A Prospective, Randomized, Double-Blind 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

IND Number: 17475

NCT03264157

Version 1.0
Version date: 26 Oct 2017

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CONFIDENTIALITY STATEMENT

Information contained within this document will be treated as confidential at all times. It shall be used for the sole information of the Investigator's team. Staff must undertake not to disclose any such information to any person not involved in the study.

PROTOCOL APPROVAL SIGNATURES

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I have carefully read this protocol and I confirm that it contains all the information necessary to perform the study. This study is to be conducted in accordance with the protocol, ICH GCP and applicable regulatory requirements.

[redacted]

Sponsor's Signatory

[redacted]

STUDY PERSONNEL

SPONSOR'S RESPONSIBLE CHIEF MEDICAL OFFICER

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REVISION HISTORY

Version Number	Version Date	Description of Changes
01	26 October 2017	Initial version

LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Aminotransferase
AUC	Area under the curve
BPL	Bio Products Laboratory Limited (The Sponsor)
Bpm	Beats per minute
CBC	Complete Blood Count
CHMP	Committee for Medicinal Products for Human Use
CD4	Cluster of differentiation 4
Cmax	Maximum/peak serum concentration
CRP	C-Reactive Protein
CRA	Clinical Research Associate
CRF	Case Report Form
CV	Curriculum Vitae
DEV	Duck embryo origin IgG
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
h	Hours
HAV	Hepatitis A Virus
Hb	Hemoglobin
HBV	Hepatitis B Virus
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HDCV	Human diploid cell vaccine
HIV	Human Immunodeficiency Virus
HRIG	Human Rabies Immunoglobulin
ICH	International Conference on Harmonisation
ID	Identity
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IgA	Immunoglobulin A
IM	Intramuscular
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IU	International Units
kg	Kilograms
LLOQ	Lower Limit of Quantification
Ltd	Limited
min	Minutes
ml	Milliliters
NAT	Nucleic Acid Amplification Technology
PCECV	Purified chick embryo cell vaccine

PEP	Post-exposure prophylaxis
PK	Pharmacokinetics
RIG	Rabies Immunoglobulin
RVNA	Rabies Virus Neutralizing Antibody
SAE	Serious Adverse Event
SAS	Statistical Analysis Software
SD	Standard deviation
SRM	Study Reference manual
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Half-life
T_{max}	Time of maximum concentration
US	United States (of America)

1. SYNOPSIS

PROTOCOL NUMBER:	RIG01
INVESTIGATIONAL MEDICINAL PRODUCT (IMP):	BPL Human rabies immune globulin (HRIG)
TITLE:	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
PHASE:	II/III
OBJECTIVES:	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.
STUDY DESIGN:	This will be a prospective, randomized, blinded, parallel-group, non-inferiority, phase II/III study of the pharmacokinetics and safety (and tolerability) of simulated post-exposure prophylaxis with BPL HRIG with co-administration of active rabies vaccine in healthy subjects. Screening visit (within 28 days prior to baseline) Screening evaluations will include viral serology, biochemistry, hematology and other tests to assess eligibility. Baseline (Day 0) Eligible subjects will be randomly assigned to one of two treatment groups:

- Treatment A: BPL HRIG + active rabies vaccine
- Treatment B: Comparator HRIG + active rabies vaccine

Pre-dose samples will be collected for anti-rabies antibody serum titer, markers of hemolysis, and long-term archiving. Subjects will then be administered their randomized treatment for Day 0.

On-Study (Days 0-140)
Pharmacokinetic assessments of anti-rabies antibody serum titer will be conducted at the following time points: days 3, 5, 7, 14, 28 (4 weeks), 49 (7 weeks) and 140 (20 weeks).

Additional doses of active rabies vaccine (will be administered, after the collection of the blood sample for anti-rabies antibody serum titer, on days 3, 7, 14, and 28.

Adverse events will be monitored from the screening visit and throughout the study.

End-of-Study Assessment (Day 140)
End-of-Study evaluations will include viral serology, biochemistry, and hematology. A sample will be collected for long-term archiving.

NUMBER OF SUBJECTS: Approximately 162 normal healthy volunteers, 81 per treatment group will be enrolled to achieve 146 evaluable subjects.

TREATMENTS:

Treatment A
Experimental:
BPL HRIG, 20 IU/kg body weight once on Day 0, administered via intramuscular injection to the deltoid and/or lateral thigh muscle in divided doses
Vaccine:
FDA-approved active rabies vaccine, 1.0 mL (2.5 IU/mL) will be given on Days 0, 3, 7, 14, and 28, administered intramuscularly in the deltoid muscle (contralateral to the HRIG).

Treatment B:
Active comparator:
Comparator HRIG, 20 IU/kg body weight once on Day 0, administered via intramuscular injection to the deltoid and/or lateral thigh muscle in divided doses.
Vaccine:
FDA-approved active rabies vaccine, 1.0 mL (2.5 IU/mL) will be given on Days 0, 3, 7, 14, and 28, administered intramuscularly in the deltoid muscle (contralateral to the HRIG).

STUDY DURATION:	24 weeks for the individual participant (20 weeks treatment plus a pre-study phase of up to 4 weeks).
STUDY POPULATION:	Healthy males and females, aged 18-75 years, not previously exposed to rabies virus or pre-or post-exposure rabies prophylaxis.
PRIMARY ENDPOINT:	The proportion of subjects with anti-rabies titer ≥0.5 IU/mL at 14 days following BPL HRIG + vaccine vs. active comparator + vaccine, using a non-inferiority margin of 10%. The above pharmacokinetic endpoint is a surrogate for efficacy, since a titer of ≥0.5 IU/mL is globally recognized as indicating adequate vaccine response.
SECONDARY EFFICACY ENDPOINT(S):	● Assessment of $AUC_{0\text{-}7d}$ for BPL HRIG and vaccine versus comparator HRIG and vaccine using a non-inferiority margin of 20%. ● Comparison of the geometric mean titers (GMTs) for rabies antibody titers at Days 3, 5, 7, 14 and 28 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine ● The proportion of subjects reaching anti-rabies titer ≥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 ● The proportion of subjects reaching anti-rabies titer of ≥ the lower limit of quantification 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 ● Comparison of the geometric mean (GMTs) for anti-rabies titer at Days 14, 28, 49 and 140 after administration of BPL HRIG and vaccine versus comparator HRIG and vaccine will be compared between treatment groups.
EXPLORATORY EFFICACY ENDPOINT:	● Pharmacokinetic (PK) parameters: C_{max}, t_{max}, area under the curve to the last measurable concentration (AUC_T) and to infinity (AUC_∞), apparent terminal rate constant (λ_z), $AUC_{0\text{-}7days}$, C_{max}/AUC, half-life ($t_{½}$) of anti-rabies antibody concentrations (both groups)

SECONDARY SAFETY ENDPOINT(S):	● Adverse events from time of signing informed consent until end of study. ● Injection site observations ● Viral serology pre-dose and at end of study ● Biochemistry, hematology and urinalysis pre-study and at end of study ● Physical examination, including ECG, pre-study and at end of study ● Vital signs
STATISTICAL METHODOLOGY	**Analysis populations:** ITT population: The intent-to-treat (ITT) population will include all randomized subjects. All analyses will be performed using the ITT population. Safety population: all subjects who receive at least one dose of BPL HRIG / comparator HRIG / active rabies vaccine. The safety population will be used for all safety analyses. Per protocol population: Primary PK population: 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 analysis and selected secondary PK analyses. Secondary PK population: 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 analyses. **Primary analysis:** The primary hypothesis is that the proportion of subjects receiving BPL HRIG + active vaccine with an anti-rabies titer 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 at a one-sided significance level of 0.025. **Secondary analysis:** Efficacy endpoints will be assessed by a combination of statistical and descriptive analyses, as appropriate. Safety parameters will be compared descriptively.

The trial will be conducted in compliance with the protocol, FDA Code of Federal Regulations 21 CFR parts 50, 54, 56, 312 and 314, EU Clinical Trial Directives 2001/20/EC and 2005/28/EC, Good Clinical Practice Guidelines and applicable local regulatory requirements BPL is committed to satisfying the requirements of the ICH-GCP Guidelines regarding the responsibilities of the Sponsor.

2. INTRODUCTION

2.1. Rabies

Rabies is a disease caused by RNA viruses in the genus *Lyssavirus* (family *Rhabdoviridae*). Currently, 14 species of lyssa-viruses have been identified. However, only 1 species, *Rabies virus,* has been detected in the western hemisphere[1] All species of mammals are susceptible to rabies virus infection, but only a few species are important as reservoirs for the disease. The vast majority of rabies cases reported to the Centers for Disease Control and Prevention (CDC) each year occur in wild animals like raccoons, skunks, bats, and foxes[1] .

Transmission of rabies virus usually begins when infected saliva of a host is passed to an uninfected animal. The virus is typically present in the saliva of clinically ill mammals and is transmitted through a bite. In humans, transmission has also been documented via other routes such as contamination of mucous membranes (i.e., eyes, nose, mouth), aerosol transmission, and corneal and organ transplantations[2] .

In the absence of prophylactic treatment, the rabies virus infects the central nervous system, ultimately causing acute, progressive encephalomyelitis which is almost invariably fatal. The incubation period in humans is usually several weeks to months, but ranges from days to years. Early symptoms of rabies are similar to those of many other illnesses, including fever, headache, and general weakness or discomfort. As the disease progresses, more specific symptoms appear and may include insomnia, anxiety, confusion, slight or partial paralysis, excitation, hallucinations, agitation, hyper salivation, difficulty swallowing, and hydrophobia. Death usually occurs within days of the onset of these symptoms[3].

Worldwide, approximately 55,000 people die of rabies each year, primarily in developing countries, where the dog is the most important animal reservoir[3]. Exposure to rabid dogs is the cause of over 90% of human exposures to rabies and of over 99% of human deaths[3].

In the United States, where vaccination of domestic animals is a component of a successful rabies prevention and control program, approximately 16,000-39,000 persons come in contact with potentially rabid animals annually[4]. However, due to the success of post-exposure prophylactic treatment, just 37 cases of human rabies were diagnosed between 2003 and 2015[1,5,6] .

2.2. Current Treatment

Human rabies can be prevented by pre- and post-exposure prophylaxis using vaccinations. Pre-exposure prophylaxis relies on active vaccination against the virus. Subsequent exposure to the rabies virus is then treated with repeat doses of the vaccine.

Pre-exposure vaccination is advised for those at increased risk of exposure, such as veterinarians, people whose activities bring them into frequent contact with rabid animals, and to international travelers if likely to come into contact with the rabies virus in regions where access to appropriate medical care might be limited.

For vaccination after exposure, post-exposure prophylaxis (PEP), people who have not received pre-exposure vaccination, should receive both passive antibody and vaccine. Passive antibodies are purified preparations of Human Rabies Immune Globulin (HRIG). Vaccines currently available in the United States include Human Diploid Cell Vaccine (HDCV) and Purified Chick Embryo Cell Vaccine (PCEC) (see Table 1)[2].

Table 1: Rabies Vaccines and Immunoglobulin Available in the United States

Type	Name	Route	Indications
Human Diploid Cell Vaccine (HDCV)	Imovax® Rabies	Intramuscular	Pre-exposure or Post-exposure
Purified Chick Embryo Cell Vaccine (PCEC)	RabAvert®	Intramuscular	Pre-exposure or Post-exposure
Human Rabies Immune Globulin	Imogam® Rabies-HT	Local infiltration at wound site, with additional amount intramuscular at site distant from vaccine	Post-exposure
Human Rabies Immune Globulin	HyperRAB® S/D	Local infiltration at wound site, with additional amount intramuscular at site distant from vaccine	Post-exposure

This post-exposure prophylaxis consists of a dose of HRIG and vaccine given on the day of the exposure (day 0), and then a dose of vaccine given again on days 3, 7, 14 and 28, following the regimen shown in Table 2[2].

HRIG is administered only once, at the beginning of anti-rabies post-exposure prophylaxis. This will provide immediate antibodies until the body can respond to the vaccine by actively producing antibodies of its own. If possible, the full dose of HRIG should be thoroughly infiltrated in the area around and into the wounds. Current guidelines recommend infiltration in and around the wound to prevent progression of rabies virus along neural pathways into the

central nervous system[7]. Any remaining volume should be injected intramuscularly at a site distant from vaccine administration.

Effectiveness of rabies treatment is measured by serological testing of the rabies virus neutralizing antibody (RVNA), of which the gold standard is the Rapid Fluorescent Focus Inhibition Test (RFFIT)[3],[8]. Animal studies have shown that survival against rabies infection is more likely to occur the higher an animal's RVNA titer was at the time of infection, but it is not a definitive indicator of survival. Nonetheless in humans a titer of 0.5 IU/mL is globally recognized as indicating adequate vaccine response[9].

Table 2: Rabies Post-Exposure Prophylaxis (PEP) Schedule for Not Previously Vaccinated Individuals

Intervention	Regimen*
Wound cleansing	All PEP should begin with immediate thorough cleansing of all wounds with soap and water. If available, a virucidal agent (e.g., povidine-iodine solution) should be used to irrigate the wounds.
Human rabies immune globulin (HRIG)	Administer 20 IU/kg body weight. If anatomically feasible, the full dose should be infiltrated around and into the wound(s), and any remaining volume should be administered at an anatomical site (intramuscular [IM]) distant from vaccine administration. Also, HRIG should not be administered in the same syringe as vaccine. Because RIG might partially suppress active production of rabies virus antibody, no more than the recommended dose should be administered.
Vaccine	Human diploid cell vaccine (HDCV) or purified chick embryo cell vaccine (PCECV) 1.0 mL, IM (deltoid area†), 1 each on days 0§ 3, 7 and 14, and 28.

* These regimens are applicable for persons in all age groups, including children.
† The deltoid area is the only acceptable site of vaccination for adults and older children. For younger children, the outer aspect of the thigh may be used. Vaccine should never be administered in the gluteal area.
§ Day 0 is the day dose 1 of vaccine is administered.

Current CDC recommendation for rabies PEP vaccination are 4 doses of vaccine on Day 0, 3, 7 and 14[7]. Manufacturers' recommendations for rabies PEP are 5 doses, which will be the regimen for the clinical trial.

Adverse reactions to rabies vaccine and immune globulin are not common. Newer vaccines in use today cause fewer adverse reactions than previously available vaccines. Mild, local reactions to the rabies vaccine, such as pain, redness, swelling, or itching at the injection site, have been reported. Rarely, symptoms such as headache, nausea, abdominal pain, muscle aches, and dizziness have been reported. Local pain and low-grade fever may follow injection of rabies immune globulin[3].

2.3. Development of HRIGs for Post-Exposure Prophylaxis

The usefulness of prophylactic rabies antibody in preventing rabies in humans when administered immediately after exposure was demonstrated in a group of persons bitten by a rabid wolf in Iran in 1954[10,11]. A series of clinical studies helped determine the optimal conditions under which anti-rabies serum of equine origin and rabies vaccine could be used in humans[12,13,14,15]. These studies showed that the anti-rabies serum could interfere with the active immunity induced by the vaccine, but could be minimized by booster doses of vaccine after the end of the usual dosage series.

Later development was the preparation of rabies immune globulin of human origin with adequate potency[16]. In carefully controlled clinical studies, this globulin was used in conjunction with rabies vaccine of duck-embryo origin[16,17]. The recommended dose for HRIG of 20 IU/kg was established in clinical studies comparing the rabies IgG titer following various doses of HRIG and vaccine[16,17,18]. A lower dose of 10 IU/kg was suboptimal for early protection and a higher dose of 40 IU/kg interfered with the development of active immunity conferred by the vaccine. At the dose of 20 IU/kg, anti-rabies antibody titers were detectable from Day 1 after the injection. Without injection of vaccine, passive antibody titers reached a peak of 30 IU/mL 13 days after Day 0 and declined with a half-life of approximately 3 weeks. However, when HRIG was administered with a course of rabies vaccine, rabies IgG levels continued to rise, peaking at Day 40 with a titer of 111 IU/mL[17].

