Official Title: Prevention of Mortality With Long-Term Administration of Human Albumin in Subjects With Decompensated Cirrhosis and Ascites

NCT Number: NCT03451292

Document Date: Statistical Analysis Plan, Version 2: 09-Sep-2024

Completion of the signature block below signifies the review and approval of this document.

Signed by:	Reason:	Date / Time (UTC):
[redacted]	[redacted]	05-Sep-2024 13:43:45
		05-Sep-2024 14:27:23
	Owner	09-Sep-2024 09:30:37

STATISTICAL ANALYSIS PLAN (SAP)

IG1601

Study Title: **Prevention of Mortality with Long-Term Administration of Human Albumin in Subjects with Decompensated Cirrhosis and Ascites**

Development Phase: 3

SAP Version: **Version 2.0**

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

Protocol Version: **IG1601 Amendment 5/Version 6 Dated 24SEP2020**

Author: [redacted] **Grifols**

Table of Contents

List of Abbreviations

ACLF	Acute-on-chronic liver failure
ADR	Adverse drug reaction
AE	Adverse event
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-C	Chronic Liver Failure-Consortium
CLIF-C ACLF	Chronic Liver Failure-Consortium Acute-on-chronic liver failure
CLIF-C AD	Chronic Liver Failure-Consortium Acute Decompensation
CLIF-C OF	Chronic Liver Failure-Consortium Organ Failure
CRP	C-reactive protein
CSR	Clinical study report
EASL-CLIF	European Association for the Study of Liver-Chronic Liver Failure
eCRF	Electronic case report form
EQ-5D-5L	EuroQoL 5 Dimensions 5 Levels
GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HCG	Human chorionic gonadotropin
HE	Hepatic encephalopathy
HRS	Hepatorenal Syndrome
ICA	International Club of Ascites
ICU	Intensive care unit
IL	interleukin
INR	International normalized ratio
IP	Investigational product
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
MAP	Mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
MELD	Model for End-stage Liver Disease
MMRM	Mixed-effects model for repeated measurement
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
SpO2	Peripheral capillary oxygen saturation
TEAE	Treatment-emergent adverse event
TIPS	Transjugular intrahepatic portosystemic shunt
TNFα	tumor necrosis factor alpha
VAS	Visual Analog Scale
WBC	White blood cells
WHO-DD	World Health Organization Drug Classification Dictionary

1 Revision History

SAP Version	Effective Date	Description of change
1.0	21Jul2023	Not Applicable
		1. Section 6: General Statistics Considerations, was updated to add the number of decimal places categorical/qualitative data percentages are displayed. 2. Section 6.1.1: updated time to event endpoints information for clarification purposes. 3. Section 6.1.2: updated definition of Day 1 for clarification purposes. 4. Section 6.1.3: updated definition of baseline for clarification purposes. 5. Section 6.1.5: Visit Windows was updated to add an option to map early discontinuation visits to a visit window for the exploratory efficacy endpoints, the addition of Appendix 4 which contains the details of the visit windows to be applied. 6. Section 6.4.1: Safety Population, removed the note regarding the demographic summary table as this will be presented using ITT population and added to 6.4.2. 7. Section 6.4.3: Per-protocol population was updated to order the criteria based on how they will be assessed. 8. Section 6.5: The fixed-sequence testing method was updated to include the ITT population to clarify which population will be assessed.

SAP Version	Effective Date	Description of change
		9. Section 7.2: Protocol Deviations was updated to provide a more detailed description of the summary tables that will be presented. 10. Section 7.3: Demographics was updated to add additional baseline characteristics that will be summarized. 11. Section 9: Efficacy Analysis section was updated to add the analysis period and Cut-off dates for each for clarity. 12. Section 9.1.1: Was updated to provide a more detailed explanation of the endpoint and analysis period. 13. Section 9.1.2: Primary Analysis, was updated to provide the details of the hypothesis test being performed that were included in the protocol, added details as to where the stratification factors are recorded i.e. IWRS, 14. Section 9.1.3: added an additional sensitivity analysis using stratification factors collected in electronic case report form (eCRF) if >3% of subjects were mis-stratified 15. Section 9.1.4: Exploratory Subgroup Analysis was updated to add an additional subgroup analysis for Europe to distinguish East and West Europe and remove history of ACLF. Appendix 3 provides details of countries included in each region of Europe 16. Section 9.2: updated to provide more details for analyses for clarification purposes 17. Section 9.2.6: Total Number of Paracenteses, was updated to provide more details on the hypothesis test and analysis being performed. 18. Section 9.2.7: Incidence of Refractory Ascites was updated to provide more details on the hypothesis test being performed and the analyses 19. Section 9.3: Exploratory Endpoints, updated to add a step to derive the exploratory

