Statistical Analysis Plan

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

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1.0	14-Oct-2021	[redacted]	Finalized
2.0	3-Nov-2021	[redacted]	1.Only for the Day 99 RVNA analysis base on PPS, the Day 99 RVNA results are treated as missing if the Day 99 RVNA blood sampling date was more than Day 110 away after the first dose of vaccine. 2.For $AUEC_{1\text{-}15}$, exploratory analysis is added. See Chapter 3.4 for details.

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List of Abbreviations

Abbreviation	Explanation
AE	Adverse Event
ANCOVA	Analysis of covariance
ATC	Anatomical Therapeutic Chemical Classification
$AUEC_{1-15}$	Area under the efficacy curve Study Day 1 to Study Day 15
BMI	Body mass index
CI	Confidence interval
CV	Coefficient of variation
eCRF	Electronic Case Report Form
GMC	Geometric Mean Concentration
HRIG	Human rabies immune globulin
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
PEP	Post-exposure prophylaxis
PPS	Per Protocol Set
PT	Preferred term
Q1	25th percentile
Q3	75th percentile
RVNA	Rabies virus neutralizing activity
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SS	Safety Analysis Set
TEAE	Treatment-emergent adverse events
WHODRUG	World Health Organization Drug Dictionary

1 Introduction

This is a randomized, double-blind, positive-controlled study (Protocol No. SYN023-006). According to the clinical study protocol (Version: 2.0, 06-Dec-2020) and case report form (Version:2.0, 05-Nov-2020) for this study, this statistical analysis plan is aimed to describe the statistical analysis methods and data handling principles that will be used in the statistical analyses of safety and efficacy endpoints.

1.1 Study Objectives

1.1.1 Primary Objectives

- To demonstrate the superiority of SYN023 plus Rabies Vaccine over Human Rabies Immune Globulin (HRIG) plus Rabies Vaccine as measured by the geometric mean concentration (GMC) of rabies virus neutralizing activity (RVNA) on Study Day 8.
- There are no cases of probable or confirmed rabies in SYN023 recipients. .

1.1.2 Secondary Objectives

- 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 AUEC1-15 for SYN023 is superior to the geometric mean RVNA AUEC1-15 for HRIG;
- 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;
- To demonstrate that the percentage of subjects with RVNA concentration $\geqslant$ 0.5 IU/mL on Study Day 99 in SYN023 recipients is not inferior to the percentage of recipients with RVNA concentration $\geqslant$ 0.5 IU/mL for HRIG;
- To describe the ratio of RVNA GMC in the SYN023 plus Rabies Vaccine group to the HRIG plus Rabies Vaccine group at each time point for subjects in the Per Protocol Set and the Intent-to-Treat Set;
- 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 in the Per-protocol and Intent-to-Treat Populations;
- To describe the effects of increasing BMI on RVNA concentrations in SYN023 recipients;
- To evaluate the safety of SYN023 in SYN023 recipients.

1.2 Study Endpoints

1.2.1 Primary efficacy endpoints

- GMC of RVNA on Day 8 post-dose.
- The incidence and survival rates of subjects with rabies up to 99 days and 1 year post-dose.

1.2.2 Secondary efficacy endpoints

- The positive rate of RVNA and GMC on Study Days 4, 8, 15, 43, 99, 183, and 365;
- $AUEC_{1\text{-}15}$ of RVNA GMC;

1.2.3 Safety endpoints

- All, related, and unrelated AEs within 30 minutes post-dose;
- AEs of injection site (local) and non-injection site (systemic) on Study Days 1~8;
- All, related, and unrelated AEs on Study Days 1~43;
- All, related, and unrelated AEs with Grade 3 or above in severity on Days 1~43;
- All, related, and unrelated SAEs during the study;
- Pregnancy events (pregnancy status and outcomes) occurring within 6 months;
- AE/SAEs leading to withdrawal.

1.3 Study Design

1.3.1 Overall Design

This is a randomized, double-blind, positive-controlled clinical study. A total of 1,000 subjects aged 18 years and older with Category III rabies exposures are planned to be enrolled and will be randomized at a 3:1 ratio into the study group and the control group. The subjects in both groups will be immunized with rabies vaccine according to the post-exposure prophylaxis (PEP) procedure of rabies. The sample size and assignment of rabies prophylaxis for both groups are shown in the following table:

Group	Sample Size	Investigational Product	Dosage and Administration	Injection Time
Study group	750	SYN023	0.3 mg/kg, infiltration injection at the wound *	Day 1
		Rabies vaccine for human use	0.5 mL, intramuscular injection into the deltoid muscle of the upper arm	Days 1, 4, 8, 15, and 29 (Essen regimen)

Control group	250	HRIG	20 IU/kg, infiltration injection at the wound *	Day 1
		Rabies vaccine for human use	0.5 mL, intramuscular injection into the deltoid muscle of the upper arm	Days 1, 4, 8, 15, and 29 (Essen regimen)

* In case there are remaining amounts of Drug after infiltration injections at all wounds, the remaining Drug should be injected into muscles remote from the Drug injection site (the dorsal muscle group ipsilateral to the wound for areas above the waist, and the mid-lateral thigh muscle group ipsilateral to the wound for areas below the waist)

At enrollment (Day 1), an infiltration injection of SYN023 or HRIG should be performed at the wound, meanwhile, 1 dose of lyophilized rabies vaccine for human use (Vero cells) should also be injected intramuscularly into the deltoid muscle of the upper arm. According to the Essen regimen, one dose of lyophilized rabies vaccine for human use (Vero cells) will also be injected on Study Days 4, 8, 15, and 29 respectively. A total of 8 venous blood samples at a volume of approximately 3.0 mL each will be collected from all subjects prior to dose and on Study Days 4, 8, 15, 43, 99, 183, 365 post-dose, and will be used for the evaluation of efficacy endpoints. In addition, the subjects will be followed up for incidence of rabies and survivability. All blood samples will be tested for RVNA using a rapid fluorescence focus inhibition test. In addition, solicited AEs occurred within Days 1-8 post-dose, all other AEs occurred within Days 1-43 post-dose, as well as pregnancies up to 6 months post-dose and all SAEs throughout the study will be collected.