2.4. BPL's Human Rabies Immunoglobulin

BPL's Human Rabies Immunoglobulin (BPL HRIG) contains human protein, 40-180 g/L, of which at least 98% is IgG. The concentration of specific IgG to rabies virus is not less than 150 IU/mL in nominal 500 IU vials. This product is prepared from plasma from screened donors, selected from the USA, who have been hyperimmunized with rabies vaccine.

BPL HRIG has been licensed in the UK since 1991. This formulation contains a solvent-detergent virus-reduction step, which is considered effective against enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV). Recently, the addition of a virus filtration step in the manufacturing process has improved the virus reduction further, providing effective reduction of small non-enveloped viruses such as parvovirus B19. For more information, see the Investigator's Brochure[19].

HRIG must always be used for post-exposure prophylaxis in combination with an approved rabies vaccine. One dose of immunoglobulin (20 IU/kg body weight) is given intramuscularly, prior to a full course of rabies vaccination, and as soon as possible after exposure. If a large volume (> 2mL for children or > 5 mL for adults) is required, it is recommended to administer

this in divided doses at different sites. The immunoglobulin and the vaccine should be administered at two different sites of the body (Table 2).

HRIG administered intramuscularly is bioavailable in the recipient's circulation after a delay of 2-3 days and has a half-life of about 3 – 4 weeks (although this may vary from patient to patient)[19]. However, the pharmacokinetics (PK) of BPL HRIG has not been studied.

2.5. Summary of Pre-Clinical and Clinical Experience with BPL HRIG

HRIG is a preparation of human plasma proteins, thus safety testing in animals is not applicable to the safety of use in man. Acute toxicity studies of BPL immunoglobulin in rat and mouse showed species specific reactions which bear no relevance to administration in humans. Repeated dose toxicity testing and embryo-fetal toxicity studies are impracticable due to the induction of, and interference with, antibodies to human protein. Clinical experience provides no sign of tumorigenic and mutagenic effects of immunoglobulins[19] .

No clinical trials have been performed with BPL HRIG. The first approval for marketing worldwide was United Kingdom on 06 June 1991. The product is currently approved in four countries (UK, Chile, Colombia and Malta). However, BPL HRIG is predominantly distributed in the UK.

The safety of this product in patients exposed to the rabies virus is well-established. Exposure data prior to 2000 is not available. From January 1, 2000 to June 28, 2017, a total of 26,716 vials of rabies immunoglobulin have been sold. The recommended dose of the product is 20IU per kg, corresponding to 1400 IU for a typical 70kg adult. Based on this assumption, a typical adult dose would be equivalent to three vials of the product. On this basis, an estimated 8,905 patients were exposed to human rabies immunoglobulin during the period and only one case report describing 3 non-serious adverse reactions (fatigue, influenza like illness, and urticaria) has been reported.

2.6. Potential Risks and Benefits to Subjects of BPL HRIG

BPL HRIG is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses, and, theoretically, the Creutzfeldt-Jakob Disease (CJD) agent that can cause disease. Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to

unknown or emerging viruses and other pathogens. The investigator will discuss the risks and benefits of this product with the participant, before administration.

BPL HRIG should not be administered into a blood vessel because of the risk of shock; investigators/site staff will be trained how to administer the BPL HRIG for this study. Although systemic reactions to immunoglobulin preparations are rare, epinephrine should be available for treatment of acute anaphylactoid symptoms. Rarely, human rabies immunoglobulin can induce a fall in blood pressure with anaphylactic reaction, even in patients who have tolerated previous treatment with human immunoglobulin. Suspicion of allergic or anaphylactic type reactions requires immediate discontinuation of the injection. In case of shock, standard medical treatment for shock should be implemented.

Although true hypersensitivity is rare, BPL HRIG should be given with caution to patients with a history of prior systemic allergic reactions following the administration of human immunoglobulin preparations. This trial will therefore exclude participants with a history of prior systemic allergic reactions following administration of blood, blood products, or human plasma-derived products.

Participants with isolated immunoglobulin A (IgA) deficiency (who have increased potential for developing antibodies to IgA and could have anaphylactic reactions to subsequent administration of blood products that contain IgA) will be excluded from the study.

As with all preparations administered by the intramuscular route, bleeding complications may be encountered in patients with thrombocytopenia or other bleeding disorders, therefore participants with thrombocytopenia or other bleeding disorders will be excluded from the study.

Other antibodies in the BPL HRIG preparation may interfere with the development of an immune response to live attenuated vaccines such as measles, mumps, varicella or rubella. Therefore, immunization with live vaccines should not be given within 3 months after BPL HRIG administration. However, inactivated influenza vaccinations may be administered.

Animal reproduction studies have not been conducted with BPL HRIG. It is also not known whether BPL HRIG can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Females of childbearing potential will have a pregnancy test prior to inclusion in the study and must be using adequate contraception for the duration of the clinical trial.

There are no robust data on the frequency of undesirable effects of BPL HRIG from clinical trials. The following undesirable effects are class effects that are common to all HRIG products [19]:

Table 3: Class effects that are common to all HRIG products

MedDRA Standard System Organ Class	Undesirable Effects	Frequency*
Immune system disorders	Hypersensitivity, anaphylactic shock	Rare
Nervous system disorders	Headache	Rare
Cardiac disorders	Tachycardia	Rare
Vascular disorders	Hypotension	Rare
Gastrointestinal disorders	Nausea, vomiting	Rare
Skin and subcutaneous disorders	Skin reaction, erythema, pruritus	Rare
Musculoskeletal and connective tissue disorders	Arthralgia	Rare
General disorders and administration site conditions	Fever, malaise, chill, fatigue, influenza like illness At injection site: swelling, pain, erythema, induration, warmth, pruritus, rash	Rare

* rare is defined as a frequency of >1/10,000 to <1/1,000

Deep intramuscular injection may reduce the risk of local induration. Subjects receiving BPL HRIG in this study will not have been exposed to the rabies virus and so the post-exposure prophylaxis will not provide any direct benefit. However, subjects who complete all vaccinations may have protection against rabies infection should they be exposed in the future, but this cannot be guaranteed. Therefore, subjects will be informed that there are no direct therapeutic benefits of participation in this study, regardless of the treatment received according to the randomized treatment schedule.

2.7. Potential Risks and Benefits to Subjects of Comparator HRIG

In this study, a licensed comparator HRIG, HyperRAB® S/D, will be used. HyperRAB® S/D is a plasma-derived product and therefore the same class effects are expected as listed in section 2.5. Refer to the prescribing information in Appendix D .

2.8. Potential Risks and Benefits to Subjects of Rabies Vaccine

In this study, a licensed vaccine RabAvert® will be used. RabAvert® is a sterile freeze-dried vaccine obtained by growing the fixed -virus strain Flury LEP in primary cultures of chicken fibroblasts. The most common adverse reactions are injection site reactions, such as injection site erythema, induration, pain, and flu-like symptoms, such as asthenia, fatigue, fever, headache, myalgia and malaise. Refer to the prescribing information in Appendix E .

2.9. The Current Study

The purpose of the current study is to obtain data required for a license application in the US. This will be achieved by comparing the safety and efficacy of BPL HRIG, administered in

conjunction with rabies vaccine in accordance with the licensed dosing schedule for post-exposure prophylaxis, with the safety and efficacy of a licensed comparator HRIG, also given in conjunction with rabies vaccine. A randomized, blinded, parallel group study design will ensure an unbiased comparison is made between treatments.

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 HRIG to be administered 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 invariably 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 (WHO, 2007) on study Day 14. A comparison of the proportion of subjects receiving BPL HRIG who meet this important clinical endpoint, with the proportion of subjects receiving FDA-licensed comparator HRIG who meet the same endpoint, is therefore the primary objective of the trial. The aim of the study will be to demonstrate the non-inferiority of BPL HRIG with a 10% margin.

Secondary endpoints will include rabies antibody titer at days 3, 5, 7, 14 and 28, for both HRIGs (in conjunction with rabies vaccine). PK sampling will take place prior to dosing of HRIG and rabies vaccine (Day 0) at each of the timepoints at which rabies vaccine is administered (Days 3, 7, 14 and 28), with an additional PK timepoint at Day 5 to study to study the early response to HRIG. Additional PK timepoints at Days 49 and 140 will enable collection of a complete the PK profile. In order to compare the effects of HRIG at early timepoints before active antibody is generated in response to the rabies vaccine, the $AUC_{0\text{-}7d}$ will be assessed. Additional secondary endpoints will be the proportion of subjects in each treatment group reaching a serum rabies antibody titer of ≥0.5 IU/mL and ≥ the Lower Level of Quantification (LLOQ) at each timepoint. PK parameters for both treatment groups will be compared in an exploratory analysis.

As mentioned in Section 2.3, a dose of 40 IU/kg was shown to interfere with the development of active immunity conferred by the vaccine[16]. At a dose of 20 IU/kg, as given during this study, any attenuation observed was insignificant and did not interfere materially with active immunity[22,23]. Moreover, any attenuation was clinically insignificant since serum anti-rabies

IgG remained considerably higher than the protective titer of 0.5 IU/mL. However, as a secondary endpoint, the possible attenuation effect of BPL HRIG on the development of the host-immune response will be studied by comparing the Day 14, 28, 49 and 140 rabies antibody titer for both treatments. Any observed attenuation will be described by comparing PK parameters of HRIGs in conjunction with rabies vaccine. Although the safety of BPL HRIG is well-established from many years of marketed use, this study will assess the safety of BPL HRIG, in conjunction with rabies vaccine.

In order to maintain blinding of treatment, the study will be blinded to the subject, investigator and site staff, to reduce bias in the identification and causality assessments of adverse events and laboratory abnormalities. An unblinded pharmacist or licensed medical professional will be responsible for preparation of the correct treatments according to the randomization code. In this study, actual (rather than nominal) HRIG potency will be used to calculate the volume of HRIG to be administered. Since there will be differences in the volume of the HRIGs the nurse administrator will also be unblinded. This modified blinding technique was successfully used in a completed study comparing PK and safety of two rabies vaccine formulations, both in conjunction with licensed HRIG[24] .

A study duration of five times the half-life of the experimental treatment is usually considered adequate to identify safety issues relating to the product. The half-life of HRIG is 3-4 weeks[19], therefore study duration of 15 to 20 weeks is considered appropriate both to obtain a full PK profile and for appropriate safety follow up. A duration of 140 days (20 weeks) has therefore been selected for this study.

3. 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.

4. STUDY DESIGN

4.1. 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 in the US.

Subjects will be randomly assigned to one of 2 treatment groups, as follows:

Table 4: Treatment groups assigned

Treatment group name	HRIG treatment	Rabies vaccine treatment	Number of subjects
A	BPL HRIG	active rabies vaccine	81
B	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.

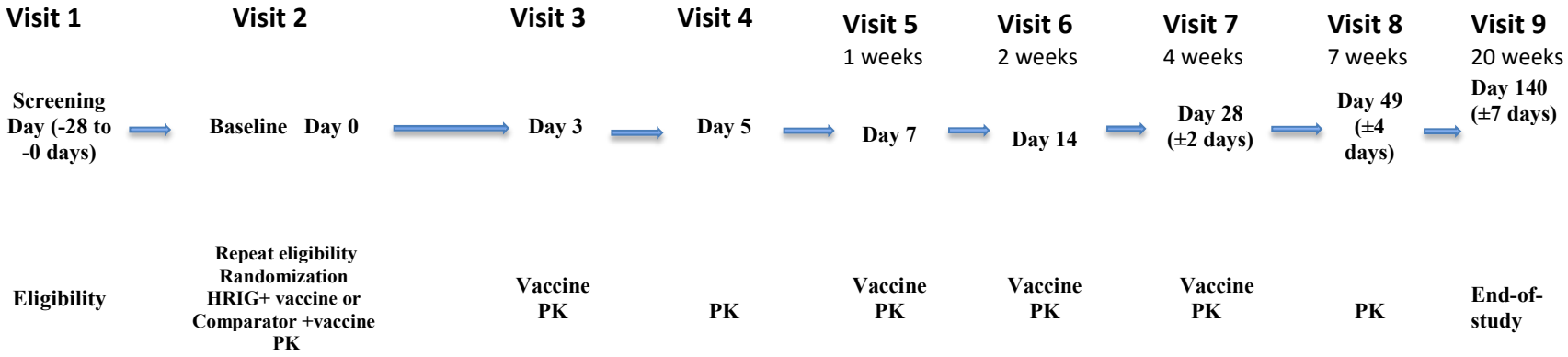
All medicinal product preparation will be performed by the unblinded pharmacist/ or licensed medical personnel using aseptic techniques and according to a standardized procedure on Day 0. The nurse administrator will quality check the calculations, and dose/treatment assignment prior to administration. Treatments on Day 0 will be administered by 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).

4.2. Study Plan

See Figure 1 .

Figure 1: Study Plan



Actual treatment by assigned Treatment Group:

A	BPL HRIG + rabies vaccine	rabies vaccine	rabies vaccine	rabies vaccine	rabies vaccine
B	comparator HRIG + rabies vaccine	rabies vaccine	rabies vaccine	rabies vaccine	rabies vaccine

4.3. Scheduled Visits

For full details of assessments performed at scheduled visits see flow chart in Appendix G.

Each subject will undergo a total of 9 visits. Subjects' eligibility will be assessed at Screening (Visit 1), which can occur up to 28 days prior to dosing. Following a repeat eligibility check at Day 0 (Visit 2), eligible subjects will be randomized and dosed with the randomized treatment (BPL 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 (Visit 3), 5 (Visit 4) (PK sampling only), 7 (Visit 5), 14 (Visit 6) and 28 (Visit 7). An additional visit for PK sampling and safety assessment will take place on Day 49 (7 weeks/Visit 8) and Day 140 (20 weeks/Visit 9). 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, see Appendix A section 4).

4.4. Endpoints

The trial's primary endpoint will be the proportion of subjects with anti-rabies antibody titer ≥ 0.5 IU/mL at 14 days following BPL HRIG + vaccine or comparator HRIG + vaccine. The primary endpoint will be designed to determine non-inferiority with a 10% margin (see Section 8.1.1).

Additional time points are included for secondary end points, including pharmacokinetic (PK) parameters of anti-rabies antibody levels in serum at time points (Days 0, 3, 5, 7, 14, 28, 49 and 140), safety and tolerability.

As the primary endpoint is assessed at Day 14, subjects who withdraw from the study after Day 14 may still be eligible for the primary analysis, if all planned assessments up to and including Day 14 were performed.

4.5. Unscheduled Visits

At the discretion of the investigator, subjects may return between visits as required, additional safety laboratory measures may be undertaken as required.

4.6. Duration of Treatment

The duration of the study for an individual participant is expected to be 24 weeks. This comprises a screening period of up to 4 weeks (28 days) followed by a treatment period of 20 weeks. The ± 7-day allowable window on the final study visit results in a maximum study duration for any subject of 25 weeks.

4.7. Assignment of Treatment

The randomization code will be prepared by a statistician. Subjects will be enrolled using an interactive web response system (IWRS), which will assign each subject to a treatment group after the demographic and eligibility data have been entered into the system. The system will allow emergency UNBLINDING, the process for which will be documented.

Manual back-up procedures and instructions are provided for use in the event that the site temporarily loses access to the Internet or the online enrollment system is unavailable.

5. TRIAL POPULATION

5.1. Subject Numbers

The trial will enroll approximately 162 healthy volunteers, 81 in each treatment arm to achieve 146 evaluable subjects

Enrolled subjects who withdraw from the study will not be replaced.

5.2. Inclusion Criteria

All the following criteria must be met for the subject to be eligible:

a) Able and willing to sign an informed consent form.

b) Healthy male or female subjects aged 18 - 75 years inclusive.

c) No previous exposure to rabies virus, rabies vaccine and/or rabies immunoglobulin.

d) No significant abnormalities in hematology, biochemistry, or urinalysis according to the Principal Investigator's judgment.

e) No significant abnormalities in ECG according to the Investigator's judgment.

f) Females of child-bearing potential (defined from the onset of menstruation to one-year post-menopause and not surgically sterilized) who are (or become) sexually active must agree to practice contraception by using a highly effective (>98%) method for the duration of the study.

g) Females of child-bearing potential (defined from the onset of menstruation to one-year post-menopause and not surgically sterilized) must have a negative result on a serum at screening visit and a urine HCG-based pregnancy test at Day 0.

