Statistical Analysis Plan

A PHASE 2 RANDOMIZED BLINDED SINGLE DOSE COMPARISON OF THE SAFETY PHARMACOKINETICS AND PHARMACODYNAMICS OF RABIES IMMUNE GLOBULIN, AND SYN023 IN HEALTHY ADULT SUBJECTS RECEIVING RABIES VACCINES

Sponsor Protocol No. SYN023-002
inVentiv Health Clinique inc. Project No. 162009

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Contract Research Organization:
inVentiv Health Clinique inc. ("inVentiv")
2500, rue Einstein
Québec (Québec)
Canada, G1P 0A2

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

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SIGNATURES

Sponsor Protocol No.: SYN023-002

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Study Title: A Phase 2 Randomized Blinded Single Dose Comparison of the Safety Pharmacokinetics and Pharmacodynamics of Rabies Immune Globulin, and SYN023 in Healthy Adult Subjects Receiving Rabies Vaccines

Author:	**Yogesh Sable, M. Sc.** Principal Statistician inVentiv	Signature: Y.C Sable Date: 27 May 2017
Senior Reviewer	**Eric Shink, Ph.D.** Principal Statistician inVentiv	Signature: Date: 29-MAY-2017
Sponsor's Representative:	**Eric Tsao, Ph.D.** Chief Executive Officer Synermore Biologics Co., Ltd	Signature: Date: 25 May 2017

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ANOVA	Analysis of variance
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the concentration- time curve from time 0 to the last measurable concentration (equivalent to AUC_{0-last})
AUC_{0-inf}	Area under the concentration-time curve from time 0 to infinity
$AUEC_{0-t}$	Area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 0 to the last measurable concentration
$AUEC_{14-t}$	Area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 14 days to the last measurable concentration
BLQ	Below the lower limit of quantitation
BMI	Body Mass Index
CI	Confidence Interval
C_{max}	Maximum observed concentration
Clp	Plasma clearance
Clp/kg	Plasma clearance normalized for the subject body weight in kg
CRF	Case report form
CPK	Creatinine phosphokinase
CSR	Clinical Study Report
CV	Coefficient of variation
ECG	Electrocardiogram
E_{max}	Maximum observed effect
GLM	Generalized Linear Model
HR	Heart Rate
IG	**Immune Globulin**
IU	International units
K_{el}	Terminal elimination rate constant (equivalent to λz)
$K_{el\ Lower}$	The actual sampling time where $_{Kel}$ calculation begins
$K_{el\ Upper}$	The actual sampling time of the last measurable concentration used to estimate the K_{el}
kg	Kilogram
Max	Maximum

MedDRA	Medical dictionary for regulatory activities
Min	Minimum
mL	Milliliter
PD	Pharmacodynamic
PK	Pharmacokinetic
PP	Per Protocol
% ≥ 0.5 IU/mL	Percentage of subjects with RVNA values ≥ 0.5 IU/mL
PT(INR)	Prothrombin time (international normalized ratio)
PTT	Partial thromboplastin time
QI	Qualified Investigator
RVNA	Rabies virus neutralizing activity
RIG	Rabies immune globulin
RVa	RabAvert®
RVi	Imovax®
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Standard Deviation
SOC	System organ class
SOP	Standard operating procedure
T_{max}	Time of maximal observed plasma concentration
$T_{max,E}$	Time of maximum observed effect
$T_{1/2\ el}$	Terminal elimination half-life
VR	Ventricular Rate
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

This statistical analysis plan (SAP) is intended to give a detailed description of the summaries and the analyses that will be generated for the present study by inVentiv. Analyses specified in this plan are based on Synermore Biologics Co., Ltd study protocol No. SYN023-002, dated June 21, 2016 (inVentiv Project No. 162009). Safety, tolerability, pharmacokinetic (PK) and Pharmacodynamic (PD) analyses will all be described.