1.3.2 Randomization and Blinding

1.3.2.1 Randomization

The subjects, who are enrolled after successful screening and informed consent, will be randomized at a 3:1 ratio using the block randomization with a stratification factor of the site to receive the test drug SYN023 or control drug HRIG according to the same injection procedure, followed by a vaccination of rabies vaccine.

In the study, subjects are randomized using the Interactive Web Response System. The blinded randomization code is generated by the independent unblinded randomization statistician of the statistical facility with the subject randomization list and the study drug randomization list (blinded randomization code) using SAS software (Version 9.4) according to the protocol. The subject randomization list includes the site number, the subject randomization number (i.e., study number), and the group of study drug (collective name for the test drug SYN023 and the control drug HRIG) corresponding to the subject randomization number. The drug randomization list includes the drug randomization number and the study drug corresponding to the drug randomization number. The subject randomization list and drug randomization list (blinded randomization code) are uploaded by the unblinded database designer to the Interactive Web Response System (IWRS) to

complete the automatic matching between the IWRS and EDC. After completion of the system setup, the investigator or his/her designee will add a subject in the EDC, and assign a randomization number in the IWRS according to the subject's site after confirming his/her eligibility. Then a drug number for use at each dosing visit will be automatically assigned according to the study drug group to which the subject is randomized, and relevant study staff on the study site will administer the subject according to the drug number assigned by the system. The entire randomization is completed in the EDC and IWRS system, where user authorization is strictly controlled to ensure the maintenance of blindness during the study. The randomization number of any randomly assigned subject, who withdraws/is withdrawn from the clinical trial for any reason, will not be reassigned to other subjects regardless of the administration of study drug.

1.3.2.2 Drug Blinding

In order to reduce/avoid procedural bias, a double-blind design is adopted, where drug assignment is blinded to the randomization statistician and other blinding personnel, and the study drugs are uniformly packaged and sealed with the same boxes so that the test drug and control drug are identical in appearance. This prevents the staff with access only to the packaging of the product from getting aware of the type of drugs received by the subject, thereby ensuring the blindness of the used study drug. Injection giver and pharmacist are unblinded in the study. Any study-related personnel, except unblinded injection giver, are not allowed to unseal and access the study drug, to ensure that the subject is blinded to the size of study drug package. The syringes are also appropriately shielded to ensure that the subject is blinded to the color and dose of study drug. In this way, the subject is kept blinded to the study drug as he/she cannot find which study drug was administered with the available information.

The randomization statistician and other staff who are not involved in conduct of the clinical trial are responsible for preparation of the blinded randomization codes of study drug at the site. Under the guidance of the randomization statistician, relevant staff will stick the printed label of randomization numbers on the corresponding container and outer package of the test/control drug according to the blinded randomization code, and seal the packages properly with sealing labels.

After preparing the blinded randomization code, the blinded randomization code should be sealed and archived by the randomization statistician. Relevant records must be kept for generating the blinded randomization code throughout the process. The staff involved in generation of the blinded randomization code shall not participate in other work relating to this clinical trial, and shall not disclose the blinded randomization code to any staff involved in conduct of the clinical trial.

1.3.2.3 Maintenance of Blinding

Due to the different doses of the test drug and the control drug (0.1 mL/kg of the test drug and 0.2 mL/kg of the control drug), blinding should be maintained for the subjects, the investigator, and the laboratory test staff throughout the study.

1) During the study, subjects, blinded investigator and project members involved in any evaluation of endpoints, data review and data analysis in the study shall be blinded to the study grouping.

2) After the drug is packaged and assigned with a blinded code, each box should be sealed with a sealing label and should not be opened at will. Before vaccination, the injection giver should check the sealing label for intactness. If any vaccine is found to have broken sealing label when handing over to the injection giver by the pharmacist, it should be disposed as damaged vaccine.

3) After the pre-injection procedures are completed, the medical guide will lead the subjects into the vaccination room one by one to ensure that only one subject is receiving drug injection in the vaccination room at one time.

4) During drug dispensing and vaccination, necessary action should be taken to ensure that the subjects cannot see any identification information of the drug to be administered (such as shape of the outer package and syringe, and color of the drug);

5) Designated staff should be assigned to give the injection and manage the study drug only, without participating in any other tasks of the study, and should sign a non-disclosure agreement, stating their non-disclose of any information that may cause leakage of the blinded code to any other staff (including investigators involved in clinical study evaluation, subjects, serum sample analysts, blinded CRAs and QC staff, data managers, etc.);

6) The injection giver should return the empty vials/boxes of the used drugs into the original packaging boxes, and timely make a reconciliation and transfer to the pharmacist for storage after completion of the work on the same day. After the site is closed out and the authorization from sponsor is obtained, the study site should uniformly transfer the empty vials/boxes to the medical waste disposal company or the sponsor for destruction and the destruction records should be retained.

7) The monitoring and quality control for drug management and injection should be completed by unblinded CRAs and QC staff.