5.3. Exclusion Criteria

Any one of the following criteria makes the subject ineligible:

a) Female subjects who are pregnant and/or lactating.

b) History of live virus vaccination, e.g., measles, mumps, varicella or rubella vaccine, within the last 3 months.

c) Planned live virus vaccination, e.g., measles, mumps, varicella or rubella vaccine, within the 3 months after Day 0.

d) History of anaphylactic or anaphylactoid hypersensitivity reactions to chicken egg; history of mild allergic reactions to chicken egg, e.g., skin rash only, is not an exclusion criterion

e) History of hypersensitivity reaction to any of the following components of active rabies vaccine (US-FDA approved) e.g.: neomycin, bovine gelatin, trace amounts of chicken protein, chlortetracycline, and amphotericin B and in accordance with the product insert of the vaccine.

f) History of life-threatening allergy, anaphylactic reaction, or systemic response to human plasma derived products.

g) History of life-threatening allergy to blood or blood products.

h) Fever at the time of the start of the injection (oral temperature >38ºC.) or acute illness at the time of the start of the injection. *

i) History of or ongoing bleeding disorder.

j) Previous organ transplant recipient.

k) Ongoing immunosuppressive illness.

l) Clinically significant illnesses including: cardiac, hepatic, renal, endocrine, neurological, hematological, neoplastic, immunological, skeletal or other) that in the opinion of the investigator, could interfere with the safety, compliance or other aspects of this study.

m) All types of malignancies except for basal and squamous cell (scaly or plate-like) skin cancer, in- situ cervical carcinoma must be in remission for a minimum of 5 years prior to Day 0. For non-melanoma skin cancers and carcinoma in-situ of the cervix may be enrolled if treated and cured at the time of screening.

n) Evidence of active systemic infection that requires treatment with antibiotics within 2 weeks prior to Day 0.

o) Currently receiving or have received within the past 6 months (prior to Day 0):

- immunosuppressive drugs
- immunomodulatory drugs

p) Currently receiving or have received oral or IV steroids within 14 days (prior to DAY 0) or expected to require oral or IV steroids during the study.

q) Evidence of uncontrolled hypertension (systolic blood pressure of >150 mmHg, and/or diastolic blood pressure of >100 mmHg).

r) Heart rate >120/min.

s) Weight > 95.5 kg

t) History of IgA deficiency.

u) Is positive for any of the following at screening: serological test for HIV 1&2, HCV or HBsAg.

v) Presence of psychiatric disorder, other mental disorder or any other medical disorder which might impair the subject's ability to give informed consent or to comply with the requirements of the study protocol.

w) Previous enrollment in this study.

x) Participation in an interventional clinical trial within 30 days prior to baseline visit (Day 0).

y) Evidence of alcohol abuse or history of alcohol abuse or illegal and/or legally prescribed drugs in the past 2 years.

z) Any other factor that, in the opinion of the investigator, would prevent the subject from complying with the requirements of the protocol.

* Subjects with fever on Day 0 may have entry to the study re-scheduled (see Section 7.3.1).

Subjects may withdraw their consent or discontinue from the study at any time (refer to Section 9).

6. INVESTIGATIONAL AND AUXILIARY MEDICINAL PRODUCTS

In this study, 'study medication' is defined as all products administered: BPL HRIG, comparator HRIG, and active rabies vaccine.

6.1. Product Presentation, Storage and Expiry

6.1.1. Investigational Medicinal Product (IMP): BPL HRIG

BPL HRIG is a liquid concentrate of rabies human immunoglobulin. BPL HRIG is obtained from blood from screened donors, who are selected from within the United States of America. BPL HRIG is manufactured, packed and labelled by the sponsor according to the requirements of FDA CFRs, Directive 2001/20/EC and Good Manufacturing Practice.

BPL HRIG is presented in 5 ml glass vials, each of which is packed in a carton. The concentration of specific IgG to Rabies virus is not less than 150 IU/mL solution for injection in nominal 500 IU vials. The actual fill volume will be printed on the vial label. The shelf-life of BPL HRIG is specified in the Investigator's Brochure. The expiry date is printed on the vial label and carton; product must not be used beyond the expiry date. Dosing for BPL HRIG will be based on the actual potency (see pharmacy manual).

Vials of BPL HRIG should be stored in the original container at 2°C to 8°C (36°F to 46°F). Storage for up to one week at 25°C (77°F) in the original container is not detrimental. DO NOT FREEZE. Store in the original vial. Keep vial in the outer carton to protect from light. The product should be brought to room or body temperature before use.

The colour can vary from colourless to pale-yellow and is either clear or slightly opalescent. Do not use solutions that are cloudy or have deposits.

Further information can be found in the Investigator's Brochure.

6.1.2. Comparator HRIG

FDA-approved HRIG comparator HyperRAB® S/D will be presented in 10 mL vials, at a nominal potency of 150 IU/mL. Dosing for HyperRAB® S/D will be based on the actual potency (see pharmacy manual).

Vials of HyperRAB® S/D should be stored at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. The expiry date is printed on the vial label; product must not be used beyond the expiry date.

Further information can be found in the approved Prescribing Information, Appendix D.

6.1.3. Active Rabies Vaccine

The FDA-approved rabies vaccine, RabAvert®, is presented as a freeze-dried vaccine containing 2.5 IU of rabies antigen for reconstitution with 1 mL diluent. Each pack contains

one vial of freeze-dried vaccine, 1 disposable pre-filled syringe of sterile diluent, 1 small needle for injection and 1 long needle for reconstitution.

RabAvert® is a white, freeze-dried vaccine for reconstitution with the water for injection diluent prior to use; the reconstituted vaccine is a clear to slightly opalescent, colorless to slightly pink solution.

RabAvert should be stored protected from light at 2°C to 8°C (36°F to 46°F). After reconstitution, the guidance in the prescribing information (PI) should be followed. The vaccine may not be used after the expiration date given on the package and container.

Further information can be found in the approved Prescribing Information, Appendix E.

6.2. Randomized Treatment

Subjects will be randomized to receive one of two treatments described below.
Treatment A: BPL HRIG + rabies vaccine (RabAvert®).

A 20 IU/kg dose of BPL HRIG will be given on Day 0 via IM injection. The volume to be injected will be based upon the subject's weight on Day 0 and BPL HRIG actual potency (see pharmacy manual). A maximum of 5 mL will be administered to each lateral thigh and a maximum 2.0 mL to the deltoid muscle. The gluteal muscle will not be used for IM injection due to the increased variability of absorption from this injection site and the risk of injury to the sciatic nerve.

The total volume will be split between the injection sites as follows:

Table 5: Treatment A -total volume to be split between the injection sites

Injection number	Volume to be injected	Site of injection
1	up to 5 mL depending on bodyweight	left lateral thigh muscle
2	up to 5 mL depending on bodyweight	right lateral thigh muscle
3 (if required)	up to 2 mL depending on bodyweight	left deltoid muscle

A 1.0 ml dose of active vaccine (2.5 IU/ml) will be given IM on 5 occasions: on Days 0, 3, 7, 14, and 28. On day 0, the vaccine will be administered to the right deltoid muscle. The subsequent doses of vaccine on days 3, 7, 14, and 28 may be administered to the right or the left deltoid muscle.

The vaccine dose should never be administered into the same anatomical site as the HRIG.

Treatment B: FDA-approved comparator HRIG (HyperRAB® S/D) + rabies vaccine (RabAvert®)

A 20 IU/kg dose of comparator HRIG will be given on Day 0 via IM injection. The volume to be injected will be based upon the subject's weight on Day 0 and BPL HRIG actual potency (see pharmacy manual). A maximum of 5 mL will be administered to each lateral thigh and a maximum 2.0 mL to the deltoid muscle. The gluteal muscle will not be used for IM injection due to the increased variability of absorption from this injection site and the risk of injury to the sciatic nerve.

The total volume will be split between the injection sites as follows:

Table 6: Treatment B -total volume to be split between the injection sites

Injection number	Volume to be injected	Site of injection
1	Up to 5 mL depending on body weight	left lateral thigh muscle
2	up to 5 mL depending on bodyweight	right lateral thigh muscle
3 (if required)	up to 2 mL depending on bodyweight	left deltoid muscle

A 1.0 ml dose of active vaccine (2.5 IU/ml) will be given on 5 occasions: on Days 0, 3, 7, 14, and 28. On day 0, the vaccine will be administered to the right deltoid muscle. The subsequent doses of vaccine on days 3, 7, 14, and 28 may be administered to the right or the left deltoid muscle.

6.3. Product Administration

HRIG will be drawn into 2 or 3 (as appropriate according to the calculated volume) 5.0 mL syringes and injected to the lateral thighs and, if required, the left deltoid muscle.

Vaccine will be drawn into a 1.0 mL syringe and injected to the right deltoid muscle.

The selection of HRIG products to be administered (BPL HRIG or comparator HRIG) as per the randomized treatment, the calculation of the volume to be administered, and the drawing up of the appropriate volume into syringe(s), will be performed by the unblinded pharmacist/or licensed medical personnel. The selection of products to be administered, calculation of volume to be administered, and the volume in the syringe will be checked by the unblinded nurse administrator prior to administration to the subject.

For the BPL HRIG, comparator HRIG, the following details will be recorded:

- name of product
- lot number

- total dose required in IU, calculated from body weight (20 IU/kg)
- total dose required in mL, calculated from the actual potency
- for each specified injection site, actual dose administered in mL (this should not exceed 5.0 mL for each lateral thigh muscle and 2.0 mL for the left deltoid muscle)
- date and time of injection on Day 0

See the pharmacy manual for additional information on calculations, potency and details to be recorded. Certificates of analysis for both products will be kept in BPL files.

For the rabies vaccine, the following details will be recorded:

- name of product
- lot number
- confirmation of actual dose given in mL (this should be 1.0 ml)
- date, time, and location of injection, on Days 0, 3, 7, 14, and 28

See the pharmacy manual for additional information on details to be recorded. For any given subject, every effort must be made to use the same lot of active rabies vaccine throughout the study.

For additional details on administration of BPL and comparator HRIG using actual potency versus nominal potency refer to Appendix F and the pharmacy manual.

6.4. Concurrent Medication

Concomitant medication is defined as any medication, other than the study drug, which is taken during the trial, including prescription and over-the-counter medicines. For the purposes of the study, nutritional supplements including vitamins and minerals are not considered concomitant medications. The generic names of medications should be used where possible.

Concomitant medication will be recorded in the subject notes with indication, dose information, and dates of administration. Any new medications taken or any changes to the form, frequency or dose of existing medication occurring during the study will also be recorded.

Corticosteroids, other immunosuppressive agents or treatments, and immunosuppressive illnesses can interfere with the development of active immunity and, in patients exposed to the rabies virus, predispose the patient to developing rabies. Immunosuppressive agents should not be administered during the study, unless essential for the treatment of other conditions. Oral or IV steroids should not be taken within 14 days prior to Day 0, and if required during the study the subject will be withdrawn from the study. Topical or inhaled steroids are permitted.

Other antibodies in the BPL HRIG or comparator preparation may interfere with the response to live vaccines such as measles, mumps, polio or rubella. Therefore, immunization with live

vaccines should not be given within 3 months of BPL HRIG administration. Inactivated Influenza vaccination is allowed, see Investigator Brochure.

6.5. Drug Accountability

The investigator is responsible for ensuring that a record is maintained for every vial of study medication and licensed product provided to the site for the study. **Accounts must be kept for each subject of the identity (lot#) and number of vials administered, used and returned to pharmacy, to demonstrate full drug accountability.** The unblinded staff at the study center will confirm receipt of the study supplies, indicating dates of receipt, expiration dates, temperature conditions, lot numbers and quantities of all study supplies received from the Central Drug Distributor. Records will be kept of medication administered to each subject, as well as amounts remaining at the study conclusion. The study monitor will arrange for the collection of unused supplies for return to the Sponsor / Central Drug Distributor upon completion of the study or before if appropriate. Alternatively, if a documented drug destruction policy exists; unused supplies may be destroyed at the investigational site.

The following records will therefore need to be maintained to provide complete accountability:

- Dispatch notes or invoice slips
- Receipt forms
- Dispensing log
- Returns to BPL / Central Drug Distributor OR destruction logs

It is essential that all study product administered to the subject is recorded in the subject's clinic notes including amount administered.

Used and partly used vials will be retained at the pharmacy and reserved for drug accountability purposes, until written confirmation is received from the monitor that they may be disposed of locally.

The products provided for the study must be used solely as indicated in the protocol and must never be used for subjects not participating in the study.

A log of daily temperatures in the pharmacy storage area must be maintained to demonstrate that the products have been stored under the specified conditions.

6.6. Randomization and Blinding

Subjects will be assigned to one of the treatment groups according to a randomization schedule prepared before the study start. Each subject's randomization number will correspond to the treatment assigned. Therefore, subjects and investigators will be blinded to the treatment received.

An unblinded pharmacist or licensed medical personnel will be responsible for preparing study treatments in accordance with the randomized treatment assignment. As the volume differs between the HRIGs, the staff responsible for administration of the treatment will be unblinded. Different, blinded study personnel will be responsible for observing any reactions and interviewing subjects about potential reactions.

Information on roles and responsibilities of blinded and unblinded study personnel will be detailed in the Blinded Project Plan.

6.7. Emergency Unblinding of Study Treatment

To maintain the integrity of the trial, emergency unblinding should occur only in exceptional circumstances when knowledge of the actual treatment is essential for further management of the subject. Investigators are encouraged to discuss with the Medical monitor if he/she believes that the unblinding is necessary.

If unblinding is deemed to be necessary, the investigator should follow the procedures for emergency unblinding as described in the Study Reference Manual (SRM).

The investigator is encouraged to maintain the blind as far as possible. The actual allocation must not be disclosed to the subject and/or other study personnel. Unblinding should not necessarily be a reason for study drug discontinuation.

7. TRIAL PROCEDURES

A detailed flowchart showing the assessments to be performed are in Appendix G. Study days are defined as calendar days.

7.1. Consent

An oral explanation of the study covering its nature, purpose, risks and requirements will be given to the subject prior to any study-specific procedures being performed. Written information will also be provided to the subject in the appropriate language.

The subject will be given adequate time to consider their participation in the study and will be given the opportunity to ask the investigator about any aspect of the study. If participation is agreed, a Consent Form will be signed. If appropriate, a letter will be sent to the subject's primary care doctor informing him/her that the subject is to participate in the study.

Consent may be obtained at the Screening Visit, if appropriate. The informed consent form must be signed before any screening procedures are performed.

7.2. Visit 1: Screening Visit (up to Day -28)

The screening visit may be performed up to 28 days before first dose of investigational product.

The following assessments will be performed:

- Medical history, concomitant medications check
- Demography, gender
- Physical examination including 12-lead ECG, height and body weight
- Vital signs: sitting blood pressure (mmHG) after a 5-min rest, pulse rate and respiration rate
- Blood samples will be taken for the following assessments:
  - virology: anti-HIV1&2, HBsAg, anti-HCV (see Section 8.2.3)
  - serum biochemistry (see Section 8.2.3)
  - hematology (see Section 8.2.5)
  - serum pregnancy test for all females of child-bearing potential
- Reserve blood samples will be taken (see Section 7.9.1)
- A urine sample will be collected for urinalysis (see Section 8.2.6).

There will be a review of eligibility criteria. At the investigator's discretion, one or more screening laboratory tests may be repeated prior to Day 0 (Visit 2) and if not clinically significant and otherwise qualifying to determine eligibility.

For full details of sample collection, labeling, processing and storage for all laboratory tests please see the separate Laboratory Manual.

7.3. Visit 2: Baseline Visit (Day 0)

Dosing will take place within 28 days of the Screening Visit.

