Clinical Trial Protocol

Safety and Pharmacokinetic Evaluation of Zika Virus Immune Globulin in Healthy Volunteers

ZK-001

Version 3.1

June 5, 2018

Emergent BioSolutions Canada Inc.

[redacted]

CONFIDENTIAL

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Trial Sponsor: Emergent BioSolutions Canada Inc.

[redacted]

Contract Research Organization (CRO): INC Research

[redacted]

CRO Reference Laboratory: Dynacare

[redacted]

Clinical Trial Scientist:

[redacted]

Sponsor's Study Medical Monitor: [redacted]

Signatory Page

Protocol ZK-001, Version 3.1: Safety and Pharmacokinetic Evaluation of Zika Virus Immune Globulin in Healthy Volunteers

Clinical Site: INC Research, Early Phase Unit

[redacted]

My signature below verifies that I have read and agree to this protocol. I am aware of my responsibilities as an Investigator under the GCP guidelines of ICH, the Declaration of Helsinki, local regulations (as applicable) and the study protocol, and I agree to conduct the study according to these regulations, documents and guidelines.

Site Principal Investigator:

Principal Investigator Name (print)	Title (print)
Principal Investigator Signature	Date (YYYY/MMM/DD)

Sponsor Signatory:

Emergent BioSolutions Canada Inc.

[redacted]

[redacted]

Sr. Director, Clinical Development and Operations

2018/[redacted]

Date (YYYY/MMM/DD)

ZK-001 Protocol Synopsis

Title	Safety and Pharmacokinetic Evaluation of Zika Virus Immune Globulin in Healthy Volunteers
Sponsor	Emergent BioSolutions Canada Inc. [redacted]
Trial Start	Q2-Q3 2018
Objectives	Primary Objective: • To assess safety of ZIKV-IG in healthy volunteers. Secondary Objective: • To determine pharmacokinetics (PK) of ZIKV-IG in healthy volunteers.
Subject Population	Healthy male and non-pregnant female volunteers
Sample Size	30 subjects
Number of Trial Sites	The clinical trial will be conducted at a single trial site.
Test Product	Zika Virus Immune Globulin (Human) (ZIKV-IG) (code name: NP-024), a purified human immunoglobulin preparation containing neutralizing antibodies to Zika virus. ZIKV-IG is supplied as a sterile liquid suitable for intravenous administration to individuals with blood type O^+ or O^-.
Reference Product	Placebo (saline solution), supplied as a sterile liquid suitable for intravenous administration.
Protocol Design	Phase 1, single-center, randomized, double blind, placebo-controlled trial design.
Dosage	One dose level of ZIKV-IG will be evaluated, along with placebo. Thirty subjects will be randomized to intravenously receive either ZIKV-IG dose (50.0 mL undiluted; n=19) or placebo (50.0 mL; n=11). Dosing of the first six subjects (group 1) will be staggered over three days, wherein two subjects per day will be randomized 1:1

	and dosed at least 3 hours apart (subgroups 1A, 1B, 1C; each subgroup to be dosed at least one day apart). If in the opinion of the principal investigator there are no identified safety concerns after the first six dosed subjects, a group of six subjects (group 2) will be randomized 2:1 and dosed (at least 30 minutes apart) over the course of one day. A safety monitoring committee will be held to evaluate safety (collected up to 72 hours post-dosing) of the first 12 dosed subjects. If there are no safety signals identified, then the remaining 18 subjects will be randomized 2:1 and dosed (at least 30 minutes apart) in three separate groups of six subjects (groups 3, 4, 5) over a period of three days; each group of six subjects will be dosed over the course of one day. Each subject will be followed-up for 85 calendar days post-study treatment administration.
Inclusion Criteria	1. Informed consent voluntarily signed by subject. 2. Age: 18–55 years of age. 3. Blood type O^+ or O^-. 4. Body mass index (BMI) of 18–30. • Note: minimum body weight of 50 kg. 5. For female subjects (with male partners) that are not surgically sterilized (e.g., did not undergo hysterectomy, bilateral oophorectomy or tubal ligation), use of an effective method of contraception throughout the trial including: • Using hormonal contraception (oral, injectable or implant) continuously for 3 months prior to screening and willing to continue to use hormonal contraception throughout the entire trial. • Intrauterine device (IUD) inserted at least 1 month prior to screening. • Double barrier type of birth control measure (e.g., condoms, diaphragms, cervical sponge with spermicide). • True abstinence. • For female subjects who are post-menopausal, documented follicle-stimulating hormone (FSH) ≥40 mIU/mL must be obtained. If the FSH is <40 mIU/mL, the subject must agree to use an acceptable form of contraception (see above). • Females of childbearing potential without male sexual partners must be willing to maintain their sexual status as it is throughout the study.

	6. For male subjects that have not had a vasectomy, use of a condom with spermicide or true abstinence for the duration of the study. Note: female partners (that are of childbearing potential) of male study subjects (that have not had a vasectomy) should use one of the effective contraception methods (eg, hormonal contraception, IUD or barrier type). Also, male subjects must not donate sperm for the duration of the study. • Males without female sexual partners must be willing to maintain their sexual status as it is throughout the study. 7. Healthy as determined by principal investigator or a qualified designate based on medical history, physical exam, vital signs, urinalysis, blood chemistry and hematology test results at screening.
Exclusion Criteria	1. Use of any investigational product within the past 30 days. 2. Use of any investigational product during the study. 3. Individuals with blood type A, B or AB. 4. Recipient of any blood product within the past 12 months. 5. Plasma donation within 7 days or significant blood loss or blood donation within 56 days of baseline. 6. Blood donation at any time during the study. 7. Females with a hemoglobin level ≤120 g/L. 8. Males with a hemoglobin level <130 g/L. 9. History of hypersensitivity to blood or plasma products. 10. History of allergy to latex or rubber. 11. History of IgA deficiency. 12. History of hypercoagulable conditions (e.g., deep vein thrombosis or pulmonary embolism). 13. History of myocardial infarction. 14. History of stroke. 15. History of renal impairment/failure. 16. Currently pregnant or lactating or planning to become pregnant during the study. 17. History of flavivirus infection [ZIKV, dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV),

	yellow fever virus (YFV)] or vaccination with licensed or investigational flavivirus vaccine. 18. Plans to travel to an area with active flavivirus (e.g., ZIKV and/or DENV) transmission during the study (and up to 10 months after the study drug administration) or has returned from an endemic area with these diseases within 30 days of screening. 19. Positive nucleic acid test (NAT) or serology for ZIKV or positive serology for WNV or DENV. 20. Positive serology test (at screening) for human immunodeficiency virus 1 and 2 (HIV), hepatitis C virus (HCV); positive test for hepatitis B virus (HBV) as determined by HBsAg. 21. History of chronic or acute severe neurologic condition (e.g., diagnosis of Guillain-Barre syndrome, epilepsy, Bell's palsy, meningitis or disease with any focal neurologic deficits). 22. Heavy smokers (≥15cigarettes a day) or electronic cigarette use. 23. History of, or suspected substance abuse problem (including alcohol). 24. Failure of drug (urine) test at screening or baseline. 25. Failure of alcohol (breath) test at screening or baseline. 26. Receipt of a live vaccine within 28 days prior to screening or anticipated receipt of a live vaccine during the study period. 27. Individuals with planned surgical procedures that will occur during the study. 28. An opinion of the investigator that it would be unwise to allow participation of the subject in the study.
Assessments	**Screening (within 35 days prior to Baseline):** • Informed consent. • Review of study criteria. • Medical history, complete physical exam, vital signs (temperature, sitting blood pressure, respiratory rate, pulse oximetry and pulse rate), concomitant medications, body weight and height. • Blood type test.

	• Electrocardiogram (ECG) assessment. • Hematology, blood chemistry and urinalysis (see Appendix I). • Viral marker testing: serology for HIV, HBV, HCV; ZIKV NAT (serum, urine) and serology for ZIKV, and serology for WNV and DENV. *Note: ZIKV IgM serology will be performed by the site's reference laboratory, while ZIKV IgG serology will be performed by the sponsor-developed non-diagnostic assay.* • Serum pregnancy test for all female subjects of child bearing potential and FSH assessment for female subjects who are post-menopausal (defined as being amenorrheic for at least 1 year). • Drug (urine) test. • Alcohol (breath) test. **Baseline (Day -1; within 24 hours prior to Day 1):** • Review of study criteria. • Complete physical exam, vital signs, body weight. • Hematology, blood chemistry (see Appendix I). • Medical history and concomitant medications. • Viral marker testing: ZIKV NAT (serum, urine) and serology for ZIKV. *Note: ZIKV IgM serology will be performed by the site's reference laboratory, while ZIKV IgG serology will be performed by the sponsor-developed non-diagnostic assay.* • Serum pregnancy test for female subjects of child-bearing potential. • Alcohol (breath) and drug (urine) assessments. • Subjects will be required to stay overnight following their baseline assessment. **Day 1 – Study Treatment Administration:** **Pre-study Treatment Administration Assessments:** • 2 hours (±15 min) prior to study-treatment administration, vital signs will be assessed (to confirm screening eligibility for vital signs).

	• 1 hour (±15 min) prior to study-treatment administration, vital signs will be assessed (to establish baseline vital signs). • Within 2 hours prior to study-treatment administration, blood sample for baseline anti-ZIKV antibody assessment (pre-dose PK sample) will be collected. After the above assessments have been completed, ZIKV-IG or placebo will be administered intravenously. **Assessments during IV Administration of Study Treatment:** **15 minutes (±5 min) into the IV infusion and at the end of IV infusion (+5 min):** • Assessment of vital signs. • Adverse events. • Concomitant medications (if applicable). **Day 1: 1 Hour (±5 min), 3 Hours (±30 min), 8 Hours (±1 hr) and 24 Hours (±3 hrs) after End of Study Treatment Administration** • Blood sample collection for anti-ZIKV antibody assessment (PK sample). • Assessment of vital signs, adverse events and concomitant medications. Subjects will stay in the clinic until 24-hour time-point post-study treatment assessments are completed. **Day 2 (Discharge Day): 24 Hours (±3 hrs after End of Study Treatment Administration** • Blood sample collection for anti-ZIKV antibody assessment (PK sample). • Assessment of vital signs, adverse events and concomitant medications. • Blood chemistry and hematology; note: if ≥2 g/dL (i.e., ≥20 g/L) hemoglobin drop from baseline (Day -1) is observed, hemolysis tests will be performed (see Appendix I). **Day 3 (48±3 hrs), Day 4 (72±3 hrs), Day 6 (120±6 hrs), Day 8 (168±6 hrs), Day 10 (216±12 hrs), Day 12 (264±12 hrs), Day 15 (336±12 hrs), Day 22 (504±24 hrs), Day 29 (672±24 hrs), Day 43 (1008±48 hrs) and Day 57 (1344±48 hrs) after Study Treatment Administration*:**