1.3.3 Sample Size

Primary study hypothesis:

The test group is superior to the control group in the geometric mean concentration of RVNA on Day 8 post-dose (the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (test group/control group) > 1.2)

Based on the study hypothesis, the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (test group/control group) is > 1.2, a final sample size of 16 subjects (12 subjects in the test group and 4 subjects in the control group) is required with a type I error of 0.025 (one-sided), a power of

90%, an estimated geometric mean concentration of RVNA (test group/control group) on Day 8 post-dose of 11.9, and a coefficient of variation (CV) of 120.5%, when assigning the subjects to the test group/control group at a ratio of 3:1 and considering a dropout rate of 20%. The current 1000 subjects are sufficient to ensure a 100% power under the same hypothesis.

Secondary study hypothesis:

1) The test group is superior to the control group in the geometric mean concentration of RVNA on Day 4 post-dose (the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (test group/control group) > 1.2)

Based on the study hypothesis, the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (test group/control group) is > 1.2, a final sample size of 12 subjects (9 subjects in the test group and 3 subjects in the control group) is required with a type I error of 0.025 (one-sided), a power of 90%, an estimated geometric mean concentration of RVNA (test group/control group) on Day 4 post-dose of 13.75, and a CV of 63.25%, when assigning the subjects to the test group/control group at a ratio of 3:1 and considering a dropout rate of 20%. The current 1000 subjects are sufficient to ensure a 100% power under the same hypothesis.

2) The test group is non-inferior to the control group in the geometric mean concentration of RVNA on Day 99 post-dose (the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (test group/control group) > 0.8)

Based on the study hypothesis, the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (test group/control group) is > 0.8, a final sample size of 308 subjects (231 subjects in the test group and 77 subjects in the control group) is required with a type I error of 0.025 (one-sided), a power of 90%, an estimated geometric mean concentration of RVNA (test group/control group) on Day 99 post-dose of 86.94, and a CV of 17.32%, when assigning the subjects to the test group/control group at a ratio of 3:1 and considering a dropout rate of 20%. The current 1000 subjects are sufficient to ensure a 100% power under the same hypothesis.

3) The test group is non-inferior to the control group in the antibody positive rate of RVNA (RVNA≥0.5 IU/mL) on Day 99 post-dose (the lower limit of 95% CI of RVNA positive rate (test group/control group) > 0.9)

Based on the study hypothesis, the lower limit of the 95% CI of the ratio of antibody positive rates (test group/control group) is > 0.9, a final sample size of 52 subjects (39 subjects in the test group and 13 subjects in the control group) is required with a type I error of 0.025 (one-sided), a power of 90%, an estimated ratio of antibody positive rates (test group/control group) on Day 99 post-dose of 1, and a CV of 98.7%, when assigning the subjects to the test group/control group at a

ratio of 3:1 and considering a dropout rate of 20%. The current 1000 subjects are sufficient to ensure a 100% power under the same hypothesis.

4) The SYN023 plus Rabies Vaccine group is superior to the HRIG plus Rabies Vaccine group in $AUEC_{1\text{-}15}$ of RVNA GMC (the lower limit of 95% CI of $AUEC_{1\text{-}15}$ ratio of RVNA GMC (test group/control group)>1.1)

Based on the study hypothesis, the lower limit of the 95% CI of $AUEC_{1\text{-}15}$ ratio of RVNA GMC (test group/control group) is > 1.1, a final sample size of 900 subjects (675 subjects in the test group and 225 subjects in the control group) is required with a type I error of 0.025 (one-sided), a power of 90%, an estimated $AUEC_{1\text{-}15}$ ratio of RVNA GMC (test group/control group) post-dose of 147.55%, and a CV of 142%, when assigning the subjects to the test group/control group at a ratio of 3:1 and considering a dropout rate of 20%. The current 1000 subjects are sufficient to ensure a 96.9% power under the same hypothesis.

2 General Statistical Considerations

2.1 General Principles

The data analysis will be performed using SAS version 9.4 or above. Two-sided tests will be performed for all statistical analysis with an $\alpha = 0.05$ and two-sided confidence interval of 95%. In addition, continuous variables will be described using the number of subjects, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), maximum, and minimum; and categorical variables will be described using the number and percentage of subjects. Table 1 shows the decimal places of statistical parameters.

Table 1. Decimal Places of Statistical Parameters

Statistics	Decimal Places
Mean, median, Q1, Q3	One more decimal place than the raw data, but no more than 3 decimal places.
Standard deviation, 95% CI	Two more decimal place than the raw data, but no more than 3 decimal places.
Max, Min	The same decimal places as the raw data, but no more than 3 decimal places.
Percentage	One decimal place; expressed as "100" if the percentage reaches 100% and "0" if the percentage is 0.
P value	Three decimal places; expressed as "< 0.001" and if P-value is less than 0.001. Expressed as ">0.999" and if P-value is greater than 0.999.

2.2 Definitions of Analysis Sets

Safety Set (SS): includes all randomized subjects who have received at least 1 dose of study drug, used as the Safety Set of the study. Based on the SS, the subjects will be analyzed for safety by actual treatment groups; and be analyzed for demographic, baseline, and efficacy endpoints by planned groups.

Per-Protocol Set (PPS): includes all randomized subjects who have received correct study drug, have been confirmed for eligibility to inclusion/exclusion criteria*, have completed the rabies vaccination on Study Day 29 as required by the protocol, have no major protocol violations affecting the efficacy evaluation, and have received sufficient wound treatment at all exposed sites and received study drug injections.

