Clinical Trial Protocol

A Randomized, Double-Blind, Placebo-Controlled Dose Ranging Study Evaluating the Safety, Pharmacokinetics and Clinical Benefit of FLU-IGIV in Hospitalized Patients with Serious Influenza A Infection

IA-001

Version 5.0

24 January 2019

NCT03315104

Emergent BioSolutions Canada Inc.

[redacted] **Manitoba R3T 5Y3**

CONFIDENTIAL

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Trial Sponsor: Emergent BioSolutions Canada Inc.
[redacted] MB R3T 5Y3

Contract Research Organization: SGS North America Inc.
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Signatory Page

IA-001 Version 5.0: A Randomized, Double-Blind, Placebo-Controlled Dose Ranging Study Evaluating the Safety, Pharmacokinetics and Clinical Benefit of FLU-IGIV in Hospitalized Patients with Serious Influenza A Infection

Clinical Site(s):

Name:

Address:

Tel:

E-mail:

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 in compliance with these regulations, documents and guidances.

Site Principal Investigator:

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

Sponsor Signatory:

Emergent BioSolutions Canada Inc.

[redacted]

Canada R3T 5Y3

[redacted] 2019/[redacted]

Date (YYYY/MMM/DD)

IA-001 Protocol Synopsis

Title	A Randomized, Double-Blind, Placebo-Controlled Dose Ranging Study Evaluating the Safety, Pharmacokinetics and Clinical Benefit of FLU-IGIV in Hospitalized Patients with Serious Influenza A Infection
Sponsor	Emergent BioSolutions Canada Inc. [redacted]MB R3T 5Y3
Trial Start	Q4 2017
Objectives	The primary objective is to determine the optimal dose of FLU-IGIV based upon evaluation of safety and pharmacokinetics (PK) in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection. The secondary objective is to evaluate the clinical benefit of FLU-IGIV in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection.
Subject Population	Patients 18 years of age or older hospitalized with serious illness caused by laboratory-confirmed influenza A infection.
Sample Size	75 (randomized 1:1:1)
Number of Trial Sites	Approximately 60 globally
Test Product	Anti-Influenza Immunoglobulin Intravenous (Human) or FLU-IGIV, is a purified immunoglobulin preparation containing a standardized amount of antibody to influenza A virus.
Reference Product	Placebo: 500 mL bag normal saline without modifications.
Dosage	Patients will be assigned into one of the three arms based on their randomization to the study treatment as follows: Arm 1: 5 vials (low dose 225 mL diluted to 500 mL with saline) FLU-IGIV; or Arm 2: 10 vials (high dose 450 mL diluted to 500 mL with saline) FLU-IGIV; or Arm 3: Placebo: 500 mL normal saline. FLU-IGIV will be administered as a single, fixed dose by volume.

	FLU-IGIV, and placebo will be administered by intravenous infusion as follows: • Starting infusion rate of 1.0 mL/min for first 30 minutes; • Incremental infusion rate if tolerated (every 15-30 minutes) of 1.0 mL/min; • Maximum Infusion Rate of 4.0 mL/min. The duration of infusion for 500 mL will be approximately 3 hours.
Protocol Design	A multi-center, double-blind, randomized, placebo-controlled, 3 arm design. For participants in all three assigned treatment groups, the randomized treatment will be administered in addition to Standard of Care (SOC). Based on current CDC guidance on Treatment Considerations for Patients Hospitalized with Suspected or Confirmed influenza (or equivalent), SOC will include a minimum 5 day course of oseltamivir 75 mg/twice a day (1), (2). Eligible patients will be randomized in a 1:1:1 ratio to receive either a low dose (5 vials) FLU-IGIV or high dose (10 vials) FLU-IGIV or placebo.
Inclusion Criteria	• Provision of voluntary informed consent in writing by patient, or legally authorized representative. • Age ≥ 18 years old. • Locally determined positive influenza A infection (Rapid Antigen (Ag) Test or PCR) from a specimen obtained within 2 days prior to randomization. • Onset of symptoms ≤ 6 days before randomization, defined as when the patient first experienced at least one respiratory symptom or fever. • Hospitalized (or in observation unit) with influenza, with anticipated hospitalization for more than 24 hours and will be/already are receiving CDC recommended antiviral SOC (oseltamivir 75 mg/twice a day x 5 days; Section 4.1.1). • Experiencing ≥ 1 respiratory symptom (ex. cough, sore throat, nasal congestion) and ≥ 1 constitutional symptom (ex. headache, myalgia, feverishness or fatigue). • For women of child-bearing potential: Through Day 60 of the study, willingness to use of at least 1 form of hormonal or barrier contraception or willingness to abstain from sexual intercourse [abstinence is not applicable to Spain].

	• Willingness to have blood and respiratory samples obtained and stored. • National Early Warning Score (NEW score) ≥ 3 at screening.

Exclusion Criteria	• Use of any investigational product within the past 30 days prior to screening.
	• History of hypersensitivity to blood or plasma products (as judged by the site investigator) or hypersensitivity to FLU-IGIV excipients (maltose, polysorbate 80).
	• History of allergy to latex or rubber.
	• Known medical history of IgA deficiency.
	• Pregnancy or lactation.
	• Medical conditions for which receipt of a 500 mL volume of intravenous fluid may be dangerous to the patient (e.g. decompensated congestive heart failure), based on investigator's medical opinion with careful consideration of lab results.
	  • Liver function LFT > 2.5 times ULN.
	  • Renal Function GFR < 60 mL/min/1.73 m^2 (age and sex adjusted).
	• A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk of thrombosis (e.g. cryoglobulinemia, severe refractory hypertriglyceridemia, or clinically significant monoclonal gammopathy).
	• An opinion of the investigator that it would be unwise to allow participation of the patient in the study (the reason for exclusion of the patient must be documented).
	• Receiving extracorporeal membrane oxygenation (ECMO).
	• Anticipated life expectancy of < 90 days.
	• Confirmed bacterial pneumonia or any concurrent respiratory viral infection that is not influenza A (ex. respiratory syncytial virus (RSV) infection).

Site Enrollment Duration	18-19 months
Participant Duration	2 months

Study Procedures and Assessments	**Screening (within 48 hours of Baseline)**
	• Informed consent.
	• Eligibility assessment.
	• Demographic assessment.
	• Medical history.
	  • Including confirmation of influenza A infection (see local labs markers of viral infection below).
	• Physical examination.
	• Vital signs (including flu symptoms).
	• NEW score assessment.
	• Concomitant medications.
	• Local lab:
	  • Markers of Viral Infection: Nasopharyngeal (NP) swab sample collection for local influenza A test (Rapid Ag Test or PCR) if not already completed as part of SOC assessment.
	  • Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
	  • Blood chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.
	• Central lab:
	  • Markers of Viral Infection/Viral Load sample collection: NP swab for laboratory confirmation of influenza A infection followed by viral load assessment by both RT-qPCR and viral culture, and additional testing to identify strain.
	• For women of child-bearing potential, a serum pregnancy test.
	
	Day 1/Baseline (Pre-Infusion)
	Prior to randomization, the following assessments must be completed:
	• Medical history (update as required from screening).
	• Physical examination (if screening and baseline do not occur on the same day).
	• Vital signs (including flu symptoms; if screening and baseline do not occur on the same day).

	• Hospital admission status.
	• Ordinal Scale assessment.
	• NEW score assessment.
	• Concomitant medications.
	• Local lab (if screening and baseline do not occur on the same day):
	  • Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
	  • Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.
	• Central lab (if screening and baseline do not occur on the same day):
	  • Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture.
	  • Pre-infusion PK sample collection: serum sample for pre-infusion hemagglutination inhibition (HAI) and micro-neutralization (MN) analysis.
	Randomization
	Randomization occurs as soon as possible (within 48 hours) after screening and Day 1 Baseline Pre-Infusion assessments are complete. Randomization should be performed as close as possible to the time of infusion. Whether or not the subject is dosed, he/she will be followed as part of the Intent to Treat (ITT) population through Day 60, see Section 9.1.3.
	Treatment Infusion
	Refer to above section on Dosage for the study treatment.
	Day 1 (Post-Infusion)
	After administration of study treatment the following assessments must be performed (within 4 hours from the end of study treatment infusion):
	• Vital signs (including flu symptoms).
	• Adverse events (AEs) & unanticipated problems.
	• Concomitant medications.
	• NEW score assessment.
	• Central Lab:

	• Post-infusion PK sample collection: **within 90 minutes after completion of study treatment infusion**, serum sample for HAI and MN analysis.
	
	Patients will be followed through Day 60 after randomization. Study visits and related procedures are to be done at the same point in time in which the study treatment infusion was completed, within the window specified for each particular visit as follows:
	
	Day 2 (+/- 4 hours; if hospitalized)
	• Ordinal Scale assessment.
	• Vital signs (including flu symptoms).
	• NEW score assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	• Local lab:
	  • Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
	  • Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.
	• Central lab:
	  • Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture.
	  • PK sample collection: serum sample for HAI and MN analysis.
	Day 3 (+/- 4 hours; if hospitalized)
	• Ordinal Scale assessment.
	• Vital signs (including flu symptoms).
	• NEW score assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	• Central lab:
	  • Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture.

	• PK sample collection: serum sample for HAI and MN analysis.
	
	Day 4 (+/- 4 hours; telephonic if discharged)
	
	The Day 4 visit needs to be performed for all subjects. If the subject has already been discharged, perform the subset of assessments by telephone that do not need to be done in person.
	
