NCT03315104

Emergent BioSolutions
STATISTICAL ANALYSIS PLAN

Study Medication
Anti-Influenza Immunoglobulin Intravenous (Human)

Protocol 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

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LIST OF ABBREVIATIONS

AE	Adverse event
AESI	Adverse event of special interest
AUC_{0-7}	Area under the serum concentration curve from time 0 to Day 7
AUC_{0-inf}	Area under the serum concentration curve from time 0 to infinity
AUC_{0-t}	Area under the serum concentration curve from time 0 to the last quantifiable concentration
BMI	Body mass index
CE	Clinically evaluable population
CI	Confidence interval
Cl	Plasma clearance
C_{max}	Maximum serum concentration
CV%	Coefficient of variation
DSMB	Data Safety Monitoring Board
EDC	Electronic data capture
FLU-IGIV	Anti-Influenza Immunoglobulin Intravenous (Human)
HAI	Hemagglutination inhibition test
ICU	Intensive care unit
IMP	Investigational medical product
ITT	Intent to treat population
IV	Intravenous
IWRS	Interactive web response system
λ_z	First order terminal elimination rate constant
KM	Kaplan-Meier
LOD	Limit of detection
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intent to treat population
MN	Microneutralization test
NEWS	National Early Warning Score
NP	Nasopharyngeal
PCR	Polymerase chain reaction
PD	Protocol deviation
PK	Pharmacokinetics
RT-qPCR	Reverse transcriptase quantitative polymerase chain reaction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SDO	Secure Data Office at SGS vendor
SMQ	Standard MedDRA query
SOC	Standard of care
$t_{½}$	First order terminal elimination half-life
t_{max}	Sampling time at which C_{max} occurs
TLF	Tables, listings and figures
vITT	Viral infection confirmed modified intent to treat population
V_z	Volume of distribution
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is based on Protocol 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" (Version 5.0, 24JAN2019). This document specifies details of the definitions of the derived variables, analysis methods, assumptions and data handling conventions. The document is accompanied by mock-up tables, listings and figures (TLF shells). Some further details on the calculation of derived variables are provided as programmer's notes in the TLF shells. The TLF shells serve only as a guide for programming the final TLF. They are working documents and can be updated as needed through TLF finalization.

2. PROTOCOL SUMMARY

2.1. Study Objectives

2.1.1. Primary Objective

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

2.1.2. Secondary Objective

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

2.2. Study Design and Conduct

Study IA-001 was designed as a multicenter, double-blind, randomized, placebo-controlled, 3-arm Phase 2 study, utilizing up to 60 clinical trial sites globally. The enrollment target was 75 hospitalized subjects, 18 years of age or older, with serious illness caused by laboratory-confirmed influenza A infection.

Eligible subjects were randomized 1:1:1 into the study in a double-blind fashion to receive either a low dose (5 vials) FLU-IGIV or high dose (10 vials) FLU-IGIV or placebo.

For participants in all 3 assigned treatment groups, the randomized treatment was administered in addition to standard of care (SOC) treatment, including a minimum 5-day course of oseltamivir (75 mg/twice per day).

Study medication (FLU-IGIV or placebo) was administered on Day 1 as a single, fixed dose by volume at prescribed intravenous infusion rates, as described in the protocol. Study treatment administration was staggered by 3 days (72 hours) between subjects for the first 9 subjects.

2.3. Study Endpoints

2.3.1 Primary Endpoints (Safety and PK)

Primary endpoint analyses include adverse event (AE) incidence and severity (see Section 7.2.1) and PK parameters (see Section 7.2.2), upon which optimal dose determination is based.

2.3.2 Secondary Safety Endpoints

Secondary safety endpoints include AEs related to study medication (FLU-IGIV or placebo), deaths, laboratory results, vital signs, influenza symptoms and physical examinations.

2.3.3 Secondary Clinical Benefit Endpoint

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

1. Death;

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

2.3.4 Exploratory Endpoints

The exploratory endpoints are:

- Ordinal scale assessment at Day 4 (72 hours post dose).
- Change from baseline to Day 4 in National Early Warning (NEW) score.
- Viral load at Days 2 and 3.
- Number of days hospitalized.
- Pharmacodynamic assessment of the relationship between PK (area under the concentration-time curve [AUC]) and log viral load.

2.4 Power and Sample Size Consideration

The planned sample size was 75 hospitalized subjects with serious illness caused by laboratory-confirmed influenza A infection. A total of 65 subjects was enrolled and randomized, with 60 of these receiving study medication (FLU-IGIV or placebo).

While no formal sample size calculation was performed, the 65 subjects randomized is adequate for determination of optimal dose based on AE and PK data, with consideration of other safety data and clinical benefit data.

2.5 Randomization and Blinding

2.3.1 Randomization

Subjects were randomized 1:1:1 into one of the 3 arms of study treatment, accompanied by SOC 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.

Randomization was stratified by site. Randomization of individual subjects occurred via interactive web response system (IWRS) within 48 hours after screening and after Day 1 baseline assessments were complete.

Randomization schedule generation and logistics were handled by a vendor (SGS Secure Data Office [SDO]). Randomization specifications and a dummy randomization schedule were created by the vendor and approved by the sponsor. Subsequently, the production unblinded randomization schedule, differing only in random number-generating seed value, was generated by the vendor and uploaded to the IWRS system for subject assignments. The randomization schedule was stored electronically by the vendor on a protected server inaccessible to blinded study team members.

The local site pharmacists were unblinded to access the randomization assignment and prepare the study medications (FLU-IGIV or placebo).

2.3.2 Blinding

Electronic data collection (EDC) data was blinded to the study team and unblinded to designated users (see next paragraph) using role-based permissions. Assigned randomization group from IWRS was integrated with the clinical

database prior to database lock, but unblinding data was removed from blinded data extracts by the vendor (SGS SDO) until after database lock to ensure maintenance of the blind. Blinded information for each subject included:

- Randomized treatment group;
- Actual number of vials of FLU-IGIV dosed;
- All PK concentration data;
- Central laboratory viral load data including nasopharyngeal swab influenza A test (RT-qPCR and/or culture) result positive for influenza A (yes or no), influenza A strain (e.g., A/H1/California), and influenza A viral load throughout the study; and
- Any unblinded protocol deviations.

