Official Title:	Effects of Plasma Exchange with Human Serum Albumin 5% (PE-A 5%) on Short-term Survival in Subjects with "Acute-On-Chronic Liver Failure" (ACLF) at High Risk of Hospital Mortality
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STATISTICAL ANALYSIS PLAN (SAP)

IG1407

Study Title: **Effects of Plasma Exchange with Human Serum Albumin 5% (PE-A 5%) on Short-term Survival in Subjects with "Acute-On-Chronic Liver Failure" (ACLF) at High Risk of Hospital Mortality**

Development Phase: 3

SAP Version: Version 3.0

SAP Effective Date: The effective date of the document is the last date of approval of the document.

Protocol Version: IG1407 Amendment 5/Version 6 Dated 21Mar 2023

Author: [redacted]

APPROVALS

[redacted]

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List of Abbreviations

ACLF	Acute-on-Chronic Liver Failure
ADR	Adverse drug reactions
AE(s)	Adverse event(s)
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
AR	Adverse reaction
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BUN	Blood urea nitrogen
CI	Confidence interval
CLIF	Chronic Liver Failure
CLIF-C ACLF	CLIF-Consortium ACLF score
CLIF-C OF	CLIF-Consortium Organ Failure
CMH	Cochran-Mantel-Haenszel
CRP	C-reactive protein
CSR	Clinical study report
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EU	European Union
FFP	Fresh frozen plasma
GGT	Gamma glutamyl transpeptidase
GI	Gastrointestinal
HCT	Hematocrit
HE	Hepatic encephalopathy
HRS	Hepatorenal Syndrome
ICU	Intensive Care Unit
IL	Interleukin
INR	International Normalized Ratio
IP	Investigational product
ITT	Intent-to-Treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWRS	Interactive Web Response System
MAP	Mean arterial pressure
MELD	Model for End-Stage Liver Disease
MMRM	Mixed-effects model for repeated measurement
NA	North America
PE	Plasma Exchange
PH	Proportional-Hazards
PP	Per Protocol
PT	preferred term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Spontaneous bacterial peritonitis
SMT	Standard medical treatment
SOC	system organ class
SpO_2	Peripheral oxygen saturation
TBV	Total blood volume
TEAE	Treatment-emergent adverse event

US	United States
WBC	White blood cell
WHO-DD	World Health Organization Drug Classification Dictionary

1 Version History

SAP Version	Effective Date	Description of Change
1.0	July 20th, 2023	Not Applicable
2.0	Sep 29th, 2025	1. Section 1: Provided early termination date of the study. 2. Section 6.1.2: Added the definition of Day 1 and clarified study drug administration. 3. Section 6.1.3: Updated the definition of baseline for clarity. 4. Section 6.1.4: Included death date as a definition of last contact date. 5. Section 6.1.5: Added detailed mapping rules and selection logic for multiple assessments of laboratory/vital sign assessments and exploratory endpoints. Added Appendix 5 with details of visit windows to be applied. 6. Section 6.4.3: Updated Per Protocol (PP) population definition to order criteria based on assessment for each treatment arm. 7. Section 6.5: Revised the fixed-sequence testing method to include the ITT population, clarifying which population will be assessed. 8. Section 7.2: Expanded Protocol Deviations to provide a more detailed

		description of summary tables to be presented. 9. Section 7.3: Added ACLF grade, Ascites Grade, Ascites, Refractory occurrences, Ascites Refractory Type, CLIF-C ACLF score, CLIF-C OF total score, Child-Pugh Score, MELD score, and country to baseline characteristics summary. Removed ACLF-AD score. 10. Section 8.1: Displayed concomitant medication summary tables by three medications. 11. Section 8.2: Removed "time since the start of use" from summary. Used safety population for analysis. 12. Section 8.4: Added expected exchange number formular since site didn't always collect that information in CRF. 13. Section 9.1/9.2/9.4: Updated Efficacy Analysis to add analysis period and cut-off dates for clarity. 14. Section 9.1.1: Provided a more detailed explanation of the endpoint, censoring, and analysis period. 15. Section 9.1.2: Updated Primary Analysis to detail the hypothesis test performed, included protocol details, and specified where

		stratification factors are recorded (i.e., IWRS). 16. Section 9.1.3: Added sensitivity analysis to consider different censoring methods and use stratification factors collected in the electronic case report form (eCRF) if more than 3% of subjects. 17. Section 9.2: Provided a more detailed explanation of the endpoint, censoring, and analysis period. Added sensitivity analysis for different censoring methods. 18. Section 9.3.1: Updated censoring event definition. Added an additional subgroup analysis for region in Exploratory Subgroup Analysis. 19. Section 9.3.2: Updated independent variables in the analysis model and specified the visits included in the analysis. 20. Section 9.3.3: Updated analysis method to use MMRM for change from baseline and specified visits included in the analysis. 21. Section 9.3.4: Updated analysis method to use MMRM for change from baseline, specified visits included, and added imputation rule for MELD score (how to

		derive the score if individual clinical parameter is <1, and generate scores if MELD is <4 or >40). 22. Section 9.3.5: Updated analysis method to use MMRM for change from baseline and specified visits included in the analysis. 23. Section 9.3.6: Updated analysis method to use MMRM for change from baseline and specified visits included in the analysis. 24. Section 9.3.7: Specified visits included in the analysis. 25. Section 9.3.7.4: Updated definition of new infections and rate of new infections, using study duration. 26. Section 9.3.8: Specified visits included in the analysis. 27. Section 10.1: Added Non-Serious Suspected ADR, Serious AR, and Non-Serious AR to TEAE categories. 28. Section 10.3: Added information regarding laboratory result imputation and summarizing laboratory results reported. Specified visits included in the analysis. 29. Section 10.4: Specified visits included in the analysis.

		30. Section 12: Changed the analysis of longitudinal outcomes, added ascites assessment as an exploratory endpoint, added sensitivity analysis where liver transplant is not considered as censoring event, added subgroup analysis on exploratory analysis, and additional categories in TEAE. 31. Section 14: Added Appendix 5 for visit windowing of exploratory endpoints.
3.0	Oct 15th ,2025	1. Section 6.1: Included the source of the death date when it is not available in the vital status eCRF. 2. Section 9.1.3: Added a sensitivity analysis for subjects whose death date was not captured on the vital status eCRF page.

2 Purpose of the Analysis

The purpose of this statistical analysis plan (SAP) is to outline the planned analyses to support the completion of the clinical study report (CSR) for protocol IG1407. The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Exploratory analyses not identified or defined in this SAP may be performed to support the clinical development program. Any post-hoc or unplanned analyses performed and not identified in this SAP will be documented in the respective CSR. The study was terminated early, and the last patient visit happened on April 14, 2025.

3 Introduction

The investigational product (IP) in this study is Human Albumin Grifols 5% (Albutein® 5%), which will be administered via plasma exchange (PE) as a treatment for Acute-on-Chronic Liver Failure (ACLF). Albutein 5% is a solution containing 50 g/L of total protein of which at least 95% is human albumin. See protocol section 4.5 Study Treatments for detail.

Cirrhosis is a progressive chronic liver disease characterized by diffuse fibrosis, severe disruption of the intrahepatic venous flow, portal hypertension, and liver failure. The natural course of cirrhosis is divided into 2 stages. The first stage is compensated cirrhosis, which is defined as the period between the onset of cirrhosis and the appearance of the first major complication of the disease. During this period, which is

relatively long in most patients (>10 years), symptoms are absent or minor, but liver lesions steadily progress. The term decompensated cirrhosis defines the period following the development of ascites, variceal bleeding, hepatic encephalopathy (HE) and bacterial infection. This period is associated with short-term survival (3 to 5 years). It is increasingly evident that patients die as a consequence of an acute deterioration in their clinical condition promoted by a precipitating event, a syndrome termed Acute-on-Chronic Liver Failure (ACLF).

Several studies suggest that PE may be effective and safe in the treatment of subjects with fulminant hepatic failure (1,2) But there is no study examining PE with human serum albumin 5% (PE-A 5%) in ACLF with the exception of a recent pilot investigation performed in the Hospital Clinic in Barcelona sponsored by Instituto Grifols S.A.(3). The main objective of the study was to assess safety of PE-A 5% in ACLF. Based on the data obtained from this trial, severe thrombocytopenia (platelet count ≤20×109/L) was observed in 3 subjects with low platelet count at baseline. No hemorrhagic events were observed. PE-A 5% treatment improved liver, renal, cardiovascular, and cerebral function and attenuated inflammatory response and endothelial dysfunction. Serum albumin concentration increased from 24 to 28 g/L, indicating that PE using 5% albumin solutions has a modest impact on serum albumin. Short-term mortality rate was 30% at 28 days and 40% at 90 days. These mortality rates were lower than those observed in 40 matched subjects with ACLF included in the CANONIC Study (57.5% and 65% respectively) (4). This pilot study suggests that PE-A 5% is safe in subjects with ACLF and may improve organ function.

The potential beneficial effects of PE-A 5% in ACLF are related to 2 features. Plasma exchange removes endogenous and exogenous substances accumulated in subjects with ACLF because of organ failure(s) and systemic inflammation. Many of these substances are normally transported in blood bound to serum albumin. However, since most binding sites of human serum albumin in subjects with cirrhosis and ACLF are presumably occupied, many of these substances circulate free in plasma and interact with specific cell sites producing adverse reactions, predisposing subjects with ACLF to bacterial infections (5). The net effect of these features is severe hypoalbuminemia and impairment in albumin function, which further increase the plasma concentration of free molecules with toxic effects.

The second potential beneficial effect of PE-A 5% is related to the substitution of the saturated endogenous albumin by exogenous albumin with preserved biological functions (6), thus improving the process of transportation and reducing the levels of free toxic molecules that accumulate in plasma as consequence of organ failure(s) and systemic inflammation.

Fluid removal and replacement during PE-A 5% will be performed simultaneously. Routine practice is to exchange 1.1 to 1.5 plasma volumes during a PE-A 5% session. Removing larger volumes will prolong the procedure, expose the patient to more replacement fluid and more anticoagulant, and thus increases the risk of complications without a relevant benefit 7).

Administering fresh frozen plasma (FFP) at the beginning of a PE-A 5% session would result in the removal of most coagulation factors administered. Therefore, the administration of FFP will be performed at the end of the PE-A 5% session to prevent coagulopathy.

4 Objectives

4.1 Efficacy Objectives

4.1.1 Primary Efficacy Objective

- To evaluate the effect of standard medical treatment (SMT) plus PE-A 5% (SMT+PE-A 5%) on 90-day overall survival

4.1.2 Secondary Efficacy Objectives

- To evaluate the effect of SMT+PE-A 5% on 90-day transplant-free survival
- To evaluate the effect of SMT+PE-A 5% on 28-day overall survival

4.1.3 Exploratory Efficacy Objectives

The effects of SMT+PE-A 5% on the following parameters will be evaluated:

- 90-day overall, 90-day transplant-free, and 28-day overall survival after randomization in subgroups of subjects with ACLF-1b, ACLF-2, or ACLF-3a
- In-patient hospital stays (including ICU stay) overall and transplant-free survival in the entire study population and in the subgroups of subjects with ACLF-1b, ACLF-2, or ACLF-3a
- 28-day transplant-free survival in the entire study population and in the subgroups of subjects with ACLF-1b, ACLF-2, or ACLF-3a
- Incidence of individual organ failures: liver, renal, brain, coagulation, circulation, and respiration as defined by the Chronic Liver Failure-Consortium Organ Failure (CLIF-C OF) score and the total CLIF-C OF score, during the treatment period and at the end of treatment and of hospitalization (or liver transplantation or death)
- ACLF course (resolution, improvement, steady course, or worsening), CLIF-C ACLF score, Child-Pugh score, and Model for End-stage Liver Disease (MELD) score
- Systemic inflammation as measured by C-reactive protein (CRP), white blood cells (WBC), and procalcitonin
- Rate of all new infections
- Time to hospital discharge
- Pre and post PE-A 5% albumin levels in serum

4.2 Safety Objectives

To determine the safety and tolerability profile of PE-A 5% in subjects with ACLF.

5 Investigational Plan

5.1 Overall Study Design and Plan

This is a phase 3, multicenter, randomized, controlled, parallel-group, open-label study to evaluate the effects of PE-A 5% in ACLF subjects. The study will involve hospitals with expertise in the management of subjects with ACLF. This clinical study is planned to be performed in approximately 40 study centers in the United States, Canada, and Europe.

