A Phase 2b Randomized Blinded Study to Evaluate SYN023 Compared to Human Rabies Immune Globulin in Post Exposure Prophylaxis of Rabies in Adults with Different Rabies Exposure Risks

Investigational Product: **SYN023**

Protocol Number: **SYN023-004**

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

Sponsor:

Synermore Biologics Co., Ltd.
6F-6, No 5, Aly 22, Ln 513, Ruiguang Rd.
Neihu Dist., Taipei City 11492
Taiwan
Phone: 011.886.202.2659.0988
Fax: 011.866.202.2659.0950

Amendments Incorporated:
Version and Date: **Version 6.0 (09/22/2020)**
Version Superseded **Version 4.0 (08/15/2019)**

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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Sponsor's Representative:

John Bruce McClain, M.D.
Medical Director
+1-202-236-6975

Dr. Eric Tsao
Chief Executive Officer

Signature _____ Date 24 SEP 2020

Printed Name **Dr. Eric Tsao**

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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
$AUC_{1\text{-last}}$	area under the curve time 0 Study Day 1 to last time point
$AUC_{1\text{-inf}}$,	area under the curve time 0 Study Day 1 to infinity
$AUEC_{1\text{-}8}$	area under the efficacy curve time 0 Study Day1 through Study Day 8
$AUEC_{1\text{-}15}$	area under the efficacy curve time 0 Study Day1 through Study Day 15
βHCG	beta human chorionic gonadotropin
BMI	body mass index
BP	blood pressure
BSR cells	a hamster cell line
BUN	blood urea nitrogen
C	Celsius
CBC	complete blood count
CDC	Centers for Disease Control
C_{max},	maximum concentration
Clp	plasma clearance
CFR	code of federal regulations
cm	Centimeter
Cr	Creatinine
CRF	case report form
CNS	central nervous system
CPK	creatinine phosphokinase
CV	coefficient of variation
DSMB	data and safety monitoring board
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	enzyme linked immunosorbent assay
ERIG	equine rabies immune globulin
FAT	fluorescent antibody test
FDA	U.S. Food and Drug Administration

GMC	geometric mean concentration
HIV	human immunodeficiency virus
HRIG	human rabies immune globulin
ICI	immune complex illness
IgG	immunoglobulin G
IUD	intrauterine device
IEC	independent ethics committee
IgA	immunoglobulin A
IgG	immunoglobulin G
IgG1κ	immunoglobulin G type 1 kappa
IM	Intramuscular
IRB	institutional review board
IU	international units
IVRS	interactive voice response system
IWRS	interactive web response system
kg	Kilogram
λ_z	terminal elimination rate constant
LD_{50}	lethal dose 50%
LLN	lower limit of normal
LRG	low risk group
MNT	mouse neutralization test
MedDRA	medical dictionary for regulatory activities
mL	Milliliter
Mab	monoclonal antibody
NRG	normal risk group
PCR	polymerase chain reaction
PD	Pharmacodynamic
PEF	peak expiratory flow
PEP	post exposure prophylaxis
PK	Pharmacokinetics
PEP	post-exposure prophylaxis
PT	preferred term
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
SAE	serious adverse event
SAP	statistical analysis plan
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
V_d	volume of distribution
WHO	World Health Organization

STUDY ABSTRACT

List of changes to Version 6.0 are in Section 12

TITLE:

A Phase 2b Randomized Blinded Study to Evaluate SYN023 Compared to Human Rabies Immune Globulin in Post Exposure Prophylaxis of Rabies in Adults with Different Rabies Exposure Risks

RATIONALES:

Rationale for SYN023 development
Effective regimens of RIG and anti-rabies vaccination exist in the US and other developed countries with close to 100% effectiveness. The available immunoglobulin preparations are produced through vaccination of humans or animals followed by a multi-step plasma collection and purification process that takes months to release product. This long production chain is vulnerable to interruption and has resulted in unavailability of the product resulting in failure to provide protection for rabies. The global use of these PEP agents is constrained by their unavailability that is as high as 10% in some surveys. (Bharti et al. 2016, Jentes et al.2013, Wilde et al. 2013, c-Equine rabies immunoglobulin soon to be available 2016) Shortages and unavailability are a risk for global PEP activities. The major clinical risks from HRIG administration are anaphylaxis at approximately 1/20,000 (Sandler et al.1995). The major risks from ERIG are immune complex disease at about 0.7% and anaphylaxis at a much lower rate (Wilde et al. 1989). The known adverse reactions to RIG are not the major risks for animal products rather it is their unavailability. When there is no ERIG, rabies death is the major risk. Thus the major reason for anti-rabies Mab development is to provide a robust supply chain to avoid deaths from unavailability.

The availability of an alternate effective, well characterized humanized IgG therapy manufactured through a well-defined industrial process will ensure the availability of anti-rabies PEP and should be an objective of global anti-rabies efforts. This trial is proposed to further the licensure of SYN023 to provide an effective PEP alternative available to those exposed persons who need such a product.

Rationale for HRIG as a control group
A placebo controlled rabies trial is unethical thus HRIG is selected as the control group. Rabies immune globulin from equine and human sources (HRIG) have been evaluated in many trials and HRIG is the standard of care in the United States (Manning 2008).

Rationale for 5 dose (Essen) dose regimen rather than the 4 dose regimen
The sponsor has selected the 5 dose Essen regimen or rabies vaccination: Days, 0, 3, 7, 14 and 28 (Study Days 1, 4, 8, 15, 29). This is the regimen in the current version of the package insert of

the rabies vaccine selected for this trial. The sponsor is aware that the WHO and the American Committee on Immunization Practices have changed their recommendations to a 4 dose regimen: Days 0, 3, 7 and 14 (WHO Background Paper 2017, Rupprecht et al. 2010). A recent survey has summarized the heterogeneity of pre-exposure prophylaxis (PEP) recommendations (Buchy 2017). The 5 dose regimen remains the standard in rabies vaccine product information. All of the regions where SYN023 will be studied in its development currently include or have included the 5 dose regimen in the recent past (Buchy 2017, Republic of the Philippines 2018, WHO Background Paper 2017). Synermore is confident that the 5 dose regimen is clinically and ethically acceptable for use in a clinical study in all jurisdictions. Since analysis of multiple vaccine regimens is not an objective of the protocol the 5 dose regimen is selected to reduce analytic difficulties when data is combined from different studies for biological licensing submissions.

Rationale for the composite efficacy endpoint
The primary objective is a composite endpoint with four elements to reflect the pharmacodynamics of administered SYN023/HRIG, the immune response to rabies vaccine and the occurrence of rabies, all important features of rabies prophylaxis.

The first composite element is superiority of the geometric mean RVNA concentration in SYN023 recipients on Study Day 8. RVNA was selected because it is a generally accepted correlate for rabies vaccine protection. Animal and human studies suggest that tissue levels of RVNA may correlate with protection by neutralizing the rabies virus before the virus is taken up into peripheral nerves from where it gains fatal access to the central nervous system (Watson et al. 1981, Schumacher et al. 1989, Shankar et al. 1991). The reason for HRIG injection in addition to vaccination is to provide immediate rabies neutralizing antibodies to prevent the entry of rabies virus into nervous tissue before rabies vaccination has elicited neutralizing antibodies through the natural immune response. This practice in historical studies seems to have reduced infection from rabies compared to rabies exposed individuals receiving only vaccination. If it is possible to demonstrate quicker and higher concentrations in the blood of RVNA from SYN023, then this may be evidence of greater potency and perhaps effectiveness. It is logical that serum levels represent passive diffusion along a concentration gradient from sites of local infiltration where the local concentration is higher than serum concentration. The pharmacodynamic variable Synermore selected to assess the prompt availability of RVNA for serum RVNA concentration (Synermore's correlate of effectiveness) on Study Day 8 after which vaccine induced antibodies will have begun to predominate as a contributor to serum RVNA. Synermore will demonstrate superiority of the GMC with an 80% power of observing a 10% margin of superiority with a p value ≤ 0.025 (Section 7.8.1).

The second element of the endpoint is noninferiority of the Study Day 99 GMC of RVNA in SYN023 recipients compared to Study Day 99 GMC of RVNA in the HRIG recipients. It is important that any immunoglobulin product administered be compatible with rabies vaccination and thus not significantly inhibit the immune response to rabies vaccination. When should this comparison of immunogenicity be performed and secondly what margin of non-inferiority

should be employed? It is Synermore's position that assessment of rabies vaccine immunogenicity should be performed on or around Study Day 99. This interval is over four times the half-lives of administered human IgG. By Study Day 99 anti-rabies antibodies including SYN023 that were administered for prophylaxis will have dissipated. Thus Study Day 99 RVNA values will reflect the long term production of natural rabies antibodies from vaccination. Synermore defines non-inferiority of a rabies vaccine response with a 20% margin of non-inferiority and equal number of SYN023 and HRIG subjects in HRIG (Section 7.8.2). The alpha value is taken to be ≤ 0.025.

The third element is the percentage of PEP recipients that have a serum RVNA concentration ≥0.5 IU/mL on Study Day 99. This is the RVNA concentration that is generally recognized to reflect protection from rabies when subjects are vaccinated. Achievement of RVNA ≥0.5 IU/mL should indicate that that the subject's vaccination has elicited a protective immune response despite the geometric mean concentration, thus any differences are not clinically important. Synermore defines non-inferiority of the percentage of SYN023 subjects with serum RVNA concentration ≥0.5 IU/mL with a 20% margin of non-inferiority and equal number of SYN023 and HRIG subjects in HRIG (7.8.3). The alpha value is taken to be ≤ 0.025.

The fourth element of the endpoint is the absence of probable or confirmed cases of rabies in the SYN032 recipients (Section 3.9.1). There is no need to specify "suspected" cases of rabies since entry into the protocol requires exposure to a possibly rabid animal and this is the factor that makes a case "probable" as opposed to "suspected." A possibly rabid animal has a "risk of rabies" according to national and local rabies policies and agreement with the research site. It is likely that there will no cases of rabies in the per protocol population of either treatment arm therefore a non-inferiority test could not be done. Synermore estimates the failure rate of properly administered PEP in adults to be between 1 in 1,000 and 1 in 10,000 (Hemachudha, 1999, Hampson 2008, Quiambao, 2008, Quiambao 2009 Shantavasinkul et al. 2010, Wilde et al. 2007). A single case of rabies in a subject properly treated with PEP meeting the per-protocol conditions in a 160 (or 184) sample of adults would be an occurrence rate of 0.6% and would be evidence for a lack of effectiveness (7.8.4).

Rationale for stratification
Bites above the level of the shoulder in the head or neck will be stratified in a 1:1 ratio by treatment arm so that there are approximately equal numbers in each treatment arm since bites in the head or neck seem to have a much higher chance of rabies transmission than bites of the trunk or extremity (Sitthi-Amorn et al. 1987, Cleveland et al. 2002, Fe'vre et al. 2005, Tenzin et al. 2011).

Rationale for extra-United States majority enrollment.
Most of the treatment allocations are to geographical areas of high rabies transmission to evaluate protection from rabies. Since this product is intended as a global product the study will occur in more than one country to examine exposure to different strains.

Rationale for per-protocol exclusion after randomization
Subjects who are randomized may be excluded from the per protocol populations after randomization if important factors that affect rabies risk or efficacy endpoint elements are discovered. PEP must not be delayed but since protocol entry criteria for patients who fail to have confirmation of inclusion/exclusion criteria such as previous rabies vaccination may not be known at the time of consent and PEP there must be some mechanism for later exclusion. All excluded subjects will be analyzed but not as part of the "per-protocol" population

- In Synermore's experience about 2% to 5% of subjects may have evidence of unknown or unrecalled rabies vaccination. Their RVNA response may be much quicker and higher than in naïve patients. Since the RVNA is a crucial efficacy element these subjects with a RVNA $\geq$ 0.1 IU that is taken to be evidence of previous vaccination must be analyzed differently.
- Subjects will be excluded for conditions discovered after randomization that impair protection such as immunodeficiency.
- Subjects will be excluded if excessive treatment delay (>54 hours) is discovered.
- Subjects will be excluded if they receive or have received protocol prohibited treatments such as RIG that will confound analysis.
- Subjects will be excluded if all of the bite wounds are discovered to have not been properly treated or injected.
- Subjects will be excluded if bites are determined to be due to non-protocol listed animals
- Subjects will be excluded if they leave the trial or their status is unknown.

Rationale for bite, broken skin lick and broken skin scratch exposure injuries eligibility for trial
Individuals with WHO Category III rabies exposures with some exceptions are eligible for the trial since they are considered WHO Category 3 exposures and RIG is indicated for these exposures. WHO Category 3 exposures include single or multiple transdermal bites or scratches or licks on broken skin, mucous membrane saliva contamination and unprotected bat exposures. Depending on the protocol defined risk substratum all observed bites, broken skin scratches and broken skin licks unprotected bat contacts and saliva contamination of mouth nose and eyes are eligible for the trial.

Rationale for bite-to-treatment interval
The bite-to-treatment interval for the administration of RIG is recommended to be as soon as possible up to 7 days by the WHO (WHO 2013). This judgment reflects the emergence of naturally produced antibodies at about 7 days. A number of surveys report that rabies cases were rare when treatment was instituted within 2 to 3 days (Si et al. 2008, Quiambao et al. 2009). Animal studies suggest that rabies virus may enter nerves within hours (Watson et al. 1981). Rabies virus may gain access to the brain within approximately 30 hours from a jaw injection (Shankar et al. 1991). Anti-rabies Mabs can interrupt this process (Schumacher et al. 1989). It is difficult to pinpoint the exact interval from studies reporting days since the counting of days may use different conventions. The interval chosen for this protocol is 48 hours plus 6 hours (54

hours) that would permit PEP to start on the third day after the bite but more likely 48 hours from the bite assuming that most bites and their PEP will occur in the daytime.

Rationale for blinding
The pharmacy will be unblinded in this study because of the need to draw up the dose based on patient weight. Since weights will be different the different volumes will not disclose identity and it will be necessary to visually blind the syringes with tubes because of slight differences in the appearance of the Study Drugs. Nevertheless it will be difficult to have absolute blinding with HRIG. Synermore judges that since the elements of the endpoint are objective the importance of blinding weaknesses in this study is secondary to adequate objective controls.

Rationale for NRG follow-up period
When the exposure time is known the incubation period of most cases occurs between 46-189 days (Noah et al.1998, Quiambao et al. 2009, Ren et al. 2015,) Some rabies incubation periods are more than a year (Boland et al. 2014). A six month follow-up will capture most cases but follow up for a year should capture almost all cases of rabies.

Rationale for interval for avoidance of pregnancy
SYN023 and HRIG are both immunoglobulins. SYN023 is not detectable in the blood by Study Day 99. Study Day 121 will be over 5 half-lives from administration and SYN023 should be eliminated from the circulation thus prohibition of pregnancy for the rest of the trial cannot be based on SYN023 exposure.

Rationale for route of administration
Immune globulins are administered by direct injection into the wound or by subcutaneous or intramuscular injection when this is not possible. Direct injection into the wound has been associated with good outcomes whereas injection at remote sites has been associated with failure of PEP (Wilde et al. 1996, Wilde et al. 1992, Shantavsinkul et al. 2010, Hemachudha et al. 1999, Bharti et al. 2016)

Rationale for SYN023 dose level
The dose level was determined by pharmacokinetic studies that demonstrated generally accepted as adequate levels of RVNA persisting for at least a month and from compatibility studies with rabies vaccines that demonstrated RVNA levels ≥ 0.5 IU/mL in rabies vaccine recipients receiving 0.3 mg/kg of SYN023 after Study Day 15 and from in vitro neutralization studies of multiple strains of rabies virus.

Rationale for photographic documentation of bite wounds
Simple uncalibrated photographs of wounds have a utility in presenting the extent number and severity of a bite wound. They will be useful during analysis with discussing individual cases and understanding safety information. They must not delay the start of PEP and thus may be recorded either before or after treatment. Interval photographs may record progress and healing. They will need to avoid recording the facial characteristics and a means must be provided for

pixilation to avoid identification of the subject. They need to be stored as a source document in a secure manner at the research site with encryption and an access roster. They will not be required for non-bite exposures. Specific consent for photography shall be obtained from the subject.

OBJECTIVES:

Primary Objective

The primary objective is a composite endpoint with four elements:

- To demonstrate that the geometric mean RVNA concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for HRIG recipients on Study Day 8 AND
- To demonstrate that the Study Day 99 geometric mean RVNA concentration for SYN023 recipients is not inferior to the geometric mean RVNA concentration for HRIG recipients AND
- To demonstrate that the percentage of subjects with RVNA concentration ≥0.5 IU/mL on Study Day 99 in SYN023 recipients is not inferior to the percentage of recipients with RVNA concentration ≥0.5 IU/mL for HRIG
  AND
- There are no probable or confirmed cases of rabies in SYN023 recipients.

Secondary Objective(s)

- To demonstrate that the geometric mean RVNA concentration for SYN023 is superior to the geometric mean RVNA concentration for HRIG on Study Day 4
- To demonstrate that the geometric mean RVNA $AUEC_{1\text{-}15}$ for SYN023 is superior to the geometric mean RVNA $AUEC_{1\text{-}15}$ for HRIG
- To describe the ratio of the geometric mean concentrations of RVNA at each time point in SYN023 recipients divided by the geometric mean concentrations of RVNA in HRIG recipients for LRG and NRG in the per-protocol and as-treated populations.
- To describe the percentage of RVNA concentration ≥0.5 IU/mL at each time point for SYN023 and HRIG recipients for LRG and NRG in the per-protocol and as-treated populations.
- To describe the pharmacokinetics of SYN023 using non-compartmental analysis. Vd, C_{max}, T_{max}, $AUC_{1\text{-}t}$, $AUC_{1\text{-}inf}$, $t_{½}$, Cl, and λ_z will be calculated when possible in the LRG and NRG protocol and as treated populations.
- To evaluate presence and effects of anti-SYN023 antibodies (anti-CTB011, anti-CTB012)
- To evaluate the safety of SYN023 compared to HyperRab® S/D
- To describe any effect of increasing BMI on SYN023 and RVNA concentrations.

DESIGN

This is a Phase 2b, double blinded, randomized study of SYN023 compared to HyperRab® S/D (a licensed HRIG) for PEP of patients who have been confirmed to have met all inclusion/exclusion criteria for their treatment group. The desired indication is the prevention of

rabies as part of PEP. The trial will be conducted in least two countries where rabies occurs. The trial will enroll sequentially two different risk substrata of WHO Category 3 rabies exposure.

Low Risk Group (LRG)

The Low Risk Group (LRG) is composed of subjects who meet the modified WHO Category 3 protocol exposure criteria (Table 2.2-1 below and Sections 3.9.4 and 3.9.5). Inclusion is limited to bites to the foot, ankle, leg or trunk and licks to broken skin, scratches with, or to broken skin, unprotected bat exposure or mucous membrane contamination by saliva or neural tissue. These exposures represent a lower rabies risk exposure within WHO Categories 3. Bites to the head, neck or genitalia are excluded from LRG Initial Enrollment and LRG General Enrollment (Section 2.2.2 to Section 2.2.4). The purpose of the LRG is to obtain early safety, pharmacodynamic and pharmacokinetic information from field sites. Since it does not have the same rabies risk as the NRG it, will be analyzed separately for clinical rabies.