Designated unblinded personnel included the vendor (SGS SDO) randomization statistician and staff, IWRS personnel, local site pharmacists, vendor unblinded monitors, an Emergent unblinded medical monitor, an independent unblinded statistical consultant supporting the Data Safety and Monitoring Board (DSMB) and the Emergent analytical group running PK assays. In addition, an Emergent QA Compliance Specialist was unblinded due to conducting site pharmacy audits and a Clinical Trial Specialist at Emergent was unblinded in order to assist in review of pharmacy closeout reports. Other personnel involved in conduct of the study, including all Emergent personnel (except the unblinded medical monitor, the two Specialists noted in the prior sentence and the analytical group running PK assays), remained blinded through database lock.

The DSMB process involved a transfer of blinded data from the clinical database to Emergent's blinded data management and statistics personnel. Programs to create DSMB outputs were written and run by Emergent's blinded statistics personnel using the dummy randomization schedule. The following were transferred to the independent unblinded statistical consultant: production unblinded randomization schedule from the vendor (SGS SDO), blinded Standard Data Tabulation Model and Analysis Data Model datasets and SAS programs to create DSMB outputs from Emergent. The unblinded statistical consultant then supervised third-party contractor creation of unblinded DSMB outputs, which were available upon request of the DSMB.

Study medication (FLU-IGIV or placebo) dosing data were reconciled with the randomized treatment group for each subject by the unblinded monitors, and any deviations are reported in the Clinical Study Report (CSR). The trial is unblinded once the clinical database (EDC) is locked. Unblinding entails Emergent approval, followed by vendor (SGS SDO) release of datasets to Emergent containing integrated unblinded treatment assignments and actual number of vials of FLU-IGIV dosed for each subject. At this point, unblinded central laboratory data on influenza strain and viral load, unblinded protocol deviations and PK concentrations are incorporated in datasets as well.

Emergency unblinding of the investigator and site staff to an individual subject's randomized treatment group via IWRS or unblinded medical monitor was possible if the subject's health or safety is at risk and knowledge of the study arm was beneficial to the medical management of the subject.

3 DATA CONSIDERATIONS

3.1 Protocol Deviations

Clinical research monitors entered protocol deviations (PDs) into a Clinical Trial Management System. PDs were graded as minor, major or critical. Minor PDs are defined as those that do not impact subject safety or the statistical analysis. Major PDs are those that potentially affect subject safety or the quality of the data evaluation. Critical PDs are those that substantially affect a subject's rights or safety or the quality of the data evaluation, or that show a pattern indicating intentional unauthorized deviation or fraud. PDs were categorized as follows:

- Investigational medical product (IMP) dispensing issue
- Informed consent issue
- Ineligible – violation of inclusion criteria
- Ineligible – violation of exclusion criteria

- Non-compliance with dosing schedule
- Study assessment not done
- Study assessment out of window
- Laboratory procedure not done
- Missed visit
- Laboratory sample collection processing issue
- Randomization error
- Safety reporting procedure not followed
- Sample storage temperature excursion
- Visit out of window
- Other

All PDs were entered into the EDC for incorporation in the clinical database for analysis and reporting. Unblinded PDs were reconciled with the clinical data immediately following database lock. Decisions affecting analysis population exclusions are finalized prior to database lock (see Section 3.2).

3.2 Analysis Populations

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

PK Population: The PK population includes all safety subjects who have adequate PK data for analysis that includes Day 1 baseline (pre-infusion) and at least one post-infusion time point. Subjects are analyzed according to the treatment received.

Intent to Treat (ITT) Population: The ITT population includes all randomized subjects regardless of study medication (FLU-IGIV or placebo) dosing, influenza type or PDs. Subjects are analyzed according to the treatment to which they were randomized. The ITT population is the primary analysis population for clinical benefit endpoints.

Modified Intent to Treat (mITT) Population: The mITT population includes those subjects from the ITT population who met eligibility criteria, received study medication (FLU-IGIV or placebo) and have confirmed influenza A by the local laboratory Rapid Ag or polymerase chain reaction (PCR) markers of viral infection test at screening. Subjects are analyzed according to the treatment to which they were randomized.

Viral Infection Confirmed Modified Intent to Treat Population (vITT): The vITT population includes any subjects from the mITT population who met eligibility criteria, received study medication (FLU-IGIV or placebo) and have confirmed influenza A by the central laboratory reverse transcriptase quantitative PCR (RT-qPCR) markers of viral infection test at screening or baseline. Subjects are analyzed according to the treatment to which they were randomized.

Clinically Evaluable Population (CE): The CE population includes any subjects from the vITT population who met eligibility criteria, received ≥ 80% of FLU-IGIV infusion (not applicable for placebo subjects) matching their randomized treatment group, received ≥ 80% of oseltamivir and have a non-missing Day 8 ordinal scale assessment. Subjects are analyzed according to the treatment to which they were randomized.

Receipt of ≥ 80% of FLU-IGIV is based on the volume administered as a percentage of the 500 mL diluted infusion volume. The clinical database collects whether the entire volume was administered or, if not, what volume in mL was administered. Receipt of ≥ 80% of oseltamivir is based on the total dose received in mg as recorded on the antiviral medication page as a percentage of the required total dose (75 mg twice per day * 5 days = 750 mg). A

subject who dies prior to receiving ≥ 80% of oseltamivir is counted in the CE population if that subject was on track to receive ≥ 80% of oseltamivir prior to the date of death.

3.3 Multicenter Study

Due to the anticipated low numbers of subjects enrolled at individual sites, subjects at all sites are pooled for analysis.