	** Note: study visits are indicated as calendar days, while time-points in relation to end of study treatment administration are indicated in the brackets.* • Blood sample collection for anti-ZIKV antibody assessment (PK sample). • Assessment of vital signs, adverse events and concomitant medications. • Blood chemistry and hematology assessments; note: if ≥2 g/dL (i.e., ≥20 g/L) hemoglobin drop from baseline (Day -1) is observed [ONLY up to Day 15 visit (336±12 hrs post-study treatment administration), hemolysis tests will be performed (see Appendix I)]. **Day 85 (2016±72 hrs after end of study treatment administration) or Early Withdrawal:** • Blood sample collection for anti-ZIKV antibody assessment (PK sample). • Assessment of vital signs, adverse events and concomitant medications. • Assessment of blood chemistry and hematology (see Appendix I). • Serum pregnancy test for female subjects of child-bearing potential. • Viral marker testing: serology for HIV, HBV, HCV and ZIKV NAT (serum, urine) and serology for ZIKV. *Note: ZIKV IgM serology will be performed by the site's reference laboratory, while ZIKV IgG serology will be performed by the sponsor-developed non-diagnostic assay.* • Complete physical exam.
Primary Endpoint(s)	The primary endpoint is the number and severity of adverse events.
Secondary Endpoints	The secondary endpoints are ZIKV-IG pharmacokinetic parameters (see below).
Safety Parameters	Safety will be evaluated based on the following parameters: • Adverse events • Laboratory test results (hematology, blood chemistry, viral marker testing)

	• Physical exams • Vital signs
Pharmacokinetic Parameters	Based on serum concentrations of ZIKV antibodies, the following PK parameters will be calculated using non-compartmental analysis: • $AUC_{0\text{-}t}$: area under the concentration-time curve from time 0 to the last quantifiable concentration. • $AUC_{0\text{-day 7}}$. • $AUC_{0\text{-inf}}$: $AUC_{0\text{-}t}$ plus the additional area extrapolated to infinity. • C_{max}: maximum observed concentration. • T_{max}: time at which C_{max} occurs. • λz: terminal elimination rate constant. • $t_{1/2}$: apparent first order terminal elimination half-life. • CL: total body clearance following IV administration. • V_Z: volume of distribution following IV administration.

Schedule of Events for ZK-001

	Screening (within 35 days of Baseline)	Baseline (Day -1; within 24 hrs of Day 1)	Post Study Treatment Administration Visits*													
			Day 1 (Dosing Day)	Day 2 (Discharge Day)	Day 3	Day 4	Day 6	Day 8	Day 10	Day 12	Day 15	Day 22	Day 29	Day 43	Day 57	Day 85 or Early Withdrawal
Informed consent	X															
Eligibility	X	X														
Medical history	X	X[1]														
Complete physical exam	X[2]	X[2]														X
Study treatment administration			X													
Vital signs[3]	X	X	X[4a]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X															
Hematology	X	X		X[5]	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	X	X		X[5]	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X															
Drug (urine) test	X	X														
Alcohol (breath) test	X	X														
Pregnancy test	X[6]	X[6]														X[6]

	Screening (within 35 days of Baseline)	Baseline (Day -1; within 24 hrs of Day 1)	Post Study Treatment Administration Visits*												
			Day 1 (Dosing Day)	Day 2 (Discharge Day)	Day 3	Day 4	Day 6	Day 8	Day 10	Day 12	Day 15	Day 22	Day 29	Day 43	Day 57	Day 85 or Early Withdrawal
Viral markers	X[7]	X[8]														X[9]
PK sample collection			X[4b]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events			X[4b]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X[4b]	X[5]	X	X	X	X	X	X	X	X	X	X	X	X

[1] Update of medical history (if necessary).

[2] Including assessment of BMI; height and body weight will be measured at Screening and only body weight again at Baseline.

[3] Vital signs include temperature, sitting blood pressure, respiratory rate, pulse oximetry and pulse.

[4a] Vital signs to be performed 2 hours (±15 min) and 1 hour (±15 min) prior to dosing, during the IV infusion at 15 minutes (±5 min) and at the end of the IV infusion (+5 min)], and post-dosing at 1 hour (±5 min), 3 hours (±30 min) and 8 hours (±1 hr).

[4b] PK sample collection, adverse events and concomitant medications assessments at 1 hour (±5 min), 3 hours (±30 min) and 8 hours (±1 hr) post-dosing. Pre-dose (i.e., baseline) PK sample to be collected within 2 hours prior to dosing.

[5] To be performed 24 hours (±3 hours) post-dosing.

[6] At screening serum pregnancy test for female subjects of child-bearing potential and FSH assessment for post-menopausal female subjects. The serum pregnancy test is required only for women of childbearing potential for Baseline (Day -1) and Day 85 study visits.

[7] Serology testing for HIV, HBV, HCV, DENV, WNV; ZIKV NAT (serum, urine) and ZIKV serology.

[8] ZIKV NAT (serum, urine) and ZIKV serology testing.

[9] Serology testing for HIV, HBV, HCV; ZIKV NAT (serum, urine) and ZIKV serology.

* Day 1 includes 1 hour (±5 min), 3 hours (±30 min) and 8 hours (±1 hr) time-points **post-dosing**, Day 2 is 24 hours (±3 hrs), Day 3 is 48 hours (±3 hrs), Day 4 is 72 hours (±3 hrs), Day 6 is 120 hours (±6 hrs), Day 8 is 168 hours (±6 hrs), Day 10 is 216 hours (±12 hrs), Day 12 is 264 hours (±12 hrs), Day 15 is 336 hours (±12 hrs), Day 22 is 504 hours (±24 hrs), Day 29 is 672 hours (±24 hrs), Day 43 is 1008 hours (±48 hrs), Day 57 is 1344 hours (±48 hrs) and Day 85 is 2016 hours (±72 hrs) **post-dosing**.

NOTE: all study laboratory assessments (for a list of all laboratory tests see Appendix I) will be performed by the Phase 1 clinic's reference laboratory, except for ZIKV IgG serology (screening, baseline and Day 85 samples) which will be performed by the sponsor-developed non-diagnostic assay. In addition, the subjects' PK samples will be tested with two types of assays (a binding ZIKV antibody assay and a neutralizing ZIKV antibody assay).

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List of Abbreviations and Definition of Terms

ADE	Antibody-dependent enhancement
AE	Adverse event
AIGIV	Anthrax Immune Globulin Intravenous (Human)
ANTHRASIL®	Anthrax Immune Globulin Intravenous (Human)
$AUC_{0\text{-day }7}$	Area under the serum concentration curve from time 0 to day 7
$AUC_{0\text{-inf}}$	Area under the serum concentration curve from time 0 to infinity
$AUC_{0\text{-t}}$	Area under the serum concentration curve from time 0 to the last measurable concentration
BMI	Body mass index
CL/F	Apparent clearance
C_{max}	Maximum serum concentration
CNJ-16®	Vaccinia Immune Globulin Intravenous (Human)
CRO	Contract research organization
CS	Clinically significant
CSR	Clinical study report
CZS	Congenital Zika syndrome
DENV	Dengue virus
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GBS	Guillain–Barré syndrome
GCP	Good Clinical Practices
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus

HepaGam B®	Hepatitis B Immune Globulin (Human)
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICH	International conference on harmonization
IRB	Institutional review board
IUD	Intrauterine device
IV	Intravenous
JEV	Japanese encephalitis virus
kDa	kilodalton
MedDRA	Medical Dictionary for Regulatory Activities
NAT	Nucleic acid testing
NCS	Not clinically significant
NP-024	Anti-Zika Virus Immune Globulin (Human)
SAE	Serious adverse event
SMC	Safety monitoring committee
US(A)	Unites States (of America)
VARIZIG®	Varicella Zoster Immune Globulin Intravenous (Human)
VIGIV	Vaccinia Immune Globulin Intravenous (Human)
V_Z/F	Apparent volume of distribution
WinRho® SDF	Rho(D) Immune Globulin Intravenous (Human)
WNV	West Nile virus
YFV	Yellow fever virus
ZIKV	Zika virus
ZIKV-IG	Anti-Zika Virus Immune Globulin (Human)

1 BACKGROUND INFORMATION

1.1 Zika Virus

Zika virus (ZIKV) is an RNA flavivirus closely related to other flaviviruses such as dengue virus (DENV), yellow fever virus (YFV), Japanese encephalitis virus (JEV) and West Nile virus (WNV). ZIKV is primarily transmitted through the bite of an infected *Aedes* species mosquito (*Ae. aegypti* and *Ae. albopictus*); however, sexual transmission has been frequently reported (1, 2). Most individuals infected by ZIKV are asymptomatic, while symptomatic individuals typically present with acute onset of fever, maculopapular rash, arthralgia, headache or nonpurulent conjunctivitis that usually last from several days to one week (1). However, ZIKV infection has been linked to Guillain–Barré syndrome (GBS) (3, 4) and other neurological impairments (5), albeit infrequently. ZIKV infection during pregnancy has been linked to adverse fetal/infant outcomes including fetal/infant microcephaly (6, 7), serious brain anomalies (8), ocular disorders (9), intrauterine growth restriction, and other congenital malformations resulting in congenital Zika syndrome (CZS) (10, 11). The percentage of fetuses/infants with possible ZIKV-associated birth defects ranges from 4-8%, depending on maternal time of ZIKV exposure during pregnancy (12). The ability of ZIKV to infect and damage developing fetuses implies that the virus can cross and/or bypass the placental barrier, but the mechanism remains unclear (13). Other flaviviruses, including DENV, are not associated with vertical transmission or congenital disorders, which suggest that this mechanism may be specific to ZIKV (14). Currently, there are no licensed or available products for prevention or treatment of ZIKV infection. Therefore, there is an unmet medical need to develop interventions against ZIKV. To that end Emergent BioSolutions Inc. is developing an Anti-Zika Virus Immune Globulin (Human) product (see Section 1.2).

1.2 Trial Drug

Emergent BioSolutions Inc. (referred to as the sponsor throughout the protocol) is developing an Anti-Zika Virus Immune Globulin (Human) (ZIKV-IG) (code name: NP-024) product as an intervention for ZIKV. The ZIKV-IG product will be manufactured using the same hyperimmune manufacturing platform process as the one used to manufacture United States (US) Food and Drug Administration (FDA)-licensed products that include CNJ-016® [Vaccinia Immune Globulin Intravenous (Human), VIGIV], ANTHRASIL® [Anthrax Immune Globulin Intravenous (Human)], WinRho® SDF [Rho(D) Immune Globulin Intravenous (Human)], HepaGam B® [Hepatitis B Immune Globulin (Human)], and VARIZIG® [Varicella Zoster Immune Globulin Intravenous (Human)][1]. ZIKV-IG is

[1] CNJ-016® (VIGIV) and ANTHRASIL® (AIGIV) and all Emergent BioSolutions Inc. brand, product, service and feature names, logos and slogans are trademarks or registered trademarks of Emergent BioSolutions Inc. in the United States or other countries. All rights reserved. WinRho® SDF, HepaGam B® and VARIZIG® are trademarks of their respective owners. All brand, product, service and feature names or trademarks of these products are the property of their respective owners.

produced with plasma collected from the FDA-licensed plasma collection centers from healthy donors with elevated levels of antibodies reactive to ZIKV antigens.