The plan may change due to unforeseen circumstances and any changes made after the plan has been finalized will be documented. If additional analyses are required to supplement the planned analyses described in the SAP, the changes and justification for the changes will be outlined in the clinical study report (CSR). No change will be made without prior approval of the study sponsor. No revision to the SAP is required for changes that do not affect the statistical analysis methods, definitions, or rules defined in this document.

When applicable, all methodology and related processes will be conducted according to inVentiv's Standard Operating Procedures (SOPs). Protocol deviations occurring during the study will be listed.

2. Study Objectives

2.1 Primary Objective

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

2.2 Secondary Objectives

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

3. Study Design

3.1 General Design

This is a Phase 2 single site, randomized, blinded comparison of the immunogenicity of RVi and RVa when administered with RIG or SYN023. Up to 160 subjects are planned to be included in this study. Subjects will be randomized into one of four treatments with a ratio of 1:1:1:1 (40 subjects per treatment). All injections will be given intramuscularly.

3.2 Study Procedures

The overall schedule of procedures and assessments is provided in the protocol.

3.3 Treatment Description

Subjects will received one of the following treatments:

Treatment RVi + RIG (A):
At Day 0, subjects will receive Imovax® 1 mL dose co-administered with HyperRab ST® 0.133 mL/kg dose. A total of five doses of the vaccine (Imovax® 1 mL dose) should be administered on Days 0, 3, 7, 14, and 28.

Treatment RVa + RIG (B):
At Day 0, subjects will receive RabAvert® 1 mL dose co-administered with HyperRab ST® 0.133 mL/kg dose. A total of five doses of the vaccine (RabAvert® 1 mL dose) should be administered on Days 0, 3, 7, 14, and 28.

Treatment RVi + SYN023 (C):
At Day 0, subjects will receive Imovax® 1 mL dose co-administered with SYN023 0.3 mg/kg dose. A total of five doses of the vaccine (Imovax® 1 mL dose) should be administered on Days 0, 3, 7, 14, and 28.

Treatment RVa + SYN023 (D):
At Day 0, subjects will receive RabAvert® 1 mL dose co-administered with SYN023 0.3 mg/kg dose. A total of five doses of the vaccine (RabAvert® 1 mL dose) should be administered on Days 0, 3, 7, 14, and 28.

3.4 Subject Withdrawal and Replacement

Subjects were advised that they were free to withdraw from the study at any time. Over the course of the study, the Sponsor and Investigator or a delegate had the right to withdraw any subject from the study for one of the reasons described below; subject withdrawal will be done in accordance with inVentiv's SOP:

- Safety reason;
- non-compliance with protocol requirements;
- significant protocol deviation;

Subjects who withdraw or are withdrawn from the study after dosing will not be systematically replaced. Subjects who fail to complete the study through Study Day 28 may be replaced at the discretion of the sponsor.

4. Changes From the Protocol

For efficacy/PD analyses, $AUC_{0\text{-last}}$ was replaced by $AUEC_{0\text{-t}}$, $AUC_{14\text{-last}}$ was replaced by $AUEC_{14\text{-t}}$, C_{max} was replaced by E_{max}, and T_{max} was replaced by $T_{max,E}$. This is standard nomenclature for such efficacy/PD parameters.

$AUC_{0\text{-inf}}$ was removed from Efficacy/PD analyses because elimination phase cannot be calculated for rabies virus neutralizing activity (RVNA).

5. Primary and Secondary Parameters

The primary parameters will be $AUEC_{0-t}$ calculated on RVNA measured above 0.5 IU/mL. All other PD parameters will be regarded as secondary parameters (refer to Sections10).

The safety, immunology and PK parameters will be regarded as secondary (refer to Sections 9, 11, and12).

6. Analysis Populations

The analysis of safety and tolerability parameters will be based on the safety population detailed in Section 6.1 below. The analysis of immunogenicity (anti-SYN023 antibodies), PK, and PD parameters will be based on the Per-Protocol population detailed in Section 6.2 below.

6.1 Safety Population

The safety population will consist of all randomized subjects who received at least one dose of a study treatment. Treatment allocation will be based on as treated principle.

