A Prospective, Randomized, Blinded, Parallel-group, Non-inferiority Phase II/III Study of the Safety and Effectiveness of BPL HRIG With Co-administration of Active Rabies Vaccine in Healthy Subjects

Study Code: RIG01

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Statistical Analysis Plan

Based on Protocol Version 1.0, 26 October 2017

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Prepared by:

APPROVAL SIGNATURES

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Protocol: RIG01

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[redacted] Date

[redacted] Oct 31, 2017

[redacted] Date

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1. SYNOPSIS

RIG01 is a randomized, blinded, parallel group study intended to obtain data required for a license application in the US and other regions. This will be achieved by comparing the safety and effectiveness of BPL HRIG, administered in conjunction with rabies vaccine in accordance with the licensed dosing schedule for post-exposure prophylaxis, with the safety and effectiveness of a licensed comparator HRIG, also given in conjunction with rabies vaccine.

The doses of BPL HRIG and comparator HRIG to be administered in this study, of 20 IU/kg, are consistent with the licensed doses. Unlike the licensed method of administration, which requires the vaccine to be administered in and around the wound, in this study HRIG will be administered to the lateral thigh muscles and, if required by the volume to be administered, to the deltoid muscle. This will result in a more consistent absorption of antibody from the intramuscular compartment between subjects and therefore allow an accurate analysis of the PK of HRIG.

It is unethical to investigate the efficacy of BPL HRIG in patients exposed to rabies virus due to the almost invariable fatal nature of the disease. Therefore, in this study, PK of HRIG when given in conjunction with active rabies vaccine to healthy volunteers will be used as a surrogate marker of HRIG efficacy. The pharmacokinetic goal of rabies post-exposure prophylaxis is to achieve a serum rabies antibody titer of ≥0.5 IU/mL on study Day 14.

2. STUDY OBJECTIVES

The objectives of this study are:

1. To demonstrate non-inferiority of BPL HRIG compared to an FDA-licensed HRIG product, in terms of the proportion of subjects achieving anti-rabies antibody titer of ≥0.5 IU/mL at Day 14 following treatment with HRIG in conjunction with active rabies vaccine.

2. To compare the PK of BPL HRIG in conjunction with active rabies vaccine, with FDA-licensed HRIG product in conjunction with active rabies vaccine.
3. To assess whether BPL HRIG interferes with the development of the host-immune response when given simultaneously with active rabies vaccine, relative to an FDA-licensed HRIG product.
4. To evaluate the safety and tolerability of BPL HRIG in comparison with FDA-licensed HRIG product.

3. SAMPLE SIZE AND POWER COMPUTATION

Statistical calculations indicate a minimum of [redacted] subjects per group is necessary. To allow for a [redacted] rate of subject withdrawal or unevaluable data, approximately 81 subjects will be enrolled per group.

This study is powered based on a [redacted] test with an overall study α of [redacted]. A total of 162 subjects will be randomized to achieve [redacted] power with a one-sided significance level of [redacted]. This computation accounts for an expected 10% dropout rate resulting in 146 evaluable subjects. The following table outlines the underlying assumptions.

	Day 14 $\geq$ 0.5 IU/mL
Non-inferiority Margin	[redacted]
Difference	[redacted]
% Success	98%

4. STUDY DESIGN

This will be a prospective, randomized, double-blind, parallel-group, non-inferiority, phase II/III study of the safety and effectiveness of simulated post-exposure prophylaxis with BPL HRIG with co-administration of active rabies vaccine in healthy subjects. This is intended to be a multi-center study. Treatment assignment is blinded until post database lock.

Subjects will be randomized 1:1 to one of the 2 treatment groups, as follows:

HRIG treatment	Rabies vaccine treatment	# of Subjects
BPL HRIG	active rabies vaccine	81
comparator HRIG	active rabies vaccine	81

Prior to randomizing a participant, all screening and baseline evaluations must be completed and the participant determined to be eligible for inclusion in the study. Randomization and the baseline visit (Day 0) should occur no later than 28 days after the completion of the screening visit.