3.4 Analysis Visits and Windowing

Scheduled visits in the study include the following (see Table 1):

- Screening
- Day 1/baseline (pre-infusion)
- Day 1 infusion/post-infusion
- Day 2 (if not discharged on this day)
- Day 3 (if hospitalized only)
- Day 4 (if hospitalized, otherwise by telephone)
- Day 6 (if hospitalized only)
- Day 8 (required in person)
- Every 48 hours up to Day 30 (if hospitalized only)
- Hospital discharge (if prior to Day 60)
- Day 15 (required in person)
- Day 30 (required in person)
- Day 60 end of study (required in person)
- Early withdrawal

Visit-based data collected at Day 4 telephone visit, hospital discharge or early withdrawal are windowed to the appropriate study visit. Visit-based data includes ordinal scale, NEW score, viral load, laboratory test results, vital signs, influenza symptoms and physical examination. Study day for windowing is calculated as (assessment date – Day 1 date + 1). If the study day falls on a scheduled visit for which scheduled visit data were collected, then the scheduled visit data are used preferentially in the analysis. If the study day falls on a scheduled visit for which scheduled visit data were not collected, then the hospital discharge or early withdrawal data are used in the analysis in place of the scheduled visit data. If the study day for the hospital discharge or early withdrawal visit does not fall on a scheduled visit, then the data are associated with the nearest scheduled visit, following the same rules as above for data priority. In case of a tie (i.e., Day 45), the data are associated with the later visit. For some domains as specified in table shells, data for the hospital discharge visit are summarized separately as its own visit and not windowed to a scheduled visit.

3.5 Definition of Baseline

Baseline data are defined as the latest data collected prior to study medication dosing (FLU-IGIV or placebo) at Day 1 for dosed subjects. For undosed subjects, baseline is defined as the latest data collected through Day 1.

3.6 Treatment Groups

Tables are presented by treatment group: FLU-IGIV 450 mL, FLU-IGIV 225 mL or placebo. A total column is included for selected tables.

3.7 Coding Dictionaries

Medical history and AEs are coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary version 22.0.

Pre-infusion medications, concomitant medications and concomitant medical procedures are coded to preferred drug name using the World Health Organization Drug Dictionary Enhanced (WHO DDE) version Mar 2019. Anatomic therapeutic class coding is not performed.

Table 1 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	X	X											
Hospital Admission		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	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).

4 STATISTICAL ANALYSIS

4.1 Statistical Software

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

4.2 Summary Statistics

Continuous endpoints are summarized by descriptive statistics including number of subjects, mean, standard deviation (SD), median, minimum and maximum. Geometric mean and geometric coefficient of variation (CV%) are added for PK parameters and logarithmic transformation is used when appropriate. Medians, minimums and maximums are rounded to the number of decimal places present in the original data as collected, while means and SDs (including geometric mean and geometric CV%) are rounded to one more decimal place than present in the original data. Categorical endpoints are summarized by the number of subjects, frequency and percentage. Time-to-event endpoints are analyzed using Kaplan-Meier (KM) estimates of the median time with confidence intervals (CIs). Unless otherwise specified, CIs are 2-sided with a 95% confidence level.

4.3 Derived Variables

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

Study Day 1 is defined as the day of study medication administration. The day prior to the study medication infusion day is Day -1 and two days prior to the study medication infusion is Day -2. There is no Day 0.

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

Age in years is auto-calculated from date of birth by EDC as the difference between date of birth and date informed consent signed.

Age group is defined as 18-54 versus 55 and over for covariate/subgroup analyses.

Analysis populations (see Section 3.2).

Antiviral treatment is defined as a medication recorded on the antiviral treatment page; likely to be considered concomitant (see also prior medication, concomitant medication, post-treatment medication in this section).

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

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

Completed study is defined as received any amount of study medication (FLU-IGIV or placebo), continued to be in touch with site through Day 60 and categorized as completed on the trial termination CRF. (Note: We are not using the trial termination CRF status alone due to two subjects randomized but not treated who were followed up throughout the study and had trial termination status of completed). Note that Day 60 visit in-person is not required to be considered completed.

Concomitant medication is defined as a medication that either starts or ends within a window defined as 6 days prior to randomization through 24 hours after the study medication infusion end time (see also prior medication and post-treatment medication in this section). If medication start or end date or start or end time is missing or partial, then any medication that could be concomitant are counted as concomitant. Concomitant medications include, but are not limited to, pre-infusion medications.

Dose, total in mg is defined as infusion proportion (e.g., 0.9 if 90% of 500 mL volume was administered) multiplied by zero for placebo recipients and, for FLU-IGIV recipients, by the number of vials * extractable volume per vial of 45 mL * IgG protein concentration in mg/mL, dependent on the lot number). IgG protein concentrations for lots 23001204, 23001968 and 23002122 are 65, 62 and 62 mg/mL, respectively.

Influenza A strain, central laboratory is A/H1/California, A/H1/Michigan, A/H1/Unspecified, A/H3/Hong Kong, A/H3/Singapore, A/H3/Hong Kong_Singapore*, A/H3/Unspecified, B/Unspecified).
*Note that some samples designated A/H3/Hong Kong_Singapore tested positive for both Hong Kong and Singapore strains and are counted in both subgroups. The strain with the higher titer is used for viral load analysis for these subjects. Subjects with no influenza A strain identified (A/H1/Unspecified, A/H3/Unspecified or negative) or positive for influenza B (B/Unspecified) are omitted from viral load analysis. For PK analysis, both assays for all strains (California, Michigan, Hong Kong and Singapore) are run for all PK population subjects.

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

PDs (see Section 3.1).

Post-treatment medication is defined as a medication with a start date and time more than 24 hours after the study medication infusion end time (see also concomitant medication and prior medication in this section).

Prior medication is defined as a medication that starts and ends before 6 days prior to randomization (see also concomitant medication and post-treatment medication in this section).

Race groups are defined as white, black/African American and others for covariate/subgroup analyses.

Receipt of ≥ 80% of oseltamivir is based on the total dose received in mg as recorded on the antiviral medication page as a percentage of the required total dose (75 mg twice per day * 5 days = 750 mg). A subject who dies prior to receiving ≥ 80% of oseltamivir is counted in the CE population if that subject was on track to receive ≥ 80% of oseltamivir prior to the date of death.

Receipt of ≥ 80% of study medication (FLU-IGIV or placebo) is based on the volume administered as a percentage of the 500 mL diluted infusion volume.

Region groups are defined as N. America and other for covariate/subgroup analyses.

Season groups (2017-2018 or 2018-2019) are derived from randomization date.