6.2 Per-Protocol Population

The PP population will consist of all randomized subjects who received all scheduled doses of a study treatment and remained on study for at least 28 days without major protocol violation. Treatment allocation will be based on as treated principle.

7. Interim Analyses

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

8. Study Population and Exposure

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in a separate document; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

No inferential analyses will be done.

8.1 Subject Disposition

Subject disposition will be summarized by treatment groups (frequency and the percentage of subjects) and overall and listed by subject. The reason for discontinuation will be also listed.

8.2 Protocol Deviations

The protocol deviations will be collected in the categories as outline on the CRF; these will be listed by subject.

8.3 Demographics and Baseline Characteristics

The descriptive statistics (mean, median, standard deviation [SD], minimum [Min], maximum [Max], and sample size) will be calculated for continuous variables (age, body mass index [BMI], height, and weight). Frequency counts and percentages will be tabulated for categorical variables (age group, gender, ethnicity, and race). All summaries will be presented overall and by treatment groups. All demographic characteristics will be listed by subject.

8.4 Medical History

All conditions that existed prior to administration of the study drug (pre-existing conditions) will be recorded in the subject's medical history to establish baseline. Medical history will be listed by subject. The Medical Dictionary for Regulatory Activities (MedDRA®) Version 19.1 will be used to classify all medical history findings by System Organ Class (SOC) and Preferred Term (PT).

8.5 Prior and Concomitant Medications

The use of concomitant medications will be monitored throughout the study. The World Health Organization Drug Dictionary Enhanced (WHO DDE) Version Sep2016, format B will be used to classify all medication reported during the study.

Prior and concomitant medications will be listed by subject.

8.6 Study Drug Administration

The study vaccine administration details, including treatment received, location of administration, and date and time of administration, will be listed by subject.

9. Safety Analyses

Safety and tolerability to SYN023 will be evaluated through the assessment of adverse events (AEs), clinical laboratory parameters, ECGs and vital signs measurements, clinical signs and symptoms from physical examination. AEs, clinical laboratory parameters, ECGs and vital signs measurements will be summarized by treatment groups and timepoint of collection.

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in a separate document; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

Safety data will be summarized but will not be subjected to inferential analysis.

9.1 Physical Examination Findings

A physical examination will be performed at screening. A focused physical examination will be performed on Day 0 till Day 112. New or worsened abnormalities will be recorded as AEs, if judged appropriate by the QI or Medical Sub-Investigator.

Any abnormal findings judged to be clinically significant will be documented as medical history or as an AE, depending upon time of observation, as appropriate. Any physical examination findings documented as AEs will be included in the AE analyses.

9.2 Solicited Adverse Events and Injection Site Reactions and Unsolicited Adverse Events

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

The MedDRA® dictionary Version 19.1 will be used to classify all AEs reported during the study by SOC and PT.

9.2.1 Solicited Adverse Events and Injection Site Reactions

Solicited AEs will be events the subject is specifically asked about. These AEs are commonly observed soon after injection of study antibody. The solicited AE reporting period begins with the day of vaccination (Day 0) through Day 28 inclusively. Solicited local AEs to be collected include the following: injection site (s) pain, tenderness, redness swelling, warmth, skin disruption and regional lymphadenopathy. Non-local solicited AEs include headache, arthralgia, myalgia, rash, pruritus, urticaria, dyspnea, chest pain, cough, fever and chills. Solicited AEs of local injection site reactions (i.e., pain at injection site, redness at injection site, or swelling at injection site) will be considered causally related to study vaccine (adverse reaction).

Summary of descriptive statistics for solicited AEs (incidence of subjects with percentages and incidence of solicited AEs) will be presented by treatment and overall, SOC, PT, by investigator-assessed relationship (Not Related, Unlikely Related, Possible, Probable, and Definite) and

severity (Mild, Moderate, and Severe). For incidence of subject calculations, each subject may only contribute once to each of the incidence rates, for a solicited AE following a given treatment, regardless of the number of occurrences; the highest severity or highest relationship will be presented, as appropriate.