SAP Version	Effective Date	Description of change
		endpoints using central laboratory results for parameters collected and if parameters are not tested by the central laboratory the eCRF information will be used. 20. Section 9.3.1: Incidence of ACLF at 3, 6 and 12 Months, updated to add more clarity for the Month 1 definition. 21. Section 9.3.3: CLIF-C ACLF Score, CLIF-C AD Score. added note to use the age collected on demographics eCRF page 22. Section 9.3.4: MELD Score, added additional information on how to derive the score if central laboratory results are <1 23. Section 9.3.5: Child Pugh Score, added additional information regarding the model used to analyze the data. Baseline score by week and stratification factors by week interactions were removed as model was over specified. 24. Section 9.3.6: Added additional information on the analyses for clarification purposes. 25. Section 9.3.7: Added additional information on the analyses for clarification purposes. 26. Section 9.3.8: added additional information for clarify regarding the type of disease related complication for "Other". Removed baseline score by week and stratification factors by week interactions as model was over specified. 27. Section 9.3.9: removal of the figure albumin concentration and functional capacity 28. Section 9.3.10: updated Day 1 to treatment start date for clarify, the occurrences will be counted while on treatment. Added note to explaining why pre-hospitalization should be removed from the model. Removed the paragraph summarizing TIPS as continuous and categorical data as only the number of subjects have an event is summarized. 29. Section 10.2: Clinical Laboratory Evaluations, added information regarding summarizing laboratory results reported.

SAP Version	Effective Date	Description of change
		30. Section 12: Updated to add region of Europe as a subgroup analysis. 31. Section 14: Appendices, added appendix 3 for further information on classifying countries in Europe into regions East and West Europe, added appendix 4 for visit windowing of exploratory endpoints.

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 IG1601. 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.

3 Introduction

The investigational product (IP) in this study is Albumin (human) USP, 20% (Albutein® 20%), which is a solution containing 200 g/L of total protein of which at least 95% is albumin.

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 rarely die as a consequence of an end-stage irreversible destruction of the liver. Rather, in most patients the cause of death is an acute deterioration in their clinical condition promoted by a precipitating event, a syndrome termed Acute-on-Chronic Liver Failure (ACLF).

Albumin is a critical determinant of the plasma oncotic pressure and therefore of circulatory homeostasis (1,2). It is also an important vehicle for the transport of water insoluble substances in plasma (i.e., bilirubin, bile salts, steroids, thyroid hormones, fatty acids, drugs) (1). Perhaps the most outstanding function of albumin is that it also captures many inflammatory inducers and mediators and by this mechanism it modulates systemic inflammation and oxidative stress (3).

Administration of albumin has shown efficacy in prevention and treatment of circulatory dysfunction in cirrhosis (4). Paracentesis is the most used treatment in cirrhotic patients with ascites but can cause a worsening of circulatory dysfunction. Administration of albumin after paracentesis can prevent this circulatory dysfunction (5). In patients with spontaneous bacterial peritonitis (SBP), the administration of intravenous (IV) albumin improves their circulatory function, reduces the presence of hepatorenal syndrome (HRS) from approximately 30 to 10% (6), and improves patient survival (3). There are also data that suggest that long term albumin administration (25 g weekly) improves the control of ascites and reduces the incidence and intensity of the muscle cramps (7).

Serum albumin in cirrhosis is saturated by a myriad of endogenous ligands resulting in severe impairment of its transport capacity (scavenger). Albumin is also markedly oxidized in patients with decompensated cirrhosis; this oxidation is irreversible and causes intense modifications of the protein structure and function and rapid clearance from the extracellular compartment (8,9). A significant reduction in the scavenger capacity of oxidized serum albumin for inflammatory inducers and mediators may participate in the exaggerated response to the pro-inflammatory precipitating events observed in ACLF patients (10). Therefore, substitution of the saturated and highly oxidized endogenous albumin molecules by exogenous albumin with higher functionality is another potentially important beneficial effect of Albutein 20% in patients with decompensated cirrhosis.