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

Study drug or study medication is FLU-IGIV or placebo.

Time duration (in days) between event A and event B is (date of event B – date of event A + 1).

T**ime duration (in days) of supplemental oxygen** is calculated as (end date – start date + 1). If supplemental oxygen is ongoing at Day 60 (or early withdrawal date), the end date is censored on the Day 60 date (or early withdrawal date) for the purposes of calculating this duration.

Time from hospital admission to hospital discharge in days is calculated per duration between event A and event B. The continuous analysis is run twice, including and excluding subjects who die during the study period. Subjects who die in the hospital or are not discharged by Day 60 (or early withdrawal date) are censored on the date of death or Day 60 date (or early withdrawal date), respectively. Duration of ICU stay in days is calculated similarly.

Time from symptom onset to oseltamivir first dose date in days is calculated per duration between event A and event B. In the event of a missing or partial symptom onset date or oseltamivir first dose date, imputation is not performed and the time from symptom onset to oseltamivir first dose date is set to missing.

Time from symptom onset to study drug administration in days is calculated per duration between event A and event B. In the event of a missing or partial symptom onset date, imputation is not performed and the time from symptom onset to study drug administration is set to missing.

Treatment-emergent AE is all AEs in the study, as AEs are collected only during or after study drug infusion.

Visit windows (see Section 3.4).

4.4 Statistical Hypotheses

Study IA-001 is designed to determine the optimal dose of FLU-IGIV based on safety and PK data. No statistical hypotheses are tested for AE and serious AE (SAE) data, although relative risks and 95% CIs for overall incidences may be calculated as specified in table shells. PK dose proportionality may be explored.

Statistical hypothesis testing is carried out only for ordinal scale analyses at Day 8 and Day 4 using a 5% significance level and 2-sided tests (see Section 6.2). Pairwise testing of each FLU-IGIV group versus placebo, of the pooled high dose and low dose FLU-IGIV groups versus placebo and of the high dose FLU-IGIV group versus the low dose FLU-IGIV group are performed without multiplicity adjustment (see Section 4.8).

4.5 Handling of Missing Data

For partial dates for hospital discharge and death only, the following conventions are used:

- For dates missing only the day, the day is imputed to 15.
- For dates missing both the month and the day, no imputation is used.
- For dates missing the year, no imputation is used.

For the ordinal scale assessment (both at Day 4 and Day 8), if partial information is available, a more conservative outcome (lower in the scale) is assigned to the subject. For example, if a subject is known to have been discharged from hospital but it is unknown whether s/he can resume normal activity at Day 8, the outcome for that subject is designated as “No longer hospitalized, but unable to resume normal activities.”

Oseltamivir SOC treatment initiation is imputed as >48 hours after symptom onset in the case of missing or partial dates.

Duration of hospitalization analysis is run twice, including and excluding subjects who die during the study period. For subjects who die, duration of hospitalization is imputed as 60 days.

For laboratory data, unless otherwise specified in laboratory manuals, values reported as below the limit of quantification (LOQ) are substituted with LOQ/2. PK values below the limit of detection (LOD) or LOQ likewise are substituted with LOD/2 or LOQ/2, respectively, for calculation of summary statistics.

No other imputation rules are used.

4.6 Adjustment for Covariates

Covariate adjustment is neither applied to AE and SAE analyses nor to PK analyses.

Adjustment for baseline prognostic factors is considered for analysis of the ordinal scale endpoint using the mITT population. Prognostic factors include age group (18-54 versus 55 or over), sex, race (white, black/African American and others), region group (N. America or other), baseline NEW score (3-4 versus 5 or over), baseline viral load and whether oseltamivir SOC treatment was initiated within 48 hours of symptom onset (in the case of missing or partial dates, oseltamivir SOC treatment initiation is imputed as >48 hours after symptom onset). For further details, see Section 6.2.

4.7 Subgroup Analysis

For AE and SAE incidences, subgroup analyses may include age group (18-54 versus 55 or over), sex and race (white, black/African American and others). Note that each of the factors (age group, sex and race) is analyzed separately, not at the same time. For clinical benefit, subgroup analyses may include any of the covariates in Section 4.6, influenza strain (A/H1, A/H3 and B/other), subjects with ARDS/COPD or respiratory distress and those with high-risk factors (e.g., cardiovascular history, diabetes or morbid obesity).

4.8 Multiplicity Adjustment

Because this is a phase 2 study, the significance level for testing the secondary and exploratory variables is not adjusted for multiplicity.

5 STUDY POPULATION CHARACTERISTICS

5.1 Subject Disposition

Subject disposition, including early withdrawal reasons, is summarized and presented by treatment group for all randomized subjects. Tabulations include number of subjects randomized to treatment, number of subjects who discontinued prior to study medication dosing and the reasons for early withdrawal and number of subjects who discontinued prior to completion of all study visits and the reasons for early withdrawal (see definition of completed study in Section 4.3). Disposition data are listed by subject.

Enrollment is summarized by site for the safety population.

In addition, subject membership in each analysis population is tabulated by treatment group as well as listed for all safety population subjects.

5.2 Protocol Deviations

Major and critical PDs as defined in Section 3.1 are presented by treatment group for the safety population. All PDs including minor PDs are listed.

5.3 Demographics and Baseline Characteristics

5.3.1 Demographics

Demographic characteristics are obtained for each subject at screening and/or baseline and include: age and age group (see definition in Section 4.3), sex, race and ethnicity, height, weight and body mass index (BMI, see definition in Section 4.3). These variables are summarized using descriptive statistics by treatment group for the safety and ITT populations and are listed.