All medicinal product preparation will be performed by the site pharmacist using aseptic techniques and according to a standardized procedure on Day 0, and administration of HRIGs + vaccine will be administered an unblinded nurse administrator. All study assessments and Post Day 0 treatment administration will be performed by blinded study personnel. Investigators and subjects will be blinded to treatment assignment.

Subjects will be identified by a unique five-digit number as follows: each site will be allocated a two-digit site number (e.g. Site 01, etc) and each subject will be allocated a three-digit subject number (e.g. 001) at the Screening Visit. Each subject will be identified by the unique site and subject number combination (e.g. 01001).

5. SCHEDULE OF ASSESSMENTS

Each subject will undergo a total of 8 visits. Subjects' eligibility will be assessed at Screening, which can occur up to 28 days prior to dosing. Following a repeat eligibility check at Day 0, eligible subjects will be randomized and dosed with the randomized treatment (HRIG/vaccine or Comparator HRIG/vaccine on Day 0. Further administration of rabies vaccine, PK sampling and safety assessments will be conducted on Days 3, 5 (PK sampling only), 7, 14 and 28. An additional visit for PK sampling and safety assessment will take place on Day 49 (7 weeks) and Day 140 (20 weeks). The last visit will be the End-of-Study Assessment which will take place on Day 140 (20 weeks). This visit will comprise the final PK sample and safety assessments. The end of the trial is

defined as the last subject's last End-of-Study Assessment (or the date of their last data collected, if the subject has an AE at the End-of-Study Assessment that needs to be followed).

Visit Number	**1**	**2**			**3**	**4**	**5**	**6**	**7**	**8**	**9**
Visit Assessment	**Screening**	**Baseline**									**End-of-Study Assessment**
Visit Timing	**up to Day -28**	**Day 0**			**Day 3**	**Day 5**	**Day 7**	**Day 14**	**Day 28 (±2 days)**	**Day 49 (±4 days)**	**Day 140 (±7 days)**
		pre-dose	dosing	30 min post-dose							
Informed Consent[a]	X										
Demography/Medical History	X										
Eligibility	X	X									
Physical Examination	X									X	X
Height	X										
Weight	X	X[b]									X
ECG	X										X
Vital Signs	X	X							X	X	X
Body Temperature (oral)		X			X		X	X	X		
Pregnancy Test[c]	X	X									X
Hematology, Serum Biochemistry, Urinalysis	X										X
Virology: HBsAg, HCV, HIV	X										X
Markers of Hemolysis: Direct Coomb's Test, LDH, Plasma Free Hemoglobin, Serum Haptoglobin, Serum bilirubin, Urine Hemosiderin		X			X[d,k]	X[d,k]	X[d,k]	X[e,k]			
Archive Serum Sample*		X									X
Randomization[f]		X									
Administration of BPL HRIG / Competitor HRIG			X								
Administration of Active Rabies Vaccine			X		X		X	X	X		
Rabies Virus Neutralizing Antibody		X			X[g]	**X**[J]	X[g]	X[g]	X[g]	X	X
Reserve Sample Collection[h]	X	X			X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X
Injection Site Observations[i]		X		X							
Concomitant Medications	X	X			X	X	X	X	X	X	X

[a] informed consent prior to screening procedures
[b] for re-assessment of eligibility and calculation of volume to be administered
[c] females of childbearing potential only: serum at screening and End-of-Study Assessment, urine dipstick pre-dose on Day 0
[d] if the Day 3 Direct Coomb's test is positive or not available by Day 5, all markers will be tested at Day 5. Subsequent testing at Day 7 and Day 14 will only be performed if results at the previous visit are suggestive of hemolysis
[e] if hemolysis is indicated at Day 7, all markers will be tested at Day 14
[f] after all screening and baseline procedures have been completed and the subject is confirmed as eligible
[g] prior to dose of active rabies vaccine