As originally designed prior to early termination, approximately 380 subjects with cirrhosis, ACLF, and high risk of hospital mortality (ACLF-1b, ACLF-2, or ACLF-3a) (Table 9-1) will be included in this study after obtaining written informed consent. In case of hepatic encephalopathy (HE), written informed consent will be obtained from a relative or a legally authorized representative (surrogate) if the subject is considered incompetent to consent.

There will be a screening period of no more than 10 days for each subject during which subjects will be screened for enrollment in the study. Subjects with ACLF-1b, ACLF-2, or ACLF-3a will be included at diagnosis of the syndrome. Subjects with ACLF-1a will be followed up and included if they deteriorate to ACLF-1b, ACLF-2, or ACLF-3a within the 10-day Screening Period. Subjects with ACLF-3b will be followed up and included if they improve to ACLF-3a, ACLF-2, or ACLF-1b within the 10–day Screening Period.

Randomization of subjects will be stratified by region (European Union [EU] or North America [NA]) and the 3 ACLF grades (ACLF-1b, ACLF-2, or ACLF-3a). Within each stratum (i.e., each unique combination of region and ACLF grade), subjects will be randomized in a 1:1 ratio into 2 treatment groups below:

- SMT+PE-A 5% (treatment group)
- SMT (control group)

The definitions for the degree of response to the intervention are the following: complete response is resolution of ACLF or improvement to ACLF-1a; partial response is reduction of 1 organ failure or more to ACLF-1b or ACLF-2; and no response is maintenance or worsening of ACLF grades. These response definitions are used by investigator to determine the number of PE-A 5% sessions for subjects in the SMT+PE-A 5% treatment group.

SMT+PE-A 5% Treatment Group

Approximately 190 subjects will be randomized to the SMT+PE-A 5% treatment group. PE-A 5% will be performed using 5% albumin (Albutein 5%) as the main replacement fluid administered intravenously. Fresh frozen plasma will be given after each PE-A 5% session to prevent coagulopathy, and the PE-A 5% session is considered completed at the end of the FFP administration. The treatment schedule consists of 2 initial PE-A 5% sessions on consecutive days followed by every other day PE-A 5% sessions. A minimum of 4 and a maximum of 9 PE-A 5% sessions will be performed in subjects randomized to receive SMT+PE-A 5% (maximum treatment period: 17 days).

The exact number of PE sessions will be determined by the pattern of response (achieving complete response or no improvement/deterioration of ACLF) to PE-A 5% therapy. IVIGs will be administered at a dose of 200 mg/kg 1 day after every 2 PE sessions in order to prevent the development of hypogammaglobulinemia and infection. For subjects ending the treatment at an odd-number PE session (e.g., #5, #7, or #9), IVIGs will be administered at a dose of 100 mg/kg 1 day after this last PE session. Initial infusion rate of IVIGs will be of 0.5 mL/kg/hour, increasing to a maximum rate of 2 mL/kg/hour if well tolerated. See Table 5-1 and Table 5-2 details.

Table 5-1 PE Schedule (Number of Sessions) according to the Clinical Response to Treatment (Complete and No Clinical Responses)

Very early complete clinical response after the first 1 or 2 PE sessions[a]												
PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■					
Day	1	2	3	4	5	6	7					
Very early complete clinical response after the first 3 PE sessions[b]												
PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■	▲ #5	●			
Day	1	2	3	4	5	6	7	8	9			
Complete clinical response after the first 4 PE sessions[c]												
PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■	▲ #5		▲ #6	■	
Day	1	2	3	4	5	6	7	8	9	10	11	
No clinical response after the first 4 PE sessions[d]												
PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■					
Day	1	2	3	4	5	6	7					

[a] These subjects will receive 3 or 2 additional PE-A 5% sessions following complete clinical response and therefore will receive a total of 4 PE-A 5% sessions.

[b] These subjects will receive 2 additional PE-A 5% sessions following complete clinical response and therefore will receive 5 PE-A 5% sessions.

[c] These subjects will receive 2 additional PE-A 5% sessions following complete clinical response and therefore will receive 6 PE-A 5% sessions.

[d] These subjects with no response after 4 PE-A 5% sessions will discontinue the treatment so the total number of PE-A 5% sessions will be 4.

▲ PE = PE-A 5% session, ■ IGIV = 200 mg/kg every 2 PE sessions, ● IGIV = 100 mg/kg 1 day after the last, odd-numbered PE session

Table 5-2 PE Schedule (Number of Sessions) according to the Clinical Response to Treatment (Partial Clinical Responses after the First 4 PE Sessions)

Achieve complete response at 5th PE session[a]

PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■	▲ #5		▲ #6	■	▲ #7
Day	1	2	3	4	5	6	7	8	9	10	11	12
PE	●											
Day	13											

Achieve complete response at 6th PE session[b]

PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■	▲ #5		▲ #6	■	▲ #7
Day	1	2	3	4	5	6	7	8	9	10	11	12
PE		▲ #8	■									
Day	13	14	15									

Achieve or do not achieve complete response after 7th PE session[c]

PE	▲ #1	▲ #2	■	▲ #3		▲ #4	■	▲ #5		▲ #6	■	▲ #7
Day	1	2	3	4	5	6	7	8	9	10	11	12
PE		▲ #8	■	▲ #9	●							
Day	13	14	15	16	17							

[a] These subjects will receive 2 additional PE-A 5% sessions following complete clinical response at the 5th PE-A 5% session and therefore will receive a total of 7 PE sessions.

[b] These subjects will receive 2 additional PE-A 5% sessions following complete clinical response at the 6th PE-A 5% session and therefore will receive a total of 8 PE-A 5% sessions.

[c] Regardless of the response after the 7th or 8th session, subjects will receive the remaining 2 or 1 PE-A 5% sessions so the total number of PE-A 5% sessions will be 9.

SMT Group

Approximately 190 subjects will be randomized to the control group and receive SMT for the length of the study or as long as needed. Standard medical treatment will be administered per institution standards. Several guidelines are published for the management of complications and comorbidities of ACLF. Subject's treatment period as specified in this protocol will be 7 days for all subjects and will then be prolonged depending on subject's ACLF evolution for up to 17 days:

- Subjects in the SMT group with ACLF-1b, -2, or -3a who achieve complete response (ACLF resolution or improve to ACLF-1a) within the treatment period (from Day 1 to Day 7), will be assessed for 4 more days after the ACLF resolution or improvement day and then will be followed up at Hospital Discharge (if applicable) and on Days 21, 28, 60, and 90.

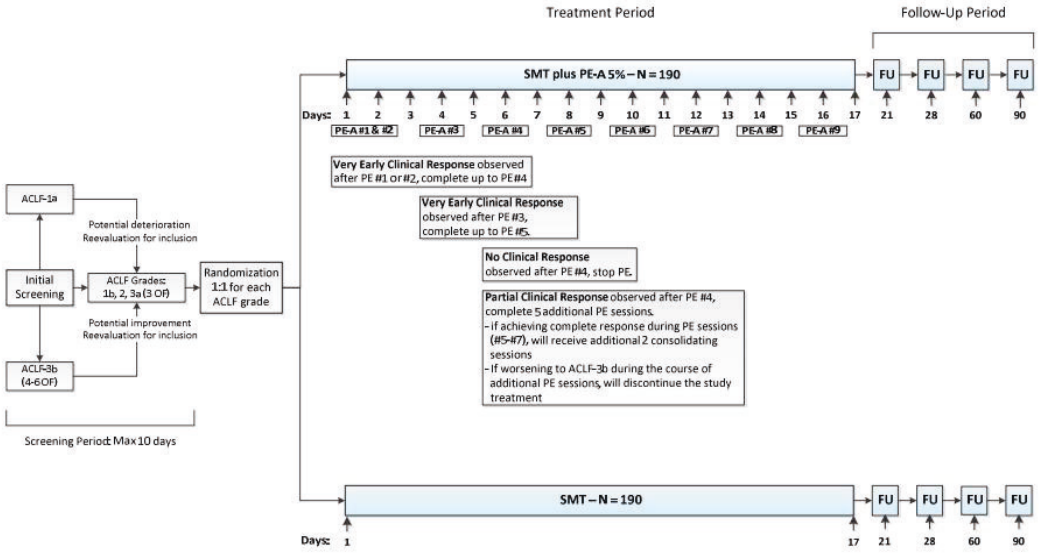
- Subjects in the SMT group with ACLF-1b, -2, or -3a who maintain or worsen their ACLF grades throughout the treatment period (from Day 1 to Day 7), will be further assessed for up to Day 17 and will be then followed up at Hospital Discharge (if applicable) and on Days 21, 28, 60, and 90.

The Treatment Period will be up to 17 days.

Subjects in both the SMT+PE-A 5% treatment group and the SMT control groups will be followed for 90 days after randomization. During the entire study, the safety of both groups will be monitored by a Data Safety Monitoring Board (DSMB).

See Figure 1 for the overall study schema.

Figure 1: Overall Study Schema



FU: follow up visit

5.2 Visits and Assessments

Refer to Appendix 1 and Appendix 2 for a detailed schedule of study procedures and events by visit. The expected study of each subject in the study beginning with the screening will be up to 100 days.

5.2.1 Screening Period (Day -10 to Day -1)

There will be a screening period of no more than 10 days for each subject during which subjects will be screened for enrollment in the study. Subjects with ACLF-1b, ACLF-2, or ACLF-3a will be included at diagnosis of the syndrome. Subjects with ACLF-1a will be followed up and included if they deteriorate to ACLF-1b, ACLF-2, or ACLF-3a within the 10-day Screening Period. Subjects with ACLF-3b will be followed up and included if they improve to ACLF-3a, ACLF-2, or ACLF-1b within the 10–day Screening Period.

For screening failure subjects, demographic data, screening evaluations, and eligibility reason(s) for screening failure will be captured.

5.2.2 Treatment Period (Day 1 to Day 17)

All screening laboratory results and assessments must be available, and all inclusion and exclusion criteria must have been satisfied prior to initiating treatment. The Treatment Period is from Day 1 until Day 17. For subjects in the SMT+PE-A 5% treatment group, PE-A 5% treatment may stop early depending on clinical response. Subjects who remain in the hospital will continue to have Treatment Period assessments performed up through hospital discharge. Follow-up assessments for Day 21, 28, 60, 90 will be performed for all subjects.

Assessments performed during the treatment period are summarized below. The detailed schedule of Study Procedure and Events can be found in Appendix 1.

5.2.2.1 Baseline/Treatment Day 1

For both treatment groups, the following will be measured and recorded: ascites assessment, weight, HE assessment, hemodynamic assessment (MAP), peripheral oxygen saturation, systemic inflammation assessment (CRP, WBC and procalcitonin), ACLF grade, illness severity scoring (CLIF-C OF score, CLIF-C ACLF score, Child-Pugh score, and MELD score), prior and concomitant medications and Adverse event(s) (AEs).

For the SMT+PE-A 5% treatment group, vital signs (temperature, blood pressure, heart rate, respiratory rate), clinical laboratory assessments (e.g., hematology, chemistry, coagulation), and serum albumin concentration will be measured immediately prior to and immediately after the end of the PE-A 5% session; these measures will be recorded once per visit for the SMT treatment group.

For the SMT+PE-A 5% treatment group only, plasma biomarker retains will be recorded after the first 15 minutes and the last 15 minutes of each PE-A 5% session.

5.2.2.2 Treatment Days 2, 4, 6, 8, 10, 12, 14, 16:

For both treatment groups, the following will be measured and recorded: ascites assessment, weight, HE assessment, hemodynamic assessment, peripheral oxygen saturation, systemic inflammation assessment (CRP, WBC and procalcitonin), ACLF grade, illness severity scoring (CLIF-C OF score, CLIF-C ACLF score, Child-Pugh score, and MELD score), prior and concomitant medications, and AEs.

For the SMT+PE-A 5% treatment group, vital signs (temperature, blood pressure, heart rate, respiratory rate), clinical laboratory assessments (e.g., hematology, chemistry, coagulation), and serum albumin concentration will be measured immediately prior to and immediately after the end of the PE-A 5% session; these measures will be recorded once per visit for the SMT treatment group.

For the SDTM+PE-A 5% treatment group only, plasma biomarker retains will be recorded after the first 15 mins and the last 15 minutes of each PE-A 5% session.