* Inclusion/exclusion criteria to be confirmed include: Category III rabies exposure with a duration of <24 hours; RVNA <0.1 IU/mL in serum collected from blood sampling at time "0" on study day 1 (WHO, 2013). In our previous clinical study experience, about 2% to 5% of enrolled subjects may have the history of vaccination with rabies vaccine. Their RVNA response may be much quicker and higher than the naive patients. Since the RVNA is a critical efficacy endpoint, the subjects with a RVNA ≥ 0.1 IU mL, which indicated the prior use of rabies vaccine, should be analyzed separately.

In addition, subjects with (not limited to) the following conditions will likely be excluded from the PPS, depending on the discussion at the blinded data review meeting prior to database lock:

• Subjects will be excluded for the conditions that may impair the protection (such as immunodeficiency) as discovered after randomization.

• Subjects will be excluded if excessive treatment delay (>24 hours) is discovered.

• Subjects will be excluded if they will receive or have received protocol prohibited treatments.

• Subjects will be excluded if all of the bite wounds are discovered to have not been properly treated or injected.

The primary analysis of the efficacy endpoints will be performed by the randomized groups of study drugs based on the PPS.

2.3 Data Handling Principles

2.3.1 Baseline Definition

Unless otherwise specified, baseline is defined as the results of the last non-missing test or evaluation prior to the injection of investigational product. Change from baseline is defined as the observed value at this visit minus baseline.

2.3.2 Definition of the Number of Study Days

The number of study days will be calculated with the study start date, and will be used to indicate the time interval between the assessments of vital signs, adverse events, and concomitant medications during the study.

The start date of the study is defined as the injection date of investigational product.

If the date of examination or event is after the injection date of investigational product, then study day will be calculated as: Study Day = date of event - study start date +1.

If the date of examination or event is before the injection date of investigational product, then study day will be calculated as: Study Day = date of event - study start date.

2.3.3 Definition of Analysis Window

Data analysis will be performed based on the data directly collected at the visits, with no analysis window.

2.3.4 Handling Rules of Missing Data

Missing data are not planned to be handled in this study, unless otherwise specified.

2.3.4.1 Date of Adverse Event

Start dates of the AEs will be imputed as follows:

- If the entire start date of an AE is missing, the date will be imputed as the study start date (the date when the subject received the investigational product);

• If the year and month are available and are equal to the year and month of the study start date, the date will be imputed as the study start date if the AE end date (including the imputed date) is on or after the study start date, or the entire end date of an AE is missing; and the date will be imputed as the AE end date if the end date (including the imputed date) is before the study start date;

• If the year and month are available, but are not equal to the year and month of the study start date, the date will be imputed as the 1st day of that month;

• If the year is available and is equal to the year of the study start date, the date will be imputed as the study start date if the AE end date (including the imputed date) is on or after the study start date, or the entire end date of an AE is missing; and the date will be imputed as the AE end date if the end date (including the imputed date) is before the study start date;

• If only the year is available, but is not equal to the year of the study start date, the date will be imputed as January 1 of that year.

End dates of the AEs will be imputed as follows:

• If the year and month are available, the date will be imputed as the last day of that month;

• If only the year is available, the date will be imputed as December 31 of that year;

For died subjects, the AE end date should be imputed as the death date if the imputed AE end date is after the death date; for survived subjects at the end of study, the AE end date should be imputed as the study end date if the imputed AE end date is after the study end date.

2.3.5 Handling of RVNA Data Below the Lower Limit of Quantitation (BLQ)

For BLQs of RVNA data, they will be calculated as zero if the samples are collected prior to the injection date of investigational product, otherwise, they will be treated as missing data and will not be included in the analysis.

2.3.6 Handling Rules of Other Data

Only data generated at scheduled visits will be summarized, and the test results at unscheduled visits will not be included in the final analysis, unless otherwise specified. The last non-missing test result will be used for analysis if two or more tests are performed at the same scheduled visit. Results of multiple tests at unscheduled and scheduled visits are present in listings.

2.4 Multiplicity Comparison

Based on multiple hypothesis testing in this study, testing of superiority of the test group over the control group in the geometric mean concentration of RVNA on Day 8 post-dose will be performed at the 0.025 (one-sided) level (testing of primary study hypothesis);

If the primary hypothesis testing is successful, testing of superiority of the test group over the control group in the geometric mean concentration of RVNA on Day 4 post-dose will be performed at the 0.025 (one-sided) level (testing the secondary hypothesis 1), otherwise, testing of all 4 secondary hypotheses will be performed for exploratory analyses;

If the secondary hypothesis testing 1 is successful, testing of non-inferiority of the test group over the control group in the geometric mean concentration of RVNA on Day 99 post-dose (test for the secondary hypothesis 2) will be performed at a level of 0.025 (one-sided), otherwise, testing of secondary hypotheses 2, 3 and 4 will be performed for exploratory analyses;

If the secondary hypothesis testing 2 is successful, testing of non-inferiority of the test group over the control group in antibody positive rate of RVNA (RVNA≥0.5 IU/mL) on Day 99 post-dose (testing of the secondary hypothesis 3) will be performed at a level of 0.025 (one-sided), otherwise, testing of secondary hypotheses 3 and 4 will be performed for exploratory analyses;

If the secondary hypothesis testing3is successful, testing of superiority of the SYN023 plus Rabies Vaccine over the HRIG plus Rabies Vaccine in $AUEC_{1\text{-}15}$of

RVNA GMC will be performed at a level of 0.025 (one-sided) (testing of the secondary hypothesis 4), otherwise, testing of secondary hypotheses 4 will be performed for exploratory analysis.

