# 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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| Study Product Name: | SYN023 |
| Clinical Trial Approval Number: | 2017L04123 |
| Clinical Trial Approval Date: | Jun. 1, 2017 |
| Registration Category: | Therapeutic Biological Products Category 2 |
| Protocol Number: | SYN023-006 |
| Version Date: | December 06, 2020 |
| Version Number: | 2.0 |
| NCT Number: | NCT04644484 |
| Sponsor (Seal) | Synermore Biologics (Suzhou) Ltd. |
| Research Institute (Seal) | Yunnan Province Center for Disease Control and Prevention |
| Research Period: | From July. 2020 to June 2022 |

**Statement**

I. This clinical trial was carried out strictly in accordance with the requirements of the Good Clinical Practice (GCP), Declaration of Helsinki and relevant China regulations on registration.

II. This document contains confidential information of Synermore Biologics (Suzhou) Ltd. Unless otherwise permitted in writing, you agree to keep this document confidential when receiving or reading it, and shall not copy it or disclose it to any third party (except as required by applicable laws), or use it for any other purpose without approval. Synermore Biologics (Suzhou) Ltd. must be immediately notified of any material violation or suspected violation of this obligation for confidentiality.

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## SPONSOR APPROVAL

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| Protocol Number | SYN023-006 |
| Version Date | December 06, 2020 |
| Version Number | Version 2.0 |
| Title | 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 |
| Sponsor | Unit: Synermore Biologics (Suzhou) Ltd.<br>Address: Building 5, Sangtiandao Biological Industrial Park, 218 Sangtian Street, Suzhou Industrial Park, Jiangsu Province<br>Postal Code: 215000 |
| Sponsor's Representative | [redacted] |
| Sponsor's Representative | [redacted] |
| Protocol Approval | [redacted] |

## APPROVAL OF PRINCIPAL INVESTIGATOR

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|---|---|
| **Protocol Number** | SYN023-006 |
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| **Title** | 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 |

I undertake to:

- Be responsible for leading the clinical research in this region;
- Ensure this research be carried out in accordance with the trial protocol and the Standard Operating Procedures (SOP) for clinical researches;
- Ensure that all staff involving in this research fully understand relevant information about the study product and other relevant duties and obligations specified in this trial protocol;
- Ensure that no change will be made to the trial protocol without the preview and written approval of the Sponsor and the Institutional Review Board (IRB), unless any such change is required to be made in order to eliminate imminent harm to the subjects or to comply with the requirements of the drug regulator (for example: in terms of project administration);
- Fully understand the correct use of the study product in the trial protocol, and fully understand other information provided by the Sponsor, including but not limited to the following: the current Investigators' Brochure or equivalent documents;
- Comply with the Good Clinical Practice (GCP), Vaccine Management Law of the People's Republic of China, Guidelines for Quality Management of Clinical Trials on Vaccines (Trial) and all other current regulations.

| Title | Name | Unit | Signature | Date of Approval |
|---|---|---|---|---|
| [redacted] | [redacted] | [redacted] | | [redacted] |

## LIST OF ABBREVIATIONS

| Abbreviations | Name |
|---|---|
| ADR | Adverse Drug Reaction |
| AE | Adverse Event |
| ADCC | Antibody Directed Cellular Cytotoxicity |
| CDC | Complement Dependent Cytotoxicity |
| CDE | National Center for Drug Evaluation of NMPA |
| $AUC_{0-14}$ | Area Under the Curve Study Day 0 to Day 14 |
| $AUEC_{0-14}$ | Area Under the Efficacy Curve Study Day 0 to Day 14 |
| BMI | Body Mass Index |
| $C_{max}$ | Maximum concentration |
| CI | Confidence Interval |
| CRA | Clinical Research Associate |
| CRC | Clinical Research Coordinator |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CV | Coefficient of Variation |
| eCRF | Electronic Case Report Form |
| D | Day |
| DM | Data Manager |
| DMP | Data Management Plan |
| DSMB | Data and safety monitoring board |
| DVP | Data Validation Plan |
| EC | Ethical Committee |
| EDC | Electronic Data Capture System |
| ERA | Equine Rabies Antiserum |
| ERIG | Equine Rabies Immune Globulin |
| FDA | U.S. Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMC | Geometric Mean Concentration |
| HRIG | Human Rabies Immune Globulin |
| ICF | Informed Consent Form |
| ICH | International Council for Harmonization |
| IgG | Immunoglobulin G |

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| IgG1κ | Immunoglobulin G type 1 kappa |
| IMP | Investigational Medical Product |
| IRB | Institutional Review Board |
| IWRS | Interactive Web Response System |
| kg | Kilogram |
| Mab, mAb | Monoclonal Antibody |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NDA | New Drug Application |
| NMPA | National Medical Products Administration |
| PEP | Post-exposure Prophylaxis |
| PK | Pharmacokinetics |
| PPAB | Per Protocol Adjudication Board |
| PPS | Per Protocol Set (Population) |
| PSUR | Periodical Safety Updated Report |
| PT | Preferred Term |
| PV | Pharmacovigilance |
| RFFIT | Rapid Fluorescent Focus Inhibition Test |
| RIG | Rabies Immune Globulin |
| RVNA | Rabies Virus Neutralizing Activity |
| SAE | Serious Adverse Event |
| SOC | System Organ Class |
| SOP | Standard Operation Procedure |
| SS | Safety Set |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| VNAs | Virus-Neutralizing Antibodies |
| TEAEs | Treatment-Emergent AEs |
| $T_{max}$ | Time Till Maximum Concentration |
| $t_{1/2}$ | Half-life |
| WHO | World Health Organization |

## GLOSSARY

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| **Case Report Form** | Refers to a printed, optical or electronic document designed in accordance with the requirements of the trial protocol, which can be used to record all information about each subject during the trial and submitted to the Sponsor. |
| **Auditing** | Refers to systematic and independent auditing on all behaviors and relevant documents in the clinical trial. The aim of auditing is to determine whether the trial implementation process and trial data recording, analysis and reporting meet the requirements of the trial protocol, Standard Operating Procedures (SOP), Good Clinical Practice (GCP) for clinical trials on drugs and relevant laws and regulations. |
| **Supervision** | Refers to supervision and review of the progress and process of the clinical trial, aiming to ensure that the clinical trial is implemented, recorded and reported in accordance with the requirements of the trial protocol, SOP, GCP and relevant laws and regulations. |
| **Blinding** | Blinding is one of the important measures for controlling the bias caused by "knowing randomized grouping information" in clinical trials, which aims to ensure the unpredictability of randomized grouping for all parties in a clinical trial. Based on different degrees, blinding is divided into double blinding, single blinding and non-blinding (open-label). |
| **Randomization** | The principle of randomization in clinical trials refers to that each subject in the clinical trial has an equal opportunity to be assigned to the implementation process or measures in the experimental group or the control group. The randomization process isn't influenced by any subjective will of any investigator and/ or subject. |
| **Study Drug** | Refers to the drug used in a clinical trial, including the study drug, control drug and placebo. |
| **Subject** | Refers to the individual participating in a clinical trial voluntarily as the recipient of the study vaccine or as the control subject, including healthy volunteer and patient. |
| **Drop-out** | Refers to that a subject cannot finish the last follow-up as required in the trial protocol for any reason. |

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| **Investigator's Brochure** | Refers to the existing clinical and non-clinical research data about the study drug during a human trial. |
| **Adverse Drug Reaction** | All noxious and unintended responses to a medicinal product related to the protocol complied dosing should be considered adverse drug reactions. A causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. |
| **Adverse Event** | Refers to any adverse medical event that occurs after a patient or a subject in a clinical trial receives a drug, which may not be causally related to treatment. |
| **Solicited Adverse Event** | Refers to any adverse event collected as a safety endpoint in a clinical research and any adverse event information actively collected by the investigators or subjects during a specific follow-up period after drug administration/vaccination, which is usually related to the study drug/vaccine and is listed in the protocol and the CRF. |
| **Unsolicited Adverse Event** | Refers to any adverse event other than the solicited adverse events and unsolicited adverse events reported in a clinical research, including any solicited adverse event reported outside the specified time window for solicitation. |
| **Serious Adverse Event** | Refers to any event that requires hospitalization or prolonged hospital stay, or causes disability, impairment in the ability to work, threat to life, death or congenital malformation during a clinical trial. |

## STUDY TEAM

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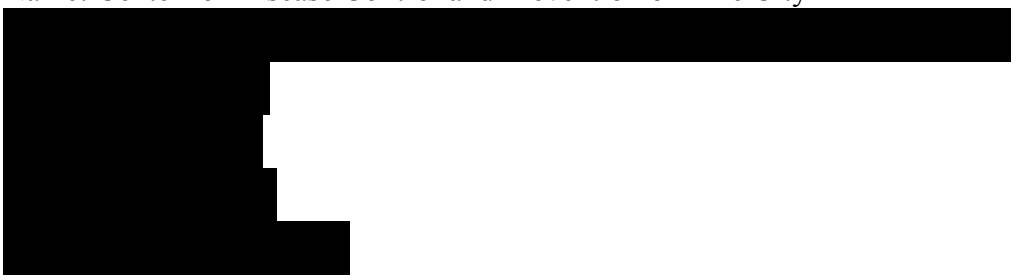
|---|---|
| **Protocol Number** | SYN023-006 |
| **Version Date** | December 06, 2020 |
| **Version Number** | Version 2.0 |
| **Title** | A Phase III Randomized Blinded Study to Evaluate SYN023 Compared to Human Rabies Immune Globulin in Post Exposure Prophylaxis of Rabies in Adults with Category III Rabies Exposure Risks |

**Clinical Trial Sites**

Name: Yunnan Province Center for Disease Control and Prevention

**Clinical Trial Site 1**

Name: Center for Disease Control and Prevention of Mile City



**Clinical Trial Site 2**

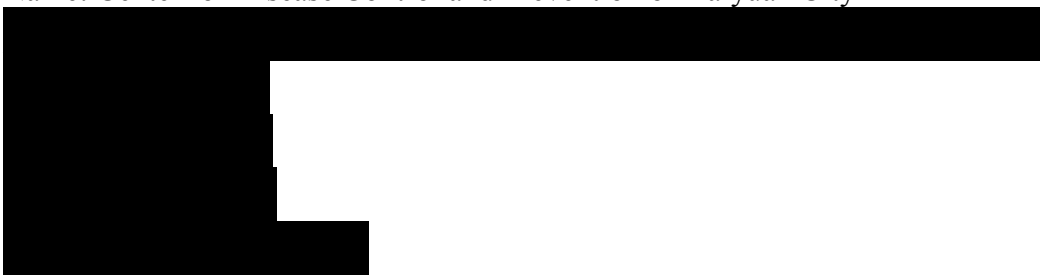
E-mail: qblcmy@163.com

**Clinical Trial Site 3**

Name: Center for Disease Control and Prevention of Yanshan City

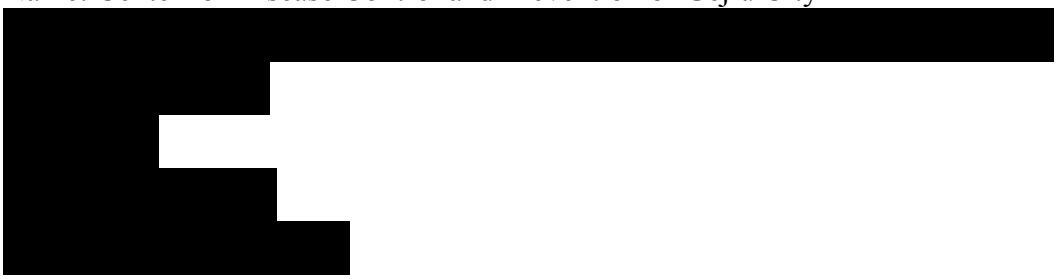
**Clinical Trial Site 4**

Name: Center for Disease Control and Prevention of Kaiyuan City



**Clinical Trial Site 5**

Name: Center for Disease Control and Prevention of Gejiu City



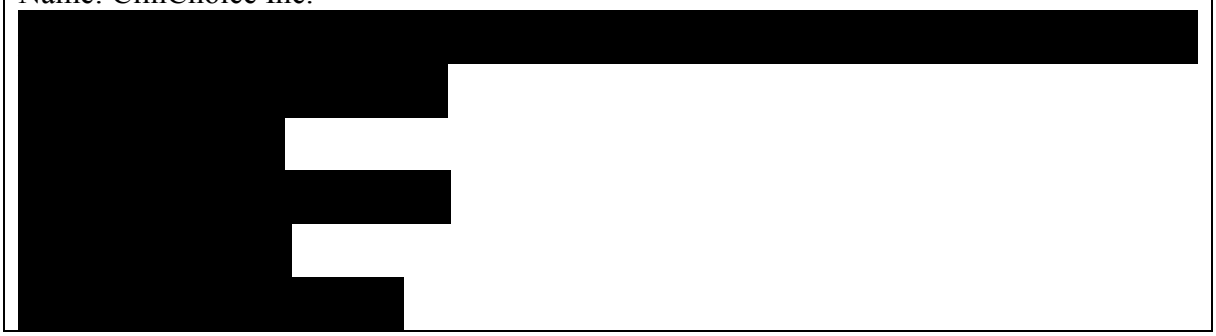
**Central Laboratory**

Name: National Center for Disease Control and Prevention

Department: Institute for Viral Disease Prevention and Control

**Biostatistical Agent**

Name: ClinChoice Inc.



| **Data Management Agent** |
| --- |
| Name: ClinChoice Inc.. [redacted] |
| **Clinical Operation Agent** |
| Name: Simoon Record Pharma Information Consulting Co., Ltd. [redacted] |

## Protocol Synopsis

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|---|---|
| **Title** | 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 |
| **Product Characteristics** | SYN023 is a mixture of two anti-rabies human monoclonal antibodies IgG1 κ CTB011 and CTB012 at a ratio of 1:1, which bind to specific and non-overlapping epitope of rabies virus glycoprotein. CTB011 and CTB012 were independently cultured in batches from SYN023 Chinese Hamster Ovary (CHO) cells in a bioreactor, and the supernatant was harvested, clarified and purified. The resulting CTB011 and CTB012 bulks were separately filtered into disposable liquid storage bags through a filter and stored at -80 °C.<br>The finished product of SYN023 is a mixture of 3.0 mg/mL CTB011 and 3.0 mg/mL CTB012 at a ratio of 1:1. SYN023 is a sterile and preservative-free injection, and the excipient contains 25 mM histidine (3.879 mg/mL), 150 mM sodium chloride (8.766 mg/mL) and 0.02% polysorbate 80 (0.2 mg/mL) and pH of 6.0. Each vial contains 2.15 mL of SYN023, or 6.45 mg of mAb. The glass bottle was closed with a 13 mm bromobutyl rubber stopper, a 13 mm aluminum crimping cap and a polypropylene flip-open lid. |
| **Indications** | SYN023 is indicated to combine with the Rabies Vaccine to confer immediate passive immunity for PEP (Post-exposure Prophylaxis) of Category III rabies exposure. |
| **Subjects** | Subjects aged 18 and above with Category III rabies exposure |
| **Principal Investigator** | [redacted] |
| **Objectives** | Primary objectives:<br>● To demonstrate the Geometric mean RVNA Concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for HRIG recipients on Study Day 8, AND<br>● There are no probable or confirmed cases of rabies in SYN023 recipients.<br>Secondary objectives:<br>● To demonstrate the Geometric mean RVNA Concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for HRIG recipients on Study Day 4;<br>● To demonstrate that the geometric mean RVNA $AUEC_{1\text{-}15}$ for SYN023 is |

<table>
<tr><td></td><td>superior to the geometric mean RVNA $AUEC_{1-15}$ for HRIG;<br>● 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;<br>● 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;<br>● 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 as-treated populations;<br>● To describe the percentage of RVNA concentration ≥0.5 IU/mL at each time point for SYN023 and HRIG recipients in the per-protocol and as-treated populations;<br>● To describe any effect of increasing BMI on SYN023 and RVNA concentrations;<br>● To evaluate the safety of SYN023 compared to HRIG.</td></tr>
<tr><td>Trial Design</td><td>Overall Design:<br><br>This is a Phase Ⅲ, randomized, blinded, and active controlled study of SYN023 compared with a China licensed HRIG for PEP of patients who have been confirmed to have met all inclusion/exclusion criteria for their treatment group.<br><br>Sample Size and Grouping:<br>1000 patients aged 18 and above with WHO Category III rabies exposure should be enrolled as planned and randomly assigned to the experimental group and the control group based on a ratio of 3:1 through on-site stratification as part of PEP. The sample size and randomization distribution of the two groups are described in below table:
<table>
<tr><th>Group</th><th>Sample Size</th><th>Study Drug</th><th>Administration Method & Dosage</th><th>Time points of Administration</th></tr>
<tr><td rowspan="2">Experimental Group</td><td rowspan="2">750</td><td>SYN023</td><td>0.3 mg/kg, wound infiltration injection*</td><td>Study Day 1</td></tr>
<tr><td>Human Rabies Vaccine</td><td>0.5 mL, intramuscular injection into the deltoid muscle</td><td>Study Days 1, 4, 8, 15, 29<br>(Essen Scheme)</td></tr>
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| | <table><tr><td rowspan="2">Control Group</td><td rowspan="2">250</td><td>HRIG</td><td>20 IU/kg, wound infiltration injection*</td><td>Study Day 1</td></tr><tr><td>Human Rabies Vaccine</td><td>0.5 mL, intramuscular injection into the deltoid muscle</td><td>Study Days 1, 4, 8, 15, 29 (Essen Scheme)</td></tr></table><br>*If the study drug isn't used up after infiltration injection for all wounds, the remaining amount should be injected into the muscles far away from the vaccine injection sites (if a wound is located above the waist, the remaining amount should be injected into the back muscles on the side where the wound is located; if a wound is located below the waist, the remaining amount should be injected into the lateral muscles in the middle thigh on the side where the wound is located). |
| | **Study Drug Administration:**<br>All subjects should receive wound infiltration injection of SYN023 or HRIG on Study Day 1 (wound conditions should be described and recorded before injection, including diameter, depth, expansion treatment, etc.), and should also intramuscularly inject one dose of the freeze-dried rabies vaccine for human use (Vero cells) into the deltoid muscle. In accordance with the Essen Scheme, each subject receives one dose rabies vaccine on Study Days 4, 8, 15, and 29 respectively. |
| | **Efficacy Evaluations:**<br>3.0 mL of venous blood should be sampled 8 times from each subject prior to administration and on Study Days 4, 8, 15, 43, 99, 183, and 365 post administration of study drug. Relevant information should be collected from the subjects through follow-up visits, such as occurrence of rabies and survival conditions.<br>RVNA should be assayed by rapid fluorescence focus inhibition test (RFFIT). |
| | **Safety Evaluations:**<br>Solicited adverse events should be collected within 8 days after administration; All adverse events occurring within 43 days after administration should be collected, and pregnant events within 6 months after IMP administration and all serious adverse events (SAE) occurring during the study period should be collected. |
| **Inclusion Criteria** | 1) Is age ≥ 18 years, on Study Day 1 with legal identification documents, and plan to live in the local administration area during the study;<br>2) Category III rabies exposure within 24 hours before Study Drug receipt ;<br>3) Completed written informed consent process, and signed the informed consent forms;<br>4) Subjects with the ability to understand the study procedure. And agreed to |

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| | complete all follow-ups;<br>5) Female subjects are not in pregnancy (with negative results of urine pregnancy tests before vaccination) and are not in the period of breast feeding, and agree to avoid pregnancy within 121 days after administration;<br>6) Those who have an armpit temperature ≤ 37.0 °C. |
| **Exclusion Criteria** | 1) Previous receipt of equine or human (rabies) globulin or rabies vaccination prior to randomization;<br>2) Clinical evidence of rabies infection;<br>3) Category I and Category II rabies exposure;<br>4) Had fever (armpit temperature ≥ 38.5 °C) within 3 days before Study Day 1, or in the acute episode of any chronic diseases;<br>5) Received immunoglobulin or blood products (except for the anti-tetanus immunoglobulin) within 43 days before Study Day 1, or plan to use any such product (except for the anti-tetanus immunoglobulin) during the study;<br>6) Received systemic immunosuppressant medication such as systemic corticosteroids but not limited to systemic corticosteroids within 43 days before Study Day 1;<br>7) History of any immunodeficiency disease (for example: AIDS, systemic lupus erythematosus, etc.); or Laboratory evidence of previous or current immunodeficiency disease, including, but not limited to, any laboratory evidence of HIV infection;<br>8) History of spleen function deficiency or function injury, such as no spleen caused by any cause (such as splenectomy);<br>9) History of any severe allergy for vaccination, such as systemic urticaria, allergic laryngeal edema, anaphylactoid purpura, local allergic necrosis (Arthus reaction), angioedema, anaphylactic shock, etc., or allergic to any ingredient of the study drug/vaccine;<br>10) Previous receipt of any study product (drug, vaccine, biological product or medical device) within 6 months before Study Day 1, or plan to participate in any other clinical study during this study period;<br>11) History of or clinical evidence of any systemic disease, acute disease or chronic disease (such as convulsions, epilepsy, encephalopathy, nephrotic syndrome, etc.) that the investigator considers to be likely to interfere with safety or efficacy assessment of the study;<br>12) Previous medical history that may compromise the safety of the subject in the study according to the opinion of the principal investigator. |

