Synermore Biologics Co., Ltd.

SYN023-004

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

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Final Statistical Analysis Plan

Version 1.0

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List of Abbreviations

ADA	anti-drug antibodies
AE	adverse event
ATC	anatomical therapeutic chemical
$AUC_{1\text{-last}}$	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
BDRM	blinded data review meeting
BLQ	below the limit of quantification
BMI	body mass index
CI	confidence interval
C_{max}	maximum concentration
Clp	plasma clearance
Cr	Creatinine
CV	coefficient of variation
CRF	case report form
DM	Data management
DSMB	data safety monitoring board
EDC	electronic data capture
ERIG	equine rabies immune globulin
GMC	geometric mean concentration
GMT	geometric mean titer
Geo SD	geometric standard deviation
HIV	human immunodeficiency virus
HRIG	human rabies immune globulin
IU	international units
kg	Kilogram
λ_z	terminal elimination rate constant
LD50	lethal dose 50%
LLN	lower limit of normal
LRG	low risk group
MNT	mouse neutralization test
MedDRA	medical dictionary for regulatory activities
mL	Milliliter
NRG	normal risk group

PD	Pharmacodynamic
PEP	post exposure prophylaxis
PK	Pharmacokinetics
PT	preferred term
RFFIT	rapid fluorescent foci inhibition test
RVNA	rabies virus neutralizing activity
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	system organ class
TEAE	treatment-emergent adverse events
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

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the procedures and statistical methods that will be used to analyze, and report results for

- subjects enrolled under Protocol version 2.0 (21Feb2019) to the initial Low Risk Group (LRG) and
- subjects enrolled under a later version of the Protocol (including, but not exclusively, version 3.0 (15Jul2019) and version 4.0 (15Aug2019)) to any of the LRG and Normal Risk Group (NRG).

2. Objectives

2.1. Primary Objective

The primary objective is a composite endpoint with four elements:

- To demonstrate that the geometric mean rabies virus neutralizing activity (RVNA) concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for human rabies immune globulin (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 cases of probable or confirmed rabies in SYN023 recipients.

2.2. 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. V_d, 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 Per-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.

3. Investigational Plan

3.1. Overall Study Design and Plan

This is a Phase 2b, double blinded, randomized study of SYN023 compared to HyperRab® S/D (a licensed HRIG) for post exposure prophylaxis (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 at least two countries where rabies occurs. The trial will enroll sequentially two different risk substrata of World Health Organization (WHO) Category 3 rabies exposure.

Table 3.1-1 Exposure Characteristics of the Low Risk Group (LRG) and Normal Risk Group (NRG)

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	+	+

Schedules of study procedures can be found in Section 15.1.

3.1.1. Low Risk Group

The LRG is composed of subjects who meet the modified WHO Categories 3 protocol exposure criteria (Protocol Section 2.2.1). 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 (Table 3.1-1). Bites to the head, neck or genitalia are excluded from LRG Initial Enrollment and General Enrollment.

3.1.2. 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 data safety monitoring board (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 will not be included in the RVNA Per-protocol Population but will be included in the 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.

3.1.3. Advancement from Initial Enrollment LRG to General Enrollment LRG

The DSMB will permit enrollment of the general LRG if safety from the As-treated Population and RVNA pharmacodynamic data from the Per-protocol Population through Study Day 29 from the initial LRG enrollment are found to be satisfactory by the DSMB.

3.1.4. General Enrollment LRG

The LRG general enrollment of an additional 60 subjects will consist of low risk WHO Category 3 exposures (Table 3.1-1). Subjects in 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.

3.1.5. Advancement from LRG General Enrollment to the NRG

If Study Day 99 efficacy (RVNA geometric mean concentration (GMC) and RVNA ≥0.5 IU/mL) and safety LRG data from the initial and general LRG 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. 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.

3.1.6. Enrollment of the NRG

The NRG will consist of all WHO Category 3 exposure (Table 3.1-1). 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.

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.

3.1.7. Study Duration and Follow-up

The 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 especially important in the last six months of the study when clinic visits are less frequent.

3.2. Study Endpoints

3.2.1. Efficacy Evaluations

Efficacy evaluations include:

- Clinical Efficacy Evaluations: a confirmed or probable case of rabies
- Pharmacodynamic Efficacy Evaluations: Serum RVNA

These are defined as the primary endpoints in Section 8.1.

3.2.2. Immunology Laboratory Evaluations

Immunology laboratory evaluations include:

Sample Type	Assay	Purpose of Assay
Serum	SYN023 concentration (CTB011 and CTB012)	Pharmacokinetics (PK) evaluations (Section 3.2.3)
Serum	RVNA by rapid fluorescent foci inhibition test (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

The RFFIT results will reported in a standardized concentration represented as international units (IU) per mL of serum (e.g., 0.5 IU/mL).

These are defined as the secondary endpoints in Section 8.2.

3.2.3. Pharmacokinetic Evaluations

For the LRG subjects, PK samples for SYN023 concentration (CTB011 and CTB012) will be obtained among all SYN023 recipients per assessment schedule (Section 15.1.1). Similarly, for the NRG subjects, PK samples will be obtained at selected timepoints per assessment schedule (Section 15.1.2). PK parameters (V_d, C_{max}, T_{max}, $AUC_{1\text{-}t}$, $AUC_{1\text{-}inf}$, $t_{½}$, Cl, and λ_z) will be calculated, when possible, for the presentation of PK activities (Section 10.3).

3.2.4. Virology Laboratory

Biting animal specimens when available from brain, skin or blood will be evaluated locally for rabies diagnosis (Section 8.1.1.4).

3.2.5. Safety Endpoints

3.3. Study Drugs

Subjects being enrolled to the study will be randomized to take either SYN023 or HRIG on Study Day 1. If a subject is enrolled under Protocol Amendment 2.0, rabies vaccinations will be administered on Study Days 1, 4, 8, and 15. If a subject is enrolled under a later version of the Protocol, vaccinations will be administrated on Study Days 1, 4, 8, 15 and 29. It is believed that there is unlikely any clinical difference in the different dosing schedules.