4 Objectives

4.1 Efficacy Objectives

4.1.1 Primary Efficacy Objective

To evaluate the effect of standard medical treatment (SMT) plus long-term Albutein 20% (SMT + Albutein 20%) administration on 1-year transplant-free survival versus SMT alone.

4.1.2 Secondary Efficacy Objectives

- To evaluate the effects of SMT + Albutein 20% administration on 3- and 6-month transplant-free and overall survival versus SMT alone
- To evaluate the effects of SMT + Albutein 20% administration on 1-year overall survival versus SMT alone
- To evaluate the effects of SMT + Albutein 20% administration on the total number of paracenteses and the incidence of refractory ascites according to the International Club of Ascites (ICA) criteria versus SMT alone

4.1.3 Exploratory Efficacy Objectives

The effects of SMT + Albutein 20% administration versus SMT alone on the following parameters will be evaluated:

- 3-, 6-, and 12-month incidence of ACLF according to the European Association for the Study of Liver -Chronic Liver Failure (EASL-CLIF) Consortium definition (11)
- Incidence of individual organ failures: liver, renal, cerebral, coagulation, respiration, and circulation as defined by the CLIF-Consortium Organ Failure (CLIF-C OF) score

- Readmissions to the hospital due to an acute complication of cirrhosis
- Admissions to intensive care units (ICU)
- Incidence of disease-related complications (anticipated disease progression includes, but not limited to HE, gastrointestinal [GI] bleeding, portal hypertension, ascites, SBP, hyponatremia and HRS)
- Serum albumin concentration and albumin functional capacity in serum (albumin binding capacity)
- Incidence of transjugular intrahepatic portosystemic shunt (TIPS) insertion for refractory ascites
- CLIF-C Acute-on-chronic liver failure (CLIF-C ACLF) score, CLIF-C Acute Decompensation (CLIF-C AD) score, Model for End-Stage Liver Disease (MELD) score, and Child-Pugh score
- Subject's quality of life according to the EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) health questionnaire

4.2 Safety Objectives

To determine the safety and tolerability profile of SMT + Albutein 20% administration in subjects with decompensated cirrhosis and ascites.

5 Investigational Plan

5.1 Overall Study Design and Plan

This is a phase 3, multicenter, randomized, controlled, parallel-group, and open-label clinical study to evaluate the efficacy of SMT + Albutein 20% administration versus SMT alone in subjects with decompensated cirrhosis and ascites.

Approximately 410 subjects with decompensated cirrhosis and ascites will be included in this study after obtaining written informed consent. The study population will consist of subjects who have been hospitalized for acute decompensation of liver cirrhosis with ascites (or with prior history of ascites requiring diuretic therapy) with or without ACLF at hospital admission or during hospitalization, but without ACLF at Screening.

There will be a screening period for enrollment of each hospitalized subject in the study. Screening should occur while the subject is hospitalized. Randomization must occur within 3 days (72 hours) of Screening, and it can occur while the subject is hospitalized or after discharge from the hospital. The first dose of Albutein 20% is to be administered on the same day as randomization (for the SMT + Albutein 20% group).

Randomization of subjects will be stratified by region (Europe or North America) and by whether or not subjects have been previously hospitalized for acute decompensation of liver cirrhosis prior to the most recent hospitalization for acute decompensation of liver cirrhosis with ascites as required by Inclusion Criterion #3v4. Within each stratum (i.e., each unique combination of region and history of hospitalization for acute decompensation of liver cirrhosis), eligible subjects will be randomized in a 1:1 ratio into 1 of 2 treatment groups:

- SMT + Albutein 20%
- SMT (control group)

SMT + Albutein 20% Treatment Group

Approximately 205 subjects will be randomized to the SMT + Albutein 20% treatment group. Screening should occur while the subject is hospitalized. Randomization must occur within 3 days (72 hours) of screening, and it can occur while the subject is hospitalized or after discharge from the hospital.

The first infusion of Albutein 20% is administered on the same day as randomization (Day 1) at the dose of 1.5 g/kg body weight (maximum 100 grams per infusion). Thereafter, subjects will receive Albutein 20% infusions at the dose of 1.5 g/kg body weight (maximum 100 grams per infusion) every 10 ± 2 days for the rest of the study (up to a maximum of 12 months). Subjects in this treatment group will also receive SMT.