[h] 2 samples will be collected at each timepoint, except for the Baseline Visit (Day 0) and the End-of-Study (EOS) Assessment (Day 140) at which 3 samples will be taken.
The additional plasma reserve samples will be taken in case viral nucleic acid testing is required to confirm viral serology results (see Section 8.2.3)
[i] to be assessed at each subsequent visit until no symptoms are observed
[j]. bloods draw only **NO** vaccine at this visit
*archive serum sample-pre-dose, Day 0 and EOS, to be archive for approximately 15 years
k routine hematology, chemistry or urinalysis can be repeated if clinically indicated or at the request of the medical monitor

6. STUDY ENDPOINTS

The PRIMARY efficacy endpoint is to demonstrate non-inferiority of BPL HRIG compared to a FDA-licensed HRIG product, in terms of:

- the proportion of subjects with anti-rabies antibody titer of $\geq$ 0.5 IU/mL on day 14 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine, using a non-inferiority margin of 10%.

The SECONDARY efficacy endpoints are as follows:

1. Assessment of AUC $_{0\text{-}7days}$ for BPL HRIG+vaccine vs. comparator HRIG+vaccine using a non-inferiority margin of 20%.
2. Comparison of the geometric mean titers (GMTs) for anti-rabies antibody titer at Days 3, 5, 7, 14, and 28 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine.
3. The proportion of subjects reaching anti-rabies antibody titer of ≥0.5 IU/mL at Days 3, 5, 7, 14, 28, 49, and 140 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine.
4. The proportion of subjects reaching anti-rabies antibody titer of ≥ the lower limit of quantitation of the assay at Days 3, 5, 7, 14, 28, 49 and 140 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine.
5. Comparison of the geometric mean titers (GMTs) for anti-rabies antibody titer at Days 14, 28, 49, and 140 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine to assess the inhibitory effects of BPL HRIG on active immunization relative to that of the comparator HRIG.

An EXPLORATORY efficacy endpoint is as follows:

The following PK parameters for anti-rabies antibody concentrations for both treatment groups:

- C_{max} [IU/mL]
- T_{max} [day]
- area under the concentration vs time curve to the last measurable concentration (AUC_{0-t}) [day*IU/mL]
- apparent terminal rate constant (λ_z) [day^{-1}]
- $AUC_{0-7\ days}$ [day*IU/mL]
- area under the concentration vs time curve to infinity ($AUC_{0-\infty}$), if appropriate
- $Cmax/AUC_{0-\infty}$ [or $Cmax/AUC_{0-t}$ if $AUC_{0-\infty}$ cannot be estimated]
- half-life ($t_{½}$), if appropriate

The following will be used to assess the SAFETY of BPL HRIG and vaccine, versus comparator HRIG and vaccine:

- Adverse events
- Injection site observations
- Viral serology
- Serum biochemistry, hematology and urinalysis
- Markers of hemolysis
- Physical examination
- Vital signs

The following additional tests will additionally be performed:

- pregnancy tests (for females of childbearing potential).

7. GENERAL ANALYSIS CONVENTIONS

All tables, figures and listings will be produced using SAS (v9.4 or a more recent version).

Unless otherwise stated, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, 95% confidence interval for the mean, standard deviation (SD), median, minimum, maximum, number of subjects (n) and number of missing subjects or data points. Minima and maxima will be quoted to the number of decimal places as recorded in the CRF; means, SDs and medians will be quoted to one further decimal place. Percentages will be rounded to one decimal place.

Subjects who withdraw from the analysis will have their data analyzed to the point of withdrawal. Subjects who complete all required assessments up to and including Day 14 will be eligible for the primary PK population. Other subjects who withdraw from the study will be eligible for the ITT population. Unblinded subjects will continue in study after being unblinded unless noted otherwise.

For the purpose of the statistical analyses visit labels may be used interchangeably as Visit and Day as in the table below regardless of actual timing of study visit. Sensitivity analyses will be performed to address any potential visit timing issues.