2.5 Subgroup Analysis

If the number of subjects in each subgroup is sufficient, the primary endpoint will be analyzed by the following subgroups:

1） Study sites

2） Sex

3） Age groups (18-59 years, 60 years and older)

2.6 Pooling of Study Sites

All data of the study sites are pooled for a direct integrated analysis, except efficacy analysis, where study sites are as the covariate.

3 Statistical Analysis

3.1 General Information of Subjects

3.1.1 Enrollment and Study Completion

The randomization, completion and early withdrawal of subjects will be described by study sites and overall population:

In the screened population, the number (percentage) of subjects who are randomized and those who are not randomized along with their reasons, and the screening results of all subjects will be tabulated.

Based on the randomized subjects, the number of subjects who included in SS and PPS, those who competed the RVNA blood sampling on Study Days 1, 4, 8, 15, 43, and 99, those who competed the neutralizing activity blood sampling on Day 183 as well as Day 365, those who completed safety observation from Day 1 to Day 99 and from Day 100 to Day 365, and those who prematurely discontinued (including the reasons for premature discontinuation) will be summarized by treatment group. Reasons for premature discontinuation will be tabulated according to the order on the electronic case report form (eCRF). In addition, the study completion status of the randomized subjects will be tabulated.

3.1.2 Protocol Deviation

In order to evaluate whether the protocol is strictly followed, all protocol deviations will be reviewed and assessed in a blinded status according to the contents and protocol requirements before database lock. The study team will assess and classify the deviations as major or minor protocol deviations. Based on the pre-defined SS, the major protocol deviations will be tabulated and summarized.

Based on randomized subjects, all protocol deviations will be tabulated by subjects and study sites.

3.1.3 Demographics and Baseline Characteristics

The demographics and baseline characteristics of subjects will be summarized descriptively based on the PPS and SS by pre-defined groups respectively. Demographics and baseline characteristics will be tabulated.

Demographics:

Categorical variables: sex (male, female), ethnic group (Han, Zhuang, Yi, Hani, Miao, others), and age grouping (18-59 years, 60 years and older).

Continuous variable: age.

Baseline characteristics:

Categorical variables:

- BMI (< 18.5 kg/m^2, 18.5-24.0 kg/m^2, ≥ 24.0 kg/m^2)
- Type of category III exposure
- Animal causing the wound
- Wound site
  - Category of wound site (high risk, low risk)
- Wound amount
  - Category of wound amount (single wound, multiple wounds)
- Are post-exposure wound cleaning and disinfection performed as required
- Is local anesthesia performed for cleaning and disinfecting the wound
- Did the subject get bitten by animals susceptible to rabies virus during the past 6 months
- Did the subject received any prior/concomitant vaccines 14 days prior to enrollment to the study
- RVNA grouping (RVNA < 0.1 IU/mL and RVNA ≥ 0.1 IU/mL) on Study Day 1

Continuous variable:

Height, weight, body mass index (BMI), and duration from rabies virus exposure to investigational product injection.

It is defined as high-risk if the wound site is any of the head, neck, face, left upper limb, right upper limb; and low-risk for the other parts. Duration of rabies virus exposure to investigational product injection time (h) = investigational product injection time – rabies virus exposure time.

3.1.4 Medical history

Based on the SS, the medical history (including history of past significant disease/ present illness) of subjects will be tabulated and summarized by treatment groups. Medical history will be coded using MedDRA 23.1 or the latest version of coding dictionary prior to database lock, and summarized by System Organ Class (SOC) or Preferred Term (PT).

All the history of past significant disease/ present illness will be tabulated; in addition, history of exposure and bites by animals susceptible to rabies virus will be presented in listing.

3.1.5 Prior/concomitant therapy

3.1.5.1 Prior/concomitant medication

Prior medications are non-investigational medications that stopped prior to the injection of investigational product.

Concomitant medications are all medications (except investigational products and concomitant vaccines) used by the subject within 1-43 days after the subject received the first dose of vaccine and the completion of the passive immunization:

- All medications that started on or after the first vaccination and within 43 days.
- All medications that started before the first dose of vaccine and continued after the first dose.

If the end date of a medication is prior to the date of first vaccination, the medication will be treated as prior medication; if the start date of a medication is on or after the date of first vaccination or the medication is “ongoing”, the medication will be treated as concomitant medication. In addition, if the end date of a medication is not complete, it will be handled according to the rules in the table below.

Table 2 Handling Rules for Missing Dates

Available Part(s)	Missing Parts(s)	Concomitant Medications or Not
[None]	Year, Month, Day	Yes
Month, Day	Year	Yes
Year	Month, Day	Yes, if the year ≥ the year of first vaccination date
Month, Year	Day	Yes, if the year > the year of first vaccination date, or if the year = the year of first vaccination date and the month ≥ the month of first vaccination date
Day, Year	Month	Yes, if year ≥ year of date of first vaccine

Based on the pre-defined SS, medications will be coded using the World Health Organization Drug Dictionary (WHODRUG, version 01-Mar-2020 or latest version at the time of database lock). The number and percentage of subjects with prior/concomitant medications will be calculated by treatment group, anatomical therapeutic class (ATC) level 2, and PN only.

Prior and concomitant medications will be tabulated.

3.1.5.2 Prior/concomitant vaccines

Based on pre-defined SS, prior/concomitant vaccines will be tabulated.

3.2 Efficacy Analyses

Efficacy analyses will be performed based on the PPS and pre-defined SS, respectively, with the PPS used for the primary analysis and SS used for the supportive analysis. In case of any inconsistency between the actual and the pre-defined groups in the study, sensitivity analyses will be performed based on actual SS.