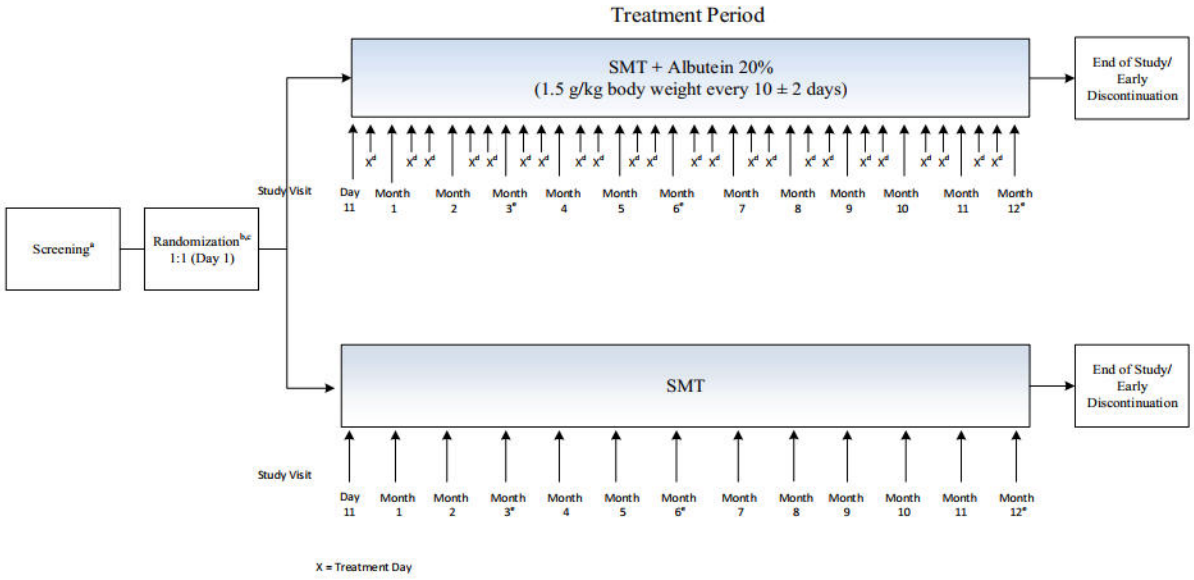
SMT Group

Approximately 205 subjects will be randomized to the control group and receive SMT. Screening should occur while the subject is hospitalized. Randomization must occur within 3 days (72 hours) of screening, and it can occur while the subject is hospitalized or after discharge from the hospital. Following randomization, subjects randomized to this group will receive SMT which will be administered per institution standards. Several guidelines are published for the management of decompensated cirrhosis (12-15).

See Figure 1 below for the diagram of the study design. The study consists of Screening for Enrollment during hospitalization, Randomization (Day 1), Treatment Period (up to 12 months), and a Follow-up Period (1 week). The screening period is 3 days (72 hours) inclusive of the day of randomization. The total duration of the study subject's participation does not exceed approximately 12 months.

Refer to Appendix 1 for detailed schedule of visits and assessments.

Figure 1: Overall Study Schema



a Screening must occur during hospitalization.

b Randomization (Day 1) must occur within 3 days (72 hours) of Screening (all efforts should be made to randomize subject as soon as they are determined eligible).

c Subjects in the SMT + Albutein 20% treatment group will receive first infusion following randomization. Randomization and first Albutein 20% infusion should occur on the same day.

d Subjects in the SMT + Albutein 20% treatment group will receive infusions at the dose of 1.5 g/kg body weight (maximum 100 grams per subject) every 10± 2 days for duration of the study (up to a maximum of 12 months).

e Overall and transplant-free survival will be assessed at 3, 6, and 12 months.

5.2 Visits and Assessments

Refer to Appendix 1 for a detailed schedule of study procedures and events by visit.

5.2.1 Screening Visit

Subjects being considered for the study will be consented prior to hospital discharge, and screening procedures will then be performed while the subject is hospitalized to determine eligibility for treatment. Local laboratory testing was to be used for screening to determine inclusion and exclusion criteria have been met, prior to initiating treatment. Local laboratory tests performed for screening purpose only will be kept in subjects' source documents but will not be entered into the eCRF. In addition, Central Laboratory testing will be collected for the purpose of safety assessment and data analyses. For ineligible subjects, demographic data and ineligibility reason(s) will be captured.