	In Hospital Assessments:
	
	• Ordinal Scale assessment.
	• Vital signs (including flu symptoms).
	• NEW score assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	• Local lab:
	  • Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
	  • Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.
	
	Telephonic Assessments (if discharged):
	
	• Ordinal Scale assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	
	Day 6 (+/- 4 hours; if hospitalized)
	
	• Ordinal Scale Assessment.
	• Vital signs (including flu symptoms).
	• NEW score assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	
	Day 8 (+/- 1 day)
	
	If the subject has been discharged prior to Day 8, the study requires the subject to return to the site for Day 8 assessments. The last NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first.

	• Ordinal Scale Assessment.
	• Vital signs (including flu symptoms).
	• Physical examination.
	• NEW score assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	• Central Lab:
	  • PK sample collection: serum sample for HAI and MN analysis.
	  • Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture. *The last NP swab collected at Day 8 or Hospital Discharge, whichever occurs first.*
	
	48 hourly (+/- 4 hours; if hospitalized)
	If the subject remains hospitalized past Day 8, continue to perform these assessments up until Day 30 every 48 hours as follows:
	• Ordinal Scale Assessment.
	• Vital signs (including flu symptoms).
	• Physical examination.
	• NEW score assessment.
	• AEs & unanticipated problems.
	• Concomitant medications.
	
	Day 15 (+/- 2 days)
	If the subject has been discharged prior to Day 15, the study requires the subject return to the site for Day 15 assessments as follows:
	• Ordinal Scale assessment.
	• Vital signs (including flu symptoms).
	• Physical examination.
	• NEW score assessment.
	• Local lab:

	• Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets. • Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT. • AEs & unanticipated problems. • Concomitant medications. **Hospital Discharge (if prior to Day 60)** If discharge occurs on a regularly scheduled visit (Day 2, 3, 4, etc.), complete the Hospital Discharge assessments instead but include the PK sample collection, as applicable. The last NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first. • Ordinal Scale assessment. • Vital signs (including flu symptoms). • Physical examination. • NEW score assessment. • AEs & unanticipated problems. • Concomitant medications. • Local lab: • Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets. • Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT. • Central lab: • Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture. *The last NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first.* *If hospital discharge occurs on Day 2, 3 or 8 also collect the PK sample:* • PK sample collection: serum sample for HAI and MN analysis. **Day 30 (+/- 2 days)** The Day 30 assessments must be done in person:

	• Ordinal Scale assessment. • AEs & unanticipated problems. • Concomitant medications. **Day 60 End of Study and/or Early Withdrawal (+/- 2 days)** The Day 60 assessments must be done in person: • Ordinal Scale assessment. • AEs & unanticipated problems. • Concomitant medications.
Pharmacokinetic Parameters	From the HAI and MN assays, the following pharmacokinetic parameters will be calculated using the non-compartmental approach: • **AUC_{0-t}**: The area under the concentration-time curve from time 0 to the last quantifiable concentration, as calculated by the linear trapezoidal method. • **$AUC_{0-day\ 7}$:** AUC from time 0 to day 7. • **AUC_{0-inf}**: AUC_{0-t} plus the additional area extrapolated to infinity, calculated using the terminal elimination rate constant. • **AUC_{0-t}/AUC_{0-inf}:** Ratio of AUC_{0-t} to AUC_{0-inf}. • **C_{max}**: Maximum observed concentration. • **T_{max}**: Sampling time at which C_{max} occurs. Where the maximum value occurs at more than one time point, T_{max} will be the first time point with this value. • **K_{el}**: Apparent first order terminal elimination rate constant calculated by linear least square regression analysis using the maximum number of points in the terminal log-linear phase. • **$t_{½}$**: Apparent first order terminal elimination half-life. • **Cl**: Plasma clearance. • **V_{ss}**: Total volume of distribution.
Primary Endpoints	• AEs. • FLU-IGIV PK parameters.

Secondary Endpoints	The secondary endpoint is an outcome based on the ordinal scale at Day 8 that has 6 mutually exclusive categories: • Death; • Hospitalization in the intensive care unit (ICU); • Non-ICU hospitalization, requiring supplemental oxygen; • Non-ICU hospitalization, not requiring supplemental oxygen; • No longer hospitalized, but unable to resume normal activities; or • No longer hospitalized with full resumption of normal activities.
Exploratory Endpoints	The exploratory endpoints are: • Ordinal scale assessment at Day 4 (72 hours post dose). • Change from baseline to Day 4 in NEW score. • Number of days hospitalized. • Pharmacodynamic (PD) assessment of the relationship between PK and viral load.
Safety Parameters	AEs related to the study treatment, lab results and concomitant medications will be collected throughout the study.

Schedule of Events

If box is greyed out, this assessment is only performed in some instances. Please review footnotes for specific details for each unique case.

Assessments	Screening (within 48 hours of baseline)	Day 1		Day 2 [b] (+/- 4 hours)	Day 3 [b] (+/- 4 hours)	Day 4 [c] (+/- 4 hours)	Day 6 [b] (+/- 4 hours)	Day 8 [d] (+/- 1 day)	48 Hourly [e] (+/- 4 hours)	Day 15 (+/- 2 days)	Hospital Discharge [f]	Day 30 (+/- 2 days)	End of Trial – Day 60 or Early Withdrawal (+/- 2 days)
		Baseline [a] (Pre-Infusion)	Infusion/ Post-Infusion										
Informed Consent	X												
Eligibility	X												
Demography	X												
Medical History	X	X											
Hospital Admission Status		X											
Physical Exam	X	X [a]						X	X	X	X		
Vital Signs/Flu Symptoms [g]	X	X [a]	X	X	X	X [c]	X	X	X	X	X		
Ordinal Scale		X		X	X	X	X	X	X	X	X	X	X
Randomization		X											
NEW score	X	X [a]	X	X	X	X [c]	X	X	X	X	X		
Hematology (local lab)	X	X [a]		X		X [c]				X	X		
Blood Chemistry (local lab)	X	X [a]		X		X [c]				X	X		
Pregnancy Test	X												
Markers of Viral Infection/Viral Load [h] (lab)	X (central & local)	X [a] (central)		X (central)	X (central)			X [f] (central)			X [f] (central)		
Treatment Infusion			X										
PK Sample		X	X	X	X			X			X [f]		

If box is greyed out, this assessment is only performed in some instances. Please review footnotes for specific details for each unique case.													
Assessments	**Screening (within 48 hours of baseline)**	**Day 1**		**Day 2 [b] (+/- 4 hours)**	**Day 3 [b] (+/- 4 hours)**	**Day 4 [c] (+/- 4 hours)**	**Day 6 [b] (+/- 4 hours)**	**Day 8 [d] (+/- 1 day)**	**48 Hourly [e] (+/- 4 hours)**	**Day 15 (+/- 2 days)**	**Hospital Discharge [f]**	**Day 30 (+/- 2 days)**	**End of Trial – Day 60 or Early Withdrawal (+/- 2 days)**
		Baseline [a] (Pre-Infusion)	**Infusion/ Post-Infusion**										
Adverse Events & Unanticipated Problems			X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Day 1: If screening and baseline do not occur on the same day, perform these assessments again at baseline.

[b] Day 2, 3 and 6: If hospitalized complete the outlined assessments. If discharged on these days, perform Hospital Discharge assessments instead.

[c] Day 4: If the subject remains hospitalized, perform ALL listed Day 4 assessments. If discharged on Day 4, perform hospital Discharge assessments instead. If discharged prior to Day 4, a subset of assessments for Day 4 can be done by telephone, including: Ordinal Scale, Adverse Events and Unanticipated Problems and Concomitant Medications.

[d] Day 8: Collect the PK sample. Complete the assessments outlined for Day 8. The last NP sample to be collected at Day 8 or at Hospital Discharge, whichever occurs first.

[e] 48 hourly assessments will be performed post-Day 8 until Day 30 while hospitalized.

[f] Hospital Discharge: The patient needs to return to the hospital for the Day 8, 15, 30 and 60 assessments. If Hospital Discharge occurs on a regularly scheduled visit (Day 2, 3, 4, etc.), complete the Hospital Discharge assessments instead and collect PK sample, if applicable. The final NP Sample to be collected at Day 8 or at Hospital Discharge, whichever occurs first. Collect the PK sample only if discharged on Day 2, 3, or 8.

[g] Vitals (Temperature, pulse and resting blood pressure).

[h] At screening, if influenza A is confirmed by the central lab, then viral load assessment and additional testing to identify strain will be performed.

Table of Contents

List of Abbreviations and Definition of Terms

AE	Adverse event
Ag	Antigen
ALT	Alanine transaminase
AST	Aspartate transaminase
$AUC_{0\text{-day }7}$	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
BUN	Blood urea nitrogen
CDC	Centers for Disease Control and Prevention
CE	Clinically evaluable population
Cl	Drug clearance rate
C_{max}	Maximum serum concentration
DSMB	Data and Safety Monitoring Board
CBC	Complete blood count
CRF	Case report form
CRO	Contract research organization
EC	Ethics Committee
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
FLU-IGIV	Anti-Influenza Immunoglobulin Intravenous (Human)
GCP	Good clinical practices
HAI	Hemagglutination inhibition
ICF	Informed consent form
ICH	International conference on harmonization
ICU	Intensive care unit
IND	Investigational New Drug Application
IRB	Institutional review board

ITT	Intent to treat population
IV	Intravenous
mITT	Modified intent to treat population
mL	Milliliter
mg	Milligram
min	Minute
MN	Microneutralization
NEW	National Early Warning
NIAID	National Institute of Allergy and Infectious Diseases
NP	Nasopharyngeal
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PPT	Partial thromboplastin time
PT	Prothrombin time
RSV	Respiratory syncytial virus
RT-qPCR	Quantitative reverse transcription
SAE	Serious adverse event
SOC	Standard of care
vITT	Virologically confirmed modified intent to treat population
V_{ss}	Volume of distribution at steady state
WHO	World Health Organization

1 BACKGROUND INFORMATION

1.1 Trial Drug

Emergent BioSolutions Canada Inc. is an innovative biopharmaceutical company with a long history of developing, manufacturing and marketing a variety of fractionated plasma products for international markets. The Sponsor will refer to Emergent BioSolutions Canada Inc. throughout this protocol.