Table 2.2-1 Exposure Characteristics of the Low Risk Group and Normal Risk Group

Exposure Type	LRG	NRG
Head and neck bite	-	+
Genitalia bite	-	+
Arms bite	-	+
Hands bite	-	+
Trunk bite	+	+
Legs bite	+	+
Ankles bite	+	+
Foot bite	+	+
Non-bite lick	+	+
Non-bite scratch	+	+
Non-bite bat contact	+	+
Non-bite mucous membrane	+	+

Initial Enrollment in the LRG (20 Subjects)

Safety and RVNA data through Study Day 29 from the initial 20 subjects of the LRG will be reviewed by the DSMB to confirm safety and the achievement of adequate RVNA levels ≥ 0.5 IU/mL on Study Day 15 and 29 from standard, wound management, Study Drug administration and rabies vaccination before LRG general enrollment is permitted. Subjects excluded for cause by the Per-protocol Adjudication Board (Section 3.2.8) will not be included in the RVNA per-protocol analysis but will be included in as-treated population. The initial 20 subjects in the LRG will be randomized on a 3:1 (SYN023 to HRIG) ratio. The size of the initial LRG

enrollment is arbitrary. The initial LRG enrollment is not part of the sample size calculations for the primary objective.

Advancement from Initial Enrollment LRG to General Enrollment LRG

The DSMB will permit enrollment of the General LRG Enrollment group if safety from the as-treated population and RVNA pharmacodynamic data from the per protocol population Study Days 8-29 from the initial LRG enrollment are found to be satisfactory by the DSMB (Section 5.1.5.2).

General Enrollment LRG

The LRG general enrollment of an additional 60 subjects will consist of low risk WHO Category 3 exposures (Table 2.2-1, Section 3.9.4 and 3.9.5). Subjects General Enrollment LRG will be allocated with a 1:1 randomization to either SYN023 or HRIG treatment arms. Bites to the head, neck or genitalia are not included in the LRG.

Advancement from LRG General Enrollment to the Normal Risk Group (NRG)

If Study Day 99 efficacy (RVNA) and safety LRG data from the initial and general enrollment have been judged to be adequate by the DSMB and there are no cases of rabies in SYN023 recipients by Study Day 183 then randomization into the NRG will be permitted (Section 5.1.5.3). It is presumed that a case of clinical rabies in the study population would become known to the DSMB promptly. Clinical rabies follow-up of the LRG will be made available to the DSMB through 6+ months on all patients for consideration of NRG commencement. The 12 months of LRG follow-up will not have ended when NRG enrollment starts.

Normal Risk Group (NRG)

The NRG will consist of all WHO Category 3 exposure (Table 2.2-1, Sections 3.9.4 and 3.9.5). The NRG includes all rabies risks. It is powered to evaluate the primary and some secondary study objectives and to contribute to the pharmacokinetic and pharmacokinetic description of SYN023.

Enrollment of the NRG

Subjects will be allocated with a 1:1 randomization to either SYN023 or HRIG treatment arms. Within the NRG group bites to the head, neck or genitalia that have the highest rabies risk will be stratified for each treatment arm in a 1:1 ratio. The DSMB will review the progress of pharmacodynamic and safety data during the NRG study period to avoid unnecessary risk or expense (Section 5.1.5.4).

Study Trial Size

Data from an initial subgroup of 20 subjects will be evaluated by the DSMB to ensure pharmacodynamic activity before the remainder of the LRG is enrolled. The size of this group was determined by non-statistical reasons (Table 2.3-1).

Safety and pharmacodynamic data from the entire LRG will be reviewed by the DSMB to ensure safety and pharmacodynamic adequacy. The size of the LRG is 80 subjects. Up to 45 LRG subjects will have received SYN023. This number was judged adequate to give a preliminary assessment of Study Drug performance in the LRG.

Three hundred and twenty patients are required in the per-protocol population to satisfy the efficacy elements of the AUEC-1-15 secondary endpoint. Synermore anticipates approximately 15% (48 patients) of loss to follow-up and exclusions resulting in a total NRG size of 368. Since PEP should not be delayed and some inclusion/exclusion criteria may not be known at the time of randomization some subjects may be excluded (but not replaced) from the per-protocol population by the Per-Protocol Adjudication Board if they are later discovered to have met an exclusion criterion.

Randomization will be adjusted by the randomization center such that patients are proportionately distributed between the trial sites and patients with wounds of the head, neck or genitalia are stratified approximately equally into the treatment groups.

Table 2.3-1 Enrollment by Risk Group and Treatment

Group	Enrollment	Dosage	Rabies Vaccination	Number of subjects
LRG	initial	HRIG 20 IU/kg	Day 1,4,8,15,29	5
LRG	initial	SYN023 0.3 mg/kg	Day 1,4,8,15,29	15
LRG	general	HRIG 20 IU/kg	Day 1,4,8,15,29	30
LRG	general	SYN023 0.3 mg/kg	Day 1,4,8,15,29	30
NRG	general	HRIG 20 IU/kg	Day 1,4,8,15,29	184
NRG	general	SYN023 0.3 mg/kg	Day 1,4,8,15,29	184
Total required for initial LRG enrollment				20
Total required for general LRG enrollment				60
Total required for NRG efficacy element				368
Total maximum enrollment				448

Study Duration

Subjects will be followed for 365 days post receipt of Study Drug unless withdrawn from the trial. It is important to have follow-up information on all study enrollees for the full duration of the study. Every effort should be made to remain in contact with study subjects in at least six-

week intervals to establish if the subject is in good health and to inquire about planned relocations. If health problems have occurred a verbal or written account of the duration and character of the difficulties should be obtained. This is specially important in the last six months of the study when clinic visits are less frequent.

Study Populations

Failure to meet inclusion/exclusion criteria at initial screening

Screening includes informed consent, satisfaction of inclusion criteria and an initial survey of exclusion criteria. Rabies exposed subjects that are known to fail inclusion criteria at initial screening or any immediately evaluable exclusion criteria will not be randomized into the study. They will be treated outside of the study protocol with the national standard of care for PEP. The minimum PEP standard will include ERIG or HRIG and rabies vaccination according to the national recommendations. Not all exclusion criteria need to be known at the time of randomization but those that are known will determine enrollment.

As-Treated Population

All subjects who are randomized and receive Study Drug are included in the "as-treated" population.

LRG Per-Protocol Population

Since PEP of rabies is urgent and should not be delayed, randomization and prophylaxis will begin after a screening event that includes informed consent and survey of inclusion criteria (including urine pregnancy test results) before some exclusion criteria have been confirmed. WHO Category 3 exposure victims that meet all initially knowable inclusion/exclusion criteria (Section 3.2.3 – 3.2.5) will be randomized receive wound treatment, receive Study Drug and begin a regimen of rabies vaccination.

NRG Per-Protocol Population

Since PEP of rabies is urgent and should not be delayed, randomization and prophylaxis will begin after a screening event that includes informed consent and survey of inclusion criteria (including urine pregnancy test) before some exclusion criteria have been confirmed. WHO Category 3 exposure victims that meet all initially knowable inclusion/exclusion criteria will be randomized receive Study Drug and begin a regimen of rabies vaccination

Randomization

LRG Initial Enrollment

Subjects in the initial enrollment group will be randomized on a 3:1 basis to treatment with SYN023 or HRIG. Eligibility for the LRG subjects is described in Section 2.2.1. The group as described in Table 2.3.1 is randomized in a 3:1 ratio. Subjects in the initial LRG may be excluded from the LRG per-protocol population but they will not be replaced.

LRG General Enrollment and NRG

Subjects in the general enrollment of LRG and NRG will be randomized on a 1:1 basis within each group to treatment with SYN023 or HRIG. Subjects will be allocated to treatment sites to approximate the ratio in Table 2.3-1. Within NRG enrollment subjects with head or neck bites or bites to genitalia will be stratified on a 1:1 basis into SYN023 or HRIG treatment groups.

Study sites wishing to randomize a subject will contact the study randomization center either telephonically or by electronic means. The study center will determine the randomization allocation and return the randomization assignment in written communication to the study site.

Non-replacement of Randomized LRG and NRG Patients

Subjects will not be replaced after randomization. They may be excluded from the per-protocol population

Adjustments to Randomization

Allocation of randomization among sites will be adjusted to accommodate stratification of head, neck or genitalia bites or site enrollment imbalances.

Protocol Deviations and Eligibility for the Per-protocol Population

Continuation in the per-protocol population depends on the absence of uncorrectable major protocol deviations. Major deviations are those that would degrade the fidelity of the data from the protocol. Protocol deviations requiring removal from the per-protocol population include but are not limited to those listed below.

- Defective informed consent
- Received the incorrect Study Drug
- Received the incorrect dose (± 20%) of Study Drug
- Failed to complete the scheduled rabies vaccinations through Study Day 29
- Are discovered to lack adequate prophylactic treatment of all exposure sites
- Are discovered to be injured by animal other than those listed
- Are discovered to have an interval > 54 hours from rabies exposure to the start of prophylaxis
- Are discovered to have RVNA ≥ 0.1 IU in serum obtained at Study Day 1
- Receives prohibited treatment during the trial
- Are found not to have a modified WHO Category 3 exposure (Table 2.2-1, Section 3.9.4)
- Are discovered to have or have developed HIV infection or other immunodeficiency state.
- Second high risk animal bite or contact requiring PEP
- Are discovered to have or have developed HIV infection or other immunodeficiency state.
- Second high risk animal bite or contact requiring PEP

Subjects who are discovered to not have satisfied any criteria for the per-protocol population may be excluded from that population by the Per Protocol Adjudication Board. Any exclusion of

randomized subjects from the per-protocol population after randomization must be made by the Per Protocol Adjudication Board (Section 3.2.8).

ANALYSIS OF EFFICACY

The absence of a confirmed or probable case of rabies in the per-protocol population is part of the composite endpoint (3.9.1). Subject will be periodically evaluated for the clinical signs and symptoms of human rabies. If these develop they will be referred for medical evaluation and laboratory or anatomic confirmation. All clinical rabies diagnostic tests may be performed locally at a qualified laboratory. All rabies cases will be reviewed by the DSMB.

The primary pharmacodynamic efficacy parameter is a composite endpoint with the following elements elements (see Section 2.1):

- the superiority of RVNA GMC RVNA on Study Day 8 in SYN-23 recipients compared. This represents early anti-rabies activity
- the noninferiority of Study Day 99 GMC RVNA in SYN023 recipients vs HRIG recipients. This represents the immune response to rabies vaccination.
- the noninferiority of the Study Day 99 percentage of SYN023 recipients with RVNA ≥ 0.5 IU/mL compared to HRIG recipients.

The criteria for a probable or definite (confirmed) rabies case in Sections 3.9.1 and 7.8.4.
The criteria for superiority for Study Day 8 GMC RVNA are described in Section 7.3 and 7.8.1
The criteria for non-inferiority of the Study Day 99 GMC RVNA and percentage of the group with RVNA ≥ 0.5 IU/mL are described in Section 7.3, 7.8.2 and 7.8.3.

Analyses of efficacy will be performed on the per-protocol and as-treated populations for each risk group.

All pharmacokinetic analyses of serum SYN023 concentrations will be done on the per-protocol and as treated populations. 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. Vd, C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{½}$, Cl, and λ_z will be calculated when possible. Effect of BMI on pharmacodynamic and pharmacokinetic parameters will be performed.

ANALYSIS OF ANTI-DRUG ANTIBODY

All analyses of anti-drug antibody (anti-SYN023) will be based on per-protocol and as-treated subjects for each risk group who received at least one dose of Study Drug. The presence and effect of anti-SYN023 antibodies (anti-CTB011, anti-CTB012) will be evaluated. Immunogenicity will be summarized for all time points as collected and as available. No imputation for missing immunology data will be performed. Data will be transformed as appropriate prior to analysis. The development of anti-SYN023 antibodies will be analyzed as a categorical variable by treatment assignment, with descriptive statistics. Any effect of anti-SYN023 antibodies on pharmacokinetics, pharmacodynamics or safety will be described.

ANALYSIS OF SAFETY

Safety analyses will be performed using the as-treated population for each risk group as defined in Section 7.1. Summaries will be presented by treatment group for all subjects in the safety population. The safety profile of Study Drug will be described by treatment group. The primary variable for evaluation of the safety profile will be the number and percentage of adverse events (AEs) recorded at all available post-Study Drug administration time points.

The number (percentage) of subjects with AEs will be summarized for each treatment arm 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 PT at the greatest severity or most related state recorded for that term.

Serious adverse events (SAEs) will be recorded through the final study visit for all subjects. SAE listings will be provided for subjects by treatment arm.

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

The number (percentage) of subjects with post-Study Drug administration clinical laboratory values or vital sign values recorded as newly abnormal or increased by a toxicity grade following Study Drug administration and meeting toxicity mild criteria (Grade 1) or above as specified in the Toxicity Table will be tabulated at each post- Study Drug administration time point and overall. Clinical laboratory and vital sign abnormalities will also be reported as AEs and will be included in the summary of AEs.

A sample size of 184 subjects per treatment group will also permit an initial estimate of general safety and tolerability. An approximation to the upper 95% confidence bound on the true rate of occurrence for a SYN023 associated AE not encountered in 160 (160 calculated minimum sample) subjects in the per-protocol receiving SYN023 is 2.2%.

1 INTRODUCTION

1.1 Background

Rabies is an acute lethal viral disease transmitted from animals to humans. Rabies is present in more than 150 countries and territories and on every continent except Antarctica. All mammals are believed to be susceptible to infection with the rabies 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 bites or scratches (WHO 2017). 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, PEP against rabies infection is of critical importance. Rabies vaccination alone is used for pre-exposure prophylaxis (Immunization Practices Advisory Committee 1980). 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 rabies vaccine have adequate rabies neutralizing activity (Grandien et al.1977, Vodopija et al.1988a)

The rabies mortality from bites to the head by the same rabid wolf in Iran in 1955 was 3/5 (60%) in subjects receiving rabies vaccine alone. The mortality fell to 1/12 (8%) when both rabies vaccination and rabies antisera were administered (Baltazard et al.1955). A study by the same group 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 et al.1976). Delays of up to 4 days in the initiation of rabies immune globulin after anti-rabies vaccination have demonstrated no inhibition of anti-rabies activity in blood (Khawplod et al.1996). There is some inhibition of the immune response to rabies vaccination by rabies immune globulin itself that has been recognized since early experience (Loofbourow et al. 1971, Hattwick et al.1974, Vodopija et al. 1988). The inhibition of immune response by RIG varied in a range generally accepted as adequate. There has not been a single case of rabies in an individual receiving proper PEP in the United States since 1980. The combination of rabies vaccine with rabies immune globulin (RIG) has continued to be used and remains the standard of care despite inhibition of rabies vaccine immune response (Manning et al. 2008, Kedrab, 2017).

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 rabies 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 ensure no significant inhibition (Vodopija et al.1988b).

Three anti-rabies immunoglobulin formulations prepared from hyperimmunized human donors have been approved by the FDA: HyperRab® S/D (Grifols Therapeutics) and Imogam® Rabies-HT (Sanofi Pasteur) and Kedrab® (Kamada Ltd.). Since all HRIG preparations are considered equivalent HyperRab® S/D will be used as the HRIG in this trial.

1.2 Description of SYN023

SYN023 is an equal mass mixture of CTB011 and CTB012, two monoclonal antibodies that exhibit a wide spectrum of activity against various wild-type rabies strains *in vitro*. CTB012 possesses a slightly broader spectrum of activity than CTB011. Both monoclonal antibodies bind to non-overlapping epitopes thus single point mutations should not escape binding by at least one Mab. The combined mixture SYN023 demonstrated medium to high neutralizing activity against most of the strains evaluated. These results were verified from two different laboratories.

1.3 Nonclinical Experience with SYN023

Nonclinical pharmacology studies included Mab binding studies, neutralizing potency studies of these Mabs by rapid fluorescent foci inhibition test (RFFIT) and mouse neutralization test (MNT), determination of the breadth of neutralization against a broad panel of street rabies virus, a study of the interference with vaccination in non-challenged mice and hamsters and PEP performance in Syrian hamster and Beagle dog rabies virus challenge models.

The preclinical pharmacology studies performed to date with the SYN023 Mab mixture (humanized Mabs CTB011 and CTB012) have examined the binding of antibodies CTB011 and CTB012 to non-overlapping determinants on the rabies virus glycoprotein antigen, and have identified amino acid residues critical for specific binding of both antibodies.

In vitro rabies virus inhibition by CTB011 and CTB012 exhibited a wide spectrum of activity against various wild-type rabies strains. CTB012 has a slightly broader spectrum of activity. The combined CRB011 and CTB012 product elicited medium to high neutralizing activity against most of the strains evaluated.

Rabies vaccine inhibition in the hamster

Studies in hamsters were performed to determine whether the SYN023 component antibodies would interfere with the immune response to rabies vaccine in non-challenged Syrian hamsters. CTB011 treatment had no adverse impact on active immunization produced by the rabies vaccine, and hamsters maintained high serum antibody levels until the end of the study. CTB012

produced higher serum RVNA concentrations following IM dosing. CTB012 treatment did not adversely impact the active immune response to rabies vaccine seen at later time points. The magnitude of the response was comparable to that produced by HRIG + rabies vaccine. Inhibitory mean antibody titers were maintained until the end of the study in all CTB012-treated groups, and these were comparable to the levels observed with HRIG + rabies vaccine.

In the SYN023-dosed hamsters, there were clear dose-dependent differences in the RVNA titers/profiles from 0.003 to 1 mg/kg SYN023. Ultimately, this study established that the RVNA response to a moderate dose of SYN023 might be capable of supplying sufficient immune protection to bridge animals/patients to the point of active immunity. Importantly, early treatment with either CTB011 or CTB012 or their combination (SYN023) did not appear to adversely impact the eventual immune response to rabies vaccine treatment.

Studies in rabies vaccine-immunized hamsters demonstrated that neither SYN023 nor HRIG adversely impacted the ability of the rabies vaccine (US approved) to induce RVNA concentrations generally accepted as adequate (≥0.5 IU/mL) in this hamster model. Comparison of the RVNA mean titers of each group by day indicates some inhibition of RVNA response, since the mean titers of the hamsters administered rabies vaccine alone or rabies vaccine and HRIG were higher at each time point than the titers of the hamsters administered SYN023 with rabies vaccine. SYN023 administration induced a high RVNA at Day 3, when the antibody response to vaccination is generally very low or undetectable. The RVNA inducing potency of the SYN023 Mab mixture is higher than the HRIG induced RVNA potency. Despite the higher potency of the SYN023 antibody mixture, the hamsters in that group were able to produce RVNA above the concentrations generally accepted as adequate (≥0.5 IU/mL) at all remaining time points.

Rabies challenge studies in Syrian hamsters

Three PEP studies were performed with the CTB011/CTB012 mixture in a Syrian hamster model of rabies infection. In the first study, three different doses of rabies virus were used for challenge. Results showed that when Syrian hamsters were challenged with the standard infection dose of 50 LD_{50}, the incubation latent period of the rabies virus was 7-8 days and PEP of hamsters with rabies vaccine at all doses of the Mab mixture resulted in 100% survival (10/10).