3.3.1. 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 (Protocol Section 3.7.1). Care must be taken NOT to administer a rabies vaccine near the study drug administration site.

3.3.2. SYN023

After thorough wound sanitation, injections of the entire calculated dose of SYN023 should be administered into and around all the bite wounds. 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.

3.4. 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). The rabies vaccine should be administered as soon as possible after dose constitution. Rabies vaccination should be administered within 75 minutes after study drug.

4. General Statistical Considerations

As it is unlikely that there is any clinical difference between the 4 and 5 dose regimens, summaries will be grouped by study group (LRG and NRG) regardless the difference in dosing schedules. In each summary where applicable, subjects will be grouped by treatment (actual study drug received). The two treatment groups for the study are SYN023 and HRIG.

Continuous data will be described using descriptive statistics (i.e. *n*, mean, standard deviation (SD), median, minimum, and maximum). Categorical data will be described using the subject count and percentage in each category. For the summary statistics of all numerical variables, unless otherwise specified, minimum and maximum will be displayed to the same level of precision as reported. Mean and median will be displayed to one level of precision greater than the data collected. SD/standard error (SE) will be displayed to two levels of precision greater than the data collected. P-values will be rounded to three decimal places. If a p-value is less than 0.001 it will be reported as "<0.001." If a p-value is greater than 0.999 it will be reported as ">0.999." Data will be displayed in all listings sorted by treatment group (actual study drug received).

Subjects will be identified in the listings by the subject identification number concatenated with the site number.

When count data is presented, the percentage will be suppressed when the count is zero to draw attention to the non-zero counts. Where applicable, a row denoted "Missing" will be included in count tabulations to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

Unless otherwise specified,

- baseline will be defined as the last non-missing assessment prior to the fist dose date (and time, if available on Study Day 1.
- Change from baseline is defined as: post-baseline value – baseline value.

The Study Day will be calculated as follows:

- If the assessment date occurs on or after the date of the first dose of study drug:
  Study Day = assessment date – first dose date + 1.
- If the date of interest occurs before the date of the first dose of study drug:
  Study Day = assessment date – first dose date
- There is no Study Day 0.

Missing data will not be imputed except for incomplete or partial dates of adverse events (AEs) and concomitant medications. Imputation rules for such will be described in the corresponding sections.

By timepoint summaries will be based on case report form (CRF) visits. For efficacy analyses, unscheduled results will not be considered but only be listed in by-subject listings. For safety analyses, unscheduled results will not be presented in by-timepoint summaries. However, it will be considered for overall post-treatment maximum or minimum values when reporting safety abnormalities.

All analyses will be conducted using SAS Version 9.4 or higher. If not pre-specified, statistical tests will be two-sided and interpreted at a 5% significance level.

4.1. Sample Size

Data from the initial 20 LRG 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.

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 $AUEC_{1\text{-}15}$ secondary endpoint. Synermore anticipates a total size of 368 subjects to be enrolled to NRG to allow a reasonable rate of loss to follow-up and exclusions. 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.

Detailed sample size considerations can be found in protocol Section 7.8 for full iterations.

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 4.1-1 Sample Sizes by Risk Group and Treatment

Group	Enrollment	Treatment	Protocol version	Rabies Vaccination	Number of subjects
LRG	initial	HRIG 20 IU/kg	2.0	Study Days 1, 4, 8, 15	5
LRG	initial	SYN023 0.3 mg/kg	2.0	Study Days 1, 4, 8, 15	15
LRG	general	HRIG 20 IU/kg	3.0	Study Days 1, 4, 8, 15, 29	30

Group	Enrollment	Treatment	Protocol version	Rabies Vaccination	Number of subjects
LRG	general	SYN023 0.3 mg/kg	3.0	Study Days 1, 4, 8, 15, 29	30
NRG	general	HRIG 20 IU/kg	3.0	Study Days 1, 4, 8, 15, 29	184
NRG	general	SYN023 0.3 mg/kg	3.0	Study Days 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

4.2. Randomization, Stratification, and Blinding

Subjects will not be replaced after randomization. They may be excluded from the Per-protocol Population. Allocation of randomization among sites will be adjusted to accommodate stratification of head, neck or genitalia bites or site enrollment imbalances.

4.2.1. 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 Protocol Section 2.2.1. The group as described in Table 4.1-1 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.

4.2.2. LRG and NRG General Enrollment 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 4.1-1. 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 randomization center will determine the randomization allocation and return the randomization assignment in written communication to the study site.

4.2.3. Blinding and Unblinding

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 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 and to inform the sponsor of the status of certain endpoint elements so that the sponsor may

make product development decisions. Since investigational agent will have been delivered, still blinded specimens for analysis collected and individual treatment assignments still unknown to the sponsor, this should not affect the conduct of the trial during the observation period required for clinical rabies surveillance.

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 AEs. 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.

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.

4.3. Analysis Set

The Per-protocol Adjudication Board will review blinded data and decide whether to exclude a subject from the Per-protocol Populations before each DSMB meeting. All analysis set definitions should be finalized prior to final study unblinding or through thorough review in the Blinded Data Review Meeting (BDRM). The list of major protocol deviations must be finalized prior to the database lock and unblinding.

Primary analyses will be performed on the Per-protocol Populations. The As-treated Population will be applied on the primary endpoints as sensitivity analyses.

4.3.1. Screen Failures

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 equine rabies immune globulin (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.

4.3.2. All Enrolled

The All Enrolled set includes every subject with recorded data in the Data Management (DM) database excluding screen failures.

4.3.3. 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 and survey of inclusion criteria before some exclusion criteria have been confirmed. High-risk bite victims that meet all initially knowable inclusion/exclusion criteria will be randomized to 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. Unless otherwise specified, summaries of adverse events, treatment compliance, laboratory results, and vital signs will be based on the As-treated Population grouped by actual treatment received and overall.