5.3.2 Influenza Symptoms and Baseline Characteristics

The following influenza symptoms and baseline characteristics are displayed by treatment group for the safety and ITT populations using descriptive statistics:

- Season (2017-2018 or 2018-2019)
- Region (N. America or other)
- Initial hospital residing unit (general ward, ICU, ER department or other)
- Presence of influenza symptoms at baseline (yes or no)
- Influenza symptom categories present (cough, diarrhea, fatigue, fever, headaches, lower RTI, muscle or body ache, nausea, runny or stuffy nose, shortness of breath, sore throat, vomiting or other)
- Duration from onset of symptoms to oseltamivir first dose date in days (see definition in Section 4.3)
- Duration from onset of symptoms to study drug administration in days (see definition in Section 4.3)
- Local laboratory influenza A test (Rapid Ag or PCR) result positive for influenza A (yes or no)
- Central laboratory influenza A test (RT-qPCR and/or culture) result positive for influenza A (yes or no)
- Central laboratory influenza A strain (A/H1/California, A/H1/Michigan, A/H1/Unspecified, A/H3/Hong Kong, A/H3/Singapore, A/H3/Hong Kong_Singapore*, A/H3/Unspecified, B/Unspecified).
  *Note that some samples designated A/H3/Hong Kong_Singapore tested positive for both Hong Kong and Singapore strains and are counted in both subgroups.
- Chest x-ray done (yes or no)
- Current seasonal vaccine status (yes or no)
- Baseline NEW score
- Baseline ordinal scale assessment

Influenza symptoms and baseline characteristics are listed.

5.3.3 Medical History and Concomitant Disease

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

5.3.4 Prior and Concomitant Medications

As stated in Section 3.5, pre-infusion medications, concomitant medications and concomitant medical procedures are coded to preferred drug name using the WHO-DDE version Mar 2019. Anatomic therapeutic class coding is not performed. Prior medications (see definition in Section 4.3) are presented for each preferred drug name using frequency counts by treatment group for the safety population. Concomitant medications and procedures, including pre-infusion medications and post-treatment medications, are presented separately in a similar manner. The following variables are summarized for concomitant antiviral medications:

- Completed 5-day oseltamivir treatment (750 mg; yes or no)
- Completed ≥80% oseltamivir treatment (yes or no)
- Total dose of oseltamivir received in mg
- Other SOC treatment by preferred drug name

Prior, concomitant, post-treatment and antiviral medications are listed together.

5.4 Treatment Compliance

Treatment compliance is not applicable to this study since the investigational treatment is administered as a single dose only in the clinic on Day 1. In the event of partial infusion of study medication, the partial volume infused (mL) is reported (see Section 7.1).

6 CLINICAL BENEFIT ANALYSIS

6.1 Primary Endpoint

The primary endpoint of study IA-001 is based on safety and PK data, upon which optimal dose determination is based. There is no primary clinical benefit endpoint. See Section 7 for safety and PK analyses.

6.2 Secondary Clinical Benefit Endpoint

The secondary clinical benefit endpoint is the 6-category ordinal scale assessment at Day 8. See imputation rules for missing data in Section 4.5. For the ordinal score, death=1 and higher scores equate to better outcomes.

Ordinal scale assessment outcomes are analyzed at Day 8 by treatment group for the ITT, mITT, vITT and CE populations using both a Wilcoxon rank-sum test and a proportional odds model investigating the effect of treatment group on ordinal outcome. The rank test is a pairwise two-sample test for location shift in median score.

```
proc npar1way data= <dataset> wilcoxon; * For each FLU-IVIG treatment group versus placebo, the pooled
FLU-IVIG treatment groups versus placebo and FLU-IVIG high dose versus low dose;
    class trt01a; * Categorical treatment variable;
    var scalen; * Variable scalen is numeric ordinal scale where death=1;
run;
```

An odds ratio is computed from the proportional odds model for each study treatment group relative to placebo, interpretable as the mean location shift across the ordinal scale attributed to FLU-IVIG treatment. The proportional odds model is used even if the proportional odds assumption is not strictly met; if the proportional odds assumption is significantly violated, then a partial proportional odds model for dose may be explored. A dose-response relationship is tested using ordinal logistic regression with a cumulative logit link and an ordinal dose variable, adjusting for significant prognostic factors using stepwise selection. Interaction terms are explored. The model may

be rerun for the pooled high dose and low dose FLU-IGIV groups versus placebo if no dose-response relationship is evident.

```
* Ordinal treatment variable trtn coded placebo='0', low dose='1', high dose='2';
* Variable scalen is numeric scale where death=1;
proc logistic data=<dataset> selection=stepwise; * Ensure that FLU-IVIG treatment value sorts before placebo;
    class trtn (param=ref ref='0') <agegp> <sex> <racegp> <bnewsgp> <socgp>;
    model scalen=trtn <bvload> <agegp> <sex> <racegp> <regiongp> <bnewsgp> <socgp>
        /aggregate scale=none expb;
    oddsratio trtn;
    lsmeans trtn/diff oddsratio cl;
run;
```

As described in Section 4.6, adjustment for baseline prognostic factors is considered for analysis of the ordinal scale endpoint using the mITT population. Prognostic factors include age group (18-54 versus 55 or over), sex, race (white, black/African American and others), region group (N. America or other), baseline NEW score (3-4 versus 5 or over), baseline viral load and whether oseltamivir SOC treatment was initiated within 48 hours of symptom onset (in the case of missing or partial dates, oseltamivir SOC treatment initiation are imputed as >48 hours after symptom onset). The model, as optimized for the mITT population, is reported for the ITT, vITT and CE populations as well.

Ordinal scale data are tabulated by visit for the ITT population by treatment group as well as listed.

6.3 Exploratory Clinical Benefit Endpoints

6.3.1 Ordinal Scale Assessment at Day 4

Ordinal scale assessment at Day 4 (72 hours post dose) is analyzed in the same manner as described above for Day 8 analysis for the ITT population only.

6.3.2 Change from Baseline to Day 4 in NEW Score

Change from baseline to Day 4 in NEW score is compared between treatment groups for the ITT population. The difference in the change from baseline between groups is reported using pairwise comparisons of the FLU-IVIG treatment groups to placebo, the pooled high dose and low dose FLU-IGIV groups versus placebo and of the high dose FLU-IGIV group versus the low dose FLU-IGIV group. Estimates of the between-group differences and their 95% confidence intervals are calculated using the Hodges-Lehmann method.

Change from baseline in NEW score data is tabulated by visit for the ITT population by treatment group as well as listed.