In each table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates). For each SOC, PT will be presented the same way.

All solicited AEs will be listed.

9.2.2 Unsolicited Adverse Events

Unsolicited AEs are any unsolicited unfavorable or unintended sign, symptom, disease, syndrome, abnormal laboratory finding, or concurrent illness that emerges or worsens after receipt of study vaccine relative to the subject's pre-treatment baseline, whether or not it is considered to be related to the medicinal product. The unsolicited AE reporting period begins with the day of vaccination (Day 0) through Day 42 inclusively. Additionally, any solicited AE (local or systemic) that persist beyond Day 28 will be recorded as an unsolicited AE.

Summary of descriptive statistics for unsolicited AEs (incidence of subjects with percentages and incidence of unsolicited AEs) will be presented by treatment and overall, SOC, PT, by investigator-assessed relationship (Not Related, Unlikely Related, Possible, Probable, and Definite) and severity (Mild, Moderate, and Severe). For incidence of subject calculations, each subject may only contribute once to each of the incidence rates, for an unsolicited AE following a given treatment, regardless of the number of occurrences; the highest severity or highest relationship will be presented, as appropriate.

In each table, SOC will be presented in descending order of overall incidence rate in terms of frequency of subjects and then in frequency of events (alphabetical order will be used in case of equal rates). For each SOC, PT will be presented the same way.

All unsolicited AEs will be listed.

9.2.3 Serious Adverse Events

A serious adverse event (SAE) is an AE meeting the outcome criteria for seriousness regardless of relationship to an administered medicinal product. SAEs are captured and recorded from the time of administration through Day 112 inclusively.

SAEs will be listed separately.

9.3 Laboratory Parameters

Clinical laboratory (serum chemistry, hematology, and urinalysis) testing will be performed at screening, on Day 0, Day 1, Day 3, Day 7, Day 14, Day 28 and Day 112. In addition Urinalysis will be performed on Day 35 and Day 42. Coagulation tests will be performed at screening, Day 0, Day 7 and Day 112.

Serum chemistry parameters should include the following: creatinine phosphokinase (CPK), troponin, total bilirubin, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Alkaline phosphatase (ALP), creatinine, blood urea nitrogen, sodium, potassium, chloride, bicarbonate, calcium.

Hematology parameters should include the following: complete blood count with differential, hemoglobin, hematocrit, and platelet.

Coagulation parameters should include the following: Prothrombin time (international normalized ratio) (PT (INR)) and Partial thromboplastin time (PTT).

Urinalysis parameters should include the following: macroscopic examination, pH, specific gravity, protein, glucose, ketones, bilirubin, occult blood, nitrite, urobilinogen, and leukocytes. Unless otherwise specified, microscopic examination will be performed on abnormal findings only and results will be listed.

Listings of all clinical test results (serum chemistry, coagulation, hematology, and urinalysis) will be provided with the abnormal values flagged with "L" for low and "H" for high for continuous parameters, and "A" for abnormal categorical parameters.

Descriptive statistics (mean, median, SD, Min, Max, and sample size) will be presented overall for screening and by the associated current treatment for on-study measurements for each clinical laboratory test (continuous variables). Change from baseline descriptive statistics for on-study measurements will also be presented. Baseline will be defined as the last results (scheduled or unscheduled) obtained prior to the first study vaccine administration. For categorical variables (urinalysis tests), the number of subjects (frequency and percentage) will be tabulated for each individual result (e.g. negative, positive, trace). Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A summary table of shifts from baseline to on-study measurements will be provided. Baseline will be defined in the same manner as described in the preceding paragraph for continuous variables. The shift tables will include normal, low, and high relative to the laboratory reference ranges (or normal-abnormal for categorical variables). Results from repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

If more than one clinical laboratory is used for the study, a formula that takes into consideration the relative normal ranges of each test of laboratories used will be applied in order to normalize these data. The conversion formula used will depend on the typical distribution of the normal range for each laboratory test; the two formulae used are presented below:

- Hemoglobin, hematocrit, and platelet count test results are considered to have a normal distribution (Chuang-Stein, 1992) and the following formula will be used (Karvanen J., 2003):

$$s = L_s + (x\text{-}L_x)\frac{U_s\text{-}L_s}{U_x\text{-}L_x}$$

where U= Upper limit; L= Lower limit; s= Primary facility result; and x= Secondary facility results.