The Sponsor is developing an Anti-Influenza Immunoglobulin Intravenous (FLU-IGIV) human product for the treatment of serious influenza infection in hospitalized patients. The FLU-IGIV product will be manufactured using the same hyperimmune manufacturing platform process as the FDA and Health Canada licensed products: CNJ-016® [Vaccinia Immune Globulin Intravenous (Human), VIGIV], ANTHRASIL® [Anthrax Immune Globulin Intravenous (Human), AIGIV], WinRho® SDF [Rho(D) Immune Globulin Intravenous (Human)], HepaGam B® [Hepatitis B Immune Globulin (Human) Injection], and VARIZIG® [Varicella Zoster Immune Globulin Intravenous (Human)]†.

Proprietary Name: To be determined (TBD)

Proper / Common Name: Anti-Influenza Immunoglobulin Intravenous (Human)

Abbreviated Name: FLU-IGIV

Code Name: NP-025

Anti-Influenza Immunoglobulin Intravenous will be formulated in multiple single-use vial(s) 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.

Anti-Influenza Immunoglobulin is produced from source plasma collected from Food and Drug Administration (FDA) licensed plasma collection establishments in the United States (US) and Health Canada/US FDA licensed plasma collection establishments in Canada from healthy donors who have recovered from influenza (convalescent) and/or were vaccinated against seasonal influenza strains. The plasma contains a relatively high concentration of antibodies directed against seasonal influenza strains, specifically influenza A strains H1N1 and H3N2. Influenza antibodies have been correlated with vaccine efficacy and the passive

transfer of anti-influenza antibodies are effective in animal models of severe influenza (2), (4), (5), (6). Clinical proof of concept from treatment with convalescent plasma and purified intravenous immunoglobulin (IGIV) suggest that FLU-IGIV can raise antibodies levels and impact the course of serious illness caused by influenza A (7), (8), (9).

FLU-IGIV is a purified immunoglobulin preparation containing antibodies to seasonal influenza A virus strains. It is a glycoprotein of 150–160 kilodaltons.

FLU-IGIV will be used in conjunction with SOC, including supportive measures, ventilator and fluid management and the prevention and treatment of secondary bacterial pneumonia, which will be captured in the case report form (CRF). Based on current CDC guidance on Treatment Considerations for Patients Hospitalized with Suspected or Confirmed influenza (or equivalent) (1), (2) it is recommended that SOC include a minimum 5 day course of oseltamivir (75 mg/twice a day). All antiviral treatments post-symptom development and during the study will be recorded in the CRF.

Immunoglobulin G molecules are glycoproteins composed of one or more units, each containing four polypeptide chains: two identical heavy chains (H) and two identical light chains (L). The amino terminal ends of each polypeptide show considerable variation in amino acid composition and are referred to as the variable (V) regions to distinguish them from the relatively constant (C) regions. The L chain consists of one variable domain V_L and one constant domain C_L. The H chain consists of a variable domain V_H, and three constant domains (CH_1, CH_2, and CH_3). The number of amino acids, along with the molecular weight of each heavy chain is approximately twice that of each light chain.

Influenza therapies target prevention and treatment of influenza illness. Currently, seasonal influenza vaccines against circulating viral strains are available for active immunization to influenza A and B. In addition, antiviral therapies, including neuraminidase inhibitors, can prevent and treat acute uncomplicated influenza by inhibiting viral replication. Yet seasonal influenza remains a significant annual disease burden in the United States and worldwide. The current vaccines and therapeutics have not proven to be adequate to prevent serious influenza illness, including the significant number of annual medical visits, hospitalizations and deaths attributed to influenza (10). While vaccination reduces influenza incidence and severity, vaccine effectiveness is dependent on vaccine coverage, individual response rates and the match between the vaccine and circulating influenza strains. While neuraminidase inhibitors are potent at inhibiting virus replication, they have limited effectiveness when used beyond 48 hours after infection and antiviral resistant strains have emerged (11). Currently there are no approved therapies for serious influenza in hospitalized patients, creating an unmet need to treat and improve outcomes in this population. The use of convalescent plasma and fractionated immunoglobulins has been suggested as a complementary strategy to treat influenza virus infection, modify the outcomes of severe disease and provide additional benefit to the standard of care (12), (13).

The safety profile for immunoglobulin products is well-established in the clinic. Immunoglobulins are normal constituents of the human body fluid, and they are used at physiological levels without creating pharmacologic/toxicologic active metabolites (14). The

planned clinical doses for FLU-IGIV fall into the range of doses used for VIGIV and ANTHRASIL, and are expected to have a similar safety and pharmacokinetic profile.

1.2 Clinical Trial Rationale

There is an unmet medical need for the treatment of serious influenza in hospitalized patients. While neuraminidase inhibitors are utilized as part of the standard of care in hospitalized influenza they are most effective when used within 48 hours of symptoms (15), however, they are not approved for use in this indication. The Sponsor is developing FLU-IGIV; an anti-influenza immunoglobulin product from high titer plasma to treat serious illness caused by influenza A in hospitalized patients.

The safety profile for immunoglobulin products is well-established in the clinic. Immunoglobulins are normal constituents of the human body fluid, and they are used at physiological levels without creating pharmacologic/toxicologic active metabolites (14). Furthermore, The Sponsor has a long history of developing immunoglobulin-based therapies, including the licensed products outlined above. Like other human immunoglobulins, The Sponsor's hyperimmune products have been studied in several healthy volunteer and patient trials; the safety profile is consistent with other immunoglobulin products and the pharmacokinetic profile is similar for each product with a half-life of approximately 24 to 28 days after intravenous administration. Taking these data and the following factors into consideration, a Phase I safety and pharmacokinetic trial in healthy volunteers is not planned for FLU-IGIV. Baseline anti-influenza titers in healthy volunteers are expected to complicate the pharmacokinetic analysis, or if a threshold of acceptable baseline anti-influenza titers is set it would significantly restrict enrolment into a Phase I study. Furthermore, determining the anti-influenza titers and pharmacokinetic profile in severe patients is expected to be more informative and may be predictive of patient outcomes rather than a Phase I study in healthy volunteers. In addition, The Sponsor is currently manufacturing an anti-influenza hyperimmune for the US National Institute of Allergy and Infectious Diseases (NIAID) using the same standardized and validated hyperimmune manufacturing process and product formulation. The NIAID anti-influenza hyperimmune has been evaluated in a pilot study in influenza patients and is currently being studied in a Phase 3 trial in hospitalized influenza patients (16, 17, 18). While a Phase 1 safety and pharmacokinetic trial in healthy volunteers is not planned for FLU-IGIV, the doses planned for FLU-IGIV are bracketed by licensed products VIGIV and ANTHRASIL that were administered in healthy volunteer studies (VA-003b, AX-001), and are expected to have a similar safety and pharmacokinetic profile.

The Sponsor's clinical development plan consists of a Phase 2 randomized, double-blind, placebo-controlled dose ranging study evaluating the safety, pharmacokinetics and clinical benefit of FLU-IGIV in hospitalized patients with serious illness caused by influenza A infection. The primary objective of this study, which initiated in the 2017–2018 flu season, is to determine the optimal dose of FLU-IGIV based upon safety and pharmacokinetics in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection. The secondary objective is to evaluate the clinical benefit of FLU-IGIV in the same population, and to examine exploratory efficacy endpoints to be used in further development.

A second study, a Phase 3 randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and pharmacokinetics of FLU-IGIV in hospitalized patients with serious influenza A infection is also planned. The primary objective of this study, which will be initiated following completion of the Phase 2 study, will be to evaluate the efficacy and clinical benefit of FLU-IGIV use in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection.

In the clinical trials, the eligible serious hospitalized population will be defined by in-patient or intensive care unit status and the severity of illness using the National Early Warning (NEW) score (19), as discussed further in section 6.7.9 National Early Warning (NEW) Score below. The NEW score will capture key symptoms and signs of respiratory tract infection including oxygen saturation, requirement for supplemental oxygen, respiration rate, as well as body temperature, blood pressure, and level of consciousness. The serious hospitalized population will include patients with risk factors for influenza and influenza-related complications. The ordinal scale will be used to evaluate the clinical status of patients based on activity levels, hospitalization status and requirements.

2 TRIAL OBJECTIVES AND PURPOSE

2.1 Hypothesis

This protocol will allow for the safe use of FLU-IGIV in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection.

2.2 Primary Objective

The primary objective is to determine the optimal dose of FLU-IGIV based upon evaluation of safety and pharmacokinetics (PK) in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection.

2.3 Secondary Objective

The secondary objective is to evaluate the clinical benefit of FLU-IGIV in hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection.

