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SAP Amendment 2 / Note to File

Protocol No. / Title: ZK-001/Safety and Pharmacokinetic Evaluation of Zika Virus Immune Globulin in Healthy Volunteers (Protocol Version 3.1 June 5, 2018)

Site Code: Not applicable **Investigator:** [redacted]

TMF Section/Artifact name: 11.01.01 Statistical Analysis Plan

Details: The purpose of this document is to outline any changes from the Statistical Analysis Plan (SAP) or important statistical analysis decisions that were made post-database lock and unblinding for study ZK-001.

The following issues are discussed:

1. Screen failure data
2. Pharmacokinetics (PK) neutralization assay deviation
3. PK analysis methodology

Assessment and Actions Taken:

1. Screen failure data were not collected in the clinical database for study ZK-001. These data were tracked by the site and shared with the Emergent clinical trial manager informally via an Excel tracker. At the end of the study, the screen failure data (total number of screen failures, 279, and associated reasons) were used in the Clinical Study Report (CSR) Section 12.1 text and Figure 2 subject disposition flow chart. It is acknowledged that these are unverified data.

2. A PK neutralization assay deviation is noted in APPENDIX I Documentation for Item #2 to this document. Briefly, the 1 hour, 3 hour and 8 hour time point concentrations for subject ZK-001-01-197 were incorrectly deemed a failed assay and repeated. The repeat data were used in the PK analysis rather than the original data; this anomaly is included in the PK Contributing Scientist report.

3. A number of changes were made to the ZK-001 PK analysis, some as a result of recommendations made by Nuventra Pharma Sciences in order to align our noncompartmental analysis (NCA) methodology to that of the industry standard Phoenix WinNonLin (Certara) software, as noted below.

    - The SAP states that, "All PK analyses include placebo subjects as well as ZIKV-IG subjects due to background antibody levels." When the PK concentration data were received, it was noted that the placebo subjects' values were all less than the lower limit of quantitation (LLOQ; 5 U/mL for binding assays and 15 U/mL for neutralization assay). This result was due to a background subtraction step applied during the assay. Consequently, PK analyses could not be performed for placebo subjects.

    - Imputation for PK analyses followed a PHUSE white paper Sections 6.2.1 and 6.2.2 to determine the following conventions: (https://www.phusewiki.org/wiki/images/e/ed/PhUSE_CSS_WhitePaper_PK_final_25March2014.pdf)
        - Predose values <LLOQ were set to zero and included in PK analyses.
        - Values prior to C_{max} (i.e., Day 1, 1 hour and 3 hour time points) and

<LLOQ were set to zero and included in PK analyses.
- Values at the end of the curve <LLOQ were set to missing and excluded from PK analyses.
- PK concentrations for the anti-E protein binding assay included one value greater than the ULOQ of 300 U/mL. This value occurred at the Day 1, 1 hour time point for subject ZK-001-01-049. In the PK analysis, the value was imputed as 1.01 * ULOQ or 303 U/mL and included in PK analysis.

- The SAP states that the "linear trapezoidal method" is used for PK analyses. In fact, the linear trapezoidal method was used for consecutive time points with level or increasing concentrations and the log-linear trapezoidal method was used for consecutive time points with decreasing concentrations per Nuventra recommendation.

- The terminal elimination constant lambda z was calculated using ln-transformed data post-C_{max} with a minimum of the last 3 points; more points were added and the adjusted r^2 was used to find the best model (except the second-best model was used if the difference in adjusted r^2 was <0.0001 and the second-best model used more data points, following https://www.lexjansen.com/pharmasug/2005/StatisticsPharmacokinetics/sp07.pdf). C_{max} was excluded from the linear regression for lambda z calculation per Nuventra advice. No lower bound was placed on the adjusted r^2 value (such as 0.8 or 0.75) as Nuventra proposed.

- Additional PK parameters not mentioned in the SAP were reported per Nuventra recommendation: AUC%extrapolated, adjusted r^2 value, number of points used in lambda z calculation, and lower and upper range of times for points used in lambda z calculation for each subject.
  Additionally per Nuventra suggestion, geometric mean and geometric percent coefficient of variation were not displayed for ordinal time variables including t_{max} and lower and upper limit of times for points used for lambda z.

- One subject, ZK-001-01-127, was removed from PK analyses as an outlier. This subject had a much later and lower C_{max} value with an apparent absorption phase present. It is hypothesized that the subject received drug administration that inadvertently missed the vein and was injected intramuscularly; this hypothesis is supported by the adverse event of tissue swelling at the injection site.

- The PK concentration tables for each assay (Tables 14.3.6.1-3) were modified by excluding placebo subjects and removing the change from predose column (since individual background subtraction was performed as part of the assay). In addition, a column was added for the PK population with subject ZK-001-01-127 removed to permit comparison of the concentrations with and without this outlying subject.

The PK parameter tables for each assay (Tables 14.3.7.1-3) were modified by adding a column for the PK population with subject ZK-001-01-127 removed to permit comparison of the parameters with and without this outlying subject. PK listings were not changed.
The PK profile figures for each assay (Figures 14.4.2.1-3) were modified by excluding subject ZK-001-01-127.
The individual PK profile Figure 14.4.2.4 was modified to overlay all three assays on the same plot for each subject; subject ZK-001-01-127 was retained.

- The SAP states that, "values reported as below the limit of detection (LOD) are substituted with LOD/2." This rule was followed relative to the LLOQ (5 U/mL for binding assays and 15 U/mL for neutralization assay) for calculation of summary statistics, but not for PK analyses.