- The remaining hematology, serum chemistry, and urinalysis test results are considered to have a non-normal distribution (Chuang-Stein, 1992) and the following formula will be used (Karvanen J., 2003):

$$s = \frac{x\,U_s}{U_x}$$

Prior to applying these formulae, if required, units will be adjusted.

9.4 Vital Signs

Vital signs measurements (blood pressure, and heart rate, respiratory rate and oral temperature) will be performed at screening, on Day 0, Day 1, Day 3, Day 7, Day 14, Day 28, and Day 112.

Descriptive statistics (mean, median, SD, Min, Max, and sample size) will be presented overall for screening and by the associated current treatment for on-study measurements and each vital sign measurement. Descriptive statistics for change from baseline for on-study measurements will also be presented. Baseline will be defined as the last results (scheduled or unscheduled) obtained prior to the first study vaccine administration. Results from on-study repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all vital signs results will be provided.

9.5 Electrocardiogram

ECGs measurements will be performed at the time of screening, on Day 0, Day 1, Day 3, Day 7, Day 14, Day 28, and 112. The quantitative ECG measurements are heart rate (HR) or ventricular rate (VR), PR interval, QRS interval, QT interval, QTcB interval (Bazett formula correction), and QTcF interval (Fridericia's formula correction).

Descriptive statistics (mean, median, SD, Min, Max, and sample size) will be presented overall for screening and by the associated current treatment for on-study measurements and each ECG measurement. Descriptive statistics for change from baseline for on-study measurements will also be presented. Baseline will be defined as the last results (scheduled or unscheduled) obtained prior to the first study vaccine administration. Results from on-study repeat tests will not be included in the summary statistics unless the repeat was required (and documented as such) due to technical reasons or an invalid initial result.

A listing of all ECG results will be presented.

10. Efficacy/Pharmacodynamic (Serum Rabies Virus Neutralizing Activity) Analyses

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in a separate document; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

Efficacy/PD analyses will be performed on PP population.

10.1 Handling of the BLQ and the No Reportable Concentration Values

All concentration values below the lower limit of quantification (BLQ) will be set to zero. Samples with no reportable value occurring prior to the first dosing will be replaced by "0.00" otherwise they will be set to missing for tabulation, graphical representation and calculation purposes.

10.2 Handling of the Difference Between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each collection time for the efficacy/PD samples will be recorded using the electronic data capture. For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times expressed in hours and rounded off to three decimal digits will be used to calculate the efficacy/PD parameters, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. Scheduled sampling times will be presented in concentration tables and mean figures, while actual sampling times will be presented in the figures of individual results in the PK section of the report. A listing of the actual times will be provided for efficacy/PD samples.

10.3 Efficacy/Pharmacodynamic Parameters

A total of 10 blood samples will be drawn from each subject for efficacy/PD analyses. Blood samples will be collected on Day 0, Day 1, Day 3, Day 7, Day 14, Day 28, Day 35, Day 42, Day 84, and Day 112.

RVNA will be used to calculate the following parameters by standard non-compartmental methods:

$AUEC_{0-t}$: area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 0 to the last measurable concentration, calculated using the linear trapezoidal method. Unit will be Day*IU/mL.

$AUEC_{0-7}$: area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 0 to 7 days, calculated using the linear trapezoidal method. In case where the 7 days RVNA value is missing, $AUEC_{0-7}$ will be interpolated at the discretion of the pharmacokineticist. Unit will be Day*IU/mL.

$AUEC_{0-14}$: area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 0 to 14 days, calculated using the linear trapezoidal method. In case where the 14 days RVNA value is missing, $AUEC_{0-14}$ will be interpolated at the discretion of the pharmacokineticist. Unit will be Day*IU/mL.