5.2.2.3 Treatment Days 3, 5, 7, 9, 11, 13, 15, 17:

For both treatment groups, the following will be measured and recorded: ascites assessment, weight, HE assessment, hemodynamic assessment (MAP), peripheral oxygen saturation, ACLF grade, illness severity scoring (CLIF-C OF score, CLIF-C ACLF score, Child-Pugh score, and MELD score), prior and concomitant medications, and AEs. In addition, if infection surveillance at screening visit has positive result, a Day 3 sample will be collected; additional samples will be obtained upon clinical suspicion. All new infections will be recorded as AEs.

For the SMT+PE-A 5% treatment group, IVIG 200 mg/kg infusion is administered after every 2 PE-A 5% sessions (Days 3, 7, 11, or 15) ; and IVIG 100 mg/kg infusion is administered following the last, odd-numbered PE session on either day 9, 13, or 17 (see Table 5-1 and Table 5-2). On the days when IVIG is administered, vital signs (temperature, blood pressure, heart rate, respiratory rate), and blood sample will be measured immediately prior to the IVIG administration. For the SMT treatment group, vital signs and blood samples will be measured one per visit.

For both treatment groups, blood biomarker retains will be obtained on Days 3, 7 and 17 only; for the SMT+PE-A 5% treatment group, the sample will be collected prior to IVIG administration.

5.2.3 Follow-Up Period

Assessments performed during hospital discharge and the follow-up period are summarized below. The detailed schedule of study procedures and events is presented in Appendix 2.

5.2.3.1 Hospital Discharge and Follow Up Visits (DAY 21 [+1 DAY], AND DAYS 28 [+ 2 DAYS], 60 [+ 2 DAYS], 90 [+ 2 DAYS])

After the treatment, all the subjects will be followed up at Hospital Discharge (if applicable) and on Days 21[+1 Day], and Days 28 [+2 Days], 60 [+2 Days], 90 [+2 Days].

For both treatment groups, the following will be measured and recorded at all visits: vital signs, full physical examinations, ascites assessment, HE assessment, hemodynamic assessment, peripheral oxygen saturation, blood sample, ACLF grade, illness severity scoring (CLIF-C OF score, CLIF-C ACLF score, Child-Pugh score and MELD score), prior and concomitant medications, AEs, data on liver transplantation, subject survival and cause of death.

All subjects who remain in the hospital will continue to have treatment period assessments performed up through Hospital Discharge. Follow-up assessments for Days 21, 28, 60, and 90 will be performed for all subjects.

At Days 28 and 90, data on liver transplant, subject survival and cause of death will be measured and recorded.

5.2.4 Follow-Up for Early Discontinued Subjects Withdrawn from the Study

Subjects who withdraw from the study early should have all Day 90 procedures performed at the time of withdrawal (preferably within 1 week of withdrawal) and will include: vital signs, full physical examinations, ascites assessment, HE assessment, hemodynamic assessment, peripheral oxygen saturation, blood sample, ACLF grade, illness severity scoring (CLIF-C OF score, CLIF-C ACLF score, Child-Pugh score and MELD score), prior and concomitant medications, AEs, data on liver transplantation, subject survival and cause of death.

If a subject receives a liver transplant, study treatment and all treatment related assessments will be discontinued upon transplant. The criteria to determine when a subject becomes a candidate for liver transplantation is described in protocol section 5.3.2.1. The subject will continue to have Days 21, 28, 60, and 90 follow-up procedures performed.

Subjects with any one of the severe AEs listed in protocol section 5.3.2 will be discontinued from study treatment and all treatment-related assessments and should continue to have subsequent planned visit assessment procedures performed.

5.3 Treatment Administration

5.3.1 PE-A 5% Dosage, Procedures, and Treatment Regimen

Plasma exchange treatment (PE-A 5%) will be performed using 5% albumin solution (Albutein 5%). Fresh frozen plasma will be administered after the 5% albumin administration to prevent coagulopathy, and the PE-A 5% session is considered completed at the end of the FFP administration. In subjects without severe coagulopathy (INR ≤3), two-thirds of the volume exchanged will be replaced with albumin 5% and one-third with FFP. In subjects with severe coagulopathy (INR >3), half of the volume exchanged will be replaced with albumin and half with FFP.

One-point-two (1.2) plasma volumes will be exchanged per PE-A 5% session. Total blood volume (TBV) will be calculated according to Nadler's formula. Plasma volume will be estimated from the calculated TBV and the Hematocrit (HCT). The volume to be exchanged will be considered as the volume to be infused (not the fluid to be removed).

A minimum of 4 and a maximum of 9 PE-A 5% sessions (maximum treatment period: 17 days) will be performed in each subject. The number of PE-A 5% sessions will be determined by the pattern of response (complete response, no response, or partial response) to PE-A 5% treatment (Table 5-1 and Table 5-2) and is described briefly below:

Treatment schedule consists of 2 initial PE-A 5% sessions on consecutive days followed by every other day PE-A 5% sessions. The aim of the intervention is to achieve complete response (resolution of ACLF or improvement to ACLF-1a):

- Subjects with very early complete response after 1 or 2 PE-A 5% sessions (resolution of ACLF or improvement to ACLF-1a) will receive 3 or 2 additional PE-A 5% sessions, respectively, to consolidate the response because the total number of PE-A 5% sessions should not be lower than 4. See Table 4-1 for details.

- Subjects with very early complete response after 3 PE-A 5% sessions (resolution of ACLF or improvement to ACLF-1a) will receive 2 additional PE-A 5% sessions to consolidate the response.

- Subjects with complete response after 4 PE-A 5% sessions (resolution of ACLF or improvement to ACLF-1a) will receive 2 additional PE-A 5% sessions to consolidate the response. See Table 4-1 for details in the protocol.

- Subjects with no response (subject with no change or worsening of ACLF grade) after 4 PE-A 5% sessions will discontinue treatment so the total number of PE-A 5% sessions will be 4.

- Subjects with partial response after the first 4 PE-A 5% sessions (reduction of 1 organ failure or more to ACLF-1b or ACLF-2) will be treated accordingly: as described below:
    - Subjects with partial response who in the course of the additional PE-A 5% sessions show complete response will receive 2 consolidating sessions after achieving complete response. See Table 4-2 for details.
    - Subjects with partial response who in the course of the additional PE-A 5% sessions worsen to ACLF-3b will be discontinued for the PE-A 5% sessions.
- In summary, regardless of the type of response, the total number of sessions should never be lower than 4 or higher than 9.

IVIGs will be administered intravenously at a dose of 200 mg/kg 1 day after every 2 PE-A 5% sessions in order to prevent the development of hypogammaglobulinemia and infection. In those subjects receiving an odd number of PE-A 5% sessions (e.g., #5, #7, or #9 PE-A 5%sessions when they are the last PE session for the subject), IVIGs will be administered 1 day after this PE-A 5% session at a dose of 100 mg/kg. Initial infusion rate of IVIGs will be of 0.5 mL/kg/hour, increasing to a maximum rate of 2 mL/kg/hour if tolerance is adequate. Refer Table 5-1 and Table 5-2 details.

The entire study duration including follow-up period will be 90 days after randomization.

5.3.2 Standard Medical Treatment

Standard medical treatment will be administered per institution standards. Subject's treatment period will be 7 days for all subjects and will be prolonged, depending on subject's ACLF evolution, to up to 17 days:

- Subjects in the SMT group with ACLF-1b, -2, or -3a who achieve complete response (ACLF resolution or improve to ACLF-1a) within the treatment period (from Day 1 to Day 7), will be assessed for 4 more days after the ACLF resolution or improvement and then will be followed up at Hospital Discharge (if applicable) and on Days 21, 28, 60, and 90.

- Subjects in the SMT group with ACLF-1b, -2, or -3a who experience no response (maintain or worsen their ACLF grades) throughout the treatment period (from Day 1 to Day 7), will be further assessed for up to Day 17 and will be then followed up at Hospital Discharge (if applicable) and on Days 21, 28, 60, and 90.

The entire study duration including follow-up period for subjects who receive SMT will be 90 days after randomization.

5.4 Study Variables

5.4.1 Efficacy Variables

The following efficacy variables will be assessed in this study:

- **Primary Efficacy**
  - Time to death through Day 90 after randomization of SMT+PE-A 5% versus SMT alone

- **Secondary Efficacy**
  - Time to liver transplant or death through Day 90 after randomization of SMT+PE-A 5% versus SMT alone
  - Time to death through Day 28 after randomization of SMT+PE-A 5% versus SMT alone

- **Exploratory Efficacy**
  - Time to death through Day 90, time to transplant or death through Day 90, and time to death through Day 28 after randomization in subgroups of subjects with ACLF-1b, ACLF-2, or ACLF-3a
  - Time to death and time to transplant or death through in-patient hospital stay (including ICU stay) in the entire study population and in the subgroups of subjects with ACLF-1b, ACLF-2, or ACLF-3a
  - Time to transplant or death through Day 28 after randomization in the entire study population and in the subgroups of subjects with ACLF-1b, ACLF-2, or ACLF-3a
  - Incidence of individual organ failures: liver, renal, brain, coagulation, circulation, and respiration, as defined by the CLIF-C OF score and the total CLIF-C OF score, during the treatment period and at the end of treatment, and of hospitalization (or liver transplantation or death)
  - ACLF course (resolution, improvement, steady course, or worsening), CLIF-C ACLF score, Child-Pugh score, and MELD score
  - Systemic inflammation as measured by CRP, WBC, and procalcitonin
  - Rate of all new infections
  - Time-to-hospital discharge
  - Albumin levels in serum measured pre and post PE-A 5% to monitor the status of infused albumin in subjects during the course of the study

- Ascites Assessment

5.4.2 Safety Variables

The following safety variables will be assessed in this study:

- **Main Safety Variables**
  - The number of suspected adverse drug reactions (ADRs), and adverse reactions (ARs), and incidence rates of subjects with suspected ADRs and ARs for the study period and within 72 hours after PE-A 5% completion (or after PE-A 5% stops).
  - The number and incidence rate of overall AEs and Serious Adverse Event(s) (SAEs), as well as deaths and discontinuations due to AEs will be also collected and analyzed.
  - According to the investigator's assessment, all clinically relevant changes in vital function and laboratory testing parameters findings will be considered AEs.

- **Other Safety Variables:**
  - Vital signs (temperature, blood pressure, heart rate, respiratory rate) recorded at each scheduled visit and in particular before and after each PE-A 5% session
  - Clinical laboratory test parameters (blood cell counts, platelet count, INR, fibrinogen, etc.)
  - Physical examinations

6 General Statistical Considerations

All analyses will be conducted using SAS Version 9.4 or higher.

Unless otherwise noted, for continuous variables, descriptive statistics for continuous/quantitative data will include the number of non-missing values, mean, standard deviation, median, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. In general, the mean, median, Q1 and Q3 will be presented to one decimal place greater than the original data, and the minimum and maximum will have the same number of decimal places as the original data. For categorical/qualitative data, descriptive statistics will include counts and percentages per category.

6.1 Data Handling

6.1.1 Missing Data Imputation

Unless otherwise noted, if an observation is missing at a specific scheduled visit/time point, the value at that visit will not be imputed and will be set to missing.

For the time to event endpoints, early discontinued subjects will be followed up at day 28 and day 90 to collect information on liver transplantation, subject survival, and cause of death, but the unobserved event date after last contact will not be imputed. If the date of death is not recorded in the vital status eCRF page but death is recorded as the reason for the early termination on the end of study/early termination eCRF page, then the early termination date can be used as the date of death for the time to event endpoints

For longitudinal efficacy outcomes, the mixed-effects model for repeated measurement (MMRM) and generalized linear model implemented in SAS proc GENMOD will be used to model the incomplete data. Missing data will be not explicitly imputed.

6.1.2 Day 1 Definition and Study Drug Administration

The Day1 visit is the planned date of randomization and typically, also the date of the first infusion of study treatment. In general, for baseline characteristics, disease history, medical history as well as efficacy endpoints, the Study Day 1 refers to the date of randomization (from the 'ELIGIBILTY' eCRF), while for previous and concomitant medications, exposure, and safety endpoints, the Study Day 1 refers

to the date of the first exchange of study treatment or the randomization date for SMT Alone. For SMT and PE-5% if the date of randomization and the date of the first exchange of study treatment are different, the study day will not be the same for all endpoints.
All efficacy and safety assessments at all visits will be assigned a study day relative to Study Day 1.

Study day or relative day for an event/assessment visit on or after the respective Study Day 1 (>= date of Study Day 1) is defined as:

Event date/Assessment Visit date - (Study Day 1 date) + 1

Study day or relative day for an event/assessment visit prior to the respective Study Day 1 (< date of Study Day 1) is defined as:

Event date/Assessment Visit date - (Study Day 1 date)

There is no ‘Day 0’.