Completed by: *(Name, role)*	[redacted] Lead Biostatistician	
Signature: [redacted]		**Date:** [redacted]

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SAP Amendment 1 / Note to File

Protocol No. / Title: ZK-001/Safety and Pharmacokinetic Evaluation of Zika Virus Immune Globulin in Healthy Volunteers (Protocol Version 3.1 June 5, 2018)

Site Code: Not applicable **Investigator:** [redacted]

TMF Section/Artifact name: 11.01.01 Statistical Analysis Plan

Details:	According to the ZK-001 protocol and SAP, subjects with "*a suitably low level of baseline anti-ZIKV E-protein binding antibodies*" are to be included in the PK analysis population. Additionally, SAP (v1.0 18-APR-2019 Section 3.2 Analysis Populations) states "*Subjects who exceed a threshold level of baseline anti-ZIKV E protein binding antibodies, to be determined **after** database lock, may be excluded from PK analysis*." This statement was based on the erroneous assumption that all PK concentrations would be blinded; in fact, screening and baseline data were unblinded. Consequently, the team decide to set the cutoff limit of baseline anti-ZIKV E-protein binding antibodies for inclusion in the PK population **prior** to database lock and examination of the blinded post-baseline PK data.
Assessment:	BIAD stated that the screening limit of 9.1 U/mL for anti-ZIKV E-protein binding antibodies was conservative and, following validation, could be confidently increased to 15-20 U/mL without affecting data integrity. The screening and baseline antibody concentrations indicated that most subjects had low background anti-ZIKV E-protein binding antibody levels, with the maximum being 11.5 U/mL. This SAP amendment 1/NTF was created to establish a baseline cutoff of **12 U/mL** anti-ZIKV E-protein concentration for subject inclusion in the PK population. This document was prepared and signed off **prior** to database lock, and thus prior to examination of the blinded post-baseline PK data.

Actions Taken:	• A limit of **≤12 U/mL** baseline anti-ZIKV E-protein concentration was established for subject inclusion in the PK population. This was done **prior** to database lock. • Application of this limit to current data indicates that no subject will be excluded from the PK analysis population due to high baseline antibody concentrations. • See also TMF Section 12.8 NTF entitled "Threshold level of baseline anti-ZIKV E-protein binding antibodies" with the same date containing substantively the same information.

Completed by: *(Name, role)*	[redacted] Lead Biostatistician
[redacted]	[redacted]

Emergent BioSolutions
STATISTICAL ANALYSIS PLAN

Study Drug
Zika Virus Immune Globulin (Human) (ZIKV-IG)

Protocol ZK-001

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

Protocol Version	Date
Protocol 1.0	30-OCT-2017
Amendment 2.0	30-NOV-2017
Amendment 2.1	10-JAN-2018
Amendment 3.0	18-APR-2018
Amendment 3.1	05-JUN-2018

SAP Version	Date
1.0 FINAL	18-APR-2019

SAP SIGNATURE PAGE

Signatures below indicate that the final version of the SAP or amended SAP is released for execution.

Study Statistician:
[redacted]
Biostatistician
Emergent BioSolutions

[redacted]
Signature / Date

Statistical Reviewer:
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Sr. Manager, Biostatistics
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Clinical Scientist:
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TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
$AUC_{0-day\ 7}$	Area under the serum concentration curve from time 0 to day 7
AUC_{0-inf}	Area under the serum concentration curve from time 0 to infinity
AUC_{0-t}	Area under the serum concentration curve from time 0 to the last measurable concentration
BMI	Body mass index
CL	Clearance
C_{max}	Maximum observed concentration
CRF	Case report form
CRO	Contract research organization
CS	Clinically significant
CSR	Clinical study report
CTMS	Clinical trial management system
DENV	Dengue virus
ECG	Electrocardiogram
EDC	Electronic data capture
FSH	Follicle-stimulating hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IV	Intravenous
LOD	Limit of detection
MedDRA	Medical Dictionary for Regulatory Activities
NAT	Nucleic acid testing
NCS	Not clinically significant
NS1	Zika virus non-structural protein 1
PD	Protocol deviation
PK	Pharmacokinetics
PR interval	Interval from the beginning of the P wave to the beginning of the Q wave

QA	Quality assurance
QRS duration	Duration from the beginning of the Q wave to the end of the S wave
QT interval	Interval from the beginning of the Q wave to the end of the T wave
QTcB interval	Bazett's correction of QT interval, $QT/(RR)^{1/2}$, where RR is one cardiac cycle from the beginning of one R wave to the beginning of the next one
QTcF interval	Fridericia's correction QT interval, $QT/(RR)^{1/3}$, where RR is one cardiac cycle from the beginning of one R wave to the beginning of the next one
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDTM	Study Data Tabulation Model
SMC	Safety monitoring committee
SMQ	Standard MedDRA query
TLF	Tables, listings, and figures
T_{max}	Time at which C_{max} occurs
$t_{1/2}$	Apparent first order terminal elimination half-life
V_Z	Volume of distribution following IV administration
WHO DD	World Health Organization Drug Dictionary
WNV	West Nile virus
ZIKV	Zika virus
ZIKV-IG	Anti-Zika Virus Immune Globulin (Human)
λ_z	Terminal elimination rate constant

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol ZK-001 "Safety and Pharmacokinetic Evaluation of Zika Virus Immune Globulin in Healthy Volunteers" (Version 3.1, 05JUN2018). This document specifies details of the definitions of the derived variables, analysis methods, assumptions and data handling conventions. The document is accompanied by mock-up tables, listings, and figures (TLF) shells. Some further details on the calculation of derived variables are provided as programmer's notes in the TLF shells. The TLF shells serve only as a guide for programming the final TLFs. They are working documents and can be updated as needed.

2. PROTOCOL SUMMARY

2.1. Study Objectives

2.1.1. Primary Objective

The primary objective of this study was to assess safety of Zika Virus Immune Globulin (ZIKV-IG) in healthy volunteers.

2.1.2. Secondary Objective

The secondary objective of this study was to determine pharmacokinetics (PK) of ZIKV-IG in healthy volunteers.

2.2. Study Design and Conduct

Study ZK-001 was a Phase 1, single-center, double-blind, randomized, placebo-controlled clinical trial to evaluate the safety and PK of ZIKV-IG in healthy non-pregnant volunteer subjects between the ages of 18 to 55 years with blood type O^+ or O^-.