Visit Label	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9
Intended Day	Day -28	Baseline, Day 0	Day 3	Day 5	Day 7	Day 14	Day 28	Day 49	Day 140

a. DEFINITION OF STATISTICAL SIGNIFICANCE

- Primary Efficacy Endpoint

The BPL HRIG treatment effect will be considered non-inferior to the active comparator HRIG treatment when the resultant p-value from the one-sided Farrington-Manning

Score Test for proportion difference is [redacted].

- Secondary Efficacy Endpoints

The secondary efficacy endpoint analyses will be considered statistically significant using a two-sided significance level of 0.05.

b. Analytic Populations

The following analysis populations will be defined for this study.

- Intent-to-Treat [ITT] Population

The intent-to-treat (ITT) population will include all randomized subjects. All analyses will be performed using the ITT population.

- Safety Population

The safety population will be defined as all subjects who receive at least one dose of BPL HRIG / comparator HRIG. Safety data will be analyzed up to the point of withdrawal for applicable subjects. The safety population will be used for all safety analyses.

- Per Protocol [PP] Population

The per protocol population will be split into the **primary** and **secondary** PK populations.

The **primary PK population** will be defined as all subjects who receive the full dose of BPL HRIG / comparator HRIG and the first 3 doses of active rabies vaccine on Visits 2, 3, and 5, and for whom the PK sample at Visit 6 is taken. This population will be used for the primary PK analysis and selected secondary PK analyses. The **secondary PK population** will be defined as all subjects who receive the full dose of BPL HRIG / comparator HRIG and all 5 doses of active rabies vaccine and for whom all required PK samples are taken. This population will be used for selected secondary PK analysis and the exploratory analysis.

Subjects with a pre-dose RVNA of ≥ the LLOQ will be excluded from the all

analyses.

[redacted]

8. ANALYSES AND SUMMARIES

a. DESCRIPTIVE STATISTICS

For continuous and pseudo-continuous variables, the number of observations, number of missing values, mean, standard deviation, median, twenty-fifth percentile, and seventy-fifth percentile will be given. For yes/no, categorical, and/or ordinal variables a simple count and percent or frequency will be given. Other statistics may be considered if necessary.

b. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristic data will include age (based on date of informed consent), sex, race, ethnicity, height, weight, and body mass index (BMI). All demographic and baseline characteristic data will be summarized. An analysis of variance [ANOVA] will be used to assess homogeneity regarding demographic characteristics between treatment groups.

c. MEDICAL HISTORY

Medical history is collected at screening and will be summarized by treatment group.

d. EFFICACY ANALYSES

PK is a surrogate for efficacy, since a titer of ≥ 0.5 IU/mL is well-established as protective against the rabies virus. RVNA titers will be listed for each subject, and summary statistics for each timepoint presented by treatment group.

e. PRIMARY EFFICACY ANALYSIS

The primary efficacy analysis will be based on the primary PK population.

The primary hypothesis is that the proportion of subjects receiving BPL HRIG + active vaccine with an anti-rabies antibody of ≥ 0.5 IU/mL will not be less than the corresponding proportion for subjects receiving comparator HRIG + active vaccine, by more than 0.1 at Visit 6. The Farrington and Manning test statistic will be used to assess the statistical comparison of the proportions at a one-sided significance level of [redacted] It will be concluded that the BPL HRIG is non-inferior to the comparator HRIG if the lower limit of an exact binomial 95% confidence interval is greater than the *a priori* set [redacted] non-inferiority margin.

HYPOTHESIS

The null hypothesis is p-p0 ≤ -0.1;

The alternative hypothesis is p-p0 > -0.1,

where p is the proportion of subjects with RVNA titer of ≥0.5 IU/mL at Visit 6 in subjects receiving BPL HRIG + vaccine and p0 is the proportion receiving comparator HRIG + vaccine

We reject the null hypothesis at the one-sided [redacted] significance level, and conclude that p-p0 > -0.1, if the lower bound of an exact 95% binomial confidence interval exceeds -0.1.