5.2.2 Treatment Day 1

Subjects will be randomized and receive treatment within 3 days (72 hours) of Screening. Randomization can occur while the subject is hospitalized or after discharge from the hospital. All assessments and activities will be performed on Day 1 prior to Albutein treatment. In the SMT + Albutein 20% treatment group, vital signs and serum albumin

concentration will also be recorded after Albutein treatment.

5.2.3 Treatment Day 11 and Monthly Visits (Month 1 through Month 11)

Subjects will have assessments on Day 11 (±2 days), Month 1 (±2 days), and then monthly (±2 days) for up to 11 months: Days, 61, 91, 121, 151, 181, 211, 241, 271, 301, 331 (See Section 5.2.5 for Day 361 assessments). All assessments and activities will be performed prior to Albutein treatment for the SMT + Albutein 20% treatment group. In addition, for the SMT + Albutein 20% treatment group, vital signs and serum albumin concentration will also be recorded after treatment.

5.2.4 SMT + Albutein 20% Treatment Days 21, 41, 51, 71, 81, 101, 111, 131, 141, 161, 171, 191, 201, 221, 231, 251, 261, 281, 291, 311, 321, 341, and 351

Subjects in the SMT + Albutein 20% treatment group will receive Albutein infusions every 10 (± 2) days for up to 12 months in the study. All assessments and activities will be performed prior to Albutein infusion, and in addition vital signs will also be recorded after Albutein infusion. These treatment day visits apply to the SMT + Albutein 20% treatment group only; subjects in the SMT treatment group will not have assessments on these study days.

5.2.5 Month 12 / Early Discontinuation

All subjects will have assessments at Month 12 (Day 361 ±2 days)/Early Discontinuation. Subjects in the SMT + Albutein 20% treatment group will receive an Albutein infusion at Month 12. All assessments and activities will be performed prior to treatment for SMT + Albutein 20% treatment group. In the SMT + Albutein 20% treatment group, vital signs and serum albumin concentration will also be recorded after Albutein infusion.

Subjects who discontinue from the study early will complete the assessments that are planned for the Month 12 visit.

5.2.6 End of Study for Completed Subjects

Subjects who complete the full 12 months of treatment will return within one week of study completion for collection of prior/concomitant medications and adverse events (AE).

5.2.7 Follow-Up for Early Discontinued Subjects (Months 3, 6, and 12)

In subjects who discontinue from the study early, data on liver transplantation, subject survival, and cause of death will be obtained at Months 3, 6, and 12.

5.3 Treatment Administration

5.3.1 Albutein 20% Dosage, Procedures, and Treatment Regimen

Randomization must occur within 3 days (72 hours) of screening, and it can occur while the subject is hospitalized or after discharge from the hospital. The first Albutein 20% infusion is administered on the same day as randomization at a dose of 1.5 g/kg body weight (maximum 100 grams per infusion). Thereafter, subjects will receive Albutein 20% infusions at the dose of 1.5 g/kg body weight (maximum 100 grams per infusion) every 10 ± 2 days for the rest of the study (up to a maximum of 12 months). At each administration, the maximum infusion rate should not exceed 4 mL/min. Reasons for any deviation from the administration of less than 100% of the IP dose as prepared by the pharmacist or designee must be recorded.

5.3.2 Standard Medical Treatment

Following randomization, subjects randomized to the SMT alone group will receive SMT, which will be administered per institution standards. Several guidelines are published for the management of decompensated cirrhosis (12-15).

5.4 Study Variables

5.4.1 Efficacy Variables

The following efficacy variables will be assessed in this study:

Primary efficacy
- Time to liver transplantation or death through 1 year after randomization

Secondary efficacy
- Time to liver transplantation or death through 3 and 6 months after randomization, and time to death through 3 and 6 months after randomization
- Time to death through 1 year after randomization
- Total number of paracenteses and incidence of refractory ascites according to the ICA criteria

Exploratory efficacy
- Incidence of ACLF (3, 6, and 12 months)
- Organ function sub-scores (liver, renal, cerebral, coagulation, circulation, and respiration), according to the CLIF-C OF score
- Number and length of hospital readmission for an acute complication of cirrhosis
- Number and length of ICU admission