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| **SYN023** | Name: SYN023<br>Manufacturer: Synermore Biologics (Suzhou) Ltd.<br>Strength: 6 mg/2 mL/vial<br>Active ingredients: A mixture of 3.0 mg/mL CTB011 and 3.0 mg/mL CTB012 (ratio: 1:1), and each vial contains 2.15 mL of SYN023 (or 6.45 mg of mAb)<br>Excipients: 25 mM histidine (3.879 mg/mL), 150 mM sodium chloride (8.766 mg/mL) and 0.02% polysorbate 80 (0.2 mg/mL) and pH 6.0.<br>Administration route: wound infiltration injection<br>Dosage: 0.3 mg/kg |
| **HRIG** | Generic name: Human Rabies Immunoglobulin (HRIG)<br>Manufacturer: Tonrol-Shanghai RAAS blood products Co., Ltd<br>Dosage form: 200 IU/2 mL/Vial<br>Active ingredients: Human rabies immunoglobulin<br>Excipients: Glucose<br>Injection site and administration route: wound infiltration injection<br>Strength: 20 IU/kg |
| **Vaccine** | Generic name: Freeze-dried Rabies Vaccine for Human Use (Vero Cells)<br>Manufacturer: Liaoning Chengda Biotechnology Co., Ltd.<br>Size: 0.5 mL/vial after dissolution. The dosage for humans should be 0.5 mL per time, and the rabies vaccine titer should not be less than 2.5 IU.<br>Active ingredients: Inactivated fixed rabies virus (PV2061)<br>Excipients: Human albumin, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, dextran 40<br>Vaccine diluent: Sterile water for injection<br>Administration route: Intramuscular injection into the deltoid muscle |
| **Endpoints** | **Primary efficacy endpoints:**<br>● The GMC of RVNA on Study Day 8 after administration;<br>● Mortality and Morbidity of rabies on subjects within 99 days and 1 year after administration.<br>**Secondary efficacy endpoints:**<br>● The protection level (percentage of subjects with RVNA concentration ≥0.5 IU/mL) and GMC of RVNA on Study Days 4, 8, 15, 43, 99, 183, and 365 after administration; |

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| | ● Geometric mean RVNA concentration of the area under the curve from Study Day 1 to 15 ($AUEC_{1-15}$).<br>**Safety endpoints:**<br>● All AEs related or unrelated to the study drug occurring within 30 minutes after administration;<br>● (Local) adverse events occurring at the drug injection sites' AE and (Systemic) adverse events occurring at sites other than the injection/vaccination sites within 8 days after administration;<br>● All AEs related or unrelated to the study drug occurring within 43 days after administration D1;<br>● All AEs above grade III related to the study drug occurring within 43 days after administration D1;<br>● All SAEs related or unrelated to the study drug occurring during the study;<br>● Pregnancy-related events occurring within 6 months after administration (pregnancy status and outcome);<br>● AEs/SAEs leading to withdrawal. |
| **Hypotheses & Statistical Strategies** | **Primary study hypotheses:**<br>1) The Geometric mean RVNA Concentration of SYN023 recipients is superior to that of the HRIG recipients on Study Day 8 after administration (the lower limit of the 95% confidence interval (CI) of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2).<br>**Secondary study hypotheses:**<br>1) The Geometric mean RVNA Concentration in the experimental group on Study Day 4 after administration should be superior to that of the control group (the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2);<br>2) The Geometric mean RVNA Concentration in the experimental group on Study Day 99 after administration should be non-inferior to that of the control group (the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 0.8);<br>3) The percentage of subjects with RVNA concentration ≥ 0.5 IU/mL of the experimental group on Study Day 15 after administration should not be inferior to that of the control group (the lower limit of the 95% confidence interval of antibody protection level ratio (experimental group/control group) should be > 0.8); |

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| | 4) The area under the curve for the GMC of RVNA from Study Day 1 to Day 15 ($AUEC_{1-15}$) of SYN023 recipients should be superior to that of HRIG recipients (the lower limit of the 95% confidence interval of the $AUEC_{1-15}$ for the GMC of RVNA from Study Day 1 to Day 15 should be > 1.1).<br>**Statistical strategies**:<br>Based on the multiple hypotheses in this study, the hypothesis that the geometric mean concentration of RVNA in the experimental group on Study Day 8 after administration should be superior to that of the control group (the test on the primary hypothesis) will be tested at the level of 0.025 (one-sided).<br>If the test is successful, the hypothesis that the geometric mean concentration of RVNA in the experimental group on Study Day 4 after administration should be superior to that of the control group will be tested at the level of 0.025 (one-sided) (the test on Secondary Hypothesis 1); otherwise, the three tests on the secondary hypotheses will be conducted as exploratory analyses at the level of 0.05 (two-sided).<br>If the test on Secondary Hypothesis 1 is successful, the hypothesis that the antibody protection level of the experimental group on Study Day 15 after administration should not be inferior to that of the control group will be tested at the level of 0.025 (one-sided) (the test on Secondary Hypothesis 2); otherwise, the tests on Secondary Hypothesis 2 and Secondary Hypothesis 3 will be carried out as exploratory analyses at the level of 0.05 (two-sided). If the test on Secondary Hypothesis 2 is successful, the hypothesis that the area under the curve for the GMC of RVNA from Study Day 1 to Day 15 ($AUEC_{1-15}$) of the SYN023 recipients should be superior to that of the HRIG recipients will be tested at the level of 0.025 (one-sided) (the test on Secondary Hypothesis 3); otherwise, the test on Secondary Hypothesis 3 will be carried out as an exploratory analysis at the level of 0.05 (two-sided). |
| **Sample Size Calculation** | In this trial, 1000 subjects aged 18 and above that had Category III exposure to rabies virus should be enrolled and randomly assigned to the experimental group and the control group based on a ratio of 3: 1.<br>**Primary study hypotheses:**<br>The geometric mean concentration of RVNA in the experimental group on Study Day 8 after administration should be superior to that of the control group (the lower limit of the 95% CI of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2). |

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| | Based on the hypotheses in this study, i.e., the lower limit of the 95% CI of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2, it is assumed that the type I error is 0.025 (one-sided) and the test power is 90%; the geometric mean concentration of RVNA (experimental group/control group) is estimated to be 11.9 on Study Day 8 after administration; CV% is 120.5%; and the randomization of the experimental group/control group is 3:1. Therefore, 16 cases are needed, including 12 cases in the experimental group and 4 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a test power of 100% when the hypotheses remain unchanged.<br>**Secondary study hypotheses:**<br>1) The RVNA GMC in the experimental group on Study Day 4 after administration should be superior to that of the control group (the lower limit of the 95% CI of the RVNA GMC (experimental group/control group) should be > 1.2).<br>Based on this hypothesis, i.e., the lower limit of the 95% CI of RVNA GMC (experimental group/control group) should be > 1.2, it is assumed that the type I error is 0.025 (one-sided) and the test power is 90%; the RVNA GMC (experimental group/control group) is estimated to be 13.75 on Study Day 4 after administration; CV% is 63.25%; and the randomization ratio of the experimental group/control group is 3:1. Therefore, 12 cases are needed, including 9 cases in the experimental group and 3 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a Power 100%.<br>2) The geometric mean concentration of RVNA in the trial group on Day 99 was not inferior to that in the control group (lower 95% confidence interval > 0.8 of the geometric mean concentration of RVNA (trial group/control group))<br>Based on the research hypothesis, the lower limit >1.2, confidence interval is set as 95%. Type I error is 0.025 (unilateral). The Power is 90%. The 99th day RVNA geometric mean concentration/control group is predicted as of 86.94%. The CV was 17.32%. The experimental group/control's sample size's ratio is designed as 3:1. Considering a 20% dropout rate, the trial's sample size is of 308, includes 231 in experimental group, 77 in control group. The sample size of 1000 would ensure a power of 100%.<br>3) The antibody protection level of the experimental group on Study Day 15 after administration should not be inferior to that of the control group (the lower limit of the 95% confidence interval of antibody protection level ratio (experimental |

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| | group/control group) should be > 0.9).<br>Based on this hypothesis, i.e., the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 0.8, it is assumed that the type I error is 0.025 (one-sided) and the Power is 90%; the estimated antibody protection level ratio (experimental group/control group) should be 1 on Study Day 15 after administration and the estimated protection level of the control group is 98.7%; and the randomization of the experimental group/control group is 3:1. Therefore, 52 cases are needed, including 39 cases in the experimental group and 13 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a Power of 100% when the hypotheses remain unchanged.<br>4)The area under the efficacy curve for the GMC of RVNA from Study Day 1 to Day 15 ($AUEC_{1-15}$) for the "SYN023 + rabies vaccine" group should be superior to that of the "HRIG + rabies vaccine" group (the lower limit of the 95% confidence interval of the $AUEC_{1-15}$ (experimental group/control group) for the GMC of RVNA from Study Day 1 to Day 15 should be >1.1);<br>Based on this hypothesis, i.e., the lower limit of the 95% CI of the $AUEC_{1-15}$ (experimental group/control group) for the GMC of RVNA from Study Day 1 to Day 15 should be >1.1, it is assumed that Type I error is 0.025 (one-sided) and the test Power is 90%; the estimated value of $AUEC_{0-14}$ (experimental group/control group) for the GMC of RVNA from Study Day 1 to Day 15 is 147.55%, and CV% is 142%; and the randomization of the experimental group/control group is 3:1. Therefore, 900 cases are needed, including 675 cases in the experimental group and 225 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a Power of 96.9%. |
| **Study Suspension or Termination** | ● Based on any new information of the IMP obtained from this study or other studies that the Sponsor, the Investigator, the IRB, and the National Drug Regulatory Authority (NMPA) determine to suspend the trial with the analysis of subject risk/benefit evaluation. When any subject dies or experiences any serious life-threatening adverse reaction related to the study drug during the study;<br>● When the number of subjects with Grade 3 or higher RELATED systemic adverse reactions accounts for 20% or more of the number of subjects receiving the study product during the trial.<br>In case of the above circumstances for suspension, the trial needs to be |

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| | suspended, and shall be reported to the Institutional Review Board for the decision of continuity. If necessary, terminate the trial as the decision.<br>If the study is terminated earlier or suspended, the (DSMB will recommend to the sponsor termination of the protocol and) Sponsor will notify the investigators, the Institutional Review Board, and the drug authorities of the reason for the suspension or termination immediately in accordance with relevant regulations.<br>Regardless of the reason for the early termination of the study, the investigators should notify all subjects immediately of such termination and carry out appropriate follow-up visits on the conditions of the subjects. |
| **Relevant Definitions** | **18 Years Old and Above:** Over 18 years old (including the 18th birthday)<br>**Protective level of Anti-rabies Virus Neutralizing Antibodies:** RVNA ≥ 0.5 IU/mL.<br>*The following definitions are quoted from "Technical Guidelines for Rabies Prevention and Control" issued by the Chinese Center for Disease Control and Prevention in 2016*<br>**Rabies Exposure:** refers to a situation in which a person is bitten or scratched by any host animal, or any suspected or uncertain host animal of the rabies virus, or any mucous membrane or damaged skin of a person is licked by any host animal, or any suspected or uncertain host animal of the rabies virus, or any open wound or mucous membrane of a person contacts any saliva or tissue that may contain the rabies virus directly. In addition, in rare cases, a person may be infected with the rabies virus through organ transplantation or inhalation of aerosol.<br>**Rabies Exposure Categorization**: Rabies exposure is classified into three categories based on nature and severity.<br>**Category I Exposure**: any exposure that meets one of the following conditions:<br>1) Touching or feeding animal<br>2) Any intact skin is licked by animal<br>3) Any intact skin contacts the secretion or excrement of any animal or person that has been infected with the rabies virus<br>*Note: Exposure to rodents, rabbits, or hares usually does not require post-exposure immunoprophylaxis. Poultry, fish, insects, lizards, turtles, and snakes cannot be infected with or spread the rabies virus.*<br>**Category II Exposure**: any exposure that meets one of the following conditions:<br>1) When any uncovered skin is nibbled |

2) Any minor scratch or abrasion without bleeding

*Note: Observe the exposed skin carefully to check whether there is any damage. If it is difficult to determine whether there is any damage, wipe the exposed skin with alcohol. Any pain indicates damaged skin (this method can only be used for checking immediately after exposure).*

**Category III Exposure:** any exposure that meets one of the following conditions:

1) A single transdermal bite or scratch or multiple transdermal bites or scratches to break the skin ("transdermal" means that the dermis and blood vessels are injured at least, and the clinical manifestation is visible bleeding or subcutaneous tissue);
2) Any damaged skin is licked (attention should be paid to small skin damages due to various reasons, such as skin cracking or scratching);
3) Any mucous membrane is contaminated by animal saliva (such as being licked)
4) Exposure to a bat (post-exposure prophylaxis should be considered after any contact with a bat unless there is no bite, scratch or exposure of any mucous membrane)

*Note: Bites on the head, face, neck, hands and external genital organs are classified as Category III Exposure.*

**Treatment after Exposure to Rabies:**

| **Type of Exposure** | **Degree of Exposure** | **Post-exposure prophylaxis** |
|---|---|---|
| I | None | No treatment is needed if the way of contact is proven to be safe |
| II | Mild | 1. Wound treatment |
| | | 2. Vaccination with rabies vaccine |
| III | Serious | 1. Wound treatment |
| | | 2. Injection of a biologics for the passive immunization against rabies (anti-rabies serum/human rabies immunoglobulin) |
| | | 3. Injection of rabies vaccine |

**WHO's Definition of Rabies**:

Clinical case: refers to a case with acute neurological syndrome (such as encephalitis), which is mainly manifested as hyperactivity (in the case of furious

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| | rabies) or paralysis syndrome (in the case of paralytic rabies). If no intensive care is provided, a patient usually falls into a coma and then dies within 7-11 days after the occurrence of the first symptom, which is usually caused by respiratory and circulatory failure. A patient can be diagnosed with rabies when one or more of the following laboratory criteria can be met:<br>A. The presence of viral antigens;<br>B. The rabies virus is detected with the cell culture method or laboratory animal inoculation;<br>C. There are virus-specific antibodies in the cerebrospinal fluid or serum of an unvaccinated person;<br>D. Viral nucleic acid is detected in any biological sample or sample for autopsy (such as brain biopsy sample, skin, saliva, and concentrated urine) with molecular biological methods.<br>**WHO's Classification of Rabies Cases**:<br>1) Suspected case: refers to a case that satisfies the definition of clinical case;<br>2) Probable case: refers to a suspected case with a reliable medical history of contact with any suspected animal infected with the rabies virus;<br>3) Confirmed case: refers to a suspected or probable case that is proved to be infected based on the lab test result.<br>In the absence of exposure to any host animal or clinically suspected encephalitis symptoms, a case can also be determined as a confirmed case if the diagnosis is sufficiently supported by the lab test result. |
| **Study Duration** | Each subject should be involved in this trial for approximately 12 months, and the total duration of this study is approximately 22 months. |
| **NDA Strategies** | **The first analysis:**<br>The first analysis will be carried out after the completion of the evaluation on safety and efficacy for all subjects within Study Day 99 after administration (the serological sampling results on Study Days 1, 4, 8, 15, 43 and 99 should be obtained), and a statistical analysis report and a clinical study report will be prepared and submitted to the National Medical Products Administration (NMPA) for review.<br>**The second analysis:**<br>The second analysis will be carried out after the completion of the evaluation on safety and efficacy for all subjects during one year after administration, and a statistical analysis report and a clinical study report will be prepared and submitted |

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| | to U.S Food and Drug Administration (FDA) for review. |
| Data and safety monitoring board (DSMB) | A DSMB will be convened in this trial. The DSMB's purpose is to monitor the death and rabies cases during the entire study period. |
| Per Protocol Adjudication Board (PPAB) | The Sponsor will create the Per-protocol Adjudication Board whose duty will be to review data and confirm the rabies cases in the study. The confirmed rabies events is one of the primary endpoints of the study. In case any rabies event in the SYN023 arm, the primary endpoint will be reached for the study failure. In case of lab-confirmed or clinically suspected rabies cases during the study, the study enrollment would be suspended and detailed information would be submitted to PPAB for reviewing and confirmation, so that PPAB can confirm the diagnosis of rabies cases. If a confirmed case of rabies occurs in the SYN023 arm (as in the per protocol set and in the SYN023 group), the clinical trial will be permanently discontinued by PPAB on a written notice. If the rabies case occurred in the control group or in the SYN023 group but PPAB deems that the case was caused by a violation of the study protocol, The study will not be stopped by the rabies case. The operating procedures in violation of the protocol include:<br>• Received the incorrect Study Drug<br>• Received the incorrect dose (± 20%) of Study Drug<br>• Fail to comply with Category III rabies exposure.<br>• Failed to complete the scheduled rabies vaccinations through the study<br>• Are discovered to lack adequate prophylactic treatment of all exposure sites<br>• Are discovered to be injured by animal other than those listed<br>• Are discovered to have an interval > 24 hours from rabies exposure to the start of Informed Consent<br>• Are discovered to have RVNA ≥ 0.1 IU in serum obtained at Study Day 1<br>• Receives prohibited treatment during the trial<br>• Are found not to have a modified WHO Category 3 exposure<br>• Second high risk animal bite or contact requiring PEP |

## STUDY PROCESS TABLE

| **Number of Follow-up Visits** | **V1** | **V2** | **V3** | **V4** | **V5** | **V6** | **V7** | **V8** | **V9** |
|---|---|---|---|---|---|---|---|---|---|
| **Time of Visit (Study Day)** | **D1** | **D4** | **D8** | **D15** | **D29** | **D43** | **D99** | **D183** | **D365** |
| **Window Period (Study Day)** | / | / | / | **+1** | **+2** | **±3** | **±5** | **±7** | **±7** |
| Informed consent for treatment after exposure | ● | | | | | | | | |
| Wound washing and disinfection | ● | | | | | | | | |
| Informed consent | ● | | | | | | | | |
| Checking the criteria for inclusion/exclusion | ● | | | | | | | | |
| Inquiry about medical history | ● | | | | | | | | |
| Medical examination | ● | | | | | | | | |
| Vital signs | ● | ● | ● | ● | | | | | |
| Urine pregnancy test[1] | ● | | | | | | | | |
| Taking photos of wounds[2] | ● | | | | | | | | |
| Random grouping | ● | | | | | | | | |
| Collecting blood samples for RVNA test (about 3.0 mL) | ● | ● | ● | ● | | ● | ● | ● | ● |
| Infiltration injection of SYN023 or HRIG | ● | | | | | | | | |
| Injection of the rabies vaccine (1-5 doses) | ● | ● | ● | ● | ● | | | | |
| Distributing and providing trainings for diary cards[3] | ● | | | | | | | | |
| Collecting and reviewing diary cards[3] | | | ● | | | | | | |
| Distributing and providing trainings for follow-up cards[4] | | | ● | ● | ● | | | | |
| Collecting and reviewing follow-up cards[4] | | | | ● | ● | ● | | | |
| Collecting pregnancy events | ● | ● | ● | ● | ● | ● | ● | ● | |
| Collecting SAEs | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Collecting information about survival conditions | ● | ● | ● | ● | ● | ● | ● | ● | ● |

1. All female subjects should receive urine pregnancy tests;

2. Photos of wounds should be taken according to the corresponding SOP, including at least photos taken prior to wound treatment, after wound treatment (before administration), and 30 minutes post administration;

3. Diary cards should be distributed after administration, which can be used for recording solicited AEs, other AEs and medications that occur within Days 1~8 after injection;

4. Each subject should be provided with a follow-up card on study Day 8, Day 15, and Day 29 during visit, which can be used for recording all AEs that occur from study Day 9 post administration to Day 14 (till Day 43) after the completion of all doses of the rabies vaccine (including those AEs that occur after the injection of the rabies vaccine on study day 8).

# 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

## 1. INTRODUCTION

The SYN023 developed by Synermore Biologics (Suzhou) Ltd. will be used in combination with a rabies vaccine for passive immunization against the rabies virus after exposure. After being reviewed by National Medical Products Administration (NMPA) according to Drug Administration Law of the People's Republic of China and Regulations for Drug Registration, this product was proven to be in compliance with the relevant regulations for the approval of new drugs, and clinical trials for the product were approved according to Approval for Clinical Trials on Drugs (number: 2017L04123).

Yunnan Province Center for Disease Control and Prevention is entrusted by Synermore Biologics (Suzhou) Ltd. to carry out a Phase III clinical trial for this product, in order to evaluate the efficacy and safety of SYN023 administered in combination with a rabies vaccine for subjects aged 18 or above after Category III exposure. This clinical trial protocol is hereby drafted according to Drug Administration Law of the People's Republic of China, Vaccine Management Law of the People's Republic of China, Regulations for Drug Registration, Good Clinical Practices (GCP), and Quality Management Guidelines for Clinical Trials for Vaccines (Trial) and Technical Guidelines for Clinical Trials for Vaccines.

## 2. STUDY OBJECTIVES

### 2.1 Primary Objective

- To demonstrate that the GMC of RVNA in the "SYN023 + rabies vaccine" group is superior to that of the "HRIG + rabies vaccine" group on Study Day 8 after administration;
- To demonstrate that during the research period, the group administered with SYN023 combined with a rabies vaccine has no probable or confirmed case of rabies.

### 2.2 Secondary Objective (s)

- To demonstrate the Geometric mean RVNA Concentration for SYN023 recipients is superior to the geometric mean RVNA concentration for HRIG recipients 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 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 ≥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;
- 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 as-treated populations;
- To describe the percentage of RVNA concentration ⩾0.5 IU/mL at each time point for SYN023 and HRIG recipients in the per-protocol and as-treated populations;
- To describe any effect of increasing BMI on SYN023 and RVNA concentrations;
- To evaluate the safety of SYN023 compared to HRIG.

**2.3 Relevant Definitions**

**Aged 18 Years and Above:** Over 18 years old (including the 18th birthday)

**Positive Activity of Anti-rabies Virus Neutralizing Antibodies:** RVNA≥0.5 IU/mL.

*The following definitions are quoted from "Technical Guidelines for Rabies Prevention and Control" issued by the Chinese Center for Disease Control and Prevention in 2016*

**Rabies Exposure:** refers to a situation in which a person is bitten or scratched by any host animal, or any suspected or uncertain host animal of the rabies virus, or any mucous membrane or damaged skin of a person is licked by any host animal, or any suspected or uncertain host animal of the rabies virus, or any open wound or mucous membrane of a person contacts any saliva or tissue that may contain the rabies virus directly. In addition, in rare cases, a person may be infected with the rabies virus through organ transplantation or inhalation of aerosol.