DERIVATION OF PRIMARY ENDPOINT

[redacted] will be performing the RFFIT test and providing the results for data analysis. Subject serum will be tested in duplicates. If either individual test in duplicated set 1 fails QC, a second duplicate set of RFFIT tests will be run. The arithmetic mean value of the appropriate duplicate set, (set 1 if QC passed, set 2 if QC failed), will be used for the final reported rabies antibody titer [IU] for primary endpoint derivation. If the final arithmetic mean value is ≥0.5 IU/mL that subject-specific time point will be coded as 1 (success); otherwise if the final arithmetic mean value is < 0.5 IU/ml the time point will be coded as 0 (failure). If both duplicate sets fail the QC test,

the subject data is deemed non-evaluable. The proportion of subjects with RVNA titer ≥0.5 IU/mL is calculated as follows:

$$\sum(successes, 1) \Big/ \sum(all\ evaluable\ subject\vdots, n)$$

Sensitivity analyses will be performed to assess impact of missing data, see section 8j.

f. SECONDARY EFFICACY ANALYSES

Secondary efficacy analyses 2 and 5 will be based on the secondary PK population. Secondary efficacy analyses 1, 3, and 4 will be based on the primary PK population, since timepoints post-Visit 6 are not included in these analyses.

The second secondary analyses will be performed using an appropriate mixed model repeated measures [MMRM] analysis to assess for differences of the slope and the change in GMT of the titers at the days described below. The correlation structure involves multiple pieces, including measurement errors, random variation, and inter-individual variability. For the longitudinal data analysis, an unstructured correlation matrix for within-subject error will be assumed. Other correlation structures, including compound symmetry, will be examined as needed. The validity of this model will be assessed via standard modeling diagnostics and goodness-of-fit measures. Comparisons of geometric mean titers [GMTs] between the treatment group at each timepoint and across all timepoints will be reported. The final output will include one row indicating the mean change [95% confidence intervals] in titer across all PK assessments from Visit 2 [baseline] through Visit 7 by treatment group and one row for every specific timepoint thereafter. Additionally, the difference in the means [or the ratio of the GMT] between treatment groups, the corresponding 95% confidence intervals, associated chi-square test statistic, and p-value will be reported. A p-value of <0.05 will signal a statistically significant difference in titers. See table below for example output:

Parameter	Treatment Group Ns			Mean Change From Baseline (95% Confidence Intervals)		BPL HRIG + Vaccine versus Comparator HRIG + Vaccine		
	N_{BPL}	N_{CP}	N_T	BPL HRIG + Vaccine	Comparator HRIG + Vaccine	Difference in Means (95% CI)	Chi-Square	P-Value
Through Day 28	x	x	x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx	0.xxx
Day 3	x	x	x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx	0.xxx
Day 5	x	x	x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx	0.xxx
Day 7	x	x	x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx	0.xxx
Day 14	x	x	x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx	0.xxx
Day 28	x	x	x	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx (x.xx, x.xx)	x.xx	0.xxx

1. a one-sided t-test will be used to assess non-inferiority of the mean of the $AUC_{0\text{-}7\,d}$ of the BPL HRIG + vaccine group to the comparator HRIG + vaccine group. The pre-specified non-inferiority margin is 20%. It will be concluded the mean $AUC_{0\text{-}7d}$ in the BPL HRIG + vaccine group is non-inferior to that in the comparator group if the lower limit of the 95% confidence interval for the mean $AUC_{0\text{-}7d}$ is greater than -20% of comparator mean $AUC_{0\text{-}7d}$. Log-transformation of the $AUC_{0\text{-}7d}$ data will be performed as necessary during statistical testing to meet assumptions for normality.

   The null hypothesis is $(\mu_T\text{-}\mu_C)/\mu_T \leq -0.2$;

   The alternative hypothesis is $(\mu_T\text{-}\mu_C)/\mu_T > -0.2$;

   Where μ_T=the geometric mean of the $AUC_{0\text{-}7d}$ in the BPL HRIG + vaccine group,

   μ_C=the geometric mean of the $AUC_{0\text{-}7d}$ in the comparator HRIG + vaccine group.