6.3.3 Change from Baseline in Log Viral Load at Days 2 and 3

Viral load data from central laboratory nasopharyngeal swabs are compared for differences between treatment groups for the ITT population at Days 2 and 3. The difference in the change from baseline (on a log scale) between groups at Day 2 and at Day 3 is reported on a pairwise basis between FLU-IVIG treatment groups to placebo, the pooled high dose and low dose FLU-IGIV groups versus placebo and of the high dose FLU-IGIV group versus the low dose FLU-IGIV group. Hodges-Lehmann estimates of the between-group differences and their 95% confidence intervals are provided.

Some subjects may not have an influenza A strain identified (A/H1/Unspecified, A/H3/Unspecified or negative) or may be positive instead for influenza B (B/Unspecified); these subjects are omitted from viral load analysis. For subjects testing positive for more than one influenza strain (i.e., both A/H3/HongKong_Singapore), the influenza A strain with higher titers is used in viral load analysis and the quantitative data for the other strain is omitted from tables and figures.

Change from baseline in viral load data (on a log scale) from central laboratory nasopharyngeal swabs is summarized by visit for the ITT population by treatment group as well as listed.

6.3.4 Duration of Hospitalization and Time to Hospital Discharge

Duration of hospitalization in days (see definition in Section 4.3) is run twice, including and excluding subjects who die during the study period. Subjects who die in the hospital or are not discharged by Day 60 (or early withdrawal date) are censored for KM analysis on the date of death or Day 60 date (or early withdrawal date), respectively. Duration of hospitalization is summarized by descriptive statistics for the ITT population along with duration of ICU and supplemental oxygen.

Median time from hospital admission to hospital discharge (see definition in Section 4.3) is estimated along with the corresponding 95% confidence interval using the Kaplan-Meier product-limit method and is presented by treatment group for the ITT population. Analyses of median time from symptom onset to oseltamivir first dose date as well as median time from symptom onset to study medication administration (see definitions in Section 4.3) are estimated and reported identically.

Kaplan-Meier plots are provided for the time from hospital admission to hospital discharge by treatment group for the ITT population.

7 SAFETY AND PHARMACOKINETIC ANALYSIS

7.1 Extent of Exposure

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

- Total dose of study medication in mg (see definition in Section 4.3)
- Total volume received (mL)
- Infusion duration in minutes
- Complete volume administered (yes or no)
- One or more infusion interruption (yes)

Study medication administration data are listed.

7.2 Primary Safety Endpoints

7.2.1 AE and SAE Incidence, Severity and Relationship

As stated in Section 3.5, AEs are coded to system organ class and preferred term using the MedDRA dictionary version 22.0. AEs are summarized by treatment group for the safety population, including the following AE summary tables:

- AE summary
- All AEs by system organ class and preferred term
- All AEs by system organ class, preferred term and maximum assessed severity
- AEs assessed as related to study medication by system organ class and preferred term
- Most frequent AEs (≥ 3% incidence) by system organ class and preferred term
- AEs leading to interruption of study medication infusion by system organ class and preferred term
- AEs leading to partial dose of study medication by system organ class and preferred term
- AEs leading to early withdrawal from study by system organ class and preferred term
- SAEs by system organ class and preferred term
- SAEs assessed as related to study medication by system organ class and preferred term
- AEs with outcome of death by system organ class and preferred term
- AEs of special interest (see Appendix I Section 10) by system organ class and preferred term
- AEs associated with a stopping rule by system organ class and preferred term *(table to be produced only in the event of a stopping rule being met)*

Each subject is counted once in each system organ class and preferred term even if multiple events in that category occurred for the subject. Assessment of causality is reported in the EDC as related or not related/no relationship. AEs where the causality assessment is missing after querying are excluded from summaries by relationship to study medication. Assessment of severity is collected in the EDC as mild, moderate or severe. AEs with missing severity assessment after querying are excluded from summaries by severity. Relative risks and 95% CIs for overall AE incidences may be calculated as specified in table shells.

Separate subgroup analyses of AE and SAE incidences by age group (18-54 versus 55 or over), sex and race (white, black/African American and others) may be performed by treatment group.

7.2.2 Pharmacokinetic Analysis

PK analysis for anti-influenza antibodies are conducted for the PK population using hemagglutination inhibition (HAI) and microneutralization (MN) concentration results for each strain (A/H1/California, A/H1/Michigan, A/H3/Hong Kong and A/H3/Singapore). For PK analysis, both assays for all strains are run for all PK population subjects.

Serum concentration versus time data are analyzed by standard noncompartmental methods (i.e., trapezoidal method with log-linear elimination phase). Actual times and not nominal times are used in the analysis. An absorption phase is modeled if indicated by the data. Concentrations below the LOD or LOQ are imputed as half of this value for summary statistics only. Calculated PK parameters include:

- **AUC_{0-t}**: The area under the concentration-time curve (AUC) from time 0 to the last quantifiable concentration, as calculated by the linear trapezoidal method with log-linear elimination phase.
- **AUC_{0-7}:** AUC from study Day 1 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.
- **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} is the first time point with this value.
- λ_Z: 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:** Total body clearance following IV administration.
- **V_z:** Volume of distribution following IV administration.

PK concentrations by visit as well as calculated PK parameters are reported using descriptive statistics for the PK population by treatment group. PK analysis includes placebo subjects unless all values for this group are below the LOD or LOQ. Serum concentration-time data are plotted by treatment group. Dose proportionality may be explored using log-transformed PK data. Dose-normalized PK parameters may be calculated, particularly in the case of numerous partial infusions of study medication. Subset analyses by age group (18-54 versus 55 or over), sex and race (white, black/African American and others) may be performed. PK concentration data are listed.

7.3 Pharmacodynamic Assessment of the Relationship Between PK and Log Viral Load

The pharmacodynamic relationship between HAI test AUC and log viral load may be investigated for subjects belonging to both the PK and ITT populations using nonparametric Spearman correlation and reported in a table and a plot, if applicable.

7.4 Deaths

AEs with outcome of death are summarized as described above in Section 7.2.1. All subject deaths during the study period, along with cause of death, are listed.

7.5 Clinical Laboratory Tests

Laboratory values including blood chemistry and hematology at each scheduled visit and change from baseline to each scheduled visit in laboratory values are summarized by treatment group for the safety population using descriptive statistics. The number and percentage of study subjects with laboratory values outside the normal range at any time on study are summarized in a similar manner. Clinical laboratory data are listed.