6.1.3 Definition of Baseline

Baseline is defined as the last measurement collected on or prior to randomization date for SMT Alone, and as the last measurement obtained before the initiation of treatment (date/time) for SMT+PE-A 5%. "For SMT+PE-A 5% subjects, two sets of vital signs assessments are collected on Day 1; the time of vital signs assessment, as well as the time for lab assessment, including chemistry, coagulation and hematology parameters will be used to determine whether the vital signs or lab were collected pre- or post- Albutein administration, if assessment time is not available, then the vital signs or lab designated by the investigator as pre-dose on the Electronic Case Report Form (eCRF) will be considered baseline.

6.1.4 Definition of Last Contact Date

The last contact date is defined as the last observation recorded in the eCRF or other sources of study data (e.g., laboratory data) which provide proof of being alive. The following lists the dates to be considered for status of being alive.

- Date of visit (regular and unscheduled visits)
- Study drug plasma exchange session start date
- Liver transplant date
- AE start date
- AE end date, with Outcome not “Fatal”
- Hospital discharge date
- Disease-related complication date
- Blood product start date
- Prior/concomitant medication start/end date
- Date of subject completion or withdrawal
- Date of liver transplant/vital status assessment, with survival status not “Dead”
- Death date

6.1.5 Visit Windows

As subjects do not always adhere to visits as scheduled in the study protocol, the following rules will be applied to map each subject’s assessment visits to analysis visits, based on the timing of their assessment visits, relative to their Study Day 1. Visit mapping is applied to all visits (scheduled, unscheduled, hospital discharge and early termination) for laboratory assessments, vital sign assessments and exploratory endpoint assessments. Due to differences in visit schedules for the

assessments, distinct mapping methods are used for each type of assessment. A detailed list of the parameters and the mapping rules to be applied is provided in Appendix 5
In cases where multiple assessments for a parameter are recorded within a single visit window, distinct rules are applied to laboratory assessments, vital signs, and exploratory endpoints, respectively because lab parameters and vital signs are measured before and after exchanges for SMT+PE 5% group.

For laboratory and vital sign assessments:

- In the treatment period, if 2 or more assessments are mapped to the same visit window where an exchange occurred. Take the assessment closest to the scheduled exchange date/time visit target day to be used in the analysis.
- If 2 or more assessments are mapped to the same visit window, then the non-missing assessment closest to the scheduled visit target day will be used in the analysis.
- If 2 assessments are equidistant from the visit target day, the later non-missing observation will be used in the analysis.
- If in the treatment period, two assessments occur on the same date and the above rules cannot be applied to identify a record to be used in the analysis, take the treatment scheduled timepoint visit in the analysis.
- For safety laboratory visits, if the screening and Treatment Day 1 visit occur on the same date and time use the ascension number to determine if this is a duplicate visit and only pick one record.

For exploratory endpoints:

- If 2 or more assessments are mapped to the same visit window, then the non-missing assessment closest to the scheduled visit target day will be used in the analysis.
- If 2 assessments are equidistant from the visit target day, the later non-missing observation will be used in the analysis.
- If in the treatment period, two assessments occur on the same date and the above rules cannot be applied to identify a record to be used in the analysis, take the treatment scheduled timepoint visit in the analysis

Analysis visits will be used for all efficacy and safety summaries. If specified in the endpoint description the hospital discharge visit will be summarized separately. All visits will be presented in the listings, and the analysis visit will be flagged.

6.1.6 Adverse Events

AEs will be classified as treatment-emergent AEs (TEAEs) or non-TEAEs based on the comparison of AE onset date/time with the start date/time of study treatment. A TEAE is defined as an AE which occurs between the start of study treatment and the final visit of the clinical study. For the SMT + PE-A 5% treatment group, start of study treatment is defined as an AE occurring during or after the first plasma exchange. For the SMT treatment group, it is assumed that subjects were already receiving SMT per institutional standards at the time of randomization; therefore, the start of study treatment will be defined as an AE occurring at or after randomization.

A non-TEAE will be defined as an AE which occurs prior to the start of study treatment.

An AE with incomplete start date/time will be determined to be a TEAE or non-TEAE using the conservative rule specified in Appendix 3.

Adverse events with missing end date will be considered ongoing.

6.1.7 Prior and Concomitant Medications and Blood Products

Prior (within 30 days prior to screening) and concomitant medications were required to be recorded in the eCRF. Prior medications and concomitant medications will be summarized separately either overall and by treatment (prior medications) and by treatment group (concomitant medications).

Prior medications are defined as any medication that ended with end date/time prior to the start of study randomization/treatment day 1 for both treatment groups.

Concomitant medications are defined as medications with start date / time on or after the subject's date / time of randomization for SMT group, or commencement of plasma exchange for SMT+PE-A 5% group. In addition, medications with start date / time prior to subject's date / time of randomization/treatment Day 1, and end date/time either ongoing or after subject's date / time of randomization/treatment Day 1 will also be deemed as a concomitant mediation.

Prior and concomitant blood products are defined in the same manner.

The following conservative imputation rules will be used for missing or partial end date / time information in order to determine whether a medication is prior or concomitant (i.e., the unknown portions of a medication end date / time will be assumed to be as late as possible):

- Note: year is required on the eCRF, except for ongoing medication
- If the entire end year, date, and time values are missing (i.e., ongoing medication), then no imputation is performed, and the medication will be assigned to the "concomitant" category
- If the month is missing, impute "December"
- If the day is missing, impute the last day of the month (i.e., "28/29/30/31" depending on the year and month)
- If the hours are missing, impute "23"
- If the minutes are missing, impute "59"

The imputed medication end date / time will then be compared with the start of study treatment to determine if the medication is prior or concomitant. Note: it is possible that the imputed end date / time could be assigned to be later in time than the data lock.
Note the imputed end date / time will only be used to determine whether a medication is prior or concomitant. The start / end dates / times reported on the eCRFs will be presented in the listings.

6.2 Sample Size

Based on the CANONIC study, the overall 90-day mortality rate is assumed to be about 50% in the whole study population (3, 6). Assuming a potential drop-out rate of 10% and 5% type-1 error for a 2-sided Chi-square test, a global sample size of 380 subjects (190 per treatment group) will allow an 80% statistical power to detect an absolute reduction of 15% (a 35% 90-day mortality rate) in subjects treated with SMT+PE-A 5%.

Alternatively, the sample size was calculated based on the log-rank test as follows. Assuming the 90-day mortality rate is 50% for the control group, or equivalently, the survival rate is 50%, which translates to a hazard rate of 0.0077 assuming an exponential distribution. Using a log-rank test at the two-sided significant level of 5%, a total of 141 events would provide at least 80% power to detect an absolute reduction of 15% in mortality rate (a 35% 90-day mortality rate, or equivalently, a 65% survival rate) in subjects treated with SMT+PE-A 5%. This absolute difference in mortality rates translates to a hazard ratio of 0.6215, or an approximate 38% risk reduction. With all subjects followed for the entire 90-day duration of the study, a total of 332 subjects would be required to obtain 141 events. Assuming a dropout rate of 10%, a global sample size of 370 subjects (185 per treatment group) is required. This sample size calculation was performed using Proc Power with the "Twosamplesurvival" statement in SAS version 9.4.

Taking a conservative approach, the larger of the 2 sample sizes (i.e., the one based on the Chi-square test) will be used to ensure the study has sufficient power.

6.3 Randomization and Blinding

This is an open-label study. Randomization will be stratified by region (EU or NA) and the 3 ACLF grades (ACLF-1b, ACLF-2, or ACLF-3a). Within each stratum (i.e., each unique combination of region and ACLF grade), subjects will be randomly assigned to 1 of the 2 treatment groups (SMT vs. SMT+PE-A 5%) in a 1:1 ratio. Randomization will be centralized and will be performed via an Interactive Web Response System (IWRS) system after subject inclusion. A computer-generated randomization list will be used for treatment allocation.

6.4 Analysis Populations

There will be 3 analysis populations in this study, Intent-to-Treat (ITT) and Per Protocol (PP) population cohorts are for efficacy assessment and Safety population is for safety evaluation.

6.4.1 Safety Population

The Safety population is defined for the SMT + PE-A 5% treatment group as the subset of subjects who received at least one PE-A 5% treatment; and is defined for the SMT alone treatment group as all subjects randomized to SMT, assuming that all subjects in the SMT arm received the SMT treatment. Safety analyses will be based on this population. Subjects will be grouped according to the treatment they actually received in all safety analyses.

6.4.2 Intent-to-Treat (ITT) Population

The ITT population is defined as subjects who are randomized. The ITT population will be used for all efficacy analyses. Subjects will be grouped according to the treatment to which they are randomized in all efficacy analyses.

6.4.3 Per Protocol (PP) Population

The primary efficacy analyses will be repeated using the per-protocol (PP) population in order to confirm the results based on the ITT population. The PP population includes all subjects in the ITT Population who meet the following criteria:

1) For SMT+PE-A 5% group:
- Subject randomized to SMT+PE-A 5% receives at least the first 2 PE-A 5% sessions
- Subject has no major protocol violations which might have an impact on the primary efficacy analysis.

2) For SMT alone group:
- Subject randomized to SMT survives more than 2 days following randomization
- Subject has no major protocol violations which might have an impact on the primary efficacy analysis.

6.5 Hypothesis Testing and Multiplicity Adjustments

All statistical tests will be two-sided with significance level fixed at 0.05.

The fixed-sequence testing method will be used to adjust for multiplicity in the analyses of the secondary efficacy endpoints (using ITT population). Specifically, the superiority of SMT+PE-A 5% versus SMT alone for the secondary efficacy endpoints will only be tested if the superiority for the primary efficacy endpoint is demonstrated at the two-sided significance level of 5% (using ITT population).

For the secondary efficacy endpoints, each subsequent hypothesis is tested only if the superiority for the previous comparison(s) has been demonstrated at a two-sided significance level of 5%. The order in which the null hypotheses will be tested is predetermined for the secondary efficacy endpoints as follows:

1. Time to transplant or death through Day 90 after randomization of SMT+PE-A 5% versus SMT alone
2. Time to death through Day 28 after randomization SMT+PE-A 5% versus SMT alone

No other adjustments for multiplicity are planned. P-values will be displayed for all the above pre-specified tests for completeness; interpretation and reporting of significant hypothesis test results will follow the fixed sequence approach described.

7 Subject Disposition and Demographics

Unless otherwise noted, all demographics listings and summaries will be based on the ITT population.

7.1 Subject Disposition

Subject disposition will include the number of all subjects screened, screen failures, number and percentage of subjects in each analysis population including the ITT population, Safety population, and PP population.

The number and percentage of subjects in the ITT population who discontinue from the study will be summarized by reason for discontinuation.

Disposition status will be listed for all subjects, including those who were screened but not randomized.

7.2 Protocol Deviations

Deviations from the protocol will be identified during the study and evaluated before the database lock. Protocol deviations will be listed and will include category, severity (i.e. minor, major, or critical), and description of deviation. Summaries of incidences of deviations and subjects experiencing deviations will be presented for the following: any deviation, critical deviations, major deviations and deviations related to COVID-19.

7.3 Demographics

Demographics (age, sex, race, and ethnicity), baseline weight, and stratification factors for randomization will be listed and summarized. Subjects who were incorrectly stratified at the time of randomization will be listed and summarized.

Baseline characteristics listed above will be compared to evaluate possible imbalance by using Student's t test for continuous variables, Chi-square test for binomial or nominal variables, and Poisson model for count variables (with adjustment for overdispersion). All demographic and baseline characteristics data will be listed. Summaries will be provided by treatment group for ITT population.

In addition, the following baseline characteristics will be summarized; ACLF grade, Ascites Grade, Ascites Refractory occurrences, Ascites Refractory Type, CLIF-C ACLF score, CLIF-C OF total score, Child-Pugh Score, MELD Score, country.

7.4 Medical History

Medical history terms are coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version within one year of data base lock), associating lower-level terms with preferred terms (PTs) and system organ classes (SOCs). All medical history information will also be listed. A medical history summary will

present the number/ percentage of subjects with at least one history event by treatment, SOC, and preferred term. Summaries will be provided by treatment group.

7.5 Disease History

Disease history including recent, recent abdominal ultrasound, and identification of cirrhosis etiology and the corresponding confirmation method of the cirrhosis will be listed and summarized by treatment group. Each subject may have more than one response selected for cirrhosis etiology; all recorded combinations will be included in the corresponding summary.