$AUEC_{14-t}$: area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 14 days to the last measurable concentration, calculated using the linear trapezoidal method. In case where the 14 days RVNA value is missing, $AUEC_{14-t}$ will be interpolated at the discretion of the pharmacokineticist. Unit will be Day*IU/mL.

$AUEC_{14-35}$: area under the effect-time curve above the minimum rabies virus neutralizing activity threshold (0.5 IU/mL) from time 14 days to 35 days, calculated using the linear trapezoidal method. In case where the 14 days or 35 days RVNA value is missing, $AUEC_{14-35}$ will be interpolated at the discretion of the pharmacokineticist. Unit will be Day*IU/mL.

E_{max}: maximum observed effect. Unit will be IU/mL.

$T_{max,E}$: time of observed E_{max}. Unit will be Day.

Some efficacy/PD parameters may not be calculated for all or some subjects, at the discretion of the inVentiv pharmacokineticist, if the concentration data is not deemed to be amenable to evaluation. Explanations for efficacy/PD parameters that could not be estimated will be provided in the CSR.

10.4 Statistical Analyses

Individual and mean RVNA versus time curves will be presented using linear and semi-log scales for RVNA. Listings and descriptive statistics (number of observations, arithmetic mean, SD, coefficient of variation [CV%], median, Min, Max, geometric mean, and the percentage of subjects with RVNA values above 0.5 IU/mL [% > 0.5 IU/mL]) of the RVNA versus time as well as all PD parameters will be provided for each treatment.

For inferential analyses, data will be analysed as a two-factor factorial design. The two factors will be Vaccine including 2 levels (RVi and RVa) and Conmed including 2 levels (RIG and SYN023) as described in Table 10-1.

Table10-1: Two-factor factorial design with Vaccine and Immune Globulin (IG) as factors

		IG	
		RIG	SYN023
Vaccine	RVi	N_A=40	N_C=40
	RVa	N_B=40	N_D=40

Where N_X is the number of subjects planned to be dosed for Treatment X (X=A, B, C, D).

10.4.1 **Similarity Acceptance**

Using GLM procedures in SAS®, ANOVA will be performed on untransformed $T_{max,E}$ and ln-transformed $AUEC_{0-t}$, $AUEC_{0-7}$, $AUEC_{0-14}$, $AUEC_{14-t}$, $AUEC_{14-35}$, and E_{max} at the alpha level of 0.05. Factors incorporated in the model will include: Vaccine, IG, and Vaccine*IG. Vaccine, IG, and Vaccine*IG will be tested against the residual mean square error. In the case of a non-statistically significant Vaccine*IG interaction term, the analysis will be rerun excluding this term from the ANOVA model in order to obtain ratios and confidence intervals where appropriate. In the case of statistically significant Vaccine*IG interaction term, the analysis will be rerun for each vaccine separately. All sums of squares (Types I, II, III and IV) will be reported. Probability (p) values will be derived from Type III sums of squares. Coefficients of variation (CV%) will be estimated.

Based on pairwise comparisons of the ln-transformed $AUEC_{0-t}$, $AUEC_{14-t}$, and E_{max} data, the ratio (RIG/SYN023) of the geometric least-squares means, calculated according to the formula "$e^{(X-Y)} * 100$", as well as the corresponding 90% geometric confidence intervals will be determined.

For $AUEC_{14-t}$, a statistically significant Vaccine*Conmed interaction term will be interpreted as a possible interference of RIG or SYN023 on the vaccines. In this case, each vaccine will be investigated separately.

Additional analyses may be performed.

Criteria for Similarity

Considering PP population, the 90% geometric confidence intervals of the ratio (RIG/SYN023) of least-squares means from the ANOVA of the ln-transformed $AUEC_{0-t}$ must be within 80.00% to 125.00%.