**Rabies Exposure Categorization:** Rabies exposure is classified into three categories based on nature and severity.

**Category I Exposure**: any exposure that meets one of the following conditions:

1) Contacting or feeding any host animal
2) Any intact skin is licked by any host animal
3) Any intact skin contacts the secretion or excrement of any animal or person that has been infected with the rabies virus

*Note: Exposure to rodents, rabbits, or hares usually does not require post-exposure immunoprophylaxis. Poultry, fish, insects, lizards, turtles, and snakes cannot be infected with or spread the rabies virus.*

**Category II Exposure**: any exposure that meets one of the following conditions:

1) When any uncovered skin is nibbled

2) Any slight scratch or abrasion without bleeding

*Note: Observe the exposed skin carefully to check whether there is any damage. If it is difficult to determine whether there is any damage, wipe the exposed skin with alcohol. Any pain indicates damaged skin (this method can only be used for checking immediately after exposure).*

**Category III Exposure**: any exposure that meets one of the following conditions:

1) A single bite or scratch or multiple bites or scratches that penetrate the skin ("penetrating" means that the dermis and blood vessels are injured at least, and the clinical manifestation is visible bleeding or subcutaneous tissue);

2) Any damaged skin is licked (attention should be paid to small skin damages due to various reasons, such as skin cracking or scratching);

3) Any mucous membrane is contaminated by animal saliva (such as being licked)

4) Exposure to a bat (post-exposure prophylaxis should be considered after any contact with a bat unless there is no bite, scratch or exposure of any mucous membrane)

*Note: Bites on the head, face, neck, hands and external genital organs are classified as Category III Exposure.*

**WHO's Definition of Rabies:**

Clinical case: refers to a case with acute neurological syndrome (such as encephalitis), which is mainly manifested as hyperactivity (in the case of furious rabies) or paralysis syndrome (in the case of paralytic rabies). If no intensive care is provided, a patient usually falls into a coma and then dies within 7-11 days after the occurrence of the first symptom, which is usually caused by respiratory and circulatory failure. A patient can be diagnosed with rabies when one or more of the following laboratory criteria can be met:

A. The presence of rabies viral antigens;

B. The rabies virus is detected with the cell culture method or laboratory animal inoculation;

C. There are rabies virus-specific antibodies in the cerebrospinal fluid or serum of an unvaccinated person;

D. Rabies Viral nucleic acid is detected in any biological sample or sample for autopsy (such as brain biopsy sample, skin, saliva, and concentrated urine) with molecular biological methods.

**WHO's Classification of Rabies Cases**:

① Suspected case: refers to a case that satisfies the definition of clinical case;

② Probable case: refers to a suspected case with a reliable medical history of contact with any suspected animal infected with the rabies virus;

③ Confirmed case: refers to a suspected or probable case that is proved to be infected based on the lab test result.

In the absence of exposure to any host animal or clinically suspected encephalitis symptoms, a case can also be determined as a confirmed case if the diagnosis is sufficiently supported by the lab test result.

## 3. CLINICAL TRIAL INSTITUTE AND SITES

The institute responsible for the clinical trial: Yunnan Province Center for Disease Control and Prevention

Trial Site 1: Center for Disease Control and Prevention of Mile City

Trial Site 2: Center for Disease Control and Prevention of Qiubei County

Trial Site 3: Center for Disease Control and Prevention of Yanshan County

Trial Site 4: Center for Disease Control and Prevention of Kaiyuan City

Trial Site 5: Center for Disease Control and Prevention of Gejiu City

See the appendix for the description of conditions in the institute responsible for the clinical trial and various trial sites.

## 4. CLINICAL TRIAL MANAGEMENT

### 4.1 Parties and Their Responsibilities in the Clinical Trial

#### 4.1.1 Sponsor

1) Provide a preliminary clinical trial protocol, and review and approve the final clinical trial protocol and various cards and forms used in the clinical trial (informed consent, diary card, follow-up card, etc.);
2) Provide documents for on-site application, such as clinical trial approval and manual for investigators, including chemical, pharmaceutical, toxicological, pharmacological, and clinical information and data about the study drug (including completed and uncompleted information and data);
3) Provide the study drug for the clinical study and issue a verification report;
4) Provide the control drug and the vaccine to be used in combination with the study drug for the clinical study; and issue certificates for the batches of the control drug and the vaccine;
5) Be responsible for the safe storage and transportation of the study drugs (including the study drug and the control drug) and the vaccine to be used in combination with the

study drug;

6) Be responsible for formulating a risk control plan for the identified and potential safety risks and implementing the plan together with all parties in this clinical trial in a strict way;
7) Designate full-time staff to be responsible for monitoring safety information of the clinical trial and managing SAE reports, learning about the latest safety information of the clinical trial, and notifying all investigators and regulatory authorities of the status in a timely manner;
8) Participate in the investigation and handling of adverse reactions and adverse events, and be responsible for providing medical treatment or relevant compensations to those cases suffering from adverse reactions and clinically proven adverse events related to the study drug/ the vaccine used in combination with the study drug according to relevant regulations;
9) Be responsible for sending qualified clinical research associates or authorizing a contracting research organization to evaluate and select clinical trial sites, perform corresponding duties for monitoring and verify research data according to the requirements of GCP;
10) Organize audits on the clinical trial to perform quality assurance, ensure that the clinical trial is carried out in accordance with the requirements of GCP and the protocol, and assume ultimate responsibilities for the quality of the clinical trial;
11) Provide funds for the clinical study.

**4.1.2 The Provincial CDC's Responsibilities for the Clinical Trial**

1) Participate in the formulation of the clinical trial protocol and organize the implementation of the clinical trial protocol;
2) Assist in the draft and review of on-site study documents, such as informed consents, vaccination and follow-up notebook, diary cards, follow-up cards and case report forms;
3) Submit ethical review documents to the Institutional Review Board and obtain approval;
4) Establish a clinical trial organization and management system and a quality management system for the clinical trial for vaccine, prepare SOPs and provide trainings;
5) Recommend clinical trial sites, organize and provide assistance in the standard construction of clinical trial sites, ensure the completion of registration for the institute and all sites and obtain an administrative approval from the Human Genetic Resource

Administration of China;

6) Have appropriate management mechanisms and measures for preventing and dealing with emergencies in clinical trials for vaccines, and have an emergency response team dealing with SAEs and the technical capabilities to deal with SAEs;
7) Provide trainings and guidance to the investigators on the clinical trial sites in terms of the use and management of the study drugs and biological samples;
8) Organize recruitment and enrollment of subjects, organize drug/vaccine administration, and supervise the implementation of various works on various sites;
9) Organize the collection of adverse events among subjects on various sites, and organize the reporting, investigation and handling of adverse events;
10) Organize the completion of all forms and electronic case report forms (eCRF) on various sites;
11) Confirm the archiving of data from this clinical trial;
12) Issue a clinical trial summary report.

**4.1.3 Clinical Trial Sites**

1) Organize a team of qualified investigators and build environmental facilities that meet the requirements of the clinical trial;
2) Recruit and enroll subjects who meet the requirements of the clinical trial protocol;
3) Complete the administration of the study drug and the vaccine, sample collection and follow-up safety evaluation;
4) Deal with all adverse events that occur during the study and report serious adverse events as required;
5) Collect raw data from the clinical trial and enter such data into eCRF;
6) Manage the study drug/vaccine and biological samples in accordance with the requirements of GCP;
7) Manage and save all data related to the clinical trial for 5 years after the closure of the clinical trial sites according to the requirements of GCP.

**4.1.4 Central Laboratory**

1) Complete a check for samples and issue the assay report;
2) Provide the RVNA (RFFIT) assay method, reference values for the interpretation of results, standard substance and assay standards, and provide a method verification, if necessary.

### 4.1.5 Statistical Agency

1) Be responsible for preparing the sections of randomization, sample size and statistical analysis in the clinical trial protocol;
2) Prepare a statistical analysis plan and statistical chart templates according to the clinical trial protocol;
3) Carry out the randomization and blinding for the clinical trial;
4) Be responsible for the data blinding review meeting before data base lock, and determine the statistical analysis population grouping and prepare a data blinding review report based on the conclusions of the meeting;
5) Carry out statistical analysis according to the statistical analysis plan and prepare a statistical analysis report;
6) Review the clinical study report.

### 4.1.6 Data Management Agency

1) Complete the data management plan and eCRF draft and amendments according to the protocol, and determine the final versions after a joint review by the Investigators, the Sponsor, the statistical agency, and the clinical operation ;
2) Formulate a data verification plan according to the protocol and eCRF;
3) Perform database design, installation, testing and revision, and carry out data cleaning, coding, database backup, version upgrade and transmission, and complete works according to the regulations of the SOPs;
4) Perform data cleaning in accordance with the data verification plan, which mainly includes: logic check, query management, SAE consistency check, combination drug check, etc.;
5) Be responsible for medical coding in this study;
6) Lock up the database after the clarification of all questions in the data and the determination of the resolution for statistical population grouping based on the opinions of the investigators, the Sponsor, the statistical agency and other related parties at the data review meeting, and deliver the data to the statisticians for statistical analysis; complete a data management report;
7) Save the XPT database and data management documents to a disk and submit it to the Sponsor after project completion.

### 4.1.7 Clinical Operation CRO

Carry out clinical trial monitoring according to GCP, the clinical trial protocol and SOP:

1) Assist the Sponsor in confirming that the research institute undertaking the clinical trial has the appropriate conditions for conducting the clinical trial, including staffing

and training, necessary functional zones such as the emergency room, and well-equipped and well-functioning laboratories that meet various conditions related to the clinical trial;

2) Verify that the vaccine doses used in the clinical trial are transported, stored, distributed, administered, returned, and handled as required by the protocol during the whole process of the clinical trial, and are controlled and documented, and check any change in the doses and drug combination for each subject;
3) Confirm that each subject signs a written informed consent prior to the trial and the selected subjects' eligibility;
4) Confirm that the investigators receive the latest versions of the Investigators' Brochure, protocol, all necessary documents related to the clinical trial, and supplies for the trial, and implement these documents according to the requirements of the regulations;
5) Verify that all investigators have received trainings and written authorizations prior to their participation into the study;
6) Confirm that all data records and reports are correct and complete, and all entries into eCRF are correct and consistent with the raw data, verify that all medical reports, records and documents provided by the investigators are accurate, complete, timely, clear and legible, dated and numbered, and verify that any correction, addition, or deletion of data is correct, dated, and signed by the investigators;
7) Confirm that all adverse events are documented, and all serious adverse events are reported and documented within the specified period;
8) Ensure that the investigators keep necessary documents according to the requirements of GCP, and all records and documents of the clinical trial are updated in real time and kept in a proper manner;
9) Determine any deviation of the clinical trial from the clinical trial protocol, SOP, GCP and relevant regulations, communicate with the investigators in a timely manner, and take appropriate measures to prevent the recurrence of such deviation;
10) Verify that any withdrawal and failure of following-up of any enrolled subject has been explained in the eCRF;
11) After each visit for inspection, the clinical research associates should prepare a written report and deliver it to the Sponsor, and explain the corrective measure that has been taken or will be taken for any problem found during the inspection; record any failure of the investigators to carry out any follow-up, test or examination truthfully, and describe whether all errors or omissions have been corrected;
12) Assist the research sites and the Sponsor in preparing all registration documents and

submit to National Medical Products Administration (NMPA) after the completion of the clinical trial, and assist in the preparation for the site inspection of registration.

Refer to the section of "Research Team" for the list of units participating in the clinical trial.

**4.2 Site Management**

This clinical trial is classified as a single-center multiple sites clinical trial in China. The institute responsible for the clinical trial is Yunnan Province Center for Disease Control and Prevention, and the clinical trial sites include Center for Disease Control and Prevention (CDC) of Mile City, Qiubei County, Yanshan County, Kaiyuan City, and Gejiu City.

Yunnan Province CDC has the vaccination management function and a team of qualified investigators, and has professional departments. The center is responsible for designating the principal investigator for clinical trial management, clinical trial manger, quality auditor, an expert panel team for the serious adverse events and other personnel for the clinical trial. The principal investigator is responsible for interpreting the clinical study protocol, organizing trainings on GCP and SOP, and the coordinators and quality controllers should be responsible for management and quality control during the whole process of the clinical trial.

The centers for disease control and prevention designated as the clinical trial sites are affiliated CDCs that accept management/guidance of the provincial CDC and have the qualification for vaccination, which should participate in the clinical trial under the leadership of principal investigator of the clinical trial, designate site manager, coordinators, quality controllers, adverse event Ad-hoc panel, and related positions for the clinical trial. etc., carry out the vaccination, evaluation and following-up, and adverse events handling according to relevant requirements.

## 5. BACKGROUND AND PRINCIPLE

### 5.1 Disease Background

Rabies is a zoonotic disease caused by rabies virus, for which the morbidity is approximately 59,000 lives and causes the reduction of more than 3.7 million disability-adjusted life years (DALYs) annually. Once the symptoms of rabies (such as acute encephalitis) occur, it is always fatal. The first rabies case has been recorded more than 4,000 years ago. Rabies mainly occurred in those regions with poor medical conditions, and could be seen in both rural areas and cities.

Most rabies cases occurred in Africa and Asia. All mammals are susceptible to Rabies Virus (RABV). In those regions where rabies is prevalent, 99% of rabies cases were infected by sick dogs, and a small proportion of these cases were infected by wild animals (such as foxes, wolves, jackals, bats, raccoons, skunks, or mongooses). Large-scale vaccination for dogs can block the spread of rabies virus among dogs and thus reduce the transmission of rabies virus from dogs to humans or from dogs to other mammals, which serves as the main strategy for rabies prevention and control. This strategy is effective in Africa, Asia, Europe, and the Americas, where the degree of prevalence of rabies varies. As the incidence of dog-mediated rabies declined thanks to the effective prevention and control strategies, rabies cases infected by other animals, which were rare although, became increasingly prominent in some regions, such as the Americas. Wild carnivores and bats (carnivora and chiroptera) are natural hosts of rabies virus, and are more likely to transmit rabies virus than other wild animals. Transplantation with tissues and organs that have been infected with rabies virus can cause rabies infection, but such cases are extremely rare. Transmission of rabies virus between humans has never been confirmed.

Most rabies cases were infected by rabid dogs. The consequences of exposure to rabies virus depend on wound severity, the locations and number of bites, the type of rabies virus (genotype), and the timeliness of post-exposure prophylaxis. Without post-exposure prophylaxis, 55% of human rabies cases were caused by bites on the head by rabid animals; 22% of the cases were caused by bites in the upper limbs; 9% of the cases were caused by bites in the trunk; 12% of the cases were caused by bites in the lower limbs. The viral load in the saliva of a rabid dog changes with the progression of the disease, which has an impact on the risk of infection faced by humans if they are bitten by the dog.

There has been no report of any human case of rabies caused by consumption of raw meat infected with rabies virus, and no rabies virus has been detected in the milk of rabid cows. No rabies case infected due to the consumption of raw milk has been reported. In extremely rare cases, humans were infected with rabies virus when handling materials containing a high concentration of live rabies virus in laboratories, or due to the inhalation of aerosols containing virus particles, or exposure to rabies virus in bat caves containing a large amount of rabies virus.

Acute encephalitis is one of the clinical manifestations of rabies. Human rabies is divided into furious rabies and paralytic rabies, of which furious rabies is the most common type. These two types of manifestation are associated with specific anatomical sites for rabies virus in the central nervous system. The typical latency for human rabies cases is 1-3 months, but a latency of one year was also reported.

Since the 1950s, there have been three epidemics of rabies in China. The first epidemic

occurred in the mid-1950s, and the annual number of reported death cases was more than 1,900. The second epidemic occurred in the early 1980s. In 1981, there were 7,037 reported death cases caused by rabies nationwide, which was the highest number of death cases since the founding of the People's Republic of China. Throughout the 1980s, the number of reported death cases caused by rabies nationwide was over 4,000, with an average annual number of 5,537. The third epidemic occurred at the beginning of the 21st century, and the rabies epidemic became serious in a continuous and rapid way. The number of reported death cases nationwide in 2007 reached 3,300; in 2018, the total number of rabies cases nationwide was 422.

Rabies occurs throughout the year, and summer and autumn are the peak seasons for rabies in China (especially in August). In recent years, the distribution of rabies cases in China shows that 32% of the patients are children aged 14 and under, indicating that rabies is more harmful to children; 58% of the patients are 14-64 years old; and 10% of the patients are elderly people aged 65 and over.

The prevention of rabies depends on the awareness of rabies among susceptible populations to a large extent. The efforts to raise the awareness of rabies should include receiving rabies-related education, participating in activities organized by relevant agencies for the prevention of animal bites, and enhancing the sense of responsibility of dog owners and timely post-exposure disposal.

Based on the quantity of rabies vaccination in China, it is estimated that the annual number of people exposed to rabies virus in China exceeds 40 million. The surveillance on some provinces with a high incidence of rabies shows that more than 90% of the exposure seeking medical attention had Category II and Category III exposure, of which Category III exposure accounted for about 40%. About 10% of the people exposed to rabies virus failed to complete vaccination; only about 15% of people with Category III exposure received passive immunization biologics.

**5.2 Pathogen Background**

Rabies virus belongs to the genus Lyssavirus under the family Rhabdoviridae of the order Mononegavirales. It consists of some genetically related enveloped viruses and contains single-stranded, non-segmented, negative-sense RNA. The virus is like a bullet with a length of 200 nm and a width of 75 nm. The International Committee on Taxonomy of Viruses pointed out that as of 2017, a total of 14 species have been found, all of which belong to the genus Lyssavirus. The virus contains the following five structural proteins: virion transcriptase (L), glycoprotein (G), nucleoprotein (N), phosphoprotein (P), and matrix protein (M). Protein L, Protein N, and Protein P bind to the RNA of the virion with non-covalent bonds, and the

resulting ribonucleoprotein (RNP) complex forms a spirally coiled nucleocapsid structure in the virion. Protein G is a trimer (about 67KD), which is the main antigen that induces the production of virus-neutralizing antibodies (VNAs) and can induce the body to produce immunogenicity against fatal rabies virus infection. Protein N antigen is the main antigen stimulating T cells to produce cellular immunity. Protein N antigen is relatively stable, which rarely varies among virus strains and thus serves as an important basis for typing and grouping. Based on the difference in antigenicity, rabies virus is categorized into 4 serotypes. Serotype I: refers to the prototype strain of CVS, including viruses separated from mammals in most regions of the world, insectivorous bats in North America, and vampire bats in South America. Serotype II: refers to the prototype strain of Lagos-bat virus, which has been separated from bats in Nigeria. Serotype III: refers to the prototype strain of Mokola virus, which has been separated from hamsters in Nigeria. Serotype IV: refers to the prototype strain of Duvenhage virus, which has been separated from patients in South Africa.

**5.3 Product Background**

According to the recommendation of WHO Expert Consultation on Rabies, for anyone having Category III Exposure to rabies virus, the wound should be thoroughly cleaned and a passive immunization biologics, i.e., Human Rabies Immunoglobulin (HRIG) or Equine Rabies Antiserum (ERA), should be injected around the wound through infiltration injection in addition to the vaccine, in order to prevent rabies virus from entering the nerve tissues and get rapid protection. In addition, if anyone with severely impaired immunological functions is exposed to rabies virus (even if for Category II exposure), a passive immunization biologics should also be used in combination with the vaccine.

At present, passive immunization biologics for rabies around the world can be divided into three types: equine rabies immune globulin (ERIG), equine purified F(ab')2 fragment product and HRIG, of which the first one and the second one are usually called "ERA" in China. Equine purified F(ab')2 fragment and HRIG have been approved for marketing in China.

ERA is a heterologous protein, so it is more likely to cause severe allergic reactions (such as serum sickness, anaphylactic shock, etc.) after administration. Although some progress has been made in reducing its allergenicity (for example, some steps have been added to the process of ERIG, such as chromatographic purification and heat inactivation of viruses), some adverse reactions still may occur in those sensitive individuals due to the fact that the heterologous protein cannot be removed completely. Moreover, ERA has a short half-life in humans, so the required dose of injection is higher than that of HRIG, which increases the risks of adverse reactions. HRIG is an anti-rabies immunoglobulin (IgG) obtained from human plasma of those

people vaccinated with rabies vaccine through the process of protein separation with low-temperature ethanol or other approved separation and manufacturing processes. Since there is no risk of reactions caused by a heterologous protein, it has a lower adverse reaction rate. However, it must be continuously obtained from healthy people with strengthened immunization, so it is difficult to secure a stable source. In addition, it is characterized by a high price, a long production cycle, a long supply chain and the risk of untimely supply. What's more, people also have safety concerns about blood products. Nowadays, it is recognized internationally that it is necessary to replace blood-borne anti-rabies antibodies used in post-exposure prophylaxis with recombinant monoclonal antibodies. Genetically engineered products are characterized by a short production cycle, a sufficient production volume, flexibility, no human component, a relatively higher degree of safety, and a stable supply chain, which can greatly improve the accessibility of PEP after exposure to rabies virus and guarantee that the demand for clinical medication after exposure can be met.

### 5.4 Trial Design Principles

#### 5.4.1 Trial Design Principle and Control Substance Selection

Monoclonal antibodies (Mab) can be used in combination with rabies vaccine for post-exposure prophylaxis. Monoclonal antibodies have the advantages of batch consistency and large-scale production, which may provide a solution for the current shortage of RIG around the world. However, there are different dominant rabies virus strains in the United States and many other regions around the world, so a single target epitope may not cover all rabies virus strains. Therefore, a single monoclonal antibody generated through point mutation may result in the phenomenon of "immune escape" arising from loss of antibody binding in terms of selectivity. As a result, the efficacy of a mixture of several monoclonal antibodies with specificity and complementary functions, such as SYN023, will be superior to that of a single monoclonal antibody. WHO Expert Consultation on Rabies recommended in 2002 that HRIG or ERIG must be replaced by at least two or three non-overlapping monoclonal antibodies used in combination, in order to ensure safety and efficacy.

SYN023 has been developed by Synermore, which is a monoclonal antibody combination therapy containing two anti-rabies human monoclonal IgG1κ antibodies, CTB011 and CTB012. These two mAbs can bind to specific and non-overlapping antigenic epitopes of the rabies virus glycoprotein respectively. SYN023 can be used in combination with a rabies vaccine for post-exposure prophylaxis. It has been proven that SYN023 can neutralize more than 15 clinically dominant rabies virus strains from China and 35 dominant strains from North America and other regions around the world. In October 2015, SYN023 was qualified as an "Orphan Drug"

in the United States.

In summary, SYN023 has a broad-spectrum neutralizing activity against different strains of rabies virus in different regions, and can replace HRIG in PEP.

For specific considerations in protocol design and sample size consideration, refer to "Section 8 Study Design" and "Section 13.3 Sample Size Calculation".

### 5.4.2 The Basis for Dosage Determination

Based on the results of pre-clinical studies on pharmacodynamics, pharmacokinetics, and the in vivo and in vitro safety, the initial dose of SYN023 is 0.3 mg/kg. After the clinical study in the US and the bridging clinical study completed in China, 0.3 mg/kg was determined to be a reasonable dose for clinical application, with RVNA protection level reaching 100% within three days. It can confer the effective protection against rabies virus 14 days after PEP without affecting the efficacy of rabies vaccination.