8 Treatments (PE-A 5%) and Other Medications

Unless otherwise noted, all listings and summaries of treatments and medications will be based on the Safety population.

8.1 Prior and Concomitant Medications

Summaries of all medications taken during the course of the study will be presented in tabular form and coded using Anatomical Therapeutic Chemical (ATC) classification codes via the World Health Organization Drug Classification Dictionary (WHO-DD), a version within one year of the data base lock will be employed. All medications will be summarized by treatment and sorted alphabetically by medication class (i.e., ATC level 2) and medication sub-class (i.e., ATC level 4). If the ATC level 2 or 4 term is missing, the higher ATC level term will be used in the medication summary table and data listing.

All medications will be listed by subject, with prior/concomitant designation as defined in section 6.1.6. Prior and concomitant medications will be summarized in separate tables by treatment (including an overall summary for prior medications), medication class and medication subclass. At each level of summarization, a subject will be counted once per medication class or subclass. The concomitant medication summary tables are displayed by standard medical therapy for management of ACLF, intravenous Immunoglobin (IVIG) after plasma exchange, and non-SMT other medications. Summaries will be provided by treatment group for safety population.

8.2 Blood Products

All blood products used will be listed by subject and summarized in separate tables by treatment. The summary includes, but not limited to the following parameters: category (Fresh Frozen plasma after PE session per protocol, SMT and other blood products), blood product type and amount. At each level of summarization, a subject will be counted once per category and blood product type. Summaries will be provided by treatment group for safety population.

8.3 Extent of Exposure to PE-A 5%

For subjects randomized to SMT+PE-A 5%, all exposure details will be listed by visit.

An overall summary of exposure will present the duration of exposure (days), total volume of Albumin 5% exchanged (mL) and number of subjects who missed any scheduled treatment with PE-A 5% per protocol. Duration of exposure in days is defined as (date of last PE-A 5% – date of first PE-A 5% + 1. Interruptions, dose changes, and compliance are not considered in the calculation of duration of exposure.

Exchange interruptions will be summarized by visit. Number of exchanges, number and percentage of exchanges with interruptions, and number and percentage of exchanges with interruptions due to TEAE will be summarized.

8.4 Treatment Compliance

Treatment compliance, plasma exchange (PE) compliance, and overall compliance will be listed and summarized for the SMT+PE-A 5% group specific to the PE-A 5% study drug treatment. In addition, the number and percentage of subjects with PE-A 5% compliance <80%, 80% to ≤120%, and >120% will be presented.

PE compliance will be calculated as (number of actual plasma exchanges / number of plasma exchanges expected or planned) *100. The expected number of exchanges be calculated as:

Expected exchanges = (Duration of exposure in days /2) + 1*

* The treatment schedule consists of 2 initial PE-A 5% sessions on consecutive days followed by every other day therefore the +1 takes the initial exchange into account

The maximum number of PE-A 5% exchanges permitted per the protocol is 9 with the last exchange scheduled to occur on treatment day 16. If the number of days on treatment is greater than 16 days, the number of expected exchanges will be 9.

The expected exchange integer value is obtained using the SAS 'Floor' function.

Treatment compliance will be calculated as (total volume exchanged/ total volume dispensed) *100. Missing visits will be excluded in the calculation.

Overall compliance will be calculated as (treatment compliance * PE compliance)/100.

Treatment compliance for the SMT alone group is not applicable for any PE-A 5% study drug compliance assessments.

9 Efficacy Analysis

All Efficacy listings and summaries will be based on the ITT population. In addition, the primary efficacy summaries and analyses will be repeated for the PP population.

9.1 Primary Endpoint

9.1.1 Time to Death Through Day 90 After Randomization

Time to 90-day overall survival will be calculated as the earlier of [(date of death) – randomization date] for those subjects who died without having liver transplant on or prior 90 days. Subjects who did not die, or had a liver transplant before death will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Liver transplant date
- Cut-off date (i.e. 90 days) for analysis

9.1.2 Primary Analysis

The analysis of the primary endpoint will be performed for the ITT population.

The objective of this is study is to demonstrate superiority of SMT + PE-A 5% over SMT alone with regards to 90-day overall survival after study randomization. The null hypothesis is that the hazard functions for death are the same for the 2 treatment groups, or equivalently, the hazard ratio is equal to 1. The alternative hypothesis is that the hazard functions for death are not the same for the 2 treatment groups, or equivalently, the hazard ratio is not equal to 1.

Null Hypothesis Ho: HR (SMT + PE-A 5% / SMT alone) = 1
Alternate Hypothesis Ha: HR (SMT + PE-A 5%/ SMT alone) $\neq$ 1

The Hazard ratio and 95% CIs will be estimated using a stratified Cox Proportional-Hazards (PH) model, where the stratification factors include the region (Europe or North America) and 3 ACLF grades (ACLF-1b, ACLF-2, or ACLF-3a) used in the randomization and recorded in IWRS.

Superiority will be demonstrated if the p-value of the estimate of the treatment effect from the PH model for SMT + PE-A 5% compared to the SMT alone group is less than or equal to 0.05 and the hazard ratio is less than 1.

The 90-day survival will be summarized by means of Kaplan-Meier survival estimates and curves. The number and percentage of subjects with events of death and subjects without events (censored) will be presented by treatment. The median, 25th percentile and 75th percentile for survival in days will be calculated by treatment using Kaplan-Meier estimates, and the 95% confidence intervals (CI) for the median of each treatment group will be calculated using the Brookmeyer-Crowley method. The probability of survival for the endpoint at day 28, and 90 for the endpoint and 95% CI will be estimated using the Kaplan-Meier product limit method and Greenwood's formula for standard error. The survival functions will be compared between treatment groups using a log-rank test stratified by region (Europe or North America) and 3 ACLF grades (ACLF-1b, ACLF-2 or ACLF-3a) as recorded in IWRS.

9.1.3 Sensitivity Analyses

The primary analysis outlined in 9.1.2 will be repeated using the per-protocol population as a sensitivity analysis.

An unstratified analysis of 90-day overall survival will be performed as a sensitivity analysis on the ITT population and PP population, respectively.

Asensitivity analysis will be conducted on both the ITT and PP populations to evaluate time to 90-day overall survival, without treating liver transplant as a censoring event. For subjects who do not die, their time to event will be censored at the earlier of the following:

- Date of last contact.
- Cut-off date (i.e. 90days) for analysis

A sensitivity analysis will be used to assess whether the magnitude of treatment effect (i.e., hazard ratio) is consistent between 3 ACLF subgroups (ACLF-1b, ACLF-2 and ALCF-3a) by a stratified Cox model, where the stratification factors include the region (Europe or North America) as recorded in IWRS only, ACLF status and treatment will be included as fixed effects, and treatment by ACLF status interaction. This will be performed on the ITT population

If the IWRS stratification factors region (Europe or North America) and ACLF grade (ACLF-1b, ACLF-2 and ALCF-3a) do not match with the corresponding information collected on the eCRF for more than 3% of subjects, the primary analysis will be repeated adjusting for the stratification variables as recorded on the eCRF. This will be performed on the ITT population only.

The primary analysis will be repeated as a sensitivity analysis censoring a subject at their last contact date if a subject is missing a death date in the vital status eCRF page, but death is recorded as the reason for early termination on the end of study/early termination eCRF page This will be performed on the ITT population only.

9.2 Secondary Endpoints

The analysis of the secondary endpoints will be performed for the ITT population using the same methodology as the primary analysis for the primary endpoint described in section 9.1.2. fixed-sequence testing method will be used for the analysis of secondary endpoints, as described in section 6.5 above. The secondary endpoint definitions are presented in the order in which testing will be performed.

9.2.1 Time to Liver Transplantation or Death Through 90-Day After Randomization

Time to 90-day liver transplant free survival will be calculated as [the earlier of the date of liver transplantation or date of death– randomization date for those subjects who died or had a liver transplant on or prior to 90 days. Subjects who neither died nor had a liver transplant, will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date(i.e. 90 days) for analysis.

This endpoint will be analyzed in the same way as outlined in section 9.1.2 for the primary analysis.

9.2.2 Time to Death Through 28-Day After Randomization

Time to 28-day overall survival will be calculated as [date of death – randomization date] for those subjects who died without having liver transplant on or prior to 28 days. Subjects who did not die or had a liver transplant before death, will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Liver transplant date
- Cut-off date (i.e. 28 days) for analysis

This endpoint will be analyzed in the same way as outlined in section 9.1.2 for the primary analysis. The probability of event-free survival for the endpoint at day 28 for the endpoint and 95% confidence interval (CI) will be estimated.

9.2.3 Secondary Efficacy Sensitivity Analyses

A sensitivity analysis will be conducted on the ITT populations to evaluate time to 28-day transplant-free survival, without treating liver transplant as a censoring event. For subjects who do not die, will have their time to event will be censored at the earlier of the following:

- Date of last contact.
- Cut-off date (i.e. 28 days) for analysis

9.3 Exploratory Endpoints

The analysis of the exploratory endpoints will be performed for the ITT population.

9.3.1 Exploratory Time to Event Endpoints after Randomization

The following endpoints will be analyzed using the same methodology as the primary analysis for the primary endpoint described in section 9.1.2.

9.3.1.1 Time to Death through in-patient hospital stay (including ICU stay)

Time to death during in-patient hospital stay will be calculated as [(date of death due to any cause) – randomization date] for those subjects who died in hospital prior to hospital discharge visit without prior liver transplant. Subjects who are alive and active in the study at their discharge date will be censored at their discharge date. Subjects who discontinue prior to their discharge visit without having death will be

censored at their last contact date or discharge date (whichever is earlier). A subject who has not been discharged before the end of study will be censored at their last contact day. A subject who had liver transplant will be censored at the last contact date, or discharge date or liver transplant date (whichever is earlier). The endpoint will be analyzed in ITT population.

9.3.1.2 Time to transplant or death through in-patient hospital stay (including ICU stay)

The time to death or liver transplant through in-patient hospital stay will be calculated as [(the date of liver transplantation or the date of death during in-patient hospitalization, whichever is first) – randomization date] for those subjects who died or had liver transplant in hospital prior to hospital discharge visit. Subjects who are alive without liver transplant and active in the study at their discharge date will be censored at their discharge date. Subjects who discontinue prior to their discharge visit without having death and liver transplant will be censored at their last contact date or discharge date (whichever is earlier). A subject who has not been discharged before the end of study will be censored at their last contact day. The endpoint will be analyzed in ITT population.

9.3.1.3 Time to liver transplant or death through Day 28 after randomization

Time to 28-day transplant-free survival will be calculated as [(the earlier of liver transplantation or death) – randomization date] for those who died or had liver transplant on or prior to 28 days. Subjects who neither died nor had a liver transplant within the cut-off date will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date (i.e. 28 days) for analysis.

The endpoint will be analyzed in ITT population.

9.3.1.4 Time to hospital discharge

Time to hospital discharge will be calculated as [discharge date -randomization date). Subjects who had a liver transplant or death during the hospitalization will be censored to the earliest date of liver transplant or death. Subjects who haven't been discharged before the end of study and have not had a liver transplant or death will be censored to their last contact date. The endpoint will be analyzed in ITT population.

9.3.1.5 Exploratory Subgroup Analysis (Exploratory Endpoints)

The primary analysis will be repeated for each ACLF subgroup (ACLF-1B, ACLF-2, or ACLF-3a) and region (Europe vs NA) All subgroup analyses will be performed using the ITT population.

In each defined subgroup category, the analysis will be carried out using the same methodology described in section 9.1.2 and the hazard ratio and CI for the subgroup will be estimated. When the subgroup is defined by a stratification factor used for the randomization, the stratification factor will not be used in the stratified Cox PH model. For example, in the analysis of ACLF subgroup, only region will be used as the stratification factor in the stratified Cox PH model. These results are considered exploratory, due to both multiplicity concerns and small sample sizes that cannot be pre-specified. Only summary statistics and CIs will be presented; p-values will not be determined. A minimum of 30 subjects must be present in each subgroup category for the analysis to be performed.

The subgroup analysis will be applied to primary, secondary and exploratory endpoint time to event endpoints after randomization.

9.3.2 CLIF-C OF Score and Sub Scores for Organ Function

CLIF-C OF scores evaluated at baseline (last measurement taken prior to treatment day 1), during and after the treatment period, and at the end of hospitalization (or before liver transplantation or death) will be listed.