Challenge with 200 LD_{50} of rabies virus resulted in an incubation period of the rabies virus of 6-7 days and PEP with Mab mixture (1000 and 5000 IU/kg) plus rabies vaccine resulted in a survival rate of 7/8 and 8/8, respectively, which was higher than the survival rate for HRIG plus rabies vaccine (50%). Challenge with the ultra-high infection dose (400 LD_{50}) resulted in a latent rabies virus period of 5-6 days and there was no survival when hamsters were treated with HRIG plus rabies vaccine. Treatment of hamsters with 1000 and 5000 IU/kg of the Mab mixture resulted in a survival rate of approximately 40% (3/8). Overall, results showed that the Mab mixture provided a level of protection against rabies comparable with that of HRIG plus rabies vaccine at the standard virus infection dose (50 LD_{50}) and protection that was superior to HRIG

plus rabies vaccine with the high and ultra-high infection doses. These data support administration of the CTB011/CTB012 Mab mixture with rabies vaccine to provide protection from rabies virus infection.

In this experiment the SYN023 Mab mixture provided dose-dependent increases in protection and survival following rabies virus challenge

A second dose response study was performed using a narrower dose range of SYN023 Mab mixture (i.e., 0.03, 0.1, 0.3, and 1 mg/kg). Findings were similar to those of the first study, and again demonstrated dose-dependent increases in protection and survival with SYN023 Mab mixture plus rabies vaccine. These results further confirmed that antibodies CTB011 and CTB012 were protective and did not interfere significantly with the immune response to rabies vaccine in the hamster model.

A third study in hamsters also suggests that PEP treatment with SYN023 in tandem with rabies vaccine provides dose-dependent protection against lethal challenge with rabies virus in Syrian hamsters. At the end of the study RVNA levels were generally elevated in surviving SYN023-treated hamsters with highest RVNA titers observed at the lower doses of SYN023 plus rabies vaccine.

Rabies challenge studies in Beagle dogs

In the first Beagle PEP experiment SYN023 was tested at doses ranging from 0.03 up to 1 mg/kg in different groups of 4 animals each. SYN023 provided higher survival against rabies virus challenge compared to the positive control of HRIG 20 IU/kg + rabies vaccine. SYN023 at both 0.1 and 1.0 mg/kg, administered with rabies vaccine, provided complete (100%) protection against virus challenge, with all dogs surviving until the end of the study. A single dog in the 4 dog group dosed with 0.3 mg/kg SYN023 died on Day 12 post-challenge. In the low-dose 0.03 mg/kg group SYN023 group, two dogs died for 50% mortality. The mortality in the HRIG group was 75%. Mortality in the negative control (saline-treated) group was 100%. SYN023 exhibited a dose response of increased survival. All SYN023 doses had increased survival compared to the HRIG group.

In the second Beagle PEP study, SYN023 was tested with rabies vaccine at doses ranging from 0.03 up to 1 mg/kg in groups of 8 Beagle dogs. In the positive control group of HRIG 20 IU/kg administered with rabies vaccine all 8 animals survived through Day 28. All animal receiving SYN023 at any dose plus rabies vaccine survived. There were three negative controls in this study: saline alone, rabies vaccine alone, and SYN023 alone without rabies vaccine. In the saline group 7/8 animal had developed rabies by the end of the study at day 28. In the rabies vaccine alone group 2/8 animal had developed rabies by the end of the study. In the SYN023 alone group none of the animals had developed rabies. There was no dose response in this study since survival was 100% in any animal receiving SYN023 plus rabies vaccine.

In the third Beagle PEP experiment a highly virulent New York City street rabies virus strain was used as the challenge in groups of 6 Beagle dogs. None (0/6) of the animal receiving rabies vaccine alone survived. All animals (6/6) receiving 0.3 mg/kg SYN023 plus rabies vaccine survived.

Toxicology

Tissue Binding
No specific binding of CTB011 or CTB012 Mabs alone or in combination to normal, frozen human tissues *in situ* human tissues was identified compared to results obtained with control groups. CTB011 and CTB012 Mabs could specifically bind with rabies virus infected BSR cells, whereas no specific binding was observed to normal human tissues for SYN023, CTB011, or CTB012. Mabs CTB011, CTB012, and SYN023 did not reveal any notable cytotoxicity at concentrations up to 40 µg/mL in either normal or rabies-infected BSR cells, nor did any of the single Mabs or the SYN023 Mab mixture produce any observable ADCC activity at concentrations up to 40 µg/mL in either normal or infected cells. Both Mabs as well as the SYN023 antibody mixture all produced dose-dependent CDC activity in rabies infected, but not normal BSR cells, suggesting that these antibodies can target cells infected with rabies virus and can destroy them via a CDC-dependent mechanism.

A Pilot Repeat-dose Intramuscular Toxicity Study in Rats
A pilot repeat-dose intramuscular study was performed with SYN023 in male and female Sprague-Dawley rats. Rats were dosed IM once weekly for two consecutive weeks (total twice) on Days 1 and 8 with either saline or SYN023 at doses of 1, 3, or 10 mg/kg. No mortality or morbidity was observed in any animals throughout the study. There were no apparent abnormalities in clinical observations, body weights, food consumption, clinical pathology, and organ weight and organ weight ratios noted in animals treated with 1, 3, and 10 mg/kg of SYN023 as compared to the concurrent control group. No abnormal macroscopic findings were noted in any animals on Day 15. SYN023 was found to be non-toxic at these doses tested in rats.

Repeat-dose Intramuscular Toxicity and Toxicokinetic Study of SYN023 in Rats
A second repeat-dose (3-dose) intramuscular toxicity and toxicokinetic study was also performed in Sprague-Dawley rats. Groups of rats were treated once weekly for three consecutive weeks with vehicle (0.9% saline) or SYN023 at 1, 3 or 10 mg/kg and were observed for either 3 days or 6 weeks following their final dose.

There were no deaths or morbidity noted in any animals treated with 1, 3, and 10 mg/kg of SYN023 throughout the study. No toxicologically significant changes in clinical observations, body weights, body temperature, food consumption, clinical pathology, ophthalmic exams, urinalysis, T-Lymphocyte subsets, and organ weight or organ weight ratios were noted in SYN023-treated rats as compared to the control group. There were no apparent abnormal changes noted at injection sites, and there were no SYN023-related changes in macroscopic or microscopic findings in rats dosed once weekly for three weeks with SYN023 at doses up to 10

mg/kg/day or in rats maintained for a further 6-week recovery period. Following repeated IM dosing of male and female rats with SYN023 for three consecutive weeks (three doses) at 1, 3 or 10 mg/kg, the no observed adverse event level (NOAEL) was considered to be equal to or greater than 10 mg/kg for both females and male Sprague Dawley rats.

During the study, totals of 3/18, 4/18, and 4/18 animals exhibited antibodies against CTB011, and 3/18, 4/18, and 4/18 demonstrated antibodies against CTB012 in Groups 6-8 at 1, 3, and 10 mg/kg, respectively. Neutralizing activity of anti-CTB011 and anti-CTB012 antibodies was observed in these animals.

Conclusions from nonclinical studies
In vitro rabies neutralization studies and *in vivo* pharmacokinetic and immunization dose response studies demonstrate that SYN023 components have anti-rabies activity and while there may be some effect on RVNA concentrations post-immunization the doses studied (0.003 to 1.0 mg/kg) do not seem to interfere with the development of RVNA concentrations generally accepted as adequate (≥ 0.5 IU/mL). Rabies challenge studies in hamsters and Beagle dogs indicate that SYN023 exhibits either a complete or dose dependent protective effect on the development of rabies compared to HRIG and rabies vaccine-only controls at clinically relevant dosages (0.03 to 1.0 mg/kg). SYN023 administered to rats at repeated doses of 10mg/kg, a dose that exceeds those found to have activity in animals suggest that SYN023 is non-toxic in the species tested.

1.4 Clinical Experience with SYN023

A total of 209 individuals have been enrolled in SYN023 studies. Of the 209 enrollees 127 have received SYN023. Doses up to 2 mg/kg were evaluated and found to have an acceptable safety profile. One hundred seventeen have received the 0.3 mg/kg dose by intramuscular or subcutaneous injection.

SYN023 administered alone to human volunteers at the 0.3 mg/kg dose by intramuscular or subcutaneous routes exceeded the ≥ 0.5 IU/mL blood inhibitory threshold RVNA levels promptly usually within 1 day. Supra-inhibitory levels at the 0.3 mg/kg dose are then maintained for 35 to 42 days.

SYN023 was co-administered with both US licensed rabies vaccines, Rabavert® and Imovax®. SYN023 achieved inhibitory blood levels faster compared to HRIG during the critical first week of a PEP regimen. Since the local tissue levels from direct injection of antibodies into the rabies wound are likely more important than blood levels in rabies prevention, the significance of these rapidly achieved blood levels is not known. Synermore speculates that rapid blood concentrations from antibodies injected into tissues imply more rapid diffusion through tissues and such tissue diffusion might be an important property. The RVNA concentrations in the SYN023 cohort were also higher than HRIG in the first week although again the significance of supra-inhibitory RVNA activity is unknown.

Many anti-rabies antibodies seem to possess some ability to lower the immune response to rabies vaccination (Loofbourow 1971, Lang 1998a, Lang 1998 b). HRIG still permits effective rabies vaccination because any lowering of RVNA is still in the adequate range. The higher RVNA concentrations from SYN023 measured early in PEP is followed by a lower but still supra-inhibitory RVNA value starting at Day 14 after SYN023 and HRIG injection. SYN023 seems to inhibit the apparent immunogenicity of the rabies vaccine more than HRIG as measured by blood RVNA concentrations. Since both SYN023 and HRIG given with rabies vaccine induced adequate RVNA activity in recipients the significance of this difference is unknown. Both HRIG and SYN023 seem to be compatible with both licensed rabies vaccines in a PEP regimen.

Antibodies to SYN023 components: anti-CTB011and anti-CTB012 antibodies were surveyed. Surprisingly about 20% of subjects with no history of exposure to CTB011 had anti-CTB011 prior to administration. Only about 3% of individuals had antibodies to CTB012 pre-exposure. When analyzed by the presence or absence of anti-CTB011 antibodies no difference in pharmacokinetics, RVNA value or AEs could be discerned. The anti-CTB011antibodies do not seem to have a pharmacokinetic, pharmacodynamic or safety effect and have an unknown significance.

SYN023 had an acceptable safety profile with no deaths, related serious adverse events or systemic injection reactions. The most common related adverse event was headache followed by local injection site manifestations.

Conclusions from human studies
SYN023 seems to provide very early serum levels of RVNA from both IM and subcutaneous administration while permitting the development of rabies vaccine induced RVNA concentrations generally accepted as adequate (≥0.5 IU/mL). Pre-existing anti-CTB011 antibodies encountered in about 20% of recipients do not seem to affect the serum RVNA activity, the pharmacokinetics or the AE profile. The safety profile is acceptable.

1.5 Clinical Experience with Products Related to SYN023

An anti-rabies Mab SII RMAB was licensed during 2017 in India for use in PEP. The product was licensed based on achievement of noninferiority of RVNA values from a 3.3. IU/kg SII RMAB dose recipients that were not inferior to those observed in 20 IU/kg HRIG dose recipients on Study Day 14. There were 200 participants in the trial. The rabies vaccine regimen was the standard 5 dose IM regimen. Clinical rabies was not an endpoint in the 84 day trial but was not mentioned in the paper (Gogtay 2018). The 84 day follow-up was long enough to have observed some rabies cases. This study indicates that some regulatory authorities believe that RVNA values are a surrogate of PEP protection from rabies. At the time of this protocol no information is available on the Indian government's pharmacovigilance site or in clinical reports regarding clinical success or failure of SII RMAB.

1.6 Rationales for Study

Rationale for SYN023 development
Effective regimens of RIG and anti-rabies vaccination exist in the US and other developed countries with close to 100% effectiveness. The available immunoglobulin preparations are produced through vaccination of humans or animals followed by a multi-step plasma collection and purification process that takes months to release product. This long production chain is vulnerable to interruption and has resulted in unavailability of the product resulting in failure to provide protection for rabies. The global use of these PEP agents is constrained by their unavailability that is as high as 10% in some surveys. (Bharti et al. 2016, Jentes et al.2013, Wilde et al. 2013, c-Equine rabies immunoglobulin soon to be available 2016) Shortages and unavailability are a risk for global PEP activities. The major clinical risks from HRIG administration are anaphylaxis at approximately 1/20,000 (Sandler et al.1995). The major risks from ERIG are immune complex disease at about 0.7% and anaphylaxis at a much lower rate (Wilde et al. 1989). The known adverse reactions to RIG are not the major risks for animal products rather it is their unavailability. When there is no ERIG, rabies death is the major risk. Thus the major reason for anti-rabies Mab development is to provide a robust supply chain to avoid deaths from unavailability.

The availability of an alternate effective, well characterized humanized IgG therapy manufactured through a well-defined industrial process will ensure the availability of anti-rabies PEP and should be an objective of global anti-rabies efforts. This trial is proposed to further the licensure of SYN023 to provide an effective PEP alternative available to those exposed persons who need such a product.

Rationale for HRIG as a control group
A placebo controlled rabies trial is unethical thus HRIG is selected as the control group. Rabies immune globulin from equine and human sources (HRIG) have been evaluated in many trials and HRIG is the standard of care in the United States (Manning 2008).

Rationale for 5 dose (Essen) dose regimen rather than the 4 dose regimen
The sponsor has selected the 5 dose Essen regimen or rabies vaccination: Days, 0, 3, 7, 14 and 28 (Study Days 1, 4, 8, 15, 29). This is the regimen in the current version of the package insert of the rabies vaccine selected for this trial. The sponsor is aware that the WHO and the American Committee on Immunization Practices have changed their recommendations to a 4 dose regimen: Days 0, 3, 7 and 14 (WHO Background Paper 2017, Rupprecht et al. 2010). A recent survey has summarized the heterogeneity of pre-exposure prophylaxis (PEP) recommendations (Buchy 2017). The 5 dose regimen remains the standard in rabies vaccine product information. All of the regions where SYN023 will be studied in its development currently include or have included the 5 dose regimen in the recent past (Buchy 2017, Republic of the Philippines 2018, WHO Background Paper 2017). Synermore is confident that the 5 dose regimen is clinically and ethically acceptable for use in a clinical study in all jurisdictions. Since analysis of multiple vaccine regimens is not an objective of the protocol the 5 dose regimen is selected to reduce

analytic difficulties when data is combined from different studies for biological licensing submissions.

Rationale for the composite efficacy endpoint
The primary objective is a composite endpoint with four elements to reflect the pharmacodynamics of administered SYN023/HRIG, the immune response to rabies vaccine and the occurrence of rabies, all important features of rabies prophylaxis.

The first composite element is superiority of the geometric mean RVNA concentration in SYN023 recipients on Study Day 8. RVNA was selected because it is a generally accepted correlate for rabies vaccine protection. Animal and human studies suggest that tissue levels of RVNA may correlate with protection by neutralizing the rabies virus before the virus is taken up into peripheral nerves from where it gains fatal access to the central nervous system (Watson et al. 1981, Schumacher et al. 1989, Shankar et al. 1991). The reason for HRIG injection in addition to vaccination is to provide immediate rabies neutralizing antibodies to prevent the entry of rabies virus into nervous tissue before rabies vaccination has elicited neutralizing antibodies through the natural immune response. This practice in historical studies seems to have reduced infection from rabies compared to rabies exposed individuals receiving only vaccination. If it is possible to demonstrate quicker and higher concentrations in the blood of RVNA from SYN023, then this may be evidence of greater potency and perhaps effectiveness. It is logical that serum levels represent passive diffusion along a concentration gradient from sites of local infiltration where the local concentration is higher than serum concentration. The pharmacodynamic variable Synermore selected to assess the prompt availability of RVNA for serum RVNA concentration (Synermore's correlate of effectiveness) on Study Day 8 after which vaccine induced antibodies will have begun to predominate as a contributor to serum RVNA. Synermore will demonstrate superiority of the GMC with an 80% power of observing a 10% margin of superiority with a p value ≤ 0.025 (Section 7.8.1).

The second element of the endpoint is noninferiority of the Study Day 99 GMC of RVNA in SYN023 recipients compared to Study Day 99 GMC of RVNA in the HRIG recipients. It is important that any immunoglobulin product administered be compatible with rabies vaccination and thus not significantly inhibit the immune response to rabies vaccination. When should this comparison of immunogenicity be performed and secondly what margin of non-inferiority should be employed? It is Synermore's position that assessment of rabies vaccine immunogenicity should be performed on or around Study Day 99. This interval is over four times the half-lives of administered human IgG. By Study Day 99 anti-rabies antibodies including SYN023 that were administered for prophylaxis will have dissipated. Thus Study Day 99 RVNA values will reflect the long term production of natural rabies antibodies from vaccination. Synermore defines non-inferiority of a rabies vaccine response with a 20% margin of non-inferiority and equal number of SYN023 and HRIG subjects in HRIG (Section 7.8.2). The alpha value is taken to be ≤ 0.025.

The third element is the percentage of PEP recipients that have a serum RVNA concentration ≥0.5 IU/mL on Study Day 99. This is the RVNA concentration that is generally recognized to reflect protection from rabies when subjects are vaccinated. Achievement of RVNA ≥0.5 IU/mL should indicate that that the subject's vaccination has elicited a protective immune response despite the geometric mean concentration, thus any differences are not clinically important. Synermore defines non-inferiority of the percentage of SYN023 subjects with serum RVNA concentration ≥0.5 IU/mL. with a 20% margin of non-inferiority and equal number of SYN023 and HRIG subjects in HRIG (7.8.3). The alpha value is taken to be ≤ 0.025.

The fourth element of the endpoint is the absence of probable or confirmed cases of rabies in the SYN023 recipients (Section 3.9.1). There is no need to specify "suspected" cases of rabies since entry into the protocol requires exposure to a possibly rabid animal and this is the factor that makes a case "probable" as opposed to "suspected." A possibly rabid animal has a "risk of rabies" according to national and local rabies policies and agreement with the research site. It is likely that there will no cases of rabies in the per protocol population of either treatment arm therefore a non-inferiority test could not be done. Synermore estimates the failure rate of properly administered PEP in adults to be between 1 in 1,000 and 1 in 10,000 **(**Hemachudha, 1999, Hampson 2008, Quiambao, 2008, Quiambao 2009 Shantavasinkul et al. 2010, Wilde et al. 2007). A single case of rabies in a subject properly treated with PEP meeting the per-protocol conditions in a 160 (or 184) sample of adults would be an occurrence rate of 0.6% and would be evidence for a lack of effectiveness (7.8.4).

Rationale for stratification
Bites above the level of the shoulder in the head or neck will be stratified in a 1:1 ratio by treatment arm so that there are approximately equal numbers in each treatment arm since bites in the head or neck seem to have a much higher chance of rabies transmission than bites of the trunk or extremity (Sitthi-Amorn et al. 1987, Cleveland et al. 2002, Fe'vre et al. 2005, Tenzin et al. 2011).

Rationale for extra-United States majority enrollment.
Most of the treatment allocations are to geographical areas of high rabies transmission to evaluate protection from rabies. Since this product is intended as a global product the study will occur in more than one country to examine exposure to different strains.