7.6 Vital Signs

Vital signs data include temperature, respiratory rate, blood pressure, pulse and oxygen saturation percentage on room air. Vital signs at each scheduled visit and change from baseline to each scheduled visit are summarized by treatment group for the safety population using descriptive statistics. The number and percentage of study subjects with vital signs values assessed as clinically significantly abnormal at any time on study are summarized in a similar manner. Vital signs data are listed.

7.7 Influenza Symptoms

Influenza symptoms at each scheduled visit are summarized by treatment group for the safety population using descriptive statistics. Influenza symptoms data are listed.

7.8 Physical Examination

Clinically significant physical examination abnormalities at each scheduled visit are summarized by treatment group for the safety population using frequency counts and percentages by body system. Physical examination data are listed.

8 DATA MONITORING AND INTERIM ANALYSES

8.1 Data Monitoring Committee

An independent DSMB provides ongoing review of safety data during the trial. The DSMB is responsible for assessing subject safety and monitoring overall conduct and integrity of the trial. A DSMB data review is planned after enrollment and data entry for 20 subjects and annually thereafter, should the study run for more than one Northern hemisphere influenza season.

The DSMB has access to unblinded data including at a minimum subject 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 safety stopping rules in the protocol or based on their clinical judgment of subject safety (see DSMB Charter).

If a safety stopping criterion as outlined in the protocol is met, a hold on recruitment is implemented until an *ad hoc* DSMB meeting is held. The DSMB reviews 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 determines whether trial termination is recommended, which would require a majority vote.

Strict procedures governing handling of unblinded data are in place to maintain the integrity of the study blind (see Section 2.5). No unblinded data are shared outside of the DSMB and the unblinded study team.

8.2 Interim Analyses

No formal interim analysis is planned apart from the DSMB data review.

9 REFERENCES

None.

10 APPENDIX I AESI PREFERRED TERM LIST

10.1 Preferred Terms for Modified Hypersensitivity SMQ

Acute generalised exanthematous pustulosis
Administration related reaction
Administration site dermatitis
Administration site eczema

Administration site hypersensitivity
Administration site rash
Administration site urticaria
Allergic bronchitis
Allergic cough
Allergic eosinophilia
Allergic hepatitis
Allergic keratitis
Allergic myocarditis
Allergic oedema
Allergic otitis media
Allergic pharyngitis
Allergic reaction to excipient
Allergic respiratory disease
Allergic respiratory symptom
Allergic sinusitis
Allergic transfusion reaction
Alveolitis allergic
Anaphylactic reaction
Anaphylactic shock
Anaphylactic transfusion reaction
Anaphylactoid reaction
Anaphylactoid shock
Angioedema
Arthritis allergic
Aspirin-exacerbated respiratory disease
Atopy
Blepharitis allergic
Bronchospasm
Circumoral oedema
Conjunctival oedema
Conjunctivitis allergic
Corneal oedema
Dermatitis
Dermatitis acneiform
Dermatitis allergic
Dermatitis atopic
Dermatitis bullous
Dermatitis exfoliative
Dermatitis exfoliative generalised
Dermatitis psoriasiform
Drug eruption

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

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

Rash follicular
Rash generalised
Rash macular
Rash maculo-papular
Rash maculovesicular
Rash morbilliform
Rash papulosquamous
Rash pruritic
Rash pustular
Rash rubelliform
Rash scarlatiniform
Rash vesicular
Reaction to excipient
Rhinitis allergic
Scleral oedema
Scleritis allergic
Scrotal oedema
Serum sickness
Serum sickness-like reaction
Skin necrosis
Skin reaction
Skin test positive
Stevens-Johnson syndrome
Swelling face
Swollen tongue
Symmetrical drug-related intertriginous and flexural exanthema
Therapeutic product cross-reactivity
Tongue oedema
Toxic epidermal necrolysis
Toxic skin eruption
Tracheal oedema
Type I hypersensitivity
Type II hypersensitivity
Type III immune complex mediated reaction
Type IV hypersensitivity reaction
Urticaria
Urticaria papular
Urticaria pigmentosa
Urticaria vesiculosa
Urticarial vasculitis
Vessel puncture site rash

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

10.2 Preferred Terms for Modified Renal Dysfunction SMQ

Glomerular vascular disorder
Hypertensive nephropathy
Ischaemic nephropathy
Malignant renal hypertension
Nephroangiosclerosis
Page kidney
Renal aneurysm
Renal arteriosclerosis

Renal arteritis
Renal artery arteriosclerosis
Renal artery dissection
Renal artery fibromuscular dysplasia
Renal artery hyperplasia
Renal artery occlusion
Renal artery perforation
Renal artery stenosis
Renal artery thrombosis
Renal embolism
Renal hypertension
Renal infarct
Renal ischaemia
Renal vascular thrombosis
Renal vasculitis
Renal vein embolism
Renal vein occlusion
Renal vein stenosis
Renal vein thrombosis
Renal vein varices
Renal vessel disorder
Renovascular hypertension
Renal cortical necrosis
Renal necrosis
Renal papillary necrosis
Renal tubular necrosis

10.3 Preferred Terms for Modified Aseptic Meningitis Syndrome SMQ

Meningitis aseptic

10.4 Preferred Terms for Modified Hemolysis SMQ

Acute haemolytic transfusion reaction
Autoimmune haemolytic anaemia
Cold type haemolytic anaemia
Coombs direct test positive
Coombs indirect test positive
Coombs negative haemolytic anaemia
Coombs positive haemolytic anaemia
Coombs test positive
Delayed haemolytic transfusion reaction
Extravascular haemolysis
Haemoglobin urine present
Haemoglobinaemia

Haemoglobinuria
Haemolysis
Haemolytic anaemia
Haemolytic transfusion reaction
Haptoglobin decreased
Intravascular haemolysis
Warm type haemolytic anaemia