The CLIF-C OF score system consists of six sub-scores for liver, kidney, brain, coagulation, circulatory, and respiratory organs/systems - each with values of 1, 2 or 3 with a higher number representing more severe disease.

Each CLIF-C OF sub-score will be summarized as a categorical variable by treatment for each visit. The CLIF-C OF sub-scores will be compared at visits when the data are collected for both treatment groups using the generalized linear models implemented in SAS GENMOD procedure, in which the CLIF-C OF sub-score is modeled by the proportional odds cumulative logit model for ordinal data with adjustment for baseline sub-score, region (Europe of North America) and ACLF subgroup (ACLF-1B, ACLF-2, or ACLF-3a) treatment, visit and treatment-by-visit interaction, as independent variables), and the robust variance estimate for the treatment effect will be estimated based on the independent working correlation structure.

The total CLIF-C OF score is a discrete numeric value in the range of 6 to 18 (inclusive) and is defined as the sum of the six organ/system sub-scores. If an individual sub-score is missing, the total score will also be missing. The total CLIF-C OF score and change in total score from baseline to each scheduled post-baseline visit will be summarized, as a continuous variable, by treatment and scheduled visit, excluding visits that follow liver transplantation. In addition, the total score change from baseline for scheduled visits with data for both treatment groups will be analyzed by MMRM, which includes change from baseline as the dependent variable; treatment, visit, region (Europe of North America) and ACLF subgroup (ACLF-1B, ACLF-2, or ACLF-3a), treatment-by-visit interaction, region-by-visit interaction, and ACLF subgroup (ACLF-1B, ACLF-2, or ACLF-3a)-by-visit interaction as fixed effects; baseline and baseline-by-visit as covariates; and measures within-subject at each visit as a repeated measure. The model employs an unstructured covariance matrix for the within-subject dependence. The treatment effect will be evaluated using the full model, with no backward or stepwise selection methods. If the model fails to converge, the mixed effects model with a compound symmetry correlation structure will be used.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.3 CLIF-C ACLF Score

The CLIF-C Acute-on-Chronic Liver Failure (ACLF) score is a continuous numeric value in the range of 0-100 with a higher number representing more severe disease, derived from the CLIF-C OF total score, and is defined as:

> CLIF-C ACLF = 10*[0.33*CLIF-C OFs + 0.04*Age {years collected on the demographics eCRF page} + 0.63*Ln(white cell count {10^9 cells/L}) - 2]

The CLIF-C ACLF score will be included in the listing of CLIF-C OF scores and will be summarized as a continuous variable. The total score and change in total score from baseline (last measurement taken prior to the start of study treatment for SMT+PE 5% group and last measurement on or prior to the randomization date for SMT alone) to each post-baseline scheduled visit will be summarized by treatment and each visit. In addition, the MMRM analysis of CLIF-C OF scores will be repeated for change from baseline CLIF ACLF total score.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.4 MELD Score

The Model for End-stage Liver Disease (MELD) score is a continuous numeric value in the range of 6-40, with a higher number representing more severe disease, and is defined as:

$$MELD = 9.57*Ln\ (Creatinine\ \{mg/dl\}) + 3.78*Ln\ (Bilirubin\ \{mg/dl\}) + 11.2*Ln\ (INR) + 6.43$$

If any of the individual clinical parameters used to derive the MELD score report results <1, the result is imputed to 1. For creatine reported >4, the result is imputed to 4(8). These parameters are then used to derive the MELD score. Any final MELD score >40 will be rounded to 40. MELD scores are evaluated monthly through Month 12 and will be listed.

The MELD score will be summarized as a continuous variable. The MELD total score and change in total score from baseline ((last measurement taken prior to the start of study treatment for SMT+PE 5% group and last measurement prior to randomization date for SMT alone) to each scheduled post-baseline visit will be summarized, as a continuous variable, by treatment and scheduled visit. In addition, the MMRM analysis of CLIF-C OF scores will be repeated for the change from baseline total scores.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.5 Child-Pugh Score

The Child-Turcotte-Pugh (Child-Pugh) classification for severity of cirrhosis consists of 5 sub-scores for encephalopathy, ascites, bilirubin, albumin, and INR – each with values of 1, 2 or 3 with a higher number representing more severe disease. Refer to Appendix 4 for details. The Child-Pugh Score is a discrete numeric value in the range of 5 to 15 (inclusive) and is defined as the sum of the five sub-scores. If an individual sub-score is missing, the total score will also be missing.

The Child-Pugh Class is derived from the Child-Pugh Score as follows: Class A = score of 5-6; Class B = score of 7-9; Class C = score of 10-15.

Child-Pugh scores are evaluated for each visit and will be listed.

Each Child-Pugh sub-score will be summarized as a categorical variable by treatment and scheduled visit. In addition, each Child-Pugh sub-score will be compared by treatment and scheduled visit using the same methods as for CLIF-C OF sub-scores (see section 9.3.2).

The Child-Pugh Total score and change in total Score from baseline (last measurement taken prior to treatment day 1) to each scheduled post-baseline visit will be summarized as a continuous variable, by treatment group and scheduled visit, In addition, the MMRM analysis of CLIF-C OF scores will be repeated for the change from baseline total scores.

The Child-Pugh Class will be summarized as a categorical variable by treatment for each visit.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.6 Systemic Inflammation Assessment

CRP [in chemistry panel], WBC [in hematology panel] and procalcitonin are analyzed by a central laboratory and collected on treatment Day1, Day2, then on every other treatment day and each follow-up visit.

A summary table will present descriptive statistics by visit for original values and change from baseline. For the SMT+PE-A 5% group, change in value from baseline to the pre-exchange timepoint will be summarized.

Moreover, the difference between pre-exchange and post-exchange within each visit will also be summarized.

The MMRM analysis of CLIF-C OF scores will be repeated here to analyze the change from baseline value for inflammatory biomarkers. for the SMT PE-A 5% group, the change from baseline to pre-exchange timepoint will be used for this analysis.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.7 ACLF Course at the End of Hospitalization

ACLF course includes resolution, improvement, steady course, or worsening from the baseline assessment. Resolution means ACLF grade changes to “No ACLF”. Improvement means ACLF grade becomes lower, steady course means ACLF grade does not change, while worsening means ACLF grade gets higher (see Table 9-1 for ACLF grades). ACLF Course will be summarized by visit, and at at the end of hospitalization i.e. hospital discharge visit . The ACLF course at the hospital discharge visit will be compared between treatment groups using the Chi-square test or Fisher’s Exact test. In addition, shifts from baseline ACLF grade with categories (No ACLF, ACLF-1b, ACLF-2 and ALCF-3a) will be presented by analysis visit and treatment and the hospital discharge visit.

Assessments after Liver transplant will be removed from summaries and analysis.

Table 9-1 Grades of ACLF

Grades of ACLF	
No ACLF	- No organ failure - One organ failure (liver failure, coagulation, circulatory or respiratory failure) with creatinine <1.5 mg/dL and no HE
ACLF grade 1a	- Single kidney failure without mild or moderate HE
ACLF grade 1b	- Single organ failure with serum creatinine ranging from 1.5 mg/dL to 1.9 mg/dL and/or mild-to-moderate HE
ACLF grade 2	- Presence of 2 organ failures
ACLF grade 3a	- Presence of 3 organ failures
ACLF grade 3b	- Presence of ≥4 organ failures

9.3.8 Organ Failure at the End of Hospitalization

Organ failure is defined according to the CANONIC study criteria for each of the following organs/systems: liver, kidney, brain, coagulation, circulatory, and respiratory. Kidney failure is defined as CLIF-C OF sub-score of 2 or 3; for all others, organ failure is defined as CLIFC-OF sub-score of 3. Refer to Appendix 4 for additional details. The number and percentage of subjects experiencing organ failure will be summarized for each organ by visit, and at the end of hospitalization i.e. hospital discharge visit. The percentage of subjects with each organ failure at end of hospitalization will be compared between treatment groups using the Fisher’s Exact or Chi-square test.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.9 New Infections at End of Hospitalization

The number of subjects with new infections by the end of hospitalization is defined as the number (and percentage) of subjects with one or more AE categorized as an infection, or any and disease related

complication i.e. spontaneous bacterial peritonitis or an infection captured as “other” and described as an infection on the disease related complications CRF page, with a start date on or after the randomization date and before the end of hospitalization i.e. hospital discharge date. The percentage is calculated for each treatment group for all subjects in the ITT population. The percentage of subjects with new infections at end of hospitalization will be compared between treatment groups using the Fisher’s Exact or Chi-square test.

9.3.10 Rate of New Infections

The annualized rate of new infections for a subject is defined as (number of infections for the subject) / (study duration in years for the subject). The study duration in days is defined as (end of study date - randomization date+1). The study duration in years also known as the person-year is defined as (study duration in days) / 365.25. A new infection is defined as an AE categorized as an infection or any disease related complication considered an infection i.e. spontaneous bacterial peritonitis or an infection captured as “other” and described as an infection on the disease related complications CRF page with a start date on or after the randomization date to the end of study. The annualized rate of new infection per subject will be summarized by treatment group as continuous variable.

The rate of new infections will be compared between treatment arms using a generalized linear model procedure for Poisson regression with adjustment for overdispersion using the Pearson statistic to estimate the scale parameter. The response variables in the model will be the number of new infections for each subject after randomization to the end of study. The model will include treatment group, region (Europe or North America) and ACLF grade (ACLF-1b, ACLF-2, or ACLF-3a) as collected from IWRS as fixed effects. The natural logarithm of the subjects’ study duration will be used as an offset variable in the model to adjust for subjects having different study durations. For each treatment group the mean yearly rate of new infections and corresponding two-sided 95% confidence intervals (CI) is presented. The estimated treatment effect (i.e. the incidence rate ratio of SMT + PE-A 5% versus SMT alone) and corresponding two-sided 95% CI will be presented also.

9.3.11 Exploratory Sensitivity Analyses

For ACLF course at end of hospitalization, specific organ failure at end of hospitalization, and percentage of new infections at end of hospitalization, a sensitivity analyses will be performed in which treatment effects will be adjusted for treatment group, region (Europe or North America) and 3 ACLF grades (ACLF-1b, ACLF-2, or ACLF-3a) as collected from IWRS by fitting an appropriate Logistic Regression model or by means of the Cochran-Mantel-Haenszel (CMH) test.

9.3.12 Serum Albumin Concentration

Serum albumin concentration is measured at each visit through the Day 90 visit and is measured before and after each PE-A 5% session at each visit during the treatment period.

Albumin level in serum will be listed for each subject and summarized by each scheduled visit for the SMT group. A summary table will present descriptive statistics for original values and change in value from baseline. For SMT+PE-A 5% group, change from baseline to the pre-exchange timepoint will be summarized. Moreover, the difference between pre-exchange and post-exchange within each visit will also be summarized.

Assessments after Liver transplant will be removed from summaries and analysis.

9.3.13 Ascites Assessment

Ascites assessment will be collected for each treatment day and follow-up visit. The grade of ascites and refractory ascites will be summarized by visit and by treatment.

10 Safety Analysis

Unless otherwise noted, all Safety listings and summaries will be based on the Safety population.

10.1 Adverse Events

Adverse Events are coded using the MedDRA coding dictionary (a version within 1 year of the data base lock).

A treatment emergent adverse event (TEAE) is defined in section 6.1.6. Non-TEAEs and TEAEs will be summarized separately.

A suspected adverse drug reaction (ADR) is an adverse event with causal relationship of “definitely related” or “possibly related”, as classified by the investigator. An adverse reaction (AR) is an adverse event with causal relationship of “definitely related”, as classified by the investigator.

An temporally associated AE is an AE that is temporally associated with PE-A 5% and is identified as an AE that occurs during a PE session, or within 72 hours following after the completion of a PE session. These definitions only apply to subjects in the SMT+PE-A 5% group.

All adverse events, both treatment-emergent and non-treatment emergent, will be included in a listing, with a flag to distinguish whether the event is treatment-emergent.