Rationale for per-protocol exclusion after randomization
Subjects who are randomized may be excluded from the per protocol populations after randomization if important factors that affect rabies risk or efficacy endpoint elements are discovered. PEP must not be delayed but since protocol entry criteria for patients who fail to have confirmation of inclusion/exclusion criteria such as previous rabies vaccination may not be known at the time of consent and PEP there must be some mechanism for later exclusion. All excluded subjects will be analyzed but not as part of the "per-protocol" population

- In Synermore's experience about 2% to 5% of subjects may have evidence of unknown or unrecalled rabies vaccination. Their RVNA response may be much quicker and higher than in naïve patients. Since the RVNA is a crucial efficacy element these subjects with a RVNA ≥ 0.1 IU that is taken to be evidence of previous vaccination must be analyzed differently.
- Subjects will be excluded for conditions discovered after randomization that impair protection such as immunodeficiency.
- Subjects will be excluded if excessive treatment delay (>54 hours) is discovered.
- Subjects will be excluded if they receive or have received protocol prohibited treatments such as RIG that will confound analysis.
- Subjects will be excluded if all of the bite wounds are discovered to have not been properly treated or injected.
- Subjects will be excluded if bites are determined to be due to non-protocol listed animals
- Subjects will be excluded if they leave the trial or their status is unknown.

Rationale for bite, broken skin lick and broken skin scratch exposure injuries eligibility for trial
Individuals with WHO Category III rabies exposures with some exceptions are eligible for the trial since they are considered WHO Category 3 exposures and RIG is indicated for these exposures. WHO Category 3 exposures include single or multiple transdermal bites or scratches or licks on broken skin, mucous membrane saliva contamination and unprotected bat exposures. Depending on the protocol defined risk substratum all observed bites, broken skin scratches and broken skin licks unprotected bat contacts and saliva contamination of mouth nose and eyes are eligible for the trial.

Rationale for bite-to-treatment interval
The bite-to-treatment interval for the administration of RIG is recommended to be as soon as possible up to 7 days by the WHO (WHO 2013). This judgment reflects the emergence of naturally produced antibodies at about 7 days. A number of surveys report that rabies cases were rare when treatment was instituted within 2 to 3 days (Si et al. 2008, Quiambao et al. 2009). Animal studies suggest that rabies virus may enter nerves within hours (Watson et al. 1981). Rabies virus may gain access to the brain within approximately 30 hours from a jaw injection (Shankar et al. 1991). Anti-rabies Mabs can interrupt this process (Schumacher et al. 1989). It is difficult to pinpoint the exact interval from studies reporting days since the counting of days may use different conventions. The interval chosen for this protocol is 48 hours plus 6 hours (54 hours) that would permit PEP to start on the third day after the bite but more likely 48 hours from the bite assuming that most bites and their PEP will occur in the daytime.

Rationale for blinding
The pharmacy will be unblinded in this study because of the need to draw up the dose based on patient weight. Since weights will be different the different volumes will not disclose identity and it will be necessary to visually blind the syringes with tubes because of slight differences in the appearance of the Study Drugs. Nevertheless it will be difficult to have absolute blinding

with HRIG. Synermore judges that since the elements of the endpoint are objective the importance of blinding weaknesses in this study is secondary to adequate objective controls.

Rationale for NRG follow-up period
When the exposure time is known the incubation period of most cases occurs between 46-189 days (Noah et al.1998, Quiambao et al. 2009, Ren et al. 2015,) Some rabies incubation periods are more than a year (Boland et al. 2014). A six month follow-up will capture most cases but follow up for a year should capture almost all cases of rabies.

Rationale for interval for avoidance of pregnancy
SYN023 and HRIG are both immunoglobulins. SYN023 is not detectable in the blood by Study Day 99. Study Day 121 will be over 5 half-lives from administration and SYN023 should be eliminated from the circulation thus prohibition of pregnancy for the rest of the trial cannot be based on SYN023 exposure.

Rationale for route of administration
Immune globulins are administered by direct injection into the wound or by subcutaneous or intramuscular injection when this is not possible. Direct injection into the wound has been associated with good outcomes whereas injection at remote sites has been associated with failure of PEP (Wilde et al. 1996, Wilde et al. 1992, Shantavsinkul et al. 2010, Hemachudha et al. 1999, Bharti et al. 2016)

Rationale for SYN023 dose level
The dose level was determined by pharmacokinetic studies that demonstrated generally accepted as adequate levels of RVNA persisting for at least a month and from compatibility studies with rabies vaccines that demonstrated RVNA levels ≥ 0.5 IU/mL in rabies vaccine recipients receiving 0.3 mg/kg of SYN023 after Study Day 15 and from in vitro neutralization studies of multiple strains of rabies virus.

Rationale for photographic documentation of bite wounds
Simple uncalibrated photographs of wounds have a utility in presenting the extent number and severity of a bite wound. They will be useful during analysis with discussing individual cases and understanding safety information. They must not delay the start of PEP and thus may be recorded either before or after treatment. Interval photographs may record progress and healing. They will need to avoid recording the facial characteristics and a means must be provided for pixilation to avoid identification of the subject. They need to be stored as a source document in a secure manner at the research site with encryption and an access roster. They will not be required for non-bite exposures. Specific consent for photography shall be obtained from the subject.

2 STUDY OBJECTIVES AND DESIGN

2.1 Objectives

Primary Objective

The primary objective is a composite endpoint with four elements:

- To demonstrate that the geometric mean RVNA concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for HRIG recipients on Study Day 8
  AND
- To demonstrate that the Study Day 99 geometric mean RVNA concentration for SYN023 recipients is not inferior to the geometric mean RVNA concentration for HRIG recipients
  AND
- To demonstrate that the percentage of subjects with RVNA concentration ≥0.5 IU/mL on Study Day 99 in SYN023 recipients is not inferior to the percentage of recipients with RVNA concentration ≥0.5 IU/mL for HRIG
  AND
- There are no probable or confirmed cases of rabies in SYN023 recipients.

Secondary Objective(s)

- To demonstrate that the geometric mean RVNA concentration for SYN023 is superior to the geometric mean RVNA concentration for HRIG on Study Day 4
- To demonstrate that the geometric mean RVNA $AUEC_{1\text{-}15}$ for SYN023 is superior to the geometric mean RVNA $AUEC_{1\text{-}15}$ for HRIG
- To describe the ratio of the geometric mean concentrations of RVNA at each time point in SYN023 recipients divided by the geometric mean concentrations of RVNA in HRIG recipients for LRG and NRG in the per-protocol and as-treated populations.
- To describe the percentage of RVNA concentration ≥0.5 IU/mL at each time point for SYN023 and HRIG recipients for LRG and NRG in the per-protocol and as-treated populations.
- To describe the pharmacokinetics of SYN023 using non-compartmental analysis. Vd, C_{max}, T_{max}, $AUC_{1\text{-}t}$, $AUC_{1\text{-}inf}$, $t_{½}$, Cl, and λ_z will be calculated when possible in the LRG and NRG protocol and as treated populations.
- To evaluate presence and effects of anti-SYN023 antibodies (anti-CTB011, anti-CTB012)
- To evaluate the safety of SYN023 compared to HyperRab® S/D
- To describe any effect of increasing BMI on SYN023 and RVNA concentrations.

2.2 Design

This is a Phase 2b, double blinded, randomized study of SYN023 compared to HyperRab® S/D (a licensed HRIG) for PEP of patients who have been confirmed to have met all inclusion/exclusion criteria for their treatment group. The desired indication is the prevention of rabies as part of PEP. The trial will be conducted in least two countries where rabies occurs. The trial will enroll sequentially two different risk substrata of WHO Category 3 rabies exposure.

2.2.1 Low Risk Group (LRG)

The Low Risk Group (LRG) is composed of subjects who meet the modified WHO Category 3 protocol exposure criteria (Table 2.2-1 below and Sections 3.9.4 and 3.9.5). Inclusion is limited to bites to the foot, ankle, leg or trunk and licks to broken skin, scratches with, or to broken skin, unprotected bat exposure or mucous membrane contamination by saliva or neural tissue. These exposures represent a lower rabies risk exposure within WHO Categories 3. Bites to the head, neck or genitalia are excluded from LRG Initial Enrollment and LRG General Enrollment (Section 2.2.2 to Section 2.2.4). The purpose of the LRG is to obtain early safety, pharmacodynamic and pharmacokinetic information from field sites. Since it does not have the same rabies risk as the NRG it, will be analyzed separately for clinical rabies.

Table 2.2-1 Exposure Characteristics of the Low Risk Group and Normal Risk Group

Exposure Type	LRG	NRG
Head and neck bite	-	+
Genitalia bite	-	+
Arms bite	-	+
Hands bite	-	+
Trunk bite	+	+
Legs bite	+	+
Ankles bite	+	+
Foot bite	+	+
Non-bite lick	+	+
Non-bite scratch	+	+
Non-bite bat contact	+	+
Non-bite mucous membrane	+	+

2.2.2 Initial Enrollment in the LRG (20 Subjects)

Safety and RVNA data through Study Day 29 from the initial 20 subjects of the LRG will be reviewed by the DSMB to confirm safety and the achievement of adequate RVNA levels ≥ 0.5 IU/mL on Study Day 15 and 29 from standard, wound management, Study Drug administration and rabies vaccination before LRG general enrollment is permitted. Subjects excluded for cause by the Per-protocol Adjudication Board (Section 3.2.8) will not be included in the RVNA per-protocol analysis but will be included in as-treated population. The initial 20 subjects in the LRG will be randomized on a 3:1 (SYN023 to HRIG) ratio. The size of the initial LRG enrollment is arbitrary. The initial LRG enrollment is not part of the sample size calculations for the primary objective.

2.2.3 Advancement from Initial Enrollment LRG to General Enrollment LRG

The DSMB will permit enrollment of the General LRG Enrollment group if safety from the as-treated population and RVNA pharmacodynamic data from the per protocol population Study Days 8-29 from the initial LRG enrollment are found to be satisfactory by the DSMB (Section 5.1.5.2).

2.2.4 General Enrollment LRG

The LRG general enrollment of an additional 60 subjects will consist of low risk WHO Category 3 exposures (Table 2.2-1, Section 3.9.4 and 3.9.5). Subjects General Enrollment LRG will be allocated with a 1:1 randomization to either SYN023 or HRIG treatment arms. Bites to the head, neck or genitalia are not included in the LRG.

2.2.5 Advancement from LRG General Enrollment to the Normal Risk Group (NRG)

If Study Day 99 efficacy (RVNA) and safety LRG data from the initial and general enrollment have been judged to be adequate by the DSMB and there are no cases of rabies in SYN023 recipients by Study Day 183 then randomization into the NRG will be permitted (Section 5.1.5.3). It is presumed that a case of clinical rabies in the study population would become known to the DSMB promptly. Clinical rabies follow-up of the LRG will be made available to the DSMB through 6+ months on all patients for consideration of NRG commencement. The 12 months of LRG follow-up will not have ended when NRG enrollment starts.

2.2.6 The Normal Risk Group (NRG)

The NRG will consist of all WHO Category 3 exposure (Table 2.2-1, Sections 3.9.4 and 3.9.5). The NRG includes all rabies risks. It is powered to evaluate the primary and some secondary study objectives and to contribute to the pharmacokinetic and pharmacokinetic description of SYN023.

2.2.7 Enrollment of the NRG

Subjects will be allocated with a 1:1 randomization to either SYN023 or HRIG treatment arms. Within the NRG group bites to the head, neck or genitalia that have the highest rabies risk will be stratified for each treatment arm in a 1:1 ratio. The DSMB will review the progress of pharmacodynamic and safety data during the NRG study period to avoid unnecessary risk or expense (Section 5.1.5.4).

2.3 Study Trial Size

Data from an initial subgroup of 20 subjects will be evaluated by the DSMB to ensure pharmacodynamic activity before the remainder of the LRG is enrolled. The size of this group was determined by non-statistical reasons (Table 2.3-1).

Safety and pharmacodynamic data from the entire LRG will be reviewed by the DSMB to ensure safety and pharmacodynamic adequacy. The size of the LRG is 80 subjects. Up to 45 LRG subjects will have received SYN023. This number was judged adequate to give a preliminary assessment of Study Drug performance in the LRG.

Three hundred and twenty patients are required in the per-protocol population to satisfy the efficacy elements of the AUEC-1-15 secondary endpoint. Synermore anticipates approximately 15% (48 patients) of loss to follow-up and exclusions resulting in a total NRG size of 368. Since PEP should not be delayed and some inclusion/exclusion criteria may not be known at the time of randomization some subjects may be excluded (but not replaced) from the per-protocol population by the Per-Protocol Adjudication Board if they are later discovered to have met an exclusion criterion.

Randomization will be adjusted by the randomization center such that patients are proportionately distributed between the trial sites and patients with wounds of the head, neck or genitalia are stratified approximately equally into the treatment groups.

Table 2.3-1 Enrollment by Risk Group and Treatment

Group	Enrollment	Treatment	Rabies Vaccination	Number of subjects
LRG	initial	HRIG 20 IU/kg	Day 1,4,8,15,29	5
LRG	initial	SYN023 0.3 mg/kg	Day 1,4,8,15,29	15
LRG	general	HRIG 20 IU/kg	Day 1,4,8,15,29	30
LRG	general	SYN023 0.3 mg/kg	Day 1,4,8,15,29	30
NRG	general	HRIG 20 IU/kg	Day 1,4,8,15,29	184
NRG	general	SYN023 0.3 mg/kg	Day 1,4,8,15,29	184
Total required for initial LRG enrollment				20
Total required for general LRG enrollment				60
Total required for NRG enrollment				368
Total maximum enrollment				448

2.4 Study Duration and Follow-up

Subjects will be followed for 365 days post receipt of Study Drug unless withdrawn from the trial. It is important to have follow-up information on all study enrollees for the full duration of the study. Every effort should be made to remain in contact with study subjects in at least six-week intervals to establish if the subject is in good health and to inquire about planned relocations. If health problems have occurred a verbal or written account of the duration and character of the difficulties should be obtained. This is specially important in the last six months of the study when clinic visits are less frequent.

2.5 Study Populations

2.5.1 Failure to Meet Inclusion/exclusion Criteria at Initial Screening

Screening includes informed consent, satisfaction of inclusion criteria and an initial survey of exclusion criteria. Rabies exposed subjects that are known to fail inclusion criteria at initial screening or any immediately evaluable exclusion criteria will not be randomized into the study. They will be treated outside of the study protocol with the national standard of care for PEP. The minimum PEP standard will include ERIG or HRIG and rabies vaccination according to the national recommendations. Not all exclusion criteria need to be known at the time of randomization but those that are known will determine enrollment.

2.5.2 As-Treated Population

All subjects who are randomized and receive Study Drug are included in the “as-treated” population.

2.5.3 LRG Per-Protocol Population

Since PEP of rabies is urgent and should not be delayed, randomization and prophylaxis will begin after a screening event that includes informed consent and survey of inclusion criteria (including urine pregnancy test results) before some exclusion criteria have been confirmed. WHO Category 3 exposure victims that meet all initially knowable inclusion/exclusion criteria (Section 3.2.3 – 3.2.5) will be randomized receive wound treatment, receive Study Drug and begin a regimen of rabies vaccination.

2.5.4 NRG Per-Protocol Population

Since PEP of rabies is urgent and should not be delayed, randomization and prophylaxis will begin after a screening event that includes informed consent and survey of inclusion criteria (including urine pregnancy test) before some exclusion criteria have been confirmed. WHO Category 3 exposure victims that meet all initially knowable inclusion/exclusion criteria will be randomized receive Study Drug and begin a regimen of rabies vaccination.

2.6 Randomization

2.6.1 LRG Initial Enrollment Randomization

Subjects in the initial enrollment group will be randomized on a 3:1 basis to treatment with SYN023 or HRIG. Eligibility for the LRG subjects is described in Section 2.2.1. The group as described in Table 2.3.1 is randomized in a 3:1 ratio. Subjects in the initial LRG may be excluded from LRG the per-protocol population but they will not be replaced.

2.6.2 LRG General Enrollment and NRG Randomization

Subjects in the general enrollment of LRG and NRG will be randomized on a 1:1 basis within each group to treatment with SYN023 or HRIG. Subjects will be allocated to treatment sites to approximate the ratio in Table 2.3-1. Within NRG enrollment subjects with head or neck bites or bites to genitalia will be stratified on a 1:1 basis into SYN023 or HRIG treatment groups.

Study sites wishing to randomize a subject will contact the study randomization center either telephonically or by electronic means. The study center will determine the randomization allocation and return the randomization assignment in written communication to the study site.

2.7 Non-Replacement of Randomized Patients

Subjects will not be replaced after randomization. They may be excluded from the per-protocol population

2.8 Adjustments to Randomization

Allocation of randomization among sites will be adjusted to accommodate stratification of head, neck or genitalia bites or site enrollment imbalances.

3 STUDY PROCEDURES

3.1 Schedule of Subject Evaluations

A Summary Schedule of Evaluations depicting all visit-specific procedures is provided in Table 3-1. A more detailed description of the tasks and evaluations by Study Day is supplied in the Appendix. A table of phlebotomy volumes by visit may be found in Appendix C.

Table 3-1 Summary Schedule of Subject Evaluations LRG Group

Study Visit Day →	1	4	8	15	29	43	71	99	127	155	183	274	365
Visit window (days)	0	0	0	0	2	4	7	7	7	7	14	14	14
Written informed consent	X												
Eligibility criteria verification	X												
Medical history	X												
Physical examination	X												
ECG	X												
Urine βHCG (all females)	X												
Hepatitis B, C [a]	4												
HIV [a]	5												5
CBC, platelets [a]	2	2		2		2							
Urinalysis [a]	X												
Serum chemistry [a, c]	4	4		4		4							
PT(INR), PTT [a]	2					2							
Bite wound washing	X												
Vital signs	X	X	X										
Interval history		X	X	X	X	X	X	X	X	X	X	X	X
Focused physical examination		X	X	X	X	X	X	X	X	X	X	X	X
Wound photographs	X												
Randomization	X												
Study Drug Wound Injection	X												
Rabies Vaccination	X	X	X	X	X								
Serum RVNA	10[a]	10[b]	10[b]	10[b]	10[b]	10	10	10	10	10	10	10	10
Confirmation visit	X	X	X										
Anti-SYN023 serum assay	5[a]			5	5			5					
SYN023 concentration	5[a]	5[b]	5[b]	5[b]	5[b]	5		5					
Adverse events (incl. con. Meds.)	X	X	X	X	X	X							
Solicited adverse events	X	X	X										
Serious adverse events (incl. con. Meds.)	X	X	X	X	X	X	X	X	X	X	X	X	X
Site of injection examination	X	X	X	X	X								
Per visit phlebotomy volume	37	21	15	26	20	23	10	20	10	10	10	10	15
Cumulative phlebotomy volume	37	58	73	99	119	142	152	172	182	192	202	212	227

a. Study Day 1 samples must be obtained before Study Drug administration
b. Samples must be obtained before vaccination.
c. Serum chemistries are total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium.
d. Numbers in lab specimen rows indicate **approximate** blood volume in mL.