3 TRIAL DESIGN

3.1 Trial Design

This trial is designed as a multi-center, double-blind, randomized, placebo-controlled, 3 arm study. For participants in all three assigned treatment groups, the randomized treatment will be administered in addition to Standard of Care (SOC) including antiviral treatment (see section 4.1.1).

3.2 Anticipated Centers

This is a multi-center trial utilizing up to 60 clinical trial sites globally.

3.3 Sample Size

The sample size will be 75 hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection. While no formal sample size calculation was performed, 75 patients are adequate for determination of optimal dose based on AE and PK data, with consideration of other safety data and clinical benefit data. Sample size was not inflated to compensate for losses to follow-up.

3.4 Randomization

Patients will be randomized 1:1:1 into the study in a double-blind fashion to receive (in addition to antiviral SOC) either a low dose (5 vials) FLU-IGIV or high dose (10 vials) FLU-IGIV or placebo.

Randomization schedule generation and logistics will be handled by a DM vendor. A dummy randomization schedule will be created by the vendor and approved by The Sponsor. Subsequently, the production unblinded randomization schedule, differing only in random number-generating seed value, will be generated by the vendor and uploaded to the IXRS system for patient assignments. The randomization schedule will be stored electronically by the IXRS system on a protected server inaccessible to blinded study team members.

Randomization will not be stratified, except by site.

3.5 Blinding

The local site pharmacist will be unblinded in order to access the randomization assignment and prepare the study medication. There will be designated unblinded monitors, and an unblinded medical monitor. Other personnel involved in conduct of the study will remain blinded through database lock. There will be blinding covers for the IV bags as described in section 5.4 Preparation.

EDC data will be blinded using role-based permissions. Randomization group and study medication 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 DM vendor until after database lock to ensure maintenance of the blind. Study medication dosing data will be reconciled with the randomized treatment group for each patient by the unblinded monitor, and any deviations will be reported in the Clinical Study Report. The trial will be unblinded once the clinical database is locked.

While this is a double-blind trial, the blind may be broken if a patient's health or safety is at risk and knowledge of the study arm may be beneficial to the medical management of the patient. In the event that unblinding is required, the IXRS will be contacted or the pharmacist or other authorized individual may disclose the patient's treatment group allocation to the

Investigator or treating health care provider. In such an event, The Sponsor must be notified, and appropriate documentation completed.

A Data and Safety Monitoring Board (DSMB) will provide another layer of patient safety assurance. The DSMB conducted a data review meeting following enrollment and data entry for the first 20 patients, and will conduct yearly reviews, as applicable. They will have access to unblinded data including at least demographics, medical history, study medication (FLU-IGIV or placebo) dosing, AEs and SAEs. The DSMB may make a nonbinding recommendation that The Sponsor stop the study based on pre-specified stopping rules or based on their clinical judgment of patient safety (Further details will be outlined in the DSMB Charter).

4 SELECTION AND WITHDRAWAL OF SUBJECTS

4.1 Subject Inclusion Criteria

Patients must meet the inclusion criteria to participate in this study.

- Provision of voluntary informed consent in writing by patient, or legally authorized representative.
- Age ≥ 18 years old.
- Locally determined positive influenza A infection (Rapid Ag Test or PCR) from a specimen obtained within 2 days prior to randomization.
- Onset of symptoms ≤ 6 days before randomization, defined as when the patient first experienced at least one respiratory symptom or fever. Earlier symptom onset is preferable.
- Hospitalized (or in observation unit) with influenza, with anticipated hospitalization for more than 24 hours and will be/already are receiving CDC recommended antiviral SOC (oseltamivir 75 mg/twice a day x 5 days; section 4.1.1).
- Experiencing ≥ 1 respiratory symptom (ex. cough, sore throat, nasal congestion) and ≥ 1 constitutional symptom (ex. headache, myalgia, feverishness or fatigue).
- For women of child-bearing potential: through Day 60 of the study, willingness to use at least 1 form of hormonal or barrier contraception or willingness to abstain from sexual intercourse [abstinence is not applicable in Spain].
- Willingness to have blood and respiratory samples obtained and stored.
- National Early Warning Score (NEW score) ≥ 3 at screening.

4.1.1 Required Standard of Care (SOC)

FLU-IGIV will be used in conjunction with SOC, including supportive measures, ventilator and fluid management and the prevention and treatment of secondary bacterial pneumonia, which will be captured in the case report form (CRF). Based on current CDC guidance on

Treatment Considerations for Patients Hospitalized with Suspected or Confirmed influenza (or equivalent) (1), (2), it is recommended that SOC include a minimum 5 day course of oseltamivir (75 mg/twice a day). All antiviral treatments post-symptom development and during the study will be recorded in the CRF. This also applies to the assigned placebo study treatment group.

It is up to the treating physician to follow SOC measures based upon their professional medical opinion. However, if patients hospitalized with serious illness caused by influenza A do not receive the antiviral SOC oseltamivir, they will not be eligible for our study.

4.2 Subject Exclusion Criteria

Patients who have any of the exclusion criteria at screening and/or baseline will be excluded from participation in this study.

- Use of any investigational product within the past 30 days prior to screening.
- History of hypersensitivity to blood or plasma products (as judged by the site investigator) or hypersensitivity to FLU-IGIV excipients (maltose, polysorbate 80).
- History of allergy to latex or rubber.
- Known medical history of IgA deficiency.
- Pregnancy or lactation.
- Medical conditions for which receipt of a 500 mL volume of intravenous fluid may be dangerous to the patient (e.g. decompensated congestive heart failure).
    - Liver function defined by a liver function test (LFT) > 2.5 times the upper limit of normal (ULN).
    - Renal function defined by a glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 (age and sex adjusted).
- A pre-existing condition or use of a medication that, in the opinion of the site investigator, may place the individual at a substantially increased risk of thrombosis (e.g. cryoglobulinemia, severe refractory hypertriglyceridemia, or clinically significant monoclonal gammopathy).
- An opinion of the investigator that it would be unwise to allow participation of the patient in the study (the reason for exclusion of the subject must be documented).
- Receiving extracorporeal membrane oxygenation (ECMO).
- Anticipated life expectancy of < 90 days.
- Confirmed bacterial pneumonia or any concurrent respiratory viral infection that is not influenza A (ex. respiratory syncytial virus (RSV) infection).

  Other infections are not explicitly exclusionary, but the Investigators shall use their best judgement to determine if the type of infection is a risk factor which makes study

participation potentially unsafe for the patient or would compromise interpretation of flu symptom improvement.

4.2.1 Subject Withdrawal

The subjects must be available, without coercion, for all required parts of the trial, including the follow-up visits post-discharge.

At any point in the study, if continued participation jeopardizes the subject's health, 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).

4.2.2 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 a concurrent 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, misses 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 into the trial.
- If an anaphylactic reaction occurs during infusion, the infusion should be stopped immediately.
- If any complication arises that requires stopping the infusion, e.g. myocardial infarction.
- If a subject is withdrawn from the trial, they will not be re-entered into the trial for any reason.

Subjects withdrawn from the trial with AEs will still require follow-up until the AE(s) are resolved.

4.2.3 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.

4.2.4 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 period, will complete all safety assessments for the early withdrawal visit as outlined in this protocol. The investigator should inform the subjects that these assessments are for their own safety.

5 TRIAL MEDICATION

5.1 Packaging and Formulation

FLU-IGIV is supplied in 50 mL Type 1 glass vials sealed with 20 mm siliconized bromobutyl rubber stoppers, aluminum seals, and plastic flip-off caps. The extractable volume per vial is 45 mL. Each vial is intended for single use only by the IV route.

FLU-IGIV should be stored at 2-8°C (35-46°F) until required for use.

FLU-IGIV is provided as a sterile liquid for IV administration. The product is a clear to slightly opalescent and colorless or pale yellow liquid essentially free of foreign particles.

FLU-IGIV contains a target of 60 mg/mL human plasma protein, of which at least 96% is human immunoglobulin G (IgG) containing a portion of specific antibodies against seasonal influenza A (H1N1, H3N2).

For more information, please refer to the Investigator's Brochure for FLU-IGIV.

5.2 Labeling

FLU-IGIV vial and shelf carton labels will include information to comply with local regulations for the country in which the trial is conducted, in the appropriate language(s).

Labeling for the shelf cartons will also include a space for patient ID (which includes the site number) to be noted by the site.

For dispensing labels for secondary receptacles, see section 5.4 Preparation.

5.3 Storage Conditions

FLU-IGIV must be stored refrigerated at 2-8°C (35-46°F) 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 as per instructions provided in the Pharmacy Manual.

For further information, refer to the Investigator's Brochure and the Pharmacy Manual for FLU-IGIV.

5.4 Preparation

The site must maintain documentation of a clear written formalized procedure for trial drug preparation activities (including any sample labels and documentation to be completed), and documented training and delegation of the activity to appropriate trial staff.

Patient identifier (patient ID number) must be recorded on the labels of the carton used to prepare the dose. Empty vials must be maintained for drug accountability. The study pharmacists will be only persons on-site who are unblinded to the treatment assignment for each patient.

To maintain the blind, all study treatments (low dose of FLU-IGIV in normal saline, high dose of FLU-IGIV in normal saline or placebo (normal saline only)) are to be dispensed in a comparable manner.

The trial drug will be prepared for administration at the appropriate dosage and transferred into IV bags before administration. The IV bag for both FLU-IGIV doses and placebo requires the dispensing label affixed to the secondary receptacle IV bag. The IV bag label will capture at a minimum the following study information: patient ID, expiry date of the prepared dose, investigator name, protocol code or identification (Protocol IA-001: FLU-IGIV Study) and caution statement "For investigational use only". The IV bag requires a cover to maintain blinding. Protective covering for the IV bags will be provided by the CRO on behalf of The Sponsor as part of the study material.