An overall summary of TEAEs will present the number of TEAEs, and the number and percentage of subjects with TEAEs, in the following categories:

- Non-TEAE (AE with Onset Prior to Treatment)
- TEAE
- Suspected ADR
- AR
- TEAE Leading to Death
- Serious TEAE
- Serious Suspected ADR
- Non- Serious Suspected ADR
- Serious AR
- Non-Serious AR
- Non-Serious TEAE
- TEAE Leading to Drug Interruption
- TEAE Leading to Drug Withdrawal
- TEAE Leading to Study Withdrawal
- Temporally Associated TEAEs

In addition, TEAEs will be summarized in the following ways:

- SOC / PT – summary of number of TEAEs and number/percentage of subjects with at least one TEAE by treatment, SOC, and preferred term
    - A select subset of TEAE summaries will also include number of events by SOC and preferred term
- SOC/PT/Severity – summary of number of TEAEs and number/percentage of subjects with at least one TEAE by treatment, SOC, preferred term, and severity

- SOC / PT / Causality – summary of number of TEAEs and number/percentage of subjects with at least one TEAE by treatment, SOC, preferred term, and causality
- PT Rates – summary of the total number of plasma exchange sessions, , the total number of temporally associated adverse events and the rate per plasma exchange session, and the total number and rate of adverse events per week on the study by preferred term.. Rate per week on the study is defined as total number of events divided by total duration of weeks on the study . This summary applies to the SMT+PE-A 5% group only.

At each level of summarization, a subject will only be counted once per SOC or preferred term, using the most severe AE or the AE with the strongest causal relationship to the treatment as applicable. Summary tables will be sorted in descending frequency within the SMT+PE-A 5% group, then descending frequency with the SMT group, and then alphabetically.

The following table identifies the sets of adverse events that will be presented for each of these types of summaries.

	TEAE Summary					
Adverse Event Subset	**SOC / PT**	**PT**	**SOC / PT / Severity**	**SOC / PT / Causality**	**PT Rates***	**Listing**
AEs with Onset Prior to Treatment	x					
TEAEs	X#		x	x	x	x
Suspected ADR	X#		x		x	
Non-Serious Suspected ADR	x					
Serious Suspected ADR	x					
AR	X#		x		x	
Non-Serious AR	x					
Serious AR	x					
TE SAEs	x			x		x
Non-serious TEAEs	x#					
TEAEs leading to Study Withdrawal	x					x
TEAEs leading to Death	x					x
Temporally Associated TEAEs*	x				x	

* This subset applies only to the SMT+PE-A 5% group.
# This summary will include number of events by SOC / PT.

10.2 Incidence of Disease-Related Complications

All disease-related complications are collected through day 90 and will be listed.

The number and percentage of subjects with at least one occurrence of each of the following disease-related complications after Day 1 will be presented by treatment and by visit, Anticipated disease progression includes, but not limited to:

- HE – including HE I, HE II, HE III, and HE IV
- Gastrointestinal (GI) Bleeding – including lower GI bleeding and upper GI bleeding
- Portal Hypertension
- Ascites
- Spontaneous Bacterial Peritonitis (SBP)
- Hepatorenal syndrome (HRS) – including Type 1 and Type 2
- Associated organ/system failure(s) – to be defined and summarized as described in 9.3.8

In addition, the number of each type of disease-related complication will be counted for each subject and presented by treatment as a continuous variable and as a categorical variable with categories 0, 1, 2, 3, 4 or more. No analysis of treatment differences will be performed. Each type of HE, Gastrointestinal (GI) Bleeding, Hepatorenal syndrome(HRS) and associated organ/system failures will be counted separately.

10.3 Clinical Laboratory Evaluations

Clinical laboratory samples will be analyzed by a central laboratory; the table below lists the planned tests for each panel. All lab tests including unplanned ones will be included in the laboratory listings and summaries.

Test Panel	Planned tests
Hematology	Hemoglobin, hematocrit, platelets, red blood cell count, white blood cell count with differential
Chemistry	Sodium, potassium, creatinine, blood urea nitrogen (BUN), calcium, magnesium, lactate dehydrogenase (LDH), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP), glucose, total bilirubin, direct and indirect bilirubin, C-reactive protein (CRP), lactate, serum albumin
Coagulation	International normalized ratio (INR), fibrinogen, platelet count, prothrombin time
Systemic inflammation assessment	Procalcitonin, WBC (hematology panel), CRP (chemistry panel)
Biomarker retains	Blood biomarker Post-PE-A 5% plasma biomarker obtained from plasma removed during the first 15 minutes and the last 15 minutes of the PE-A 5% session

Laboratory parameters will be presented in alphabetical order within test panel; the differential of WBC counts will be presented alphabetically following the WBC results.

All results and normal ranges will be displayed in SI units. All data will be listed for each subject. Values outside of normal range will be flagged.

Systemic inflammation assessment summaries are described in section 9.3.6.

For all other continuous/quantitative laboratory parameters (hematology, chemistry, coagulation), summary tables will present descriptive statistics for original values and change in value from baseline by parameter, treatment, and scheduled visit. For SMT+PE-A 5% group, change from baseline to the pre-exchange timepoint will be summarized. Moreover, the difference in value between pre-exchange and post-exchange within each visit will also be summarized. Assessments after Liver transplant will be removed from summaries and analysis but will be provided in the listing.

For summarization, concentration values that are reported as "<X.XX" the concentration will be imputed using the X.XX value multiplied by a factor of 0.9. For concentration values that are reported as ">X.XX" the concentration will be imputed by using the X.XX value multiplied by a factor of 1.1.

For example:

Standard lab result =<0.2 then analysis result=0.2*0.9

Standard lab result =>0.2 then analysis result=0.2*1.1

Shifts from baseline (with categories L/N/H for low/normal/high) will be presented by parameter, scheduled visit, and treatment.

Laboratory results that are outside of the normal range will be evaluated by the investigator, and if determined to be clinically significant, will be reported as an adverse event. Clinical significance will not be reported in the laboratory listings or summaries.

Biomarker retains will be drawn for potential analysis of cytokines (interleukin [IL] 6 (IL-6), IL-8, IL-10, and tumor necrosis factor alpha [TNFα]) and other candidate biomarkers found in the blood which may correlate with disease activity. These samples will be frozen and stored for possible future use and will not be included in this analysis. All biomarker sample results obtained will be provided in a listing.

10.4 Vital Signs

Vital signs for systolic and diastolic blood pressure (mmHg), heart rate (bpm), temperature (°C), and respiration rate (breaths/min) will be listed for each subject.

For each vital sign parameter, absolute values and changes from baseline will be summarized descriptively by visit for SMT group. For SMT+PE-A 5% group, change from baseline to the pre-exchange timepoint will be summarized. Moreover, the difference between pre-exchange and post-exchange within each visit will also be summarized.

Assessments after Liver transplant will be removed from summaries and analysis.

10.5 Physical Assessment

Physical assessment findings (normal and abnormal) will be listed for each subject and summarized by treatment and visit. Any clinically significant abnormality, as determined by the investigator, experienced by a subject during the clinical study and not already present at baseline will be reported as an AE.

11 Interim Analysis

No interim analysis is planned.

12 Changes in Planned Analysis

Changes in the analysis of longitudinal outcomes

The MMRM will be used to analyze the longitudinal continuous outcomes [e.g., CLIF-C OF score, CLIF-C ACLF score, MELD score, Child-Pugh score and Systemic inflammation assessment], and a general linear model implemented in SAS Proc GENMOD will be used to analyze the longitudinal binary or ordinal outcomes [Child-Pugh Sub-Score, CLIF-C OF Sub-Score]. However, protocol section 9.1.2.4 stated that exploratory endpoints would be analyzed by means of analysis of covariance (ANCOVA); this method is not suitable for longitudinal outcomes with missing data.

Adding Ascites Assessment as an exploratory endpoint

Although not included as an exploratory objective in the protocol an Ascites assessment is performed at each visit. The Ascites assessments will be summarized by visit and presented as an exploratory efficacy endpoint. This has been added for completeness.

Exploratory Endpoints

The protocol states the analyses of the primary and secondary efficacy endpoints and exploratory time to event endpoints will be repeated for each sub-group of subjects with ACLF-1b, ACLF-2, or ACLF-3a for exploratory purposes. *Additional subgroup analyses by age group, sex, race, and region (EU versus NA) may be performed for the* primary endpoint. Region was pre-specified as the only additional sub-group analysis on the primary endpoint and this sub-group analyses will also be performed on the secondary and exploratory time-to-event endpoints. This additional by region sub-group analyses is performed to determine if there are treatment effect differences in regions.

Adding a sensitivity analysis in which liver transplant is not a censoring event for the endpoints

A sensitivity analysis will be added to not consider liver transplant as a censoring event in time to death endpoints. This analysis is incorporated in the appropriate sections above (see section 9.1.3, 9.2.3)

Adding additional categories in treatment emergent adverse event (TEAE)

Non-serious suspected ADR and Non-serious AR are added in TEAE categories to provide more granular summary for discussion in the CSR report.

13 References

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14 Appendices

Appendix 1 – Schedule of Study Procedures and Events

Procedures and Evaluation / Study Period	Screening	Treatment Period[a]																
Study Day	-10 to -1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Inclusion/exclusion criteria	X																	
Medical history & demographics	X																	
Chest X-ray	X																	
ECG	X																	
Abdominal ultrasound	X																	
Urine pregnancy test	X																	
Physical exam[b]	X																	
Randomization		X																
Vital signs[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Ascites assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HE assessment[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hemodynamics assessment[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peripheral oxygen saturation (SpO_2) assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory assessments[g]	X	X	X		X		X		X		X		X		X		X	
Infection surveillance[h]	X			X		X		X		X		X		X		X		X
Microbiology tests[i]	X																	
Record ACLF grade[ki]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Illness severity scores[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Systemic inflammation assessment[lk]		X	X		X		X		X		X		X		X		X	
Blood biomarker retains[m]	X			X				X										X
Post-PE-A 5% biomarker retains[n]		X	X		X		X		X		X		X		X		X	
PE-A 5% (1.2 plasma vol) [o]		X	X		X		X		X		X		X		X		X	
IVIG infusion[p]				X				X		X		X		X		X		X
Prior and concomitant medications[p]	X[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Depending on clinical response, subjects may not complete all treatment days. For subjects in the SMT+PE-A 5% treatment group, PE-A 5% treatment may stop early depending on clinical response. For all subjects, if a subject receives a liver transplant, study treatment will be discontinued. All subjects who remain in the hospital will continue to have Treatment Period assessments performed up through Hospital Discharge. Follow-up assessments for Days 21, 28, 60, and 90 will be performed for all subject

[b] Full physical examination (excluding breast and genitourinary examination).

[c] Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and respiratory rate. For subjects in the SMT+PE-A 5% treatment group, vital signs will be measured immediately before and immediately after each PE-A 5% session.

[d] HE assessment as per Protocol Appendix 9.

[e] Hemodynamics (MAP) will be monitored.

[f] Clinical laboratory assessments will include hematology, chemistry, and coagulation. For subjects in the SMT+PE-A 5% treatment group, assessment will be performed immediately before and immediately after each PE-A 5% session. For subjects in the SMT group, clinical laboratory assessments will be performed on Days 1 and 2, followed by every other day.

[g] Infection surveillance if positive result obtained at Screening Visit using microbiology (cultures) including blood, urine, ascetic fluid, sputum, and pleural fluid. If a positive result occurs at screening, a Day 3 result will be collected. If a thoracentesis or paracentesis has been performed within the last 5 days prior to screening, results of the fluid cultures should be documented in the medical notes. Microbiology cultures will be performed at local labs and the results will be captured in the subject's source documents but will not be the entered into the eCRF. All new infections will be recorded as AEs and recorded in subject's source documents and the eCRF. Additional samples will be obtained upon clinical suspicion.

[h] Microbiology testing includes cytomegalovirus, polymerase chain reaction, and galactomannan antigen index.

[i] ACLF grade (Table 8-1).

[j] Illness severity scores include CLIF-C OF score, CLIF-C ACLF score, Child-Pugh score, and MELD score criteria

[k] Systemic inflammation assessment includes testing for procalcitonin, WBC (part of hematology panel), and CRP (part of chemistry panel).

[l] For subjects in the SMT+PE-A 5% treatment group, blood biomarker retain samples will be collected prior to IVIG infusion (Screening, Days 3, 7, and 17).

[m] Applies to subjects in the SMT+PE-A 5% treatment group only. Post-PE-A 5% plasma biomarker retains will be collected after each PE-A 5% session from the plasma bag on Days 1, 2, 4, 6, 8 10, 12, 14, 16.

[n] Applies to subjects in the SMT+PE-A 5% treatment group only.

[o] IVIG 200 mg/kg will be administered every 2 PE sessions on Day 3, 7, 11, or 15. IVIG 100 mg/kg will be administered 1 day after the last, odd-numbered PE session on Days 9, 13, or 17.

[p] Record prior (30 days prior to screening) and concomitant medications.