4.3.4. LRG Per-Protocol Population

All subjects who

- are randomized
- receive the correct study drug
- have inclusion/exclusion criteria confirmed
- complete all rabies vaccinations scheduled
- lack major protocol deviations
- 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.

4.3.5. NRG Per-Protocol Population

All subjects who

- are randomized
- receive the correct study drug
- have inclusion/exclusion criteria confirmed

- complete all rabies vaccinations scheduled
- lack major protocol deviations
- have adequate wound treatment and study drug injection of all exposure sites
- are not part of the LRG enrollment

will be included in the "Per-protocol" Population. Initial 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.

5. Subject Disposition

5.1. Disposition

The subject disposition table summarizes the counts for each analysis set and summarizes the reason for discontinuation from study by total and frequency.

5.2. Protocol Deviations

All protocol deviations (including violations) will be assessed and reviewed at the BDRM prior to the database lock. Any exclusion of randomized subjects from the Per-protocol Population after randomization must be made by the Per-protocol Adjudication Board. Subjects with the following significant deviations will be excluded from the Per-protocol Populations:

- 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
- Receive prohibited treatment during the trial
- Are found not to have a modified WHO Category 3 exposure
- Are discovered to have or have developed HIV infection or other immunodeficiency state
- Second high-risk animal bite or contact requiring PEP

As the study is ongoing, additional significant protocol deviations can also be identified or defined by the Per-protocol Adjudication Board. The list of significant protocol deviations can be updated accordingly.

Significant deviations categorized according to the list will be summarized in a table for the As-treated Population. All protocol deviations will be presented in a listing and an additional listing

of deviations for the randomized subjects who missed any dose of study drug or rabies vaccine will be provided.

6. Demographics and Baseline Characteristics

Demographic parameters (age, gender, race and ethnicity), randomization factors (including study site and bite location) and other baseline characteristics will be summarized by treatment group for all subjects in the As-treated Population. The summary can be used to check potential imbalance between treatment groups.

6.1. Demographics

Demographics for all subjects in the As-treated Population will be presented in a listing. Listings of randomized subjects who missed any dose of study drug or rabies vaccine and of subjects with protocol deviations will be provided.

The age and body mass index (BMI) collected in CRF will be used for analysis if it is non-missing. If the age is not collected in the CRF, the age in years is calculated using the date of the informed consent and date of birth.

Age (years) = [(Informed Consent Date – Date of Birth + 1) / 365.25].

6.2. Baseline Disease Characteristics

All rabies related characteristics as captured on the ‘Confirmation Visit’ and ‘Bite Wound Washing or Irrigation’ CRF pages will be summarized as recorded based on the As-treated Population.

6.3. Medical History

Medical history will include, but is not limited to, events recorded on the Medical History CRF page. Any event that is proven to have ended before the first dose of study drug will also be categorized as a medical history. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 or later (the actual MedDRA version used will be specified in the actual outputs). The number and percentage of subjects with any medical history will be summarized by treatment group and overall for each system organ class (SOC) and preferred term (PT). Percentages will be calculated based on the number of subjects in the As-treated Population.

6.4. Inclusion and Exclusion Criteria

Prior to enrollment, the investigator will assess if the subject fulfills all the inclusion and none of the exclusion criteria outlined in the protocol. The specific inclusion criterion not met or exclusion criterion which was met will be recorded in the CRF. This information and whether the sponsor granted a waiver will be presented in a listing.

6.5. Electrocardiogram

Baseline ECG results and overall interpretation will be listed and summarized by risk group and treatment based on the As-treated Population. If abnormal, clinically significant findings should be considered a pre-existing condition and be indicate on the Medical History CRF page.

7. Treatments and Medications

7.1. Prior and Concomitant 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' CRF. The indication recorded on the 'Concomitant Medications' CRF must correspond to a medical term/diagnosis recorded on the 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.

All prior and concomitant medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHO-DD) and summarized by treatment group based on the As-treated Population. The actual dictionary version used will be specified in the actual outputs.

7.1.1. Prior Medications

Prior medications are defined as medications taken and stopped prior to the first dose of study drug. Prior medications will only be presented in a data listing.

7.1.2. Concomitant Medications

Concomitant (including post-treatment) medications are defined as medications with a start date or a stop date occurring on or after the first dose. If the medication start/stop date is missing or partial, the medication will be considered concomitant unless there is evidence to the contrary (e.g., month and year of stop date is present and is less than the month and year of the first dose of study drug). (Section 15.3.2)

A frequency summary table based on the drug class (Anatomical Therapeutic Chemical (ATC) level 2 terms) and standardized medication names will be produced. At each level of

summarization, a subject is counted once if he/she received one or more medications at that level.

A by-subject listing of concomitant medications will be provided.

7.2. Treatment Exposure and Compliance

7.2.1. Extent of Exposure

Extent of exposure including number of doses, cumulative number of doses, duration of exposure, and cumulative dose will be summarized for the As-treated Population as well as the Per-protocol Population. Percentages will be calculated based on number of subjects in the specified population.

Duration of treatment exposure (days) will be calculated as (date study drug last applied minus date study drug first applied) plus 1.

7.2.2. Treatment Compliance and Modifications

Compliance will be summarized for rabies vaccinations. Treatment compliance is defined as the ratio of total number of vaccinations to the planned number of vaccinations, in terms of percentage. Treatment compliance will be summarized descriptively for both the As-treated and the Per-protocol Populations.

8. Efficacy Analysis

The primary and secondary efficacy endpoints may be performed on the As-treated and the Per-protocol Populations. The Per-protocol analyses will be considered primary; the As-treated analyses will be considered supportive. The denominator for all percentages will be the number of subjects in that treatment within the analysis set of interest, unless otherwise specified.

8.1. Primary Efficacy Endpoint

The primary objective will be evaluated by 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 geometric mean titer (GMT) noninferiority SYN023 vs HRIG
- the response to rabies vaccine on Study Day 99: RVNA ≥0.5 IU/mL % noninferiority SYN023 vs HRIG
- the absence of clinical rabies.