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

- Normal saline – in 500 mL IV bags or in bulk
- Empty IV bags (if bulk saline is used)

For further information, refer to the Investigator's Brochure and the Pharmacy Manual for FLU-IGIV.

5.5 Medication Shipment

FLU-IGIV will be shipped to the site at a temperature of 2-8°C (35-46°F). 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 or designate. 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. Study treatment 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.

5.6 Drug Accountability

The investigator is responsible for maintaining accurate inventory records of FLU-IGIV. 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 or designate. 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 or a designated individual not involved in FLU-IGIV administration will maintain a current inventory and ongoing record of test material supplies using the Drug Accountability Form provided by The Sponsor. This inventory record for the FLU-IGIV 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.

These records will be reviewed by representatives of The Sponsor and may be reviewed by regulatory agencies.

6 TRIAL PROCEDURES

6.1 Screening Assessments (within 48 hours of Baseline)

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

- Informed consent.
- Eligibility assessment.
- Demographic assessment.
- Medical history.

  - Including confirmation of influenza A infection (see Local Labs: Markers of Viral Infection below).
- Physical examination.
- Vital signs (including flu symptoms).
- NEW score assessment.
- Concomitant medications.
- Local lab:
  - Markers of Viral Infection sample collection: Nasopharyngeal (NP) swab for local influenza A test (Rapid Ag Test or PCR) if not already completed as part of SOC assessment.
  - Hematology: complete blood count (CBC) with differential white cell count, hemoglobin, hematocrit, platelets.
  - Blood chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.
- Central lab:
  - Markers of Viral Infection/Viral Load sample collection: NP swab for laboratory confirmation of influenza A infection followed by viral load assessment by both RT-qPCR and viral culture, and additional testing to identify strain.
- For women of child-bearing potential, a serum pregnancy test.

6.2 Day 1 Assessments: Baseline (Pre-Infusion of Study Treatment)

Prior to randomization, the following assessments must occur.

- Medical history (update as required from screening).
- Physical examination (if screening and baseline do not occur on the same day).
- Vital signs (including flu symptoms, if screening and baseline do not occur on the same day).
- Hospital admission status.
- Ordinal Scale assessment.
- NEW score assessment.
- Concomitant medications.
- Local lab (if screening and baseline do not occur on the same day):
  - Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
  - Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.

- Central lab (if screening and baseline do not occur on the same day):
  - Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture.
  - Pre-infusion PK sample collection: serum sample for pre-infusion HAI and MN analysis.

6.3 Randomization

Randomization occurs as soon as possible (within 48 hours) after screening and Day 1 Baseline Pre-Infusion assessments are complete. Randomization should be performed as close as possible to the time of infusion. Study treatment administration was staggered by 3 days (72 hours) between patients for the first 9 patients.

6.4 Study Treatment Administration (Day 1)

The study treatment is to be administered for the first 30 minutes under the direct supervision of the investigator or a qualified sub-investigator or designate. Under no circumstances will the investigator allow FLU-IGIV to be used other than as specified in the protocol. For full details on FLU-IGIV preparation, storage, and administration refer to the Investigator's Brochure.

Patients will be assigned into one of the three arms based on their randomization to study treatment as follows:

Arm 1: 5 vials (225 mL diluted to 500 mL with saline) FLU-IGIV;

Arm 2: 10 vials (450 mL diluted to 500 mL with saline) FLU-IGIV; or

Arm 3: Placebo: 500 mL normal saline.

Taking into consideration the maximum protein concentration (refer to IB), the high dose group would receive a maximum IgG protein dose of 31.5 g. Assuming a patient weight range of 60 kg to 100 kg, patients will receive approximately 0.32 – 0.53 g/kg of IgG protein for the high dose and approximately 0.16 – 0.26 g/kg for the low dose, in a single infusion. For participants in all three assigned treatment groups, the randomized treatment will be administered in addition to SOC as defined above in section 4.1.1 Required Standard of Care (SOC). Eligible patients will be randomized in a 1:1:1 ratio to receive either a low dose (5 vials) FLU-IGIV or high dose (10 vials) FLU-IGIV or placebo.

Both FLU-IGIV doses must be diluted with saline solution to a final volume of 500 mL to match the placebo volume administered in order to maintain blinding.

All IV bags must be covered with a sleeve to maintain blinding.

FLU-IGIV and placebo will be administered by intravenous infusion as follows:

- Starting infusion rate of 1.0 mL/min for first 30 minutes.
- Incremental infusion rate if tolerated (every 15-30 minutes) of 1.0 mL/min.

- Maximum Infusion Rate of 4.0 mL/min.
- The duration of infusion for 500 mL will be approximately 3 hours.

A lower maximum infusion rate of 2 mL/min should be used for patients with increased risk of acute renal dysfunction or thrombotic events, based on investigator's medical opinion with careful consideration of lab results. If there is a tolerance issue during infusion, the rate can be scaled back.

If adverse events occur, such as flushing, headache, nausea, changes in pulse rate or blood pressure, the rate of infusion should be slowed or temporarily stopped. When events resolve, the infusion rate may be resumed at a rate that is comfortable to the subject (start at half of the last tolerated rate and increase gradually). Refer to the IB (section 3.4.3 Administration) for more information.

6.5 Day 1 (Post-Infusion of Study Treatment)

After administration of the study treatment, the following assessments must occur (within 4 hours from when the infusion is complete).

- Vital signs (including flu symptoms).
- Adverse events (AEs) & unanticipated problems.
- Concomitant medications.
- NEW score assessment.
- Central lab
    - Post-infusion PK sample collection: **within 90 minutes after completion of study treatment infusion**, serum sample (two 2 mL transport tubes per time point) will be collected for HAI and MN analysis.

6.6 Additional Assessments

Patients will be followed through Day 60 after randomization. Study visits and related procedures are to be done at the same point in time in which the study treatment infusion was completed, within the window specified for each particular visit.

6.6.1 Day 2 Assessments (+/- 4 hours; if hospitalized)

- Ordinal Scale assessment.
- Vital signs (including flu symptoms).
- NEW score assessment.
- AEs & unanticipated problems.
- Concomitant medications.
- Local lab:

- Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
- Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.

- Central lab:
  - Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture.
  - PK sample collection: serum sample for HAI and MN analysis.

6.6.2 Day 3 Assessments (+/- 4 hours; if hospitalized)

- Ordinal Scale assessment.
- Vital signs (including flu symptoms).
- NEW score assessment.
- AEs & unanticipated problems.
- Concomitant medications.
- Central lab:
  - Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture.
  - PK sample collection: serum sample for HAI and MN analysis.

6.6.3 Day 4 Assessments (+/- 4 hours; telephonic if discharged)

The Day 4 visit needs to be performed for all subjects. If the subject has already been discharged, perform the subset of assessments by telephone that do not need to be done in person.

In Hospital Assessments:

- Ordinal Scale assessment.
- Vital signs (including flu symptoms).
- NEW score assessment.
- AEs & unanticipated problems.
- Concomitant medications.
- Local lab:
  - Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.

- Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.

Telephonic Assessments (if discharged):

- Ordinal Scale assessment.
- AEs & unanticipated problems.
- Concomitant medications.

6.6.4 Day 6 (+/- 4 hours; if hospitalized)

If the subject remains hospitalized at Day 6, complete assessments as follows:

- Ordinal Scale Assessment.
- Vital signs (including flu symptoms).
- NEW score assessment.
- AEs & unanticipated problems.
- Concomitant medications.

6.6.5 Day 8 (+/- 1 day)

If the subject has been discharged prior to Day 8, the study requires the subject to return to the site for the Day 8 assessments. The last NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first.

- Ordinal Scale Assessment.
- Vital signs (including flu symptoms).
- Physical examination.
- NEW score assessment.
- Adverse events & unanticipated problems.
- Concomitant medications.
- Central lab:
  - PK sample collection: serum sample for HAI and MN analysis.
  - Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture*. The final NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first.*

6.6.6 48 hourly (+/- 4 hours; if hospitalized)

If the subject remains hospitalized past Day 8, continue to perform these assessments up until Day 30 every 48 hours as follows:

- Ordinal Scale Assessment.
- Vital signs (including flu symptoms).
- Physical examination.
- NEW score assessment.
- AEs & unanticipated problems.
- Concomitant medications.

6.6.7 Day 15 Assessments (+/- 2 days)

If the subject has been discharged prior to Day 15, the study requires the subject return to the site for Day 15 assessments as follows:

- Ordinal Scale assessment.
- Vital signs (including flu symptoms).
- Physical examination.
- NEW score assessment.
- Local lab:
  - Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.
  - Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.
- AEs & unanticipated problems.
- Concomitant medications.

6.6.8 Hospital Discharge (if prior to Day 60)

If discharge occurs on a regularly scheduled visit (Day 2, 3, 4, etc.), complete the Hospital Discharge assessments instead but include the PK sample collection, as applicable. The last NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first.

- Ordinal Scale assessment.
- Vital signs (including flu symptoms).
- Physical examination.
- NEW score assessment.
- AEs & unanticipated problems.
- Concomitant medications.
- Local lab:
  - Hematology: CBC with differential white cell count, hemoglobin, hematocrit, platelets.

- Blood Chemistry: sodium, potassium, serum bicarbonate, BUN, creatinine, glucose, albumin, ALT, AST, total bilirubin, PTT, PT.