10.4.2 **RIG vs. SYN023 Comparison by Timepoint**

Using GLM procedures in SAS®, ANOVA will be performed separately on ln-transformed RVNA at Day 1, Day 3, Day 7, Day 14, Day 28, Day 35, Day 42, Day 84, and Day 112 at the alpha level of 0.05. Factors incorporated in the model will include: Vaccine, Conmed, and Vaccine*Conmed. Vaccine, Conmed, and Vaccine*Conmed will be tested against the residual mean square error. In the case of a non-statistically significant Vaccine*Conmed interaction term, the analysis will be rerun excluding this term from the ANOVA model in order to obtain ratios and confidence intervals where appropriate. In the case of statistically significant Vaccine*Conmed interaction term, the analysis will be rerun for each vaccine separately. All sums of squares (Types I, II, III and IV) will be reported. Probability (p) values will be derived from Type III sums of squares. Coefficients of variation (CV%) will be estimated.

Based on pairwise comparisons of the ln-transformed Day 1, Day 3, Day 7, Day 14, Day 28, Day 35, Day 42, Day 84, and Day 112 data, the ratio (RIG/SYN023) of the geometric least-squares means, calculated according to the formula "$e^{(X-Y)} * 100$", as well as the corresponding 90% and 95% geometric confidence intervals will be determined.

Additional analyses may be performed.

11. Immunogenicity: Anti-SYN023 Antibodies Analyses

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in a separate document; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

Immunogenicity analyses will be performed on PP population. No inferential analysis will be done.

11.1 Immunogenicity Parameters

A total of 8 blood samples will be drawn from each subject for anti-SYN023 antibodies analyses (anti-CTB011 and anti-CTB012). Blood samples will be collected on Day 0, Day 7, Day 14, Day 28, Day 35, Day 42, Day 84, and Day 112.

A figure presenting the proportion of subjects with positive anti-CTB011 and anti-CTB012 results over time will be provided.

No formal parameter will be calculated.

11.2 Statistical Analyses

For anti-CTB011 and anti-CTB012, the number of subjects (frequency and percentage) will be tabulated for each individual result (e.g. negative or positive)

Additional analyses may be performed.

12. Pharmacokinetic Analyses

Shells for all summary descriptive statistic tables and listings referred to in this section are displayed in a separate document; the shells may be revised as they are presented to illustrate the general layout of data to be included in the final report.

PK analyses will be performed on PP population. No inferential analysis will be done.

12.1 Handling of the BLQ and the No Reportable Concentration Values

All concentration values below the lower limit of quantification (BLQ) will be set to zero. Samples with no reportable value occurring prior to the first dosing will be replaced by “0.00” otherwise they will be set to missing for tabulation, graphical representation and calculation purposes.

12.2 Handling of the Difference Between the Scheduled and the Actual Sampling Times

The actual clock time for dosing and the actual clock time for each collection time for the PK samples will be recorded using the electronic data capture. For all sampling times, the actual sampling times will be calculated as the difference between the sample collection actual clock time and the actual clock time of dosing. The actual post-dose sampling times expressed in

hours and rounded off to three decimal digits will be used to calculate the PK parameters, except for pre-dose samples occurring prior to dosing, which will always be reported as zero (0.000), regardless of the time difference. Scheduled sampling times will be presented in concentration tables and mean graphs, while actual sampling times will be presented in the individual graphs in the PK section of the report. A listing of the actual times for PKs will be provided for PK samples.

12.3 **Pharmacokinetic Parameters**

A total of 9 blood samples will be drawn from each subject for PK analyses. Blood samples will be collected on Day 0, Day 1, Day 3, Day 7, Day 14, Day 28, Day 35, Day 42, and Day 84.