Appendix 2 – Schedule of Study Procedures and Events (Hospital Discharge through Day 90)

Procedures and Evaluation / Study Period / Study Day	Hospital Discharge[a]	Follow-Up Period			
		Day 21	Day 28[a]	Day 60	Day 90[a,b]
Vital signs[c]	X	X	X	X	X
Physical exam[d]	X	X	X	X	X
Ascites assessment	X	X	X	X	X
HE assessment	X	X	X	X	X
Hemodynamics assessment[e]	X	X	X	X	X
Peripheral oxygen saturation (SpO_2) assessment	X	X	X	X	X
Clinical laboratory assessments[f]	X	X	X	X	X
Record ACLF grade[g]	X	X	X	X	X
Illness severity scores[h]	X	X	X	X	X
Systemic inflammation assessment	X	X	X	X	X
Blood biomarker retains[i]	X		X	X	X
Prior and concomitant medications[j]	X[i]	X	X	X	X
Adverse events	X	X	X	X	X

[a] On Hospital Discharge, Day 28, and Day 90, data on liver transplantation, subject survival, and cause of death will be recorded either by a medical visit or by telephone contact.

[b] Subjects who discontinue from the study early should have all Day 90 study procedures performed at the time of withdrawal (preferably within 1 week of withdrawal).

[c] Vital signs include systolic blood pressure, diastolic blood pressure, body temperature, heart rate, respiratory rate.

[d] Full physical examination (excluding breast and genitourinary examination).

[e] Hemodynamics (mean arterial pressure) will be monitored.

[f] Clinical laboratory assessments will include hematology, chemistry, and coagulation.

[g] ACLF grades (Table 9-1).

[h] Illness severity scores include CLIF-OF score, CLIF-C ACLF score, Child-Pugh score, and MELD score.

[i] Blood biomarker retains.

[j] Record prior (30 days prior to screening) and concomitant medications.

Appendix 3 – A Rule for Determining Whether an AE with Incomplete Start Date/Time is TEAE

The following procedure will be used to determine whether an AE with incomplete start date/time is TEAE in the SMT+PE-A 5% treatment group. In the AE start/end date/time, the observed value in the lower time frame (day, hour, minute) will not be used if the value in a higher time frame (e.g., month) is missing.

Step 1: to determine whether an AE with incomplete start date/time is non-TEAE based on the AE end date/time in the SMT+PE-A 5% treatment group

1a. If the AE end year value is less than the treatment starts year value, it is a non-TEAE

1b. otherwise, if years under comparison in step 1a) are equal, but the AE month value is less than the treatment start month value, the AE is a non-TEAE

1c. otherwise, if months under comparison in step 1b) are equal, but the AE end day value is less than the treatment start day value, the AE is a non-TEAE

1d. otherwise, if the days under comparison in step 1c) are equal, but AE end hour value is less than the treatment start hour value, the AE is a non-TEAE

1e. otherwise, if the hours under comparison in step 1d) are equal, but AE end minute value is less than the treatment minute value, the AE is a non-TEAE

Step 2: If the AE with incomplete start date cannot be determined to be non-TEAE based on the AE end date/time in step 1), the following conservative rule will be used to determine whether it is TEAE

2a. if the AE start year value is missing, it is an TEAE

2b. otherwise, when the year of AE start date/time is not missing, it is a non-TEAE if the AE start year value is less than the treatment starting year value, and the AE is a TEAE if the AE start year value is larger than the treatment start year

2c. otherwise, if the AE start year value is equal to the treatment start year value, but the AE start month value is missing, the AE is a TEAE

2d. otherwise, when the AE start month value is not missing, it is a non-TEAE if the AE start month value is less than the treatment starting month value, and the AE is a TEAE if the AE start month value is larger than the treatment starts month value

2e. otherwise, if the AE start month value is equal to the treatment start month value, but the SE start day value is missing, the AE is a TEAE

2f. otherwise, when the AE start day value is not missing, it is a non-TEAE if the AE start day value is less than the treatment starting day value, and the AE is a TEAE if the AE start day value is larger than the treatment starting day value

2g. otherwise, if the AE start day value is larger than the treatment starting day value, but the AE start hour value is missing, the AE is a TEAE

2h. otherwise, when the AE start hour value is not missing, it is a non-TEAE if the AE start hour value is less than the treatment starting hour value, and the AE is a TEAE if the AE start hour value is larger than the treatment starts hour value

2i. otherwise, if the AE start hour value is equal to the treatment start hour value, but the AE start minute value is missing, the AE is a TEAE

2j. otherwise, when the AE start minute value is not missing, it is a non-TEAE if the AE start minute value is less than the treatment starting minute value, and the AE is a TEAE if the AE start minute value is equal to or larger than the treatment starts minute value

2k. otherwise, if the AE status cannot be determined in steps 2a)- 2j), the AE would be treated as a TEAE

The procedure can be similarly applied to the SMT group except that the randomization date/time instead of the treatment start date/time is used in the SMT arm.

Appendix 4 – Illness Severity Score Details

CLIF-Organ Failure score system.			
Organ / System	**Sub-score = 1**	**Sub-score = 2**	**SUB-Score = 3**
Liver	Bilirubin <6mg/dL	6 ≤ Bilirubin <12mg/dL	Bilirubin ≥12mg/dL
Kidney	Creatinine <2mg/dL	2 ≤ Creatinine <3.5 mg/dL	Creatinine ≥3.5 mg/dL or renal replacement
Brain (West-Haven grade for HE*)	Grade 0	Grade 1-2	Grade 3-4
Coagulation	INR <2.0	2.0 ≤ INR <2.5	INR ≥2.5
Circulatory	MAP ≥70 mm/Hg	MAP <70 mm/Hg	Use of vasopressors
Respiratory PaO_2/FiO_2	>300	≤300 - >200	≤200 (#)
or SpO_2/FiO_2	>357	>214- ≤357	≤214 (#)

*The shaded area describes criteria for diagnosing organ failures; *HE: Hepatic Encephalopathy; # patients enrolled in the study with MV were considered as presenting respiratory failure (respiratory sub-score=3) except for patients intubated due to severe HE or to other reasons and not to a respiratory failure, in whom respiratory failure is defined according to the PaO2/FiO2 ratio.# Other patients enrolled in the study with MV were considered as presenting a respiratory failure (respiratory sub-score=3).*

CLIF-C ACLF Score

CLIF-C ACLFs = 10*[0.33*CLIF-C OFs + 0.04*Age {years} + 0.63*Ln(white cell count {10^9 cells/L}) - 2]

Child-Pugh Score

Child-Turcotte-Pugh Classification for Severity of Cirrhosis			
	Points*		
	1	2	3
Encephalopathy	None	Grade 1-2 (or precipitant induced)	Grade 3-4 (or chronic)
Ascites	None	Mild to moderate (diuretic responsive)	Severe (diuretic refractory)
Bilirubin (mg/dL)	< 2	2-3	>3
Albumin (g/dL)	> 3.5	2.8-3.5	<2.8
INR	<1.7	1.7-2.3	>2.3
*Child-Turcotte-Pugh Class obtained by adding score for each parameter (total points)			
Class A = 5 to 6 points (least severe liver disease)			
Class B = 7 to 9 points (moderately severe liver disease)			
Class C = 10 to 15 points (most severe liver disease)			

MELD Score

MELD Score = 9.57 Ln(Creatinine {mg/dl}) + 3.78 Ln(Bilirubin {mg/dl}) + 11.2 Ln(INR) + 6.43

Appendix 5 – Visiting Mapping to all Visits

Lab Assessment: **Analysis Period**	**Scheduled Timepoint**	**Analysis Visit**	**Target Day (ADY)**	**AVISITN**	**Analysis Visit Window (Days)**
Baseline	Screening/Treatment Day 1	Baseline	1	1	<=1*
	Treatment Day 2	Treatment Day 2	2	2	[2 to 3]
	Treatment Day 4	Treatment Day 4	4	4	[4 to 5]
	Treatment Day 6	Treatment Day 6	6	6	[6 to 7]
	Treatment Day 8	Treatment Day 8	8	8	[8 to 9]
	Treatment Day 10	Treatment Day 10	10	10	[10 to 11]
	Treatment Day 12	Treatment Day 12	12	12	[12 to 13]
	Treatment Day 14	Treatment Day 14	14	14	[14 to 15]
	Treatment Day 16	Treatment Day 16	16	16	[16 to 17]
	Follow-Up Day 21	Follow-Up Day 21	21	21	[18 to 24]
	Follow-Up Day 28	Follow-Up Day 28	28	28	[25 to 44]
	Follow-Up Day 60	Follow-Up Day 60	60	60	[45 to 75]
	Follow-Up Day 90	Follow-Up Day 90	90	90	[76 and above]

* If the visit is a scheduled Treatment Day 1 timepoint, the Pre-Dose sample is considered baseline, and the post dose will be considered post baseline
* If 2 or more assessments are mapped to the same visit window where an exchange occurred assign Pre and Post based on the exchange date/time.

Vital Sign Assessment:

Analysis Period	**Scheduled Timepoint**	**Analysis Visit**	**AVISITN**	**Target Day (ADY)**	**Analysis Visit Window (Days)**
Baseline	Treatment Day 1	Baseline	1	1	<=1*
	Treatment Day 2	Treatment Day 2	2	2	2
	Treatment Day 3	Treatment Day 3	3	3	3
	Treatment Day 4	Treatment Day 4	4	4	4
	Treatment Day 5	Treatment Day 5	5	5	5
	Treatment Day 6	Treatment Day 6	6	6	6
	Treatment Day 7	Treatment Day 7	7	7	7
	Treatment Day 8	Treatment Day 8	8	8	8
	Treatment Day 9	Treatment Day 9	9	9	9
	Treatment Day 10	Treatment Day 10	10	10	10
	Treatment Day 11	Treatment Day 11	11	11	11
	Treatment Day 12	Treatment Day 12	12	12	12
	Treatment Day 13	Treatment Day 13	13	13	13
	Treatment Day 14	Treatment Day 14	14	14	14
	Treatment Day 15	Treatment Day 15	15	15	15
	Treatment Day 16	Treatment Day 16	16	16	16
	Treatment Day 17	Treatment Day 17	17	17	17
	Follow-Up Day 21	Follow-Up Day 21	21	21	[18 to 24]
	Follow-Up Day 28	Follow-Up Day 28	28	28	[25 to 44]
	Follow-Up Day 60	Follow-Up Day 60	60	60	[45 to 75]
	Follow-Up Day 90	Follow-Up Day 90	90	90	[76 and above]

* If the visit is a scheduled Treatment Day 1 timepoint, the Pre Dose sample is considered baseline, and the post dose will be considered post baseline

* If 2 or more assessments are mapped to the same visit window where an exchange occurred assign Pre and Post based on the exchange date/time.

Exploratory Endpoints:

Analysis Period	Scheduled Timepoint	Analysis Visit	AVISITN	Target Day (ADY)	Analysis Visit Window (Days)
Baseline	Screening/Treatment Day 1	Baseline	1	1	<=1*
	Treatment Day 2	Treatment Day 2	2	2	2
	Treatment Day 3	Treatment Day 3	3	3	3
	Treatment Day 4	Treatment Day 4	4	4	4
	Treatment Day 5	Treatment Day 5	5	5	5
	Treatment Day 6	Treatment Day 6	6	6	6
	Treatment Day 7	Treatment Day 7	7	7	7
	Treatment Day 8	Treatment Day 8	8	8	8
	Treatment Day 9	Treatment Day 9	9	9	9
	Treatment Day 10	Treatment Day 10	10	10	10
	Treatment Day 11	Treatment Day 11	11	11	11
	Treatment Day 12	Treatment Day 12	12	12	12
	Treatment Day 13	Treatment Day 13	13	13	13
	Treatment Day 14	Treatment Day 14	14	14	14
	Treatment Day 15	Treatment Day 15	15	15	15
	Treatment Day 16	Treatment Day 16	16	16	16
	Treatment Day 17	Treatment Day 17	17	17	17
	Follow-Up Day 21	Follow-Up Day 21	21	21	[18 to 24]
	Follow-Up Day 28	Follow-Up Day 28	28	28	[25 to 44]
	Follow-Up Day 60	Follow-Up Day 60	60	60	[45 to 75]
	Follow-Up Day 90	Follow-Up Day 90	90	90	[76 and above]

* If the date/time is collected for the assessment and Screening and Treatment Day 1 occur on the same date/time then take the screening visit in the analysis. If only the date is collected for the assessment and Screening and Treatment Day 1 occur on the same date, then take the screening visit in the analysis.