## 5.5 Benefits/Potential Risks to Subjects

### 5.5.1 Known Potential Benefits and Risks

Subjects obtain potential benefits from the use of SYN023 or HRIG and the rabies vaccine, i.e., prophylactic of rabies virus.

The potential risks arising from the study drug and the vaccine in combination are the common adverse reactions arising from injection. Common adverse reactions of SYN023: pain, redness and swelling at the injection site, and systemic reactions such as headache, nausea, vomiting, and dizziness. Common adverse reactions of HRIG: swelling at the injection site, and fever, headache, nausea, vomiting, urticaria, etc. Common adverse reactions of the vaccine: pain, redness, swelling and induration at the injection site, and fever, fatigue, headache, dizziness, arthralgia, vomiting, abdominal pain, etc. The expected common adverse reactions are mostly mild and transient, which are generally self-healing; serious adverse reactions, such as allergies and neurological symptoms, are rarely seen. For detailed information about potential benefits/risks to subjects, refer to the informed consent forms and Investigators' Brochure.

### 5.5.2 Potential Risks and Benefits towards the subjects

Data from the pre-clinical studies and the Phase I and Phase II clinical studies show that SYN023 has favorable safety and efficacy. The purpose of this study is to evaluate the safety and efficacy of SYN023 on Category III rabies exposure subjects. Three quarters of the subjects in this study will be randomized in the study drug group and one quarter of the subjects will be randomized in the HRIG control group. Simultaneously, a China approved rabies vaccine will be vaccinated with the study drugs. Therefore, the subjects will benefit

from rabies prophylaxis. All subjects should voluntarily participate in the trial, otherwise they choose to receive rabies immunoglobulin and rabies vaccine at their own expense. During the course of the study, any subject can voluntarily withdraw from the study at any time.

During the study, the investigators will closely monitor the adverse reactions of the study drug. Any discomfort or adverse reaction of the subjects should be reported to investigators timely. If the investigator or the subject deems the adverse reactions intolerable, the subject may be withdrawn from the trial. The safety of the subject will be closely monitored and evaluated through stringent following-up.

## 6. PRODUCT PROPERTIES & PRE-CLINICAL STUDIES/LABORATORY EVALUATION

### 6.1 Product Properties

#### 6.1.1 Physical Properties

SYN023 is a mixture of two anti-rabies human monoclonal antibodies IgG1 κ CTB011 and CTB012 at a ratio of 1:1, which bind to specific and non-overlapping antigenic sites of rabies virus glycoprotein.

CTB011 and CTB012 were independently cultured in batches from SYN023 Chinese hamster ovary (CHO) cells in a bioreactor, and the harvested liquid was clarified and then purified. The resulting CTB011 and CTB012 bulks were separately filtered into disposable liquid storage bags through a filter and stored at -80 °C.

The finished SYN023 product is a mixture of 3.0 mg/mL CTB011 and 3.0 mg/mL CTB012 made at a ratio of 1:1. SYN023 is a sterile and preservative-free injection, and the excipient contains 25 mM histidine (3.879 mg/mL), 150 mM sodium chloride (8.766 mg/mL) and 0.02% polysorbate 80 (0.2 mg/mL) and has a pH of 6.0. Each bottle contains 2.15 mL of SYN023, or 6.45 mg of mAb. The vial was closed with a 13 mm bromobutyl rubber stopper, a 13 mm aluminum crimping cap and a polypropylene flip-open lid. The finished SYN023 product is a clear, colorless, particle-free and sterile liquid for injection.

#### 6.1.2 Pharmacological Properties

SYN023 is a mixture of two human monoclonal antibodies, CTB011 and CTB012, which can bind to two non-competitive epitopes on the rabies virus glycoprotein. SYN023 is used for post-exposure prophylaxis of people exposed to rabies virus during the unprotected stage after rabies vaccination. Table 1 lists the physical, chemical and biological properties of SYN023.

**Table 1 Physical, Chemical and Biological Properties of SYN023**

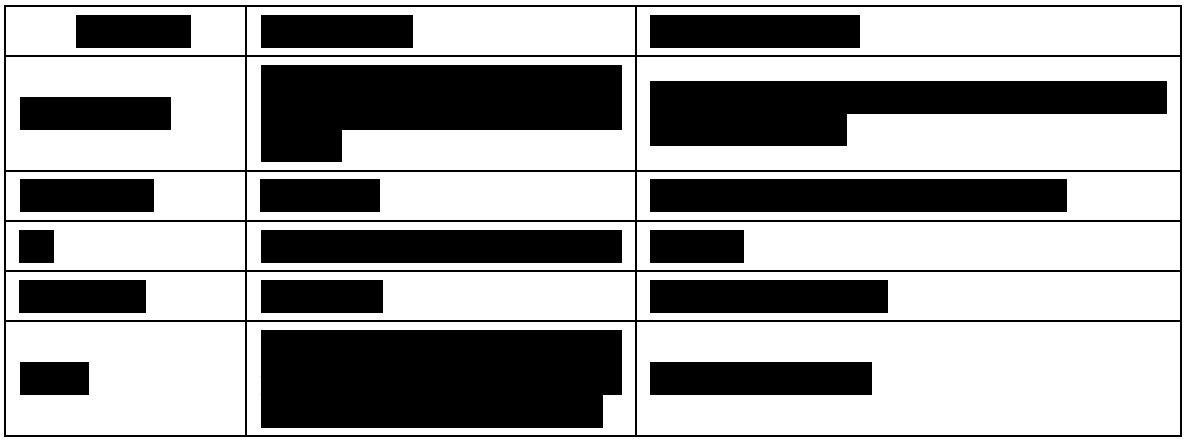
| Test Item | Analysis Method | Acceptance Criteria |
|---|---|---|
| Identification | Ion exchange chromatography (IEX-HPLC) | Consistent with the chromatogram of the reference product |
| General inspection | Appearance | Clear liquid |
| General inspection | pH | 5.8 - 6.2 |
| Safety | Osmolarity | 280 - 350 mOsmol/Kg |
| Identification and purity | Size exclusion chromatography (SEC-HPLC) | In terms of peak area, the main peak: > 95.0% |
| Identification and purity | Ion exchange chromatography (IEX-HPLC) | CTB011: The acid peak: ≤50.0%; the main peak: ≥45.0%<br>CTB012: The acid peak: ≤50.0%; the main peak: ≥45.0% |
| Purity | Insoluble particles | The number of particles with a size ≥ 10 μm in each vial should not be greater than 6000;<br>The number of particles with a size ≥ 25 μm in each vial should not be greater than 600; |
| Protein content | Ion exchange chromatography (IEX-HPLC) | 2.7-3.3 mg/mL |
| Content uniformity | Volumetric method | No less than the labeled amount. |
| Safety | Bacterial Endotoxin Test (LAL) | < 2.5 EU/mL |
| Safety | Sterility test | The growth shall be sterile. |
| Safety | Abnormal toxicity | All mice and guinea pigs should be alive and sound and gain weight, without any abnormalities. |
| Titer | RFFIT (Rapid Fluorescent Focus Inhibition Test) | 1492 ± 522 IU/mg |

Abbreviation: IU: IU; kg: Kg; mOsmol: mmol

### 6.1.3 Formulation Standards

The finished product of SYN023 is a mixture of CTB011 and CTB012 by equal mass, containing 3.0 mg/mL active ingredients for each. The excipients contain 25 mM histidine (3.879 mg/mL), 150 mM sodium chloride (8.766 mg/mL) and 0.02% polysorbate 80 (0.2 mg/mL), with a PH of 6.0. Each bottle contains 2.15 mL of SYN023, or 6.45 mg of mAb. Release standards for finished product of SYN023 are listed in Table 2.

**Table 2 Release Standards for Finished Product of SYN023**



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| [redacted] | [redacted] | [redacted] |
| [redacted] Titer of anti-rabies virus neutralizing antibody | [redacted] | [redacted] |

### 6.1.4 Storage Conditions

SYN023 shall be transported at 2–8°C with a continuous temperature monitoring device. Any damage or temperature variation shall be reported to the Sponsor in time. Bottled final product of SYN023 shall be stored at 2–8°C upright.

## 6.2 Preclinical Study/Laboratory Evaluation

Non-clinical pharmacological evaluation, non-clinical pharmacokinetics evaluation, and toxicological evaluation are detailed in Investigator's Brochure.

### 6.2.1 Safety Evaluation

#### 6.2.1.1 Toxicity Study

SYN023 safety studies included toxicity studies in rats intramuscularly injected with SYN023, repeated dose studies in rats that met GLP requirements, toxicological and toxicokinetics studies on cynomolgus monkeys with repeated doses of SYN023 by intramuscular injection, and in vitro studies of latent cytotoxicity, as well as tests of ADCC and DCD activity of SYN023 and its component antibodies in BSR cells of healthy and rabies-infected hamsters. Meanwhile, a tissue cross-reaction test was also conducted to explore the possibility of SYN023's binding to or interacting with normal human tissues.

##### 6.2.1.1.1 Repeated Dose Studies

#### 6.2.1.1.1.1 Preclincial Study on Toxicology in Rats Given Repeated Doses of SYN023 by Intramuscular Injection

The study intramuscularly injected multiple-dosages of SYN023 in male and female Sprague-Dawley rats. The rats were intramuscular injected normal saline or SYN023 weekly in three dosage groups (1, 3, 10 mg/kg) for two consecutive weeks (on Study Day 1 and Day 8).

Throughout the study, no rats were dead or moribund in Group 1, Group 2, Group 3, and Group 4. Compared with rats in the control group, the rats that received 1, 3, and 10 mg/kg of SYN023 showed no significant abnormalities in terms of weight, food consumption, clinicopathologic features, organ weight and organ-to-body weight ratio. On Study Day 15, no general abnormalities were observed in all rats.

In short, no significant clinical abnormalities, changes in clinicopathologic parameters, organ weight, or general pathological features were observed in both male and female rats intramuscularly injected with 1, 3 or 10 mg/kg SYN023 once a week for two consecutive weeks (twice in total) under the conditions of the study.

#### 6.2.1.1.1.2 Toxicological and Toxicokinetic Study on Rats Given Repeated Doses of SYN023 by Intramuscular Injection

The toxicological and toxicokinetic study was conducted in SD rats given repeated doses (three doses) of SYN023 by intramuscular injection. The rats were given 0.9% normal saline or 1, 3, 10 mg/kg SYN023 once a week for three consecutive weeks, and observed for three days or six weeks afterwards.

Throughout the study, no rats given with 1, 3, 10mg/kg SYN023 were dead or moribund. Compared with rats in the control group, the rats given with 1, 3, and 10 mg/kg of SYN023 showed no significant abnormalities in toxicological indicators, including weight, body temperature, food consumption, clinicopathological features, ophthalmic examination, urine analysis, T lymphocyte subsets, organ weight or organ-to-body weight ratio. And no obvious abnormal changes were observed on the injection sites. No SYN023-related changes were observed at the macro or micro level in Sprague Dawley rats during the 3-week administration of SYN023 at 10mg/kg/day, or during the subsequent 6-week recovery period.

During the study period, 3/18, 4/18, 4/18 of rats in Group 6, Group 7, and Group 8 given the drug at 1, 3 and 10 mg/kg developed anti-CTB011 antibodies, respectively, and 3/18, 4/18, 4/18 of rats in the above three groups developed anti-CTB012 antibodies, respectively. Neutralizing activity of anti-CTB011 and anti-CTB012 antibody was also observed in these rats.

The NOAEL of male and female rats was approximately equal to or greater than 10 mg/kg. On Study Day 15, $AUC_{0\text{-}168h}$ and $C_{max}$ of CTB011 in female rats were 10881.06 h•μg /mL and 79.42 μg/mL, respectively, and those of male rats were 9172.50 h•μg/mL and 67.37 μg/m, respectively; $AUC_{0\text{-}168h}$ and $C_{max}$ of CTB012 in female rats' were 12001.99 h•μg /mL and 94.24 μg/mL, respectively, and those of male rats were 9504.10 h•μg/mL and 70.38 μg/mL, respectively.

**6.2.1.1.1.3 Toxicological and Toxicokinetic Study on Cynomolgus Monkeys Given Repeated Doses of SYN023 by Intramuscular Injection**

The toxicological and toxicokinetic study on cynomolgus monkeys, in which the monkeys were given with SYN023 for three weeks and then given a recovery period of six weeks, was conducted together with the immunotoxicity test and safety pharmacology test. 30 cynomolgus monkeys were randomly divided into three groups by weight: solvent control group, low-dose SYN023 group and high-dose SYN023 group, with each group consisting of 10 monkeys (female: male = 1: 1). The monkeys were administrated with SYN023 once a week for three consecutive weeks, and then given a recovery period of six weeks. The low-dose SYN023 group and high-dose SYN023 group were given the drug at 2 mg/kg and 10 mg/kg, respectively, with a volume of administration of 4 mL/kg, and corresponding concentration levels of 0.5 mg/mL and 2.5 mg/mL, respectively. The solvent control group was given sodium chloride injection.

No abnormal changes in body weight, food consumption, food intake, body temperature, ECG system, respiratory state, blood pressure, ophthalmic examination, coagulation index, hematological index, serum chemistry index, urine index, immunotoxicity index, bone marrow examination, histopathological examination, etc., related to the test drug were observed. No obvious irritations were observed at the injection sites.

According to the toxicokinetic study on cynomolgus monkeys, there was no gender difference in systemic exposure ($AUC_{last}$ and $C_{max}$) of CTB011 and CTB012 in female and male cynomolgus monkeys in each group. The exposure of CTB011 in the low-dose group was significantly accumulated and that in the high-dose group showed a trend of accumulation; the exposure of CTB012 in the low-dose group and high-dose group was significantly accumulated. After administration, the exposure ($AUC_{last}$ and $C_{max}$) of CTB011 and CTB012 increased in proportion to dose.

According to the immunotoxicity study in cynomolgus monkeys, SYN023 had no obvious impact on the immune system.

**6.2.1.1.2 Other Toxicity Studies**

In vitro cytotoxicity, ADCC and CDC of SYN023 and its component antibodies in healthy and rabies-infected BSR cells were evaluated.

In addition to in vivo studies, in vitro studies of SYN023 and its component antibodies were also conducted to evaluate the potential cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC), and complement-dependent cytotoxicity (CDC). The in vitro studies were conducted in BRS cells from healthy and rabies-infected young hamsters.

At 40 μg/mL, CTB011 and CTB012 antibodies and SYN023 did not show any significant cytotoxicity in the healthy or rabies-infected BSR cells, nor did any antibody or SYN023 antibody mixture in the healthy or infected cells produce observable ADCC activity.

Instead, both antibodies and SYN023 antibody mixture produced dose-dependent CDC activity in the rabies-infected cells, but not in healthy BSR cells, suggesting that these antibodies could target at rabies-infected cells and kill them through CDC's dependent mechanism. CDC activity was not observed in any of the healthy cells, which was consistent with our previous in vivo findings, and no adverse effects were observed in the healthy tissues or animals.

Finally, the possibility of SYN023's binding or interacting with normal and frozen human tissues was also tested. Compared with the results obtained in each control group, SYN023 or its component antibody, CTB011 or CTB012, was not specifically bound to these human tissues, indicating that SYN023 and individual CTB011 or CTB012 antibody can specifically bind to the BSR cells infected with rabies, but not to normal human tissues.

### 6.2.2 Stability

Real-time stability of GMP batch of SYN023 samples is still under test. Long-term stability data support that the drug can be stored for 12 months at 5°C ± 3°C.

## 6.3 CLINICAL EVALUATIONS

### 6.3.1 SYN023-001 Clinical Trial

| **Abstract** | |
|---|---|
| **Items** | **Descriptions** |
| Title | A Phase-Ia, Single-Center, Open Study on the Safety, Pharmacokinetics, and Pharmacodynamics of Dose-Increasing SYN023 in Healthy Subjects Given SYN023 by Intramuscular Injection. |
| Address | PPD Clinical Research Center, Austin, TX, USA |
| Number of subjects | 15 |
| Gender | Males & females |
| Dose groups | 0.3 mg/kg; 1.0 mg/kg; 2.0 mg/kg |
| Formula | 10 mg/mL liquid |

| Abstract | |
|---|---|
| **Items** | **Descriptions** |
| Control | Not applicable |
| Volume of administration | Variable |
| Administration route | Intramuscular injection |
| Administration frequency | Single dose |
| Follow-up period | 84 days |
| Indicators | RVNA, PK specimens (on study days 0, 1, 3, 7, 14, 28, 35, 84): $C_{max}$, $T_{max}$, $AUC_{0-48}$, $AUC_{0-\infty}$, $t_{1/2}$, $\lambda_{½}$, $V_c$, CL; anti-CTB011 and anti-CTB012 antibodies, AE |
| Research status | Completed |
| Conclusion | **Efficacy/pharmacodynamics evaluation:**<br>There was no clinical endpoint efficacy evaluation. The efficacy evaluation was based on the pharmacodynamics evaluation of RVNA with RFFIT. On the first day of administration, the RVNA of all SYN023 groups achieved the protective level. The 0.3 mg/mL group was the minimum dose group, in which the RVNA of subjects had maintained positive for more than 35 days. The RVNA of subjects in higher dose groups had stayed at the protective level for more than 84 days. The RVNA levels of different dose groups were approximately linear.<br>**Pharmacokinetics evaluation:**<br>The PK concentration levels of SYN023 components, CTB011 and CTB012, were measured separately, which reached the peaks within 4–7 days, and the half-life observed was consistent with that of typical human immunoglobulin G1.<br>**Anti-SYN023 antibody:**<br>Four subjects developed anti-CTB011 antibodies before SYN023 injection. The other subjects were found of transient production of anti-CTB011 antibodies. Anti-CTB011 antibodies did not seem to be associated with adverse events. There were no anti-CTB012 antibodies.<br>**Conclusions on safety:**<br>Only one of the 7 AEs reported, muscle cramp, was deemed to be related to the study. All AEs in the three dose groups were mild. No death or SAE occurred in the study, so the safety of the drug was acceptable. SYN023 at 0.3 mg/kg presented favorable pharmacodynamic and pharmacokinetic parameters and the conclusions on safety could provide basis and support for the subsequent clinical studies. |

### 6.3.2 SYN023-003 Clinical Trial

| Abstract | |
|---|---|
| **Items** | **Descriptions** |
| Title | A Phase-Ib Study on The Safety, Pharmacokinetic and Pharmacodynamic Characteristics of SYN023 in Healthy Subjects Given SYN023 by Intramuscular Injection and Subcutaneous Injection |

| **Abstract** | |
|---|---|
| **Items** | **Descriptions** |
| Address | inVentiv Health Inc., 1951 NW 7th Avenue, Suite 450, Miami, Florida, USA, 33136 |
| Number of subjects | 30 |
| Gender | Males & females |
| Dose groups | Intramuscular injection at 0.3 mg/kg<br>Subcutaneous injection at 0.3 mg/kg |
| Formula | 10 mg/mL liquid |
| Control | Not applicable |
| Volume of injection | Adjustable |
| Administration route | Intramuscular injection or subcutaneous injection |
| Administration frequency | Single dose |
| Follow-up period | 84 days |
| Indicators | RVNA, PK specimens (on study days 0, 1, 3, 7, 14, 28, 35, 84): $C_{max}$, $T_{max}$, $AUC_{0-48}$, $AUC_{0-\infty}$, $t_{1/2}$, $\lambda_{1/2}$, $V_c$, CL, anti-CTB011 and anti-CTB012 antibodies, AE |
| Research status | Completed |
| Conclusion | **Efficacy/pharmacodynamics evaluation:**<br>The efficacy evaluation was performed through the pharmacodynamics evaluation of RVNA with RFFIT. The RVNA level of subjects given SYN023 in both ways reached protective level (RVNA≥0.5 IU/mL) in three days and maintained positive for more than 42 consecutive days. The concentration of RVNA in subjects given the drug by subcutaneous injection was higher than that of subjects given the drug by intramuscular injection.<br>**Pharmacokinetics evaluation:**<br>The concentration levels of both CTB011 and CTB012 reached peak levels in the same time range. The concentration levels of CTB011 and CTB012 (on day 3 and day 6) given by subcutaneous injection might reach peak levels slightly faster than those of CTB011 and CTB012 given by intramuscular injection. The half-life of CTB011 was 21–23 days, while that of CTB012 was 26–29 days, which was within the typical human immunoglobulin range.<br>**Anti-SYN023 antibody:**<br>Eight subjects developed anti-CTB011 antibodies before SYN023 injection. Other subjects were found of transient production of anti-CTB011 antibodies. Two subjects developed anti-CTB012 antibodies. Anti-CTB011 antibodies may be irrelevant to AEs.<br>**Conclusions on safety:**<br>Eight of the 20 AEs reported headache. SYN023 at 0.3 mg/kg presented ideal pharmacodynamic and pharmacokinetic characteristics under both methods of administration. There was no death or SAE. The safety of the drug was acceptable. All AEs were mild and the AEs related to the study drug were nonspecific symptoms, such as headache and reactions at the injection sites. |