2. The geometric mean titers (GMTs) for RVNA titer up to peak serum level after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine. Due to the observed change in relationship between time and titer level, only PK timepoints up to peak serum level will be included in this analysis.

A generalized estimating equation [GEE] for a repeated measures analysis will be used to assess the difference in proportions between the treatment groups for the third and fourth secondary efficacy analyses. Standard model building methods, diagnostics, and goodness-of-fit measures will be performed as appropriate. Proportions of subjects reaching set anti-rabies antibody titer will be compared at each timepoint as well as throughout all timepoints.

3. The proportion of subjects reaching anti-rabies antibody titer of ≥0.5 IU/mL at Visits 3-6 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine.

4. The proportion of subjects reaching anti-rabies antibody titer of ≥ the lower limit of quantitation of the assay at Visit 3-6 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine. This titer threshold corresponds to the lower limit of quantitation of the assay.

The GEE analysis will include timepoints through Visit 6 for endpoints 3 and 4, at which point all or nearly all subjects are expected to have reached the stated thresholds. There is no clinical benefit of including subsequent timepoints in this analysis.

5. The geometric mean titers (GMTs) for anti-rabies antibody titer at Visit 6-9 will be compared between treatment groups. Descriptive statistics and visual inspections will be reported as appropriate. No formal hypotheses testing will be performed.

g. EXPLORATORY PK ANALYSES

The following PK parameters for anti-rabies antibody concentrations will be summarized for both treatment groups:

- C_{max} [IU/mL]
- T_{max} [day]
- area under the concentration vs time curve to the last measurable concentration (AUC_{0-t}) [day*IU/mL]
- apparent terminal rate constant (λ_z) [day^{-1}]
- $AUC_{0-7\,d}$ [day*IU/mL]
- area under the concentration vs time curve to infinity ($AUC_{0-\infty}$), if appropriate

- $C_{max}/AUC_{0-\infty}$ [or $Cmax/AUC_{0-t}$ if $AUC_{0-\infty}$ cannot be estimated]
- half-life ($t_{½}$), if appropriate

Non-compartmental PK methods will be utilized to calculate the subject level PK parameters. C_{max}, AUC_{0-t}, $AUC_{0-7d\backslash}$, $AUC_{0-\infty}$, apparent terminal rate constant (λ_z), and $t_{1/2}$ will be dose normalized by dividing the raw PK parameters by the actual dose the subject received. A t-test will compare the PK and dose-normalized PK parameters between treatment groups. Log-transformations will be performed as necessary during statistical analysis when appropriate.

h. ADVERSE EVENT REPORTING

Adverse events (AEs) will be reported by the MedDRA system organ class and preferred term. Only treatment emergent AEs (i.e. beginning after dosing with BPL HRIG / vaccine or comparator HRIG / vaccine) will be included in the summary tables. All AEs will be included in the data listings.

Treatment-related AEs will be defined as events recorded as having a possible, probable or very likely/certain causality to treatment. AEs leading to withdrawal will be defined as events where the subject's participation in the study was discontinued as a result of the AE.

AEs will be summarized descriptively for all subjects and by treatment group. The denominator used for the calculation of percentages will be the number of subjects in the safety population per treatment group. For all AE summaries described below, counting will be performed by subject and event. For counts by subject, subjects experiencing the same event more than once will have that event counted only once within each system organ class and once within each preferred term.

The following summaries of treatment-emergent AEs will be provided:

Summary of AEs

- The number and percentage of subjects reporting AEs, serious AEs, study medication-related AEs, AEs leading to withdrawal and AEs leading to death.
- The number of AEs, serious AEs, study medication-related AEs, AEs leading to withdrawal and AEs leading to death.

Summary of AEs by Severity of Event

The number and percentage of subjects reporting AEs, and study medication-related AEs, will be summarized by the system organ class and by the preferred term. The severity of event will be recorded once per subject for each term as the maximum severity experienced by each subject (i.e. where the order of most severe to least severe is given by: severe, moderate and then mild).