ZIKV-IG is a purified human immune globulin preparation containing neutralizing antibodies to ZIKV. It is a glycoprotein of approximately 160 kilodaltons (kDa). The final ZIKV-IG product will be formulated in multiple single-use vials as a sterile liquid stabilized with 10% maltose and 0.03% polysorbate 80 (pH between 5.0 and 6.5) and free of any preservatives.

Due to the limited number of plasma donors used to generate the plasma pool for manufacture of the ZIKV-IG clinical lot, donor plasma with high isoagglutinin titers (e.g. anti-A antibodies) were not excluded from plasma pools used for the manufacture of ZIKV-IG. Therefore, ZIKV-IG is intended for intravenous (IV) administration only to individuals with blood type O^+ or O^-.

The safety profile for immune globulin products is well-established due to a long history of their use in the clinical practice for a range of medical conditions (for more details refer to ZIKV-IG Investigator's Brochure). Immune globulins are normal constituents of the human body fluid, and they are used at physiological levels without creating pharmacologic and toxicologic active metabolites (15). The planned ZIKV-IG dose for this clinical trial falls into the range of doses used for products manufactured with Emergent's hyperimmune platform; hence, ZIKV-IG is expected to have a similar safety and pharmacokinetic (PK) profile to these hyperimmune products.

1.3 Clinical Trial Rationale

ZK-001 clinical trial is designed to evaluate safety and PK of ZIKV-IG in healthy volunteer subjects. The trial will be conducted in compliance with this protocol, GCP and the applicable regulatory requirement(s).

ZIKV-IG is an immune globulin (human IgG) product enriched with ZIKV antibodies. The general safety profile for immune globulin products is well-established in the clinic due to extensive use of these products for various types of medical conditions and infections (16). Furthermore, the sponsor has a long history of developing immune globulin based therapies, including the licensed products outlined in Section 1.2. Like other human immune globulins, the sponsor's products manufactured on the hyperimmune platform have been studied in several healthy volunteer and patient clinical trials; the safety profile of these immune globulin products is consistent with other commercial immune globulin products and the PK profile is similar among the sponsor's licensed immune globulin products with a half-life of approximately 24 to 30 days after IV administration. The proposed dose for this clinical trial [50 mL undiluted, total of 4.65 g of protein; administered as an IV infusion) is within the dose levels tested in clinical trials of the sponsor's other licensed immune globulin products (outlined in Section 1.2) and is expected to display similar safety and PK profile to those products.

Based on non-clinical studies with ZIKV-IG, a single dose of ZIKV-IG [50 mL dose (total of 4.65 g of protein), to be administered as an IV infusion] was selected for evaluation in ZK-001; the clinical ZIKV-IG dose is in the range of efficacious doses evaluated in lethal mouse model of ZIKV infection [refer to Investigator's Brochure for ZIKV-IG (NP-024)]. In addition, the levels of excipients in the selected ZIKV-IG dose for ZK-001 are well below the animal maximum tolerated doses, hence these substances are not expected to pose any health risks to humans [refer to Investigator's Brochure for ZIKV-IG (NP-024)].

Results from ZK-001 clinical trial will provide safety information on the intravenously administered ZIKV-IG dose, as well as PK parameters such as peak ZIKV-IG plasma levels, trough titers of ZIKV antibodies and ZIKV-IG half-life; these PK parameters will be used for dose selection in subsequent clinical trials with ZIKV-IG.

2 TRIAL OBJECTIVES

2.1 Primary Objective

The primary objective of ZK-001 is to assess safety of ZIKV-IG in healthy volunteers.

2.2 Secondary Objective

The secondary objective of ZK-001 is to determine pharmacokinetics (PK) of ZIKV-IG in healthy volunteers.

3 TRIAL DESIGN

3.1 Trial Design

ZK-001 is designed as a Phase 1, single-center, double-blind, randomized, placebo-controlled clinical trial to evaluate safety and PK of ZIKV-IG in healthy volunteer subjects.

3.2 Anticipated Centers

ZK-001 clinical trial will be conducted at a single Phase 1 clinical site, located in [redacted].

3.3 Sample Size

Sample size for ZK-001 will be 30 healthy volunteers who will be randomized to receive either one dose level of ZIKV-IG (n=19) or placebo (n=11). While there was no formal sample size calculation as this is a Phase 1 clinical trial evaluating safety and PK of only one dose level of ZIKV-IG, up to 19 subjects treated with ZIKV-IG will allow for safety evaluation and calculation of PK parameters.

3.4 Randomization

Dosing of the first six subjects will be staggered over three days, wherein two subjects per day will be randomized 1:1 and dosed to receive either ZIKV-IG or placebo, while the remaining 24 subjects will be randomized 2:1 (four groups with six subjects in each group) in a double-blind fashion to receive either ZIKV-IG or placebo as described in Section 6.2.

Randomization schedule generation and logistics will be handled by a designated individual (an unblinded statistician) at the Phase 1 CRO who will not be involved in study treatment administration or subject assessments. A dummy randomization schedule will be created by the CRO for review and approval by the sponsor. Subsequently, the production of unblinded randomization schedule will be generated by the CRO's unblinded statistician for subject assignments. The randomization schedule will be stored in a locked room in a locked vault inaccessible to blinded personnel.

3.5 Blinding

The pharmacy staff assigned to ZK-001 clinical trial at the CRO's Phase 1 clinical site will be unblinded to access the randomization assignment and prepare the study treatment. There will be designated (subcontracted) unblinded clinical trial monitors, a segregated unblinded medical monitor and an independent unblinded Quality Assurance (QA) representative. In addition, designated personnel at the sponsor's bioanalytical laboratory who will be assigned to perform PK sample testing will indirectly become unblinded due to nature of test results, but measures will be implemented not to disseminate this information until database lock (see Section 6.8). Other personnel involved in the conduct of ZK-001 trial will remain blinded until database lock.

Access to information in electronic data capture (EDC) system will be blinded using role-based permissions. Randomization group and study treatment dispensing data will be integrated with the clinical database prior to database lock, but unblinding data will be removed from blinded data extracts by the CRO until after database lock to ensure maintenance of the blind. Study treatment dosing data will be reconciled with the randomized treatment group for each subject by the unblinded monitor, and any deviations will be reported in the Clinical Study Report (CSR). The ZK-001 trial will be unblinded once the clinical database is locked.

While this is a double-blind trial, the blind may be broken if a subject's health or safety is at risk and knowledge of the study treatment administered may be beneficial to the medical management of the subject. The pharmacist or other authorized individual may disclose the allocation of an individual subject's study treatment if unblinding is required. In such an event, the sponsor must be notified and appropriate documentation completed.

A Safety Monitoring Committee (SMC) will be implemented to assure subject safety (for details on SMC see Section 0). The SMC will at a minimum consist of two blinded medical reviewers (Phase 1 clinic's medical monitor and sponsor's medical monitor) and one segregated unblinded medical monitor.

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Inclusion Criteria

Subjects must meet the inclusion criteria to participate in ZK-001 trial. The inclusion criteria include the following:

1. Informed consent voluntarily signed by subject.
2. Age: 18–55 years of age.
3. Blood type O^+ or O^-.
4. Body mass index (BMI) of 18–30.
   - Note: minimum body weight of 50 kg.
5. For female subjects (with male partners) that are not surgically sterilized (e.g., did not undergo hysterectomy, bilateral oophorectomy or tubal ligation), use of an effective method of contraception throughout the trial including:
   - Using hormonal contraception (oral, injectable or implant) continuously for 3 months prior to screening and willing to continue to use hormonal contraception throughout the entire trial.
   - Intrauterine device (IUD) at least 1 month prior to screening.
   - Double barrier type of birth control measure (e.g., condoms, diaphragms, cervical sponge with spermicide).
   - True abstinence.
   - For female subjects who are post-menopausal, documented follicle-stimulating hormone (FSH) ≥40 mIU/mL must be obtained. If the FSH is <40 mIU/mL, the subject must agree to use an acceptable form of contraception (see above).
   - Females of childbearing potential without male sexual partners must be willing to maintain their sexual status as it is throughout the study.
6. For male subjects with female partners that have not had a vasectomy, use of a condom with spermicide or true abstinence for the duration of the study. Note: female partners (that are of childbearing potential) of male study subjects (that have not had a vasectomy) should use one of the effective contraception methods (e.g., hormonal contraception, IUD or barrier type). Also, male subjects must not donate sperm for the duration of the study.
   - Males without female sexual partners must be willing to maintain their sexual status as it is throughout the study.
7. Healthy as determined by the principal investigator or a qualified designate based on medical history, physical exam, vital signs, urinalysis, blood chemistry and hematology test results at screening.

Note: for a list of specific laboratory tests (e.g., blood chemistry, hematology), refer to Appendix I.

4.2 Subject Exclusion Criteria

Subjects who have any of the following exclusion criteria at screening and/or baseline will be excluded from participation in ZK-001 trial:

1. Use of any investigational product within the past 30 days.
2. Use of any investigational product during the study.
3. Individuals with blood type A, B or AB.
4. Recipient of any blood product within the past 12 months.
5. Plasma donation within 7 days or significant blood loss or blood donation within 56 days of baseline.
6. Blood donation at any time during the study.
7. Females with a hemoglobin level ≤120 g/L.
8. Males with a hemoglobin level <130 g/L.
9. History of hypersensitivity to blood or plasma products.
10. History of allergy to latex or rubber.
11. History of IgA deficiency.
12. History of hypercoagulable conditions (e.g., deep vein thrombosis or pulmonary embolism).
13. History of myocardial infarction.
14. History of stroke.
15. History of renal impairment/failure.
16. Currently pregnant or lactating or planning to become pregnant during the study.
17. History of flavivirus infection [ZIKV, dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), yellow fever virus (YFV)] or vaccination with licensed or investigational flavivirus vaccine.
18. Plans to travel to an area with active flavivirus (e.g., ZIKV and/or DENV) transmission during the study (and up to 10 months after study drug administration) or has returned from an endemic area with these diseases within 30 days of screening.
19. Positive nucleic acid test (NAT) or serology for ZIKV (at screening) or positive serology for WNV or DENV (at screening).