The primary efficacy analyses will be performed on the Per-protocol Population for the NRG group. Standard log transformation on GMC can be found in Section 15.2.

8.1.1. Primary Analysis

8.1.1.1. Superiority Testing on Study Day 8

The first element is superiority of the geometric mean concentration of RVNA (serum) in SYN023 recipients on Study Day 8. RVNA was selected because it is a generally accepted surrogate for rabies vaccine protection. 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.

GMC for a group of subjects is calculated by multiplying all values and taking the *n*th root of this number, where *n* is the number of subjects with available data. Because concentrations are often approximately log-normally distributed, they are customarily analyzed on a logarithmic (log) scale; a difference in arithmetic means (Δ) on a log scale becomes a ratio of geometric means (∅) when the results of analysis are converted back to the original data scale. Thus, each hypothesis is a statement regarding ∅. The alternative hypothesis (H_a) is that the SYN023 vaccine is superior to HRIG.

$$H_a: \emptyset = \frac{GMC_{SYN023}}{GMC_{HRIG}} > 1$$

The null hypothesis is the complement of the alternative, meaning that the SYN023 vaccine is inferior or equal to HRIG.

$$H_0: \emptyset = \frac{GMC_{SYN023}}{GMC_{HRIG}} \leq 1$$

The null hypothesis will be rejected at a significance level of 2.5% ($\alpha = 0.025$) if the lower bound of the one-sided 97.5% confidence interval (CI) for the GMC ratio is greater than 1.

In the summary table, by-treatment GMCs and geometric standard deviations (Geo SDs) will be displayed, where Geo SD is calculated by converting the normal concentration values in to log-normal values, calculating the typical standard deviation of log transformed concentrations and then taking its antilog for the geometric standard deviation. GM ratio along with its coefficient of variation (CV) and 95% CI will also be displayed in the summary table.

8.1.1.2. Non-inferiority Testing on Study Day 99

The second element is immune response to the rabies vaccine on Study Day 99 measured by the noninferiority of the Study Day 99 GMC of RVNA in SYN023 recipients compared to Study Day 99 GMC of RVNA in the HRIG recipients. Synermore defines non-inferiority rabies vaccine response 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 alternative hypothesis (H_a) is that the SYN023 vaccine is non-inferior to HRIG by a 20% margin.

$$H_a: \emptyset = \frac{GMC_{SYN023}}{GMC_{HRIG}} > 0.8$$

The null hypothesis is:

$$H_0: \emptyset = \frac{GMC_{SYN023}}{GMC_{HRIG}} \leq 0.8$$

The null hypothesis will be rejected at a significance level of 2.5% ($\alpha = 0.025$) if the lower bound of the one-sided 97.5% confidence interval for the GMC ratio is greater than the non-inferiority bound 0.8. Descriptive statistics will be displayed in a summary table following the same presentation for Section 8.1.1.1.

8.1.1.3. Non-inferiority on RVNA Response Rate

The third element is immune response to the rabies vaccine on Study Day 99 measured by the noninferiority percent of the study population RVNA ≥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 alternative hypothesis (H_a) is that the response rate in SYN023 vaccine (r_{SYN023}) is non-inferior to HRIG (r_{HRIG}) by a 20% margin (0.8 in terms of a ratio). Given that the statistics can be defined as the rate ratio $\emptyset = \frac{r_{SYN023}}{r_{HRIG}}$, the alternative hypothesis can be written as:

$$H_a: \emptyset = \frac{r_{SYN023}}{r_{HRIG}} > 0.8$$

and the null hypothesis as:

$$H_0: \emptyset = \frac{r_{SYN023}}{r_{HRIG}} \leq 0.8.$$

As the rate ratio $\emptyset$ and the rate difference $\Delta = r_{SYN023} - r_{HRIG}$ are interchangeable with log transformation, it is equivalent to test on the test statistic Δ with Pearson's chi-square test or, in case of small sample sizes (responders in either group is less than 5 subjects), Fisher's exact test. This can be achieved by using SAS procedure FREQ (use the option *riskdiff* and additional option *Newcombe* with the *tables* statement). In the summary table, by-treatment risk rates with corresponding SDs, risk ratio and the asymptotic CI for the risk ratio based on the Wilson score method will be back transformed and displayed. In case of small sample sizes, an exact CI based on the Clopper-Pearson method will be presented instead. The null hypothesis will be rejected at a significance level of 2.5% ($\alpha = 0.025$) if the lower bound of the two-sided 95% CI for the risk ratio is greater than the non-inferiority bound 0.8.

8.1.1.4. Probable or Confirmed Cases of Rabies

The fourth element is the absence of probable or confirmed cases of clinical rabies in the SYN023 recipients. 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.

Study drug administration will be paused for DSMB confirmation of rabies diagnosis and review. Unblinded data will be presented to the DSMB during the closed sessions. If a confirmed case of rabies occurs in the per-protocol SYN023 group, the DSMB will issue a written communication to permanently stop study enrollment and study drug administration. A descriptive summary table with counts of cases will be prepared after receiving DSMB confirmation for the end of study report after database lock and unblinding.

8.1.2. Sensitivity Analyses

The as-treated analyses will be performed for the four elements of the primary analysis as the sensitivity analyses.

8.2. Secondary Efficacy Endpoints

The below secondary efficacy analyses will be performed on the Per-protocol Population for the NRG group. Descriptive statistics will be displayed in a summary table following the same presentation for Section 8.1.1.1.

- To test that the GMC of RVNA in the SYN023 group is superior to the GMC of RVNA in the HRIG group on Study Day 4.
- To test that the GM ratio of RVNA $AUEC_{1\text{-}15}$ for SYN023 to HRIG is superior.

The below secondary efficacy analyses will be performed on the As-treated Population and the Per-protocol for the LRG and NRG, separately. Descriptive statistics will be displayed in a summary table following the same presentation for Sections 8.1.1.1 and 8.1.1.3; however, hypothesis testing will not be performed.