### 6.3.3 SYN023-002 Clinical Trial

| **Abstract** | |
|---|---|
| **Items** | **Description** |
| Title | A Phase II, Randomized, Blinded, Single-Dose Study on the Safety and Pharmacokinetic and Pharmacodynamic Characteristics of Rabies Vaccine and SYN023 in Healthy Subjects Receiving Rabies Vaccines. |
| Address | inVentiv Health Inc., 1951 NW 7th Avenue, Suite 450, Miami, Florida, USA, 33136 |
| Number of subjects | 164 |
| Gender | Males & females |
| Dose | Rabies vaccine (Imovax)+human rabies immune globulin (HRIG)<br>Rabies vaccine (RabAvert)+human rabies immune globulin (HRIG)<br>Rabies vaccine (Imovax)+SYN023<br>Rabies vaccine (RabAvert)+SYN023 |
| Formula | 10 mg/mL liquid |
| Control drug | HRIG |
| Volume of administration | To be adjusted according to weight |
| Administration route | Intramuscular injection |
| Administration frequency | Single dose |
| Follow-up period | 112 days |
| Indicators | AEs, anti-CTB011 and anti-CTB012 antibody, PK specimens (at 0.1, 0.25, 0.5, 0.75, 1.0, 1.5, 2, 3, 4, 6, 12, 24 and 48 h): $C_{max}$, $T_{max}$, $AUC_{0-48}$, $AUC_{0-\infty}$, $t_{1/2}$, $\lambda_{z}$, $V_c$, CL. |
| Research status | Completed |
| Conclusion | **Efficacy/pharmacodynamics evaluation:**<br>The generally accepted pharmacodynamic surrogate of vaccine protection level is RVNA≥0.5 IU/mL. The RNVA levels of all subjects in the HRIG and SYN023 group reached the protection level. In the first week of post-exposure prophylaxis (PEP), the RNVA level of the SYN023 group reached the protection level faster than that of the HRIG group. In the first week, the RVNA peak concentration of the SYN023 group was higher than that of the HRIG group. Because the immune response of rabies vaccine could provide continuous immune protection, HRIG shall be used together with rabies vaccine. On the 14th day after injection of SYN023 and HRIG, the activity of RVNA of the SYN023 group reached the peak and then decreased, which was still much higher than the antibody protection level. Both HRIG and SYN023 seemed to be compatible with both licensed rabies vaccines in post exposure prophylaxis.<br>**Pharmacokinetic evaluation:**<br>The pharmacokinetic analysis of SYN023 components was similar to the previous two phase-I clinical studies. The concentration of CTB011 reached the peak (about 650 ng/mL) in about three days. The concentration of CTB012 reached the peak (about 920 ng/mL) in about seven days. The half-life periods of the two groups were within the |

| Abstract | |
|---|---|
| **Items** | **Description** |
| | range of 19–23 days, which were within the typical human immunoglobulin range.<br>**Anti-SYN023 antibody:**<br>In the SYN023 group, 20% of the subjects developed anti-CTB011 antibodies, and about 3% of the subjects developed anti-CTB012 antibodies. The presence of the antibody had no effect on pharmacokinetics and AE.<br>**Conclusions on safety:**<br>There were altogether 255 AEs, in which 177 AEs were present in the SYN023 group, and 37 AEs were identified to be related to the study drug. The most common drug-related AEs were headache and reaction at the injection site. Five AEs were identified as severe, including fracture, elevated protein kinase level, and elevated troponin level. One case of severe elevation of the protein kinase level was identified to be related to SYN023 and others were related to HRIG. No death occurred in the study. One SAE was identified to be irrelevant to the study drug. The subject had an elevated troponin level before withdrawal from the study and was hospitalized for treatment, so it was identified to be SAE, which was attributed to moving house. The safety of SYN023 in healthy subjects was acceptable.<br>As a mixture of anti-rabies monoclonal antibody that could be rapidly produced, SYN023 had desirable safety, which if used together with rabies vaccine produced in the United States, could be used for rabies PEP. |

### 6.3.4 SYN023-005 Clinical Trial

| Abstract | |
|---|---|
| **Items** | **Description** |
| Title | A Phase I, Single-Center, Parallel and Open Bridging Clinical Trial to Evaluate The Safety, Pharmacokinetics and Pharmacodynamics of SYN023 in Healthy Subjects Given a Single Intramuscular Injection of SYN023 or Given SYN023 and Rabies Vaccine |
| Address | Phase I Research Center, First Hospital of Jilin University, Changchun, Jilin Province, China |
| Number of subjects | 33 |
| Gender | Males & females |
| Dose | Group A: SYN023 0.3 mg/kg<br>Group B: SYN023 0.3 mg/kg + freeze-dried rabies vaccines for human use (Vero cells, Liaoning Cheng Da Co., Ltd) |
| Formula | The finished product of SYN023 is a mixture of CTB011 and CTB012 by equal quantity, containing 3.0 mg/mL active ingredients in both. The excipient buffer contains 25 mM histidine (3.879 mg/mL),150 mM sodium chloride (8.766 mg/mL) and 0.02% polysorbate 80 (0.2 mg/mL), with a PH of 6.0. Each bottle contains 2.15 mL of SYN023, or 6.45 mg of mAb. |
| Control | Contrast of Group A (SYN023) and Group B (SYN023+rabies vaccine) |
| Volume of administration | To be adjusted according to weight of the subjects |

<table>
<tr><th colspan="2">Abstract</th></tr>
<tr><th>Items</th><th>Description</th></tr>
<tr><td>Administration route</td><td>Intramuscular injection</td></tr>
<tr><td>Administration frequency</td><td>Single dose</td></tr>
<tr><td>Follow-up period</td><td>85 days, including 8-day in hospital observation after administration.</td></tr>
<tr><td>Indicators</td><td>Safety, pharmacokinetics, anti-drug antibody</td></tr>
<tr><td>Research status</td><td>Completed</td></tr>
<tr><td>Conclusion</td><td>
Efficacy/pharmacodynamics evaluation:<br>
The activity of RVNA of Group A (SYN023) reached concentration peak on Study Day 7 after administration, 4.55±1.55 IU/mL; the antibody protection level (RVNA≥ 0.5 IU/mL) maintained at 100% from 48h to Study Day 42 after administration.<br>
The activity of RVNA of Group B (SYN023+rabies vaccine) reached concentration peak on Study Day 14 after administration, which was strong positive with an activity value of 53.27±52.66 IU/mL; the antibody protection level maintained at 100% from 48h to Study Day 84 after administration.<br>
Although Chinese and American subjects differed in serological protection from SYN023, they had similar profiles in pharmacodynamic characteristics as suggested by pharmacodynamic data.<br>
Pharmacokinetics evaluation:<br>
Both Chinese and American subjects presented similar dose-effect relationship and PK pattern. Although there were some differences in the PK of Chinese and American subjects, the safety and tolerance of drugs were not affected.<br>
PK characteristics of CTB-011 and CTB-012 are described as follows:
<table>
<tr><th rowspan="2">Parameters</th><th rowspan="2">Statistics</th><th colspan="2">Group A (SYN023)</th><th colspan="2">Group B (SYN023+rabies vaccine)</th></tr>
<tr><th>CTB011</th><th>CTB012</th><th>CTB011</th><th>CTB012</th></tr>
<tr><td>$AUC_{0-t}$ (h*ng/mL)</td><td>Mean (SD)</td><td>690713.69 (91433.40)</td><td>468955.56 (129362.11)</td><td>779026.35 (138435.66)</td><td>487821.52 (156758.07)</td></tr>
<tr><td>$AUC_{0-\infty}$ (h*ng/mL)</td><td>Mean (SD)</td><td>774711.08 (111041.26)</td><td>507604.98 (122741.74)</td><td>872700.78 (176114.53)</td><td>565246.72 (141633.10)</td></tr>
<tr><td>$C_{max}$ (ng/mL)</td><td>Mean (SD)</td><td>730.48 (145.74)</td><td>614.83 (186.73)</td><td>784.77 (230.46)</td><td>613.17 (132.85)</td></tr>
<tr><td>$T_{max}$(h)</td><td>Median （Min, Max）</td><td>252.33 (72.00,336.67)</td><td>168.00 (120.00,336.67)</td><td>167.50 (48.00,335.53)</td><td>167.50 (48.00,335.53)</td></tr>
<tr><td>$t_{1/2}$(h)</td><td>Mean (SD)</td><td>572.14 (85.87)</td><td>333.23 (34.19)</td><td>577.40 (114.27)</td><td>424.12(152.69)</td></tr>
<tr><td>CL/f(mL/h)</td><td>Mean (SD)</td><td>24.55 (4.82)</td><td>39.04 (12.52)</td><td>22.96 (5.29)</td><td>35.78 (8.28)</td></tr>
<tr><td>Kel(1/h)</td><td>Mean (SD)</td><td>$1.24\times10^{-3}$ ($2.29\times10^{-4}$)</td><td>$2.10\times10^{-3}$ ($2.13\times10^{-4}$)</td><td>$1.24\times10^{-3}$ ($2.40\times10^{-4}$)</td><td>$1.80\times10^{-3}$ ($5.34\times10^{-4}$)</td></tr>
</table>
Anti-SYN023 antibody:<br>
4.2% of the subjects in Group B developed anti-SYN023 antibodies before administration, and no new ADA was produced after administration. No anti-SYN023 antibody was detected in CTB011 and CTB012 of Group A. One subject in Group B developed anti-CTB011 antibodies and two subjects developed anti-CTB012 antibodies before administration. The CTB012 antibodies of both subjects turned negative after administration, and turned positive 36 days and 64 days after administration, respectively, and maintained ADA-positive afterwards. Antigenicity of the two monoclonal antibody components of SYN023 was not strong by referring to the ADA results of American clinical studies.
</td></tr>
</table>

| Abstract | |
|---|---|
| **Items** | **Description** |
| | **Safety:**<br>Both SYN023 (0.3mg/kg) alone and SYN023 (0.3mg/kg) + rabies vaccine PEP were quite safe for the Chinese subjects. No SAE, or AE of Grade-3 (CTCAE5.0) or above that were related to the study drug occurred. No death occurred.<br>Five subjects (62.5%) in Group A reported fourteen AEs, and AEs with a relatively high incidence (incidence ≥ 25%) were elevated alanine aminotransferase, elevated aspartate aminotransferase, elevated blood creatinine, and hypertriglyceridemia. Three subjects (37.5%) in Group A reported four AEs that were related to the study drug, including elevated alanine aminotransferase, elevated aspartate aminotransferase, hypertriglyceridemia and anemia, each with an incidence of 12.5%. One subject (12.5%) experienced two Grade-3 AEs (nephrolithiasis and hydronephrosis) due to recurrence of kidney stones, which was identified to be irrelevant to the study drug, and recovered after lithotripsy treatment, and then dropped out of the test; two subjects (25.0%) experienced three Grade-2 AEs, including one case of hypertriglyceridemia that might be related to the drug, which was an unintended adverse reaction; the remaining AEs were Grade-1 events.<br>21 subjects (87.5%) in Group B reported 76 AEs, and AEs with a relatively high incidence (incidence ≥ 25%) was decreased white blood cell count. 13 subjects (54.2%) in Group B reported 30 AEs that were related to the study drug, and AEs with a relatively high incidence (incidence ≥ 12.5%) were decreased neutrophil count, decreased leukocyte count and back pains. Two subjects (8.3%) experienced two Grade-3 or higher-grade AEs (hypertriglyceridemia and increased creatine phosphokinase), which were identified to be irrelevant to the study drug, and recovered without any treatment; seven subjects (29.2%) experienced 15 Grade-2 AEs; the remaining events were Grade-1 AEs; four subjects (16.7%) reported six unintended adverse reactions.<br>The incidence of AEs in Group B was higher than that in Group A, which might be related to the administration of the rabies vaccine.<br>No death occurred in the Chinese and American studies; one SAE occurred in the American study, which was not related to the study drug based on evaluation, and no SAE occurred in the Chinese study. There were four and three Grade-3 and higher-grade AEs in the Chinese study and American study, respectively, which were identified to be irrelevant to the study drug; there were no anemia, acute injection reactions and other unusual AEs. In terms of drug-related AEs, no headache, pains at the injection site and other reactions that were common in the American study were reported in the Chinese study, but the Chinese study showed higher incidences of decreased neutrophil count and leukocyte count than the American study. |

### 6.3.5 SYN023-004 Clinical Trial

This study is a randomized blinded phase-IIb clinical trial on the effect of rabies vaccine+SYN023 and rabies vaccine+HRIG in people aged 18 years and over and exposed to rabies to different degrees. Intending to recruit 448 subjects, this study has completed the enrollment and patients are in the follow-up status.

# 7. STUDY ENDPOINTS

## 7.1 Primary Endpoints

- GMC of RVNA on Day 8 after administration.
- The incidence and survival rate of rabies in subjects within 99 days and 1 year after administration.

## 7.2 Secondary Endpoints

- The protection level (percentage of RVNA concentration ≥0.5 IU/mL) and GMC of RVNA on Study Days 4, 8, 15, 43, 99, 183, and 365 after administration;
- AUEC of RVNA GMC from Study Day 1 to Day 15 after administration ($AUEC_{1-15}$);

## 7.3 Safety Endpoints

- All AEs regardless of related or un-related with IMPs within 30 minutes post administration will be collected ;
- Injection/vaccination sites (local)'s AE and (Systemic) adverse events occurring at sites other than the injection/vaccination sites within 1~8 days post administration;
- All AEs related or unrelated to the study drug occurring within 1~43 days post administration;
- Grade 3 or higher AEs occurring within 1~43 days post administration;
- All SAEs related or unrelated to the study drug occurring during the study;
- Pregnancy events occurring within 6 months after administration (pregnancy status and outcome);
- AEs/SAEs leading to withdrawal.

# 8. TRIAL DESIGN

## 8.1 Overall Design

A randomized, blinded and controlled design is adopted in this clinical trial.

### 8.1.1 Sample Size and Grouping

In this study, 1000 subjects aged 18 and over who had Grade 3 exposure to rabies virus were intended to be enrolled, and randomly assigned to the experimental group and the control group (3:1). Both groups were immunized according to PEP procedures for rabies. Specific sample size and distribution of rabies vaccines are described as follows:

| **Group** | **Sample Size** | **Study Drug** | **Administration Method & Dosage** | **Time of Injection** |
|---|---|---|---|---|
| Experimental Group | 750 | SYN023 | 0.3 mg/kg, wound infiltration injection* | Study Day 1 |

| | | | | |
|---|---|---|---|---|
| | | Rabies vaccine for humans | 0.5 mL, intramuscular injection into the deltoid muscle | Study Days 1, 4, 8, 15, 29 (Essen Scheme) |
| Control Group | 250 | HRIG | 20 IU/kg, wound infiltration injection* | Day 1 |
| | | Rabies vaccine for humans | 0.5 mL, intramuscular injection into the deltoid muscle | Study Days 1, 4, 8, 15, 29 (Essen Scheme) |

*: If the drug isn't used up after infiltration injection for all wounds, the remaining amount should be injected into the muscles far away from the vaccine injection sites (if a wound is located above the waist, the remaining amount should be injected into the back muscles on the side where the wound is located; if a wound is located below the waist, the remaining amount should be injected into the lateral muscles in the middle thigh on the side where the wound is located).

### 8.1.2 Study Drug's Administration

All subjects were given SYN023 or HRIG by infiltration injection at the wound site, and the first dose of freeze-dried rabies vaccine for human use (Vero cells) was intramuscularly injected at the deltoid of upper arm on Study Day 1, followed by dosing on Study Days 4, 8, 15 and 29.

Note: If the drug isn't used up after infiltration injection for all wounds, the remaining amount should be injected into the muscles far away from the vaccine injection sites (if a wound is located above the waist, the remaining amount should be injected into the back muscles on the side where the wound is located; if a wound is located below the waist, the remaining amount should be injected into the lateral muscles in the middle thigh on the side where the wound is located).

### 8.1.3 Efficacy Evaluations

3.0 mL of venous blood should be sampled 8 times from each subject prior to administration and on Days 4, 8, 15, 43, 99, 183, and 365 after administration respectively for the evaluation of RVNA levels. Relevant information should be collected from the subjects through follow-ups, such as occurrence of rabies and survival conditions.

RVNA should be tested for all blood samples through rapid fluorescence focus inhibition test (RFFIT).

### 8.1.4 Safety Evaluations

All solicited adverse events should be collected within 1~8 days post administration; all adverse events occurring within 1~43 days post administration should be collected, and all pregnant events occurring within 6 months post administration and all SAE during the study period should be collected.

## 8.2 Randomization & Blinding Methods

### 8.2.1 Randomization

In this trial, the block randomization method is adopted. After providing informed

consents, the enrolled subjects should be randomly assigned to the SYN023 group (the study drug group) or the HRIG group (the control drug group) at a ratio of 3:1, with the site as a stratification factor. Each subject should be injected with the corresponding drug based on the same procedures and then with the rabies vaccine.

In this study, a web based central randomization system is used to carry out random grouping for all subjects. The randomized blinded codes refer to the list of randomly assigned subjects and the list of randomly assigned study drugs (blinded codes) generated by an independent non-blinded randomization statistician from the statistical agency with the SAS software (version 9.4 or above) according to the protocol. The list of randomly assigned subjects contains the site number, random number (namely study number) and the study drug group corresponding to the random ID number of each subject (the study drugs herein generally refer to the study drug SYN023 and the control drug HRIG). The list of randomly assigned study drugs contains the random drug number and the study drug corresponding to the random drug number. Non-blinded database designers should upload the list of randomly assigned subjects and the list of randomly assigned study drugs (blinded codes) to the IWRS and complete the automatic interfacing setup for the interactive net response system, IWRS, and the EDC system, the Medidata Blance and Rave. After system setup, the investigators or other qualified personnel designated by the investigators should create subject information in the EDC and assign a random number for each eligible subject with the IWRS based on the study site after confirming that the subject's eligibility for enrollment. After the completion of random assignment of the subjects, the system will automatically assign the drug number in each visit for drug administration according to the corresponding drug group. Relevant investigators on each study site should provide treatment to each subject in accordance with the drug number assigned by the system. The entire randomization process should be completed in the EDC and IWRS, and the authority of users is strictly controlled in both systems to ensure the maintenance of blindness during the study. If a randomly assigned subject withdraws from/drops out of the clinical trial for any reason, regardless of whether the subject has been given any study drug, his/her random number cannot be reassigned to another subject.

### 8.2.2 Blinding

In order to reduce/avoid bias in operations, a double-blinded design will be adopted in this study. The randomization statistician and other personnel responsible for blinding should perform blinding for the drugs, in which the drugs used in this study should be packaged with same boxes and sealed up, in order to make sure that there is no difference in the packages of the study drug and the control drug. Therefore, one cannot figure out the drug given to any subject based on the package only, thereby ensuring blindness of the drugs used in the study. In

this study, personnel responsible for non-blinded drug injection and drug administration are arranged. Except for these personnel, anyone cannot unseal and get access to any study drug, and any subject cannot observe the size of the drug vial. In addition, the syringes should be appropriately masked so as to ensure that a subject cannot observe the color and dosage of the study drug, and thus cannot figure out the drug given to him/her based on its color or the size or appearance of the vial. In this way, the blindness of the drugs used in this study can be ensured.

Blinding for drugs should be carried out by the randomization statistician and other personnel who will not be involved in the implementation of the clinical trial. Under the guidance of the randomization statistician, blinding operators attach the printed labels with numbers to the outer packages of the study drug/control drug according to the blinded codes and seal the packages with sealing stickers.

After the completion of blinding for drugs, the blinded codes shall be sealed and kept by the randomization statistician. The entire blinding process must be documented. The personnel responsible for blinding must not participate in other relevant works during this clinical trial, and must not disclose the blinded codes to any person participating in this clinical trial.

**8.2.3 Maintenance of Blindness**

The dosage of the study drug is different from that of the control drug (the dosage of the study drug is 0.1 mL/kg; the dosage of the control drug is 0.2 mL/kg), the "blindness" in this trial applies to the subjects, observers, investigators and laboratory testers.

1) The package must be kept sealing before use; otherwise the drug inside the package will be deemed to be used drug.
2) The personnel responsible for drug injection should prepare drugs prior to drug injection. Other personnel are not allowed to be present when these works are being done. After the completion of drug preparation, the subjects should be guided by specific triage staff to the vaccination rooms one by one for vaccination. One vaccination room can only accommodate one subject for drug/vaccine injection each time, and the syringe should be appropriately masked to ensure that the subject cannot observe any identification information of drug and vaccine given to him/her (such as outer package, drug color, etc.);
3) The personnel responsible for drug preparation should put the empty vials/boxes back to the original packages, check them in a timely manner after the completion of work every day, and seal them up for storage together with the drug administrator. After a study site is closed and the Sponsor's authorization is obtained, the study site should transfer these packages to the provider of medical waste disposal services or the

Sponsor for destruction, and destruction record should be kept;

4) The inspection and quality control related to drug management and drug injection should be performed by non-blinded CRAs and quality controllers;
5) The blood samples collected during the study can only be identified by the study number.

**8.2.4 Emergency Unblinding**

Unless it is necessary to meet medical needs, unblinding of the treatment for subjects isn't allowed without the consent of the Sponsor and the investigators and should be with the recommendation of DSMB. In case of any serious adverse event that requires emergency treatment during the study, emergency unblinding can be performed through IWRS if the investigator believe that it is necessary to learn about the drug group and it is beneficial for the handling of the adverse event. The investigator must enter relevant information into the IWRS, such as the reason(s) for emergency unblinding, and reconfirm the necessity of unblinding prior to emergency unblinding. If possible, every effort should be made to notify the principal investigator, CRA, and relevant personnel of the Sponsor of such unblinding before emergency unblinding, and the specific grouping information of the subject can be obtained only with the approvals of the Sponsor and the principal investigator. If the Sponsor cannot be reached before emergency unblinding, it is necessary to contact the Sponsor, the principal investigator, and the CRA within 24 hours after emergency unblinding. The subject requiring emergency unblinding will be deemed as a drop-out case.

Refer to the separate operation manual for the specific emergency unblinding procedures. Please also refer to the DSMB 14.3 chapter.

**8.2.5 Regulations on Unblinding**

The one-time unblinding method is adopted in this study. Unblinding will be carried out after the completion of the follow-up on Study Day 99 after drug injection, signing and confirmation of the statistical analysis plan and the data review report by all parties and database locking. Unblinding refers to the revelation of the group code corresponding to each random number and the study drug corresponding to each group code. The unblinding documents should be jointly signed by the Sponsor and statisticians.

After data locking and unblinding on Study Day 99, blindness should still be maintained for the investigators responsible for the follow-ups on safety and efficacy analysis (in one year after administration).

**8.3 Amendments to the Study Protocol**

Any amendment to the study protocol should be discussed with and approved by the

Sponsor. If an agreement is reached on the necessity of any amendment, the Sponsor will make a written record and the revised version of the study protocol will replace the earlier version. All amendments to the protocol need to be submitted to the Institutional Review Board (IRB), and important amendments (such as those that may affect the implementation of the study and the safety of subjects) need to be approved by the IRB. Those amendments to the section of management, which do not affect the design or purposes of the study, or the safety of subjects, should be sent to the IRB for registration or quick review (as required by the IRB). If any amendment to the protocol involves study design, attention should be paid to the revision of the informed consent forms and other relevant forms.

The investigators should be responsible for ensuring that if any amendment needs to be made to the study protocol, such amendment must not be implemented prior to the review and approval of the IRB, unless it is necessary to implement such amendment in order to remove any immediate danger to any subject.