Table 3-2 Summary Schedule of Subject Evaluations NRG Group

Study Visit Day →	1	4	8	15	29	43	71	99	127	155	183	274	365
Visit window (days)	0	0	0	0	2	4	7	7	7	7	14	14	14
Written informed consent	X												
Eligibility criteria verification	X												
Medical history	X												
Physical examination	X												
ECG	X												
Urine βHCG (all females)	X												
Hepatitis B, C [a]	4												
HIV [a]	5												5
CBC, platelets [a]	2	2		2		2							
Urinalysis [a]	X												
Serum chemistry [a, c]	4	4		4		4							
PT(INR), PTT [a]	2					2							
Bite wound washing	X												
Vital signs	X	X	X										
Interval history		X	X	X	X	X	X	X	X	X	X	X	X
Focused physical examination		X	X	X	X	X	X	X	X	X	X	X	X
Wound photographs	X												
Randomization	X												
Study Drug Wound Injection	X												
Rabies Vaccination	X	X	X	X	X								
Serum RVNA [a]	10[a]	10[b]	10[b]	10 [b]	10 [b]	10	10	10	10	10	10	10	10
Confirmation visit	X	X	X										
Anti-SYN023 serum assay	5[a]			5[b]				5					
SYN023 concentration	5[a]	5[b]	5[b]	5 [b]				5					
Adverse events (incl. con. Meds.)	X	X	X	X	X	X							
Solicited adverse events	X	X	X										
Serious adverse events (incl. con. Meds.)	X	X	X	X	X	X	X	X	X	X	X	X	X
Site of injection examination	X	X	X	X	X								
Per visit phlebotomy volume	37	21	15	26	10	18	10	20	10	10	10	10	15
Cumulative phlebotomy volume	37	58	73	99	109	127	137	157	167	177	187	197	212

a. Study Day 1 samples must be obtained before Study Drug administration
b. Samples must be obtained before vaccination.
c. Serum chemistries are total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium.
d. Numbers in lab specimen rows indicate **approximate** blood volume in mL. May differ from actual.

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 subjects at the time of consent. 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 subjects on the day of study entry.

3.2.2 Screening

After informed consent is obtained, a unique screening number will be assigned to each subject for identification purposes, and 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. Screening log will record name, birth date, sex, ethnicity and race. 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.

Eligibility for entry into the study will be based on the inclusion and exclusion criteria described below. Results of the urine pregnancy test must be known before enrollment. The investigator must document confirmation of eligibility prior to randomization

3.2.3 LRG Inclusion Criteria

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

1. History of dog, cat, mongoose, fox, ferret, skunk, bat or raccoon bite to trunk, leg, ankle or foot, or lick or scratch with, or of broken skin or mucous membrane saliva or neural tissue contamination, unprotected physical bat contact, scratch or saliva contamination of the head or neck without broken skin all ≤ 54 hours (Section 3.9.4 and 3.9.5)
2. Has completed the written informed consent process and signed informed consent document
3. Males and females
4. Is age ≥18 years on Study Day 1
5. Agrees to stay in contact with the study site for the duration of the study, provide updated contact information as necessary, and has no current plans to move from the study area for the duration of the study
6. Lives within 2 hour journey by available transportation to study center
7. For female subjects: agrees to avoid pregnancy from Study Day 1 through Study Day 121. Women physically capable of pregnancy (not sterilized and still menstruating or within 1 year of the last menses if menopausal) in sexual relationships with men must use an acceptable method of avoiding pregnancy during this period. Acceptable methods of avoiding pregnancy include a sterile sexual partner, sexual abstinence (not engaging in sexual intercourse), hormonal contraceptives (oral, injection, transdermal patch, or implant), vaginal ring, intrauterine device (IUD), or the combination of a condom or diaphragm with spermicide

3.2.4 NRG Inclusion Criteria

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

1. History of dog, cat, mongoose, fox, ferret, skunk, bat or raccoon bite to any body part, lick or scratch with, or of broken skin, mucous membrane saliva or neural tissue contamination, or unprotected physical bat contact all ≤ 54 hours from PEP (Section 3.9.4 and 3.9.5)
2. Has completed the written informed consent process and signed informed consent document.
3. Males and females
4. Is age ≥18 years on Study Day 1
5. Agrees to stay in contact with the study site for the duration of the study, provide updated contact information as necessary, and has no current plans to move from the study area for the duration of the study
6. Lives within 2 hour journey by available transportation to study center
7. For female subjects: agrees to avoid pregnancy from agrees to avoid pregnancy from Study Day 1 through Study Day 121. Women physically capable of pregnancy (not sterilized and still menstruating or within 1 year of the last menses if menopausal) in sexual relationships with men must use an acceptable method of avoiding pregnancy during this period. Acceptable methods of avoiding pregnancy include a sterile sexual partner, sexual abstinence (not engaging in sexual intercourse), hormonal contraceptives (oral, injection, transdermal patch, or implant), vaginal ring, intrauterine device (IUD), or the combination of a condom or diaphragm with spermicide

3.2.5 Exclusion Criteria LRG and NRG

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

1. Clinical evidence of rabies infection
2. Category 3 exposure > 54 hours before Study Drug receipt
3. History or serological evidence of previous rabies vaccination
4. Previous receipt of equine or human rabies globulin
5. History of hypersensitivity reaction to equine or human immunoglobulin.
6. Received immunoglobulin or blood products within 42 days before Study Day 1
7. Received any investigational drug therapy or investigational vaccine within 60 days before Study Day 1
8. Planned participation in any other investigational study during the study period.
9. Receiving systemic immunosuppressant medication such as systemic corticosteroids but not limited to systemic corticosteroids
10. History or laboratory evidence of any past, present, or possible immunodeficiency state including but not limited to any laboratory indication of HIV infection
11. Previous medical history that may compromise the safety of the subject in the study according to the opinion of the principal investigator
12. History or evidence on physical examination of any systemic disease or any acute or chronic illness that, in the opinion of the investigator, may interfere with the evaluation of the safety or activity of SYN023
13. Pregnancy (results of the urine pregnancy test MUST be known before enrollment)

3.2.6 Major Protocol Deviations and Eligibility for the Per-protocol Population

Continuation in the per-protocol population depends on the absence of uncorrectable major protocol deviations. Major deviations are those that would degrade the fidelity of the data from the protocol. Protocol deviations requiring removal from the per-protocol population include but are not limited to those listed below.

- Defective informed consent
- Received the incorrect Study Drug
- Received the incorrect dose (± 20%) of Study Drug
- Failed to complete the scheduled rabies vaccinations through Study Day 29
- Are discovered to lack adequate prophylactic treatment of all exposure sites
- Are discovered to be injured by animal other than those listed
- Are discovered to have an interval > 54 hours from rabies exposure to the start of prophylaxis
- Are discovered to have RVNA ≥ 0.1 IU in serum obtained at Study Day 1
- Receives prohibited treatment during the trial
- Are found not to have a modified WHO Category 3 exposure (Table 2.2-1, Section 3.9.4)
- Are discovered to have or have developed HIV infection or other immunodeficiency state.
- Second high risk animal bite or contact requiring PEP

Subjects who are discovered to not have satisfied any criteria for the per-protocol population may be excluded from that population (Section 3.2.8). These deviations may become known at different intervals from randomization. Likely intervals for discovery of these deviations are listed in Table 3.2.6-1 based on the occurrence of site review, monitoring visits and vaccination schedules.

Table 3.2.6-1 Intervals for Per-protocol Exclusions (approximate)

Major Protocol Deviation	Rationale	Likely Interval Days
Defective consent	Data without effective consent cannot be used	43
Diagnosis of HIV after enrollment	New HIV may affect PEP response	365
Received incorrect study drug	Mixes SYN023 and HIRG results	43
Incorrect dose (± 20%) of Study Drug	Arbitrary but reasonable dose margin. Used for biosimilars.	43
> 54 hr from rabies exposure to the Study Drug	Early PEP initiation is important Should be discovered early from wound state and investigation	15
Failed to complete all rabies vaccinations	Important feature of PEP. Should be known by Study Day 29	29

Failure to treat all exposure sites	Documented cause of treatment failure. Should be discovered early from wound state and investigation	15
Exposure from animal not in inclusion criteria	Some not animals don't transmit rabies. Should be discovered early from wound state and investigation	15
Serum RVNA ≥ 0.1 IU at Study Day 1	Indicates previous Rabies vaccination. Results from central reference laboratory needs shipment, processing and return of results	43
Receives prohibited treatment during the trial	Has potential to increase or decrease vaccine protection. Will turn up in monitoring visit	365
Are found not to have a modified WHO Category 3 exposure (Table 2.2-1, Section 3.9.4)	Different rabies risks. Should turn up in local investigation or monitoring	15
Second high risk animal bite or contact requiring PEP	Subjects should have same rabies risk. Should turn up in monitoring.	365

3.2.6.1 Pregnancy During Study

Results of the urine pregnancy test MUST be known before enrollment. Subjects who have a positive pregnancy test on Study Day 1 should not be enrolled since this is an exclusion criteria. If a subject becomes pregnant during the study, she will continue in the study. She will not be withdrawn from the per-protocol population by the Per Protocol Adjudication Board unless she declines phlebotomy. If she wishes to withdraw study consent she should be asked to complete follow-up visits without phlebotomy. Follow-up should continue for pregnancy outcome including premature terminations, and data are to be included in the safety reports.

3.2.7 Screening Clinical Assessments and Laboratory Tests

Subjects will provide a detailed medical history and will undergo a physical examination. 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. Subjects who are discovered to have newly diagnosed HIV will undergo formal counseling and referral.

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.

Screening laboratory tests will be collected on Study Day 1. Results from these laboratory tests will serve as study-entry baseline values. Findings that might later make the subject ineligible such HIV status will be discussed with the subject and the subject will be referred for follow-up care with their healthcare provider if necessary. Urine Pregnancy test results MUST be known before randomization.

The study has inclusion and exclusion criteria that are required for entry on the study. Those that are knowable on Study Day 1 prior to study entry will determine eligibility for randomization. Since the results of all of the screening assessments may not be known at the time of randomization subjects may be found to be ineligible for the per protocol population after randomization. For example an individual may be found to have serological evidence of previous rabies immunization when the RVNA results are returned. This subject may continue on the trial but will be excluded from the per protocol population.

3.2.7.1 Window Period for Screening Laboratory Tests

There is no window for screening laboratory evaluations. These must be collected on Study Day 1. Because of the necessity for prompt anti-rabies care the results may be known and eligibility confirmed after study entry and randomization. This means that some subjects may be found to be ineligible for the study or the per protocol population after randomization.

3.2.8 Per-protocol Adjudication Board (exclusion from the per-protocol population)

Since all inclusion/exclusion criteria are not able to be known at the time of study randomization the per-protocol status of some randomized subjects may need to be changed based on review of blinded screening information that becomes available at a later time. The Sponsor will create the Per-protocol Adjudication Board whose duty will be to review screening data, management information and initial determination of eligibility for the per-protocol population. The Per-protocol Adjudication Board will review blinded data and will not be able to unblind subjects or data. Based on inclusion/exclusion criteria, the protocol deviation and the impact of the deviation on protocol data, the Per-protocol Adjudication Board may exclude randomized subjects from the per-protocol population. Its judgments will be forwarded to the DSMB and the study enrollment center for the adjustment of randomization to maintain stratification and distribution of cases at the different sites. The subjects excluded from the per-protocol population will continue on the study in the “as-treated” population unless they withdraw consent. The Sponsor will maintain a roster of its actions and the reasoning behind them.

3.3 Study Randomization

Subjects will be randomized to the study by and IVRS/IWRS. The procedure for randomization will require CRO contract before completion. Since a CRO has not been contracted this information is not yet available for this version.

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 1.

3.4 Blinding

3.4.1 Blinding at the Study Level

The LRG and the NRG are both blinded until Study Day 365. If the last subject in LRG reaches Study Day 365 even if the NRG is still in progress, then the LRG group may be unblinded. The LRG may be unblinded to the extent recommended or required by the DSMB for analysis of safety or efficacy data for Study Day 99 DSMB review. The NRG group will remain blinded until Study Day 365. The DSMB will conduct unblinded analyses before Study day 365 as specified by the protocol and inform the sponsor of the overall results of those analyses. The purpose of these analyses is to permit advancement of the study risk groups and to inform the sponsor so that product development decisions can be made. Since investigational agent will have been administered to the NRG, blinded specimens for analysis collected and individual treatment assignments still unknown to the sponsor for the NRG, this should not affect the conduct of the trial during the observation period required for clinical rabies surveillance.

The NRG is powered for the efficacy outcomes of the study. The smaller LRG's purpose is primarily pharmacodynamic and pharmacokinetic. The LRG will remain blinded for safety and clinical efficacy through Study Day 365. The sponsor will know without blinding that there are no rabies cases but the rabies risk in the LRG is much lower than from the NRG so the clinical efficacy results from the LRG do not mean the same thing. The DSMB must give permission for advancement to the NRG. The combined LRG and NRG study will take years to complete without information for Synermore. The sponsor will be able to infer meager pharmacodynamic characteristics from the progress of the blinded study. The LRG pharmacodynamic and pharmacokinetic data will help in planning and maintaining support for SYN023 development. Once this cohort has final data there is no reason to continue to blind the LRG study cohort since its efficacy results are objective, separately analyzed and cannot affect the efficacy conclusions from the NRG.

3.4.2 Blinding at the Site Level

The site's investigational pharmacist or product manager (or designee) will need to be unblinded in order to manage Study Drug inventory and prepare doses. Other unblinded persons on the study are the unblinded study monitor that will need to audit Study Drug stocks 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 investigational pharmacist or product manager must be a designated study team member who is not an employee of the sponsor and who will have no other clinical or regulatory

responsibilities associated with the conduct of the study during the entire study period. 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.

Labels accompanying the syringes of prepared Study Drug will not indicate which Study Drug is in the syringe but will only contain the study identification and subject ID number. Identical syringes and needles will be used for preparation and administration of each Study Drug.

3.4.3 Individual 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 to the investigational pharmacist or product manager for urgent unblinding of a subject's treatment. The request must include the subject ID number, the date, a brief justification of the clinical requirement to the Study Drug 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 investigational pharmacist or product manager 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 Clinical Evaluation, Photography, Decontamination and Treatment of Wounds

The correct management of rabies bite wounds in animals has as much influence on the development of rabies as vaccination and wound immunoglobulins (Dean et al. 1963). Regardless of the risk for rabies, the optimal medical treatment of animal bite wounds includes the evaluation and treatment of serious nerve, tendon and vascular lacerations. Avoidance of infection through wound debridement and irrigation will yield the best possible cosmetic results. Care should be taken not to damage skin or tissues (Manning et al. 2008). Immediate gentle irrigation with at least 200 mL of sterile water or normal saline with either commercially available wound cleansing solutions, mild soap or povidone-iodine (10%) diluted to 1-2% concentration in water. Gentle cleaning of the wound with gauze may be required. Irrigation should involve gentle cleaning with irrigation fluid expressed through 20 to 21 gauge plastic catheter tip from a 30 to 50 mL syringe. The tip of the catheter should be held approximately 2 cm from the wound surface. (Gouin et al. 2001, Singer et al. 2008). Eye protection and splash guards should be employed for protection of medical staff. Puncture wounds should be gently cleaned with cotton swabs and irrigation solution. Wound cleansing is especially important in rabies prevention because wound cleansing alone without other PEP markedly reduces the likelihood of rabies in animal studies (Kaplan et al. 1962, Dean et al. 1963).

Local anesthetics may be employed to assist in wound management.

Complete primary wound closure should be avoided with delayed closure employed when necessary. Partial closure may be individualized on the basis of wound size and location of the wound(s), and time interval since the bite with delayed closure at a later time. Suturing should be avoided when possible. When wounds require some closure (such as suturing) this should occur only after administration of Study Drug.

Decisions regarding the use of antibiotic prophylaxis and management of infection (both local and systemic) should be individualized based on the wound and the biting animal.

If the subject has received the primary tetanus immunization series and has not received a tetanus booster within 10 years (or five years for severely contaminated bite wound) a tetanus vaccine booster immunization should be given. Tetanus immunization should be begun if the subject has not received a primary tetanus vaccination series.

Uncalibrated photographs of all wounds should be recorded if possible within 48 hours of PEP start. The photograph should record the date and the subject number but no other personal identification. The photos with facial characteristics should be pixilated before permanent storage to avoid identification. All photos will be stored in a locked secure location at the research site and if stored electronically should be encrypted and access limited by an access roster. The photographs are for medical use only and may not be used commercially.

3.6 Decontamination of Mucous Membranes

Mucous membranes of the eyes nose and mouth may be decontaminated by copious irrigation with potable water or sterile saline.

3.7 Study Drug Infiltration for Bite and Non-bite Exposures

After decontamination and before wound dressing the wound surface itself should be injected with the calculated dose of Study Drug through a 25 gauge needle or similar of approximately 2.5 to 3 cm in length. Study drug should be injected through the skin subcutaneously as if local anesthesia were being administered creating a wheal of fluid within a centimeter of the wound margin. After creation of the first wheal the needle should be withdrawn with the tip remaining in the injection hole and the needle redirected to accomplish infiltration of a different axis. If the wound involves muscle tissue, injection of the muscle should be performed. If the wound surface has been thoroughly injected and there is remaining Study Drug it should be injected subcutaneously as close to the wound as anatomically possible.

Care should be taken to avoid intravenous or intra-arterial injection by aspiration and looking for blood return before infiltration. Remove the needle and re-insert it in a new location and repeat the aspiration step before administering. All bite injuries and breaks in the skin related to bites should be infiltrated with Study Drug. Infiltration of finger compartments or other anatomic

compartments should be done with a volume appropriate to the anatomic volume to avoid compartment syndrome. Study drug should be administered within 45 minutes of when the dose is constituted. Study drug volume may be expanded with dilution of normal saline if the extent of the wound area to be injected is large and may require extra injection volume. All Study Drug must be injected. Subjects must be observed for at least 60 minutes after the end of Study Drug administration.

For the non-bite exposures the calculated doses of Study drug should be administered intramuscularly as above without regard to proximity to exposure.

3.7.1 Human Rabies Immune Globulin (HyperRab® S/D)

There are two dosage forms of HRIG that may be used in the study a presently available 150 IU/mL preparation and a newly available 300 IU/mL preparation. All stocks of 150 IU/mL HRIG (HyperRab) should be used at a study site before the study site can switch to the 300 IU/mL preparation. Once a study site has switched to the 300 IU/mL preparation it cannot again use the 150 IU/mL.

The dose of HRIG (HyperRab) 20 IU/kg should be calculated based on body weight. The dose for the 150 IU/mL potency preparation is 0.133 mL/kg. The dose for the 300 IU/mL potency is 0.0665 mL/kg.

The calculated dose should be administered into the wound whether in subcutaneous tissue or muscle. For example, a 70 kg person receiving the 150 IU/mL potency has a calculated dose of 9.31 mL. The entire calculated dose must be given. If the fluid volume of the injection needs to be increased to enable all sites to be injected the pharmacy may dilute the calculated dose with saline when the syringe is prepared. Doses up to 3 mL may be given in at a single injection site (Hopkins et al. 2013).

Care must be taken NOT to administer a rabies vaccine near the Study Drug administration site.

3.7.2 SYN023

After thorough wound sanitation, injections of the entire calculated dose of SYN023 should be administered into and around all the bite wounds on Study Day 1. The dose of SYN023 should be calculated based on body weight: 0.3 mg/kg. For example, a 70 kg person has a calculated dose of 21 mg. The entire calculated dose should be given. Doses up to 3 mL may be given at a single injection site. Care must be taken NOT to administer a rabies vaccine near the Study Drug administration site.