- By-treatment GMT ratio of RVNA at each time point
- By-treatment response rate (RVNA ≥0.5 IU/mL) at each time point

Subjects with increased BMI or not will be presented with RVNA concentrations over time for the two risk groups based on the As-treated and Per-protocol Populations in SYN023 recipients.

Any probable or confirmed rabies case that is identified in subjects with SYN023 administered within 54 hours of rabies exposure will be reported following the summary for Section 8.1.1.4.

9. Safety Analysis

Safety evaluations include adverse events, clinical laboratory, vital signs and physical examination assessments. Safety analyses will be performed using the As-treated Population. Summaries will be presented by risk group (LRG and NRG) and treatment group (SYN023, HRIG and overall). The safety profile of study drug will be described by treatment group.

9.1. Adverse Events

The primary variable for evaluation of the safety profile will be the number and percentage of AEs recorded after study drug administration. For selected of AE tables, additional summaries based on reporting period of adverse events following each vaccination (RabAvert® or Rabipur®) will also be presented.

The collection periods for adverse events are:

- Solicited AEs: Through Study Day 8
- Unsolicited AEs: (After Study Day 8) Through Study Day 43
- SAEs: Entire study period (i.e., 365 days)

All AEs will be classified by SOC and PT according to MedDRA, Version 21.0 or later. Summaries of the total number of treatment-emergent AEs (TEAEs) and the number and percentage of subjects with at least one TEAE will be provided by treatment. TEAEs will be presented by SOC and PT. At each level of subject summarization, a subject is counted once if the subject reported one or more events. Percentages will be calculated out of the number of subjects in the As-treated Population.

The summary of TEAEs will be presented in alphabetical order of SOC. Within each SOC, PTs will be sorted in descending order from the PT with the highest total frequency (that is, summed across all treatment groups) to the PT with the lowest total frequency. If the total frequency for any two or more PTs is equal, the PTs will be presented in alphabetical order.

SAEs will be recorded through the final study visit for all subjects. Listings will be provided for subjects with SAEs. Listings will also be provided for subjects who have discontinued prematurely due to an AE.

All AE summaries will be restricted to TEAEs only. A TEAE is defined as any event not present before exposure to study drug or any event already present that worsens in either intensity or frequency after exposure to study drug.

For inclusion in TEAE tables, incomplete AE start and end dates will be imputed following rules specified in Section 15.3.1.

9.1.1. 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 through Study Day 8. The non-local symptoms that will be solicited include:

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

Summary of solicited TEAEs will be provided. All solicited AEs will be presented in a listing.

9.1.2. Unsolicited Adverse Events

An overview summary of the number and percentage of subjects with any unsolicited TEAE, unsolicited serious TEAE, unsolicited treatment-related TEAE, unsolicited treatment-related serious TEAE, unsolicited TEAE leading to study drug discontinuation, unsolicited TEAE leading to study discontinuation, and unsolicited AE leading to death will be provided by treatment group.

All unsolicited AEs will be presented in a listing.

Summary of unsolicited TEAEs will also be repeated for the following:

- Serious Adverse Events;
- Treatment-Related Adverse Events;
- Treatment-Related Serious Adverse Events;
- Adverse Events Leading to Study Discontinuation.

9.1.3. Relationship of Adverse Events to Study Drug

Summary of TEAEs (solicited/unsolicited) by relationship to study drug will be presented. The investigator will provide an assessment of the relationship of the event to the study drug. 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 related. Not related and unlikely related are considered unrelated.

In the TEAE relationship table, if a subject reports multiple occurrence of the same TEAE, only the most closely related occurrence will be presented. Treatment-emergent AEs that are missing a relationship will be presented in the summary table as “Related” but will be presented in the data listing with a missing relationship.

Treatment-emergent SAEs by relationship to study drug will also be presented in a table. Treatment-emergent SAEs that are missing a relationship will be presented in the table as “Related” but will be presented in the data listing with a missing relationship.

9.1.4. Severity of Adverse Event

Summaries of TEAEs (solicited/unsolicited) by severity will be presented. The severity that will be presented represents the most extreme severity captured on the CRF page. The possible severities are “Mild”, “Moderate”, and “Severe”.

In the TEAE severity table, if a subject reported multiple occurrences of the same TEAE, only the most severe will be presented. An additional row “Missing” must be added for the missing severity.

Treatment-emergent SAEs by severity will also be presented in a table.

9.1.5. Death

All subjects who have an AE with an outcome of death will be presented in a listing.

9.2. Clinical Laboratory Evaluations

All clinical laboratory test results will be presented in listings.

Clinical laboratory evaluations include hematology, serum chemistry, coagulation and urinalysis assessments. Summaries will be based on the As-treated Population.

Unscheduled assessment results will be listed and considered when deriving by-subject maximum and minimum values; however, these will not be included in the by-time-point summary tables. An average value will be derived for repeating assessment values taken on the same day for the by-time-point summary tables.

Observed and change from baseline values at each study visit with by-subject post-baseline maximum and minimum values among all visits will be summarized for numeric test results. Frequency summaries (number of subjects and percentages) will be provided for categorical tests. The number of subjects (*n*) with a non-missing result at each time point will be presented by treatment group and overall.

Shift summaries for baseline to post-baseline new abnormality (normal to ≥ grade 1 or increase in toxicity grade) will be provided at each post-baseline time point for tests (Protocol Appendix B). For tests with available normal ranges, shift summaries for baseline to post-baseline new abnormality (normal to low, normal to high, low to high and high to low) will be provided at each post-baseline time point. By-subject maximum and minimum values (with unscheduled values considered) will be used to produce an overall shift for tests with at least one post-baseline assessment.

When available, clinical significance (normal, abnormal but not clinically significant, or abnormal and clinically significant) and shifts from baseline to post-baseline will be provided at each post-baseline time point.

For shift summaries, the number of subjects with at least one non-missing post-baseline assessments will be presented. Percentages will be calculated based on the number of subjects. At each level of anomalies (low or high; abnormal but not clinically significant, or abnormal and clinically significant), a subject is counted once if he/she reports multiple anomalies at that level. However, a subject might appear multiple times if he/she reports anomalies at multiple levels.