20. Positive serology test (at screening) for human immunodeficiency virus 1 and 2 (HIV), hepatitis C virus (HCV); positive test for hepatitis B virus (HBV) as determined by HBsAg.
21. History of chronic or acute severe neurologic condition (e.g., diagnosis of Guillain-Barre syndrome, epilepsy, Bell's palsy, meningitis or disease with any focal neurologic deficits).
22. Heavy smokers (≥15cigarettes a day) or electronic cigarette use.
23. History of, or suspected substance abuse problem (including alcohol).
24. Failure of drug (urine) test at screening or baseline.
25. Failure of alcohol (breath) test at screening or baseline.
26. Receipt of a live vaccine within 28 days prior to screening or anticipated receipt of a live vaccine during the study period.
27. Individuals with planned surgical procedures that will occur during the study.
28. An opinion of the investigator that it would be unwise to allow participation of the subject in the study.

Note 1: with respect to exclusion criterion no. 18, subjects will recommend to their partner(s) (if applicable) not to travel to flavivirus (e.g., ZIKV and/or DENV) endemic regions for the duration of the study and up to 10 months after the study drug administration.

Note 2: for a list of specific laboratory tests (e.g., blood chemistry, hematology), refer to Appendix I.

4.3 Subject Withdrawal

The subjects must be available, without coercion, for all parts of the trial.

If continued participation jeopardizes the subject's health at any point in the study, the subject should be withdrawn from the trial. The investigator is encouraged to consult the sponsor prior to the withdrawal of any subject, except in the event of a medical emergency. The reason for withdrawal of any subject must be clearly documented on the trial source documents and the appropriate Case Report Form (CRF).

4.3.1 Subject Withdrawal Criteria

All subjects are free to withdraw from participation in this trial at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

In addition, subjects may be withdrawn from the trial for any of, but not limited to, the following reasons:

- The subject develops an intercurrent illness that prevents completion of the trial.

- The subject develops severe or serious adverse events.
- It is the opinion of the Principal Investigator that it is unwise for the subject to continue in the study
- The subject is not compliant with the requirements of the trial to the satisfaction of the investigator and/or sponsor (e.g. non-cooperative, subject misses study visits/appointments, unreported use of concomitant medications).
- The subject is lost to follow-up.
- The subject does not meet the entry criteria for the trial but was erroneously entered in the trial.

Subjects withdrawn from the trial due to AEs will require follow-up until the AE(s) are resolved or stabilized (as per the investigator's discretion).

4.3.2 Subject Replacement

Subjects withdrawn from the trial or who withdraw consent prior to randomization will be replaced. Subjects withdrawn from the trial or who withdraw consent after randomization will not be replaced.

4.3.3 Follow-up for Withdrawn Subjects

Every attempt will be made to ensure that subjects who are withdrawn, or who withdraw from the trial during the active treatment or follow-up study period, will complete at a minimum all safety assessments for the early withdrawal visit as outlined in this protocol (see Section 6.5). The investigator should inform the subjects that these assessments are for their own safety.

5 TRIAL MEDICATION

5.1 Packaging and Formulation

ZIKV-IG (NP-024) is supplied in 3 cc (3 mL) glass vials with 2 mm siliconized bromobutyl rubber stoppers, aluminum seals and plastic flip-off caps. The extractable volume per vial is 2 mL. Each vial is intended for single use.

ZIKV-IG should be stored at 2–8ºC until required use (do not freeze ZIKV-IG).

ZIKV-IG is provided as a sterile liquid stabilized with 10% maltose and 0.03% polysorbate 80 (pH between 5.0 and 6.5) and free of any preservatives for IV administration. The final product is a clear to slightly opalescent and colorless liquid essentially free of particles.

ZIKV-IG contains 30–130 mg/mL human plasma proteins (clinical lot for this trial contains 93 mg/mL), of which at least 96% is human immune globulin G enriched with antibodies to ZIKV.

ZIKV-IG activity against ZIKV (product potency) is determined by a cell-based ZIKV microneutralization assay (potency release assay) that measures neutralization titer of ZIKV cytopathic effects.

For more information, refer to the Investigator's Brochure for ZIKV-IG.

5.2 Labeling

ZIKV-IG vial labels will include information to comply with local regulations for the country in which the trial is conducted (Canada), in the appropriate language(s).

Vial labels for Canada will include the following information in English and French:

- "Investigational Drug to Be Used by Qualified Investigator Only" or similar wording
- "For use in blood type O subjects only"
- The name, number or identifying mark of the drug
- The product's protein concentration
- The lot number
- The expiration date
- The protocol code or identification
- The recommended storage conditions
- The name and address of the sponsor

Labeling for the shelf cartons will also bear this information.

For dispensing labels for secondary receptacles, see Section 5.4 below.

5.3 Storage Conditions

ZIKV-IG must be stored refrigerated at 2–8ºC in a secured area until prepared by the pharmacist for use. The temperature in the storage area should be monitored with properly calibrated instruments and recorded on a temperature log. Temperature excursions must be reported to the sponsor or designate.

For further information, refer to the Investigator's Brochure for ZIKV-IG.

5.4 Preparation

The site will maintain documentation of a clear written formalized pharmacy study-specific procedure for study treatment preparation and blinding activities (including any sample labels and documentation to be completed), and documented training and delegation of the activity to appropriate trial staff.

Subject identifier (subject randomization number) must be recorded on the labels of the vial(s) used to prepare the study treatment. Empty vials must be maintained for drug accountability. The study pharmacy staff will be only persons on-site who are unblinded to the study treatment assignment for each subject.

To maintain the blind, all study treatments [ZIKV-IG or placebo (normal saline)] will be dispensed in a comparable manner. Both, the trial drug and placebo have the same administration volume and the site's pharmacy staff who will prepare the study treatments will ensure that they are indistinguishable to maintain the blinding (details on preparation and maintaining the blind will be outlined in the site's study-specific pharmacy procedure).

The study treatments will be prepared for IV administration in secondary receptacles (syringes); hence, the dispensing label affixed to the syringes will capture the subject identifier (subject randomization number), visit number, expiry date of the prepared dose, principal investigator's name, and protocol code (ZK-001).

The trial drug (ZIKV-IG) will be prepared for administration at the appropriate dosage (total volume of 50 mL undiluted, prepared into a syringe) for an IV infusion; visual check to be completed to ensure total volume of 50 mL. The placebo (normal saline) will be prepared in the same manner for an IV infusion.

The site pharmacy will be responsible for ensuring that the following supplies are available:

- Normal saline
- Syringes for study treatment dose preparation/administration

For further information on ZIKV-IG dose preparation, refer to the Investigator's Brochure for ZIKV-IG. In addition, details on study treatment preparation and handling will be outlined in the site's study-specific pharmacy procedure.

5.5 Administration

Administer ZIKV-IG within 3 hours of preparation into a syringe.

Administer ZIKV-IG only under the supervision of the investigator and/or qualified designate(s).

Once the ZIKV-IG dose is prepared into the syringe (50 mL total volume), connect it to an IV line and secure it on the infusion pump apparatus.

Set the starting infusion rate at 1 mL/min for the first 15 minutes. If there are no adverse events (AEs), increase the rate to 2 mL/min for the remainder of the IV infusion (ie, at the recommended infusion rates and if no interruptions/reduction of the infusion rates, the IV infusion of 50 mL ZIKV-IG should be completed within 33 minutes).

Note: the same administration procedure applies to IV infusion of the placebo.

Monitor subjects closely during the IV infusion and for at least 1 hour after the study treatment administration.

If AEs occur during the IV infusion, such as flushing, headache, nausea, changes in pulse rate or blood pressure, the rate of infusion may be slowed or temporarily stopped until symptoms subside, at discretion of the investigator. The infusion rate may be resumed at a rate that is comfortable to the subject at discretion of the investigator [ie, if deemed necessary, infusion rate of less than 1 mL/min (eg, 0.5 mL/min) is permissible].

Details on administration of study treatment (ZIKV-IG or placebo) will be outlined in the site's study-specific procedure.

The study subjects will be housed in the Phase 1 clinic for 24 hours after study treatment administration and will be regularly monitored throughout that period.

5.6 Medication Shipment

ZIKV-IG will be shipped to the site at a temperature of 2–8ºC. During shipment, the temperature of the drug will be monitored to ensure the required temperature conditions are maintained. The site pharmacist or designate will be responsible for checking the number of vials and the condition of the vials received and entering this information into the drug accountability records, reporting the condition to the sponsor. The site pharmacist or designate will be responsible for assessment of the shipping temperature including upload of temperature data from the electronic temperature monitoring device, as well as returning of the shipping container and all required documentation to the sponsor or designate.

Trial drug will be released for use by the site only after the data logger results are reviewed and written authorization has been issued to the Investigator/designate by the sponsor or designate. At the end of the trial, or upon request of the sponsor, all unused, partially used or empty vials will be returned to the sponsor or destroyed at the site as directed by the sponsor.

5.7 Drug Accountability

The principal investigator is responsible for maintaining accurate inventory records of ZIKV-IG. The investigator or designate will inventory all Investigational Product shipments upon receipt; acknowledge possession by signing all required documentation, and returning these to the sponsor. The investigator must ensure that all drug supplies are kept in a secure location in the site pharmacy in accordance with recommended storage conditions. For blinded trials, a research pharmacist will maintain a current inventory and ongoing record of test material supplies using the Drug Accountability Form(s) approved by the sponsor. This inventory record for ZIKV-IG will include:

- Protocol name, number and sponsor
- Product name and description
- Trial site and investigator name
- Product lot number and date of manufacture and/or Use-by/Expiry/Re-test date

- Number of vials dispensed, date and time of dispensing and study subject for whom product was dispensed
- Product balance
- Name and title of qualified individual dispensing product.

The inventory record will be stored in a locked pharmacy room at the site.

These records will be reviewed by representatives of the sponsor, and may be reviewed by regulatory agencies.

6 TRIAL PROCEDURES

6.1 Screening (within 35 days prior to Baseline)

Eligible subjects will first undergo informed consent counselling. Once informed consent has been obtained, subjects will undergo a screening visit to ascertain their eligibility in this trial. The screening visit assessments will include:

- Written informed consent
- Review of inclusion/exclusion criteria
- Medical history
- Complete physical exam, vital signs (temperature, pulse rate, pulse oximetry, respiration rate, sitting blood pressure), height and body weight (for BMI calculation)
- ECG assessment.
- Laboratory assessments:
  - Blood type test.
  - Blood chemistry, hematology and urinalysis (see Appendix I)
  - Serum pregnancy test for female subjects of child-bearing potential; FSH assessment for post-menopausal female subjects
  - Viral marker testing: serology for HIV, HBV, HCV; ZIKV NAT (serum, urine) and serology for ZIKV, serology for WNV and DENV

    Note: serology for ZIKV IgM testing will be performed by the site's reference laboratory, while ZIKV IgG testing will be performed by the sponsor-developed non-diagnostic assay.
  - Drug (urine) test.
  - Alcohol (breath) test.
- Review of concomitant medications

Note: for a list of specific laboratory tests (e.g., blood chemistry, hematology), refer to Appendix I.