3.2.1 Primary Efficacy Analysis

3.2.1.1 GMC of RVNA on Day 8 post-dose

3.2.1.1.1 Primary Analysis

Null hypothesis: $GMC_{SYN023}/GMC_{HRIG} \leq 1.2$.

Alternative hypothesis: $GMC_{SYN023}/GMC_{HRIG} > 1.2$.

GMC_{SYN023} represents the geometric mean concentration of RVNA on Day 8 post-dose in the test group and GMC_{HRIG} represents the geometric mean concentration of RVNA on Day 8 post-dose in the control group with a type I error of 0.025 (one-sided).

RVNA concentrations on Day 8 will be summarized for each treatment group with median, minimum, maximum, geometric mean, 95% CI of geometric mean,

and geometric coefficient of variation. The RVNA concentration at each scheduled visit for each subject is the geometric mean of the duplicate results.

In addition, with the treatment group and the study site used as fixed variables, the mean and standard error of adjusted RVNA (log-transformed) concentrations in two groups will be summarized using analysis of variance, and the ratio of RVNA geometric mean concentrations, 95% CI, and P-value in two groups will be calculated at the two-sided 0.05 level.

3.2.1.1.2 Subgroup Analysis

The following subgroup analyses will be performed for RVNA on Day 8 post-dose. With treatment group used as a fixed variable, and the adjusted ratios and standard errors of the two groups will be calculated using analysis of variance, and the ratios and 95% CIs of the two groups by site will be summarized.

- Study sites
- Sex
- Age groups (18-59 years, 60 years and older)
- RVNA grouping (SS only) on Study Day 1: RVNA < 0.1 IU/mL and RVNA ≥ 0.1 IU/mL

3.2.1.1.3 Sensitivity Analysis

Based on the PPS only, a sensitivity analysis of the primary efficacy endpoints will be performed after excluding the deviations in post-dose RVNA from geometric mean concentration ± 3 times the geometric SD using the same method as the primary analysis.

3.2.1.2 Incidence and Survival Rate of Subjects with Rabies within 99 Days and 1 Year Post-Dose

The incidence and survival rate of subjects with rabies within 99 days and 1 year post-dose will be described by number and percentage of subjects.

3.2.2 Secondary Efficacy Analysis

Only for the Day 99 RVNA analysis base on PPS, the Day 99 RVNA results are treated as missing if the Day 99 RVNA blood sampling date was more than Day 110 away after the first dose of vaccine.

3.2.2.1 GMC of RVNA on Days 4, 15, 43, 99, 183, 365 Post-Dose

The primary analysis, subgroup analysis, and sensitivity analysis are performed using the same methods as that used for RVNA on Day 8 post-dose. In addition, mean RVNA versus time profiles (linear and semi-logarithmic) and scatter plots of BMI versus RVNA at each scheduled visit post-baseline will be created with scheduled sampling time points.

3.2.2.2 Positive Rate of RVNA on Days 4, 8, 15, 43, 99, 183, and 365 Post-Dose

3.2.2.2.1 Primary Analysis

The positive rates of RVNA on Days 4, 8, 15, 43, 99, 183, and 365 post-dose will be described by the number and percentage of subjects, and the inter-group differences will be compared using a chi-square test or an exact probability test (expected value < 5 in either cell), and inter-group differences in positive rates and their 95% CIs will be calculated based on Wald or Clopper-Pearson.

In addition, rate differences and P-values adjusted for the stratification factor of study site will be calculated using the CMH. A bar graph of RVNA concentrations will be created by scheduled visits.

3.2.2.2.2 Subgroup Analysis

Same as those in Section 3.2.1.1.2.

3.2.2.2.3 Sensitivity Analysis

Based on the PPS only, a sensitivity analysis will be performed after excluding the deviations in post-dose RVNA from geometric mean concentration ± 3 times the geometric SD using the same method as the primary analysis.

3.2.2.3 $AUEC_{1\text{-}15}$ of RVNA GMC post-dose

The $AUEC_{1\text{-}15}$ of RVNA GMC will be calculated using the trapezoidal method. The primary analysis, subgroup analysis, and sensitivity analysis will be performed using the same method as that used for RVNA on Day 8 post-dose.

3.3 Safety Analysis

Based on the actual SS, the safety analysis will be performed by different treatment groups.

3.3.1 Drug Exposure

Based on the actual SS and PPS, the treatment compliance of lyophilized rabies vaccine for human use will be descriptively by treatment groups. The treatment compliance is equal to the actual number of doses divided by the planned number of doses multiplied by 100%, with the result rounded to one decimal place.

For “whether the investigational products were injected” and “whether there were any vaccination abnormalities”, these 2 questions will be summarized descriptively by the number and percentage of subjects who receive investigational products (including SYN023 and HRIG) and lyophilized rabies vaccine for human use. In addition, the number of doses and duration of exposure of lyophilized rabies vaccine for human use will be summarized by treatment groups.

The duration of exposure (days) is equal to last dose date minus first dose date plus 1. The duration of exposure includes the in-between period of discontinuation.

In addition, the administration information of the investigational product will be tabulated, mainly including: date of administration, time of administration, route of injection, injected wound site, occurrence of injection abnormalities, etc.

3.3.2 Adverse Events

Adverse events (AEs) will be coded using MedDRA 23.1 or the latest version of the dictionary prior to database lock. A treatment-emergent adverse event (TEAE) is defined as an adverse event that occurs on or after the injection date of investigational product and within 43 days after the investigational product injection, or an adverse event that worsens during the treatment compared with the condition prior to treatment, or an SAE that occurs 43 days after investigational product injection. If the start date of an AE is incomplete, it will be handled according to Section 2.3.4.2 Handling Rules of Missing Data.