Summary of AEs by Causality

The number and percentage of subjects reporting AEs will be summarized by the system organ class and by the preferred term. The causality will be recorded once per subject for each term giving the most likely relationship to study medication (i.e. in the order: very likely/certain, probable, possible, unlikely and then unrelated).

i. Sensitivity Analyses

Sensitivity analyses will be performed to assess the impact on the primary PK analysis of non-compliers within the ITT population, missing primary endpoints, and timing of vaccine dosing.

Potential Interaction

Before treatment unblinding, timing of vaccine dosing and PK sampling, if not performed on the designated day, will be assessed as potential effect modifiers on the association between RVNA levels and treatment group in the primary and secondary PK analysis. A chi-square or fisher's exact test, as appropriate, will be used to measure the association between the dichotomous indicator of receiving dose/PK sampling on the intended day

[yes/no] and target level of RVNA titer reached [yes/no]. If the association is significant at the 0.05 level, a subgroup analysis including only subjects who were dosed/sampled on the target day will be reported in addition to the full analysis.

NON-COMPLIERS AND MISSING DATA

Non-compliers will be defined as subjects who meet one of the following:

- subjects who did not receive the full dose of BPL HRIG/comparator HRIG [not eligible for primary PK population];
- all 3 doses of active rabies vaccine at the time specified [not eligible for primary PK population];
- randomized without meeting all eligibility criteria [[redacted];
- subjects with any major protocol deviations reported [[redacted]].

Specifically, the following two analyses will be performed to assess impact on primary PK analysis:

- The primary PK analysis will be repeated assuming that non-compliant subjects did not attain an RVNA titer of $\geq$ 0.5 IU/mL at Visit 6. [worst case scenario]
- The primary PK analysis will be repeated assuming that non-compliant subjects successfully attain an RVNA titer of $\geq$ 0.5 IU/mL at Visit 6. [best case scenario]

j. SUBGROUP ANALYSES

Subgroup analyses will be performed as appropriate, due to either imbalance randomization in baseline subject demographics and/or clinical relevance to primary and secondary PK analyses and safety analysis. Factors including, but not limited to, age, race, BMI, and sex will be considered. Subgroups will be defined based on population median.

k. Missing Values

No missing value imputation methods will be applied, e.g. the analyses are based on a valid case basis.

l. Injection Site Observations

Injection site observations data will be summarized as appropriate.

Summary by Product

The number and percentage of subjects reporting injection site reactions will be summarized by preferred term and product (HRIG or vaccine).

Summary by Number of Injections

The number and percentage of subjects reporting injection site reactions will be summarized by preferred term, product (HRIG or vaccine) and number of injections.

m. Viral Serology Variables

Viral serology variables will be summarized. Shift tables for virology will present the number of subjects with positive and negative results and those for whom the results change during the study.

n. Hematology, Serum Biochemistry, Urinalysis

Hematology, serum biochemistry and urinalysis variables will be summarized, including changes from baseline. Shift tables for hematology and biochemistry variables will be provided for the number and percentage of subjects with values below, within and above the reference range.

o. Markers of Hemolysis

Markers of hemolysis will be summarized, including changes from baseline.

p. Vital Signs and Body Temperature

Sitting diastolic and systolic blood pressure, pulse rate, body temperature and respiration rate will be summarized, including changes from baseline (i.e. pre-dose on Visit 2 for body temperature, Screening for all other parameters). In addition, the number of subjects with "substantial" increases or decreases from baseline in blood pressure (>20 mmHg) and pulse (>15 b.p.m.) will be summarized.

q. Physical Examination

Physical Examination and ECG findings will be summarized. The shift from Screening to Visit 8 and Screening to the End-Study Assessment will be summarized. Body weight data will be fully listed.

r. Other Safety Parameters

Pregnancy test results will be listed.

s. Interim Analysis

No interim analysis is planned.