- Central lab:
  - Markers of Viral Infection/Viral Load sample collection: NP swab for RT-qPCR and viral culture. *The last NP swab sample is collected at Day 8 or Hospital Discharge, whichever occurs first.*

If hospital discharge occurs on Day 2, 3 or 8 also collect the PK sample:
  - PK sample collection: serum sample for HAI and MN analysis.

6.6.9 Day 30 (+/- 2 days)

The Day 30 assessments must be done in person as follows:

- Ordinal Scale assessment.
- Adverse events & unanticipated problems.
- Concomitant medications.

6.6.10 Day 60 End of Study and/or Early Withdrawal (+/- 2 days)

The Day 60 assessments must be done in person as follows:

- Ordinal Scale assessment.
- Adverse events & unanticipated problems.
- Concomitant medications.

6.7 Trial Assessment Details

The investigator should attempt to perform trial assessments, or if delegated, should ensure that the individual performing the task is qualified by education, training, and experience. Licensing requirements may vary by jurisdiction. Investigators should take such qualifications/licensing requirements into account when considering delegation of specific trial assessment tasks. In all cases, as a qualified physician, the Investigator should be responsible for all trial-related medical decisions and care.

6.7.1 Informed Consent

Details of informed consent are discussed in section 10.2 Informed Consent.

6.7.2 Eligibility

Eligibility will be assessed at screening by ensuring that the subject meets all inclusion criteria while not meeting any exclusion criteria (4.1 Subject Inclusion Criteria and 4.2 Subject Exclusion Criteria). In order for the subject eligibility to be determined, all screening

assessments must be completed with the exception of those for PK/central lab that do not occur at the clinical trial site.

6.7.3 Demography

Demographic information will be obtained for each subject at screening and will include age/ date of birth, sex, race, and ethnicity.

6.7.4 Medical History

Medical history will be collected at screening and updated at Day 1 (Baseline). Collect if the subject has received the seasonal influenza vaccine for the present season. Ensure any medical history collected doesn't affect the eligibility of the subject.

6.7.5 Hospital Admission Status

The hospital admission status (residing unit: general/ICU/other) will be obtained at baseline and throughout the study.

6.7.6 Physical Exam

A physical exam (including but not limited to eyes, ears, nose, throat, lymph nodes, heart, pulse, lungs, and abdomen assessments), will be performed throughout the study and the patient's height, weight and body mass index (BMI) will be collected at screening.

6.7.7 Vital Signs/Flu Symptoms

Vital signs will be collected for subject including temperature, respiratory rate, blood pressure, pulse and solicitation of flu symptoms (fever, cough, sore throat, runny or stuffy nose, muscle or body aches, headaches, fatigue, vomiting or diarrhea). If a patient has required chest x-rays or other diagnostic methods during their hospitalization to determine the extent of infection in the respiratory tract (pneumonia), the available images should be redacted and the assessment details should be collected and input into the CRF for that subject at the next study visit. If a site is not able to provide redacted image files, clearly enter detailed assessment information (from the radiologist report) into the eCRF. At screening, baseline oxygen saturation on room air will be collected.

6.7.8 Ordinal Scale

The ordinal scale will be used to assess clinical improvement, which categorizes patients into one of six mutually-exclusive categories based on activity levels, hospitalization status and requirements as follows:

- Death;
- Hospitalization in the intensive care unit (ICU);
- Non-ICU hospitalization, requiring supplemental oxygen;

- Non-ICU hospitalization, not requiring supplemental oxygen;
- No longer hospitalized, but unable to resume normal activities; or
- No longer hospitalized with full resumption of normal activities.

The Hospital Discharge visit ordinal scale assessment should be one of the two "No longer hospitalized" options.

6.7.9 National Early Warning (NEW) Score

The NEW score will be collected for patients and will be defined by in-patient or intensive care unit status and the severity of illness. The NEW scoring system will capture key symptoms and signs of respiratory tract infection including oxygen saturation, requirement for supplemental oxygen, respiration rate, as well as body temperature, blood pressure, and level of consciousness. The NEW score parameters can be obtained from patient hospital medical records, nursing notes, etc. and will be recorded in the CRF. Screening NEW score can be calculated using values from hospital admission prior to medical intervention, as provided treatment (ex. Acetaminophen) may confound NEW scoring parameters (ex. fever). For more information on NEW score interpretation, please see Appendix I for the NEW Scoring Guide.

6.7.10 Markers of Viral Infection/Viral Load Sample Collection

To collect and ship samples for assessment for markers of viral infection and viral load for FLU-IGIV, collect nasopharyngeal (NP) swab samples according to the instructions provided in section 6.8.2 Markers of Viral Infection/Viral Load Samples and the Laboratory Manual. Nasal saline should not be administered prior to collecting the NP sample.

6.7.11 Pharmacokinetic (PK) Sample Collection

To collect and ship PK samples for assessment, follow instructions specified in section 6.8.1 Pharmacokinetic (PK) Samples and in the Laboratory Manual.

6.7.12 Adverse Events (AE) and Unanticipated Problems

Collect any AE and unanticipated problem for patients as outlined in section 8 ASSESSMENT OF SAFETY.

6.7.13 Concomitant Medications

Concomitant medications for patients will be collected from time of first symptom onset until end of study. The concomitant medications should be assessed and reported according to section 6.9 Concomitant Medications and 6.10 Excluded Concomitant Medications, and will include SOC antiviral treatment (section 4.1.1 Required Standard of Care (SOC)).

6.7.14 Blood Chemistry

Clinical chemistry assessments for patients will include:

- Serum sodium, potassium, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, albumin, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, partial thromboplastin time (PPT), prothrombin time (PT).

6.7.15 Hematology

Hematology assessments obtained for patients will include:

- A complete blood count (CBC) with differential white cell count, hemoglobin, hematocrit, platelets.

6.7.16 Pregnancy Test

Pregnancy tests (serum) will be performed once at screening for all females of child bearing potential. A woman is considered of child-bearing potential/age i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A pregnancy test is not required for female subjects who are postmenopausal > 2 years, or surgically sterilized. If a subject becomes pregnant prior to Day 60 this should be reported to the sponsor as a serious AE for appropriate follow-up.

6.8 Handling of Samples

6.8.1 Pharmacokinetic (PK) Samples

6.8.1.1 PK Sample Collection

To obtain samples for analysis of PK for FLU-IGIV, refer to the provided Laboratory Manual.

Briefly, sufficient blood will be drawn per time point to yield two 2 mL aliquots of serum. PK sampling kits will be provided for this purpose by the central laboratory. Each sample tube must be labelled as per instructions in the Laboratory Manual. Label information will be recorded in the CRF and into a logbook as described in the Laboratory Manual.

Samples will be stored frozen at ≤ -15 °C until they are shipped to the designated central lab. The Sponsor or designate must be notified of any deviations in the storage temperature of the samples within 48 hours of occurrence.

Samples collected for PK analysis will be retained according to The Sponsor's standard procedures.

6.8.1.2 PK Sample Shipment

The trial central lab will initiate shipment of PK samples and arrange the date and method of shipment.

Samples will be divided into two shipments. The second shipment (backup samples) will be initiated by the central laboratory once the first shipment has been received and inventory verified. Shipment must be arranged such that the central laboratory will have staff on duty to receive the samples. Refer to Laboratory Manual for details on PK sample shipment.

6.8.1.3 PK Sample Analysis

The pharmacokinetic analysis will be performed using HAI and MN assays by The Sponsor's bioanalytical laboratory.

6.8.2 Markers of Viral Infection/Viral Load Samples

6.8.2.1 Viral Marker/Load Sample Collection

To collect and ship samples for markers of viral infection and viral load assessments for FLU-IGIV, collect nasopharyngeal (NP) swab samples according to the Laboratory Manual. NP collection kits will be provided by the central lab.

6.8.2.2 Viral Marker/Load Shipment

The trial central lab will initiate shipment of viral load/marker samples and arrange the date and method of shipment. Shipment must be arranged such that the central laboratory will have staff on duty to receive the samples. Refer to Laboratory Manual for details on sample shipment.

6.8.2.3 Viral Marker/Load Analysis

The local lab will determine if there is influenza A infection at screening, by a Rapid Ag test or PCR, according to their procedures.

The central lab will confirm if there is influenza A infection from the screening sample before performing any further testing. The central lab will perform viral load analysis by RT-qPCR and viral culture and additional testing to identify the strain (ex. H1N1/H3N2) for all samples listed in the schedule of assessments and section 6 Trial Procedures and confirmed as influenza A positive.

6.9 Concomitant Medications

The administration of concomitant medications is permitted during the trial period in keeping with the standard of care for subjects with serious illness due to influenza A infection. Any medication taken by the subject, including transfusions, herbal preparations and non-prescription medications within 6 days prior to treatment assignment and/or during the course of the trial and the reason for use will be recorded on the trial source documents and concomitant medications page of the CRF.

FLU-IGIV will be used in conjunction with SOC, including supportive measures, ventilator and fluid management and the prevention and treatment of secondary bacterial pneumonia, which will be captured in the CRF. Based on current CDC guidance (or equivalent) on Treatment Considerations for Patients Hospitalized with Suspected or Confirmed Influenza (1), (2) it is recommended that SOC include a minimum 5 day course of oseltamivir (75 mg/twice a day). All antiviral treatments post-symptom development and during the study will be recorded in the CRF. This also applies to the assigned placebo study treatment group.