### 8.4 Study Duration

The study duration for each subject is about 12 months, while the total duration of this study is approximately 22 months.

## 9. HUMAN SUBJECTS

### 9.1 Population & Number of Enrolled Subjects for the Study

The population for the study includes all people aged 18 and over, regardless of sex or nation.

Please refer to the section "Sample Size Calculation" for details.

### 9.2 Inclusion Criteria

1) Is age 18 years, on Study Day 1 with legal identification documents, and plan to live in the local administration area during the study;
2) Category III rabies exposure within 24 hours before Study Drug receipt ;
3) Completed written informed consent process, and signed the informed consent forms;
4) Subjects with the ability to understand the study procedure. And agreed to complete all follow-ups;
5) Female subjects are not in pregnancy (with negative results of urine pregnancy tests before vaccination) and are not in the period of breast feeding, and agree to avoid pregnancy within 6 months after administration;
6) Those who have an armpit temperature $\leqslant$ 37.0 °C.

### 9.3 Exclusion Criteria

1) Previous receipt of equine or human (rabies) globulin or rabies vaccination prior to randomization;
2) Clinical evidence of rabies infection;

3) Category I and Category II rabies exposure ;
4) Had fever (armpit temperature ≥ 38.5 °C) within 3 days before Study Day 1, or in the acute episode of any chronic diseases;
5) Received immunoglobulin or blood products (except for the anti-tetanus immunoglobulin) within 43 days before Study Day 1, or plan to use any such product (except for the anti-tetanus immunoglobulin) during the study;
6) Received systemic immunosuppressant medication such as systemic corticosteroids but not limited to systemic corticosteroids within 43 days before Study Day 1;
7) History of any immunodeficiency disease (for example: AIDS, systemic lupus erythematosus, etc.); or Laboratory evidence of previous or current immunodeficiency disease, including, but not limited to, any laboratory evidence of HIV infection;
8) History of spleen function deficiency or function injury, such as no spleen caused by any cause (such as splenectomy);
9) History of any severe allergy for vaccination, such as systemic urticaria, allergic laryngeal edema, anaphylactoid purpura, local allergic necrosis (Arthus reaction), angioedema, anaphylactic shock, etc., or allergic to any ingredient of the study drug/vaccine;
10) Previous receipt of any study product (drug, vaccine, biological product or device) within 6 months before Study Day 1, or plan to participate in any other clinical study during this study period;
11) History of or clinical evidence of any systemic disease, acute disease or chronic disease (such as convulsions, epilepsy, encephalopathy, nephrotic syndrome, etc.) that the investigator considers to be likely to interfere with safety or efficacy assessment of the study;
12) Previous medical history that may compromise the safety of the subject in the study according to the opinion of the principal investigator.

## 9.4 Study Completion and Withdrawal

### 9.4.1 Study Completion

Those subjects who have completed all visits as required by the protocol should be deemed to have completed the study.

### 9.4.2 Study Withdrawal

The subjects enrolled in this clinical study are eligible patients with Category III exposure to rabies virus. Each subject who has received wound cleaning and the injection of SYN023 or HRIG should complete subsequent rabies vaccination unless the subject requests to withdraw from the study voluntarily. In principle, the investigators must not suspend the subsequent rabies vaccination for any subject for any reason.

Any subject can stop his/her participation in the trial at any time for any reason. All

subjects should be informed of their right to withdraw from the study at any time, and those subjects who withdraw from the study will not be replaced. The investigators must distinguish those subjects who withdraw from this study due to adverse events from those who withdraw from this study for other reasons.

Withdrawal from the study (drop-out) means that a subject cannot complete the last follow-up as required by the trial protocol for any reason.

The investigators should make every effort to get in touch with those subjects who fail to return for follow-up visits within the specified period of time. After the withdrawal of any subject from the study, the investigators should provide necessary guidance to the subject about his/her clinical conditions, and carry out follow-ups on AE/SAE until the subject has a definite diagnosis/stable condition/full recovery.

All data collected before the date when a subject withdraws from the study/the date when a subject is contacted should be used for analysis, and relevant information about such withdrawal should be recorded in the eCRF, such as whether the subject or an investigator makes the decision of withdrawal and the possible reasons for the withdrawal. For example:

- Serious Adverse Event
- Other adverse events
- Death
- Others (detailed description should be provided)

If a subject withdraws from the study after the injection of the study drug/the first dose of vaccine before the completion of the vaccination with 5 doses of rabies vaccine, an investigator should inform the subject of the risks of his/her withdrawal and give recommendations for subsequent preventive measures.

### 9.4.3 Handling of Missing Visits

If a subject cannot return to the site for a follow-up examination on time, the investigators should make efforts to contact the subject to make a confirmation or recall the subject, or at least determine the subject’s health status, and record such efforts (such as, phone call and SMS records).

## 9.5 Deviation From/Violation against the Protocol

Deviation from the protocol: refers to any behavior that does not conform to the clinical study protocol design or process and hasn't been approved by the Institutional Review Board. A behavior that does not affect the rights, safety and benefits of the subjects, or the integrity, accuracy and reliability of the study data and the evaluation of safety or main indexes should be deemed as a minor deviation from the protocol; a behavior that affects the rights, safety and

benefits of the subjects, or the integrity, accuracy and reliability of the study data and the evaluation of safety or main endpoints should be deemed as a serious deviation from the protocol (violation against the protocol).

It is unnecessary to report minor violation against the protocol (i.e., a deviation from the protocol), such as that the fifth dose of vaccine isn't injected within the window period, to the Institutional Review Board.

The on-site investigators should report to the principle investigator's unit, the Sponsor, the Institutional Review Board, and the Clinical Monitoring about the fact, process, cause, and impact of any serious deviation from the protocol (violation against the protocol) that occurs during the study process. The principal investigator and the Sponsor should give their opinions on the handling of such deviation.

The investigators should provide a corresponding training on relevant procedures to those personnel involved in any violation against the protocol in order to prevent similar incidents from happening again, and should record the training process.

**9.6 Pregnancy-related Events**

Pregnancy is a criterion of exclusion for subject enrollment, so female subjects are required to take effective contraceptive measures during the study; however, they may still get pregnant unexpectedly during their participation in this study. All pregnancy-related events of the subjects during the study period should be reported, and investigators should fill in the "Pregnancy-related Event Report Form".

Investigators should conduct close follow-up on any pregnant subject and collect information about the outcome of pregnancy (for example, detailed information about childbirth, conditions of the newborn baby or termination of pregnancy), and update the "Pregnancy-related Event Report Form".

The starting date of pregnancy should be the first day of the last menstruation.

Pregnancy shouldn't be considered as an adverse event/serious adverse event, but any complication that occurs during pregnancy will be considered as an adverse event, and will even be considered as a serious adverse event in some cases, such as: spontaneous abortion, fetal death, stillbirth, and congenital abnormalities. If no abnormality is found in the fetus, and the mother decides to have induced abortion, such event should not be considered as an adverse event.

**9.7 Study Suspension/Termination**

In case of any of the following circumstances, the trial needs to be suspended, and the circumstance should be reported to the Institutional Review Board and the drug authorities in

accordance with relevant regulations. An expert meeting will be held for safety demonstration. If necessary, earlier unblinding can be performed in order to determine whether the trial should be continued:

- When any subject dies or experiences any serious life-threatening adverse reaction related to the study drug during the study;
- When the number of subjects with Grade 3 or higher-grade systemic adverse reactions accounts for 20% or more of the number of subjects taking the study product during the follow-up period

If the study is terminated early or suspended, the Sponsor will notify the investigators, the Institutional Review Board, and the drug authorities of the reason for the suspension or termination immediately in accordance with relevant registration regulations.

Regardless of the reason for the early termination of the study, the investigators should notify all subjects immediately of such termination and carry out appropriate follow-up visits on the conditions of the subjects.

## 10. Study Drug/Control and Vaccine in combination

### 10.1 SYN023

- Drug Name: SYN023
- Manufacturer: Synermore Biologics (Suzhou) Ltd.
- Dosage: 6 mg/2 mL/vial
- Active ingredients: a 1:1 mixture of 3.0 mg/mL CTB011 and 3.0 mg/mL CTB012. Each vial contains 2.15 mL of SYN023 (or 6.45 mg mAb of SYN023)
- Excipients: 25 mM histidine (3.879 mg/mL), 150 mM sodium chloride (8.766 mg/mL) and 0.02% polysorbate 80 (0.2 mg/mL) and has a pH of 6.0.
- Administration route: wound infiltration injection
- Strengths: 0.3 mg/kg
- Inspection unit: Synermore Biologics (Suzhou) Ltd.

### 10.2 Human Rabies Immunoglobulin (HRIG)

- Common name: Human Rabies Immunoglobulin (HRIG)
- Manufacturer: Tonrol-Shanghai RAAS blood products Co., Ltd
- Strength: 200 IU/2.0 mL/Vial
- Active ingredients: Human Rabies Immunoglobulin
- Excipients: Glucose
- Administration route: wound infiltration injection
- Strength: 20 IU/kg

### 10.3 Rabies Vaccine

Generic Name: Freeze-dried Rabies Vaccine for Human Use (Vero Cells)

Manufacturer: Liaoning Chengda Biotechnology Co., Ltd.

Strength: 0.5 mL/vial after dissolution. The dosage for humans should be 0.5 mL, and each rabies vaccine titer should not be less than 2.5 IU.

Active ingredients: Inactivated fixed rabies virus (PV2061)

Excipients Human albumin, disodium hydrogen phosphate, sodium dihydrogen phosphate, sodium chloride, dextran 40

Vaccine diluent: Sterile water for injection

Administration Method: Intramuscular injection into the deltoid muscle

Batch Release: National Institutes for Food and Drug Control

### 10.4 Packages & Labels

#### 10.4.1 Packages & Labels of Study Drugs

The small boxes and each vial of the study drugs will be labeled, and a printed adhesive label (an extra label) with the same drug number will be placed in the small box, which also will be pasted on the Vaccination Record Form for each subject. The form should be kept by non-blinded staff independently, and other blinded investigators and staff must not get access to the form.

The label shall contain following information:

Carton label: clinical study approval number, drug name, protocol number, strength, storage and transportation, company name, batch number and expiration date (the batch numbers and expiration dates of the study drug and the control drug should be listed), usage and dosage, and drug number. An example of the outer package label of the study drug is provided as follows:

**Drug for Use in the Phase III Clinical Study on SYN023/Human Rabies Immunoglobulin (HRIG) Combined with Rabies Vaccine**
(Only for Clinical Trial)
NMPA Approval #: 2017L04123
Protocol #: SYN023-006 Kit #:
Indication: Category III Exposure to Rabies Virus

Strength: See vial label
Method: Administer according to protocol. Must Sit at R.T. for 15 minutes before use
Lot #: XXX/XXX; Expiry: XXX (the earlier one in the expiry date of the study drug and the expiry date of the control drug);
Storage: Upright at 2 - 8°C;

Note: Please keep the empty bottle. Unused drug will be collected. Please consult investigators for any concern.
Sponsor: Synermore Biologics (Suzhou) Ltd.
Add.: No.5 Building, 218 Sangtian St., Suzhou Industrial Park, China. Tel.: 0512-87658266

An example of the vial label of the study drug:

SYN023 (Only for Clinical Trial)
Protocol #: SYN023-006
Kit #: Strength: 6 mg/2 mL
Lot #: XXX/XXX Expiry: XXX

Method: Administer according to protocol. Must Sit at R.T. for 15 minutes before use.
Storage: Upright at 2 - 8°C

Sponsor: Synermore Biologics (Suzhou) Ltd.
Tel.: 0512-87658266

**10.4.2 Labels of the Rabies Vaccine for Human Use**

1) The label on the outer box of the vaccine: clinical study approval number, protocol number, product name, strength, serial number range, storage and transportation, batch number and expired date, instructions for use, "Only for Clinical Trial" and the Sponsor's name should be printed on the outer package box.
2) The label on the carton of each vial: product name, strength, serial number, batch number and expiration date of the vaccine, storage and transportation, protocol number, the subject's initials, and "Only for Clinical Trial".
3) The label on each bottle: serial number of the vaccine.
4) The built-in label (to be pasted on the vaccination and follow-up record sheets): serial number of the vaccine, the subject's initials.

The study number on the package label of the standby vaccine should be the "serial number of standby vaccine", and other items should be the same as the above.

After the outer package is unsealed, the subject’s initials must be written on the outer package label of the dose and the built-in label (to be pasted on the vaccination and follow-up records), and the vaccination personnel will give the dose with the corresponding number to the subject after check.

**10.5 Storage and Transportation**

The study drugs and the vaccine in combination should be stored and transported at 2-8 °C, upright and avoid sun-light. Freezing is strictly prohibited. The storage temperature should be monitored and recorded in the morning and in the afternoon every day (when the temperature is automatically monitored and an alarm will be triggered in case of any abnormality, temperature monitoring and recording can be arranged based on the specific circumstances on the site). If the storage and transportation conditions fail to meet the requirements, the on-site investigators should contact the agency responsible for the study and

the Sponsor, and must not use the study drugs (SYN023/HRIG) and the vaccine to be used in combination with them until the Sponsor's instruction is obtained.

### 10.6 Administration Method

#### 10.6.1 Vaccination Site and Route

A wound should be the injection site of the study drug, and the injection route should be wound infiltration injection. If the calculated dose is not enough for infiltration injection for all wounds, normal saline can be used to dilute the drug in order to obtain a sufficient volume for infiltration injection.

Note: If the drug isn't used up after infiltration injection for all wounds, the remaining amount should be injected into the muscles far away from the vaccine injection sites (if a wound is located above the waist, the remaining amount should be injected into the back muscles on the side where the wound is located; if a wound is located below the waist, the remaining amount should be injected into the lateral muscles in the middle thigh on the side where the wound is located).

The rabies vaccine used in combination should be shaken to mix before use and can only be used for intramuscular injection. The first dose of vaccine should be injected in the deltoid muscle on the opposite side. Gluteal injection is strictly prohibited. Each subject should receive one dose of vaccine on Study Days 1, 4, 8, 15, and 29.

The study drug and the rabies vaccine must not be injected on a single site; the study drug and the rabies vaccine must not be injected with a single syringe.

#### 10.6.2 Administration Dosage

The dosage of SYN023 should be 0.3 mg/kg (or 0.1 mL/kg).

The dosage of HRIG should be 20 IU/kg (or 0.2 mL/kg).

The dosage of the rabies vaccine should be 0.5 mL per subject.

### 10.7 Reminders and Precautions

Appropriate first-aid treatment measures should be provided on the site where the drugs and the vaccine are injected, and epinephrine and other necessary drugs should be prepared for any severe allergic reaction after vaccination. A subject should stay at the site for 30 minutes after injection for safety.

### 10.8 Concomitant Medications

After the injection of the study drugs, an investigator should ask the subject whether he/she took any other drug or received any other vaccine during each visit/contact, until the diary card and the follow-up card are returned. All concomitant medications (except for vitamins and/or

food supplements for health care) should be recorded on the diary card and the follow-up card. The investigators should enter information about all concomitant medications into the eCRF.

**Concomitant Medications:** Refer to drugs (except for the study drugs) used by a subject within 43 days post to the first dose of the vaccine, including antibiotics, antiviral drugs, antipyretics and analgesics, anti-allergy drugs, biological products (vaccines), traditional Chinese herbal medicines, etc. (except for vitamins and/or food supplements for health care).

**Allowable vaccines:** The vaccines should meet the inclusion/exclusion criteria. Emergency vaccination, such as tetanus antitoxin or tetanus toxoid, etc., should not be prohibited, but the use of vaccines should be recorded as required.

**Allowable drugs:** If any subject experiences any adverse event during this study, necessary medication should be allowed, and information about such medication should be truthfully recorded as required. Subjects are required to take contraceptive measures during this study, so use of contraceptives should also be allowed; however, use of any drug should be truthfully recorded.

**Restricted drugs:** A prophylactic drug is a drug given in the absence of any symptoms or when an expected adverse reaction to the experimental drug or a combination of vaccines (for example, when fever is not present, an antipyretic is taken for the prophylactic of fever, in which case an antipyretic is considered to be a prophylactic drug). Subjects should be asked whether they are on any medication during the enrollment procedures, in order to confirm that they are not using antipyretics, analgesics or anti-allergy drugs. Use of prophylactic antibiotics is not recommended for all cases with Category III exposure. Use of antibiotics for prophylactic or therapeutic purposes is allowed for those cases with high-risk factors or wound infections. If any subject suffers from any disease that requires medication during the study, there should be no limit on such medication.

**Prohibited drugs:** Any non-protocol immunoglobulin with anti-rabies activity and any non-protocol anti-rabies vaccines should be prohibited. The systemic immunosuppressive drugs was prohibited to the enrolled subjects until Day 29 post administration. Vaccination with live attenuated virus vaccine such as measles is prohibited within 3 months post administration. If any subject suffers from any disease that requires medication during the study, there should be no limit on such medication.

## 11. STUDY PROCEDURES

### 11.1 Patient Reception & Wound Treatment

The research site should be qualified for treatment of rabies injuries, equipped with professional wound washing equipment and washing liquid, and the medical professionals

should be qualified with adequate rabies training.

After the reception of a patient, medical staff should inform the patient of the treatment after exposure to rabies virus. If the patient has Category III exposure, he/she should be briefly informed of the option of participating in this clinical study or receiving the corresponding vaccine at his/her own expense. After learning about the patient's intention to participate in this study and obtaining a signed informed consent for post-exposure treatment, the investigators should give post-exposure wound treatment in a timely manner. If the patient intends to participate in this study, the wound should be irrigated in accordance with the standard washing procedures in this study; if the patient has no intention to participate in this study, the wound should be washed in accordance with the conventional washing procedures. It is necessary to carry out wound washing and disinfection treatment in a correct and timely manner.

The two main objectives of post-exposure wound treatment include prevention of rabies and prevention of secondary bacterial infections, aiming to promote wound healing and functional recovery.

Wound treatment procedures include thorough washing, disinfection and subsequent surgical treatment of each wound. Local wound treatment should be provided as soon as possible. In case of severe pain during washing or disinfection, local anesthesia may be given.

① Wound washing: washing equipment and special washing solution should be equipped to rinse inside the wound. The wound should be rinsed with saline to remove any residual of the washing solution.

② Disinfection: After thorough washing, dilute povidone iodine (0.025% -0.05%), benzalkonium chloride (0.005% -0.01%) or other skin and mucous disinfectants inactive the virusby wiping or disinfecting the inside of the wound.

③ Subsequent surgical treatment: After at least 2 hours from the wound washing, disinfection and injection of passive immunization biologics as required, follow-up surgical treatment can be provided based on the actual situation. Surgical treatment should be provided based on many considerations, such as animal species, wound type and location, and the basic health status of the patients. See relevant SOPs for specific operations.

**11.2 Informed Consent**

Before enrollment, subjects should be informed of relevant information about this clinical study by the investigators. An informed consent should be signed in duplicate by each patient and the investigator. The patient should keep the copy, while the study site should keep the original.

### 11.3 Screening

Investigators should inquire about relevant information in accordance with the "inclusion and exclusion criteria", learn about each patient's medical history (including history of exposure to rabies virus, diseases/concomitant diseases and allergy, etc.), vaccination history and other medications, and carry out examination of vital signs (axillary temperature, pulse and blood pressure) and physical examination, including height, weight, overall skin conditions and skin condition at the wound. Female subjects should be required to collect urine samples for urine pregnancy test, which must be completed prior to blood sample collection on the day of vaccination. Investigators should fill relevant information about selection and demographic data (such as birth date, gender, and ethnicity) in the "Vaccination and Follow-up Records". Eligible patients should enter the next study procedure, and those ineligible patients should receive the injection of a RIG and/or a rabies vaccine at their own expense in accordance with routine clinical procedures.

### 11.4 Study Randomization

Refer to Section 8.2 for study randomization and blinding.

### 11.5 Blood Sampling Prior to Dosing

All subjects should be tested on the activity of rabies virus neutralizing antibodies. Approximately 3.0 mL of venous blood should be sampled prior to administrate the study drug and the first dose of vaccine, and serum should be aliquoted into two microtubes (one for testing, containing at least 0.5 mL of serum, while another is the backup), which should be stored at -20 °C or below.

### 11.6 Administration & Vaccination

#### 11.6.1 Administration of the First Dose of Vaccine

The study drug with the corresponding number should be prepared and administered according to the assigned randomization study number. After the randomization study number on the "Vaccination and Follow-up Records Sheet" is reviewed, the subject's initials should be written on the outer package label, and the enclosed label should be filled in and pasted on the specified position on the "Vaccination Record Form". The information about the subject should be checked again before vaccination.

The dosage adjusted based on body weight: the strength of SYN023 should be 0.1 mL/kg, a maximum of 3 mL can be injected once, while the dosage of HRIG should be 0.2 mL/kg. The study drug should be injected into the wound through infiltration injection (If it isn't used up after infiltration injection for all wounds, the remaining amount should be injected into the muscles far away from the vaccine injection sites (if a wound is located above the waist, the

remaining amount should be injected into the back muscles on the side where the wound is located; if a wound is located below the waist, the remaining amount should be injected into the lateral muscles in the middle thigh on the side where the wound is located)). The injection volume of SYN023/HRIG should be not exceed 3mL at any single injection site.

After injection of the study drug, the rabies vaccine should be injected as soon as possible (the injection should be completed within 75 minutes). The vaccine should be used based on the serial number of rabies vaccine on the vaccine box, and the subject's initials should be written on the enclosed label, which should then be pasted on the specified position of the "Vaccination and Follow-up Records". The information about the subject should be checked again before vaccination. The vaccine should be shaken up, and 0.5 mL of vaccine should be injected into the deltoid muscle on opposite side relative to the wound. It must be noted that the rabies vaccine should not be injected near the injection site of the study drug.

Note: If any other drug, such as tetanus antitoxin, is also needed for treatment, such treatment should be performed in accordance with clinical standards.

**11.6.2 Administration of Subsequent Dosage of Rabies Vaccine**

Each subject should receive one dose of vaccine on Study Days 4, 8, 15, and 29 respectively. The interval between two doses should be calculated based on the time of the previous dose. In case of any delay of injection, the injection time of the next dose should be postponed accordingly based on the original interval between immunization procedures. The window period for Study Day 15 is +1 day, and the window period for Study Day 29 is +2 days.