Sample size for ZK-001 was 30 subjects randomized to receive either one dose level of ZIKV-IG (n=19) or placebo (n=11; normal saline), referred to as study medication or treatment.

Dosing of the first 6 eligible subjects was staggered over three days, wherein 2 subjects per day were randomized 1:1 and dosed at least 3 hours apart with ZIKV-IG or placebo. The remaining subjects were randomized 2:1 in 4 cohorts of size 6 subjects. The protocol states that cohorts 2 through 5 were each to be dosed on a single day. However, scheduling constraints resulted in dosing of cohorts 2, 3 and 4 subjects spread over 3 days each (see Section 4.3 definition of cohort). A Safety Monitoring Committee (SMC) was convened after cohort 2 to review safety data through 72 hours post-dosing for the first 12 dosed subjects.

On Day 1, subjects received intravenous (IV) administration of either 50 mL of ZIKV-IG or 50 mL of placebo. The administered dose of ZIKV-IG was planned to be 4650 mg (93 mg/mL * 50 mL).

Each subject was to be followed-up for 85 calendar days post-study treatment administration for safety (adverse events [AEs], laboratory tests, viral markers, vital signs and physical examinations) and pharmacokinetic assessments.

2.3 Study Endpoints

2.3.1 Efficacy Endpoints

There are no efficacy endpoints for this study.

2.3.2 Safety Endpoints

2.3.2.1 Primary Safety Endpoint

The primary safety endpoint is the number and severity of AEs.

2.3.2.2 Secondary Safety Endpoints

Safety is evaluated based on the following endpoints:

- Adverse events
- Laboratory test results (hematology, blood chemistry)
- Viral markers (human immunodeficiency virus 1 and 2 [HIV], hepatitis B and C virus [HBV, HCV], Zika virus [ZIKV] IgM/IgG and nucleic acid testing [NAT] in serum and urine)
- Vital signs
- Physical examinations

2.3.3 Pharmacokinetic Endpoints

Primary PK analysis is based on the validated MagPix anti-ZIKV E-protein binding assay serum antibody concentrations. Analysis parameters include:

- $AUC_{0\text{-}t}$: area under the concentration-time curve from time 0 to the last quantifiable concentration
- $AUC_{0\text{-day }7}$: area under the serum concentration curve from time 0 to 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
- λ_z: 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

PK parameters are calculated using non-compartmental analysis (see Section 7.4).

In addition, results from a second, unvalidated binding assay are investigational only. This assay measures serum concentrations of antibodies that bind recombinant Zika virus non-structural protein 1 (NS1). NS1-binding PK parameters may be calculated if data permit.

Finally, PK parameters derived from ZIKV neutralizing antibody concentrations are estimated as a secondary PK analysis. See Section 7.4 for further details.

2.4 Power and Sample Size Considerations

Sample size for ZK-001 was 30 healthy volunteers; subjects were 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 was a Phase 1 clinical trial evaluating safety and PK of one dose level of ZIKV-IG, 19 subjects treated with the study medication allows for safety evaluation and for calculation of PK parameters.

2.5 Randomization and Blinding

Subjects were randomized by cohort, except that the first 6 subjects (cohort 1A, 1B and 1C) were randomized 1:1 in pairs dosed at least 3 hours apart on the same day over the course of 3 days. The remaining subjects were randomized 2:1 in 4 cohorts of size 6 subjects. The protocol states that cohorts 2 through 5 were each to be dosed on a single day. However, scheduling constraints resulted in dosing of cohorts 2, 3 and 4 subjects spread over 3 days each (see Section 4.3 definition of cohort).

The contract research organization's (CRO) unblinded statistician created the final randomization schedule. A paper copy was shared with unblinded pharmacists at the CRO's Phase 1 clinical site for dispensation. Other unblinded personnel included subcontracted unblinded clinical trial monitors and a segregated sponsor unblinded medical monitor (who subsequently joined the sponsor company during the course of the trial). The segregated sponsor unblinded medical monitor served on the SMC (see Section 8.1). In addition, designated personnel at the sponsor's bioanalytical laboratory assigned to perform PK sample testing were unblinded, but PK data were stored in a protected server location. All other sponsor and CRO personnel involved in the conduct of the trial remained blinded until database lock and unblinding.

Access to information in the Medidata RAVE electronic data capture (EDC) system was blinded using role-based permissions. Randomization group and study treatment dispensing data were integrated with the clinical database prior to database lock, but unblinding data were removed from blinded data extracts by the CRO until after database lock to ensure maintenance of the blind. Study treatment dosing data were reconciled with the randomized treatment group for each subject by the unblinded monitors, and any deviations were reported in a separate repository from the blinded EDC.

Data external to the EDC included safety laboratory test results and PK concentration data. Laboratory data were converted to Study Data Tabulation Model (SDTM) datasets and were not considered unblinding. PK concentration data, considered unblinding, were retained by the sponsor's bioanalytical laboratory until after database lock and unblinding, when they were converted to SDTM for analysis and inclusion in the Clinical Study Report (CSR).

3 DATA CONSIDERATIONS

3.1 Protocol Deviations

Protocol deviations (PDs) were documented by the monitors and captured directly in the EDC; there were no unblinding PDs. There is no Clinical Trial Management System (CTMS) for the ZK-001 study.

PDs were graded as minor, major or critical. Minor PDs are defined as those that do not impact subject safety or the statistical analysis. Major PDs are those that potentially affect subject safety or the quality of the data evaluation. Critical PDs are those that do affect a subject's rights or safety or the quality of the data evaluation, or that show a pattern indicating intentional unauthorized deviation or fraud. PDs were categorized as follows:

- Missed procedures/assessments
- Procedures/assessments outside protocol window
- Order of procedures/assessments
- Missed visit
- Visit outside protocol window
- Inclusion/exclusion
- Randomization
- Informed consent
- Study drug administration
- Documentation
- Study restrictions
- Other

3.2 Analysis Populations

Safety Population: The safety population includes all subjects who receive any amount of study medication (ZIKV-IGIV or placebo) per the clinical database. In the case of incorrect treatment administration, subjects are analyzed according to the treatment received. The safety population is the primary analysis population for all non-PK analyses.