The solicited AEs occurring within 7 days after injection include AEs at injection site (local) and non-injection site (systemic), among which, injection site (local) AEs include: injection site pain, pruritus, swelling, induration, redness, and rash. AEs at non-injection site (systemic) include: pyrexia, headache, rash, pruritus, urticaria, dyspnea, cough, chills, chest pain, arthralgia, myalgia.

The investigator should assess the severity of adverse events with reference to the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007 and in combination with clinical practice (hereinafter referred to as Severity Criteria 1), see Solicited Adverse Events and Other Adverse Events in CRF for details; In addition, further assessment of severity will be performed based on Appendix 1 (hereinafter referred to as Severity Criteria 2) for pyrexia, injection site swelling, redness, induration only, and rash under solicited adverse events.

The number and percentage of subjects with at least 1 TEAEs and number of episodes of TEAEs will be summarized as follows:

- Any TEAEs
    - TEAEs within 30 minutes after investigational product injection
    - TEAEs within 7 days after investigational product injection
    - TEAEs within 8-43 days after investigational product injection
    - TEAEs unrelated to investigational product
    - TEAEs related to investigational product
        - TEAEs with Grade 3 or above in severity (Severity Criteria 1/ 2)
        - SAEs
    - TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
    - SAEs

- TEAEs leading to withdrawal
- TEAEs leading to death

- Solicited TEAEs
  - TEAEs within 30 minutes after investigational product injection
  - TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
  - SAEs
  - TEAEs leading to withdrawal
  - TEAEs related to investigational product
    - TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
    - SAEs
  - TEAEs unrelated to investigational product
  - Solicited local TEAEs
    - TEAEs within 30 minutes after investigational product injection
    - TEAEs related to investigational product
      - TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
      - SAEs
    - TEAEs unrelated to investigational product
    - TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
  - Solicited local TEAEs
    - TEAEs within 30 minutes after investigational product injection
    - TEAEs related to investigational product
      - TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
      - SAEs
    - TEAEs unrelated to investigational product

- TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
- TEAEs at the injected wound site
- TEAEs within 30 minutes after investigational product injection
- TEAEs related to investigational product
- TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
- SAEs
- TEAEs unrelated to investigational product
- TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
- TEAEs at injection site other than the wound site(s)
- TEAEs within 30 minutes after investigational product injection
- TEAEs related to investigational product
- TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
- SAEs
- TEAEs unrelated to investigational product
- TEAEs with Grade 3 or above in severity (Severity Criteria 1/2)
- Unsolicited TEAEs
- TEAEs within 30 minutes after investigational product injection
- TEAEs within 7 days after investigational product injection
- TEAEs within 8-43 days after investigational product injection
- TEAEs related to investigational product
- TEAEs with Grade 3 or above in severity (Severity Criteria 1)
- SAEs
- TEAEs unrelated to investigational product

- TEAEs with Grade 3 or above in severity (Severity Criteria 1)
- SAEs
- TEAEs leading to withdrawal

The number and percentage of subjects with TEAEs and number of episodes of TEAEs will be summarized by SOC and PT, respectively, as follows:

- Any TEAEs
- Unsolicited TEAEs
- TEAEs with Grade 3 or above in severity (Severity Criteria 1)
- TEAEs related to investigational product
- TEAEs related to investigational product and with Grade 3 or above in severity (Severity Criteria 1)
- TEAEs leading to withdrawal
- Unsolicited TEAEs with Grade 3 or above in severity (Severity Criteria 1)
- Unsolicited TEAEs Related to Investigational Product
- Unsolicited TEAEs related to investigational product and with Grade 3 or above in severity (Severity Criteria 1)
- SAEs
- SAEs related to investigational product
- Unsolicited TEAEs Leading to Withdrawal

In addition, the number and percentage of subjects with TEAEs will be summarized by the maximum severity reported (severity criteria 1/severity criteria 2), SOC, and PT; and the number and percentage of subjects with TEAEs will also be summarized by the reported causal relationship with investigational products (definitely related > probably related > possibly related > unlikely related > unrelated), SOC and PT. If the causal relationship with investigational products is missing, it should be imputed as “possibly related”. The details are as follows:

- Summary of unsolicited TEAEs by causal relationship with investigational product, SOC, and PT
- Summary of TEAEs by causal relationship with investigational product, SOC, and PT
- Summary of unsolicited SAEs by causal relationship with investigational product, SOC, and PT

- Summary of SAEs by causal relationship with investigational product, SOC, and PT
- Summary of unsolicited TEAEs with Grade 3 or above in severity by causal relationship with the investigational product, SOC, and PT
- Summary of TEAEs with Grade 3 or above in severity by causal relationship with the investigational product, SOC, and PT
- Summary of unsolicited TEAEs by maximum severity, SOC, PT (Severity Criteria 1)
- Summary of TEAEs by maximum severity, SOC, PT (Severity Criteria 1)
- Summary of unsolicited TEAEs related to investigational product by maximum intensity, SOC, and PT (Severity Criteria 1)
- Summary of TEAEs related to investigational product by maximum intensity, SOC, and PT (Severity Criteria 1)

In addition, the number and percentage of subjects with solicited TEAEs and number of episodes of such TEAEs will be summarized by symptom as follows:

- Summary of solicited TEAEs by symptom
- Summary of solicited TEAEs related to investigational product by symptom
- Summary of solicited TEAEs unrelated to investigational product by symptom
- Summary of solicited TEAEs by symptom and severity (Severity Criteria 1/2)

The number of AEs will be calculated with the actually occurred total number of episodes of the AE when calculating the TEAEs of a subject who has more than one episode of one TEAE (as determined by PT). Similarly, when calculating the TEAEs of a subject who has more than one TEAEs in a SOC, the number of AEs will also be calculated with the actually occurred number of episodes if the AE in that system organ class. Causal relationship with investigational products will be classified as “related” and “unrelated” when calculating the AEs. The “related” includes “definitely related”, “probably related”, and “possibly related”; and “unrelated” includes “unlikely related” and “unrelated”.