3.8 Rabies Vaccine (RabAvert® or Rabipur®) Administration

Rabies Vaccine (RabAvert® or Rabipur®) must be administered in a different area from the Study Drug infiltration to reduce interference. The 1 mL dose of the chicken fibroblast rabies vaccine should be administered in deltoid muscle. If not possible, then vaccination may be administered in the vastus lateralis (thigh) or rectus femoris (thigh). Five doses of the rabies vaccine should be administered on Study Days 1, 4, 8, 15 and 29. The rabies vaccine should be administered as soon as possible after dose constitution. Rabies vaccination should be administered within 75 minutes after Study Drug.

3.9 Study Efficacy Evaluations

3.9.1 Clinical Efficacy Evaluations

The absence of a confirmed or probable case of rabies in the per-protocol population is part of the composite endpoint. Subject will be periodically evaluated for the clinical signs and symptoms of human rabies. If these develop they will be referred for medical evaluation and laboratory or anatomic confirmation. All clinical rabies diagnostic tests may be performed locally at a qualified laboratory. All rabies cases will be reviewed by the DSMB.

Human Rabies Clinical Case Definition:

A person presenting with an acute neurological syndrome (encephalitis) dominated by forms of hyperactivity (furious rabies) or paralytic syndromes (dumb rabies) progressing towards coma and death, usually by respiratory failure, within 7-10 days after the first symptom if no intensive care is instituted.

A subject who is alive and not hospitalized is presumed not to have rabies. Contact with a non-hospitalized subject on any date is evidence that rabies has not occurred on that date. If a subject is discharged from hospital rabies has not occurred.

Case Classification Human Rabies

- Suspected: A case that is compatible with the clinical case definition
- Probable: A suspected case (above) plus history of contact with a suspected rabid animal.
- Confirmed: A suspected case that is laboratory-confirmed.

Rabies Laboratory Diagnosis Confirmation Criteria

One or more of the following:

- Rabies viral isolation from clinical specimens
- RVNA in the CSF
- Detection of rabies viral RNA by RT/PCR in clinical specimens, saliva,
- Detection of rabies by FAT on skin biopsy such as from neck (ante mortem).
- Detection of rabies by FAT preferably brain tissue (collected post mortem).

- Detection of rabies by FAT after inoculation of brain tissue, saliva or CSF in cell culture, or after intracerebral inoculation in mice or in suckling mice.
- Detection of viral nucleic acids by PCR on tissue collected before or after death in a clinical specimen (brain tissue or skin, cornea, urine, saliva or other).

3.9.2 Pharmacodynamic Efficacy Evaluations

The serum RVNA ≥ 0.5 IU/mL for the 365 day trial duration is the pharmacodynamic efficacy parameter. These specimens will be collected and forwarded to the study laboratory at the University of Kansas. These measurements will be used to calculate both superiority for Study Day 8 GMC RVNA and non-inferiority for Study Day 99 GMC RVNA and % population RVNA ≥ 0.5 IU/mL. A missing RVNA datapoint or RVNA data point less than 0.5 IU/mL preceded and followed by RVNA concentrations ≥ 0.5 IU/mL will be considered to be in the protective range.

3.9.2.1 The Window Interval for Collection of Efficacy Evaluation Specimens

The time window for collection of efficacy evaluation specimens is listed in Table 3-1 and 3-2.

3.9.3 Efficacy: Confirmation of Anti-rabies Activity in the Initial Enrollment LRG

This study includes the first administration of SYN023 in the setting of animal exposures. All subjects should have a WHO Category 3 rabies exposure (Section 3.9.4). The first twenty subjects in the LRG (the Initial Randomization) will have serum RVNA concentrations (Section 3.9.5) reviewed through Study Day 29. The DSMB will ensure that RVNA concentrations are ≥0.5 IU/mL on the Study Day 15 visit in all subjects before the remainder of the site's subjects are enrolled. Enrollment will be paused at the site until this review is completed.

3.9.4 Modified WHO Rabies Risk Exposure Categories

In countries or areas enzootic for rabies, exposure to suspected or confirmed rabid (domestic or wild) animals is categorized as follows (WHO 2013):

Category I: touching or feeding animals, licks on intact skin, contact of intact skin with secretions or excretions of a rabid animal or human. These are not regarded as exposures, and no PEP is required.

Category II: nibbling of uncovered skin, minor scratches or abrasions without bleeding. Vaccine should be administered as soon as possible.

Category III: single or multiple transdermal bites OR scratches to broken skin OR licks

on broken skin OR contamination of mucous membrane with saliva or neural tissue from licks or exposure to bats. Vaccine and rabies immune globulin should be administered as soon as possible.

For this protocol "exposure to bats" means a subject with unprotected (e.g. without gloves or other similar barriers) physical contact with a bat. Mucous membrane contamination means the transfer of saliva or neural tissue from the suspect animal into the eyes, nose or mouth of the victim.

3.9.5 WHO Category III Rabies Risk Substrata

Within the WHO Category III four additional risk sub-strata based on the probability of rabies development by bitten or exposed body part have been described (Sitthi-Amorn et al. 1987, Cleveland et.al. 2003, Fe'vre et al., 2005, Knobel et al. 2005, Tenzin et al. 2011). These sub-strata are listed in Table 3.9-1. These Category III substrata also serve as the basis for selection of an initial cohort. Bites to the head, neck, arms, hands and genitalia are considered the highest risk from empirical and enervation density estimates. These highest risk espouses are excluded from the LRG. The LRG is enrolled into the trial to confirm pharmacokinetics and pharmacodynamics in a field setting by DSMB before enrollment of the NRG. This is the basis for restriction of enrollment by bite or exposure location for the LRG Initial Enrollment (Section 2.6.1) and also the basis for stratification by bite or exposure location in the NRG (Section 2.6.2) randomization.

Table 3.9-1 Relative Probability of Rabies by Bite Location

Bite Location	Risk Estimate 1= highest	Probability (mode)	Maximum/ minimum
Head and neck	1	0.45	0.6/ 0.3
Genitalia	1	n/a	n/a
Arms	2	0.28	0.4/ 0.15
Hands	2	n/a	n/a
Trunk	3	0.05	0.1/ 0.0
Legs	3	0.05	0.1/ 0.0
Ankles	3	n/a	n/a
Foot	3	n/a	n/a
Non-bite lick	4	n/a	n/a
Non-bite scratch	4	n/a	n/a
Non-bite bat physical contact	5	n/a	n/a
Non-bite Mucous membrane contamination with saliva or neural tissue	5	n/a	n/a

n/a: not available

For this protocol bites to the foot and ankle are considered to be in the same risk stratum as bites to the leg. The absolute risk is unknown for the following categories of exposure but they are held to be lower than the bite risk to the lower extremity:

- non-bite exposure of broken skin to licks by suspect animal
- non-bite exposure by scratch to broken skin or that breaks the skin by suspect animal
- non-bite mucous membrane contact with saliva or neural tissue from a suspect animal
- non-bite unprotected physical bat exposure.

3.10 Immunology Laboratory Evaluations

A summary of immunological laboratory evaluations is presented in Table 3.10-1.

Table 3.10-1 Summary of Immunology Laboratory Evaluations

Sample Type	Assay	Purpose of Assay
Serum	SYN023 concentration (CTB011 and CTB012)	Pharmacokinetics
Serum	Rabies virus neutralizing activity (RVNA) by RFFIT	Rabies neutralizing antibody concentration from Study Drug and vaccination, surrogate of protection
Serum	Anti-SYN023 antibodies (CTB011 and CTB012)	Effect on safety and efficacy analysis

3.11 Virology Laboratory Evaluations

Biting animal specimens when available from brain, skin or blood will be evaluated locally for rabies diagnosis.

3.12 Safety Evaluations

3.12.1 Adverse Event Reporting Intervals

The collection periods for adverse events are:
Unsolicited adverse events: Through Study Day 43
Solicited adverse events: Through Study Day 8
Serious adverse events: Entire study period (i.e., 365 days)
For this study, solicited adverse events to be collected are listed in section 5.7 Solicited Adverse Events.

3.12.2 Pre-Study Drug and Post-Study Drug Monitoring of Subjects

Hypersensitivity reactions are a potential adverse effect both Study Drugs administered in this protocol. Allergic reactions to vaccination are also 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 Study Drug and 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 antiarrhythmics and pressors. Appropriate equipment includes devices for blood pressure monitoring, oximetry, maintenance of airway and intratracheal intubation and, removal of secretions and cardiac defibrillation.

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 60 minutes after receiving rabies vaccination that is administered after Study Drug. Vital signs and oximetry will be repeated every 30 minutes during and at the end of the monitoring period before subjects leave the clinic.

Electrocardiograms are performed as a baseline to monitor subject safety (Table 3-1 and 3-2). Laboratory evaluations for subject safety are clinical chemistry evaluations, CBC, platelet counts and differential counts, PT (INR) and PTT and urinalyses. Please refer to Table 3-1 and 3-2 for a list of laboratory tests for monitoring of safety. Window intervals for specimen collection are also listed in Table 3-1 and 3-2.

3.12.3 Clinical Assessments and Laboratory Tests

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.

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 B for toxicity grading scales) from pre-vaccination 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.

3.12.4 Concomitant Medications and Prohibited Medications

The collection of information on concomitant medications used by subjects following Study Drug administration will coincide with the collection period of adverse events. The collection period for concomitant medications associated with the treatment of adverse events will be 42 days following the last Study Drug. The collection period for concomitant medications associated with the treatment of serious adverse events (SAE) will be Study Days 1-365. The collection period for prohibited medications will be Study Days 1-365.
Concomitant medication includes prescription and non-prescription drugs or other treatments, and any vaccines other than rabies or tetanus vaccines specified by the protocol. 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.

Prohibited medications include any vaccination or immunoglobulin directed against rabies. Systemic corticosteroids or other immunosuppressants administered within 29 days of first rabies vaccination are prohibited.

3.12.5 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, subjects 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.

3.12.6 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 365 visit date, then a determination of "lost to follow-up" can be made.

3.13 Pharmacokinetic Evaluations LRG and NRG

Pharmacokinetic evaluations (Sections 2.1 "secondary objectives" and Table 3-1) on samples obtained on all subjects will be performed on SYN023 recipients in the LRG and compared to pharmacodynamic activity over time.

Pharmacokinetic evaluations (Sections 2.1 "secondary objectives" and Table 3-2) will be obtained at selected time points from all NRG subjects but will be performed only on SYN023 recipients and compared to pharmacodynamic activity.

3.14 Preservation of Clinical and Veterinary Materials

On some cases there may be diagnostic clinical and veterinary materials available. Every effort should be made to preserve these materials for review by investigators at the end of the trial.

4 STUDY DRUGS

There are three substances administered as part of this study. There are two Study Drugs SYN023 and HRIG (HyperRab® S/D Grifols) and rabies vaccines RabAvert® or Rabipur® that are used in rabies PEP. SYN023 is investigational agent that has been administered previously to human subjects and tolerated in a Phase 1 and Phase 2 trials. HyperRab® S/D is an HRIG that is licensed in the US and commercially available for PEP. RabAvert® is a rabies vaccine licensed in the US. Rabipur® is the same GSK rabies vaccine licensed in the Philippines.

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 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 HRIG (HyperRab® S/D)

HRIG (HyperRab® S/D, Grifols Therapeutics) will be supplied by 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. HRIG 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. HRIG liquid will be stored at 2-8° C in a secured location. HRIG 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 HRIG Preparations

There are two HRIG preparations that may be used in this trial (Section 3.7): the 150IU/mL preparation is packaged in 2 mL and 10 mL single dose vials. HRIG 300IU/mL is packaged in 1 and 5 mL single dose vials. After cleaning of the vial top with an alcohol swab, the proper dose of HRIG is withdrawn slowly from the vial with a 21 gauge needle to avoid foaming. Study drug should be inspected for particulate matter and discarded if present. If more than one vial of HRIG is required the dose may be accumulated from a second vial. HRIG must be allowed to sit at room-temperature for at least 15 minutes before intramuscular administration to allow the HRIG to warm before administration. A constituted HRIG 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 HRIG 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 Study Rabies Vaccine U.S. (RabAvert®)

RabAvert® will be supplied by the sponsor.

4.3.1 Receipt and Storage

Upon receipt of Study Drug supplies, the Study Drug manager must immediately inspect all vials of Study Drug for damage. The RabAvert® 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 vaccine 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 Rabies Vaccine (RabAvert®) Preparation

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. A constituted dose of rabies vaccine 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.

4.3.3 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 Study Rabies Vaccine Philippines (Rabipur®)

Study Drug will be supplied by the sponsor

4.4.1 Receipt and Storage

Upon receipt of Study Drug supplies, the Study Drug manager must immediately inspect all vials of vaccine for damage. The Rabipur® 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 vaccine 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 Rabies Vaccine (Rabipur®) Preparation

Rabipur® 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. A constituted dose of rabies vaccine 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 will provide for disposal of unused supplies 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 SYN023 sponsor, Synermore, the institution 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 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 two medical monitors (one local medical monitor and one global medical monitor) and a DSMB.

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, like the principal investigator, is blinded for a blinded study.

5.1.4 Global Medical Monitor

The purpose of the global medical monitor is to permit SUSAR (suspected unexpected serious adverse reaction, see Section 5.10) reporting to regulatory agencies (that generally do not permit placebo or control "suspect drugs" in their safety databases) without unblinding the sponsor personnel or the clinical sites in a systematic way. The sponsor will retain a global medical monitor through the contract research organization PPD. The global medical monitor reviews and unblinds all SUSAR reports and, if he or she deems it necessary, may review and unblind selected SAE reports. If the global medical monitor suspects that there is an unrecognized pattern in reported SUSARs and SAEs, then the global medical monitor will notify the local medical monitor who will convene the DSMB (this committee is normally responsible for unblinded SAE review). If the SUSAR is reported for the active investigational study agent, the report is forwarded to the MedWatch database, or other regulatory databases. If the SUSAR is reported for an active control medicinal product, then it is reported to the manufacturer. **For all SUSARS the global medical monitor will make available to the sponsor and the clinical trial sites a completed CIOMS II form with the suspect drug absent or blacked out so that the sites and the sponsor may remain blinded.**

5.1.5 Data and Safety Monitoring Committee (DSMB)

The study will have a DSMB composed of a physician chairman/chairwoman, three member physicians and a DSMB statistician all of which may vote. At least one physician should be an Infectious Disease or rabies expert. The voting members will not be directly involved with the conduct of the study. Voting members will not be employees of the sponsor. Additional non-voting subject area experts may be present at meeting to provide expertise if requested by the DSMB. The DSMB will operate according to its charter.

The DSMB will have five responsibilities

1. Review of Study Drug pharmacodynamic activity in the Initial Enrollment of the LRG subjects and granting permission for general LRG enrollment (5.1.5.2).
2. Review of safety and pharmacodynamics through Study Day 99 in the initial and general enrollment groups of the LRG (5.1.5.3)
3. Review of Study Drug safety after 80 subjects have reached Study Day 9 (5.1.5.4)
4. Review and confirmation of any possible rabies cases in trial participants.
5. Management of safety issues during the trial.

The DSMB will not determine exclusions from the per protocol population. Exclusions from the per protocol population are determined by the Per Protocol Adjudication Board. The DSMB may request review of any case by this board.

5.1.5.1 DSMB Confirmation of Rabies Cases in the Trial

A confirmed or probable case of rabies is an element of the composite endpoint for the trial (Section 3.9.1). If a case of rabies occurs in the SYN023 treatment group of the per protocol population in the trial it will result in the failure of the primary objective and the cessation of Study Drug administration in the trial. The DSMB will review and confirm a rabies diagnosis in any study participant and determine if trial enrollment or Study Drug administration should be stopped. The DSMB may require additional subjects in the Initial Enrollment.

5.1.5.2 DSMB Evaluation of Safety and Pharmacodynamic Activity in the Initial Enrollment LRG

The sponsor will collect blinded RVNA results and adverse events through Study Day 29 from the subjects in the LRG initial enrollment group and provide this information to the DSMB. Permission to enroll the General Enrollment of the LRG may be granted if

- no protocol stopping rules are met (Section 6.3) and if
- no severe related adverse events other than local injection site manifestations are encountered due to SYN023 in the initial enrollment of the LRG
- the serum RVNA values are all in the protective range (≥ 0.5 IU/mL Section 3.9.2) on Study Days, 8 through 29 in the SYN023 recipients.

The DSMB will issue a written determination permitting enrollment of the general enrollment group of the LRG and inform the sponsor of this determination. It is acknowledged that some HRIG recipients may not have achieved ≥ 0.5 IU/mL RVNA by Study Day 8.

5.1.5.3 DSMB Review of Safety and Pharmacodynamic Activity in the Initial and General Enrollment LRG

The sponsor will collect blinded RVNA results and adverse events through Study Day 99 from all subjects in the LRG General and Initial enrollment groups and provide them to the DSMB. Permission to enroll the General Enrollment of the NRG may be granted at Study Day 183 if

- no protocol stopping rules are met (Section 6.3) and if
- no severe related adverse events other than local injection site manifestations are encountered due to SYN023 in the initial and general enrollment of the LRG
- The RVNA values are in the protective range in ≥ 75% of SYN023 recipients on Study Day 99 (Section 3.9.2).

5.1.5.4 DSMB Review of Safety in the NRG

The DSMB will assess the safety (while enrollment continues) after 80 subjects have completed Study Day 99. If there are no adverse events or patterns of concern it will issue permission for the trial to continue.

5.1.5.5 DSMB Management of Safety Issues in the Trial

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, the DSMB will be convened. The DSMB 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 DSMB may request unblinding any amount of safety information needed to conduct its safety assessment. Only the DSMB 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 DSMB minutes.

Based on its review and the protocol stopping rules (Section 6) the DSMB will make recommendations in the DSMB minutes to the sponsor regarding further conduct of the study, changes to the study protocol and further administration of Study Drugs. The conclusions of the DSMB 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 DSMB and any directives issued by the national regulatory authority, the Institutional Review Board or Ethics Committee.

If Study Drug administration is paused by the medical monitor or the global medical monitor, the DSMB will be convened. Based on its review and the protocol stopping rules (Section 6) the DSMB will make recommendations in the DSMB minutes to the sponsor regarding further conduct of the study and further administration of Study Drug. The DSMB 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 DSMB may unblind any amount of safety information needed to conduct their assessment. All procedures associated with this review, including objectives, data handling, and elements to be included for review will be documented in DSMB minutes. The conclusions of the DSMB will be communicated to the investigators and the IRB/Ethical Committees and the national regulatory authorities. The

sponsor agrees to abide by the decision of its DSMB and any directives issued by the national regulatory authorities, the Institutional Review Boards or Ethics Committees.

5.1.6 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.

5.1.7 National Regulatory Authority

Since the national regulatory authority (such as the US FDA for the 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 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.

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 relative to the subject's pretreatment baseline, whether or not it is considered to be related to the medicinal product. All adverse events will be assessed for severity, causal relationship, expectedness and seriousness (below).