Clinical laboratory being reported as adverse events will only be included in the summary of adverse events.

9.3. Vital Sign Measurements

Summaries for vital signs results on the As-treated Population including change from baseline and will be provided following the same presentation for numeric clinical laboratory tests. Shift summaries for baseline to post-baseline new abnormality (normal to ≥ grade 1 or increase in

toxicity grade) will be provided at each post-baseline time point for tests (Protocol Appendix B). By-subject maximum and minimum values (with unscheduled values considered) will be used to produce an overall shift for tests with at least one post-baseline assessment.

9.4. Physical Examination

Summaries for physical exam results on the As-treated Population including shifts will be provided following the same presentation for categorical clinical laboratory tests.

10. Pharmacokinetics

To describe the pharmacokinetics of SYN023 using non-compartmental analysis, V_d, 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 Per-protocol and As-treated Populations.

10.1. Handling Missing Data

Concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and coefficient of variation (CV) will be reported as not applicable. Missing concentrations will be excluded from the calculation.

10.2. Pharmacokinetic Concentrations

Blood samples will be obtained during the course of the study for use in determining the PK concentrations of CTB011 and CTB012 in serum. These will be collected before administration of study drug on Study Day 1 for all subjects, then on Study Days 4, 8, 15, 29, 43, 71, 127, 155, 183 and 274 for the LRG; and on Study Days 4, 8, 15 and 99 for the NRG.

Individual serum concentrations of CTB011 and CTB012 will be presented in the data listings and summarized by nominal time point for ease of presentation using descriptive statistics (*n*, mean, SD, CV, min, median, and max), by ADA status, and also by Per-protocol (LRG and NRG) and As-treated Populations. The mean serum concentrations of CTB011 and CTB012 will be plotted versus nominal collection time, and the individual serum concentration of CTB011 and CTB012 will be plotted versus actual collection time on both linear and semilogarithmic scales, by ADA status.

10.3. Pharmacokinetic Parameters

The serum concentration-time data for CTB011 and CTB012 will be analyzed by non-compartmental analysis using WinNonlin Phoenix Version 8.0 or higher. For PK analysis, actual sampling times and actual doses administered will be used. For the calculation of PK parameters, all serum concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. The BLQ values that occur at the end of the profile after the last quantifiable concentration will be set to missing.

If data allow, the following PK parameters will be derived from the individual serum concentrations of CTB011 and CTB012 over time profile using non-compartmental methods:

$AUC_{1\text{-}t}$	Area under the serum concentration-time curve from time 0 on Study Day 1 to the last quantifiable concentration, calculated using the linear trapezoidal linear interpolation rule
$AUC_{1\text{-}inf}$	Area under the serum concentration-time curve from time 0 on Study Day 1 extrapolated to infinity, calculated using the formula: $AUC_{1\text{-}inf} = AUC_{1\text{-}t} + [C_t / \lambda_z]$, where C_t is the last measurable serum concentration and λz is the terminal elimination rate constant. If the extrapolated area (C_t/λ_z) is greater than 20% of $AUC_{1\text{-}inf}$, then $AUC_{1\text{-}inf}$ and its associated parameters (CL/F and Vd/F) will be set to missing.
C_{max}	Maximum observed serum concentration
T_{max}	Time of maximum observed serum concentration
λ_z	Terminal elimination rate constant, where λ_z is the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase. λ_z will only be retained if $R^2 \geq 0.80$ and 3 points in the terminal phase that do not include C_{max} are included in determining the regression line.
t1/2	Terminal half-life (whenever possible), calculated as $\ln(2)/\lambda_z$
CL/F	Apparent clearance, calculated as $Dose/AUC_{1\text{-}inf}$
Vd/F	Apparent volume of distribution, calculated as $(CL/F)/\lambda_z$

Individual serum PK parameters of CTB011 and CTB012 will be presented in the data listings. Further, CTB011 and CTB012 PK parameters will be summarized using descriptive statistics (*n*, mean, SD, CV, min, median, and max) by ADA status, and also by Per-protocol (LRG and NRG) and As-treated Populations.

11. Pharmacodynamics

11.1. Handling Missing Data

Concentrations that are below the limit of quantification (BLQ) will be treated as zero for descriptive statistics. Mean BLQ concentrations will be presented as BLQ, and the SD and coefficient of variation (CV) will be reported as not applicable. Missing concentrations will be excluded from the calculation.

11.2. Pharmacodynamic Concentrations

Blood samples will be obtained during the course of the study for use in determining the concentration of RVNA in serum. These will be collected before administration of Study Drug on Day 1, before administration of vaccination on Days 4, 8, 15, and 29, and Days 43, 71, 99, 127, 155, 183, 274, and 365.

Individual serum concentrations of RVNA will be presented in the data listings and summarized by nominal time point for ease of presentation using descriptive statistics (*n*, mean, SD, CV, min, median, and max), by ADA status, and also by Per-protocol (LRG and NRG) and As-treated

Populations. The mean serum concentrations of RVNA will be plotted versus nominal collection time, and the individual serum concentrations of RVNA will be plotted versus actual collection time on both linear and semilogarithmic scales, by ADA status.

11.3. Pharmacodynamic Parameters

The serum concentration-time data for RVNA will be analyzed by non-compartmental analysis using WinNonlin Phoenix Version 8.0 or higher. For PD analysis, actual sampling times and actual doses administered will be used. For the calculation of PD parameters, all serum concentrations that are BLQ prior to the first measurable concentration will be set to zero. The BLQ values that are between measurable concentrations will be set to missing. The BLQ values that occur at the end of the profile after the last quantifiable concentration will be set to missing.