In summary of each type of TEAEs, TEAEs will be displayed by SOCs in descending order of the total numbers of subjects in all SOCs. In case there are equal number of subjects in certain SOCs, TEAEs will be displayed by SOCs in alphabet order of initials of the SOCs; in case there are equal number of subjects in one SOC, TEAEs will be displayed by PT in descending order of the total number

of subjects in all PTs; and in case there are equal number of subjects in certain PTs, TEAEs will be displayed in alphabet order of initials of the PTs.

All AEs will be displayed in listing, including the AE term, start date, end date, occurring within 30 minutes or not, maximum severity, serious adverse event or not, SAE classification, causal relationship with the investigational product. At the same time, solicited adverse events, AEs leading to withdrawal, SAEs, and AEs leading to death will be displayed in separate listings.

3.3.3 Pregnancy

The number of subjects with pregnancy in each group during the study will be counted and the final pregnancy outcomes will be described according to the following categories:

- Pregnancy outcome (in pregnancy, delivered, termination)
- Neonatal status (normal, congenital anomaly, other complications or abnormalities)
- Reason for termination of pregnancy

3.3.4 Vital signs

Vital signs include: body temperature, pulse, blood pressure (systolic, diastolic).

Observations and changes from baseline at scheduled visits will be summarized descriptively. At the same time, clinical assessment will be performed for each test result (normal < abnormal but not clinically significant < abnormal and clinically significant), and a crossover table will be presented showing the worst post-baseline results (including results at unscheduled visit) and the change of test results from baseline at each scheduled visit. In addition, vital sign findings of increased toxicity or new toxicity (Grade≥1) from baseline will be summarized by visit. Refer to toxicity grading in Appendix 2.

3.4 Exploratory analysis

Considering that the current number of PPS subjects does not reach the sample size of $AUEC_{1\text{-}15}$ in the protocol for the hypothesis of superiority, and the RVNA before immunization in China clinical trial is limited by 0.5 IU/mL, the only reason for the inclusion of $AUEC_{1\text{-}15}$ analysis is that the PPS is excluded because the RVNA before immunization is $\geqslant$ 0.1 IU/mL and the RVNA before immunization is less than 0.5 IU/mL, and the exploratory analysis is performed on the subjects with the same analysis method as the RVNA on Day 8 after medication.

4 Interim Analysis

No interim analysis will be performed in this study. However, after all subjects have completed the safety and efficacy observations up to Day 99 post-dose (serology results on Days 1, 4, 8, 15, 43, 99 are available), the first analysis will be performed, and a statistical analysis report and a clinical study report will be drafted

and submitted to the NMPA for review. After all subjects have completed the safety and efficacy observations 1 year post-dose, a second analysis will be performed, and a statistical analysis report and a final clinical study report will be drafted and submitted to the NMPA as supplementary documents and submitted to the FDA US for review.

5 Modifications to Statistical Analysis Plan in the Study Protocol

"The difference in RVNA rates will also be analyzed using Wald" and "rate differences and P-values adjusted for stratification factor of study site will be calculated using the CMH method" are added in the SAP compared to the clinical study protocol (version: 2.0, 06-Dec-2020).

6 References

7 Appendices

Appendix 1. Adverse Event Severity Grading Criteria

Symptoms/Signs	Grade 1	Grade 2	Grade 3	Grade 4
Induration *, swelling (optional) * * #				
> 14 years	2.5 ~ < 5 cm in longest diameter or 6.25 ~ < 25 cm^2 in area	5 ~ < 10 cm in longest diameter or 25 ~ < 100 cm^2 in area	≥10 cm in longest diameter or ≥100 cm^2 in area	/
Rash *, redness (optional) * * #				
> 14 years	2.5 ~ < 5 cm in longest diameter or 6.25 ~ < 25 cm^2 in area	5 ~ < 10 cm in longest diameter or 25 ~ < 100 cm^2 in area	≥10 cm in longest diameter or ≥100 cm^2 in area	/

Signs	Grade 1	Grade 2	Grade 3	Grade 4
Pyrexia * [Axillary temperature (℃)]				
> 14 years	37.3 ~ < 38.0	38.0 ~ < 38.5	38.5 ~ < 39.5	≥ 39.5

Note: Area is calculated as: π*A (longest diameter) *B (shortest diameter)/4

Appendix 2. Vital Signs Toxicity Grading

Vital Signs	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Very severe (Grade 4)
Pyrexia	38.0-38.4℃	38.5-38.9℃	39.0-40℃	>40℃
Tachycardia (beats/min)	101-115	116-130	>130	
Bradycardia (beats/min)	50 – 54	45 – 49	< 45	
Hypertension (systolic blood pressure) - mmHg	141 – 150	151 – 155	> 155	
Hypertension (diastolic blood pressure) - mmHg	91 – 95	96 – 100	> 100	
Hypotension (systolic blood pressure) - mmHg	85 – 89	80 – 84	< 80	