**11.7 Medical Evaluation**

After the injection of the study drug and the vaccines, a subject needs to remain on the site for 30 minutes. The investigator should provide a diary card, a thermometer, and a ruler to the subject, instruct the subject about how to measure and record solicited and other adverse events and treatment's effect before the next follow-up visit, train the subject how to use the thermometer and the ruler, give instructions about how to observe adverse events and fill out the diary card, and specify when the diary card will be collected. The diary card should be collected and reviewed before the third dose of vaccine, and a follow-up card should be given to the subject after the injection of the dose. The follow-up card should be collected and reviewed before the injection of the fourth and fifth doses (another follow-up card should be given after the injection of the doses).

The investigator should emphasize his/her phone number on the copy of the informed consent form and the diary card/follow-up card and require the subject to contact the investigator immediately after the occurrence of any serious sign or symptom, or any event that

requires medical attention in his/her opinion.

### 11.8 Wound Photography

Photographs of wounds should be recorded if possible before treatment, after treatment (prior to administration) and 30 minutes after administration at least.

### 11.9 Vital Signs

Vital signs parameters (fever (axillary temperature), pulse, blood pressure) need to be measured before vaccine injection on Study Days 4, 8, and 15.

### 11.10 Post-vaccination Sampling

About 3.0 mL of venous blood should be collected from each subject prior to the administration and on Study Days 4, 8, 15, 43, 99, 183, and 365 respectively post administration, and serum should be aliquoted into two tubes (one tube for testing, containing at least 0.5 mL of serum, while another tube is a backup), which should be stored at -20 °C or below. The window period for Study Day 15 is ± 1 day; the window period for Study Day 43 is ±3 days; the window period for Study Day 99 is ± 5 days; the window period for Study Day 183 and Day 365 is ± 7 days. The interval between the times of sample collection on Study Days 4, 8, 15, and 43 should be calculated based on the time of injection of the previous dose, and the time of blood samples 'collection on Study Days 99, 183 and 365 should be calculated based on the time of drug injection on Study Day 1 and the time of initial injection of the vaccine.

### 11.11 Safety Follow-up and Evaluation

#### 11.11.1 Definition of AE

AE: Refers to any adverse medical event that occurs after a patient or a subject in a clinical trial receives a study drug, which may not be causally related to treatment.

Adverse Reactions: Refers to any unexpected or harmful reaction that occurs during the injection of a vaccine (or a study drug) based on the prescribed dose and procedures, which is usually have a causality to the vaccination or study drug, including the causality assessment as "Definite", "Probable", "Possibly"

SAE: Refers to any event that requires hospitalization or prolonged hospital stay, or causes disability, impairment in the ability to work, threat to life, death or congenital malformation during a clinical trial.

#### 11.11.2 Follow-up Time and Method

- ✓ Each subject should be asked to stay on the site for 30 minutes after administration in order to observe any adverse event that occurs during the first 30 minutes;
- ✓ After administration, a diary card with information about adverse events should be given to each subject. Each subject should measure his/her body temperature and record all

local and systemic adverse events based on the requirements on the diary card every day (Study Day 1 – Study Day 8);

- ✓ The diary card should be collected on Study Day 8 after administration, and the investigators should review and record the adverse reactions described on the diary card. Meanwhile, a follow-up card should be given to each subject, on which all adverse events that occur after the injection of the third dose of the rabies vaccine and before the injection of the next dose. The follow-up card should be collected before the injection of the fourth dose, and another follow-up card should be provided, which should be collected 14 days after the injection of the fifth dose;
- ✓ During the study, serious adverse events, survival conditions, and pregnancy-related events should be collected through active reporting by subjects and regular follow-ups by investigators. If a subject dies, the subject's family member should report his/her death to an on-site investigator promptly. Investigators should collect relevant data, such as death certificate, medical record, autopsy report (if any), and record necessary information such as time of death, cause of death, and diagnosis;
- ✓ During each visit, the investigator should emphasize that the subject may contact the investigator at any time via the phone number on the diary card/follow-up card/copy of informed consent.

**11.11.3 Follow-up Contents**

Safety evaluations include all solicited AEs, other AEs, and SAEs and pregnant status during the study.

**11.11.3.1 Solicited AEs**

Solicited AEs refer to any of the following events occurring within 1~8 days post administering of the study drug and the first dose of vaccine:

| | |
|---|---|
| (Systemic) adverse events occurring at sites other than the vaccination site | Fever, headache, rash, itching, urticaria, dyspnea, cough, chills, chest pain, joint pain, and myalgia |

**11.11.3.2 Other AEs**

Other AEs refer to any adverse event other than the solicited adverse events.

**11.11.3.3 SAEs**

**SAEs** refer to any medical event that:

a) causes death;
b) threatens life;
c) results in hospitalization or prolonged hospital stay;

d) causes any permanent or significant disability/function loss;

e) causes any congenital abnormality or defect;

f) Leads to any other significant medical event.

### 11.11.4 Safety Evaluations

#### 11.11.4.1 Assessing Severity

Investigators should refer to "Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials 2007" to determine the severity of any adverse event that occurs during the trial. Simultaneously, the injection sites' fever, swelling, redness, sclerosis, and rash will be assessed for severity in the statistical analysis in accordance with the Guidelines for the Adverse Events Assessment in Prophylactic Vaccines Clinical Trials.

#### 11.11.4.2 Assessing Causal Relationship (Relatedness)

It is the responsibility of the investigator and the sponsor to determine the correlation of all AE/SAE and the IMPs. The correlation assessment includes five aspects: 1) whether the occurrence AE/SAE has a reasonable time sequence with administering of IMPs; 2) Whether AE/SAE conforms to known types of AEs of IMPs; 3) After drug withdrawal or dose reduction, if the AE/SAE decreased or disappeared; 4) Whether the same AE occurs again after the suspect drug is used again; 5) Whether AE/SAE can be explained by the effect of combination drugs? The progress of subjects' diseases or other treatment measures. Based on the above five aspects, the following assessment are made:

| **RELATEDNESS** | **1** | **2** | **3** | **4** | **5** |
|---|---|---|---|---|---|
| DEFINITE | + | + | + | + | - |
| PROBABLE | + | + | + | ? | - |
| POSSIBLY | + | - | ±? | ? | ±? |
| UNLIKELY RELATED | - | - | ±? | ? | ±? |
| UNLIKELY | - | - | - | - | + |
| NOTE：1-5 REPRESENTING THE ABOVE 5 ITEMS TO BE ANALYZED；+ COMPLIES WITH；- NO COMPLIES；±INDICATES DIFFICULTY IN DETERMINING COMPLIANCE OR NONCOMPLIANCE；？INDICATE UNCLEAR | | | | | |

General principles for relevance causality assessment:

- ✓ **Definite** relationship to Study Drug (i.e., the Study Drug is known to be the cause of the adverse event. The evidence establishes a causal relationship; an association exists

between the event and receipt of the Study Drug and there is a plausible mechanism for the event to be related to the Study Drug, and causes other than the Study Drug have been ruled out).

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

For statistical analysis, AE that is defined as "definitely", "probably" and "possibly related" is considered "related" to the study drug/vaccine, and AE that is defined as "unlikely related" and "not related" is considered "unrelated" to the study drug/vaccine.

Since investigators' understanding of AE/SAE is a dynamic deepening process, the initial report may contain inaccurate relevance information. As more information is generated or updated in subsequent visits, the investigator may change his/her initial judgment of relevance, in which case the investigator shall follow up the AE/SAE, and update relevant information, especially for the SAE subject.

#### 11.11.4.3 Anticipation

Investigators and the Sponsor shall confirm whether a serious adverse reaction is anticipated or unanticipated. If the nature, severity or frequency of a serious adverse reaction is inconsistent with the previously described risk information related to the test, it shall be considered unanticipated.

### 11.12 Efficacy Evaluations

Blood samples from all subjects will be collected eight times (on Study Days 1, 4, 8, 15,

43, 99, 183 and 365), and by measuring the activity of RVNA in their blood samples, the efficacy of SYN203 + rabies vaccine and HRIG + rabies vaccine will be compared for PEP of rabies in subjects with Category III rabies exposure.

### 11.13 Clinical Samples' Handling and Assay

#### 11.13.1 Clinical Samples' Handling

Hemolysis of blood samples shall be avoided. Venous blood shall be placed at room temperature (R.T.) without agitation until stratified, and if it could not centrifuge within 2 hours of sampling, the blood sample shall be transferred to a place with an ambient temperature of 2 - 8°C and centrifuged within 24 hours of sampling.

The separated serum shall be divided into two aliquots to a microtube (with a minimum serum volume of 0.5 mL) and a spare tube respectively, and the aliquot of test tube serves as the priority. The serum aliquots shall be refrigerated at -20°C or below, and be transported in a frozen state.

#### 11.13.2 Numbering Rules of Clinical Samples

The collected blood samples shall be labeled with the study number and specific sampling time in principle; and the specific numbering procedures are described in relevant SOPs.

#### 11.13.3 Assay of Biological Samples

All serum samples are transported to the National Institutes for Food and Drug Control for test. Rabies virus antibody is detected by rapid fluorescent focus inhibition test (RFFIT), with neutralizing antibody concentration ≥ 0.5 IU/mL as the protection level.

## 12. DATA MANAGEMENT

1) Data managers shall draft a data management plan (DMP) based on project requirements and the clinical trial protocol, and carry out specific data management work according to DMP to ensure the reliability, completeness and accuracy of clinical trial data.
2) In this study, an electronic data capture system (EDC) is used for data collection and management, and an interactive web response system (IWRS) is used for randomized distribution and drug management. The system shall be well-verified, and could support preservation of audit trails and account and authority management. System administrators shall create different accounts for data managers (DM), investigators, clinical research associates (CRA), clinical research coordinators (CRC), etc., grant different permissions to their accounts, strictly manage and control the application and cancellation of accounts.

3) Data managers shall design an electronic case report form (eCRF) and draft a database building direction by referring to CDISC, and make a data verification plan (DVP) based on eCRF; database designers shall build up a database and set up its logical verification program; data managers shall test the database and the logical verification program therein, and bring the database online after passing the test. Data managers shall compile notes and explanations for eCRF filling and provide training on the use of EDC.
4) Investigators shall collect the data of subjects according to GCP and the study protocol. Investigators or CRCs shall input the data of subjects into the EDC system in a faithful, accurate, complete and normative manner according to the notes and explanations for eCRF filling within the specified time, and save the data well. The EDC logical verification program will verify the data automatically, and generate a query if there is any logical problem with the data. Investigators or CRCs shall check the data and respond to the query according to raw data, modify the data if necessary, and provide necessary explanation. Data managers shall review the modified data or response to the query, raise secondary query if necessary until all queries are resolved or clarified.
5) During the test, CRAs shall confirm that all data in the EDC system are filled in correctly and properly, and consistent with the raw data (source data/source files); data managers shall check whether the data are integrate, consistent and accurate; medical personnel shall perform necessary medical audit on the data. All of the above personnel can input their queries into the EDC system during the review process. Investigators or CRCs could respond to the above queries in the system and even modify the data if necessary. When reviewing the updated data and responses to the queries, the reviewer may query the data again if necessary, until all queries are resolved or clarified. All data modification and query records shall be kept in the EDC audit trails.
6) Upon the completion of data collection and verification and resolution of queries, the principal investigator shall give an e-signature to all eCRF in the EDC system as a confirmation of the authenticity of data. If there is any updated data upon the investigator's signing, a renewed signature shall be made for the updated eCRF.
7) During the test, the data management team shall use coded dictionaries (MedDRA 22.1 or above and WHODrug Sep1, 2019 or above) for medical coding of past medical history, AEs, and combined medication. If there is any doubt to the data in the coding process, the doubt shall be resolved or clarified in the way of questioning according to the query management process.

8) After data cleaning is completed, a data review meeting will be held, and the principal investigator, medical personnel, statistical analysts, data managers, and project managers will attend the meeting to review the data, discuss the data in question and settle the problems to be solved, define and divide the analysis population, and authorize data managers to lock the database.
9) In principle, no change shall be allowed after the database is locked. If data errors still exist after the database locked, the project team (medical staff, statistical analysts, data managers, project managers, etc.) shall carefully evaluate the potential impact of errors on safety and efficacy analysis, and discuss how to deal with the errors. Data errors can be recorded in statistical analysis reports, clinical reports, etc. If it is necessary to modify the data in the locked database, the project team can unlock the database and modify the data after signing relevant documents. After the completion of data modification and re-cleaning, data managers shall lock the database again. All locked data shall be exported by data managers and submitted to statistical analysts for analysis.
10) After the test, data managers shall draft a data management report according to the actual implementation of the project, archive all paper and electronic documents, and save and back up the data. EDC system administrators could shut down the EDC system (bring it offline).
11) It is necessary to save the XPT database and data management documents to a disk and submit it to the Sponsor after project completion.

## 13. STATISTICAL CONSIDERATIONS

### 13.1 Study Hypothesis

**Primary study hypotheses:**

1) The geometric mean concentration of RVNA in the experimental group on Study Day 8 after administration should be superior to that of the control group (the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2).

**Secondary study hypotheses:**

1) The geometric mean concentration of RVNA in the experimental group on Study Day 4 after administration should be superior to that of the control group (the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2).
2) The antibody protection level of the experimental group on Study Day 15 after

administration should be non-inferior to that of the control group (the lower limit of the 95% confidence interval of antibody protection level ratio (experimental group/control group) should be > 0.8).

3) $AUEC_{1-15}$ of RVNA GMC of SYN023+rabies vaccine is superior to that of HRIG+rabies vaccine (the lower end of the 95% confidence interval for RVNA GMC $AUEC_{0-14}$ (experimental group/control group) > 1.1).

**Testing strategy:**

Based on the multiple hypotheses in this study, the hypothesis that the geometric mean concentration of RVNA in the experimental group on Study Day 8 after administration should be superior to that of the control group (the test on the primary hypothesis) will be tested at the level of 0.025 (one-sided). If the test is successful, the hypothesis that the geometric mean concentration of RVNA in the experimental group on Study Day 4 after administration should be superior to that of the control group will be tested at the level of 0.025 (one-sided) (the test on Secondary Hypothesis 1); otherwise, the three tests on the secondary hypotheses will be conducted as exploratory analyses at the level of 0.05 (two-sided). If the test on Secondary Hypothesis 1 is successful, the hypothesis that the antibody protection level of the experimental group on Study Day 15 after administration should be non-inferior to that of the control group will be tested at the level of 0.025 (one-sided) (the test on Secondary Hypothesis 2); otherwise, the tests on Secondary Hypothesis 2 and Secondary Hypothesis 3 will be carried out as exploratory analyses at the level of 0.05 (two-sided). If the test on Secondary Hypothesis 2 is successful, the hypothesis that the area under the curve for the GMC of RVNA from Study Day 1 to Day 15 ($AUEC_{1-15}$) of the group receiving SYN023 combined with the rabies vaccine should be superior to that of the group receiving HRIG combined with the rabies vaccine will be tested at the level of 0.025 (one-sided) (the test on Secondary Hypothesis 3); otherwise, the test on Secondary Hypothesis 3 will be carried out as an exploratory analysis at the level of 0.05 (two-sided).

## 13.2 Study Endpoints

Details of the study endpoint are provided in Chapter 7.

## 13.3 Sample Size Calculation

**Primary study hypotheses:**

The geometric mean concentration of RVNA in the experimental group on Study Day 8 after administration should be superior to that of the control group (the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2).

Based on the hypotheses in this study, i.e., the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2, it is assumed that the type I error is 0.025 (one-sided) and the test power is 90%; the geometric mean concentration of RVNA (experimental group/control group) is estimated to be 11.9 on Study Day 8 after administration; CV% is 120.5%; and the randomization the experimental group/control group is 3:1. Therefore, 16 cases are needed, including 12 cases in the experimental group and 4 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a test power of 100% when the hypotheses remain unchanged.

**Secondary study hypotheses:**

1) The geometric mean concentration of RVNA in the experimental group on Study Day 4 after administration should be superior to that of the control group (the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2).

Based on this hypothesis, i.e., the lower limit of the 95% confidence interval of the geometric mean concentration of RVNA (experimental group/control group) should be > 1.2, it is assumed that the type I error is 0.025 (one-sided) and the test power is 90%; the geometric mean concentration of RVNA (experimental group/control group) is estimated to be 13.75 on Study Day 4 after administration; CV% is 63.25%; and the randomization of the experimental group/control group is 3:1. Therefore, 12 cases are needed, including 9 cases in the experimental group and 3 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a test power of 100% when the hypotheses remain unchanged.

2) The antibody protection level of the experimental group on Study Day 15 after administration should not be inferior to that of the control group (the lower limit of the 95% confidence interval of antibody protection level ratio (experimental group/control group) should be > 0.8).

Based on this hypothesis, i.e., the lower end of the 95% confidence interval for antibody protection level ratio (experimental group/control group) > 0.8, assuming that type I error is 0.025 (one-sided), study power is 90%, estimated antibody protection level ratio (experimental group/control group) on Study Day 15 of administration is 1, estimated protection level of control group is 98.7%, distribution ratio of samples is 3:1 (experimental group/control group), and sample exclusion rate is 20%, 52 samples will be required (39 samples for experimental group and 13 samples for control group). The existing 1,000 cases will ensure a test power of 100% when the hypotheses remain unchanged.

3) $AUEC_{1\text{-}15}$ of RVNA GMC of SYN023+rabies vaccine is superior to that of HRIG+rabies vaccine (the lower end of the 95% confidence interval for RVNA GMC

$AUEC_{1\text{-}15}$ (experimental group/control group) > 1.1).

Based on this hypothesis, i.e., the lower limit of the 95% confidence interval of the $AUEC_{1\text{-}15}$ (experimental group/control group) for the GMC of RVNA from Study Day 1 to Day 15 should be >1.1, it is assumed that Type I error is 0.025 (one-sided) and the test power is 90%; the estimated value of $AUEC_{1\text{-}15}$ (experimental group/control group) for the GMC of RVNA from Study Day 1 to Day 15 is 147.55%, and CV% is 142%; and the randomization of the experimental group/control group is 3:1. Therefore, 900 cases are needed, including 675 cases in the experimental group and 225 cases in the control group, given a drop-out rate of 20%. The existing 1,000 cases will ensure a test power of 96.9% when the hypotheses remain unchanged.

**13.4 Analysis Set**

As-Treated Population (Safety Population or Set)

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

Per-Protocol Population (Set)

All subjects who

1) randomized

2) receive the Study Drug

3) have inclusion/exclusion criteria confirmed

4) complete the rabies vaccinations schedule by Study Day 28

6) lack major protocol deviations

7) have adequate wound treatment and Study Drug injection of all exposure sites

will be included in the "per-protocol" population. Initial exclusion criteria that must be confirmed are the nature of the exposure including the species of the animal; a high risk exposure (WHO Category 3); interval ≤ 24 hours from the bite to the start of prophylaxis; the absence of RVNA ≥ 0.1 IU in serum obtained at Study Day 1, time "1" 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.

* Inclusion/exclusion criteria to be confirmed include: Category III exposure to rabies virus<24 h; in the serum collected at "1" (WHO, 2013) on the first day of the study, the

RVNA<0.1 IU/mL.

In addition, subjects that have (not limited to) the following conditions may be removed from the PPS, which are subject to the result of discussion on the Blinded Data Review Meeting before the locking of database:

- Subjects will be excluded if there are conditions that may impair protection, such as immunodeficiency, after randomization.
- Subjects will be excluded if treatment is long-delayed (> 24 h).
- Subjects will be excluded if they receive or have received treatment prohibited by the protocol.
- Subjects will be excluded if the bite is not properly treated.

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

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

SS and PPS subjects will be used for efficacy analysis, with the results of the PPS subjects as the main, and the efficacy analysis will be subject to the group of patients planning to take the study drug.

### 13.5 Statistical Analysis

#### 13.5.1 General Principle

All statistical analyses are done with SAS 9.4 or updated versions.

Unless specifically stated, all tests are performed at the two-sided alpha level of 0.05 with 95% confidence interval.

For continuous variables, descriptive statistics include the number of non-missing values,

the mean, median, quartile, and standard deviation, maximum and minimum values. For categorical variables, descriptive statistics include frequency and composition or incidence. Unless otherwise stated, missing values will not be included in the calculation of percentage.

### 13.5.2 Demographic and Baseline Characteristics

On-site subject screening, random grouping and completion of each trial site are summarized; the distribution of subjects in each treatment group and each analysis set is summarized; the main reasons for subject's withdrawal from the test and the reasons for not entering the analysis set are analyzed.

Demographic parameters (age, gender, ethnicity) and other baseline characteristics of subjects in each treatment group will be summarized based on the safety analysis set. Descriptions of demographic characteristics and baseline characteristics will be based on as-treated population and PPS, respectively.

Major violations of the protocol will be classified and summarized, and a list of violating subjects will be made.

### 13.5.3 Efficacy Analysis

Efficacy analysis will be based on Per-Protocol Set (PPS) and Safety Set (SS). The PPS is the major analysis set, and the SS will be the support analysis set.

**Analysis of primary efficacy indicators**

1) Geometric mean concentration (GMC) of RVNA on Study Day 8

The comparison of RVNA GMC on Study Day 7 between the two groups (Arms) will be analyzed by ANOVA, with the treatment group and sites as the fixed variables. Meanwhile, the mean, standard deviation, median, minimum and maximum values of their respective RVNA GMC, as well as their mean, standard error of the corrected RVNA GMC will be provided for the ratio, standard deviation, 95% confidence interval and P value of the two groups at the two-sided alpha level.

For primary efficacy indicators, a subgroup analysis will also be carried out in each trial site to obtain the difference of GMC and the 95% confidence interval between the two groups in each trial site.

2) 99-day and one-year incidence and survival rates of rabies in subjects post administration;

The incidence and survival state of subjects with rabies treatment within 99 days and 1 year are described, and the incidence and survival rates are calculated.