6.2 Randomization

Following written informed consent, successful completion of the screening assessments and attendance at baseline study visit, 30 subjects will be randomized to receive an IV infusion of either ZIKV-IG or placebo (normal saline).

The subjects will be randomized and dosed in the following manner: the first six subjects (group 1) will be randomized 1:1 and dosed over three days (two subjects per day, dosed at least 3 hours apart; subgroups 1A, 1B and 1C; each subgroup to be dosed at least one day apart); the principal investigator will review the available safety information (adverse events, vital signs, concomitant medications) between each subject's dosing interval. If in the opinion of the principal investigator there are no identified safety concerns after the first six dosed subjects, a group of six subjects (group 2) will be randomized 2:1 and dosed (at least 30 minutes apart) over the course of one day. After review of safety data collected up to 72 hours post study treatment administration for the first 12 dosed subjects by the Safety Monitoring Committee (SMC) and confirmation of no safety signals by the SMC (see Section 8.7 for details), the remaining 18 subjects will be randomized 2:1 and dosed (at least 30 minutes apart) in three separate groups of six subjects (groups 3, 4 and 5) over a period of three days; each group of six subjects will be dosed over the course of one day.

Randomization should occur after screening and as close as possible to study treatment administration on Day 1.

6.3 Baseline Assessments (Day -1; within 24 hours prior to Day 1)

- Review of inclusion/exclusion criteria
- Medical history [including updates (if applicable)] and concomitant medications.
- Complete physical exam, vital signs (temperature, pulse, pulse oximetry, respiration rate, sitting blood pressure) and body weight
- Laboratory assessments:
  - Blood chemistry and hematology
  - Serum pregnancy test for female subjects of child-bearing potential
  - Drug (urine) test and alcohol (breath) test
- Viral marker testing: ZIKV NAT (serum, urine) and serology (IgM and IgG) for ZIKV

  Note: ZIKV NAT testing and IgM serology for ZIKV will be performed by the site's reference laboratory, while ZIKV IgG testing will be performed by the sponsor-developed non-diagnostic assay.

- Collection of a blood sample for baseline (pre-dose) anti-ZIKV antibody assessment (PK sample); see Section 6.4 on timing for this pre-dose PK sample collection.

The results of the baseline laboratory assessments for ZIKV viral marker testing (NAT/serology) will not be known prior to dosing of the subjects; however, this will not preclude the dosing of the subjects as study eligibility is determined by the screening assessments. The trial site must inform the sponsor of any aberrant baseline ZIKV NAT/serology assessments once the results are received. If the results of the baseline ZIKV (NAT and/or serology) laboratory tests confirm that the subject does not meet the clinical trial criteria for PK analysis (i.e., defined as ZIKV negative by NAT and serology test results and suitable level of baseline antibodies that bind ZIKV antigens), the subject(s) will be excluded from the PK analysis (also, the collection of PK samples will not take place at the remaining follow-up study visits). These subjects will continue to be followed for safety reasons and will be included in the safety analyses (i.e., all scheduled assessments and laboratory tests will be performed for these subjects in the follow-up visits, except for collection of PK samples).

Since all subjects in group 1 may be admitted at the same time to the Phase 1 clinic (approximately 24 hours prior to Day 1), the group 1 subjects may have their baseline assessments performed on the admission day. For subgroup 1A, baseline assessments will be done approximately 24 hours prior to Day 1. However, for subjects who are not randomized into group 1A and who remain eligible for the study may remain in the Phase 1 clinic to await possible randomization into subgroups 1B or 1C, for which randomization may occur approximately 24 and 48 hours later, respectively. The baseline assessments for these subjects may not be repeated (eg, blood chemistry, hematology), at the discretion of the investigator, since they will be housed in a controlled environment and it is expected their baseline assessments will not significantly change over the course of one to two days.

For subjects who are not randomized into subgroup 1A and who are randomized into subgroups 1B or 1C, pre-dose assessments on Day 1 may be performed more than once, at the discretion of the investigator (see Section 6.4 below).

Note 1: laboratory assessments and related activities will be described in the site's study-specific laboratory procedure.

Note 2: for a list of specific laboratory tests (e.g., blood chemistry, hematology), refer to Appendix I.

6.4 Study Treatment Administration (Day 1)

The study treatment is to be administered only under the supervision of the principal investigator or a qualified sub-investigator(s) identified on the 1572 FDA form and/or Health Canada qualified investigator undertaking form (as applicable) or a designate listed on Delegation of Authority form (signed by the principal investigator). Under no circumstances will the investigator allow ZIKV-IG to be used other than as specified in the protocol.

Prior to study-treatment administration, the following will be performed:

- 2 hours (±15 min) prior to study-treatment administration, vital signs will be assessed (to confirm screening eligibility for vital signs).
- 1 hour (±15 min) prior to study-treatment administration, vital signs will be assessed (to establish baseline vital signs).
- Within 2 hours prior to study-treatment administration, blood sample for baseline anti-ZIKV antibody assessment (pre-dose PK sample) will be collected.

After the above assessments have been completed, ZIKV-IG or placebo will be administered intravenously.

Subjects will be assigned (randomized) to receive either 50 mL of undiluted ZIKV-IG or 50 mL of placebo, administered by an IV infusion. For details on study treatment administration refer to Section 5.5 of the protocol and the Investigator's Brochure for ZIKV-IG.

Physical activity will be maintained at a minimal level during the first 24 hours following study treatment administration. *Note: study treatment preparation (including measures to prevent unblinding), administration and other activities related to study treatment handling will be described in the site's study-specific procedure*.

Subjects will stay in the Phase 1 clinic until assessments within the first 24 hours post-study treatment are completed (ie, subjects will be discharged on Day 2). Each subject will be followed up to Day 85 after study treatment administration (see Section 6.5).

6.5 Trial Assessments during/following Study Treatment Administration

Day 1: 15 minutes (±5 min) into the IV infusion and at the end of the IV infusion (+5 min):

- Assessment of vital signs.
- Adverse events.
- Concomitant medications (if applicable).

Day 1: 1 Hour (±5 min), 3 Hours (±30 min), 8 Hours (±1 hr) and 24 Hours (±3 hrs) after End of Study Treatment Administration

- Blood sample collection for anti-ZIKV antibody assessment (PK sample).
- Assessment of vital signs, adverse events and concomitant medications.

Day 2 – Discharge Day (24±3 hrs after end of study treatment administration)

- Blood sample collection for anti-ZIKV antibody assessment (PK sample).
- Assessment of vital signs, adverse events and concomitant medications.
- Blood chemistry and hematology.

Note: if ≥2 g/dL (i.e., ≥20 g/L) hemoglobin drop from baseline (Day -1) is observed, hemolysis tests (see Appendix I) will be performed.

Day 3 (48±3 hrs), Day 4 (72±3 hrs), Day 6 (120±6 hrs), Day 8 (168±6 hrs), Day 10 (216±12 hrs), Day 12 (264±12 hrs), Day 15 (336±12 hrs), Day 22 (504±24 hrs), Day 29 (672±24 hrs), Day 43 (1008±48 hrs) and Day 57 (1344±48 hrs):

Note: study visits are indicated as calendar days, while time-points in relation to end of study treatment administration are indicated in the brackets.

- Blood sample collection for anti-ZIKV antibody assessment (PK sample).
- Assessment of vital signs, adverse events and concomitant medications.
- Blood chemistry and hematology.

  Note: if ≥2 g/dL (i.e., ≥20 g/L) hemoglobin drop from baseline (Day -1) is observed (ONLY up to Day 15 visit (336±12 hrs post-study treatment administration), hemolysis tests (see Appendix I) will be performed.

Day 85 (2016±72 hrs after end of study treatment administration) or Early Withdrawal:

- Blood sample collection for anti-ZIKV antibody assessment (PK sample).
- Assessment of vital signs, adverse events and concomitant medications.
- Blood chemistry and hematology.
- Serum pregnancy test for female subjects of child-bearing potential
- Viral marker testing: serology for HIV, HBV, HCV; ZIKV NAT (serum, urine) and serology for ZIKV.

  Note: serology for ZIKV IgM testing will be performed by the site's reference laboratory, while ZIKV IgG testing will be performed by the sponsor-developed non-diagnostic assay.
- Complete physical exam.

Note: for a list of specific laboratory tests (e.g., blood chemistry, hematology), refer to Appendix I.

6.6 Handling of Samples for PK Analysis

To obtain samples for PK analysis of ZIKV-IG, 12 mL blood sample at Baseline (pre-dose) and 6 mL blood samples for subsequent PK time-points will be drawn into serum collection containing tubes.

The blood will be allowed to clot for 15–30 minutes at room temperature and the clotted cells will be removed by centrifugation at room temperature for 15 minutes at 1,500 x g. The serum will be transferred (as 3 approximately equal aliquots) into 3 sterile screw-cap cryotubes. Each tube should be labelled with the following information:

- Trial Protocol Number
- Sample Name (e.g., D1, 3 h: Day 1 visit, 3-hour sampling time point)
- Subject Trial ID# (Randomization/Enrollment Number)
- Date and time of sample collection

Label information will be recorded into the eCRF and into a logbook. Samples will be stored at ≤ -15ºC until they are shipped on dry ice to the sponsor. The sponsor must be notified of any deviations in the storage temperature of the samples within 48 hours of occurrence.

Back-up samples collected for PK analysis will be retained according to the sponsor's standard procedures.

6.7 Shipment of Samples for PK Analysis

The Phase 1 clinical site designate will initiate shipment of samples (to the sponsor) and arrange the date and method of shipment with the sponsor.

Samples will be divided into two shipments. The second shipment (back-up samples) will be initiated by the site designate once the first shipment has been received and inventory verified by the sponsor.

Shipment must be arranged such that the sponsor's facility will have staff on duty to receive the samples (e.g., ship on Monday through Wednesday).

Shipments of samples for PK analysis will be maintained at the storage temperature indicated in Section 6.6, and will include chain of custody signed and dated by the sender, and sample log/list/inventory documents. Temperature data loggers are required for all PK sample shipments.

The site will provide the shipping waybill number and, if possible, an electronic inventory of samples to the recipient in advance of shipment.

6.8 Pharmacokinetic Sample Analysis

The pharmacokinetic sample analysis will be performed using a binding ZIKV antibody assay and a neutralizing ZIKV antibody assay at the sponsor's facility:

Emergent BioSolutions Inc.