6.10 Excluded Concomitant Medications

There are no known excluded concomitant medications. Refer the Investigator's Brochure for full details on potential impaired efficacy for vaccines.

7 ASSESSMENT OF PK

7.1 PK Parameters

From the HAI and MN assays the following pharmacokinetic parameters will be calculated using the non-compartmental approach:

- **$AUC_{0\text{-}t}$**: The area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration, as calculated by the linear trapezoidal method.
- **$AUC_{0\text{-}day\ 7}$:** AUC from time 0 to day 7.
- **$AUC_{0\text{-}inf}$**: $AUC_{0\text{-}t}$ plus the additional area extrapolated to infinity, calculated using the terminal elimination rate constant.
- **$AUC_{0\text{-}t}/AUC_{0\text{-}inf}$:** Ratio of $AUC_{0\text{-}t}$ to $AUC_{0\text{-}inf}$.
- **C_{max}**: Maximum observed concentration.
- **T_{max}**: Sampling time at which C_{max} occurs. Where the maximum value occurs at more than one time point, T_{max} will be the first time point with this value.
- **K_{el}**: Apparent first order terminal elimination rate constant calculated by linear least square regression analysis using the maximum number of points in the terminal log-linear phase.
- **$t_{½}$**: Apparent first order terminal elimination half-life.
- **Cl**: Plasma clearance.
- **V_{ss}**: Total volume of distribution.

7.2 Assessment of PK Parameters

PK will be assessed in all subjects, including those subjects assigned to the placebo group, who will have natural antibody production. Due to the buildup of anti-influenza antibodies

from subjects' natural immunity, PK parameters will be estimates only and cannot quantify precisely the levels of FLU-IGIV in dosed subjects.

8 ASSESSMENT OF SAFETY

The safety of the trial drug will be assessed by monitoring closely adverse events (AE) defined as related to study treatment, lab results for chemistry and hematology and concomitant medications collected throughout the study. Any lab results and concomitant medications will be monitored regularly.

8.1 Adverse Event/Serious Adverse Event Definition

The occurrence of AEs will be monitored throughout all phases of the trial and will cover all participating subjects. AE capture will begin after randomization, and any medical history changes that occur after baseline assessments during randomization and before dosing should be updated as medical history.

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

8.1.1 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 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 AEs. 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 CRF. All adverse events will be examined by a physician investigator or sub-investigator for assessment of both severity and causality using the following criteria:

8.1.2 Assessment of Severity (Intensity)

The adverse event severity should be assessed based on the MedDRA Lowest Level Term (LLT) scale below.

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.

8.1.3 Assessment of Causality (ICH Classification)

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.

8.2 Description of Known AE Profile for FLU-IGIV

The safety of human IV immunoglobulins is well established. The incidence of AEs associated with administration of IV immunoglobulin products is reported by the manufacturers to be in the range of 1 to 15%, usually less than 5% (20, 21). Non-anaphylactic reactions are most common and the majority of AEs are mild and self-limiting in nature.

A complete list of risks with details are outlined in the Investigator's Brochure which includes:

- Hypersensitivity
- Renal dysfunction/failure
- Aseptic Meningitis Syndrome (AMS)
- Hemolysis
- Thrombotic events
- Transfusion-Related Acute Lung Injury (TRALI)
- Infusion rate reactions
- Interference with blood glucose testing

8.3 Adverse Event Reporting

Occurrence of adverse events will be monitored throughout the trial and will cover all participating patients, including any randomized subject. Trial subjects will be provided with a 24 hour telephone number to contact trial personnel in case of an untoward reaction after hospital discharge.

All AEs must be followed to resolution, or up to 60 days after the patient has completed the trial, whichever occurs first. The investigator will follow serious related adverse events to resolution, or in the case of disability or incapacity, until the condition has stabilized. In the event that a patient does not complete the trial, efforts must be made to obtain information regarding all AEs, with a minimum follow-up of 60 days post-dosing.

If a subject becomes pregnant during a clinical trial, these pregnancies will be considered as SAEs and will be followed until termination of pregnancy or birth. 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.

8.4 Reporting of SAEs

The investigator will report all serious adverse events to The Sponsor's Pharmacovigilance Department by telephone or e-mail (with the Medical Monitor in copy) 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, with the Medical Monitor in copy. 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 reports should be made to:

Emergent BioSolutions Canada Inc.	AND	**Medical Monitor** [redacted] SGS North America Inc. [redacted]
Toll free phone: [redacted] Toll free fax [redacted]		

8.5 Safety Data Monitoring

Study treatment administration was staggered by 3 days (72 hours) between patients for the first 9 patients. An independent Data Safety and Monitoring Board (DSMB) will provide on-going review of safety data during the trial. The DSMB will be responsible for assessing safety and monitoring overall conduct and integrity of the trial. In fulfilling these responsibilities, the DSMB may make recommendations concerning continuation and/or stopping of the trial as it relates to safety and risk to the patient population as outlined in section 9.2.5 Criteria for Early Termination of the Trial.

9 STATISTICAL ISSUES IN TRIAL DESIGN AND PK ASSESSMENT

9.1 Sample Size Calculation

The sample size will be 75 hospitalized patients with serious illness caused by laboratory-confirmed influenza A infection. While no formal sample size calculation was performed, 75 patients are adequate for determination of optimal dose based on AE and PK data, with consideration of other safety data and clinical benefit data.

9.1.1 Safety Population

The safety population will include all patients who receive any amount of study medication (FLU-IGIV or placebo).

9.1.2 PK Population

The PK population will include all patients who have adequate PK data for analysis that includes day 1 pre-infusion/baseline, post-infusion plus at least one additional time point.

9.1.3 Intent to Treat Population (ITT)

The intent to treat population will include all randomized patients regardless of study medication treatment status, influenza type or protocol deviations. Patients will be analyzed according to the treatment to which they were randomized.

9.1.3.1 Modified Intent to Treat Population (mITT)

The mITT population will include those patients from the ITT population who met eligibility criteria, received study medication (FLU-IGIV or placebo) and have confirmed influenza A by the local lab Rapid Ag or PCR markers of viral infection test from the screening NP swab sample. Patients will be analyzed according to the treatment to which they were randomized.

9.1.3.2 Virologically Confirmed Modified Intent to Treat Population (vITT)

The vITT population will include any patients from the mITT population who met eligibility criteria, received study medication (FLU-IGIV or placebo) and have confirmed influenza A by the central lab RT-qPCR markers of viral infection test from the screening NP swab sample. Patients will be analyzed according to the treatment to which they were randomized.

9.1.4 Clinically Evaluable Population (CE)

The CE population will include all patients who met eligibility criteria, received ≥ 80% of study medication (FLU-IGIV or placebo) infusion matching their randomized treatment group, ≥ 80% of the oseltamivir and have a non-missing Day 8 ordinal scale assessment.

9.2 Trial Endpoints

9.2.1 Primary Endpoint

Primary endpoint analyses will include AE incidence and severity and PK parameters, upon which optimal dose determination will be based.

9.2.2 Secondary Endpoints

The secondary endpoint is an outcome based on the ordinal scale at Day 8 that has six mutually exclusive categories:

- Death;
- Hospitalization in the intensive care unit (ICU);
- Non-ICU hospitalization, requiring supplemental oxygen;
- Non-ICU hospitalization, not requiring supplemental oxygen;
- No longer hospitalized, but unable to resume normal activities; or
- No longer hospitalized with full resumption of normal activities.

9.2.3 Exploratory Endpoints

The exploratory endpoints are:

- Ordinal scale assessment at Day 4 (72 hours post dose).
- Change from baseline to Day 4 in NEW score.
- Number of days hospitalized.
- Pharmacodynamic (PD) assessment of the relationship between PK and viral load.

9.2.4 Safety Endpoints

Adverse events related to the study treatment, lab results and concomitant medications will be collected throughout the study.

9.2.5 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. Meeting a safety stopping criterion will not automatically trigger study termination, but a hold on recruitment will be implemented until an ad hoc DSMB meeting is held. If any of the following criteria are fulfilled, the DSMB will review the unblinded safety data to assess the evidence for an excess of events in the FLU-IGIV treatment groups relative to the placebo group. The DSMB will determine whether trial termination is recommended, which would require a majority vote.

- Two or more subjects experience related rare reactions reported for immunoglobulin intravenous (human) (IGIV), such as thrombotic events, hemolysis or transfusion related acute lung injury (TRALI).
- Three or more subjects experience the same related SAE (per sponsor assessment).
- Five or more subjects experience the same related severe AE.
- Ten or more subjects experience a related moderate or higher AE associated with the same organ system.

- Eight or more patients who were not able to tolerate the entire 500 mL IV infusion, but were administered a partial study medication infusion (FLU-IGIV or placebo).
- Proportion of deaths due to complications from worsened primary conditions or co-morbidities ≥ 10% higher than that reported for the influenza season by CDC FLUVIEW (https://www.cdc.gov/flu/weekly/fluviewinteractive.htm).
- Any other findings that, at the discretion of the medical monitors, indicate that the study should be halted.

Administrative issues affecting one or more sites may constitute grounds for stopping the trial at that site(s). Examples include, but are not limited to, non-adherence to the protocol, 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 the trial treatment (or 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; the investigational treatment is found to be ineffective; recruitment is poor; research strategy or management priorities change; or a clinical hold is imposed by a regulatory authority, to name a few.

Any decision to voluntarily suspend or terminate a clinical trial will be carefully reviewed and fully justified. The Sponsor will notify the regulatory authorities and the Institutional Review Boards (IRB)/Ethics Committees (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 DSMB data review occurred in March 2018, after enrollment and data entry for 20 subjects. Thereafter, the DSMB will conduct yearly reviews, as applicable.