10.5 Preferred Terms for Modified Thrombosis SMQ

Amaurosis
Amaurosis fugax
Aortic thrombosis
Arterial occlusive disease
Arterial thrombosis
Basal ganglia infarction
Basilar artery occlusion
Basilar artery thrombosis
Blindness transient
Brachiocephalic artery occlusion
Carotid arterial embolus
Carotid artery occlusion
Carotid artery thrombosis
Cerebellar artery occlusion
Cerebellar artery thrombosis
Cerebral artery embolism
Cerebral artery occlusion
Cerebral artery thrombosis
Coronary artery embolism
Coronary artery occlusion
Coronary artery reocclusion
Coronary artery thrombosis
Embolism arterial
Femoral artery embolism
Hepatic artery embolism
Hepatic artery occlusion
Hepatic artery thrombosis
Iliac artery embolism
Iliac artery occlusion
Ischaemic cerebral infarction
Ischaemic stroke
Lacunar infarction
Leriche syndrome

Mesenteric arterial occlusion
Mesenteric arteriosclerosis
Mesenteric artery embolism
Mesenteric artery thrombosis
Myocardial infarction
Myocardial necrosis
Papillary muscle infarction
Penile artery occlusion
Peripheral arterial occlusive disease
Peripheral arterial reocclusion
Peripheral artery occlusion
Peripheral artery thrombosis
Peripheral embolism
Popliteal artery entrapment syndrome
Post procedural myocardial infarction
Postinfarction angina
Precerebral artery occlusion
Precerebral artery thrombosis
Pulmonary artery occlusion
Pulmonary artery thrombosis
Renal artery occlusion
Renal artery thrombosis
Renal embolism
Retinal artery embolism
Retinal artery occlusion
Retinal artery thrombosis
Silent myocardial infarction
Spinal artery embolism
Spinal artery thrombosis
Splenic artery thrombosis
Splenic embolism
Subclavian artery embolism
Subclavian artery occlusion
Subclavian artery thrombosis
Superior mesenteric artery syndrome
Thrombotic microangiopathy
Thrombotic thrombocytopenic purpura
Transient ischaemic attack
Truncus coeliacus thrombosis
Vascular pseudoaneurysm thrombosis
Vertebral artery occlusion
Vertebral artery thrombosis

Axillary vein thrombosis
Brachiocephalic vein occlusion
Brachiocephalic vein thrombosis
Budd-Chiari syndrome
Cavernous sinus thrombosis
Cerebral venous thrombosis
Deep vein thrombosis
Deep vein thrombosis postoperative
Embolism venous
Hepatic vein embolism
Hepatic vein occlusion
Hepatic vein thrombosis
Homans' sign positive
Iliac vein occlusion
Inferior vena cava syndrome
Inferior vena caval occlusion
Intracranial venous sinus thrombosis
Jugular vein occlusion
Jugular vein thrombosis
Mesenteric vein thrombosis
Mesenteric venous occlusion
Obstetrical pulmonary embolism
Obstructive shock
Ophthalmic vein thrombosis
Ovarian vein thrombosis
Pelvic venous thrombosis
Penile vein thrombosis
Portal vein occlusion
Portal vein thrombosis
Portosplenomesenteric venous thrombosis
Post procedural pulmonary embolism
Post thrombotic syndrome
Postoperative thrombosis
Postpartum venous thrombosis
Pulmonary embolism
Pulmonary infarction
Pulmonary microemboli
Pulmonary thrombosis
Pulmonary vein occlusion
Pulmonary veno-occlusive disease
Pulmonary venous thrombosis
Renal vein embolism

Renal vein occlusion
Renal vein thrombosis
Retinal vein occlusion
Retinal vein thrombosis
Splenic vein occlusion
Splenic vein thrombosis
Subclavian vein occlusion
Subclavian vein thrombosis
Superior sagittal sinus thrombosis
Superior vena cava occlusion
Superior vena cava syndrome
Thrombosed varicose vein
Thrombosis corpora cavernosa
Transverse sinus thrombosis
Vena cava embolism
Vena cava thrombosis
Venoocclusive disease
Venoocclusive liver disease
Venous occlusion
Venous thrombosis
Venous thrombosis in pregnancy
Venous thrombosis limb
Visceral venous thrombosis
Administration site thrombosis
Adrenal thrombosis
Application site thrombosis
Arteriovenous fistula occlusion
Arteriovenous fistula thrombosis
Arteriovenous graft thrombosis
Atrial thrombosis
Basal ganglia stroke
Bone infarction
Brain stem embolism
Brain stem infarction
Brain stem stroke
Brain stem thrombosis
Cardiac ventricular thrombosis
Catheter site thrombosis
Cerebellar embolism
Cerebellar infarction
Cerebral infarction
Cerebral ischaemia

Cerebral microembolism
Cerebral septic infarct
Cerebral thrombosis
Cerebral vascular occlusion
Cerebrospinal thrombotic tamponade
Cerebrovascular accident
Choroidal infarction
Coronary bypass thrombosis
Disseminated intravascular coagulation
Embolic cerebral infarction
Embolic pneumonia
Embolic stroke
Embolism
Graft thrombosis
Haemorrhagic adrenal infarction
Haemorrhagic cerebral infarction
Haemorrhagic infarction
Haemorrhagic stroke
Haemorrhagic transformation stroke
Haemorrhoids thrombosed
Heparin-induced thrombocytopenia
Hepatic infarction
Hepatic vascular thrombosis
Infarction
Infusion site thrombosis
Inner ear infarction
Intestinal infarction
Intracardiac thrombus
Mesenteric vascular occlusion
Microembolism
Optic nerve infarction
Pancreatic infarction
Paradoxical embolism
Paraneoplastic thrombosis
Pituitary infarction
Placental infarction
Post procedural stroke
Postpartum thrombosis
Prosthetic cardiac valve thrombosis
Renal infarct
Renal vascular thrombosis
Retinal infarction

Retinal vascular thrombosis
Shunt occlusion
Shunt thrombosis
Spinal cord infarction
Splenic infarction
Splenic thrombosis
Stoma site thrombosis
Stroke in evolution
Testicular infarction
Thalamic infarction
Thromboangiitis obliterans
Thrombosis
Thrombosis mesenteric vessel
Thrombotic cerebral infarction
Thrombotic stroke
Thyroid infarction
Tumour embolism
Tumour thrombosis

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

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