**Analysis of secondary efficacy indicators**

1) GMC of RNVA on Study Days 4, 8, 15, 43, 99, 183 and 365 post administration;

Analysis method of the secondary efficacy indicators is the same as that of the major

efficacy indicators;

2) Protection level of RNVA on Study Days 4, 8, 15, 43, 99, 183, 365 post administration;

The number of RVNA positive cases in each group and the protection level at each time point after administration will be described respectively. The comparison between the two groups will be performed by chi-square test or Fisher exact test, and the difference of protection level between the two groups as well as the 95% confidence interval calculated based on Clopper-Pearson are also provided;

3) Area under the Curve Study Day 1 to Day 15, $AUEC_{1-15}$

The comparison of $AUEC_{1-15}$ of RVNA GMC between the two groups will be performed using chi-square test, with the treatment group and the trial site as fixed effects. Meanwhile, the mean, standard deviation, median, minimum and maximum values of their respective $AUEC_{1-15}$ of RVNA GMC, as well as their respective ratio, standard deviation, 95% confidence interval and P value at the two-sided alpha level of 0.05 are also provided.

**13.5.4 Safety Analysis**

All subjects that have taken the study drug and have safety follow-up data are included in the safety analysis set. Analysis of the end point of safety evaluation is carried out in the safety analysis set, and the safety analysis is subject to the study drug actually accepted by the subject.

**13.5.4.1 AEs**

The system organ classification and preferred term classification of AE will be coded by the current edition of MedDRA. Analysis of AE will be based on treatment-emergent AE (TEAE), i.e., an undesirable event not present prior to medical treatment, or an already present event that worsens during the treatment. The number of TEAE subjects and TEAE cases, and TEAE incidence will be summarized by treatment group, system organ class and preferred term:

Any TEAE that occur within 43 days post administration, n TEAE of Grade 3 or above, TEAE related to the study drug, TEAE leading to subject's suspension of treatment, and TEAE leading to subject's withdrawal from the test; solicited local adverse response, solicited systemic adverse response, SAE, and SAE related to the IMPs.

In addition, the severity of TEAE occurring within 43 days after injection and its correlation with the study drug will also be summarized by treatment group, system organ class and preferred term. For each subject, only the most severe or the most relevant term is recorded.

List of SAE by treatment group and list of TEAE leading to withdrawal within 43 days after administration are provided.

Solicited systemic events (Fever, headache, rash, itching, urticaria, dyspnea, cough, chills, chest pain, joint pain, myalgia) that occur within 8 days post administration in each group will be described and analyzed according to symptoms. Solicited systemic events that lead to the

suspension of study are analyzed in the same manner.

#### 13.5.4.2 Pregnancy

The number of pregnancies in each group during the study period is collected, and the final pregnancy results are classified and described.

#### 13.5.4.3 Vital Signs Assessment

A descriptive analysis of vital sign measurements and changes of the measurements after treatment as compared to baseline is performed by visits and treatment groups. Meanwhile, the abnormal values of vital signs are tabulated.

### 13.6 Registration and Declaration Strategy

**Initial analysis**

After all subjects complete a 99-day safety and efficacy evaluation after administration (based on the serological results on Study Days 1, 4, 8, 15, 43 and 99), the first analysis will be conducted, and a statistical analysis report and clinical research report will be formed and submitted to the National Medical Products Administration (NMPA) for review.

**Secondary analysis**

After all subjects complete a one-year safety and efficacy evaluation after administration, the secondary analysis will be conducted, and a statistical analysis report and clinical research report will be formed and submitted to the National Medical Products Administration (NMPA) as a supplement, and also to the U.S. Food and Drug Administration (FDA) for review.

### 13.7. Data and safety monitoring board (DSMB)

A DSMB will be convened in this trial. The DSMB's purpose is to monitor the death and rabies cases during the entire study period.

The DSMB's composition and working contents will be specified in the DSMB charters.

### 13.8 Per Protocol Adjudication Board (PPAB)

The Sponsor will create the Per-protocol Adjudication Board whose duty will be to review data and confirm the rabies cases in the study. The confirmed rabies events is one of the primary endpoints of the study. In case any rabies event in the SYN023 arm, the primary endpoint will be reached for the study failure. In case of lab-confirmed or clinically suspected rabies cases during the study, the study enrollment would be suspended and detailed information would be submitted to PPAB for reviewing and confirmation, so that PPAB can confirm the diagnosis of rabies cases. If a confirmed case of rabies occurs in the SYN023 arm (as in the per protocol set and in the SYN023 group), the clinical trial will be permanently discontinued by PPAB on a written notice. If the rabies case occurred in the control group or in the SYN023 group but PPAB deems that the case was caused by a violation of the study protocol, The study will not

be stopped by the rabies case. The operating procedures in violation of the protocol include:

- Received the incorrect Study Drug
- Received the incorrect dose (± 20%) of Study Drug
- Fail to comply with Category III rabies exposure.
- Failed to complete the scheduled rabies vaccinations through the study
- 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 > 24 hours from rabies exposure to the start of Informed Consent
- Are discovered to have RVNA ≥ 0.1 IU in serum obtained at Study Day 1
- Receives prohibited treatment during the trial
- Are found not to have a modified WHO Category 3 exposure
- Second high risk animal bite or contact requiring PEP

## 14. SAFETY MANAGEMENT

### 14.1 Safety Precautions

Clinical test shall be conducted at county-level and municipal-level medical institutions that are eligible for rabies vaccination. Before the initial of the trial, the Sponsor shall inspect the research site strictly according to the GCP, especially on the facilities complying with the Quality Management Guidelines for Clinical Trials for Vaccines (Trial) and to ensure the first-aid facility and equipment in emergency rooms are effective, the first-aid drugs are in valid period with the qualified and capable first-aid doctors. The Sponsor shall ensure that once an AE occurs, the subject could get timely treatment at the site. If emergency hospitalization is required, after the disease becomes stable, the subject could be sent to the assigned hospital by the ambulance vehicle of the site. The site shall sign the Green Channel Contracts with assigned local county or municipal-level general hospitals. The investigator shall notify the assigned hospital during the enrollment period, and make out qualified SOP for related personnel's duties, contact information, rescue measures and so on to ensure timely treatment of unexpected AEs and effective communication between the subject and the investigator, and further ensure a quick and timely report and handling of AEs. If the subject needs the emergent treatment after an SAE, the assigned hospital shall be able to provide green channel medical services, including treatment, hospitalization, and health care to ensure that the subject can be treated in a timely manner.

The Sponsor shall appoint the special personnel for monitoring of safety in clinical trial and the management of SAE. Both the Sponsor and the investigator shall establish SOPs for

the safety monitoring and SAE in clinical trial, and provide training for all relevant personnel. The monitoring and reporting of AEs in the vaccine clinical trial shall be performed by subjects, medical monitor and researchers at its time points evaluation and specific duties.

**14.2 Detection and Collection of AEs**

For the subjects with solicited and non-solicited AEs, the investigator shall ask whether they have received hospitalization, outpatient treatment, etc., for any reason, or taken drugs by themselves, and record such information.

The investigator shall remind the subjects to report AE in time during the training of subjects, always keep a vigilant eye on AEs, and investigate and deal with AEs in a timely manner.

When an AE occurs, the investigator is obliged to review all documents related to the event (e.g. progress notes and medical orders, laboratory reports and diagnosis reports), or arrange a clinical examination/test as requested by the Sponsor to clarify the nature and relevance of the SAE. If a subject is confirmed dead during the study period or the follow-up period, the investigator shall collect the final conclusion provided by the hospital regarding the subject, and also a copy of autopsy results, including histopathological results, if an autopsy is performed.

The investigator shall try to collect a complete copy of the medical history of the subject, but shall not replace the study record with medical history copy. Besides this, the investigator shall also record all information related to the SAE on the original record, eCRF, and SAE report page.

If medical records need to be disclosed for the purpose of medical identification, all contents that may reveal the identity of the subject shall be obscured before disclosure.

**14.4 Reporting of SAEs**

**14.4.1 Reporting Time**

After learning of SAE, the investigator shall make an initial report by filling in the SAE Report Form within 24 hours, and submit the form to the Sponsor by fax, email or web. Once received a SUSAR cases confirmed by the sponsor, the investigator shall submit related information to the EC in a timely manner.

**Reporting Contents as following:**

1) Types of report and reporting time (initial report, follow-up report, summary report and corresponding reporting time);
2) Information of subjects (initials, study number, date of birth, gender);
3) Information of reporter (name of the working medical institution and profession,

telephone, position/professional title of the reporter);

4) Information of suspected drugs (drug names in Chinese and English, registration classification and dosage form);
5) Study related information (clinical study approval number, clinical study classification, clinical indications);
6) Complications and treatment information (name of disease diagnosed, name, usage and dosage of drugs used);
7) Details of SAE (diagnosis name, time of occurrence, end time, laboratory test results, treatment process, outcome, measures taken against the experimental vaccine, the correlation with the experimental vaccine and so on);
8) Time of knowing by investigators;
9) Signature of investigators.

**14.4.2 Sponsor**

**14.4.2.1 Suspected Unexpected Serious Adverse Reaction (SUSAR)**

Sponsors should analyze and evaluate all SAEs reported from the investigator timely, including the severity, relatedness, and anticipation of the IMPs. The sponsor shall promptly report suspected and unexpected SAE to all investigators participating in the clinical trial, the Institutional Management Office, and the ethics committee (EC); The Sponsor shall report SUSAR to the drug regulatory authorities and the health authorities.

For other potential serious safety risk information, the sponsor should also report to the national center of drug evaluation as soon as possible.

**14.4.2.2 Periodical Safety Updated Report (PSUR)**

The sponsor should submit the PSUR to the CDE, all the researchers participating in the clinical trials, and EC in accordance with the requirements of the regulatory authorities and the EC. The PSUR shall include risk and benefit evaluation in the clinical trial.

**14.5 Treatment and Handling of AEs**

Investigators should prepare an emergency plan for the handling of SAEs in clinical trials, provide trainings to all relevant personnel, have measures to promptly know any clinically significant diseases/events after the vaccination of the subjects, and cause the subjects to receive appropriate treatment at the designated hospital in accordance with the relevant national regulations and the current medical administration regulations. Drugs used to treat any AE should be recorded in the original records and eCRFs of the subjects.

In case of any disagreement or dispute during the handling of an adverse event, the investigators should be obliged to cooperate with the Sponsor in handling and assist the subjects

in medical identification.

The Sponsor has the obligation and responsibility to unconditionally ensure the safety of subjects, and provide humane care and compensation to subjects who suffer adverse events related to the study drug/vaccine during the clinical trial.

The investigators should pay continuous attention to the adverse events that are terminated due to an adverse event or continue after the end of each visit. Any adverse event related to drug/vaccine injection should be followed up until the end of the event, while the follow-up visits concerning non-related events such as disease may be stopped after such disease is diagnosed by a doctor.

### 14.8 Individual Emergency Unblinding

If any serious adverse event occurs during the study period, individual emergency unblinding should be performed only if the subjects involved require medical emergency or treatment and the information of the product studied is critical to the clinical treatment of the said subjects. Investigators should complete the recordation of the unblinding process and promptly report it to the Sponsor and the Institutional Review Board.

## 15. QUALITY ASSURANCE AND MONITORING OF CLINICAL TRIALS

### 15.1 Investigators

Institutions responsible for clinical trials should establish a sound organization management system and a quality management system, set up the management mechanism and measures to prevent and deal with emergencies in clinical trials of vaccines, have an expert team for SAE emergency handling and the technical ability to handle serious adverse events, and have perfect cold-chain equipment for transporting and storing study drugs/vaccines.

The clinical trial sites should have the qualification for prophylactic vaccination as approved by the health and family planning administrative department, equipped with a relatively fixed and sufficient number of clinical trial investigators and the standard operating procedures related to the clinical trials of vaccines. Trainings should be provided and training records should be prepared. A green channel for the medical treatment of SAE in clinical trials of vaccines should be set up in cooperation with local medical institutions. According to the vaccination and visit procedures for the clinical trials of vaccine, functional divisions such as reception area, informed consent room, inquiry and physical examination room, biological specimen collection room, drug injection/vaccine inoculation room, emergency room, medical observation room, drug/vaccine storage room, archives room, sample processing and preservation room, case screening laboratory, and temporary storage place for medical wastes should be set up, and a green channel for emergencies should be established. Ambulances and

relevant ambulance men and first-aid materials should be available on the trial site.

The division of labors of all investigators should be confirmed by the principal investigator to make sure that all investigators involved in the project are qualified, trained and authorized, clearly know their respective work to be assumed, master and implement the relevant standard operating procedures. Trainings on GCP and vaccine clinical trial technologies should be provided to the investigators of the responsible institution and the trial site, and training records should be prepared. The support staff should have records of receiving the corresponding work training.

**15.2 Sponsor**

The Sponsor is ultimately responsible for the quality of the clinical trials. The Sponsor should establish a sound clinical trial quality management system, formulate the corresponding SOP, organize inspection against clinical trials, check clinical trial related activities and documents systematically, including trial site, laboratory, CRO company, so as to assess whether the tests are performed in line with the test plan, SOP and the relevant regulations, and whether the test data is recorded in time and recorded truly, accurately and completely. Inspections should be performed by persons who are not directly involved in clinical trials.

The trial site should cooperate with the inspections against the clinical trial project, keep the relevant records, formulate improvement plans for problems found in inspection, and take corresponding management measures to improve test quality.

**15.3 Clinical Research Associate**

In accordance with Article 50 of the Quality Management Guidelines for Clinical Trials for Vaccines (Trial), the Sponsor should assign a sufficient number of CRA to supervise the clinical trial process. The CRAs should have education background and work experience in medicine, pharmacy or related professions. The number of CRAs designated by the Sponsor for clinical trials should be determined according to the monitoring frequency of the test and the complexity of the test plan designed. The CRAs should conduct clinical trial supervision and submit supervision report according to the requirements of the supervision plan.

The CRAs should supervise the whole clinical trial process, make sure that the clinical trials are performed in line with the test plan, SOP, GCP and the relevant regulations and are completed within the expected time limit.

**15.4 Clinical Sample Management**

The serum samples of subjects used for antibody neutralization activity should be managed by the assigned persons, and the records for sample preservation and temperature should be established. The preservation temperature should be monitored daily and recoded (which may be arranged according to the concrete situation of the site on holidays under the premise that

automatic temperature monitoring and alarming is maintained).

Serum samples should be sent to the test laboratory under the condition of freezing (dry ice/low-temperature ice floe/other frozen methods). The backup samples should not be sent together with the samples to be tested and should be properly kept by the investigators (≤-20°C) until the clinical report is completed, and should then be handled upon confirmation by the Sponsor.

The handover management should be done strictly in the whole process, and the records should be properly kept by the investigators, the sample carriers and the laboratory.

**15.5 Study Drug Management**

The institution responsible for clinical trials should guide the trial site to formulate the management regulations for study drugs. The receipt, storage, preparation, recovery, return/destruction of study drugs/vaccines should meet the relevant laws and regulations. The institution responsible for clinical trials and the trial site should both designate persons who have received GCP and related trainings to be responsible for the administration of study drugs.

**Study drug delivery:** the whole drug/vaccine administration process should meet the cold chain requirements, and there should be conditions for the study drug transportation and preservation which meet the plan. Delivery document and temperature monitoring should be available in the delivery process of vaccines. The packaging and the unpacking temperature should be recorded upon arrival. Upon acceptance check against the study drugs, the receiver should sign on and fax the delivery document to the Sponsor or copy it to the Sponsor, and both parties should properly keep the delivery document.

**Storage, distribution and use of the study drugs:** the study drugs should be managed by storing in separate divisions and in separate lockers by specially assigned persons. Blinded management should be maintained for blinding. The receiver of the study drugs must verify the delivery and set up a form for the delivery, registration, use and recovery, which is to be filled in as required and kept in the work record.

**Study drug handover record:** the Sponsor provides the study drugs, and the investigators verify the name, quantity and packaging while receiving the study drugs and well make handover record.

**Registration and use record of study drugs:** the registration and use records of the study drugs should be established by investigators. Investigators should keep a record of the use of the study drugs distributed to each subject, including the study number, initials of the subjects, and signatures of persons who administer the study drugs.

**Study drug recovery record:** the study drug administrator should recover the remaining study drugs in time, check the inventory at regular intervals, make records, and add explanations

if the sum of the quantity of the study drugs that have been used and the remaining quantity of the study drugs is not equal to the total quantity. All rejected, expired and remaining study drugs in this trial should be returned to the Sponsor. The Sponsor should verify the quantity of the study drugs while receiving them and make records in a proper way, which should be signed by the study drug administrator and the representative of the Sponsor.

**Cold chain failure:** once the cold-chain equipment for storing study drugs has an abnormal temperature which is lower than 2°C or higher than 8°C, it will be considered as a cold chain failure. The Sponsor needs to describe the information related to the stability of vaccines in Investigators' Brochure. Once a cold chain failure occurs, the investigators should transport the study drugs concerned to a dark environment with a temperature of 2 - 8°C for storage, stop using the study drugs involved in the cold chain failure, report to the Sponsor as soon as possible, and then decide to stop or continue using such study drugs according to the official advice of the Sponsor.

The study drugs are not allowed to be used in people other than the subjects of the clinical trial.

**15.6 Calibration of Instruments and Equipment**

- The thermometer for monitoring the temperature of refrigerator has been validated. The refrigerator should have a monitoring record of normal temperature for three consecutive days before starting to be used.
- The thermometer has been standardized;
- The syringes for study drug injections and blood collection are disposable sterile syringes, whose manufacturer should have the production license granted by the State and whose batch number and period of validity should be recorded;
- The refrigeration equipment for storing study drugs and samples at the site have passed annual inspection and are in use;
- The height measuring instrument, weight scale, blood pressure gauge and other measuring equipment have been proven to be qualified and are in use.

**15.7 Management of Original Materials**

The original materials such as informed consents, vaccination and follow-up visit records, dairy cards, contact cards, and SAE report forms are important bases for tracing the clinical trial, and should be recorded accurately, completely, and truly in a timely and standardized manner and be properly kept in the study site.

The study data should be entered in the eCRF by the authorized and specially trained investigators according to the original materials and should not be changed without permission during entry. In case of any error in entry, the data should be modified according to the entry

guide. To ensure the authenticity and reliability of the clinical trial data, the eCRF shall be jointed reviewed by the clinical research associate and the investigators. Upon being signed by the investigators, all the materials shall be statistically processed by the statisticians entrusted by the institution responsible for clinical trial or the Sponsor.

**15.8 Research Materials**

The Sponsor and the investigators should provide clinical trial materials according to the Regulations for Drug Registration and the GCP.

The materials that record the real information of the subjects such as the informed consents, vaccination and follow-up visit records, diary cards, contact card and medical records should all be sealed in each site and managed by the site archivist.

Archives management shall be performed based on the SOP. The project name, completion date, Sponsor and storage period need to be well labeled. Safety measures such as insect prevention, damp-proof and fireproof measures and theft prevention should be in place. The use of and access to the materials of this project are limited to the concerned personnel of this project, the concerned personnel of the Sponsor (including clinical research associates) and the inspectors of the NMPA project. All materials should be kept for five years from the date of closure of the site. A notice should be given to the Sponsor when the five-year long period expires. No one may dispose of the materials without prior written notice from the Sponsor.

**16. INSTITUTIONAL REVIEW BOARD**

**16.1 Clinical Trial Review**

The Institutional Review Board needs to review the scientific and ethical rationality of the clinical trial project for the drug, aiming to guarantee the dignity, safety and interests of the subjects, promote the scientific and healthy development of clinical trials for drugs, and enhance the trust and support of the public to clinical trials for drugs.

The Institutional Review Board may review the trial protocol, informed consents, recruitment materials and other written materials provided to the subjects. Any modification to the protocol needs to be negotiated with the Sponsor. For contents that involve the informed consents but do not violate the protocol and conform to the local actuality, the opinions of the Institutional Review Board may be adopted.

**16.2 Intermediate Process Review**

**16.2.1 Tracking Review**

The Institutional Review Board should carry out tracking review against all the approved clinical trials until these trials are completed.

**16.2.2 Amendment Review**

Any amendment of the trial protocol during clinical trials should be submitted to the

Institutional Review Board for review and approval/filing before implementation. The Institutional Review Board should require the Sponsor and/or investigators to submit relevant information concerning the amendment review, including (but not limited to):

(I) The contents of and reasons for modification;

(II) The impacts of protocol modification on the expected risks and benefits;

(III) The impacts of protocol modification on the interests and safety of the subjects.

The Institutional Review Board mainly assesses the trial risks and benefits after protocol modification and then gives review opinions. If the protocol is modified to avoid causing emergency harm to the subjects, the investigators may implement the modified protocol before submitting it to the Institutional Review Board for review and approval and submit a written report to the Institutional Review Board in a timely manner afterwards.

**16.2.3 Annual/Regular Review**

The Institutional Review Board should determine the frequency of annual/regular review according to the risk level of the trial at the time of initial review, at least once a year. The Institutional Review Board should require the investigators to submit reports on schedule. The annual/regular tracking review report should include (but is not limited to):

(I) Progress of the trial;

(II) The number of cases included, the number of cases completed, the number of cases withdrawing from the trial and so on;

(III) Confirming that serious adverse events are reported in a timely manner and are properly handled;

(IV) Any event or new information that may affect the risks and benefits of the trial.

The Institutional Review Board will re-assess the risks and benefits of the trial after reviewing the progress of the trial.

**16.2.4 Review of SAEs**

The Institutional Review Board needs to review the serious adverse events reported by the Sponsor and/or investigators, including the extent and scope of such serious adverse events, the impacts on the risks and benefits of the trial and the medical protections to subjects.

**16.2.5 Noncompliance and Protocol Deviation/Violation Review**

For any noncompliance with/violation of the protocol that occurs in the clinical trial, the Institutional Review Board will require the Sponsor and/or investigators to explain the cause, impacts and treatment measures, and review whether the said noncompliance or violation affects the safety and interests of the subjects or affects the risks and benefits of the trial.

**16.2.6 Review of Early Termination of Trial**

In case of early termination of the trial by the Sponsor and/or investigators, it needs to be

reported to the Institutional Review Board for review. The Institutional Review Board should require the Sponsor and/or investigators to report the reasons for such early termination and the subsequent treatment to the subjects, and review whether the safety and interests of the subjects are guaranteed.

### 16.2.7 Completion Review

The Institutional Review Board should require the Sponsor and/or investigators to report the completion situation of the trial and review the protection to the safety and interests of the subjects.

## 17. PUBLICATIONS

After completion of the trial, the research site may publish the summary report or research results involving this clinical trial after obtaining the written authorization of the Sponsor, and the investigators of the research sites share the right of authorship for the publishing. Negative or inconclusive research results should also be published or made public the same as the positive results.

## 18. REFERENCES

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