7.3.1. Before Dosing (Day 0)

The following procedures will be performed prior to dosing:

- Review of continued eligibility, including:
  - elements of informed consent
  - interim medical history
  - concomitant medications
  - Vital Signs
    - Oral temperature. If the participant is febrile (oral temperature >38.0°C [100.4°F]) or has an acute illness, their enrollment must be re-scheduled. The decision to delay vaccinations because of a current or recent acute illness depends on the severity of the symptoms and their cause. Although a moderate or severe acute illness is sufficient reason to postpone vaccination, minor illnesses are not necessarily contraindications to vaccination. If re-scheduled. Day 0 must be within 28 days of all screening procedures; if greater than 28 days the subject must undergo a repeat screening visit. A new subject number will be assigned for repeat screening visits (see Study Reference Manual (SRM) for instructions on repeat screening).
- Body weight will be measured for reassessment of eligibility and calculation of the dose of HRIG in IU/kg
- A urine pregnancy test in females of childbearing potential
- A urine sample will be taken for urine hemosiderin (see Section 8.2.7)
- Blood samples will be taken for the following assessments:
  - rabies virus neutralizing antibodies (see Section 8.1.4)
  - markers of hemolysis (DCT, LDH, plasma free hemoglobin, serum haptoglobin and serum bilirubin) (see Section 8.2.7)
- Reserve blood samples will be taken (see Section 7.9.1)
- An archive serum sample will be taken (see Section 7.9.2) for long-term storage at -70ºC for approximately 15 years.

The subject will then be randomized to treatment Group A or B, as described in Section 6.2 .

7.3.2. Dosing on Day 0

Immediately prior to dosing, each injection site for the HRIG will be examined for pain, tenderness, erythema and induration (see Section 8.2.2) by the blinded site personnel, to establish a baseline for local tolerance.

According to the subject's randomized treatment, an IM injection of 20 IU/kg body weight BPL HRIG or HyperRAB® S/D will be administered. This will be followed by an IM injection of 1.0 ml licensed active rabies vaccine. Treatments for injection will be prepared and administered by unblinded site staff, who will remain separate to the study team as described in Section 6.6).

The volume and location of administration of HRIG to each injection site will be recorded. The location of administration of active rabies vaccine, which must be a separate site to the HRIG injections, will also be recorded.

7.3.3. After Dosing

Study subjects will be observed in the clinic for a minimum of 30 minutes post-dose. Any adverse events will be assessed by the clinic staff and will be recorded in the subject notes.

At 30 minutes (± 5 minutes), all injection sites will be examined for pain, tenderness, erythema and induration by qualified clinical staff. (see Section 8.2.2).

7.4. Visits 3 to 7: Injections of Rabies Vaccine

The subject will return to the clinic on the following days:

Day 3 (Visit 3)

Day 7 (Visit 5)

Day 14 (Visit 6)

Day 28 ± 2 days (Visit 7)

7.4.1. Before Dosing

The following assessments will be performed at all visits:

- Check for any new or changed adverse events and concomitant medications since the last visit
- Oral temperature. If the participant is febrile (oral temperature >38.0°C (100.4°F) or has an acute illness, active rabies vaccine must not be given. The subject may continue in the study but should receive no further doses of active rabies vaccine and will not be eligible for the per protocol population.

- Injection site assessment (only if symptoms were observed at the previous visit)
- Blood samples will be taken for rabies virus neutralizing antibodies (see Section 8.1.4)

Reserve blood samples will be taken (see Section 7.9.1)

In addition, the following assessments will be performed at the specified visits (see also the Schedule of Assessments in Appendix G):

- Vital signs: sitting blood pressure (mmHg) after a 5-min rest, pulse rate and respiration rate – Day 28 (see Section 8.2.8)
- Blood samples will be collected for the following assessments:
  - markers of hemolysis (DCT, LDH, plasma free hemoglobin, serum haptoglobin and serum bilirubin) on Day 3. These tests including CBC may be repeated on Day 5, Day 7 and Day 14 depending on results obtained at the previous visit (see Section 8.2.7).
- A urine sample for hemosiderin – Day 3. This test may be repeated on Day 5, 7 and Day 14 depending on results obtained at the previous visit (see Section 8.2.7).

7.4.2. Dosing of Active Rabies Vaccine

According to the subject's randomized treatment, an IM injection of 1.0 ml licensed active rabies vaccine will be administered. It may be administered to either the left or the right deltoid muscle, as long as there are no injection symptoms from previous HRIG or active rabies vaccine injections. The location of administration of active rabies vaccine will be recorded.

7.4.3. After Dosing

Study subjects will be observed in the clinic for a minimum of 30 minutes post-dose. Any adverse events will be assessed by the clinic staff and will be recorded in the subject notes.

7.5. Visit 4: Day 5 PK sample

The subject will return to the clinic on Day 5. The following assessment will be performed:

- Check of any new or changed adverse events and concomitant medications since the last visit.
- Blood sample will be taken for rabies virus neutralizing antibodies (see Section 8.1.4)
- Blood samples will be collected for markers of hemolysis (DCT, LDH, plasma free hemoglobin, serum haptoglobin and serum bilirubin), and CBC if the Day 3 DCT result was positive or missing (see Section 8.2.7).
- A urine sample for hemosiderin will be collected if the Day 3 DCT result was a positive or missing (see Section 8.2.7).

- Reserve blood samples will be taken (see Section 7.9.1)

7.6. Visit 8: Day 49 PK sample

The subject will return to the clinic on Day 49 (± 4 days). The following assessments will be performed:

- Check of any new or changed adverse events and concomitant medications since the last visit
- Physical examination (see Section 8.2.9)
- Vital signs: sitting blood pressure (mmHg) after a 5min rest, pulse rate and respiration rate (see Section 8.2.8)
- Blood samples will be taken for the following assessments:
  - rabies virus neutralizing antibodies (see Section 8.1.4)
- Reserve blood samples will be taken (see Section 7.9.1)

7.7. Visit 9: End-of-Study Assessment

An End-of-Study assessment will be conducted at Day 140 (±7 days). The following assessments will be performed:

- Check of any new or changed adverse events and concomitant medications since the last visit
- Physical examination including 12-lead ECG and body weight
- Vital signs: sitting blood pressure (mmHg) after a 5 min rest, pulse rate and respiration rate (see Section 8.2.8)
- Blood samples will be taken for the following assessments:
  - hematology and serum biochemistry (see Sections 8.2.4 and 8.2.5)
  - Serum Pregnancy
  - virology: anti-HIV1&2, HBsAg, anti-HCV (see Section 8.2.3)
  - rabies virus neutralizing antibodies (see Section 8.1.4)
- Reserve blood samples will be taken (see Section 7.9.1)
- A urine sample will be collected for urinalysis

- An archive serum sample will be taken (see Section 7.9.2) for long-term storage at -70°C or lower for 15 years.

7.8. Unscheduled Visits

Subjects will also attend the investigational site as required for collection of repeat blood samples.

7.9. Blood Sample Collection, Handling and Labeling

Full details on blood sampling collection, handling, storage and shipment of samples can be found in the Laboratory Manual.

7.9.1. Reserve Samples

Two reserve plasma/serum samples will be collected at all timepoints, for re-analysis if needed, e.g. if an original sample is spoiled or if results are discrepant. Additional reserve plasma samples will be taken pre-dose at Day 0 and Day 140 in case viral nucleic acid testing is required to confirm viral serology results (see Section 8.2.3). Human DNA testing will not be performed on any samples. Reserve samples will be stored at the study site at -70°C or lower for the duration of the study and sent to the central laboratory when requested by the sponsor (BPL). Reserve samples may be stored at a central laboratory archive until the license for BPL HRIG is granted in the US and EU (European Union) or other territories and will be used, if required, for repeat assays at the request of a regulatory agency.

7.9.2. Archive Sample

An archive serum sample will be collected pre-dose on Day 0 and at the End-of-Study Assessment. Archive serum samples will be sent to the central laboratory for storage at -70°C and later by batch shipment to a central laboratory archive for storage at -70°C or lower for 15 years. The archive sample serves as a safety measure for subjects receiving human plasma-derived product, for investigation of risk factors which may potentially be identified in the future.

7.10. Recording Laboratory Results

All laboratory tests, except for the urine dipstick pregnancy test on Day 0, will be performed at a central laboratory. Test results will be emailed to the investigator. All reports must be reviewed by the investigator as soon as possible after receipt, and printed, signed and dated by the investigator.

Abnormal laboratory values considered to be clinically significant by the Investigator must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Any values outside the normal range should be assessed for clinical significance, and any clinically significant results must be commented upon by the investigator.

7.11. Restrictions

There are no restrictions on study subjects, except for certain concurrent medications (Section 6.4).

8. OUTCOME MEASURES

8.1. Efficacy Measures

8.1.1. Primary efficacy endpoint

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

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

8.1.2. Secondary efficacy endpoints

The following secondary efficacy endpoints will be assessed:

1) Assessment of $AUC_{0\text{-}7d}$ for BPL HRIG and vaccine versus comparator HRIG and 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 quantification (LLOQ) 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.

8.1.3. Exploratory efficacy endpoints

The following PK parameters for anti-rabies antibody concentrations for both treatment groups will be assess as an exploratory endpoint:

- 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}]
- $AUC_{0\text{-}7\ days}$ [day*IU/mL]
- area under the concentration vs time curve to infinity ($AUC_{0-\infty}$), if appropriate
- $C_{max}/AUC_{0-\infty}$ [or C_{max}/AUC_{0-t} if $AUC_{0-\infty}$ cannot be estimated]
- half-life ($t_{½}$), if appropriate

8.1.4. Rabies virus neutralizing antibody

Rabies virus neutralizing antibody (RVNA) levels will be measured at [redacted] by the rapid fluorescent focus inhibition test (RFFIT). This serum neutralization test measures the ability of rabies specific antibodies to neutralize rabies virus and prevent the virus from infecting cells, and is the current gold standard serological assay[3,8]. The WHO 2nd international reference serum for rabies immunoglobulin will be used to titrate as a standard reference each time serum samples are tested. This reference serum can vary in titer level for each batch of testing. Therefore serum samples at each PK timepoint (pre-dose on Days 0, 3, 5, 7, 14, 28, 49 and 140) will be batched by subject, tested for rabies RVNA titer after the subject's study completion, and reported in IU/ml.

The lowest RVNA level that can be accurately and precisely (the lower limit of quantification) measured at [redacted] is approximately 0.1 IU/mL. A RVNA level of equal to or above 0.5 IU/mL is globally recognized as indicating adequate vaccine response[4,9] .

The laboratory staff will be blinded to study treatment. Details for collection and processing of each blood sample will be documented separately in the Laboratory Manual.

8.2. Safety Assessments

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).

8.2.1. Adverse Events

All adverse events that appear or worsen during the study, from the time of signing informed consent, will be recorded in the CRF. If a subject has a recurring condition, then this should be recorded at the Screening Visit in the Medical History pages of the CRF. Fluctuations or re-occurrences of the condition, that are considered normal for that subject and are recorded in the medical history, and need not be reported as an adverse event. However, if the condition were to deteriorate during the study this would then be recorded as an adverse event.

Adverse events will be reported in terms of their type, duration, treatment and/or severity.

For further information on the definition and reporting of adverse events, see Appendix A.

8.2.2. Injection Site Observations

Each HRIG and vaccine injection site will be examined, and injection site observations will be assessed, pre-dose and 30 min [± 5 min] post-dose on Day 0 and at each subsequent clinic visit unless no symptoms are observed.

For injection site reaction (ISR) assessment criteria, refer to the table below:

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non- narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/ Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/ Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

For the complete guidance (see Appendix A, Section 7): Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials[25] :

All injection site reactions (ISR) will be recorded and graded on the ISR eCRF page. However, the investigator will determine if these are AEs. Injection site reactions will be recorded as AEs when the sign/symptoms require concomitant medications, or have an impact on the general condition of the subject as judged by the Investigator. The investigator will use their judgement to record the severity of the AE, using the appended toxicity scale to guide their assessment.

8.2.3. Viral Serology

Serum samples for viral serology testing will be collected at the Screening Visit and at the End-of-Study Assessment. Subjects with a positive serological test for HIV 1&2, HCV or HBsAg at the Screening Visit will be excluded from the study.

Samples will be tested for the following panel of serological markers:

- Anti-HIV1
- Anti-HIV2
- HBsAg
- Anti-HCV

In addition, a reserve sample will be taken pre-dose at the Baseline Visit and at the End-of-Study Assessment specifically for nucleic acid testing (NAT) if required (see below).

If any of the above serological tests are positive at the End-of-Study Assessment, suggesting a change in viral status of the subject, the sample will be tested by NAT (reflex testing). If a change in viral status is confirmed by NAT, the central laboratory will inform the investigator, Sponsor and the designated CRO within one business day. The reserve samples taken pre-dose at the Baseline Visit and at the End-of-Study Assessment will then be tested in the same laboratory in the same batch.

8.2.4. Serum Biochemistry

Blood samples for serum biochemistry assessments will be collected at the Screening Visit and at the End-of-Study Assessment. Results at the Screening Visit will be used to determine eligibility for the study. The following variables will be assessed for each biochemistry sample collected:

- Albumin

- Alkaline phosphatase (ALP)
- Alanine transferase (ALT)
- Aspartate aminotransferase (AST)
- Blood Urea Nitrogen (BUN)
- bicarbonate
- Bilirubin (direct and total)
- Calcium
- Chloride
- Creatinine
- Creatinine Phosphokinase (CPK)
- Gamma-glutamyl-transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Potassium
- Sodium
- Total protein

8.2.5. Hematology

Blood samples for hematology assessments will be collected at the Screening Visit and at the End-of-Study Assessment. Results at the Screening Visit will be used to determine eligibility for the study. The following variables will be assessed for each hematology sample collected:

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count (total and differential)
- Mean cell volume
- Mean corpuscular hemoglobin concentration
- Platelet count

8.2.6. Urinalysis

Urine samples will be collected for urinalysis, including microscopic examination, at the Screening Visit and at the End-of-Study Assessment. Microscopic examination will be

performed in case of positive dipstick results or abnormal findings. Significant abnormalities at the Screening Visit will exclude the subject from the study.

8.2.7. Markers of Hemolysis

Blood samples for the following markers of hemolysis will be collected pre-dose on Days 0 and 3:

- direct Coomb's test (DCT)
- serum lactate dehydrogenase (LDH)
- plasma free hemoglobin
- serum haptoglobin
- serum bilirubin

A urine sample for urine hemosiderin will be collected at the same timepoints.

If the DCT result at Day 3 is positive or not available by Day 5, blood and urine samples will be collected pre-dose on Day 5 for testing of all the above markers, as well as an unscheduled CBC. If any result at Day 5 is suggestive of hemolysis (*i.e.*, positive DCT; plasma free hemoglobin, LDH, serum bilirubin, or urine hemosiderin above the normal reference range; haptoglobin below the normal reference range) all markers including CBC will be tested pre-dose at Day 7. Similarly, if any result at Day 7 is suggestive of hemolysis; all markers including CBC will be tested pre-dose at Day 14.

Markers of hemolysis will be reviewed regularly by the medical monitor, and any potential signs of hemolysis will be reported to the investigator, sponsor and dedicated CRO by the central laboratory within one business day.

8.2.8. Vital Signs and Body Temperature

Vital signs will be assessed at Screening, Day 0, Day 28, and Day 49 and at the End-of-Study Assessment. Vital signs will include the following assessments:

- Sitting blood pressure (mmHg) after a 5-min rest.
- Pulse rate (bpm).
- Respiration rate (breaths/respirations per minute).

Results at the Screening Visit will be used to determine eligibility for the study. Evidence of uncontrolled hypertension (systolic blood pressure of >150 mmHg, and/or diastolic blood pressure of >100 mmHg), or heart rate >120 beats/min will exclude the subject from the study.

Oral body temperature will be assessed pre-dose on Days 0, 3, 7, 14 and 28. If the subject is febrile (oral temperature >38.0°C [100.4°F]) or has an acute illness at Day 0, their enrollment must be re-scheduled (see Section 7.3.1). If re-scheduled, Day 0 must be within 28 days of all screening procedures; if outside of this window the subject must undergo a repeat screening visit. A new subject number will be assigned. (See SRM for instructions on repeat screening).