[redacted]

The assay methodology and the testing strategy will be described in the study-specific Analytical Plan (including measures to prevent unblinding due to PK sample testing at the sponsor's bioanalytical laboratory).

6.9 Concomitant Medications

Subjects should not take prescription medications (except for hormonal contraceptives for females), over-the-counter drugs, vitamins and herbal preparations for at least 7 days before baseline and during the trial.

The use of concomitant medication that the investigator considers unnecessary will be discouraged. No premedication will be permitted. Medications to treat minor ailments (e.g., headache, nausea, etc.) after the study treatment has been administered will be allowed at the discretion of the investigator. Trial subjects will be questioned about all concomitant medications including all herbal preparations and non-prescription medications that they are receiving. This information will be recorded by the investigator (or designate) in the eCRF. Concomitant medications taken in relation to adverse events will be denoted.

Blood- or plasma-derived products/plasma exchange procedures during the study are allowed only for emergency reasons; the use of these types of products/procedures and the reason for such use will be recorded by the investigator (or designate) in the eCRF.

7 ASSESSMENT OF PHARMACOKINETICS

7.1 PK Parameters

Based on serum concentrations of ZIKV antibodies, the following PK parameters will be calculated using non-compartmental analysis:

- $AUC_{0\text{-}t}$: area under the concentration-time curve from time 0 to the last quantifiable concentration.
- $AUC_{0\text{-day 7}}$.
- $AUC_{0\text{-inf}}$: $AUC_{0\text{-}t}$ plus the additional area extrapolated to infinity.
- C_{max}: maximum observed concentration.
- T_{max}: time at which C_{max} occurs.
- λz: terminal elimination rate constant.
- $t_{1/2}$: apparent first order terminal elimination half-life.
- CL: total body clearance following IV administration.
- V_Z: volume of distribution following IV administration.

7.2 Assessment of PK Parameters

Analysis of pre-dose (baseline) and post-dose samples at 1 hour, 3 hours, 8 hours (all part of Day 1 visit), 24 hours (Day 2 visit), Day 3, Day 4, Day 6, Day 8, Day 10, Day 12, Day 15, Day 22, Day 29, Day 43, Day 57 and Day 85 with anti-ZIKV antibody assays will determine serum concentrations of ZIKV antibodies over time, which will be used for calculation of PK

parameters (ie, PK analysis will be based on binding PK assay test results; however, PK analysis based on neutralizing PK assay test results will also be explored to the extent that the data permit). The full PK analysis will be performed for subjects that received ZIKV-IG and may be performed for placebo subjects (if needed).

8 ASSESSMENT OF SAFETY

The safety of the trial drug will be assessed by monitoring adverse events (AE), laboratory results for blood chemistry, hematology and concomitant medications collected throughout the study.

Note: for a list of specific laboratory tests (e.g., blood chemistry, hematology), refer to Appendix I.

8.1 Adverse Event/Serious Adverse Event Definition

The capture of AEs will begin during and after dosing, and any medical history changes that occur after baseline assessments during randomization and before dosing should be updated as medical history.

Adverse events are spontaneously reported by the subject and/or elicited by the investigator (or designate) by asking the subject non-leading questions. The association of the AE to ZIKV-IG is to be judged by the investigator as related or not-related/no relationship.

8.2 Definitions

An Adverse Event (AE): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

NOTE: A diagnosis should be preferentially captured as an adverse event term and signs and symptoms should be captured only in the absence of a unifying diagnosis. In the event that there are multiple diagnoses, then all diagnoses should be captured. The worsening of an existing sign, symptom or disease is also considered to be an AE. An abnormal laboratory finding deemed by the Principal Investigator and/or sub-investigator(s) as not clinically significant will not be captured as an AE, but an abnormal laboratory finding that worsens after dosing with the study drug, from not clinically significant to clinically significant, is considered an AE. Surgical procedures are not AE's. They are the action taken to treat a medical condition. Interventions that were planned prior to study entry for medical conditions that started prior to study entry, but did not worsen during the clinical trial are not reported as AEs.

A Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

Important medical events which may not result in death, be life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

NOTE: Death is an outcome and not an event. The condition leading to death is the event. Death will be considered an event only when no other information regarding the cause of death is available.

Hospitalization that is planned before inclusion into the study or outpatient treatment without overnight hospitalization is not considered a SAE. Hospitalization that occurs during a trial for social reasons (e.g., transportation difficulties, respite care) is not considered to be a SAE.

Adverse Drug Reaction: Any noxious and unintended response to a medicinal product related to any dose.

Expected Adverse Drug Reaction/Event: An adverse reaction, the nature or severity of which is consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Unexpected Adverse Drug Reaction/Event: 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 package insert/summary of product characteristics for an approved product).

All adverse events, including those that are not of a serious nature and those that are expected, will be documented by the investigators (or designates) in the source documents and appropriately transcribed into the eCRF.

8.3 Assessment of Severity (Intensity)

All adverse events will be examined by a principal investigator or sub-investigator for assessment of severity using the following criteria:

Mild: awareness of a sign or symptom but subject can tolerate.

Moderate: discomfort enough to cause interference with normal daily activity.

Severe: resulting in an inability to do work or do usual daily activity.

8.3.1 Assessment of Causality (ICH Classification)

All adverse events will be examined by a principal investigator or sub-investigator for assessment of causality (relatedness) using the criteria below.

In accordance with ICH E2A and 21.CFR.312, the following definitions are used to assess causality (relatedness) of the adverse events:

Related: There is a reasonable possibility that the AE was caused by the product in question. The expression "reasonable possibility" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

Not-related / No relationship: The AE is clearly or most probably caused by other etiology such as the patient's underlying condition, therapeutic intervention or concomitant therapy, or the delay between the administration of the product and the onset of the AE is incompatible with a causal relation, or the AE started before the administration of the product.

8.4 Description of Known Adverse Event Profile for ZIKV-IG

Although no clinical studies have been performed to date using ZIKV-IG, extensive clinical experience is available with immune globulin products (16). The safety profile of ZIKV-IG is expected to be comparable to other commercially available immune globulin products, including those manufactured at Emergent by the same manufacturing platform process and with IV route of administration (17, 18, 19).

A potential risk of antibody-dependent enhancement (ADE) of ZIKV and/or DENV infection may exist in those individuals with pre-existing levels of flavivirus antibodies (such as antibodies to ZIKV, DENV or WNV), but this risk is undefined for products such as ZIKV-IG. The sponsor has conducted preliminary *in vivo* ADE experiments in a mouse model of ZIKV infection and has not observed evidence of *in vivo* ZIKV ADE [refer to Investigator's Brochure for ZIKV-IG (NP-024)]. Currently, there is no clinical evidence to suggest that pre-existing flavivirus (DENV) antibodies enhance ZIKV infection (20-22) or that ZIKV antibodies clinically enhance other flavivirus infections such as DENV or WNV (23, 24).

Nevertheless, to mitigate the potential risk of ADE for study subjects that will receive ZIKV-IG, this clinical trial was designed to reduce exposure of subjects to ZIKV and/or DENV or other flaviviruses after administration of ZIKV-IG by conducting the study in ZIKV/DENV non-endemic region where the mosquito viral transmission vector is not present (in Canada), by requiring the subjects not to travel to ZIKV and/or DENV regions for the duration of the study (from screening until end of study) and by requiring subjects to use highly effective contraceptive methods throughout the study period. Also, subjects will recommend to their partner(s) (if applicable) not to travel to these endemic regions for the duration of the study. Collectively, these measures during the study period will mitigate the potential risk of ZIKV and DENV ADE for the study subjects who receive ZIKV-IG. In addition, the clinical dose intended for the Phase 1 study is expected to maintain ZIKV-IG levels well above the levels

that elicited *in vitro* ZIKV/DENV ADE effect (and presumably for WNV, which circulates in Canada during summer months); refer to Investigator's Brochure for ZIKV-IG.

The general safety profile of human immune globulins is well established and the most common types of adverse reaction (related AEs) to immune globulin intravenous products (IGIVs) are non-anaphylactic infusion reactions, such as back or abdominal pain, nausea and vomiting within the first 30 minutes of the infusion. Fever, headache, chills, rash, fatigue may begin at the end of the IV infusion and continue for several hours. More severe reactions of this type may require treatment with corticosteroids or acetaminophen. The incidence of adverse reactions associated with IV administration of immune globulin products is typically in the range of 1-15%(17-19, 25-27). Infrequent events associated with IV immune globulin administration (ie, product class-specific) have also been reported, typically in individuals who have significant, underlying risk factors for the development of the following: hypersensitivity reactions, renal failure, aseptic meningitis syndrome (AMS), hemolysis, transfusion-related acute lung injury (TRALI) and thrombotic events, (28).

8.5 Adverse Event Reporting

Occurrence of AEs will be monitored throughout the trial and will cover all participating subjects. Trial subjects will be provided with a telephone number to contact trial personnel in case of an untoward reaction.

All AEs must be followed to resolution, or up to 30 days after the subject has completed the trial, whichever occurs first. The investigator will follow SAEs to resolution, or in the case of disability or incapacity, until the condition has stabilized. If a patient does not complete the trial, efforts must be made to obtain information regarding all AEs, with a minimum follow-up of 30 days post-dosing.

All laboratory tests with values considered clinically significantly abnormal during participation in the study will be reported as AEs. These tests will be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor. If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified. If laboratory values from non-protocol specified laboratory assessments performed at the institution's reference laboratory require a change in participant management or are considered clinically significant by the investigator, then the results must be recorded in the eCRF as AEs.

If a subject becomes pregnant or if a subject's partner becomes pregnant during the clinical trial, this should be reported by the subject to the site within 24 hours of the subject becoming aware of their pregnancy/their partner's pregnancy. The pregnancies will be recorded as AEs and will be followed until termination of pregnancy or birth (as per sponsor's follow-up procedure): a separate pregnancy follow-up consent form for subject's partner will be required. If a pregnancy results in an abnormal outcome that the reporting health care professional considers might be due to the trial drug, then the guidelines for

expedited reporting of serious, unexpected adverse drug reactions should be followed (see Section 8.6).

8.6 Reporting of SAEs

The investigator will report all SAEs to the sponsor by telephone or e-mail (also informing the study medical monitor) within 24 hours of the investigator's knowledge of occurrence. This will be followed by a fax or e-mail copy of the SAE Form.

A written SAE report by the investigator to the sponsor (including medical summary of the SAE) must follow within 3 days of the investigator's knowledge of occurrence of the SAE.

All SAE reports should be made to:

Sr. Specialist, Pharmacovigilance	AND	**Medical Monitor**
[redacted]		[redacted]
Toll free phone: [redacted]		
Toll free fax: [redacted]		

The sponsor will report every SAE to the regulatory agencies (FDA and Health Canada), while the investigator must report SAE(s) to the Institutional Review Board (IRB)/Ethics Committee (EC).