If data allow, the following PD parameter will be derived from the individual serum concentrations of RVNA over time profile using non-compartmental methods:

$AUEC_{1\text{-}15}$	Area under the effect-time curve from time 0 on Study Day 1 to Study Day 15 calculated using the linear trapezoidal linear interpolation rule

Individual serum PD parameters of RVNA will be presented in the data listings. Further, RVNA PD parameters will be summarized using descriptive statistics (*n*, mean, SD, CV, min, median, and max) by ADA status, and also by Per-protocol (LRG and NRG) and As-treated Populations.

12. Immunology Laboratory other than PK and PD

As part of the secondary objectives of the study, all immunogenicity analyses will be based on per-protocol and as-treated subjects 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 initial LRG subjects, general LRG subjects and NRG subjects, separately. The summary will take forms of GMC or GMT and be based on standard log transformations (Section 15.2) for all time points as collected and as available. If the assay read-out does not occur at the starting dilution – indicating a very low amount of antibodies, below the detection limit of the assay – then the antibody titer for the sample is set to D/2, half of the starting dilution. No imputation for missing data will be performed. Data will be transformed as appropriate prior to analysis. GM, Geo SD and 95% CI will be provided in summary tables. Inferential testing will not be performed. In case of pre-vaccination immunogenicity levels are not zero, GM fold increase will be presented as the alternative statistics to GMC or GMT. Let v_{pre} be a subject's pre-vaccination (baseline) immunogenicity value and v_{post} be the post-vaccination value, then the fold increase is

$$f_{\text{i}} = v_{\text{post}}/v_{\text{pre}}.$$

Fold increases express intra-individual relative increases in immunogenicity values. Just like immunogenicity values, log transformed fold increases tend to be normally distributed, and for the statistical analysis of fold increases the methods described for the analysis of immunogenicity values can be used.

13. Interim Analysis

Not applicable. Regarding summaries planned for DSMB meetings, please refer to a standalone DSMB Charter.

14. Changes in the Planned Analysis

Not applicable in this version.

15. Appendices

15.1. Schedule of Study Procedures

15.1.1. LRG group

	Study Day												
Study Procedure	**1**	**4**	**8**	**15**	**29 ±2**	**43 ±4**	**71 ±7**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±14**	**274 ±14**	**365 ±14**
Obtain informed consent	X												
Eligibility	X												
Medical history	X[a]												
Physical examination	X	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]					X[i]
Vital signs	X	X	X										
EKG/ECG	X												
Urine samples	X[b]												
Hepatitis B, C	X												
HIV-1, 2	X												X
PT (INR), PTT	X					X							
Serum chemistry[c]	X	X		X		X							
Hematology[d]	X	X		X		X							
Serum RVNA	X	X[k]	X[k]	X[k]	X[k]	X	X	X					X
SYN023 concentrations	X	X[k]	X[k]	X[k]	X[k]	X	Protocol 2.0	Protocol 3.0 and later					
Anti-SYN023 antibodies	X			X[k]	X[k]	Protocol 2.0	Protocol 2.0	X	Protocol 2.0				
Bite wound washing	X[e]												
Photographs of all wounds	X												
Concomitant medications	X	X	X	X	X	X	X	X					X
Randomization	X												
Interval history		X	X	X	X	X	X	X					X

	Study Day												
Study Procedure	**1**	**4**	**8**	**15**	**29 ±2**	**43 ±4**	**71 ±7**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±14**	**274 ±14**	**365 ±14**
Confirmation visit findings[j]		X	X										
Study drug administration	X[f]	X[f]	X[f]	X[f]	X[f]								
Adverse Events	X[g]	X[h]	X[h]	X[l]	X[l]	X[l]	X[m]	X[m]					X[m]
Wound or injection site Examination	X	X[k]	X[k]	X[k]	X[k]								

a. Record medical history including date of last immunization for tetanus.
b. Include urine βHCG (females only) and baseline urinalysis for all LRG subjects; Baseline urine toxicology for initial LRG subjects.
c. Include total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel.
d. CBC including differential and platelets
e. Or irrigation if no wound present
f. Include study drug injection to wound (or muscle if no wound) and rabies vaccination #1 on Study Day 1 for all LRG subjects, rabies vaccinations #2, #3, and #4 on Study Days 4, 8, and 15 for all LRG subjects and rabies vaccination #5 on Study Day 29 for general LRG subjects.
g. Include AEs, SAEs and Solicited AEs.
h. Include AEs, SAEs and Solicited AEs prior to rabies vaccination.
i. Focused Physical Exam
j. Include bite time, animal capture, location animal specimens, immunization records etc.
k. Prior to rabies vaccination on Study Days 4, 8, 15 for all LRG subjects and Study Day 29 for general LRG subjects
l. AEs and SAEs only; Prior to rabies vaccination on Study Day 15 for all LRG subjects and Study Day 29 for general LRG subjects
m. SAEs only

15.1.2. NRG group

	Study Day												
Study Procedure	**1**	**4**	**8**	**15**	**29 ±2**	**43 ±4**	**71 ±7**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±14**	**274 ±14**	**365 ±14**
Obtain informed consent	X												
Eligibility	X												
Medical history	X[a]												
Physical examination	X	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]				X[g]
Vital signs	X	X	X										
ECG	X												
Urine samples	X[b]												
Hepatitis B, C	X												
HIV-1, 2	X												X
PT (INR), PTT	X					X							
Serum chemistry[c]	X	X		X		X							
Hematology[d]	X	X		X		X							
Serum RVNA	X	X	X	X	X	X	X	X	X				X
SYN023 concentrations	X	X	X	X				X					
Anti-SYN023 serum assay	X			X				X					
Bite wound washing or irrigation	X												
Photographs of all wounds	X												
Concomitant medications	X	X[j]	X[j]	X[j]	X	X	X		X				X
Randomization	X												
Interval history		X	X	X	X	X	X	X	X				X