If the subject is febrile at any subsequent visit, active rabies vaccine must not be given. The subject may continue in the study but should receive no further doses of active rabies vaccine and will not be eligible for the per protocol population.

8.2.9. Physical Examination

A physical examination will be performed at the Screening Visit, on Day 49, and at the End-of-Study Assessment. The following body systems will be examined: Head, ears, eyes, nose, throat, chest, cardiovascular, respiratory, abdomen, musculoskeletal, skin and general appearance.

In addition, a 12-lead ECG in a semi-recumbent position following at least 5 minutes of rest will be performed at Screening and the End-of-Study Assessment. Results at the Screening Visit will be used to determine eligibility for the study. Based upon the investigator's judgement, significant abnormalities will exclude the subject from the study.

Any changes in physical examination or ECG from the Screening assessment will be recorded, and any adverse changes will be reported as adverse events.

Body weight and height will be measured at Screening, and body weight only will be repeated pre-dose on Day 0 and at the End-of-Study Assessment. Body weight at Screening or Day 0 which exceeds 95.5 kg will exclude the subject from the study.

8.2.10. Pregnancy Test

A pregnancy test will be performed on all females of child-bearing potential (*i.e.* all those who are not more than 1 year post-menopausal or surgically sterilized). Pregnancy testing will be performed on a serum sample at the Screening Visit, by the central laboratory. Pregnancy testing will be repeated on a urine sample pre-dose at the Baseline visit (Day 0) and serum sample at End-of-Study Assessment by the central laboratory. A negative result at screening and Day 0 must be obtained to confirm the subject is eligible for the study.

9. WITHDRAWAL OF SUBJECTS

Subjects may stop study treatment for any of the following reasons:

- Withdrawal of consent.
- Significant protocol deviation.
- Occurrence of an adverse event which interferes with the subject's ability to continue in the trial.
- Occurrence of adverse events (AEs) not compatible with the continuation of subject participation in the study, in the investigator's opinion (e.g. anaphylactic or other severe/serious reaction to injection).
- Investigator's request.
- Pregnancy. If pregnancy occurs, the subject should be monitored and the outcome of delivery reported.
- Requirement for therapeutic intervention prohibited by the protocol, for example, immunosuppressive agents.
- Potential exposure to the rabies virus during the study, which would necessitate treatment with licensed HRIG.
- Presenting with fever (oral temperature >38.0°C [100.4°F]) on Day 3, 7, 14 or 28.
- Premature termination of the trial by BPL (e.g. if special circumstances concerning the IMP or BPL occur, making further treatment of subjects impossible, or if serious adverse events occur that are considered to make further treatment of subjects impossible). If this occurs, BPL or BPL's representatives will notify the regulatory authorities, ethics committees and investigators of the reason for premature study termination, within 15 days from the study being halted.
- Reason not provided (subject lost to follow-up)

The clinical investigator may also remove a subject if, in his/her opinion, it is in the best interests of the subject. In exceptional circumstances relating to safety, the sponsor may withdraw subjects at any time.

Subjects are free to withdraw from the study at any time without providing reason(s) for withdrawal and without prejudice to further treatment. The reason(s) for withdrawal will be documented where possible, particularly where withdrawal is a consequence of an adverse event (see Appendix A). The subject's primary care physician will be informed of the reason for withdrawal if follow-up care is needed for safety. The subject will be informed if this is required.

Data collected up until a subject's withdrawal from the study will be used in the analysis. Data on screen failures will be collected.

Subjects withdrawing from the study will be requested to complete the same End-of-Study assessments as subjects completing the study according to the protocol, particularly safety assessments. If there is a medical reason for withdrawal, the subject will remain under the supervision of the investigator until in satisfactory health or the subject's condition has stabilized.

Reasonable efforts will be made to contact subjects who are lost to follow-up. These efforts must be documented in the subject's medical records.

10. DATA ANALYSIS

10.1. Source Data

The collection and analysis of high quality data is dependent on accurate documentation in the study subjects' hospital notes, to allow accurate verification of CRF data. See Appendix B (Administrative Requirements) for more detail on the recording of data in subject notes and maintenance of other study documents.

10.2. Data Recording

All data from the study will be entered into a eCRF at the study site. All key data must be entered into the subjects' medical records before they are entered in eCRF (see Appendix B, Section 11.4).

10.3. Statistical and Analytical Plans

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.

All data will be listed. More information is in the statistical analysis plan for the study.

10.4. Analysis 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 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 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 analyses and the exploratory PK analysis.

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

Subjects not meeting eligibility criteria or for whom major protocol deviations are reported may be excluded from the per protocol population if considered to potentially impact on the PK analysis. Any such cases will be fully justified in the clinical study report.

10.5. Efficacy Analysis

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.

10.5.1. Primary PK 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 titer 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 at a one-sided significance level of 0.025. 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 calculated from the Farrington-Manning score test is greater than the *a priori* set -10% non-inferiority margin.

An additional analysis will be performed to assess the impact of dosing/PK sampling not being performed on the designated day. See Section 10.7.2.

10.5.2. Hypothesis for the Primary PK Analysis

The null hypothesis is $p-p_0 \leq -0.1$;

The alternative hypothesis is $p-p_0 > -0.1$,

where p is the proportion of subjects with anti-rabies titer of ≥0.5 IU/mL at Visit 6 in subjects receiving BPL HRIG + vaccine and p_0 is the proportion receiving comparator HRIG + vaccine.

We reject the null hypothesis at the one-sided 0.025 significance level, and conclude that $p-p_0 > -0.1$, if the lower bound of an exact 95% binomial confidence interval exceeds -0.1.

10.5.3. Secondary PK Analysis

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 secondary PK endpoints will be analyzed as follow:

1) the assessment AUC_{0-7d} for BPL HRIG and vaccine versus comparator HRIG and vaccine using a non-inferiority margin of 20%.
2) the geometric mean titers (GMTs) for RVNA titer up to peak serum level after administration of BPL HRIG and vaccine or comparator HRIG and vaccine will be assessed using a mixed model repeated measure [MMRM] analysis.
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 will be assessed using a generalized estimated equation [GEE] for a repeated measure analysis.
4) the proportion of subjects reaching anti-rabies antibody titer of ≥ the lower limit of quantification (LLOQ) of the assay at Visit 3-6 after administration of BPL HRIG and

vaccine versus comparator HRIG and vaccine will be assessed using a generalized estimating equation [GEE] for a repeated measure analysis.

5) the GMTs for anti-rabies antibody titer at Visits 6-9 will be compared between treatment groups. Descriptive statistics and visual inspections will be reported as appropriate. No formal hypothesis testing will be performed.

10.5.4. Exploratory PK Analysis

The PK parameters for anti-rabies antibody concentrations as described in Section 8.1.3 will be statistically compared as appropriate between treatment groups.

Non-compartmental PK methods will be utilized to calculate the subject level PK parameters. C_{max}, $AUC_{0\text{-}t}$, $AUC_{0\text{-}7d}$, $AUC_{0\text{-}\infty}$, 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.

10.6. Safety Analysis

The safety analysis will be based on the safety population. The general strategy of the safety evaluation will be to examine the summaries for any clinically relevant imbalance of safety events between the treatment groups. Safety parameters for the two treatment groups will be compared descriptively. Summary data will be presented by Treatment Group. No formal hypothesis testing will be carried out.

10.6.1. Adverse Events

Adverse events (AEs) will be reported by the MedDRA system organ class and preferred term. Only treatment-emergent AEs, defined as those events with onset date from 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

1) The number and percentage of subjects reporting AEs, serious AEs, study medication related AEs, AEs leading to withdrawal and AEs leading to death.
2) 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).

10.6.2. 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.

10.6.3. 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.

10.6.4. 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.

10.6.5. Markers of Hemolysis

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

10.6.6. 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 bpm) will be summarized.

10.6.7. 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.

10.6.8. Other Safety Parameters

Pregnancy test results will be listed.

10.7. 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.

10.7.1. Potential Interaction

Before treatment unblinding, timing of vaccine dosing at Visits 3-5 and PK sampling at visit 6, 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 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.

10.7.2. 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];
- subjects who did not receive the first 3 doses of active rabies vaccine at the time specified [not eligible for primary PK population];
- randomized without meeting all eligibility criteria [may be eligible for primary PK population];
- subjects with any major protocol deviations reported [may be eligible for primary PK population].

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]

10.8. Subgroup Analysis

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, and sex will be considered. Subgroups will be defined based on population median.

10.9. Determination of Sample Size

Statistical calculations indicate a minimum of 73 subjects per group is necessary. To allow for subject withdrawals or unevaluable data, approximately 81 subjects will be enrolled per group.

This study is powered based on a one-sided test with an overall study α of 0.05. A total of 162 subjects will be randomized to achieve 85% power with a one-sided significance level of 0.025.

This computation accounts for an expected 10% dropout rate resulting in 146 evaluable subjects. The following table outlines the underlying assumptions:

Table 7: The underlying assumptions

	Day 14 ≥ 0.5 IU/mL
Non-inferiority margin	10%
Difference	0%
% success	98%

10.10. Interim Analysis

An interim analysis is not planned.

11. INVESTIGATOR'S STATEMENT

A Prospective, Randomized, Double-Blind, 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

Version 1.0
Date: 26 Oct 2017

I have carefully read this protocol and the clinical investigator's brochure and I confirm that they contain all the information necessary to perform the study I agree to carry out the study in compliance with the protocol, ICH GCP and applicable regulatory requirements.

Signature: _____ Date: _____

Principal Investigator

Name: _____

(Printed)

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APPENDIX A. - ADVERSE EVENT DEFINITIONS AND REPORTING PROCEDURES

1. ABBREVIATIONS

ADR - Adverse Drug Reaction
AE - Adverse Event
BPL - Bio Products Laboratory Limited
CRF - Case Record Form
CRO - Contract Research Organisation
eCRF - Electronic Case Record Form
ECG - Electrocardiogram
FDA - Federal Drug Agency
ICF - Informed Consent Form
IEC - Independent Ethics Committee
IRB - Institutional Review Board
IMP - Investigational Medicinal Product
SAE - Serious Adverse Event
SmPC - Summary of Product Characteristics
SUSAR - Suspected Unexpected Serious Adverse Reaction

2. DEFINITIONS OF ADVERSE EVENTS

2.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign including an abnormal laboratory (or vital sign, ECG, etc.) finding, symptom or disease temporally associated with the use of study medication. All adverse events, whether considered by the investigator to be related to study medication must be described and recorded on the appropriate Adverse Event forms in the CRF/e-CRF. Where possible, a diagnosis should be made. Anticipated fluctuations of pre-existing conditions, including the disease under study that does not represent a clinically significant exacerbation or worsening need not be considered AEs.

2.2 Adverse Events Temporally Associated with the Injection

Unless clearly attributable to other causes any AEs that occur from the injection until Day 3 after the injection will be recorded as temporally related to the injection.

2.3 Clinical Laboratory and Other Adverse Events

If a laboratory result is considered by the investigator to be clinically significant or have a clinically significant pathological change from baseline it should be recorded as an AE.

Other abnormal results (e.g. x-rays, scans, physical examination findings) that worsen from baseline and/or are considered clinically significant should also be recorded as AEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

AEs should be reported and documented in accordance with the procedures outlined below. All AEs occurring during the study must be documented on the relevant CRF/e-CRF pages. The following data should be documented for each AE:

- Description of the symptom event
- Classification of 'serious' or 'not serious'
- Severity
- Date of first occurrence and date of resolution (if applicable)
- Action taken
- Causal relationship
- Outcome of event (unknown, recovered, not recovered, recovered with sequelae, death [with date and cause reported])

2.4 Pregnancy

Subjects will be instructed that known or suspected pregnancy occurring during the study should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. If a subject is found to be pregnant after inclusion in the study, the subject must be withdrawn from the study. Any pregnancy will be followed to term and the status of mother and child will be reported to the Sponsor after delivery.

Full details of any pregnancy will be recorded on the AE page of the CRF/eCRF, and a Pregnancy & Outcome Report Form will be completed. A copy of the Pregnancy Report Form must be completed and faxed to the appropriate contact (as detailed in the Study Reference Manual (SRM)) within 24 hours.

2.5 Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose administered. The phrase 'response to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

2.6 Serious Adverse Event (SAE) or Drug Reaction

A **Serious Adverse Event or reaction** is any untoward medical occurrence that at any dose:

- **results in death,**
- **is life-threatening (patient at risk of death at time of event; not hypothetically life-threatening),**
- **requires inpatient hospitalization or prolongation of existing hospitalisation,**
- **results in persistent or significant disability or incapacity,**
- **is a congenital anomaly or birth defect?**
- **is an important medical event (see below for definition)?**

The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Medical and scientific judgement must be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

The following medical conditions will be automatically regarded as serious, regardless of the classification assigned by the clinical trial investigator reporting the case:

- Anaphylaxis or anaphylactoid reaction
- Myocardial infarction
- Stroke
- Pulmonary embolism
- Infection with any blood borne virus
- Any transmissible spongiform encephalopathy

In general, information that might materially affect the risk-benefit assessment of a medicinal product or that would suggest changes in the way it is to be administered or to the way a clinical investigation should be conducted should be reported in an expedited manner. Examples include:

- Single case reports of an expected adverse reaction with an unexpected outcome e.g. fatal outcome
- For an expected serious adverse reaction, an increase in the rate of occurrence which is judged to be clinically important.

- A significant hazard to the patient population, such as lack of efficacy in treating life-threatening diseases or an event which is significant enough to lead to important changes in the way a medicine is developed e.g. change in dose, monitoring, consent forms.
- A major new safety finding from a newly completed animal study.
- A serious adverse event associated with a study procedure that could modify the conduct of the trial.

2.7 Unexpected ADRs

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). Reports which add significant information on specificity, severity or frequency about a listed ADR would be classed as 'unexpected', for example, a report of interstitial nephritis when acute renal failure is the listed ADR or a report of fulminant hepatitis when the product information only lists hepatitis.

Expectedness for BPL HRIG will be assessed against the Investigator's Brochure, for HyperRAB® will be assessed against the USPI (Appendix D) and rabies vaccine will be assessed against the USPI (Appendix E).

2.8 Suspected Unexpected Serious Adverse Reactions (SUSARs)

All suspected adverse reactions related to an IMP (the tested IMP, comparators or active vaccine) which occur that are both unexpected and serious (SUSARs) are subject to expedited reporting. BPL and / or the designated CRO will be responsible for reporting these to the concerned Competent Authorities and to the Ethics Committee concerned, as detailed in the Study Reference Manual.

3. DETECTING ADVERSE EVENTS

Subjects will be carefully monitored for adverse events that occur after the Informed Consent Form (ICF) has been signed until the last day of the study. The Investigator or delegate will question the subjects about adverse events using a non-leading question such as "How are you feeling?" The Investigator will also record adverse events reported spontaneously by the subjects. **Clinically significant** changes in the findings of physical examination, and clinically significant abnormalities in the result of objective tests (e.g. laboratory variables, ECG) should be recorded as AEs.

3.1 Causality

All AEs will be recorded in the CRF/eCRF, whether considered to be related or unrelated to the treatment. The record will include the following: brief description of event (preferably a diagnosis), date and time started and stopped severity, outcome, actions taken and classification of the AE. The Investigator should also evaluate the probability of a causal relationship of the AE to each medication administered during the study according to the following criteria as:

1. Unrelated	Clinical event with an incompatible time relationship to study medication administration, or that could be explained by underlying disease or other drugs or chemicals, or is incontrovertibly not related to the IMP.
2. Unlikely	Clinical event whose time relationship to study medication administration makes a causal connection improbable, but that could plausibly be explained by underlying disease or other drugs or chemicals.
3. Possible	Clinical event with a reasonable time relationship to study medication administration, but that could also be explained by concurrent disease or other drugs or chemicals.
4. Probable	Clinical event with a reasonable time relationship to study medication administration, and is unlikely to be attributed to concurrent disease or other drugs or chemicals.
5. Very likely / certain	Clinical event with plausible time relationship to study medication administration, and that cannot be explained by concurrent disease or other drugs or chemicals.

Study medication is defined as those investigational compounds or their controls and vaccines used in the study.