8.7 Safety Monitoring Committee

A Safety Monitoring Committee (SMC) consisting at a minimum of two blinded medical reviewers (Phase 1 clinic's medical monitor and sponsor's medical monitor) and one unblinded segregated medical monitor will provide another layer of subject safety assurance.

Dosing of the first six subjects (group 1) will be staggered over the period of three days, wherein two subjects per day will be randomized 1:1 and dosed at least 3 hours apart (subgroups 1A, 1B and 1C; each subgroup to be dosed at least one day apart). Based on the information available [i.e., reported adverse events within 3-hour period after study treatment administration, concomitant medications and vital signs 15 min into the IV infusion, at the end of the IV infusion, 1 hour and 3 hours after study treatment IV administration], the principal investigator will decide on subsequent dosing of each subject. If in the opinion of

the principal investigator no safety concerns are identified after the first six subjects are dosed, a group of six subjects (group 2) will be randomized 2:1 and dosed (at least 30 minutes apart) over the course of one day.

The two blinded medical reviewers will then conduct a safety review following enrollment and data entry completion (up to 72 hours post-study treatment administration) of the first 12 subjects dosed to monitor for any unexpected safety signals. The safety review will include blinded data on demographics, medical history and adverse events (AEs). A safety signal is defined as follows:

- Two or more subjects report rare reactions for immune globulin intravenous products (such as hypersensitivity, hemolysis, thrombotic events).
- Occurrence of two or more unexpected related AEs.
- Two or more subjects report same related SAEs.
- Two or more subjects experience a related moderate or higher severity AE associated with the same organ system.
- Any other findings that, at the discretion of the medical monitor(s), that would indicate a safety signal.

If there is no safety signal identified by the blinded safety data review, the remaining 18 subjects will be randomized 2:1 and dosed (at least 30 minutes apart) in three separate groups over a period of three days (each group consisting of six subjects to be dosed over the course of one day). However, if there is a safety signal based on the blinded review of safety data from the first 12 dosed subjects, the safety review of the same data by the segregated unblinded medical monitor will be triggered (randomization scheme will be provided by the unblinded statistician at the CRO to the unblinded independent medical monitor to decode subject assignment) to determine if affected subject(s) received the trial drug (ZIKV-IG).

The segregated medical monitor may recommend stopping the trial if the safety review identifies unforeseen adverse effects that impact subject safety (see Section 9.2.4). Only in the case where the independent medical monitor recommends stopping the trial (based on their safety review) would the other two medical monitors' concurrence be required.

The SMC process will be further outlined in the Medical Monitoring Plan for this study.

9 STATISTICAL ISSUES IN TRIAL DESIGN AND PK ASSESSMENT

9.1 Sample Size Calculation

Sample size for ZK-001 will be 30 healthy volunteers; subjects will be randomized to receive either one dose level of ZIKV-IG (n=19) or placebo (n=11). While there was no formal sample size calculation as this is a Phase 1 clinical trial evaluating safety and PK of only one dose level of ZIKV-IG, up to 19 subjects treated with trial drug will allow for safety evaluation and for calculation of PK parameters.

9.1.1 Safety Population

The safety population will include all subjects who received any amount of study treatment (ZIKV-IG or placebo).

9.1.2 PK Population

The PK population will include all subjects who received ZIKV-IG with adequate number of PK samples (a suitable pre-dose sample and at least one measurable post-dose sample).

9.2 Trial Endpoints

9.2.1 Primary Endpoint

The primary endpoint is the number and severity of adverse events.

9.2.2 Secondary Endpoints

Secondary endpoints are ZIKV-IG PK parameters, including:

- $AUC_{0\text{-}t}$: area under the concentration-time curve from time 0 to the last quantifiable concentration.
- $AUC_{0\text{-day 7}}$.
- $AUC_{0\text{-inf}}$: $AUC_{0\text{-}t}$ plus the additional area extrapolated to infinity.
- C_{max}: maximum observed concentration.
- T_{max}: time at which C_{max} occurs.
- λz: terminal elimination rate constant.
- $t_{1/2}$: apparent first order terminal elimination half-life.
- CL: total body clearance following IV administration.
- V_Z: volume of distribution following IV administration.

9.2.3 Safety Endpoints

Safety will be evaluated based on the following endpoints:

- Adverse events
- Laboratory test results (hematology, blood chemistry, viral marker testing; refer to Appendix I for the list of specific laboratory tests)
- Physical exams
- Concomitant medications
- Vital signs

9.2.4 Criteria for Early Termination of the Trial

The Sponsor and/or the principal investigator may elect to terminate the trial early as defined by the clinical trial agreement. This may be done at any time provided there is reasonable cause, and sufficient notice is given in advance of the intended termination.

Meeting a safety stopping criterion will not automatically trigger study termination, but a hold on recruitment will be implemented until an ad hoc Safety Monitoring Committee (SMC) meeting is held. If any of the following safety criteria outlined below are fulfilled, the unblinded member of the SMC will review the unblinded safety data to assess the evidence for an excess of events in subjects who received ZIKV-IG relative to those subjects that received placebo. The SMC will determine whether trial termination is recommended.

The safety criteria for early termination of the trial include:

- Two or more subjects experience related rare reactions reported for immune globulin products such as thrombotic events or hypersensitivity.
- Two or more subjects experience the same related SAE (per sponsor assessment).
- Three or more subjects experience a related moderate or higher severity AE associated with the same organ system.
- Any other findings that, at the discretion of the medical monitor(s), indicate that the study should be halted.

Administrative issues affecting the Phase 1 clinical site may constitute grounds for stopping the trial. Examples include, but are not limited to, non-adherence to the trial protocol, sponsor's procedures, GCP guidelines, requirements of IRB/EC/regulatory authorities, unavailability of the principal investigator or staff for the sponsor's (or their authorized representative) monitoring personnel, inadequate evidence of the principal investigator's personal conduct or supervision of the trial, relocation of the investigator or reallocation of investigator's responsibilities or disqualification of the investigator by the regulatory authority.

The Sponsor and the site principal investigator(s) may elect to terminate the trial early for a variety of other reasons. A decision to terminate the trial early may be based on data suggesting that subject participation in the trial may be unsafe; the protocol or conduct of the trial is flawed such that the safety or rights of the trial subjects may be adversely affected; the ethics committee withdraws the approval for the trial and denies reconsideration; recruitment is poor; research strategy or management priorities change; or a clinical hold is imposed by a regulatory authority.

Any decision to voluntarily suspend or terminate a clinical trial will be carefully reviewed and fully justified. The sponsor will notify the FDA and Health Canada and the IRB/EC of any suspension or termination, along with justification for restarting or terminating the study as applicable.

The principal investigator must notify the IRB/EC in writing of the trial's completion or early termination. The sponsor must receive a copy of the notification letter from the IRB/EC indicating receipt of the completion or early termination letter.

9.3 Interim Analyses

A safety monitoring committee will review blinded data for the first 12 dosed subjects.

No formal interim analysis is planned.

9.4 Planned Method of Analyses

In general, continuous endpoints will be summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum and maximum. Categorical endpoints will be summarized by the total number of subjects, frequencies and percentages.

Adverse events will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), using the most current version at the time of coding. AEs will be defined as events beginning during and after study treatment administration that were not present prior to study treatment administration or those that were present prior to study treatment administration and subsequently worsened in severity. AE incidence for each system organ class and preferred term will be summarized for the safety population by study treatment overall and by gender, as well as separately by severity and for events related to study treatment (ZIKV-IG or placebo). SAEs will be summarized separately for the safety population overall and by study treatment.

PK analysis for anti-ZIKV antibodies will be conducted for the PK population using the binding ZIKV antibody assay results; the PK analysis using neutralizing ZIKV antibody assay results will be performed to the extent that the data permit; hence this PK analysis will be exploratory. ZIKV-IG serum concentration versus time data will be analyzed by standard non-compartmental methods (i.e., trapezoidal method). Actual times and not nominal times will be used in the analysis, and concentrations below the limit of quantitation (LOQ) and/or detection (LOD) will be imputed as half of this value. Calculated PK parameters will include those listed in Section 9.2.2. The PK analysis will be performed for the PK population overall. Subjects with elevated baseline levels of ZIKV antibodies or subjects with inadequate number of PK time-points (e.g., no pre-dose sample, or no measurable post-dose samples) may be excluded from the PK analysis. Baseline correction will be implemented, if necessary.

Subject disposition, including early termination reasons, will be summarized by study treatment for all subjects. Major and critical protocol deviations will be presented for the safety population. Subject demographics, medical history and study treatment (ZIKV-IG or placebo) dosing data will be tabulated for the safety population.

Pre-infusion medications, concomitant medications and concomitant medical procedures will be coded using the WHO Drug Dictionary and displayed by treatment group for the safety population.

Laboratory test results will be summarized by time point and study treatment using descriptive statistics for the safety population. Changes in laboratory values and 'clinically significant' (as assessed by the investigator) abnormal values will be analyzed descriptively. Vital signs parameters will be presented in the same manner.

The details of analyses will be further described in the study-specific Statistical Analysis Plan (SAP).

10 REGULATORY AND ETHICAL ISSUES

10.1 Declaration of Helsinki

The investigator shall ensure that this trial is conducted in accordance with the "Declaration of Helsinki."

10.2 Informed Consent

The investigator (or designates) will explain the nature of the study to the participant, answer all questions related to the study and obtain written informed consent from prospective trial candidates before enrolment or the performance of any trial procedures. The proper completion of consent forms will be monitored by sponsor personnel and the original signed informed consent form(s) (ICF) will be maintained in the Investigator site file.

A copy of the signed ICF must be given to the subject. If the ICF is revised, all trial subjects who are ongoing in the trial must be re-consented to the current IRB/EC-approved version of the ICF at their next trial visit. While obtaining informed consent from these subjects, the investigators (or designates) will inform the subject of the following:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The type and amount of biological samples to be collected for PK analysis, and the retention period for these samples.
- The subject's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.

- The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks, if applicable.
- The compensation and/or treatment available to the subject in the event of trial related injury.
- The anticipated prorated payment, if any, to the subject for participating in the trial.
- The anticipated expenses, if any, to the subject for participating in the trial.
- That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
- The consequences of a subject's decision to withdraw from the study and procedures for orderly termination of participation by the subject.
- That the monitor(s), the auditor(s), the IRB/EC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial 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.
- 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 trial are published, the subject's identity will remain confidential.
- That the subject 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 trial.
- The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial related injury.
- The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
- The expected duration of the subject's participation in the trial.
- The approximate number of subjects involved in the trial.
- In FDA-regulated clinical trials, the following statement shall be provided to each clinical trial subject in informed consent documents and processes: "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

10.3 Institutional Review Board (IRB)

Before the start of the trial, the Investigator's Brochure for ZIKV-IG, the ZK-001 protocol, proposed ICF, subject compensation (if any), sponsor-approved trial materials and advertisements, and any other written information to be provided to the subject will be submitted to a properly constituted IRB for review. The sponsor must receive a copy of the written approval from the IRB/EC for all of the above applicable documents prior to recruitment of subjects into the trial and shipment of ZIKV-IG.