PK Population: The PK population includes subjects who have adequate PK data for analysis (a pre-dose sample and at least one measurable post-dose sample), are ZIKV-negative by NAT and serology testing and have a suitably low level of baseline anti-ZIKV E-protein binding antibodies. Subjects who exceed a threshold level of baseline anti-ZIKV E-protein binding antibodies, to be determined after database lock, may be excluded from PK analysis. Subjects are analyzed according to the treatment received.

3.3 Multicenter Study

This study was conducted at a single Phase 1 clinical center, located in Toronto, Ontario, Canada.

3.4 Analysis Time Points

Scheduled visits and assessment time points in the study include the following (see Table 1):

- Screening
- Baseline
- Day 1 – 2 hr pre-dose, 1 hr pre-dose, 15 min after start of dosing, end of dosing and 1, 3 and 8 hr post-dosing
- Day 2 – 24 hr post-dosing
- Day 3 – 48 hr post-dosing
- Day 4 – 72 hr post-dosing
- Day 6 – 120 hr post-dosing
- Day 8 – 168 hr post-dosing
- Day 10 – 216 hr post-dosing
- Day 12 – 264 hr post-dosing
- Day 15 – 336 hr post-dosing
- Day 22 – 504 hr post-dosing
- Day 29 – 672 hr post-dosing
- Day 43 – 1008 hr post-dosing
- Day 57 – 1344 hr post-dosing
- Day 85 or early withdrawal – 2016 hr post-dosing

Early withdrawal data is not windowed to a scheduled visit and may be summarized separately as its own visit in selected tabulations.

3.5 Definition of Baseline

Baseline data are defined as the latest data collected prior to study medication dosing (ZIKV-IGIV or placebo).

3.6 Treatment Groups

Tables are presented by treatment group: ZIKV-IG or placebo. A total column is included for selected tables.

3.7 Coding Dictionaries

Medical history and AEs are coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 21.0.

Concomitant medications are coded to preferred drug name using World Health Organization Drug Dictionary (WHO-DD) version March 2018. Anatomic therapeutic class coding is not performed.

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Table 1 Schedule of Events

	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	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]
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

	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
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 (±12 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 will be performed by the Phase 1 clinic's reference laboratory, except for ZIKV IgG serology (screening and baseline samples) which will be performed by the sponsor's ZIKV IgG binding assay. The sponsor will evaluate subjects' PK samples with two in-house assays (a binding ZIKV antibody assay and a neutralizing ZIKV antibody assay).

4 STATISTICAL ANALYSIS

4.1 Statistical Software

Statistical analyses are implemented using SAS® v9.4 or higher.

4.2 Summary Statistics

Continuous endpoints are summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum and maximum. Categorical endpoints are summarized by the number of subjects, frequency and percentage. Precision is rounded to the number of decimal places in the original data, except mean and SD are rounded to one additional decimal place.

4.3 Derived Variables

This section provides definitions of the derived variables. In some cases, the definitions are provided in the relevant sections.

Age in years is defined as integer part of ([date of informed consent – date of birth] / 365.25). If date of informed consent is missing or partial, then the screening visit date will be used.

AEs of special interest (AESI) is defined as a preferred term in the modified Standard MedDRA Query (SMQ) lists contained in Appendix I, Section 10. These include the following categories: hypersensitivity, acute renal dysfunction/failure, aseptic meningitis syndrome, hemolysis or hemolytic anemia, thrombotic events and transfusion-related acute lung injury.

Analysis populations (see Section 3.2)

Body mass index (BMI) is defined as weight (kg) divided by height squared (m^2).

Change from baseline is defined as (value at post-baseline assessment – value at baseline). Percent change from baseline is defined as (change from baseline / value at baseline) * 100.

Cohort is not collected in the case report form (CRF) but derived as follows based on randomization date and time:

- Cohort 1 comprises the first 6 subjects randomized. Two subjects per day dosed on 3 separate days are cohorts 1A, 1B and 1C, respectively (subjects 021 and 040 for 1A, 030 and 013 for 1B and 038 and 049 for 1C).
- Cohort 2 comprises the second 6 subjects randomized. Two subjects per day were dosed on 3 separate days (subjects 080 and 085 for 2A, 127 and 129 for 2B and 160 and 171 for 2C).
- Cohort 3 comprises the third 6 subjects randomized. One subject was dosed (subject 198 for 3A), then 3 subjects were dosed (subjects 197, 210 and 212 for 3B) and 2 subjects were dosed (subject 224 and 225 for 3C) on 3 separate days.

- Cohort 4 comprises the fourth 6 subjects randomized. Two subjects (subjects 226 and 232 for 4A) were dosed on the same day as the last 2 subjects in Cohort 3. Three subjects were dosed (subjects 088R, 231 and 240 for 4B) and one more subject was dosed (subject 249 for 4C) on 2 separate days.
- Cohort 5 comprises the last 6 subjects randomized. All 6 subjects were dosed on the same day as the last subject in Cohort 4 (subjects 273, 274, 277, 284, 001R and 309 for 5A).

Completion of study is defined as no primary reason for study discontinuation present on the end of study CRF page. The question, "Did the subject complete the study per protocol?" is not used because this question may be answered no for a completed subject with a PD.

Concomitant medication is defined as a medication that either starts before dosing and is ongoing at the study treatment dosing start time or a medication that starts during the study. If medication start or end date or start or end time is missing or partial, then any medication that could be concomitant is counted as concomitant.

Duration of infusion is defined as the difference between end time and start time of infusion (minus any interruption time) in minutes.