- Incidence of disease-related complications (anticipated disease progression includes, but not limited to HE, GI bleeding, portal hypertension, ascites, SBP, hyponatremia, and HRS)
- Serum albumin concentration and albumin functional capacity in serum (albumin binding capacity)
- Incidence of insertion of TIPS for refractory ascites
- CLIF-C ACLF score, CLIF-C AD score, MELD score, and Child-Pugh score
- Quality of life: EQ-5D-5L health questionnaire

5.4.2 Safety Variables

The following safety variables will be assessed in this study:

- The number of suspected adverse drug reactions (ADRs; defined as possibly and or definitely drug related), including ARs (defined as definitely drug related), and incidence rate of subjects with suspected ADRs during the treatment period and within 72 hours after Albutein 20% infusion completion (or after Albutein 20% infusion stops) will be considered as the main safety variables. Due to the open label design of this trial, ADRs will be assigned causality to Albutein and ADRs will not be applicable to SMT.
- The number and incidence rate of overall treatment-emergent adverse events (TEAEs) and Serious AEs (SAEs), in addition deaths and discontinuations due to AEs will be also collected and analyzed.
- Clinically significant/relevant changes in vital function and clinical laboratory testing parameters, as determined by the investigator, will be documented as AEs and reported as part of the adverse event summaries.
- Vital signs (temperature, blood pressure, heart rate, respiratory rate) at each scheduled visit and, in particular before and after each Albutein 20% administration.
- Clinical laboratory test parameters including:
- 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), serum albumin [pre and post albumin 20% infusion in the SMT + A20% group])
- Hematology (Hemoglobin, hematocrit, platelets, red blood cell count, white blood cell (WBC) count with differential, total neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Lactate
- Coagulation (International normalized ratio (INR), fibrinogen, prothrombin time)
- Albumin functional capacity assessment (Albumin binding capacity)
- Urine pregnancy test (Qualitative urine β-human chorionic gonadotropin [β-HCG])
- Procalcitonin
- Biomarker (interleukin [IL] 6 (IL-6), IL-8, IL-10) and tumor necrosis factor alpha [TNFα])

- Plasma biomarker retains and transcriptome
- 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, standard deviation will be 2 decimal places 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 (rounded to 1 decimal place) 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 month 3, 6, and 12 to collect information on liver transplantation, subject survival, and cause of death, subjects who do not have an event relating to an event endpoint within the analysis period will have their time to event censored at the earlier of date of last contact or cut-off date for analysis.

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

Subjects randomized to SMT + Albutein 20% are scheduled to have their first infusion on the date of randomization. For SMT + Albutein 20% subjects, Study Day 1 will be considered as the first infusion date. Subjects randomized to SMT are assumed to already be receiving SMT per institutional standards at the time of randomization. They receive treatment per the investigator's treatment plan for the subject under their institutional standards for SMT and the Day 1 study visit is considered as the Study Day 1.

For primary and secondary time to event endpoints the date of randomization will be used as the start of the time period.

All concomitant medications for both treatment groups are collected and classified as either SMT or other in the electronic case report form (eCRF). The first post-randomization date of any medication(s) given as SMT is collected.

6.1.3 Definition of Baseline

Baseline is defined as the last measurement taken prior to the start of study treatment for the SMT +Albutein 20% group and for the SMT alone group baseline is the last measurement taken on or prior to the Day 1 visit. For SMT + Albutein 20% subjects, two sets of vital signs assessments are collected on day of first infusion; the vital signs assessment time will be used to determine whether the vital signs were collected pre- or post-Albutein administration if assessment time is not available, then the vital signs designated by the investigator as pre-dose on the eCRF will be considered baseline. For all other assessments, if time of assessment is not available then an assessment that occurs on the same date as randomization is assumed to be prior to randomization and considered baseline.

6.1.4 Definition of Last Subject 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 infusion start date
- Liver transplant date
- AE start date
- AE end date, with Outcome not “Fatal”
- TIPS insertion date
- Hospital admission date
- Paracentesis procedure date
- Hospital admission 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”

6.1.5 Visit Windows

For safety analyses (laboratory and vital signs data) and efficacy analyses, by-visit summaries and analyses will analyze assessments by visit as designated on the CRF; visit remapping based on study day to an analysis visit window won’t be applied. Unscheduled visits will be excluded from by-visit summaries and analyses. The Early Discontinuation

visit will be summarized as a separate visit, without adjusting for the timing of assessments for subjects that discontinue early.
For the analyses of exploratory endpoints, the early discontinuation visit will be mapped to an assessment visit. The mapping will be based on the timing of a subject's assessment visit, relative to their Study Day 1. A detailed list of the parameters and the mapping rules to be applied is provided in Appendix 4.