It will be assumed that for all adverse events classified as "probably related", "possibly related" or "very likely / certainly related" to the study medication, there is reasonable likelihood that the adverse event was causally related to the product. All such adverse events will be regarded as "causally related" to the study medication.

3.2 Outcome of AEs

The outcome of the AE should be documented as:

- Recovered / resolved
- Recovering / resolving
- Not recovered / not resolved
- Recovered / resolved with sequelae
- Fatal
- Unknown

3.3 Action taken

The action taken by the Investigator or study staff should be documented as:

- Drug withdrawn
- Dose reduced
- Dose increased
- Dose not changed
- Unknown

- Not applicable

3.4 Grading Severity of AE**

Severity refers to the grading of adverse events to assess the severity of symptoms as evaluated by the Investigator or as experienced by the subject. The Investigator will make an assessment of severity (e.g. Grade 1 (mild)-Grade 4 (potentially life threatening)) for each AE and SAE reported during the study in accordance with the following definitions:

Mild/Grade 1: No interference with activity

Moderate/ Grade 2: Some interference with activity not requiring medical intervention

Severe/ Grade 3: Prevents daily activity and requires medical intervention.

Potentially Life Threatening/Grade 4: Emergency room visit or hospitalization

**Any adverse event resulting in Death will be classified as a Grade 5
For further information (see Appendix A, Section 7): *FDA Guidance on Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials*[25]

4. ADVERSE EVENT FOLLOW UP

All adverse events will be followed:

- to resolution

  or
- until an underlying condition has been diagnosed

  or
- until the patient's condition has stabilised

  or
- for a period of 28 days following the last administration of the study drug (HRIG or rabies vaccine) or the last study visit, whichever is soonest.

Any new or unresolved AEs noted at the last study visit will be followed up for a further 28 days unless they fulfil the above criteria.

All pregnancies will be followed up until birth and any birth defects will be reported as in the procedures for SAEs (see section 3 and 4).

If the subject becomes pregnant while participating in the study, the pregnancy will not be recorded as an SAE, but will be captured on a Pregnancy Report Form and followed through until delivery or elective/spontaneous termination.

5. REPORTING SERIOUS ADVERSE EVENTS

When an Adverse Event occurs, which fulfils the definition of serious (see Section 2.6 for definition) the Investigator must complete and sign the serious adverse event form and send it within 24 hours to the appropriate contact.,

Medical cover for urgent queries relating to adverse events will be provided on 24 hours / 7 days a week by the following:

[redacted]

All SAE reports must be e-mailed or faxed directly to [redacted] *at* [redacted] *or* [redacted] *(see study reference manual for guidance on providing documentation of SAE).*

The Investigator is responsible for expedited reporting of all Serious Adverse Events immediately to BPL and / or the designated CRO except for those that the protocol or Investigator's Brochure identifies as not requiring immediate reporting. This reporting requirement covers any serious adverse events that develop at any point between the date when a subject provides informed consent and up to 28 days after the last administration of the investigational medicinal product (HRIG or rabies vaccine). The investigator is also responsible for reporting to BPL and / or the designated CRO any serious adverse events with an onset date more than 28 days after the last administration of the product if he/she judges the serious adverse event to be possibly, probably or very likely/certainly related to the product.

The immediate report should contain the following as a minimum:

- a suspected investigational medicinal product
- study subject number
- details of the serious adverse event
- classification of SAE
- causality of SAE (if available)

The immediate SAE form should be followed by a detailed, complete SAE form as soon as possible. The immediate report and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

Adverse events and/or laboratory abnormalities identified in the protocol as critical to the evaluation of safety must be reported to BPL and / or the designated CRO by the Investigator according to the reporting requirements within the time periods specified in this protocol.

The investigator must not wait to receive additional information to document fully the event before notification of a SAE, though additional information may be requested. Where applicable, information from relevant laboratory results, hospital case records and autopsy reports should be obtained.

Instances of death, congenital abnormality or an event that is of such clinical concern as to influence the overall assessment of safety, if brought to the attention of the investigator at any time after cessation

of IMP administration and linked by the investigator to this study should be reported to BPL or the designated CRO.

BPL and / or the designated CRO will promptly notify all relevant investigators and the regulatory authorities of findings that could adversely affect the safety of patients, affect the conduct of the study or alter the IEC/IRB approval/favourable opinion of the study. In addition, the sponsor (or designated CRO), will expedite the reporting to all concerned investigators, to the IECs/IRBs, where required, and to the regulatory authorities of all adverse events that are serious, unexpected, and in the opinion of the investigator, related to the IMP.

The investigator will comply with local requirements related to the reporting of SAEs, IND Safety Notification Letters, and other safety information related to the trial to their local IRB.

For reported deaths of a subject, the investigator shall supply BPL and / or the designated CRO (as stated in the Study Reference Manual) and the Independent Ethics Committee (IEC) / Institutional Review Board (IRB) with any additional information requested.

5.1 Completing Serious Adverse Event Forms

Serious Adverse Event (SAE) forms must be completed in a timely manner and contain the following information:

- subject number, randomization number, sex, date of birth, study centre, trial code,
- description of event (where possible a diagnosis should be made rather than just listing symptoms),
- dose, route, date and time of start and last dose,
- date and time of adverse event,
- **all** concomitant medication (copy of concomitant medication page can be appended),
- causal relationship to study medication (as in Section 3.1),
- outcome (as in Section 3.2),
- action taken and treatment given (as in Section 3.3),
- severity (as in Section 3.4),
- classification of serious adverse event (as in Section 2.6),

The SAE form must be signed and dated by the person reporting the SAE. The final report must be signed and dated by the Principal Investigator from the site.

6. BPL'S RESPONSIBILITIES

BPL and / or the designated Contract Research Organisation (CRO) will be responsible for reporting all relevant safety information (including a listing of all SUSARs) to the competent authorities and to the IEC / IRB concerned. In the case of blinded studies, the IEC / IRB and Competent Authority will be provided with an unblinded listing and in order not to bias the study the listing will be provided by

an independent person. Safety reports will be issued in accordance with local relevant procedures (as a minimum on an annual basis).

BPL and / or the designated CRO will inform the relevant Competent Authority(ies) in line with regulatory guidelines on adverse events occurring during the trial. The investigator retains the right to inform the relevant Competent Authority(ies) if he/she so desires but must inform BPL and / or the designated CRO (as stated in the Study Reference Manual) so that duplicate reports to the competent authority(ies) can be highlighted.

BPL and / or the designated CRO will inform all investigators of all suspected unexpected serious adverse reactions occurring during the study or findings that could adversely affect the safety of subjects.

7. TOXICITY GRADING SCALE FOR HEALTHY ADULT AND ADOLESCENT VOLUNTEERS ENROLLED IN PREVENTIVE VACCINE CLINICAL TRIALS

Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

Additional copies of this guidance are available from the Office of Communication, Training and Manufacturers Assistance (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or from the Internet at http://www.fda.gov/cber/guidelines.htm.

For questions on the content of this guidance, contact the Division of Vaccines and Related Products Applications, Office of Vaccines Research and Review at 301-827-3070.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
September 2007

Contains Nonbinding Recommendations

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Guidance for Industry

Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the appropriate FDA staff. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

Preventive vaccines are usually developed to prevent disease in a healthy population. The Office of Vaccines Research and Review, Center for Biologics Evaluation and Research, regulates preventive vaccines under authority of section 351 of the Public Health Service Act (42 U.S.C. 262), as well as specific sections of the Federal Food, Drug, and Cosmetic Act, and reviews investigational new drug applications (INDs) and biologics license applications (BLAs). (See, for example, Title 21 Code of Federal Regulations (CFR) Parts 312, 600, and 601). Most of the clinical trials of preventive vaccines conducted to support INDs and BLAs enroll healthy volunteers in all phases of vaccine testing. The enrollment of healthy volunteers warrants a very low tolerance for risk in those clinical trials.

This guidance provides you, sponsors, monitors, and investigators of vaccine trials, with recommendations on assessing the severity of clinical and laboratory abnormalities in healthy adult and adolescent volunteers enrolled in clinical trials. The grading system described in the table can also be useful in defining a particular study's stopping rules (e.g., a certain number of adverse events, as defined in the table, may call for stopping the study). Less extreme observations (e.g., mild) may not require discontinuing the study vaccine but can still contribute to evaluating safety by identifying parameters to focus upon in subsequent product development. Uniform criteria for categorizing toxicities in healthy volunteers can improve comparisons of safety data among groups within the same study and also between different studies. We, FDA, recommend using toxicity grading scale tables, provided below, as a guideline for selecting the assessment criteria to be used in a clinical trial of a preventive vaccine. We recommend incorporation of such appropriate, uniform, criteria into the investigational plan, case report forms, and study reports and correspondence with FDA, sponsors, monitors, investigators, and IRBs.

This guidance finalizes the draft guidance of the same title dated April 2005 (70 FR 22664, May 2, 2005).

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FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Standardized toxicity assessment scales have been widely used to evaluate products treating specific diseases. For example, the National Cancer Institute's Common Toxicity Criteria Scale and the Division of AIDS' Toxicity Grading Scale standardize the evaluation of adverse events among patients with cancer and HIV/AIDS, respectively (Refs. 1, 2). The defined toxicity parameters in those scales are designed for patients who may already experience mild, moderate, or severe adverse clinical or laboratory events due to the disease process, and may not be appropriate for healthy volunteers.

In the development of the toxicity grading scales for healthy volunteers, we chose parameter limit values based on published information, when such values were available (Refs. 1-6). For example, the Brighton Collaboration has developed case definitions and guidelines to evaluate some adverse events associated with administering vaccines (Ref. 3). In some cases, parameter limit values were based on clinical experience and experience reviewing vaccine clinical trials that enroll normal healthy subjects.

Toxicity grading scales for laboratory abnormalities should consider the local laboratory reference values when the parameter limit values are defined. The characterization of laboratory parameters among some populations of healthy adults and adolescents may require the exercise of clinical judgment, for example, consideration of the potential for ethnic differences in white blood cell (WBC) counts or gender differences in creatine phosphokinase (CPK) values.

III. TOXICITY GRADING SCALE TABLES

Adverse events in a clinical trial of an investigational vaccine must be recorded and monitored and, when appropriate, reported to FDA and others involved in an investigation (sponsors, IRBs, and investigators). (See, for example, 21 CFR 312.32, 312.33, 312.50, 312.55, 312.56, 312.60, 312.62, 312.64, 312.66). Although the use of a toxicity grading scale for adverse events would not replace these regulatory requirements, using a scale to categorize adverse events observed during a clinical trial may assist you in monitoring safety and making required reports. Nonetheless, we believe that categorization or grading of data as outlined in this document is supplementary to and should not replace full and complete data analysis.

These guidelines for toxicity grading scales are primarily intended for healthy adult and adolescent volunteers. The parameters in the tables below are not necessarily applicable to every clinical trial of healthy volunteers. The parameters monitored should be appropriate for the specific study vaccine. For some preventive vaccines under development, it may be appropriate

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to include additional parameters to be monitored during a clinical trial or to alter the choice of values in the toxicity table. For example, additional parameters might be added based on one or more of the following: safety signals observed in pre-clinical toxicology studies, the biological plausibility of the occurrence of certain adverse events, or previous experience with a similar licensed product.

As discussed above, the tables do not represent a recommendation to monitor all the listed parameters in all clinical trials of healthy volunteers, nor do the tables represent all possible parameters to be monitored. In addition, these tables do not represent study inclusion or exclusion criteria. We recommend that the parameters monitored be appropriate for the study vaccine administered to healthy volunteers participating in the clinical trial.

A. Tables for Clinical Abnormalities

Local Reaction to Injectable Product	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room (ER) visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	ER visit or hospitalization
Erythema/Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration/Swelling **	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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Vital Signs *	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) ** (°F) **	38.0 – 38.4 100.4 – 101.1	38.5 – 38.9 101.2 – 102.0	39.0 – 40 102.1 – 104	> 40 > 104
Tachycardia - beats per minute	101 – 115	116 – 130	> 130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	< 45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	> 155	ER visit or hospitalization for malignant hypertension
Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	> 100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate – breaths per minute	17 – 20	21 – 25	> 25	Intubation

* Subject should be at rest for all vital sign measurements.
** Oral temperature; no recent hot or cold beverages or smoking.
*** When resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Systemic (General)	Mild (Grade 1)	Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1 – 2 episodes/24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2 – 3 loose stools or < 400 gms/24 hours	4 – 5 stools or 400 – 800 gms/24 hours	6 or more watery stools or > 800gms/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever > 24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

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Systemic Illnes	Mild (Grade 1)	(Moderate(Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Illness or clinical adverse event (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization

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B. Tables for Laboratory Abnormalities

The laboratory values provided in the tables below serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Serum *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)**
Sodium – Hyponatremia mEq/L	132 – 134	130 – 131	125 – 129	< 125
Sodium – Hypernatremia mEq/L	144 – 145	146 – 147	148 – 150	> 150
Potassium – Hyperkalemia mEq/L	5.1 – 5.2	5.3 – 5.4	5.5 – 5.6	> 5.6
Potassium – Hypokalemia mEq/L	3.5 – 3.6	3.3 – 3.4	3.1 – 3.2	< 3.1
Glucose – Hypoglycemia mg/dL	65 – 69	55 – 64	45 – 54	< 45
Glucose – Hyperglycemia Fasting – mg/dL Random – mg/dL	 100 – 110 110 – 125	 111 – 125 126 – 200	 >125 >200	Insulin requirements or hyperosmolar coma
Blood Urea Nitrogen BUN mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Calcium – hypocalcemia mg/dL	8.0 – 8.4	7.5 – 7.9	7.0 – 7.4	< 7.0
Calcium – hypercalcemia mg/dL	10.5 – 11.0	11.1 – 11.5	11.6 – 12.0	> 12.0
Magnesium – hypomagnesemia mg/dL	1.3 – 1.5	1.1 – 1.2	0.9 – 1.0	< 0.9
Phosphorous – hypophosphatemia mg/dL	2.3 – 2.5	2.0 – 2.2	1.6 – 1.9	< 1.6
CPK – mg/dL	1.25 – 1.5 x ULN***	1.6 – 3.0 x ULN	3.1 –10 x ULN	> 10 x ULN
Albumin – Hypoalbuminemia g/dL	2.8 – 3.1	2.5 – 2.7	< 2.5	--
Total Protein – Hypoproteinemia g/dL	5.5 – 6.0	5.0 – 5.4	< 5.0	--
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	> 10 x ULN
Liver Function Tests –ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
Bilirubin – when accompanied by any increase in Liver Function Test increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	> 1.75 x ULN
Bilirubin – when Liver Function Test is normal; increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	> 3.0 x ULN
Cholesterol	201 – 210	211 – 225	> 226	---
Pancreatic enzymes – amylase, lipase	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.1 – 5.0 x ULN	> 5.0 x ULN

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** The clinical signs or symptoms associated with laboratory abnormalities might result in characterization of the laboratory abnormalities as Potentially Life Threatening (Grade 4). For example, a low sodium value that falls within a grade 3 parameter (125-129 mE/L) should be recorded as a grade 4 hyponatremia event if the subject had a new seizure associated with the low sodium value.