The IRB must provide written approval for all amendments to any of the above documents prior to implementation of these amendments at the investigational site. The investigator is obliged to report SAEs, as well as any unanticipated problems, to the IRB/EC in addition to other information as required by the IRB/EC.

The names (or title, if IRB procedures prohibit publishing of names) and associated backgrounds of the members of IRB/EC (to assist in assuring that the board membership is properly constituted and operates according to 21 CFR part 56 and local regulatory requirements) will be given to the sponsor prior to the start of the trial along with a signed and dated statement stating that the protocol and ICF and, where applicable, any other document listed above, have been approved by the IRB/EC.

All correspondence between the investigator and the IRB/EC will be available for review by the sponsor (or designate), representatives of the sponsor (monitors) and the applicable regulatory authority(ies).

10.4 Documentation Required Prior to Trial Initiation

The investigator (or designate) is responsible for forwarding the following documents to the sponsor for review prior to trial initiation:

- Signed protocol signature page, form FDA 1572 (or an equivalent form depending on local regulatory requirements), financial disclosure form, debarment certification statement, Clinical Trial Agreement, and any other required regulatory documents.
- Copy of IRB/EC-approved informed consent form.
- Copy of the written IRB approval for the ZK-001 protocol, ZIKV-IG Investigator's Brochure, ICF, subject compensation (if any), any trial materials and advertising, and any other written information to be provided to the subject.
- Current Curriculum Vitae and a photocopy of medical license (if applicable) of the principal investigator, co/sub investigators and other site personnel as required.
- Written statement that the IRB is properly constituted and operates according to 21 CFR part 56 regulations. Investigators participating in this study, if IRB members, should state in writing that they have abstained from voting in regard to this protocol.
- Laboratory normal ranges and documentation of laboratory certification.

10.5 Subject Confidentiality

The investigator must ensure the anonymity of each subject is maintained at all times. Subjects should only be identified by their initials and subject trial ID (randomization, enrollment) number on the CRF, or on any other trial documents provided to the sponsor or their designate(s). Any documents that identify the subject should be kept in strict confidence by the principal investigator.

Based on ICH GCP guidelines and regulatory requirements, the investigator is required to allow authorized personnel of the sponsor (or its designate), the IRB, and members of the appropriate regulatory authority(ies) to review subject's files that are related to ZK-001. Subjects must be informed that his/her records at the site may be reviewed by the sponsor, its designate(s), the IRB and the appropriate regulatory authority(ies) through direct access to the subject's original medical records at the site.

11 ADMINISTRATIVE AND LEGAL REQUIREMENTS

11.1 Sponsorship

This clinical study is sponsored by Emergent BioSolutions Canada Inc., [redacted] who is the manufacturer of ZIKV-IG.

11.2 Protocol Amendments

Protocol amendments will only be made by the sponsor. Any change to the protocol must be made in the form of a formal amendment to the protocol and must be approved in writing by the principal investigator, the sponsor, and the IRB/EC prior to implementation. The investigator must receive written IRB/EC approval for all protocol amendments prior to implementing protocol amendments at the trial site, and the investigator must send a copy of any IRB/EC correspondence and all approval/disapproval letters from the IRB/EC to the sponsor. Minor changes (e.g., change of contact details or logistic arrangements) to the protocol will be submitted to the IRB/EC as a non-substantial amendment for information only.

11.3 Deviations from the Protocol

The investigator agrees to conduct the clinical trial in compliance with the protocol agreed to by the sponsor and approved by the IRB/EC. The investigator and the sponsor shall sign the protocol to confirm this agreement.

The investigator will not deviate from this protocol for any reason without prior approval of the sponsor and the IRB/EC, except in cases of medical emergencies. The investigator may deviate from the protocol without the prior approval of the IRB/EC or the sponsor only when the deviation is necessary to eliminate an apparent immediate hazard to the subjects. In that event, the investigator must notify the IRB/EC and the sponsor in writing as soon as possible

and no more than 5 working days after the deviation is implemented. The investigator shall document and explain any deviation from the approved protocol.

11.4 Source Documentation and Storage

The source documentation requirements described below apply to all source documentation and trial records in any form, including those maintained in the institution's Electronic Health Record system, if applicable.

The investigator should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry and should be explained if necessary (e.g., via an audit trail).

The principal investigator will maintain the following information:

- Medical history/physical condition of the trial subject before involvement in the trial sufficient to verify protocol entry criteria.
- Dated and signed notes on the day of entry into the trial including the trial number, the drug being evaluated, subject trial ID number assigned, and a statement that informed consent was obtained, noting the time the consent was obtained.
- Dated and signed notes from each trial subject visit that refer to the protocol or eCRF for further information, if appropriate (i.e., for specific procedures and exams).
- The investigator will assess each abnormal lab result as clinically significant (CS) or not clinically significant (NCS). For clinically significant results, a brief explanation will be written on the laboratory report. These assessments will be noted on the laboratory report source document, and signed and dated on the date of the investigator's review.
- Notes regarding concomitant medications taken during the trial (including start and stop dates).
- Source documents regarding adverse events occurring during the trial including date of onset and cessation, seriousness, severity, causality, action taken and related concomitant medications.
- Trial subjects' condition upon completion or withdrawal from the trial.
- All communications with the IRB/EC responsible for the trial.
- Drug accountability records.
- Any other records as required by the sponsor/designate, the IRB/EC or the regulatory authority(ies).

The investigator must arrange for the retention of the subject identification codes for at least 25 years after the completion or discontinuation of the trial (Revised Canadian CTA Regulations, September 2001). Subject files and other source data must be securely stored

and kept for the maximum time permitted by the hospital, institution or private practice but not less than 25 years after completion or termination of the trial. Archival data may be held on microfiche or electronic record, provided that a backup exists and that hard copy can be obtained from it if required. If source documents are to be destroyed as per hospital or local regulatory policy, the investigator is requested to contact the sponsor.

Records from the trial that identify the subject will be confidential except that they may be given to and inspected by the sponsor of the trial or designate(s), the IRB/EC, the FDA, other government agencies as appropriate (Health Canada), and will not otherwise be released except as required by law. All information provided to the investigator by the sponsor is to be considered confidential unless otherwise stated.

11.5 Electronic Data Forms

The investigator (or designate) will record data collected in ZK-001 on electronic CRFs (eCRFs) [i.e., via electronic data capture (EDC) system]. The eCRFs are to be completed on a contemporaneous basis. Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained.

The data are the property of the sponsor of the trial. Questions arising from eCRF data will resolved by the issuance of data queries within the EDC system by the sponsor's Clinical Data and Statistics personnel (or designate) to the investigator.

11.6 Monitoring

At the time the trial is initiated, monitors from the sponsor/CRO will thoroughly review the protocol and data forms with the investigators and their staff. During the trial, the monitors will be available to discuss by telephone, e-mail, or in person (during site visits), questions regarding adverse reactions, removal of subjects from the trial, conduct of the trial and other clinical trial matters. Monitors from the sponsor (or their representatives) will visit at the initiation of the trial, during the trial and at the completion of the trial. At the time of each monitoring visit, the monitors will check eCRFs of the subjects to ensure that items have been completed, that the data are accurate and obtained in the manner specified in the protocol and that data recorded on the data forms for the trial agree with medical records at the site. The monitors will also check for general protocol and regulatory compliance by subjects and site personnel.

To ensure maintenance of the blind, independent subcontracted unblinded monitors will be utilized for monitoring for verifying the unblinded drug accountability at the site pharmacy.

The Phase 1 clinical site will be provided with the trial related training/ instructions at the initiation and throughout the conduct of the trial.

11.7 Quality Control and Quality Assurance

The sponsor's Quality Assurance (QA) department (or authorized representatives) may conduct onsite audits of all aspects of the clinical trial prior to, during the trial, or after the trial has been completed. The clinical trial may also be inspected by regulatory authorities or the IRB to verify that the trial is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

11.7.1 Quality Management

The sponsor maintains a quality management oversight through encompassing SOPs, risk assessment, risk management with defined data management plans, monitoring plans and audit plans to assure regulatory compliance, subject safety, robust data management and scientific integrity.

11.8 Publication Policy

Data arising from this trial are the sole property of the sponsor of the trial. The sponsor must provide written, prior agreement to any publication based, in whole or in part, on data from this trial. All proposed abstracts, manuscripts or presentations from the study must be provided to the sponsor for review at least 60 days prior to submission for publication/presentation. Any information identified by the sponsor as confidential must be deleted prior to submission.

The Publication Policy applicable to this protocol is the one agreed upon and described in the Clinical Trial Agreement between the sponsor and the principal investigator.

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13 APPENDIX I

Below is the listing of laboratory tests for ZK-001 clinical trial. All laboratory tests will be performed/managed by the Phase 1 CRO's reference laboratory (Dynacare), except where noted.

Laboratory Assessment Category	**List of Specific Tests**
Blood type	ABO/Rh blood typing
Blood chemistry	Glucose, urea, calcium, albumin, total bilirubin, sodium, potassium, chloride, alkaline phosphatase, lactate dehydrogenase (LD), gamma-glutamyl transferase (CGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), thyroid stimulating hormone (TSH), creatinine.
Hematology	White blood count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, neutrophils, blood smear (morphology: platelets, red blood cells, white blood cells), hemoglobin*, hematocrit, red blood cells, platelets.
Pregnancy	Chorionic gonadotropin (CG) for females of child bearing potential
	Follicle-stimulating hormone (FSH) for post-menopausal females
Urinalysis	Micro: red blood cells, squamous epithelial, white blood cells, bacteria. Chemical: glucose, bilirubin, ketones, specific gravity, blood, pH, protein, urobilinogen, nitrite, leukocytes.
Viral marker serology	HIV-1/HIV-2, Hep B Ag, Hep C, ZIKV (IgM, IgG**), DENV (IgM, IgG), WNV (IgM, IgG).
Viral marker nucleic acid test (NAT)	ZIKV (serum, urine).
Urine drug test	Amphetamine, benzodiazepine, cannabinoids, cocaine, opiates, oxycodone.

* If hemoglobin drops ≥2 g/dL (i.e., 20 g/L) from baseline (up to Day 15 study visit), the following hemolysis tests will be performed: direct Coombs test, serum haptoglobin, plasma-free hemoglobin, and urinalysis testing including urine hemosiderin.

** ZIKV IgG test will be performed by the sponsor-developed non-diagnostic assay.