For cases where multiple assessments are recorded for a parameter within a single visit window, the following rules will be applied for each parameter:

- 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.

6.1.6 Adverse Events

Adverse events will be classified as TEAEs or non-Treatment-Emergent AEs (non-TEAEs), based on the comparison of the AE onset date/time with the start date/time of study treatment. For the SMT + Albutein 20% treatment group, TEAE is defined as an AE occurring during or after the first Albutein dose administration. For the SMT treatment group, it is assumed that subjects were already receiving SMT per institutional standards at the time of randomization; therefore, a TEAE will be defined as an AE occurring at or after randomization.

A non-TEAE will be defined as an AE which starts during screening and prior to the start of the first administration of study treatment in the SMT + Albutein 20% treatment group. For the SMT group, a non-TEAE is an AE that starts during screening and prior to randomization.

An AE with incomplete start date/time will be determined to be a TEAE or non-TEAE using the conservative rule specified in Appendix 2.

Any AE with a 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 treatment (i.e., start of the infusion for the SMT+ Albutein treatment group, or end date/time prior to randomization for the SMT group).

Concomitant medications are defined as medications with start date / time on or after the subject's date / time of randomization (for the SMT group) or commencement of Albutein (SMT+ Albutein treatment group). In addition, medications with start date / time prior to subject's date / time of randomization for the SMT group or commencement of Albutein for the SMT + Albutein treatment group, and end date/time either ongoing or after subject's date / time of randomization for the SMT group or commencement of Albutein in the SMT + Albutein treatment group 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 1-year transplant-free mortality rate in the current study population is assumed to be about 46% (11,16). Assuming a potential drop-out rate of 20% and 5% type-1 error for a 2-sided Chi-square test, a global sample size of 410 patients (205 per treatment group) will allow an 80% statistical power to detect an absolute reduction of 15% (17) for the 1-year mortality rate in subjects treated with SMT + Albutein 20%.

Alternatively, the sample size was calculated based on the log-rank test as follows. Assuming the 1-year transplant or mortality rate is 46% for the control group, or equivalently, the transplant-free survival rate is 54%, which translates to a hazard rate of 0.0017 assuming an exponential distribution. Using a log-rank test at the 2-sided significant level of 5%, a total of 125 events would provide at least 80% power to detect an absolute reduction of 15% in transplant or mortality rate (a 31% 1-year transplant or mortality rate, or equivalently, a 69% transplant-free survival rate) in subjects treated with SMT + Albutein 20%. This absolute difference in transplant or mortality rates translates to a hazard ratio of 0.6022, or an approximate 40% risk reduction. With all subjects followed for the entire 1-year duration of the study, a total of 322 subjects would be required to obtain 125 events. Assuming a dropout rate of 20%, a global sample size of 404 subjects (202 per treatment group) is required. This sample size calculation was performed using Proc Power with the two-sample survival statement in SAS version 9.4.

Taking a conservative approach, the larger of the 2 sample sizes (i.e., 410 subjects 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. Subjects will be randomized into one of two groups (SMT + Albutein 20% versus SMT alone) in a 1:1 ratio based on a computer-generated randomization schedule. Randomization of subjects will be stratified by region (Europe or North America) and by whether or not subjects have been previously hospitalized for acute decompensation of liver cirrhosis prior to the most recent hospitalization for acute decompensation of liver cirrhosis with ascites as required by Inclusion Criterion #3v4. Within each stratum (i.e., each unique combination of region and history of hospitalization for acute decompensation of liver cirrhosis), eligible subjects will be randomized in a 1:1 ratio into 1 of 2 treatment groups.

6.4 Analysis Populations

6.4.1 Safety Population

The Safety Population is defined for the SMT + Albutein 20% as the subset of subjects who receive any amount of Albutein 20% treatment while on SMT, and is defined for the SMT alone treatment as all subjects randomized to SMT, assuming that all subjects in the SMT arm received the SMT treatment. The Safety Population will be used for all safety analyses. Subjects will be grouped according to the treatment they actually received in all safety analyses.