For subjects receiving Treatment C (RVi + SYN023) or Treatment D (RVa + SYN023), serum concentrations from CTB011 and CTB012 will be used to calculate the following parameters separately by standard non-compartmental methods:

AUC_{0-t}:	area under the concentration-time curve from time zero to the last non-zero concentration, calculated using the linear trapezoidal method. Unit will be Day*ng/mL.
AUC_{0-inf}:	area under the concentration-time curve from time zero to infinity (extrapolated), calculated as $AUC_{0-t} + C_t / K_{el}$, where: C_t = the last observed non-zero concentration. Unit will be Day*ng/mL.
C_{max}:	maximum observed concentration. Unit will be ng/mL.
T_{max}:	time of observed C_{max}. Units will be Day
$T_{½\ el}$:	elimination half-life, calculated as ln(2)/ K_{el}. Unit will be Day.
K_{el}:	elimination rate constant. This parameter will be the negative of the estimated slope of the linear regression of the ln-transformed concentration versus time profile in the terminal elimination phase. At least 3 concentration points will be used in estimating K_{el}. The actual sampling time where ln-linear K_{el} calculation begins ($K_{el\ Lower}$) and the actual sampling time of the last quantifiable concentration used to estimate the K_{el} ($K_{el\ Upper}$) will be reported with the correlation coefficient from the linear regression to calculate K_{el} (Correlation). Unit will be /Day.
Clp:	Plasma clearance, calculated as Dose/AUC_{0-inf}. Units will be L.
Clp/kg:	Plasma clearance normalized for the subject body weight in kg, calculated as Dose/AUC_{0-inf}/weight. Units will be L/kg.

The K_{el}, $T_{½\ el}$, AUC_{0-inf}, Clp and Clp/kg parameters will not be estimated for serum concentration-time profiles where the terminal linear phase is not clearly defined.

Some PK parameters may not be calculated for all or some subjects, at the discretion of the inVentiv pharmacokineticist, if the concentration data is not deemed to be amenable to

evaluation. Explanations for PK parameters that could not be estimated will be provided in the CSR.

12.4 Statistical Analyses

No statistical analysis is planned on samples obtained from subjects who received Treatment A (RVi + RIG) and Treatment B (RVa + RIG), but any cases of detectable and quantifiable levels observed in these subjects (for those who were analyzed) will be addressed descriptively in the PK report.

For Treatment C (RVi + SYN023) and Treatment D (RVa + SYN023), individual and mean serum concentration versus time curves will be presented using linear and semi-log scales for SYN023. Listings and descriptive statistics (number of observations, arithmetic mean, SD, coefficient of variation [CV%], median, Min, Max, and geometric mean) of the concentrations versus time as well as all PK parameters will be provided for each treatment.

Only descriptive statistics will be used to compare Treatment C and Treatment D.

A table and figures (individual and mean versus time curves) presenting RVNA on SYN023 concentrations ratios over time will be provided. For a given scheduled timepoint, the ratio will be defined as

$$\text{Ratio} = \frac{\text{RVNA}}{\text{CTB011 concentration} + \text{CTB012 concentration}}$$

No attempt will be made to extrapolate or interpolate to correct any concentrations in case of time deviations for ratios calculation. Results will be presented using scheduled times.

Additional analyses may be performed.

13. Data Handling

Safety, tolerability, immunogenicity, efficacy/PD and PK data will be received as SAS® datasets from the data management facility

14. Handling of Missing Data

Only observed data will be used in the data analysis except for concentration values BLQ and samples with no reportable value occurring prior to dosing as described in Section 10, 11, and 12 No attempt will be made to extrapolate or interpolate estimates for missing data.

15. Software to be Used

Efficacy/PD and PK analysis will be performed using Phoenix WinNonlin® version 6.4, which are validated for bioequivalence/bioavailability studies by inVentiv. The inferential statistical analyses, the safety data tables and listings, the efficacy/PD data tables and listings, the immunogenicity data tables and listings as well as PK tables and listings will be created using SAS®, release 9.2 or a higher version. PK figures will be created using R version 3.2.2 (or

higher). The PK report text will be created using Microsoft® Office Word 2010, or a higher version.

16. Reference List

- Chuang-Stein C. Summarizing laboratory data with different reference ranges in multi-center clinical trials. Drug Information Journal. 1992; 26:77-84.
- Karvanen J. The statistical basis of laboratory data normalization. Drug Information Journal. 2003; 37:101-107