***"ULN" is the upper limit of the normal range.

Contains Nonbinding Recommendations

Hematology *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - gm/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	< 8.0
Hemoglobin (Female) change from baseline value - gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
Hemoglobin (Male) - gm/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	< 8.5
Hemoglobin (Male) change from baseline value – gm/dL	Any decrease – 1.5	1.6 – 2.0	2.1 – 5.0	> 5.0
WBC Increase - cell/mm^3	10,800 – 15,000	15,001 – 20,000	20,001 – 25, 000	> 25,000
WBC Decrease - cell/mm^3	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	< 1,000
Lymphocytes Decrease - cell/mm^3	750 – 1,000	500 – 749	250 – 499	< 250
Neutrophils Decrease - cell/mm^3	1,500 – 2,000	1,000 – 1,499	500 – 999	< 500
Eosinophils - cell/mm^3	650 – 1500	1501 - 5000	> 5000	Hypereosinophilic
Platelets Decreased - cell/mm^3	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	< 25,000
PT – increase by factor (prothrombin time)	1.0 – 1.10 x ULN**	1.11 – 1.20 x ULN	1.21 – 1.25 x ULN	> 1.25 ULN
PTT – increase by factor (partial thromboplastin time)	1.0 – 1.2 x ULN	1.21 – 1.4 x ULN	1.41 – 1.5 x ULN	> 1.5 x ULN
Fibrinogen increase - mg/dL	400 – 500	501 – 600	> 600	--
Fibrinogen decrease - mg/dL	150 – 200	125 – 149	100 – 124	< 100 or associated with gross bleeding or disseminated intravascular coagulation (DIC)

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

** "ULN" is the upper limit of the normal range.

Urine *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Protein	Trace	1+	2+	Hospitalization or dialysis
Glucose	Trace	1+	2+	Hospitalization for hyperglycemia
Blood (microscopic) – red blood cells per high power field (rbc/hpf)	1 - 10	11 – 50	> 50 and/or gross blood	Hospitalization or packed red blood cells (PRBC) transfusion

* The laboratory values provided in the tables serve as guidelines and are dependent upon institutional normal parameters. Institutional normal reference ranges should be provided to demonstrate that they are appropriate.

Contains Nonbinding Recommendations

IV. REFERENCES

1. National Cancer Institute Common Toxicity Criteria, April 30, 1999. (http://ctep.cancer.gov/reporting/CTC-3.html)

2. Division of AIDS Table for Grading Severity of Adult Adverse Experiences; August 1992. (http://rcc.tech-res-intl.com/tox_tables.htm)

3. The Brighton Collaboration. Finalized Case Definitions and Guidelines. (http://brightoncollaboration.org/internet/en/index/definition___guidelines.html)

4. HIV Vaccine Trials Network Table for Grading Severity of Adverse Experiences; September 18, 2002. (http://rcc.tech-res-intl.com/tox_tables.htm)

5. Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, December 2004. (http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf)

6. Kratz A, Ferraro M, Sluss PM, Lewandrowski KB. Laboratory Reference Values. New England Journal of Medicine. 2004;351:1548-1563.

APPENDIX B. - ADMINISTRATIVE REQUIREMENTS

1. ABBREVIATIONS AND DEFINITIONS

ARSAC - Administration of Radioactive Substances Committee
BPL - Bio Products Laboratory Limited
CA - Competent Authority
COI - Coordinating Investigator
CI - Chief Investigator
CRA - Clinical Research Associate
CRF - Case Record Form
e-CRF - Electronic Case Record Form
CV - Curriculum Vitae
DQF - Data Query Form
EU - European Union
FDA - Food and Drug Administration
GCP - Good Clinical Practice
GMC - General Medical Council
HIV - Human Immunodeficiency Virus
ICH - International Conference on Harmonisation
ID - Identification
IEC - Independent Ethics Committee
IMP - Investigational Medicinal Product
IRB - Institutional Review Board
PI - Principal Investigator
R&D - Research and Development
SOP - Standard Operating Procedure

CA – 'Competent Authority', synonymous with 'Regulatory Authority': the Government body that has the power to regulate. In the context of ICH GCP, the term 'Competent Authority' includes the authorities that review submitted clinical data and those that conduct inspections.

CI – 'Chief Investigator': in relation to a clinical trial conducted at a single trial site, the Investigator for that site. In relation to a clinical trial conducted at more than one trial site, the authorised health care professional, whether or not he/she is an Investigator at any site, who takes primary responsibility for the conduct of the trial.

COI – 'Coordinating Investigator': an investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

PI - 'Principal Investigator': a doctor or person following a profession for investigations because of the scientific background and the experience in subject care it requires. The Principal Investigator is responsible for the conduct of the trial at the trial site. If a trial is conducted by a team of individuals at a trial site, the Principal Investigator is the leader responsible for the team.

IEC – 'Independent Ethics Committee': a review board or a committee, institutional, regional, national or supranational, constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the Investigator(s), facilities and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IRB – 'Institutional Review Board': an independent body constituted of medical, scientific and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a clinical trial by, among other things, reviewing, approving and providing continuing review of the trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

IMP – 'Investigational Medicinal Product': a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorisation but used or assembled in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

2. ETHICAL CONSIDERATIONS

The study will be performed in accordance with the guidelines of the Declaration of Helsinki on biomedical research involving human subjects and in accordance with GCP guidelines (ICH), EU Directives 2001/20/EC[1] and 2005/28/EC[2] and FDA's Code of Federal Regulations (CFR)[3] 21 CFR parts 50, 54, 56, 312 and 314 as well as the demands of national drug and data protection laws, other applicable regulatory requirements and any new directives or regulations which become enforceable during the course of the study.

Before the study can begin the Investigator must have submitted to an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) the study protocol, Investigator's Brochure, subject

information leaflet, consent form (and any updates), subject recruitment procedures and any other relevant study documentation as outlined in the guidance document ('Detailed guidance on the application format and documentation to be submitted in an application for an Ethics Committee opinion on the clinical trial on medicinal products for human use', ENTR/CT 2) for EU Directive 2001/20/EC[1]. Written approval of the study must be obtained before the study centre can be initiated or the investigational medicinal product (IMP) can be released to the Investigator. Any necessary extensions or renewals of IEC / IRB approval must be obtained for changes to the study such as modification of the protocol, the informed consent form, the written information provided to subjects and/or other procedures.

The Investigator will report promptly to the IEC / IRB any new information that may adversely affect the safety of the subjects or the conduct of the study. The Investigator will submit written summaries of the study status to the IEC / IRB annually, or more frequently if requested by the IEC / IRB, in accordance with local regulatory requirements. On completion of the study, the sponsor will notify the IEC / IRB that the study has ended.

3. INFORMED CONSENT

No study-related procedures will be performed prior to the subject's and subject's parent/legal guardian's (if applicable) signed consent to participate in the study being obtained. Before the decision to participate, the Investigator or a duly authorised deputy will provide both an oral and a written full explanation of the study and the subject's rights. The written consent must be given by the subject and the parent/legal guardian (if applicable) of the subject, after detailed information about the study has been given as outlined above in EU Directive 2001/20/EC[1] and in accordance with any national provisions on the protection of clinical study subjects. The verbal explanation will cover all the elements specified in the written information provided for the subject.

For subjects not qualified to give legal consent, written consent must be obtained from the subject's parent/legal guardian. If appropriate, children old enough to understand the risks and benefits of the study (generally for children above 6 years of age) should also be informed and provide their written assent. In addition, the subject/subject's parent or legal guardian will sign consent and child's assent form authorizing release of the subject's HIV test results to appropriate authorities. All consent and assent forms must be approved in advance by the IRB/IEC.

If the legal guardian is unable to read, an impartial witness should be present during the entire informed consent discussion. After the informed consent form and any other written information is provided, read, and explained to the subject or their legal guardian, and after oral consent has been obtained, if

capable of doing so, the subject's legal guardian should sign and date the informed consent form, and where appropriate written assent should be obtained from the subject. The witness should also sign and date the consent form. In addition, the subject's legal guardian should, if possible, sign an additional form confirming that the materials provided have been read and explained to them. The witness should also sign and date this additional form.

The Investigator or designated personnel will inform the subject of the objectives, methods, anticipated benefits and potential risks and inconveniences of the study. The subject and parent/legal guardian (if applicable) must be given every opportunity to clarify any points they do not understand and, if necessary, to ask for more information. At the end of the interview, the subject and parent/legal guardian (if applicable) will be given time to consider the study if this is required, or if they request more time. Subjects and parents/legal guardians (if applicable) will be required to sign and date the informed consent form. After signatures are obtained, the informed consent forms will be kept and archived by the Investigator in the Investigator's study file for possible inspection by regulatory authorities, the IEC or IRB, BPL or BPL's representative's personnel, auditors. The subject will keep an identical signed copy. A letter will be sent to the subject's primary care physician informing him/her that the subject is to participate in the study, as appropriate.

It should be emphasised to the subject that he/she is at liberty to withdraw from the study at any time, without penalty or loss of benefits to which the subject is otherwise entitled. Subjects who withdraw consent should not continue in the study, but will be asked to attend an end-of-study visit, if possible.

The IEC / IRB will review and approve the subject information sheet and informed consent form. If the Investigator intends to use his/her own information leaflet (for non-interventional studies only) he/she must ensure that it contains all the information outlined in Section 4.8 of the ICH-GCP guidelines.

4. CONFIDENTIALITY

The investigator will ensure that the subject's anonymity is preserved.
In order to protect the subject's identity, identification codes will be used in lieu of subject's name. Personal information will be treated as confidential but may need to be reviewed by BPL or BPL's representatives such as the CRA or auditor, or by representatives of IEC / IRBs or regulatory authorities. The subject's consent to direct access to their personal notes must be obtained prior to participation in the trial. Each subject's Primary Care Physician will be informed of the nature and timing of the study, as appropriate.

All unpublished documents including the protocol, the case record form (CRF/eCRF) and the Investigator's Brochure are confidential. Those documents cannot be disclosed to a third party without the written consent of BPL. However, submission of those documents to the IEC / IRB is expressly permitted.

5. COMPENSATION/INDEMNITY

Compensation will not be provided for injury or medical conditions that are unrelated to this study. BPL will indemnify the Institute and the Investigator with respect to [redacted] brought against it resulting from the administration to subjects, of source materials supplied by BPL, provided that the protocol and Investigator Agreement have been adhered to, and the event has not been occasioned by malpractice or negligence. BPL will take out private insurance in respect of its potential liability.

6. PROTOCOL ADHERENCE

Adherence to the protocol is a fundamental part of the conduct of the study. Deviations from the protocol, including deviations from the inclusion / exclusion criteria, might erode the scientific and ethical value of the protocol and its authorization and might have an impact on the processes put in place for the care and safety of the study subjects.

Where a deviation has been made to eliminate an immediate hazard, the Investigator must submit a report of the implemented deviation and the reasons for it to the IEC / IRB and must notify relevant members of the **Medical Department of BPL or the designated Contract Research Organisation**. All deviations must be adequately documented.

7. PROTOCOL AMENDMENTS

A decision will first be made by BPL as to whether a protocol amendment is 'Substantial' or 'Non-substantial'. Amendments to the protocol are regarded as 'Substantial' where they are likely to have significant impact on:

- the safety or physical or mental integrity of the subjects;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any investigational medicinal product (IMP) used in the trial.

Competent Authority (CA) and IEC / IRB written approval (if applicable) will be obtained prior to any protocol amendment being adopted.

When a sponsor and/or Investigator must take urgent safety measures to protect the trial subjects from immediate hazard BPL or the designated CRO must be notified within 24 hours and the IEC / IRB and CA must be notified within 3 calendar days after appropriate safety measures have been taken. For any period during which a disease is pandemic and is a serious risk to human health or potentially a serious risk to human health, the IEC/IRB and CA should be informed as soon as possible. Where the amendment affects the risk/benefit ratio of continued participation for subjects already enrolled in the study, informed consent should be obtained again from such subjects using the new information leaflet/consent form. The updated version of the information leaflet/consent form should be used for all new subjects recruited on to the trial.

8. SERIOUS BREACHES

A Serious Breach is a breach which effects to a significant degree either the safety or physical or mental integrity of the subjects in the clinical trial or the scientific value of the clinical trial. The Investigator or participating laboratory must notify BPL or the designated Contract Research Organisation promptly (within 24 hours) of becoming aware of any Serious Breaches of the conditions and principles of GCP or the clinical trial protocol and any protocol amendment(s). BPL (or designated Contract Research Organisation) will be responsible for informing the CA and IEC / IRB of any Serious Breach in line with applicable national laws and regulations.

9. TRIAL TERMINATION

BPL reserve the right to stop the trial if:

- Recruitment is too slow to allow accrual of an adequate number of subjects within a reasonable length of time.
- Evidence is gained that the subjects are being exposed to an unacceptable risk.
- For any reason, it is not possible to continue to supply trial material.
- An advancement in knowledge makes the trial redundant.

If the study is terminated, BPL, the CRO and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

10. MONITORING VISITS

The BPL Clinical Research Associate (CRA) or representative CRA will monitor the study by telephone, correspondence, and regular visits to the investigational sites. In accordance with ICH-GCP guidelines, the study monitor will carry out source document verification at regular intervals to ensure that the data collected in the CRF/eCRF are accurate, to carry out drug accountability and to ensure all documentation and study procedures comply with the protocol and with ICH-GCP. The frequency of monitoring visits will be determined by the rate of subject recruitment.

The CRA will ensure that:

- the facilities remain adequate
- the Investigator adheres to the protocol and ethical responsibilities
- source documents are legible and agree with entries in the CRF/eCRF
- adverse events are adequately documented and reported
- investigational medicinal product is properly stored and accountability is being maintained
- laboratory samples are identified, handled and stored appropriately.

The Investigator must permit the CRA, the IEC / IRB, BPL appointed auditors and representatives from regulatory authorities direct access to all study-related documents and pertinent hospital or medical records for confirmation of data contained within the CRF/eCRFs. The Investigator will agree to make himself/herself available to correct or discuss any discrepancies. Subject confidentiality will be protected at all times.

A “Site Delegation of Duties and Signature Log” will be completed and signed by the responsible investigator. In accordance with this authority log, study site staff (e.g. co-investigators and nurses) will be authorised to enter data into the CRF/eCRF. The monitor will visit the study centres as required.

11. AUDIT/INSPECTION

Access to documentation and facilities used during the study may be required by BPL appointed auditors or by regulatory authorities.

In the event that the regulatory authorities schedule an audit the Investigator must notify BPL immediately. BPL will in turn notify the Investigator if they are informed of an audit at an Investigator’s site.

The main purposes of an audit or inspection are to confirm that the rights and welfare of the subjects have been adequately protected, and that all data relevant for the assessment of safety and effectiveness of the investigational product have been reported to the sponsor.

The verification of the CRF/e-CRF data may be performed by direct inspection of source documents, after the investigator has protected all confidential personal subject information not related to the study, in accord with local regulations.

12. REQUIRED PRE-STUDY DOCUMENTATION

Before the start of the study, BPL will require, as a minimum, the following documentation:

1. A signed copy of the protocol and signed amendments approved by the IEC/IRB.
2. A signed Clinical Trial Agreement, including any host R&D approval.
3. Other signed financial agreements (e.g. laboratory, pharmacy).
4. Signed Confidentiality Agreements for study team.
5. A signed Secrecy Agreement (if applicable).
6. A completed Investigator Financial Disclosure / Certification Statement and a Statement of Investigator (Form FDA 1572), if applicable.
7. An Indemnity Form signed and dated by both parties unless indemnity is covered by other signed agreements for the study.
8. Insurance policy or statement that this is not required.
9. IEC / IRB written approval.
10. Assurance that the IEC / IRB is organised and operates according to GCP and the applicable laws and regulations.
11. ARSAC approval (if applicable).
12. CA Approval.
13. Signed CVs of Investigators and sub-Investigators showing current position and Licence/ registration number, as appropriate.
14. Normal Ranges for:
    Laboratory parameters.
    Medical or technical procedures.
    Tests included in the protocol.
15. Evidence of validation of procedures/tests to be performed e.g.:
    Accreditation
    Certification
    SOPs for specialised tests
16. IEC / IRB approved subject information sheet and consent forms, identified with version number and date, plus any other written information given to subjects.
17. Investigator's Brochure, the edition clearly identified plus any updates.
18. Master randomisation list (if appropriate).
19. Decoding procedures for blinded trials.

20. Sample case record form.

If any of these documents are issued in a language other than English then verified translations are required.

11. COMPLETION AND RETURN OF CASE RECORD FORMS AND DATA QUERY FORMS

11.1 Recording Data in Case Record Forms (CRF/eCRFs)

All study data will be recorded on CRFs/e-CRFs provided by BPL or the designated Contract Research Organisation. These must be completed by the Investigator or a duly authorised assistant.