Exposure, total = defined as total volume (mL) administered.

One month = (365.25/12) days = 30.4375 days.

PDs (see Section 3.1)

Study Day 1 is defined as the day of study treatment administration. The day prior to the study treatment infusion day is Day -1. There is no Day 0.

Study day = (assessment date – Day 1 date + 1) if the assessment is on or after the date of study drug administration. Study day = (assessment date – Day 1 date) if the assessment is before the date of study drug administration.

Study medication or study treatment = ZIKV-IG or placebo.

Treatment, actual is defined as the actual treatment given field on the study drug administration CRF.

Treatment-emergent AE = not defined for this study because AEs are collected only during or after study drug administration (i.e., all AEs are treatment-emergent).

Treatment, randomized is defined as the treatment assigned to the subject on the randomization schedule.

4.4 Statistical Hypotheses

Study ZK-001 was designed to assess safety of ZIKV-IG in healthy volunteers by examining the number and severity of AEs. No statistical hypotheses are tested for AE and serious AE (SAE) data.

4.5 Handling of Missing Data

For PK and laboratory data, values reported as below the limit of detection (LOD) are substituted with LOD/2; values reported as ">xx" or "<xx" are substituted with xx.

No other imputation rules are used, and no dates are imputed.

4.6 Adjustment for Covariates

Not applicable because no formal hypothesis is being tested.

4.7 Subgroup Analysis

For AE and SAE incidences, no formal subgroup analyses is performed.

4.8 Multiplicity Adjustment

Not applicable due to no formal hypothesis tests being conducted.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject Disposition

Subject disposition, including early withdrawal reasons, are summarized and presented by treatment group for all randomized subjects. Tabulations include number of subjects randomized to the treatment, number of subjects who discontinued prior to study treatment administration and the reasons for early withdrawal and number of subjects who discontinued prior to completion of all study visits and the reasons for early withdrawal. Disposition data are listed by subject. In addition, subject membership in each analysis population is tabulated by treatment group as well as listed for the safety population. A disposition flow chart is provided.

5.2 Protocol Deviations

All PDs defined in Section 3.1 are presented by treatment group for the safety population. All PDs are listed.

5.3 Demographics and Other Baseline Characteristics

5.3.1 Demographics

Demographic variables include: age (see definition in Section 4.3), sex, whether or not subject is female of child-bearing potential, race and ethnicity, height, baseline weight, body mass index (BMI; see definition in Section 4.3) and blood type (O^+ or O^-). These variables are summarized using descriptive statistics by treatment group for the safety population and are listed. Eligibility data is listed only.

5.3.2 Baseline Viral Markers

Screening serology results for dengue virus (DENV) and West Nile virus (WNV) pass or fail, are reported along with baseline ZIKV NAT results for serum and urine and baseline ZIKV IgM and IgG serology results. These variables are summarized using descriptive statistics by treatment group for the safety population and are listed.

5.3.3 Medical History

Medical history is coded to system organ class and preferred term using MedDRA dictionary version 21.0 and is tabulated for each system organ class and preferred term using frequency counts by treatment group for the safety population. Each subject is counted once in each system organ class and preferred term even if multiple events in that category occurred for the subject. Medical history is listed.

5.3.4 Screening Smoking History

Smoking history is solicited from each subject at screening and includes whether the subject currently smokes. If the subject is a current smoker the type (cigarettes or e-cigarettes) is recorded as well as the number of units per day. Smoking history results are listed only.

5.3.5 Breath Alcohol Test at Screening and Baseline

Breath alcohol test is performed for each subject at screening and baseline visits and includes if the test was performed, if not performed reason why and result of the test (positive or negative). Breath alcohol test results are listed only.

5.3.6 Urine Drug Test at Screening and Baseline

Urine drug test is performed for each subject at screening and baseline visits and includes if the test was performed, if not performed reason why, test name (amphetamine, benzodiazepine, cannabinoids, cocaine, opiates, oxycodone) and result of the test (positive or negative). Urine drug screen results are listed only.

5.3.7 Pregnancy Test at Screening and Baseline

Serum pregnancy test and follicle stimulating hormone (FSH) results at screening and baseline visits for female subjects of child-bearing potential are listed only.

5.3.8 Screening Urinalysis

Clinical laboratory tests for urine are performed at screening. Parameters to be tested include red blood cells, white blood cells, blood, bacteria, specific gravity, pH, glucose, bilirubin, urobilinogen, ketones, protein, nitrite, leukocyte esterase and squamous epithelial cells.

Assessments include whether a urine sample was collected, if not reason why, and the investigator's interpretation of these parameters as clinically significant or not clinically significant. Urinalysis results are listed only.

5.3.9 Screening Electrocardiogram

Electrocardiogram (ECG) test including ventricular rate, PR interval, QRS duration, QT interval, QTcF interval, and QTcB interval (see List of) is performed at screening. Assessments include whether the test was performed, if not reason why and the investigator's interpretation of these parameters as normal, abnormal but not clinically significant, or abnormal and clinically significant. ECG test results are listed only.

5.3.10 Concomitant Medications

Concomitant medications are coded to preferred drug name using WHO-DD March 2018. Concomitant medications are tabulated for the safety population by preferred drug name and by treatment group.

6 EFFICACY ANALYSIS

There is no efficacy analysis for this study.

7 SAFETY ANALYSIS

7.1 Extent of Exposure

The following study treatment (ZIKV-IG or placebo) infusion variables are summarized by treatment group for the safety population:

- Was study drug administered (yes or no)?
- Status of infusion (complete or incomplete).
- Was infusion interrupted (yes or no)?
- Total volume infused (mL).
- Duration of infusion (min).
- Randomized treatment (ZIKV-IG or placebo).

Study drug administration data are listed.

Treatment compliance is not applicable to this study since the investigational treatment is administered as a single dose only in the clinic on Day 1.