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 patients, mean, standard deviation (SD), median, minimum and maximum. Categorical endpoints will be summarized by the total number of patients, frequencies and percentages.

AEs will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), using the current version at the time of coding. AEs will be defined as events beginning after first study medication administration that were not present prior to first study medication administration or those that were present prior to first study medication administration and subsequently worsened in severity. AE incidence for each system organ class and preferred term will be summarized for the safety population by treatment group overall as well as separately by severity and for events related to study medication (FLU-IGIV or placebo). Serious AEs will be summarized separately for the same population, as will deaths. Separate subgroup analyses of AE and SAE incidences by sex, race (Caucasians, African Americans, and others) and age (over 55 versus 18-54) will be performed by treatment group.

PK analysis for anti-influenza antibodies will be conducted for the PK population using HAI and MN analysis. Serum concentration versus time data will be analyzed by standard noncompartmental 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 maximum serum concentration (C_{max}), time of maximum serum concentration (t_{max}), half-life ($t_{1/2}$), area under the concentration-time curve (AUC) for 0-t (time 0 to the last concentration), AUC_{0-7} (time 0 to Day 7), AUC_{0-inf} (time 0 to infinity), ratio of AUC_{0-t}/AUC_{0-inf}, terminal elimination rate constant (K_{el}), clearance (Cl) and volume of distribution (V_{ss}).

PK parameters will be reported using descriptive statistics by treatment group for the PK population. Dose proportionality will be explored using log-transformed PK data. Serum concentration-time data will be plotted by treatment group. Relevant subset analyses may be performed.

Patient disposition, including early termination reasons, will be summarized by treatment group for all patients. Major protocol deviations will be presented by treatment group for the safety population. Patient demographics, medical history and study medication (FLU-IGIV or placebo) dosing data will be tabulated by treatment group for the safety population. Important baseline values such as ordinal score assessment, NEW score and flu symptoms will be summarized by treatment group for the safety and ITT populations. 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.

Ordinal scale assessment will be analyzed at Days 4 and 8 for the ITT and CE populations using a proportional odds model investigating the effect of treatment group on ordinal outcome. An odds ratio will be computed for each study treatment group relative to placebo, interpretable as the mean location shift across the ordinal scale attributed to IVIG treatment. After verification of the proportional odds assumption for dose, a dose-response relationship will be tested using ordinal logistic regression with a cumulative logit link and an ordinal dose variable, adjusting for significant prognostic factors using stepwise selection. If the proportional odds assumption is significantly violated, then a partial proportional odds model for dose will be explored. Relevant subset analyses may be performed.

Change from baseline to Day 4 in NEW score will be compared between treatment groups for the ITT and CE populations using nonparametric rank analysis. Viral load data from central laboratory NP swabs will be summarized by time point for the ITT and CE populations by treatment group and tested for differences between treatment groups at key time points (e.g, Days 2 and 3). The relationship between PK and viral load will be investigated for patients belonging to both the PK and ITT populations.

Central clinical laboratory test results will be summarized by time point and treatment group using descriptive statistics for the safety population. Vital signs parameters will be presented in the same manner.

10 REGULATORY AND ETHICAL ISSUES

10.1 Declaration of Helsinki

The investigator shall ensure that this trial is conducted in accordance with the ethical principles that have their origin in the "Declaration of Helsinki."

10.2 Informed Consent

The investigator (or his/her representative) will 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. If applicable, identify different consent forms that are needed for the study (e.g. future use of specimen, assent from minors, etc.). 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, and the fate of these samples whether analyzed or not (backup).
- 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.
- 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 or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the 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."
- Considering other jurisdictions, the following statement shall be provided to each clinical trial subject in informed consent documents and processes: "This description will be

available on other Clinical Trial registration sites specific to the jurisdictions this study is being carried out in (ex. https://eudract.ema.europa.eu/ in Europe, https://health-products.canada.ca in Canada, etc.), according to their respective laws. These Web sites will not include information that can identify you. At most, these Web sites will include a summary of the results. You can search this Web site at any time."

10.3 Institutional Review Board (IRB)/Ethics Committee (EC)

Before the start of the trial, the Investigator's Brochure, the protocol, proposed informed consent form(s), subject compensation (if any), The Sponsor-approved trial materials and advertisements, and any other written information to be provided to the subject, will be submitted to a properly constituted Institutional Review Board (IRB) or Ethics Committee (EC) for review. The Sponsor must receive a copy of the written approval from the IRB for all of the above applicable documents prior to recruitment of subjects into the trial and shipment of FLU-IGIV.

The IRB/EC 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/EC 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 (or equivalent local regulations) and ICH GCP guidelines 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 Informed Consent Form and, where applicable, any other document listed above, have been approved by them.

All correspondence between the investigator and the IRB/EC will be available for review by The Sponsor (or designate), contract research organization (CRO) personnel, 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 equivalent, 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/EC approval for the protocol, Investigator's Brochure, informed consent form(s), 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 by the Sponsor/CRO.
- Written statement that the IRB/EC is properly constituted and operates according to 21 CFR part 56 regulations and/or ICH GCP, as applicable. Investigators participating in this study, if IRB members, should state in writing that they have abstained from voting in regards 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, enrolment) 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 IA-001. Subjects must be informed that his/her records may be reviewed by The Sponsor, its designate(s), the IRB/EC and the appropriate regulatory authority(ies) through direct access to the subject's original medical records.

11 ADMINISTRATIVE AND LEGAL REQUIREMENTS

11.1 Sponsorship

This clinical study is sponsored by Emergent BioSolutions Canada Inc., Winnipeg, MB, Canada, who is the manufacturer of FLU-IGIV.

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 (ex. 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 CRFs 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 Food and Drug Administration, other relevant regulatory agencies as appropriate, 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

The investigator (or designate) will record data collected in this clinical trial on electronic CRFs (eCRFs). The electronic forms are to be completed on a contemporaneous basis.

The data are the property of The Sponsor of the trial. Questions arising from eCRF data will be dealt with by the issuance of Data Queries within the EDC environment by The Sponsor Clinical Data and Statistics (or designate) to the investigator.

11.6 Monitoring

Safety will be monitored using a risk-based monitoring approach. 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/CRO 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 the case report forms of the subjects to ensure that all 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, each clinical site will have two separate monitors assigned- one for monitoring the blinded portion of the study and the other for verifying the

unblinded drug accountability at the site pharmacy. The clinical sites will be provided with the trial related training/ instructions at the initiation and throughout the conduct of the trial.

11.6.1 Medical Monitoring

Medical Monitor(s), appointed by the Sponsor, will be available during the trial to assist sites with study related questions such as medically relevant conduct issues, questions regarding inclusion/exclusion, safety trending analysis, safety reporting issues, and patient management questions. Medical Monitor(s) will collaborate with study project, medical, and pharmacovigilance teams, as well as data safety monitoring board with regard to all project-specific medical and safety-related questions. An unblinded Medical Monitor will also be involved to provide consultation/ guidance to the unblinded study team. Roles and responsibilities for the Medical Monitoring team will be further defined in the Medical Monitoring Plan.

11.7 Quality Control and Quality Assurance

The Sponsor Quality Assurance 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/EC to verify that the trial is being or has been conducted in accordance with protocol requirements, GCP, as well as the applicable regulatory requirements.

11.8 Quality Management

The Sponsor maintains a Quality Management System encompassing SOPs, risk assessment, risk management with defined data management plans, monitoring plans and audit plans to assure regulatory compliance, patient safety, robust data management and scientific integrity.

11.9 Publication Policy

Data arising from this trial are the sole property of The Sponsor of the trial, The Sponsor. 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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APPENDIX I

APPENDIX I

A Randomized, Double-Blind, Placebo-Controlled Dose Ranging Study Evaluating the Safety, Pharmacokinetics and Clinical Benefit of FLUIGIV in Hospitalized Patients with Serious Influenza A Infection

Version 4.0
24 May 2018
NCT03315104

NEW SCORING GUIDE

Protocol No. / Title	**IA-001** / A Randomized, Double-Blind, Placebo-Controlled Dose Ranging Study Evaluating the Safety, Pharmacokinetics and Clinical Benefit of FLU-IGIV in Hospitalized Patients with Serious Influenza A Infection

Category	Score	Value
Respiratory Rate (breaths/min)	3	≤ 8
	1	9-11
	0	12-20
	2	21-24
	3	≥ 25
Temperature	3	≤ 35 °C ≤ 95 °F
	1	35.1-36 °C 95.1-96.8 °F
	0	36.1-38 °C 96.9-100.4 °F
	1	38.1-39 °C 100.5-102.2 °F
	2	≥ 39.1 °C ≥ 102.3 °F
Heart Rate (BPM)	3	≥ 131
	2	111-130
	1	91-110
	0	51-90
	1	41-50
	3	≤ 40

Category	Score	Value
SpO_2 (%)	3	≤ 91
	2	92-93
	1	94-95
	0	≥ 96
Inspired O_2 (%)	2	Yes: Any supplemental O_2
	0	Not receiving supplemental O_2
Systolic Blood Pressure (mmHg)	3	≥ 220
	0	111-219
	1	101-110
	2	91-100
	3	≤ 90
Level of Consciousness	0	Alert
	3	Voice (V) Pain (V) Unresponsive (U)
TOTAL: _____	**Add up all assigned score values in each category* to obtain the total NEW score.**	