	Study Day												
Study Procedure	**1**	**4**	**8**	**15**	**29 ±2**	**43 ±4**	**71 ±7**	**99 ±7**	**127 ±7**	**155 ±7**	**183 ±14**	**274 ±14**	**365 ±14**
Confirmation visit		X	X										
Study drug administration	X[e]	X[j]	X[j]	X[j]	X[j]								
Adverse Events	X[f]	X[f]	X[f]	X[m]	X[hk]	X[k]	X[l]	X[l]	X[l]				X[l]
Wound or injection site Examination	X	X	X	X	X[h]								

a. Record medical history including date of last immunization for tetanus.
b. Include urine βHCG (females only) and baseline urinalysis.
c. Include total bilirubin, AST, ALT, ALP, creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium and others if part of panel.
d. CBC including differential and platelets
e. Include study drug injection to wound (or muscle if no wound) and rabies vaccination #1 on Study Day 1.
f. Include AEs, SAEs and Solicited AEs.
g. Focused Physical Exam
h. Prior to rabies vaccination
i. Rabies vaccination only
j. Post rabies vaccination
k. AEs and SAEs only
l. SAEs only

15.2. Standard Log Transformations

The standard statistic to summarize immunogenicity values is the geometric mean (GM), the geometric mean titer (GMT) if the observations are titers, or the geometric mean concentration (GMC) if the observations are concentrations.

Let $v_1, \ldots, v_n$ be a group of n immunogenicity values. The geometric mean is defined as

$$GM = (v_1 \times \ldots \times v_n)^{1/n}.$$

An equivalent formula is

$$GM = \exp \sum_{i=1}^{n} (log_e v_i / n).$$

The geometric mean response is thus on the same scale as the immunogenicity measurements.

The transformation of the immunogenicity values need not to be log_e, it can be any logarithmic transformation, log_2, log_{10}, etc. Thus, if log_{10} is used, the geometric mean should be computed as

$$GM = 10^{\sum_{i=1}^{n} (log_{10} v_i / n)}$$

If antibody titers t_i are reciprocals of twofold serial dilutions with 1: D as the lowest tested dilution, then a convenient log transformation (generally referred as the standard log transformation for antibody titers) is

$$u_i = log_2 [t_i / (D/2)]$$

The $u_i's$ are then the dilution steps: 1, 2, 3, etc. The geometric mean should be computed as

$$GM = (D/2)\, 2 \sum_{i=1}^{n} (u_i / n)$$

Example 15.2.1

Assume that in an antibody test the lowest dilution is 1:8. Then the antibody titers can take on the values 8, 16, 32, 64, etc. The standard log-transformed values of the titers are $log_2[8/4] = 1$, $log_2[16/4] = 2$, $log_2[32/4] = 3$, $log_2[64/4] = 4$, etc.

Example 15.2.2

Assume that in an antibody test the lowest dilution is 1:8. The GMT of the five titers 8, 8, 16, 32, 64 is 18.379

$$GMT = 4 \times 2^{(1+1+2+3+4)/5}$$

A statistic often reported with the geometric mean response is the geometric standard deviation (Geo SD), which is the antilog of the sample standard deviation of the log_e transformed immunogenicity values. Let SD be the sample standard deviation of the log_e transformed immunogenicity values, then the geometric standard deviation is

$$Geo\ SD = \exp(SD)$$

Example 15.2.3 (continued)

The sample SD of the five log_e transformed antibody titers is 0.904. Thus, the Geo SD is 2.469

$$Geo\ SD = \exp(0.904)$$

The lower and upper limit of the two-sided $100(1-\alpha)\%$ confidence interval for the underlying GM e^{μ} are

$$LCL_{e^{\mu}} = GMT / Geo\ SD^{\,t_{n-1;1-\alpha/2}/\sqrt{n}}$$

and

$$UCL_{e^{\mu}} = GMT \times Geo\ SD^{\,t_{n-1;1-\alpha/2}/\sqrt{n}}$$

where $t_{n-1;1-\alpha/2}$ is the $100(1-\alpha/2)$th percentile of the Student t distribution with (n-1) degrees of freedom. Percentiles of Student t distributions can be obtained with the SAS procedure TINV.

Example 15.2.4 (continued)

The lower 95% confidence limit for the underlying GM is 5.98

$$GMT/Geo\ SD^{\mathrm{TINV}(0.975,4)/\sqrt{5}}$$

$$= 18.379/2.469^{2.776/\sqrt{5}}.$$

The upper 95% confidence limit is 56.4

$$GMT \times Geo\ SD^{\mathrm{TINV}(0.975,4)/\sqrt{5}}$$

$$= 18.379 \times 2.469^{2.776/\sqrt{5}}.$$

with TINV(0.975,4)=2.776.

15.3. Missing and Incomplete Dates

15.3.1. Adverse Events

Missing onset dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: If the month and year are different from the month and year of the date of first dose, assume 01-MMM-YYYY. If the month and year are the same as the month and year for the date of first dose, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the month and year are the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.
- DD-UNK-YYYY/UK-UNK-YYYY: If the year is different from the year of the date of first dose, assume 01-JAN-YYYY of the collected year. If the year is the same as the date of first dose year, and the end date (after any imputation) is on or after the date of first dose, then assume the date of first dose. If the year is the same as the date of first dose, and the end date (after any imputation) is prior to the date of first dose, then assume the end date for the start date.

Missing end dates (where UK and UNK indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume the last day of the month;
- DD-UNK-YYYY/UK-UNK-YYYY: Assume 31-DEC-YYYY.

15.3.2. Medications

The table below illustrates how a medication with missing or partial dates should be categorized to a prior, concomitant, or post-treatment medication.

Start Date	Ongoing?	End Date					
		missing	<FD	=FD	(FD, LD+1)	=LD+1	>LD+1
Missing	Yes	2					
	No/Missing	2	1	2	2	2	2
<FD	Yes	2					
	No/Missing		1	2	2	2	2
=FD	Yes	2					
	No/Missing			2	2	2	2
(FD, LD)	Yes	2					
	No/Missing				2	2	2
=LD+1	Yes	2					
	No/Missing					2	2
>LD+1	Yes	2					
	No/Missing						2

Abbreviations: FD, first dose; LD, last dose.
1=Prior Medication, 2=Concomitant Medication