7.2 Primary Safety Analysis

7.2.1 Adverse Events

AEs are coded to system organ class and preferred term using MedDRA dictionary version 21.0. AEs are summarized by treatment group for the safety population, including the following AE summary tables:

- AEs by system organ class and preferred term (includes serious and nonserious AEs)

- AEs by system organ class, preferred term, and maximum severity (includes serious and nonserious AEs)
- Treatment-related AEs by system organ class and preferred term (includes serious and nonserious AEs)
- Serious AEs
- Treatment-related serious AEs by system organ class and preferred term
- AEs of special interest (see definition in Section 4.3)

Each subject is counted once in each system organ class and preferred term even if multiple events in that category occurred for the subject. Assessment of causality is reported in the EDC as related or not related/no relationship. AEs where the causality assessment is missing after querying are excluded from summaries by relationship to study treatment. Assessment of severity is collected in the EDC as mild, moderate or severe. AEs with missing severity assessment after querying are excluded from summaries by severity.

7.3 Secondary Safety Analysis

7.3.1 Clinical Laboratory Tests

Laboratory values for hematology include white blood cell count, neutrophils, lymphocytes, monocytes, eosinophils, basophils, neutrophils, blood smear (morphology: platelets, red blood cells, white blood cells), hemoglobin, hematocrit, red blood cells, and platelets. Laboratory values for blood chemistry include 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.

At each scheduled visit, values and change from baseline to each scheduled visit are summarized by treatment group for the safety population using descriptive statistics. The number and percentage of study subjects with hematology values clinically significantly outside the normal range at any time on study are summarized. Clinical laboratory data are listed.

7.3.2 Viral Markers

Viral marker testing including HIV serology, HBV HBsAg, HCV serology, DENV serology, WNV serology, ZIKV NAT (serum, urine) and ZIKV serology (IgM and IgG) are performed at screening and at Day 85/ early withdrawal. ZIKV NAT (serum, urine) and ZIKV IgM and IgG serology testing results are updated at baseline. The test result (pass/fail) is summarized using frequency counts by treatment group for the safety population at each visit. Viral marker results are listed.

7.3.3 Vital Signs

Vital signs data include sitting systolic blood pressure, sitting diastolic blood pressure, respiratory rate, pulse, oral temperature and pulse oximetry. The investigator's interpretation of these parameters as normal, abnormal but not clinically significant, or abnormal and clinically significant is also collected. Vital signs at each scheduled visit and time point and change from

baseline to each scheduled visit and time point are summarized by treatment group for the safety population using descriptive statistics. The number and percentage of study subjects with vital signs values assessed as clinically significantly abnormal at any time on study are summarized. Vital signs data are listed.

7.3.4 Physical Examinations

A complete physical examination including general appearance, eye, ear, nose, throat, head and neck, respiratory, cardiovascular, gastrointestinal, musculoskeletal, dermatological, peripheral vascular, lymphatic, neurological, and mental status is performed at screening, baseline and upon study completion/ early withdrawal. Assessments include the investigator's interpretation of these parameters as normal, abnormal but not clinically significant, or abnormal and clinically significant. Physical examination results are listed only.

7.4 Pharmacokinetic Analyses

PK analyses are based on serum concentrations of binding and neutralizing ZIKV antibodies as described in this section. All PK analyses include placebo subjects as well as ZIKV-IG subjects due to background antibody levels.

7.4.1 Anti-ZIKV E-protein Binding Antibodies

The primary binding assay is a validated MagPix assay targeting anti-ZIKV antibodies that bind a recombinant Zika virus glycoprotein (E-protein). PK analysis using data from this assay comprises the primary PK analysis.

Serum concentration versus time data are analyzed by standard non-compartmental methods (i.e., linear trapezoidal method). Actual times and not nominal times are used in the analysis, and concentrations below the LOD are imputed as half of this value. The following PK parameters are calculated using non-compartmental analysis:

- $AUC_{0\text{-}t}$: area under the concentration-time curve from time 0 to the last quantifiable concentration
- $AUC_{0\text{-day }7}$: area under the serum concentration curve from time 0 to 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
- λ_z: 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

PK concentrations by visit and time point as well as calculated PK parameters are reported using descriptive statistics for the PK population by treatment group, including the placebo group, for E-protein binding antibodies. Serum concentration-time data are plotted by treatment group means ± standard deviation for E-protein binding antibodies, and individual subject profiles are provided. PK concentration and parameter data are listed.

7.4.2 Anti-ZIKV NS1 Binding Antibodies

An unvalidated, experimental MagPix binding assay measures serum concentrations of antibodies that bind to a recombinant Zika virus NS1 protein. PK analysis using data from this assay are investigational only. NS1-binding PK parameters may be calculated as described above if data permit.

7.4.3 Anti-ZIKV Neutralizing Antibodies

The neutralization assay is an xCelligence functional assay that assesses the ability of anti-ZIKV antibodies to kill the virus. PK analysis using data from this assay are considered secondary. PK parameters derived from ZIKV neutralizing antibody concentrations are estimated as described above.

8 SAFETY MONITORING COMMITTEE AND INTERIM ANALYSES

8.1 Safety Monitoring Committee

An 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 (who subsequently joined the sponsor company during the course of the trial) may recommend stopping the trial if the safety review identifies unforeseen adverse effects that impact subject safety.

The SMC process is further outlined in the Medical Monitoring Plan for this study. Strict procedures governing handling of unblinded data are in place to maintain the integrity of the study blind (see Section 2.5).

8.2 Interim Analyses

No interim analysis is planned.

9 REFERENCES

None.