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 1 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, 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 Section 3.12.1. 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 (SAER) 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 local medical monitor) will determine a **causal relationship,** to the Study Drug without knowledge, for blinded studies, of whether SYN023 or active control, HRIG was administered. 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 1 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 1 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

Local Study Drug injection will be made in the immediate area of an animal bite. Since the trauma and wound management will create confounding local findings they will not be solicited in this trial. The reporting period during which *solicited* adverse events will be evaluated is specified in Section 3.12.1. The non-local symptoms that will be solicited include:

- headache,
- arthralgia,
- myalgia,
- rash,
- pruritus,
- urticaria,
- dyspnea,
- chest pain,
- cough,
- fever
- chills

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. SUSARs may occur for marketed products such as HRIG if a reaction is not described in the product labeling. SUSARS for marketed products should be reported to the manufacturer of the product who has an obligation to notify the National Regulatory Authority through periodic pharmacovigilance.

5.11 Reporting of Serious Adverse Events

***Serious adverse events,* which include SUSARs, are reported to the sponsor and to the pharmacovigilance (PVG) for the entire study period (see protocol appendix A).**

Pharmacovigilance (PVG), PPD Global Ltd.
24 Hour Safety Hotline: +44 122 337 4240
24 Hour Safety Hotline Fax: +44 122 337 4102
EMEAASIASafetyCentral.SM@ppdi.com

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 the Pharmacovigilance (PVG) at PPD (Appendix A). 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 local medical monitor immediately upon the investigator's awareness of the event. If the local 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 pharmacovigilance (PVG) 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 the PPD to be the pharmacovigilance (PVG) 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 DSMB 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 Immediately Reportable Events

These are events that might affect randomization or analysis. The investigator must report the following events by faxing the appropriate form to the local 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 applied measures 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 1, 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 Pregnancy Safety Reporting

Pregnancy is not an adverse event. 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. Follow-up should continue for pregnancy outcome including premature terminations, and data are to be included in the safety reports.
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 Study 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. (Section 3.2.6.1 Pregnancy During The Study)

5.15 Immunological Adverse Events

Adverse events that have a potential immunological cause should be investigated as safety risks. Blood tests such as anti-SYN023 antibodies and others as clinically indicated should be drawn to help understand the mechanism of the event.

5.16 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 subject* (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 subject* (minutes to several hours):

  - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

5.17 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 receptor antagonists,

corticosteroids, and glucagon for individuals on β adrenergic blocking agents. (Sampson et al. 2006)

5.18 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 complement 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 be observed. 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).

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 DSMB Efficacy Pausing Rules

6.1.1 Confirmation of Initial LRG Pharmacodynamic activity

If the RVNA is found to be not adequate in the SYN023 initial LRG enrollment population then general LRG enrollment at that site will not be permitted by the DSMB until this has been resolved (Section 5.1.5.2).

6.1.2 Confirmation of Rabies in Trial Participants

Any laboratory confirmed or clinically suspected case of rabies occurs in the blinded trial the administration of Study Drug will be paused for DSMB confirmation of rabies diagnosis and review. The DSMB must confirm rabies in a case of the per protocol population before

unblinding of that case is considered. If a confirmed case of rabies occurs in the per-protocol unblinded SYN023 treated group the DSMB will issue a written communication permanently stopping enrollment and Study Drug administration. A rabies case will not be reported as an adverse event since it is an element of the primary objective.

6.2 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 an adverse event pattern of grave 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 DSMB. If additional clinical information becomes available during this pausing process that reduces the principal investigator's or local medical monitor's assessment of causality, severity or toxicity grade such that study pausing is no longer required by pausing rules, in other word if the PI or medical monitor recognizes their pausing of the study was in error, then the principal investigator, with the agreement of the medical monitor, and DSMB chairman/chairwoman may resume Study Drug administration, record this in a memorandum to the study file, and notify the sponsor.

Since the global medical monitor is unblinded and 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 grave 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 DSMB.

6.3 Safety Stopping Rules

The DSMB must make a determination of relationship of death (or other below) to the Study Drug before determining a need for unblinding to discover if the subject was a SYN023 recipient. The rules for stopping further enrollment and Study Drug administration by the DSMB are below:

- Death in any subject unless the DSMB determines it is UNRELATED to a SYN023 adverse event.
- A life-threatening adverse event in any subject unless the DSMB 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 grave safety concern in the opinion of the investigator or the medical monitor and are judged by the DSMB to be DEFINITELY, PROBABLY or POSSIBLY related to SYN023

The DSMB may recommend resumption of Study Drug administration if the study pause was for reasons less severe than those in the DSMB stopping rules. The DSMB 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 DSMB must follow the study safety stopping rules.

If a decision to resume study enrollment and Study Drug administration is made the DSMB will record their judgment in a memorandum to the study file and notify the sponsor. The DSMB memorandum will be forwarded to the medical monitors and principal investigators. The clinical site will be allowed to resume activities upon receipt of written notification from the sponsor.

The appropriate regulatory authority will be informed in writing when:
1. The study is stopped
2. The decision is made by the DSMB to 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 7.9).

7.1 Subject Populations

As-Treated Population (Safety Population)

Since post-exposure treatment of rabies is urgent and should not be delayed, randomization and prophylaxis will begin after a screening event that includes informed consent, urine pregnancy test and survey of inclusion criteria before some exclusion criteria have been confirmed. High-risk rabies exposure victims that meet all initially knowable inclusion/exclusion criteria will be randomized receive Study Drug and begin a regimen of rabies vaccination. All subjects who are randomized and receive Study Drug are included in the “as-treated” population.

LRG Per-Protocol Population (Initial Enrollment)

The LRG initial enrollment group is described in all subjects who
1) are randomized as part of the initial enrollment group
2) receive the correct Study Drug

3) have inclusion/exclusion criteria confirmed
4) complete the rabies vaccinations schedule by Study Day 29
6) lack major protocol deviations
7) have adequate wound treatment and Study Drug injection of all exposure sites

will be included in the "per-protocol" population. Exclusion criteria that must be confirmed are the species of the biting animal; a high risk exposure (WHO Category 3); interval ≤ 54 hours from the bite to the start of prophylaxis; the absence of RVNA ≥ 0.1 IU in serum obtained at Study Day 1, time "0" blood collection (WHO, 2013). Subjects who are discovered to not have satisfied criteria for the per-protocol population may be excluded from that population by the Per-protocol Adjudication Board.

LRG Per-Protocol Population (General Enrollment)

All subjects who
1) are randomized as part of the LRG general enrollment
2) receive the correct Study Drug
3) have inclusion/exclusion criteria confirmed
4) complete the rabies vaccinations schedule by Study Day 29
6) lack major protocol deviations
7) have adequate wound treatment and Study Drug injection of all exposure sites

will be included in the "per-protocol" population. Exclusion criteria that must be confirmed are the species of the biting animal; a high risk exposure (WHO Category 3); interval ≤ 54 hours from the bite to the start of prophylaxis; the absence of RVNA ≥ 0.1 IU in serum obtained at Study Day 1, time "0" blood collection (WHO, 2013). Subjects who are discovered to not have satisfied criteria for the per-protocol population may be excluded from that population by the Per-protocol Adjudication Board.

NRG Per-Protocol Population

All subjects who
1) are randomized to the NRG
2) receive the correct Study Drug
3) have inclusion/exclusion criteria confirmed
4) complete the rabies vaccinations schedule by Study Day 29
6) lack major protocol deviations
7) have adequate wound treatment and Study Drug injection of all exposure sites
8) are not part of the LRG enrollment

will be included in the "per-protocol" population. Initial exclusion criteria that must be confirmed are the nature of the exposure including the species of the animal; a high risk exposure (WHO Category 3); interval ≤ 54 hours from the bite to the start of prophylaxis; the absence of RVNA ≥ 0.1 IU in serum obtained at Study Day 1, time "0" blood collection (WHO, 2013).

Subjects who are discovered to not have satisfied criteria for the per-protocol population may be excluded from that population by the Per-protocol Adjudication Board.

7.2 Demographics and Protocol Compliance

Demographic parameters (age, gender, and race/ethnicity) and other baseline characteristics will be summarized by treatment group for all subjects in the safety population.

Subject enrollment to each study group will be conducted based on timing of completion of study eligibility requirements. Randomization will be adjusted by the randomization center to maintain stratification and site allocation. Any resulting imbalance in baseline characteristics between study groups will be examined.

Listings of randomized subjects who missed any dose of Study Drug or rabies vaccine and of subjects with protocol deviations (to be defined in the statistical analysis plan) will be provided.

7.3 Primary Objective: Efficacy Analyses

The primary objective is a composite endpoint with four elements in three areas:

- the geometric mean RVNA concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for HRIG recipients on Study Day 8
- the immune response to rabies vaccine on Study Day 99: RVNA GMT noninferiority SYN023 vs HRIG
- the response to rabies vaccine on Study Day 99: RVNA $\geq$ 0.5 IU/mL % noninferiority SYN023 vs HRIG
- the absence of clinical rabies.

A similar analyses will be performed for both the per-protocol and the as-treated population for sensitivity analysis.

- The first element is superiority of the geometric mean SYN023 on study Day 8 in serum. RVNA was selected because it is a generally accepted surrogate for rabies vaccine protection. Animal and human studies suggest that tissue levels of RVNA may correlate with protection by neutralizing the rabies virus before the virus is taken up into peripheral nerves from where it gains fatal access to the central nervous system even in the presence of neutralizing antibodies (Watson et al. 1981, Schumacher et al. 1989, Shankar et al. 1991). It is logical that serum levels represent passive diffusion along a concentration gradient from sites of local infiltration. Tissue RVNA concentrations are likely higher than serum RVNA concentrations. The reason for HRIG injection in addition to vaccination is to provide immediate rabies neutralizing antibodies in tissues to prevent the entry of rabies virus into nervous tissue before rabies vaccination has elicited neutralizing antibodies. This practice in historical studies seems to have reduced infection from rabies compared to rabies exposed individuals receiving only vaccination.

If it is possible to demonstrate quicker and higher concentrations in the blood of RVNA from SYN023 then this may be evidence of greater potency and perhaps effectiveness.

The pharmacodynamic variable Synermore selected to assess the prompt availability of RVNA is the area under the curve for serum RVNA concentration (Synermore's correlate of effectiveness) from Study Day 1 through Study Day 15 when vaccine antibodies will have begun to predominate. Synermore will demonstrate superiority of the $AUEC_{1\text{-}8}$ with an 80% power of observing a 10% margin of superiority with a p value ≤ 0.025.

- The second element is immune response to the rabies vaccine on Study Day 99 measured by the noninferiority of the Study Day 99 geometric mean concentrations of RVNA in SYN023 recipients compared to Study Day 99 geometric mean concentrations of RVNA in the HRIG recipients. It is important that any immunoglobulin product administered be compatible with rabies vaccination and not significantly inhibit the immune response to rabies vaccination. When should this comparison of immunogenicity be performed and secondly what margin of non-inferiority should be employed? It is Synermore's position that assessment of rabies vaccine immunogenicity should be performed on or around Study Day 99. This interval is over four half-lives of human IgG. Anti-rabies antibodies administered for prophylaxis will have largely dissipated and Study Day 99 GMC RVNA values will reflect the long term immunogenicity of rabies vaccination. Synermore defines non-inferiority rabies vaccine response of the as a 20% margin of non-inferiority and equal allowance (number of subjects in SYN023 = number of subjects in HRIG) and alpha is taken to be ≤ 0.025.

- The third element is immune response to the rabies vaccine on Study Day 99 measured by the noninferiority percent of the study population RVNA $\geq$ 0.5 IU/mL SYN023 vs HRIG. This approach assesses the noninferiority of the percent of subjects who have a serum RVNA concentration that is generally recognized as protective, the more important measure of vaccine compatibility.

- The fourth element is the absence of probable or confirmed cases of clinical rabies in the SYN023 recipients (Section 3.9.1). There is no need to specify "suspected" cases of rabies since entry into the protocol requires exposure to a possibly rabid animal and this is the factor that makes a case "probable" as opposed to "suspected." It is likely that there will no cases of rabies in the per protocol population of either treatment arm therefore a non-inferiority test could not be done. Synermore estimates the failure rate of properly administered PEP in adults to be between 1 in 1000 and 1 in 10,000 (Hemachudha et al. 1999, Hampson et al. 2008, Quiambao et al. 2008, Quiambao et al. 2009 Shantavasinkul et al. 2010, Wilde et al. 2007). A single case of rabies in a subject properly treated with PEP meeting the per-protocol conditions in a 160 subject sample of adults would be an occurrence rate of 0.63% and the 95% confidence interval extends from 0 to 2%. This rate of failure would be evidence for a lack of effectiveness.

7.4 Secondary Objectives: Clinical and Pharmacodynamic Efficacy.

To demonstrate that the proportion of SYN023 recipients with blood RVNA concentrations that meet the generally accepted as adequate threshold ≥ 0.5 IU/mL, for Study Days 8-99 in the per-protocol population is not inferior to the same proportion in HRIG recipients. A similar analysis will be performed for the as-treated population for sensitivity analysis.

To demonstrate that SYN023 administered within 54 hours of rabies exposure with rabies vaccinations prevents all probable or confirmed clinical rabies cases.

To describe the ratio of the geometric mean concentrations of RVNA at each time point in SYN023 recipients divided by the geometric mean concentrations of RVNA in HRIG recipients for the per-protocol and as-treated populations for each risk group.

To describe ant effect of increasing BMI on RVNA concentrations.

7.5 Secondary Objective Pharmacokinetic Analysis

To describe the pharmacokinetics of SYN023 in enrollees using non compartmental analysis, Vd, C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{½}$, Cl, and λ_z will be calculated when possible in the per-protocol and as treated populations. 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. Vd, C_{max}, T_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}inf}$, $t_{½}$, Cl, and λ_z will be calculated when possible in the per-protocol and as treated populations.

7.6 Secondary Objective: Immunogenicity Anti-SYN023 Antibodies

All immunogenicity analyses will be based on per-protocol and as-treated subjects for each risk group who received at least one dose of Study Drug. The presence and effect of anti-SYN023 antibodies (anti-CTB011, anti-CTB012) will be evaluated. 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. 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. Any effect of anti-SYN023 antibodies on pharmacokinetics, pharmacodynamics or safety will be described.

7.7 Secondary Objective Safety Analyses

Safety analyses will be performed using the safety population as defined in Section 7.1. Summaries will be presented by risk group and treatment group for all subjects in the safety population. The safety profile of Study Drug will be described by treatment group. The primary variable for evaluation of the safety profile will be the number and percentage of adverse events

recorded at all available post- Study Drug administration time points. For all presentations of adverse events, additional summaries based on reporting period of adverse events following each Study Drug administration 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 PT at the greatest severity or most related state recorded for that term.

Separate summaries of the number (percentage) of subjects with adverse events will also be presented. 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.

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- Study Drug administration clinical laboratory values or vital sign values recorded as newly abnormal or increased by a toxicity grade following Study Drug administration and meeting toxicity mild criteria (Grade 1) or above as specified in the Toxicity Table will be tabulated at each post- Study Drug administration 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.

The sample size of 190 subjects per treatment group will also permit an initial estimate of general safety and tolerability. An approximation to the upper 95% confidence bound on the true rate of occurrence for a Study Drug-associated adverse event not encountered in 190 subjects is 1.6%.

7.7.1 Adverse Events

The safety profile of the Study Drugs 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 Drug 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 PT 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 PT 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 B) 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.

7.7.2 Clinical Laboratory and Vital Sign Parameters

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

7.8 Sample Size Considerations Primary Objective: Composite Endpoint Element

Since the primary objective is composite multiple endpoints will be determined. Each endpoint will have different requirements on the Study sample size determination. The contribution of various endpoints to sample size is tabulated in Table 7.8-1. The specific analyses are discussed in Sections 7.81 - .

Table 7.8-1 Sample Size Estimates for Pharmacodynamic Endpoints (all 80% power, alpha ≤0.025)

RVNA GMC	Priority	Sample Size total 1:1	Mean ratio SYN/HRIG	Margin	CI	CV %
Superiority Study Day 8	Primary	<10	>10.0	10%	95	16.11
Non inferiority Study Day 99 GMC	Primary	138	0.88	20%	95	17.00
Non inferiority Study Day 99 percent subjects ≥ 0.5 IU/mL	Primary	72	1.0	10%	95	NA
Superiority Study Day 3	Secondary	<10	>10.0	10%	95	9.83
Superiority $AUEC_{1\text{-}15}$	Secondary	320	1.45	10%	90	108.78

7.8.1 Superiority of Geometric Mean of RVNA Study Day 8

Superiority test for the ratio of two geometric means is used for determining the sample size. The null hypothesis is that the ratio for the two treatments is less than the defined margin that is expressed as:

$H_0: \emptyset \leq \emptyset_L \; where \; \emptyset_L > 1$

Where, $\emptyset = \frac{GM_{SYN023}}{GM_{HRIG}}$; GM is the geometric mean.

The alternative hypothesis for superiority is expressed as: $H_1: \emptyset > \emptyset_L$. The ratio of superiority is more than ten-fold. The sample size required for this comparison is less than 10.

7.8.2 Non-inferiority of Geometric Serum RVNA on Study Day 99

The timepoint selected for non-inferiority in the current trial is based on need for a "later" timepoint at which to evaluate vaccine immunogenicity is from historical data from protocol SYN023-002 for which there are Study Day 84 and Study Day 112 timepoint (Table 7.8.2-1). The Study Day 99 is selected as being between these timepoints and closest for estimation.

The 20% margin was selected since it is a recommended bioequivalence margin for a lower bound of 0.8 (FDA 2001). Applying this margin to historical data near the Study Day 99 timepoint shows RVNA concentrations both well above the 0.5 IU/mL and should provide protective concentration in all subjects (Table 7.8.2-1).

Table 7.8.2-1 RVNA Historical Values by Timepoint for SYN023-002 Protocol

Visit	SYN023			HRIG		
	N	Geometric Mean	95% CI	N	Geometric Mean	95% CI
Day 42	73	8.05	(6.58, 9.85)	76	9.18	(7.91, 10.66)
Day 84	72	2.33	(1.79, 3.03)	75	2.75	(2.27, 3.33)
Day 112	73	1.43	(1.09, 1.87)	76	1.71	(1.38, 2.11)

Non-Inferiority test for ratio of two geometric means is used for determining the sample size. The null hypothesis is that the ratio for the two treatments is less than the defined margin which is expressed as:

$H_0: \emptyset \leq \emptyset_L \; where \; \emptyset_L < 1$

The alternative hypothesis for superiority is $H_1: \emptyset > \emptyset_L$. The calculated ratio between SYN023/RIG and the 95% confidence intervals for the ratio are presented in Table 7.8.2-2 and were used as inputs for the sample size calculation in PASS 15 software.

Table 7.8.2-2: Ratio (SYN023/HRIG) and 95% Geometric Confidence Intervals for Each Time-point for RVNA from SYN023-002 Protocol, Historical Data

Time Point	Ratio (SYN023/HRIG) for RVNA- SYN023-002	95% Geometric Means Ratio CI		CV
Day 35	81.28%	62.19%	106.23%	13.59%
Day 42	88.94%	68.79%	114.99%	13.04%
Day 84	88.50%	64.04%	122.30%	16.47%
Day 112	86.94%	61.88%	122.15%	17.32%

The sample size is calculated at 80% power with 20% margin of non-inferiority and equal allowance (number of subjects in group 1 = number of subjects in group 2) and alpha is taken to be 0.025.