11.2 Electronic CRF

In the case of an e-CRF, errors occurring in the e-CRFs will be corrected directly in the data field of the e-CRF. An audit trail capturing the original entry, the new entry, the user ID of the entry personnel, and the date and time of each action will be maintained in the data capture system. Likewise, the interchange of queries between the CRO and the site, as well as query replies, will be maintained within the audit trail of the data capture system. Any changes to the data in the data capture system that occur after the investigator or authorised co-investigator have electronically signed the e-CRF will require that the investigator or authorised co-investigator review and re-sign the e-CRF.

11.3 Signing off CRF/eCRFs and DQFs and return to BPL or the designated Contract Research Organisation

In the case of e-CRFs for each subject enrolled, e-CRFs will be completed and signed electronically by the investigator or an authorised co-investigator.

All paper source documents will be filled out using an indelible pen, and must be legible.

11.4. Handling of clinical trial data

All clinical trial data will be recorded, handled and stored in such a way that it can be accurately reported, interpreted and verified, whilst maintaining the confidentiality of the subjects' records.

11.5 Source Documents

Source data are defined as all information related to clinical findings, observations, or other activities in the study, written in original records or consisting of certified copies of original records. The investigator will permit trial-related monitoring, audit(s), IRB review(s) and regulatory inspection(s).

Source documents or data to be entered directly into the Case Record Form will be defined prior to study start in an appropriate plan e.g. definition of source data document.

12. MAINTENANCE AND ARCHIVING OF STUDY RECORDS

12.1 Investigator Site File

The Investigator will be supplied with an Investigator Site File by BPL or the designated Contract Research Organisation at the start of the study, containing copies of required pre-study essential documents. It is the responsibility of the Investigator and study team members at site to maintain these essential documents and ensure their secure storage. The Investigator Site File will comprise the following documentation, although certain sections may be kept in a separate file with certain study team members e.g. laboratory or pharmacy staff:

Agreements

- Signed Confidentiality Agreements for study team.
- Signed Clinical Trial Agreement, including any host R&D approval (and submission documentation where applicable) detailing versions of the documents approved.
- Other signed financial agreements specific to the site (e.g. laboratory, pharmacy).
- Indemnity Form (if used) signed and dated by both parties, unless indemnity is covered by other signed agreements for the study.
- Insurance statement if applicable.
- A completed Investigator Financial Disclosure / Certification Statement and a Statement of Investigator (Form FDA 1572), if applicable.

Protocol

A signed copy of the protocol and signed amendments approved by the IEC/IRB.

Product Information

- Investigator's Brochure, the edition clearly identified plus any updates.
- Supporting publications and information.
- Safety updates from BPL, including any aggregated line listings of SUSARs and summary safety reports, in accordance with local regulatory requirements.

CRF/eCRF and Supporting Information

- Sample case record form.
- Other blank forms used in the study e.g. diary cards.
- Data transmittal forms.

CVs

- Signed CVs of Investigators and sub-Investigators showing current position and GMC registration number, as appropriate.

- Site Delegation of Duties Log.
- Reference to training records of study site personnel / Site training log.

Ethics Committee

- IEC / IRB written approval.
- CA Approval.
- ARSAC approval (if applicable).
- Relevant correspondence with IEC/IRB.
- Copies of progress reports to IEC/IRB.
- Copies of annual safety reports to IEC/IRB, in accordance with local regulatory requirements.
- Copies of IEC/IRB approved consent forms.
- Copies of IEC/IRB approved information leaflets.
- Final letter and report to IEC/IRB documenting study completion.

Laboratory Details

- Central laboratory manual, if applicable.
- Local laboratory normal ranges both current and previous if changed during study, if applicable.
- Local laboratory certification / accreditation both current and any updates.
- Local laboratory validation or SOPs for specialized tests both current and any updates.
- Sample storage log.
- Local sample handling procedures, unless included in a central laboratory manual
- Laboratory parameters
- Medical or technical procedures
- Tests included in the protocol.

Subject Details

- Master randomisation list (if appropriate).
- Subject screening log (if appropriate).
- Subject enrollment log (if appropriate).
- Signed informed consent forms; informed consent checklist, if used.
- Template of letter to primary physician.
- If applicable, completed subject identification code list for randomized studies (at study completion).

Adverse Events

- Reports of Serious Adverse Events and SUSARs.
- Correspondence relating to SAEs and SUSARs.
- Notification of SUSARs to IEC/IRB.

General Correspondence

Investigational Medicinal Product

- IMP receipt forms.
- Procedure for temperature monitoring.
- Certificates of Analysis, if requested.
- IMP accountability records.
- Instructions for handling IMP.
- Example prescription form (if applicable).
- Documentation of destruction of IMP.
- Randomisation code location (if not kept in Investigator Site File).

Monitoring

- Pre-study and Initiation Site Visit Report forms.
- Case Record Form correction notes.
- Data query forms.

Reports

- Any interim clinical study report.
- The final Clinical Study Report. A synopsis will suffice.

Completed CRF/eCRFs

- Copies of completed CRF/eCRFs or reference if stored separately.
- Copy of any CRF/eCRF and data query tracking and acknowledgement forms.

Meetings

Minutes of meetings, agenda and correspondence relating to meetings.

Publications

- Any publications of trial results available before site closure.
- If any of these documents are issued in a language other than English then verified translations are required.

12.2 Subject notes

The Investigator must maintain adequate records of subject participation for the duration of the study. These records must be available for inspection upon reasonable request by the sponsor, members of the regulatory authorities or other authorised individuals. The Investigator must detail in the subject notes that the subject is eligible for the study prior to enrollment. The Investigator must also ensure that worksheets provided for the study that form part of the source data must always be included in the subject notes.

12.3 Availability of data for inspection

The Investigator is obliged to provide BPL, or BPL's representative, with complete test results and all data and reports within the timeframe agreed by both parties.

After completion of the study, all documents and data relating to the study will be kept in an orderly manner by the Investigator in a secure study file. This file will be available for inspection by the sponsor or its representatives.

12.4 Archiving study documentation

The Investigator must make proper provision for archiving study documentation. Essential documents must be retained in accordance with ICH-GCP. Essential documents must be retained for two years after the last marketing approval in an ICH region or until at least two years have elapsed since the discontinuation of clinical development of the IMP. It is BPL's responsibility to inform the Investigator or Institute as to when these documents no longer need to be retained. It is the Investigator's responsibility to notify BPL, or BPL's representative, in writing if they are unable to make suitable provisions for archiving study documents at the study centre. Prior to archive, subject ID codes should be kept in a suitable place to enable easy access at the Investigator site. Subject ID codes must be retained for a period of at least 15 years after issue of the final study report. Subject consent forms and other study related documentation must be retained for a maximum period permitted by the hospital, institution or private practice

Essential documents from trials which are not to be used in regulatory submissions should be retained for at least five years after completion of the trial. These documents should be retained for a longer period if required by the applicable regulatory requirements or by agreement with BPL.

No study document should be destroyed without prior written agreement between the investigator and the sponsor. Should the investigator elect to assign the study documents to another party, or move them to another location, the sponsor must be notified.

13. REPORT AND PUBLICATION

BPL's standard report and publication policy is detailed below. In the case of the agreement between BPL and the Investigator differing from this policy, what is stated in the agreement will override what is stated below.

In accordance with relevant guidelines, a final clinical study report will be prepared after the completion of the study.

BPL recognises that the Investigator might wish to publish the results of the study. The Investigator and members of the Investigator's team engaged in the study shall not be permitted to present at symposia and professional meetings or to publish journals, theses or dissertations, or otherwise of their choosing, methods and results of the Study (all of which hereinafter referred to as "the Publication") without the consent of BPL.

In the case that the Investigator or members of the Investigator's team engaged in the study wish to pursue the Publication, the Investigator shall furnish BPL with copies of the Publication at least two months in advance of the intended date of whichever is the earliest submission of the Publication or presentation of the Publication or publication of the Publication or the making of a commitment to do any of the foregoing. The Investigator agrees, if BPL requests a meeting between the Investigator and BPL, to discuss in good faith the comments.

BPL shall have two months, after receipt of said copies, to object to such proposed Publication on reasonable grounds. For the avoidance of doubt the grounds that the subject matter is patentable or commercially sensitive shall constitute reasonable grounds.

Authorship should reflect work done by the investigators and BPL personnel, in accordance with generally recognised principles of scientific collaboration.

14. REFERENCES

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorization of the manufacturing or importation of such products.

FDA guidelines CFR 21 (www.fda.gov) which dictates the regulations and principles for conducting clinical trials in the USA.

APPENDIX C. - INVESTIGATOR'S RESPONSIBILITIES BASED ON THE GUIDELINES FOR GOOD CLINICAL PRACTICE

1. LOCAL INVESTIGATOR

1.1 Investigator's Qualifications and Agreements

1.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the study, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the Regulatory Authority(ies).

1.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

1.1.3 The investigator should be aware of, and should comply with, ICH GCP and the applicable regulatory requirements.

1.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate Regulatory Authority(ies).

1.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.

1.2 Adequate Resources

1.2.1 The investigator should be able to demonstrate (e.g. based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

1.2.2 The investigator should have sufficient time to properly conduct and complete the study within the agreed study period.

1.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.

1.2.4 The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, the investigational product(s), and their study-related duties and functions.

1.3 Medical Care of Study Subjects

1.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the study, should be responsible for all study-related medical (or dental) decisions.

1.3.2 During and following a subject's participation in a study, the investigator/institution should ensure that adequate medical care is provided to a subject for any AE's, including clinically

significant laboratory values, related to the study. The investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

1.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the study if the subject has a primary physician and if the subject agrees to the primary physician being informed.

1.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

1.4 Communication with IRB/IEC

1.4.1 Before initiating a study, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the study protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements), and any other written information to be provided to subjects.

1.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the study, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

1.4.3 During the study the investigator/institution should provide to the IRB/IEC all documents subject to review.

1.5 Compliance with Protocol

1.5.1 The investigator/institution should conduct the study in compliance with the protocol agreed to by the sponsor and, if required, by the Regulatory Authority(ies) and which was given approval/favorable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

1.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g. change in monitor(s), change of telephone number(s)).

1.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

1.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior IRB/IEC approval/favorable opinion. As

soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted;

a) to the IRB/IEC for review and approval/favorable opinion,

b) to the sponsor for agreement and, if required

c) to the Regulatory Authority(ies).

1.6 Investigational Product(s)

1.6.1 Responsibility for investigational product(s) accountability at the study site(s) rests with the investigator/institution.

1.6.2 Where allowed/required, the investigator/institution may/should assign some or all the investigator's/institution's duties for investigational product(s) accountability at the study site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

1.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the study site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and study subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

1.6.4 The investigational product(s) should be stored as specified by the sponsor and in accordance with applicable regulatory requirement(s).

1.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

1.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the study, that each subject is following the instructions properly.

1.7 Randomization Procedures and Unblinding

The investigator should follow the study's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the study is blinded, the investigator should promptly document and explain to the sponsor any premature Unblinding (e.g. accidental Unblinding, Unblinding due to a SAE) of the investigational product(s).

1.8 Informed Consent of Study Subjects

1.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to ICH GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to subjects.

1.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favorable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information should be documented.

1.8.3 Neither the investigator, nor the study staff, should coerce or unduly influence a subject to participate or to continue to participate in a study.

1.8.4 None of the oral and written information concerning the study, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

1.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the study including the written information given approval/favorable opinion by the IRB/IEC.

1.8.6 The language used in the oral and written information about the study, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

1.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the study and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

1.8.8 Prior to a subject's participation in the study, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

1.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject's legally acceptable representative has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

1.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

a) That the study involves research.

b) The purpose of the study.

c) The study treatment(s) and the probability for random assignment to each treatment.

d) The study procedures to be followed, including all invasive procedures.

e) The subject's responsibilities.

f) Those aspects of the study that are experimental.

g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.

j) The compensation and/or treatment available to the subject in the event of study-related injury.

k) The anticipated prorated payment, if any, to the subject for participating in the study.

l) The anticipated expenses, if any, to the subject for participating in the study.

m) That the subject's participation in the study is voluntary and that the subject may refuse to participate or withdraw from the study, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.

n) That the CRA(s), the auditor(s), the IRB/IEC, and the Regulatory Authority(ies) will be granted direct access to the subject's original medical records for verification of clinical study procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access

o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the study are published, the subject's identity will remain confidential.

p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the study.

q) The person(s) to contact for further information regarding the study and the rights of study subjects, and whom to contact in the event of study-related injury.

r) The foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.

s) The expected duration of the subject's participation in the study.

t) The approximate number of subjects involved in the study.

1.8.11 Prior to participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the study, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

1.8.12 When a clinical study (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the study with the consent of the subject's legally acceptable representative (e.g. minors, or patients with severe dementia), the subject should be informed about the study to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

1.8.13 Except as described in 1.8.14, a non-therapeutic study (i.e. a study in which there is not anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

1.8.14 Non-therapeutic studies may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:

a) The objectives of the study cannot be met by means of a study in subjects who can give informed consent personally.

b) The foreseeable risks to the subjects are low.

d) The negative impact on the subject's well-being is minimized and low.

e) The study is not prohibited by law.

f) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/favorable opinion covers this aspect.

Such studies, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these studies should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

1.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrollment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the study as soon as possible and consent to continue and other consent as appropriate (see 1.8.10) should be requested.

1.9 Records and Reports

1.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

1.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

1.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit study should be maintained): this applies to both written and electronic changes or corrections (see 1.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are

endorsed by the investigator. The investigator should retain records of the changes and corrections.

1.9.4 The investigator/institution should maintain the study documents as specified in Essential Documents for the Conduct of a Clinical Study and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

1.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

1.9.6 The financial aspects of the study should be documented in an agreement between the sponsor and the investigator/institution.

1.9.7 Upon request of the monitor, auditor, IRB/IEC, or Regulatory Authority, the investigator/institution should make available for direct access all requested study-related records.

1.10 Progress Reports

1.10.1 The investigator should submit written summaries of the study status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

1.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC and, where applicable, the institution on any changes significantly affecting the conduct of the study, and/or increasing the risk to subjects.

1.11 Safety Reporting

1.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the study subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the Regulatory Authority(ies) and the IRB/IEC.

1.11.2 AE's and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

1.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. autopsy reports and terminal medical reports).

1.12 Premature Termination or Suspension of a Study

If the study is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the study subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the Regulatory Authority(ies). In addition:

1.12.1 If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

1.12.2 If the sponsor terminates or suspends a study, the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

1.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a study, the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

1.13 Final Report(s) by Investigator

Upon completion of the study, the investigator, where applicable, should inform the institution: the investigator/institution should provide the IRB/IEC with a summary of the study's outcome, and the Regulatory Authority(ies) with any reports required.

APPENDIX D. – COMPARATOR HRIG PRESCRIBING INFORMATION (2012 VERSION)

Adobe Acrobat Document

APPENDIX E. – ACTIVE RABIES VACCINE PRESCRIBING INFORMATION (2015 VERSION)

Adobe Acrobat Document

APPENDIX F. – HRIG DOSING FOR CLINICAL TRIAL

The concentration of specific IgG to Rabies virus is nominally 150 IU/mL solution for injection in nominal 500 IU vials.

The recommended dose of rabies immunoglobulin is 20IU/kg of body weight

Dosing for the trial will be calculated using the actual potency versus the nominal potency.

The potency of each lot of BPL HRIG and comparator HRIG will be provided.

To calculate the Day 0 dose; used the subject's body weight to calculate the total IUs per body weight. Then use the potency per vial to calculate the volume to be administered.

Example:

*The subject weighs 75 kg, the recommended dose is 20 IU/mL, so based on subject weight the total IUs to be administered is 1500 IU. Actual potency on the vial is 230 IU/mL, [1500 IU ÷ 230 IU/mL] =6.5 mL of product to be administered. Volume per vial is 3.4 mL, [6.5 ÷ 2.17] = 2 vials are required. ***

****REFER TO THE PHARMACY MANUAL FOR DETAILED DOSING INSTRUCTIONS**

APPENDIX G. –TRIAL PLAN FLOW CHART

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									

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							
Administration of BPL HRIG / Competitor HRIG			X								
Administration of Active Rabies Vaccine			X		X		X	X	X		
Rabies Virus Neutralizing Antibody Titer		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 including CBC 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, including CBC 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
[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