10 APPENDIX I AESI PREFERRED TERM LIST

10.1 Preferred Terms for Modified Hypersensitivity SMQ

Acute generalised exanthematous pustulosis
Administration related reaction
Administration site dermatitis
Administration site eczema
Administration site hypersensitivity
Administration site rash
Administration site urticaria
Allergic bronchitis
Allergic cough
Allergic eosinophilia
Allergic hepatitis
Allergic keratitis
Allergic myocarditis
Allergic oedema
Allergic otitis media
Allergic pharyngitis
Allergic reaction to excipient
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Allergic transfusion reaction
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Arthritis allergic
Aspirin-exacerbated respiratory disease
Atopy
Blepharitis allergic
Bronchospasm
Circumoral oedema
Conjunctival oedema
Conjunctivitis allergic
Corneal oedema
Dermatitis
Dermatitis acneiform

Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis psoriasiform
Drug eruption
Drug hypersensitivity
Drug reaction with eosinophilia and systemic symptoms
Eczema
Eczema nummular
Eczema vesicular
Eczema weeping
Encephalitis allergic
Encephalopathy allergic
Epidermal necrosis
Epidermolysis
Epidermolysis bullosa
Epiglottic oedema
Erythema multiforme
Erythema nodosum
Exfoliative rash
Eye allergy
Eye oedema
Eye swelling
Eyelid oedema
Face oedema
Fixed eruption
Giant papillary conjunctivitis
Gingival oedema
Gingival swelling
Gleich's syndrome
Haemorrhagic urticaria
Hand dermatitis
Henoch-Schonlein purpura
Henoch-Schonlein purpura nephritis
Hypersensitivity
Hypersensitivity myocarditis
Hypersensitivity vasculitis
Idiopathic urticaria
Immediate post-injection reaction
Immune-mediated adverse reaction

Infusion related reaction
Infusion site dermatitis
Infusion site eczema
Infusion site hypersensitivity
Infusion site rash
Infusion site recall reaction
Infusion site urticaria
Infusion site vasculitis
Injection related reaction
Injection site dermatitis
Injection site eczema
Injection site hypersensitivity
Injection site rash
Injection site recall reaction
Injection site urticaria
Injection site vasculitis
Interstitial granulomatous dermatitis
Intestinal angioedema
Kounis syndrome
Laryngeal oedema
Laryngitis allergic
Laryngospasm
Laryngotracheal oedema
Limbal swelling
Lip oedema
Lip swelling
Mouth swelling
Mucocutaneous rash
Multiple allergies
Nephritis allergic
Nodular rash
Oculomucocutaneous syndrome
Oculorespiratory syndrome
Oedema mouth
Oral allergy syndrome
Oropharyngeal blistering
Oropharyngeal oedema
Oropharyngeal spasm
Oropharyngeal swelling
Palatal oedema
Palatal swelling
Palisaded neutrophilic granulomatous dermatitis

Palpable purpura
Perioral dermatitis
Periorbital oedema
Pharyngeal oedema
Pruritus allergic
Rash
Rash erythematous
Rash follicular
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to excipient
Rhinitis allergic
Scleral oedema
Scleritis allergic
Scrotal oedema
Serum sickness
Serum sickness-like reaction
Skin necrosis
Skin reaction
Skin test positive
Stevens-Johnson syndrome
Swelling face
Swollen tongue
Symmetrical drug-related intertriginous and flexural exanthema
Therapeutic product cross-reactivity
Tongue oedema
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal oedema
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction

Type IV hypersensitivity reaction
Urticaria
Urticaria papular
Urticaria pigmentosa
Urticaria vesiculosa
Urticarial vasculitis
Vessel puncture site rash
Vessel puncture site vesicles
Asthma
Asthma late onset
Asthmatic crisis
Auricular swelling
Bronchial hyperreactivity
Bronchial oedema
Ear swelling
Eosinophilic bronchitis
Erythema
Flushing
Generalised erythema
Generalised oedema
Genital rash
Genital swelling
Haemolytic transfusion reaction
Localised oedema
Oedema mucosal
Orbital oedema
Penile oedema
Penile swelling
Perineal rash
Pneumonitis
Pruritus
Pruritus generalised
Respiratory tract oedema
Scrotal swelling
Seasonal allergy
Skin swelling
Sneezing
Status asthmaticus
Wheezing

10.2 Preferred Terms for Modified Renal Dysfunction SMQ

Glomerular vascular disorder

Hypertensive nephropathy
Ischaemic nephropathy
Malignant renal hypertension
Nephroangiosclerosis
Page kidney
Renal aneurysm
Renal arteriosclerosis
Renal arteritis
Renal artery arteriosclerosis
Renal artery dissection
Renal artery fibromuscular dysplasia
Renal artery hyperplasia
Renal artery occlusion
Renal artery perforation
Renal artery stenosis
Renal artery thrombosis
Renal embolism
Renal hypertension
Renal infarct
Renal ischaemia
Renal vascular thrombosis
Renal vasculitis
Renal vein embolism
Renal vein occlusion
Renal vein stenosis
Renal vein thrombosis
Renal vein varices
Renal vessel disorder
Renovascular hypertension
Renal cortical necrosis
Renal necrosis
Renal papillary necrosis
Renal tubular necrosis

10.3 Preferred Terms for Modified Aseptic Meningitis Syndrome SMQ

Meningitis aseptic

10.4 Preferred Terms for Modified Hemolysis SMQ

Acute haemolytic transfusion reaction
Autoimmune haemolytic anaemia
Cold type haemolytic anaemia
Coombs direct test positive

Coombs indirect test positive
Coombs negative haemolytic anaemia
Coombs positive haemolytic anaemia
Coombs test positive
Delayed haemolytic transfusion reaction
Extravascular haemolysis
Haemoglobin urine present
Haemoglobinaemia
Haemoglobinuria
Haemolysis
Haemolytic anaemia
Haemolytic transfusion reaction
Haptoglobin decreased
Intravascular haemolysis
Warm type haemolytic anaemia