The non-inferiority of serum GMC RVNA on study day 84 in SYN023 recipients (above) with respect to HRIG recipients would require the sample size of 138 for 80% power with an expected true geometric means ratio 88.00%. Note that based on historic data from protocol SYN023-002 the geometric ratio from Study Day 42 through Study Day 112 is stable and therefore it is expected that a true ratio of 88.00% is reasonable to determine non-inferiority at Study Day 99.

7.8.3 Non-inferiority of Percentage of Subjects with Serum RVNA ≥ 0.5 IU/mL on Study Day 99

20 % margin of noninferiority was selected since it is a recommended bioequivalence margin for a lower bound of 0.8 (FDA 2001). Historical SYN023 data is presented In Table 7.8.3-1.

Table 7.8.3-1 Historical Percentage of Subjects with RVNA ≥ 0.5 IU/mL

DAY	SYN023 + Vaccine		RIG + Vaccine	
	≥ 0.5 IU/mL Count (percentage)	Total	≥ 0.5 IU/mL Count (percentage)	Total
0	3 (4.0%)	75	1 (1.3%)	76
1	67 (90.5%)	74	1 (1.3%)	75
3	74 (98.7%)	75	1 (1.3%)	76
7	75 (100.0%)	75	6 (7.9%)	76
14	75 (100.0%)	75	75 (98.7%)	76
28	75 (100.0%)	75	76 (100.0%)	76
35	74 (100.0%)	74	74 (100.0%)	74
42	73 (100.0%)	73	76 (100.0%)	76
84	72 (100.0%)	72	75 (100.0%)	75
112	70 (95.9%)	73	75 (98.7%)	76

Non-Inferiority test for ratio of two proportions is used for determining the sample size. The null hypothesis is that the ratio for the two treatments is less than the defined margin which is expressed as:

$H_0: \emptyset \leq \emptyset_L \; where \; \emptyset_L < 1$

The sample size is estimated for an 80% power of demonstrating noninferiority of a 20% margin of non-inferiority and equal allowance (number of subjects in group1 = number of subjects in group 2) with a p value = 0.025 (Table 7.8.3-2).

7.8.3-2 Noninferiority Sample Size and Percentage of Subjects with RVNA ≥ 0.05 IU/mL

Assumed SYN023 Proportion	Assumed HRIG Proportion	Margin	Total Sample Size
1	1	0.2	32
1	1	0.1	72

Samples sizes are shown for noninferiority for two proportions using a 20% margin that requires a total of 32 and a 10% margin that requires a total sample of 72 both of which can be demonstrated with the current 368 subject sample.

7.8.4 Superiority of Secondary endpoint AUEC1-15

$H_0: \emptyset \leq \emptyset_L \; where \; \emptyset_L > 1$

Where, $\emptyset = \frac{GM_{SYN023}}{GM_{HRIG}}$; GM is the geometric mean.

The alternative hypothesis for superiority is expressed as: $H_1: \emptyset > \emptyset_L$.

The calculation of the sample size requires defining the range of the true mean ratio [$AUEC_{1\text{-}15}$ (SYN023/RIG): 147.55%, 90% CI: 115.10%, 189.14%], margin of superiority [10%], power [80%], coefficient of variation [CV: 108.78%] and alpha [0.025]. The calculation is done in PASS 15 software for the defined range of the true mean ratio and the results are presented for only those values for which the sample size is considered feasible.

A true $AUEC_{1\text{-}5}$ geometric mean ratio of SYN023/ HRIG of at least 1.45 and 80% power would therefore require a sample size of 320 with equal number of subjects in two groups for detecting the superiority with 10% of margin. Based on a true geometric mean ratio of at least 1.45, a total sample size of 320. A higher total sample of 368 allows for drop-outs and lost to follow up.

7.8.5 Absence of Rabies:

Synermore estimates that any PEP failure rabies cases occurring in the trial will be more likely due to a failure of clinical management or failure to follow protocol specified procedures or less likely intrinsic resistance to post-exposure prophylaxis. Synermore estimates this possibility of rabies at approximately 0.1% to 0.01%. This means there is a small chance of a single case of confirmed rabies occurs in the 184 subjects in the SYN023 NRG group. If one case of PEP failure occurs the point incidence of PEP failure will be 0.6% and the 95% confidence interval will extend from 0% to 2.0%. A 0.6% failure rate is high enough to be evidence of lack of efficacy and thus a failure of the primary objective.

7.9 Plan for Statistical Summaries and Analyses

7.9.1 Preliminary Data Reviews

A preliminary blinded data review of RVNA immunogenicity data may be performed following completion of immunogenicity assessments through Study Day 365. This review may present

individual and aggregate (mean or median [95% CI], as appropriate) RVNA immune response data, as well as change from pre-Study Drug to each post-Study Drug 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.

A preliminary unblinded review of RVNA immune response and safety data will be conducted following completion of Study Day 365. The database will be locked and the study will be unblinded for the preparation of this review. The purpose of this review is to obtain preliminary immunogenicity and safety data for use in the decision-making process regarding Study Drug dose level and dosing regimens to be employed in future studies of the Study Drug. This review will include all safety data, immune response data, clinical assessments, and concomitant medications through Study Day 365. 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. 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 365 data have been collected, reviewed and queries resolved.

7.9.2 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.

7.10 Computer Methods

Statistical analyses will be performed using SAS® version 9.1 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, 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 (or CTA, etc.). 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 the informed consent document will be reviewed and approved by the IRB or IEC of each participating clinical site prior to any protocol-specified procedures being conducted. All documents given to the subject will be reviewed and approved by the IRB/IEC. 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 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. Personal information may be difficult to remove from safety information but this data is kept under additional measures of data protection and is not part of the study database.

After the study has been unblinded, the subject should be informed by letter which treatment (SYN023 or HRIG) the subject received. The text of this letter will be submitted and approved by the relevant IRB/IEC before issuance to subjects.

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 other than administrative changes and typographical errors in 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. Subjects 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.

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.

9.4 Payments and Reimbursement of Human Research Subjects

Trial participants will not be paid for participation in the trial. Trial participants will be reimbursed for expenses that are incurred due to participation in the trial.
These expenses may include but are not limited to: transportation costs, child care costs, costs of missed wages due to trial related activities, clinic appointments and other expenses at the discretion of the principal investigator and site IRB/IEC. The amounts and payment schedules for payment shall be determined by the principal investigator and the IRB/IEC at each site.

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(s) 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. From the sponsor. All changes to the protocol must be submitted to the IRB/IEC and must be approved by the IRB/IEC unless they are administrative changes, typographical errors or required for subject safety prior to their implementation. This is the third version of the protocol.

12 CHANGES IN THE CURRENT VERSION OF THE PROTOCOL

The changes to Version 6.0 of the protocol are listed in Table 12-1. Version 5.0 was never submitted to any clinical site but was used in discussions with the US FDA thus the last clinical protocol was Version 4.0. Minor grammatical or orthographic changes may not be listed. The major changes to the protocol are:

- The operation of the DSMB to permit enrollment of the NRG is revised to recognize that all subjects need not have a RVNA ≥ 0.5 IU/mL.

Table 12-1 Table of Changes for Version 6.0 of Protocol

Section Modified	Version 4.0	Version 6.0	Page
3.4.1 Blinding at the Study Level	The LRG and the NRG are both blinded until Study Day 365. If the last subject in LRG reaches Study Day 365 even if the NRG is still in progress, then the LRG group may be unblinded	The LRG and the NRG are both blinded until Study Day 365. If the last subject in LRG reaches Study Day 365 even if the NRG is still in progress, then the LRG group may be unblinded. The LRG may be unblinded to the extent recommended or	49

Section Modified	Version 4.0	Version 6.0	Page
		required by the DSMB for analysis of safety or efficacy data for Study Day 99 DSMB review.	
4.4 Study Rabies Vaccine in Philippines	Study rabies vaccine in Philippines and Thailand	Study rabies vaccine in Philippines	62
5.1.5.3 DSMB Review of Safety and Pharmacodynamic Activity in the Initial and General Enrollment LRG	The sponsor will collect blinded RVNA results and adverse events through Study Day 99 from all subjects in the LRG General and Initial enrollment groups and provide them to the DSMB. Permission to enroll the General Enrollment of the NRG may be granted at Study Day 183 if • no protocol stopping rules are met (Section 6.3) and if • no severe related adverse events other than local injection site manifestations are encountered due to SYN023 in the initial and general enrollment of the LRG • The RVNA values are all in the protective range in SYN023 recipients Study Days 8 through 99 (Section 3.9.2).	The sponsor will collect blinded RVNA results and adverse events through Study Day 99 from all subjects in the LRG General and Initial enrollment groups and provide them to the DSMB. Permission to enroll the General Enrollment of the NRG may be granted at Study Day 183 if • no protocol stopping rules are met (Section 6.3) and if • no severe related adverse events other than local injection site manifestations are encountered due to SYN023 in the initial and general enrollment of the LRG • The RVNA values are in the protective range in ≥ 75% of SYN023 recipients on Study Day 99 (Section 3.9.2).	65-66
5.1.5.4 DSMB Review of Safety in the NRG	The DSMB will assess the safety after 80 subjects have completed Study Day 99. If	The DSMB will assess the safety (while enrollment continues) after 80 subjects	66

Section Modified	Version 4.0	Version 6.0	Page
	there are no adverse events or patterns of concern	have completed Study Day 99. If there are no adverse events or patterns of concern it will issue permission for the trial to continue.	

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APPENDIX A Protocol Facilities and Contact List

Role in Study	Name	Contact Information
Institutional Review Boards	To be determined	USA Philippines
Clinical Study Manager	Paul Grostal	PPD Level 9, 5 Queens Road Melbourne VIC 3004, Australia (mobile) +61 (0)413 625 763
Responsible Physicians	To be determined	USA Philippines
Medical Monitor (Emergency Contact)	J. Bruce McClain, M.D. James Fan, M.D.	11673 Garnet Road Lovettsville, VA 20180 (Mobile) 202-236-6975 PPD No 155, Tianjin Road, Huangpu District, Shanghai, China +86 136 7198 4640
Study Monitoring	To be determined	PPD local branches in USA, Philippines,
Biomedical Laboratory Facilities (clinical safety laboratory tests)	Edward Xue	PPD® Laboratories 25/F, Raffles City Beijing Office Tower No.1 Dongzhimen South Street Dongcheng District Beijing 100007, China Mobile +86 13601383815
Safety Reporting	Rowena Gracia Blaza (or PVG assigned personnel)	Pharmacovigilance (PVG), PPD 24H Safety Hotline: +44 122 337 4240 24H Safety Hotline Fax:+44 122 337 4102 EMEAASIASafetyCentral.SM@ppdi.com
Clinical Sites	To be determined	USA Philippines
Data Safety Monitoring Board	Gil Price, M.D. Chief Medical Officer	ProPharma Group 2635 University Ave W Suite 195 St. Paul, MN 55114 M: 240-426-4695 gil.price@propharmagroup.com

Rabies Virus Neutralizing Activity (RVNA)	Stephanie Gatrell/ Hunter Wilkens	Rabies Laboratory, Mosier Hall, Kansas State University, 1800 Denison Avenue, Manhattan KS 66506-5600
Bioanalytical Laboratory Facility (PK/ADA)	Korin Cofsky	Syneos Health 301D College Rd East, Princeton, NJ 08540 Phone: +1 609 806 4815 korin.cofsky@syneoshealth.com

APPENDIX B Toxicity Table

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

8. * In addition to grading the local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
9. ** 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

10. * 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

11. ** 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.
12. *** 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)

13. ** "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

APPENDIX C Phlebotomy Volume by Visit

Low Risk Group (volumes are approximate)

Study Visit Day →	1	4	8	15	29	43	71	99	127	155	183	274	365
Hepatitis B, C [a]	4												
HIV [a]	5												5
CBC, platelets [a]	2	2		2		2							
Serum chemistry [a, c]	4	4		4		4							
PT(INR), PTT [a]	2					2							
Serum RVNA	10[a]	10[b]	10[b]	10[b]	10	10	10	10	10	10	10	10	10
Anti-SYN023 serum assay	5[a]			5	5			5	5	5	5	5	5
SYN023 concentration	5[a]	5[b]	5[b]	5[b]	5	5		5					
Per visit phlebotomy volume	37	21	15	26	20	23	10	20	10	10	10	10	15
Cumulative phlebotomy volume	37	58	73	99	119	142	152	172	182	192	202	212	227

Normal Risk Group (volumes are approximate)

Study Visit Day →	1	4	8	15	29	43	71	99	127	155	183	274	365
Hepatitis B, C [a]	4												
HIV [a]	5												5
CBC, platelets [a]	2	2		2		2							
Serum chemistry [a, c]	4	4		4		4							
PT(INR), PTT [a]	2					2							
Serum RVNA [a]	10	10	10	10	10	10	10	10	10	10	10	10	10
Anti-SYN023 serum assay	5[a]			5[b]				5					
SYN023 concentration	5[a]	5[b]	5[b]	5 [b]				5					
Per visit phlebotomy volume	37	21	15	26	10	18	10	20	10	10	10	10	15
Cumulative phlebotomy volume	37	58	73	99	109	127	137	157	167	177	187	197	212

APPENDIX D Listing of Procedures by Study Visit

LRG Group Study Day Procedure of Subject Evaluations

LRG Study Day 1 (Randomization Date, Baseline)

Before Study Drug administration

Obtain informed consent

Verify eligibility by review of inclusion/exclusion criteria

Record medical history Including date of last immunization for tetanus

Conduct and record physical examination and vital signs

Perform Baseline EKG

Collect urine sample for:

Urine βHCG (females only) must be confirmed negative before randomization

Baseline Urinalysis

Blood for: Baseline Hepatitis B, C, HIV-1, 2,

Blood for Baseline PT (INR), PTT

Blood for Baseline serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for Baseline hematology: CBC including differential and platelets

Blood for Baseline serum RVNA, SYN023 concentration and anti-SYN023 antibodies

Bite wound washing or irrigation if no wound present

Photographs of all wounds

Confirmation visit scheduling if required

Record concomitant medications

Randomization

Study Drug Administration

Study Drug injection to wound or muscle if no wound

Rabies Vaccination #1

After Study Drug Administration

Record AEs/SAEs and

Record Solicited AEs

Wound or Site of injection examination

LRG Study Day 4

Blood for hematology: CBC including differential and platelets

Blood for serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for Serum RVNA, and SYN023 concentration

Interval history

Record solicited AEs

Vital signs, focused physical examination

Confirmation visit findings (bite time, animal capture, location animal specimens, immunization records etc.)

Record AEs/SAEs

Record concomitant medications

Wound or site of injection examination

Rabies vaccination #2

LRG Study Day 8

Blood for Serum RVNA and SYN023 concentration

Interval history,

Record solicited AEs

Vital signs, focused physical examination

Confirmation visit findings (bite time, animal capture, location animal specimens, immunization records etc.)

Record AEs/SAEs

Record concomitant medications

Wound or site of injection examination

Rabies vaccination #3

LRG Study Day 15

Blood for hematology: CBC including differential and platelets

Blood for serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for Serum RVNA, SYN023 concentration and anti-SYN023 antibodies

Interval history

Focused physical examination

Record AEs/SAEs

Record concomitant medications

Wound or site of injection examination

Rabies vaccination #4

LRG Study Day 29 (Visit window ± 2 days)

Interval history

Wound or site of injection examination

Focused physical examination

Blood for Serum RVNA, SYN023 concentration and anti-SYN023 antibodies

Record AEs/SAEs

Record concomitant medications

Rabies vaccination #5

LRG Study Day 43 (Visit window ± 4 days)

Blood for hematology: CBC (including differential and platelets)

Blood for PT (INR), PTT

Blood for serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for Serum RVNA, and SYN023 concentration

Interval history

Focused physical examination

Record AEs/SAEs

Record concomitant medications

LRG Study Day 99 (Visit window ± 7 days)

Interval history

Focused physical examination

Blood for Serum RVNA

Record SAEs

Record concomitant medications

LRG Study Day 71, 127, 155, (Visit window ± 7 days), 183, 274 (Visit window ± 14 days)

Interval history

Focused physical examination

Blood for Serum RVNA, SYN023 concentration and anti-SYN023 antibodies

Record SAEs

Record concomitant medications

LRG Study Day 365 (Visit window ± 14 days)

Blood for HIV-1, 2

Interval history

Focused physical examination

Blood for Serum RVNA and anti-SYN023 antibodies

Record SAEs

Record concomitant medications

NRG Group Study Day Procedure of Subject Evaluations

NRG Study Day 1 (Randomization Date, Baseline)

Before Study Drug administration

Obtain informed consent

Verify eligibility by review of inclusion/exclusion criteria

Record medical history including date of last immunization for tetanus

Conduct physical examination and vital signs

Perform EKG

Collect urine sample for:

βHCG (all females)

Baseline Urinalysis

Blood samples for baseline Hepatitis B, C, HIV-1, 2

Blood for baseline PT (INR), PTT

Blood for baseline serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for baseline Hematology: CBC including differential and platelets

Blood for baseline Serum RVNA, Anti-SYN023 antibody assay, SYN023 concentration

Bite wound washing or irrigation

Photographs of all wounds

Schedule confirmation visit

Record concomitant medications

Randomization

Study Drug Administration

Study Drug Wound injection

Rabies Vaccination #1

After Study Drug Administration

AEs/SAEs

Record Solicited AEs

Wound or site of injection examination

NRG Study Day 4

Blood for hematology: CBC including differential and platelets

Blood for serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for Serum RVNA SYN023 concentration

Vital signs

Interval history

Focused physical examination

Rabies vaccination #2

Confirmation visit

AEs/SAEs

Solicited AEs

Record concomitant medications

Wound or Site of injection examination

NRG Study Day 8

Vital signs

Interval history

Focused physical examination

Blood for Serum RVNA and SYN023 concentration

Confirmation visit

Rabies vaccination #3

AEs/SAEs and concomitant medications

Solicited AEs

Wound or Site of injection examination

NRG Study Day 15

Hematology: CBC including differential and platelets

Serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Interval history

Focused physical examination

Blood for Serum RVNA, Anti-SYN023 serum assay, SYN023 concentration

Rabies vaccination #4

AEs/SAEs

Record concomitant medications

Wound or Site of injection examination

NRG Study Day 29 (Visit window ± 2 days)

Interval history

Focused physical examination

Blood for Serum RVNA

Record AEs/SAEs

Record concomitant medications

Wound or Site of injection examination

Rabies vaccination #5

NRG Study Day 43 (Visit window ± 4 days)

Blood for Hematology: CBC including differential and platelets

Blood for Serum chemistry: total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel

Blood for PT (INR), PTT

Interval history

Focused physical examination

Blood for Serum RVNA

Record AEs/SAEs

Record concomitant medications

NRG Study Day 71 (Visit window ± 7 days)

Interval history

Focused physical examination

Blood for Serum RVNA

SAEs

Record concomitant medications

NRG Study Day 99 (Visit window ± 7 days)

Interval history

Focused physical examination

Blood for Serum RVNA, Anti-SYN023 serum assay, SYN023 concentration

SAEs

Record concomitant medications

NRG Study Day 127, 155 (Visit window ± 7 days), 183, 274 (Visit window ± 14 days)

Interval history

Focused physical examination

Blood for Serum RVNA

SAEs

Record concomitant medications

NRG Study Day 365 (Visit window ± 14 days)

Blood for HIV-1, 2

Blood for Serum RVNA

Interval history

Focused physical examination

SAEs

Record concomitant medications