10.5 Preferred Terms for Modified Thrombosis SMQ

Amaurosis
Amaurosis fugax
Aortic thrombosis
Arterial occlusive disease
Arterial thrombosis
Basal ganglia infarction
Basilar artery occlusion
Basilar artery thrombosis
Blindness transient
Brachiocephalic artery occlusion
Carotid arterial embolus
Carotid artery occlusion
Carotid artery thrombosis
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery thrombosis
Coronary artery embolism
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery thrombosis
Embolism arterial
Femoral artery embolism
Hepatic artery embolism

Hepatic artery occlusion
Hepatic artery thrombosis
Iliac artery embolism
Iliac artery occlusion
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Leriche syndrome
Mesenteric arterial occlusion
Mesenteric arteriosclerosis
Mesenteric artery embolism
Mesenteric artery thrombosis
Myocardial infarction
Myocardial necrosis
Papillary muscle infarction
Penile artery occlusion
Peripheral arterial occlusive disease
Peripheral arterial reocclusion
Peripheral artery occlusion
Peripheral artery thrombosis
Peripheral embolism
Popliteal artery entrapment syndrome
Post procedural myocardial infarction
Postinfarction angina
Precerebral artery occlusion
Precerebral artery thrombosis
Pulmonary artery occlusion
Pulmonary artery thrombosis
Renal artery occlusion
Renal artery thrombosis
Renal embolism
Retinal artery embolism
Retinal artery occlusion
Retinal artery thrombosis
Silent myocardial infarction
Spinal artery embolism
Spinal artery thrombosis
Splenic artery thrombosis
Splenic embolism
Subclavian artery embolism
Subclavian artery occlusion
Subclavian artery thrombosis

Superior mesenteric artery syndrome
Thrombotic microangiopathy
Thrombotic thrombocytopenic purpura
Transient ischaemic attack
Truncus coeliacus thrombosis
Vascular pseudoaneurysm thrombosis
Vertebral artery occlusion
Vertebral artery thrombosis
Axillary vein thrombosis
Brachiocephalic vein occlusion
Brachiocephalic vein thrombosis
Budd-Chiari syndrome
Cavernous sinus thrombosis
Cerebral venous thrombosis
Deep vein thrombosis
Deep vein thrombosis postoperative
Embolism venous
Hepatic vein embolism
Hepatic vein occlusion
Hepatic vein thrombosis
Homans' sign positive
Iliac vein occlusion
Inferior vena cava syndrome
Inferior vena caval occlusion
Intracranial venous sinus thrombosis
Jugular vein occlusion
Jugular vein thrombosis
Mesenteric vein thrombosis
Mesenteric venous occlusion
Obstetrical pulmonary embolism
Obstructive shock
Ophthalmic vein thrombosis
Ovarian vein thrombosis
Pelvic venous thrombosis
Penile vein thrombosis
Portal vein occlusion
Portal vein thrombosis
Portosplenomesenteric venous thrombosis
Post procedural pulmonary embolism
Post thrombotic syndrome
Postoperative thrombosis
Postpartum venous thrombosis

Pulmonary embolism
Pulmonary infarction
Pulmonary microemboli
Pulmonary thrombosis
Pulmonary vein occlusion
Pulmonary veno-occlusive disease
Pulmonary venous thrombosis
Renal vein embolism
Renal vein occlusion
Renal vein thrombosis
Retinal vein occlusion
Retinal vein thrombosis
Splenic vein occlusion
Splenic vein thrombosis
Subclavian vein occlusion
Subclavian vein thrombosis
Superior sagittal sinus thrombosis
Superior vena cava occlusion
Superior vena cava syndrome
Thrombosed varicose vein
Thrombosis corpora cavernosa
Transverse sinus thrombosis
Vena cava embolism
Vena cava thrombosis
Venooccclusive disease
Venoocclusive liver disease
Venous occlusion
Venous thrombosis
Venous thrombosis in pregnancy
Venous thrombosis limb
Visceral venous thrombosis
Administration site thrombosis
Adrenal thrombosis
Application site thrombosis
Arteriovenous fistula occlusion
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Atrial thrombosis
Basal ganglia stroke
Bone infarction
Brain stem embolism
Brain stem infarction

Brain stem stroke
Brain stem thrombosis
Cardiac ventricular thrombosis
Catheter site thrombosis
Cerebellar embolism
Cerebellar infarction
Cerebral infarction
Cerebral ischaemia
Cerebral microembolism
Cerebral septic infarct
Cerebral thrombosis
Cerebral vascular occlusion
Cerebrospinal thrombotic tamponade
Cerebrovascular accident
Choroidal infarction
Coronary bypass thrombosis
Disseminated intravascular coagulation
Embolic cerebral infarction
Embolic pneumonia
Embolic stroke
Embolism
Graft thrombosis
Haemorrhagic adrenal infarction
Haemorrhagic cerebral infarction
Haemorrhagic infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Haemorrhoids thrombosed
Heparin-induced thrombocytopenia
Hepatic infarction
Hepatic vascular thrombosis
Infarction
Infusion site thrombosis
Inner ear infarction
Intestinal infarction
Intracardiac thrombus
Mesenteric vascular occlusion
Microembolism
Optic nerve infarction
Pancreatic infarction
Paradoxical embolism
Paraneoplastic thrombosis

Pituitary infarction
Placental infarction
Post procedural stroke
Postpartum thrombosis
Prosthetic cardiac valve thrombosis
Renal infarct
Renal vascular thrombosis
Retinal infarction
Retinal vascular thrombosis
Shunt occlusion
Shunt thrombosis
Spinal cord infarction
Splenic infarction
Splenic thrombosis
Stoma site thrombosis
Stroke in evolution
Testicular infarction
Thalamic infarction
Thromboangiitis obliterans
Thrombosis
Thrombosis mesenteric vessel
Thrombotic cerebral infarction
Thrombotic stroke
Thyroid infarction
Tumour embolism
Tumour thrombosis

10.6 Preferred Terms for Modified Transfusion-related Acute Lung Injury SMQ

Acute respiratory distress syndrome
Non-cardiogenic pulmonary oedema
Transfusion-related acute lung injury
Acute lung injury