6.4.2 Intent-to-Treat Population

The intent-to-treat (ITT) population includes all subjects who are randomized. The ITT Population will be used for all efficacy analyses and all baseline demographics. Subjects will be grouped according to the treatment to which they are randomized in all efficacy analyses. This population will be used for the primary efficacy analysis, demographics, and baseline characteristics.

6.4.3 Per-Protocol 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 fulfill the following criteria:

- Subject randomized to the SMT + Albutein 20% arm will be excluded from the PP population if:
    1. the subject does not receive at least 80% of the expected doses prior to the date of events (death or transplantation) or study discontinuation / completion date,
    2. the subject misses 4 or more consecutive weeks
- Subject has no major protocol violations which might have an impact on primary efficacy analysis.

6.5 Hypothesis Testing and Multiplicity Adjustments

All statistical tests will be 2-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 the ITT population). Specifically, the superiority of SMT + Albutein 20% versus SMT alone for the secondary efficacy endpoints will only be tested if the superiority for the primary efficacy endpoint is demonstrated at the 2-sided significance level of 5% (for ITT population).

For the secondary efficacy endpoints, each subsequent hypothesis is tested only if the superiority for the previous comparison(s) listed below has been demonstrated at a 2-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 death through 1 year after randomization
2. Time to liver transplantation or death through 6 months after randomization
3. Time to death through 6 months after randomization
4. Time to liver transplantation or death through 3 months after randomization
5. Time to death through 3 months after randomization
6. Total number of paracenteses
7. Incidence of refractory ascites according to the ICA criteria

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. Subjects who were incorrectly stratified at the time of randomization will be listed and summarized.

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. Deviations related to COVID-19 will also be summarized as described above.

7.3 Demographics

Demographics (age, sex, race, ethnicity, country and region in Europe), 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 will be used 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.

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 AD Score, CLIF-C OF Total Score, Child-Pugh Score, MELD Score.

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 endoscopic procedures, 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 (Albutein) 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 6.1.7. 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.

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

(SMT and other blood products), blood product type, amount, time since the start of use. At each level of summarization, a subject will be counted once per category and blood product type.

8.3 Extent of Exposure to Albutein 20%

For subjects randomized to SMT + Albutein 20%, all Albutein exposure details will be listed by visit.

An overall summary of exposure will present the duration of exposure (weeks), number of infusions received, number of subjects who had 4 or more missing consecutive infusions, and the total volume infused (mL). Duration of exposure is defined as [(date of last infusion – date of first infusion) + 10]/7. Interruptions, dose changes, and compliance are not considered in the calculation of duration of exposure.

Albutein infusion interruptions will be summarized by visit. Number of infusions, number and percentage of infusions with interruptions, and number and percentage of infusions with interruptions due to TEAE will be summarized.

8.4 Treatment Compliance for Albutein 20% Administration

Treatment compliance, infusion compliance, and overall compliance will be listed and summarized for the SMT + Albutein 20% group specific to the Albutein study drug treatment. In addition, the number and percentage of subjects with Albutein compliance <80%, 80% to ≤120%, and >120% will be presented. Infusion compliance will be calculated as (number of actual infusions / number of infusions expected or planned) *100. For subjects that complete the study, the number of infusions expected is 37. For subjects who drop out from the study early, the number of infusions expected or planned will be calculated as [(date of end of study visit – date of randomization) / 10 + 1].

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

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

Treatment compliance for the SMT alone group is not applicable for any Albutein study drug compliance assessments.

9 Efficacy Analysis

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

For the purposes of defining the analysis period for each of the efficacy analysis timepoints the following will be applied:

Analysis Timepoint	Analysis Period	Cut-Off Date
1 Year	362 Days	Randomization Date + 361 Days
6 Months	182 Days	Randomization Date + 181 Days
3 Months	92 Days	Randomization Date + 91 Days

9.1 Primary Endpoint

9.1.1 Time to Liver Transplantation or Death Through 1 Year After Randomization

Time to one-year transplant-free survival will be calculated as the earlier of [(date of liver transplantation or date of death) – randomization date + 1] for those subjects who died or had a liver transplant within the analysis period. Subjects who neither died nor had a liver transplant within the analysis period will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date for analysis.

9.1.2 Primary Analysis

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

The objective of this study is to demonstrate superiority of SMT + Albutein 20% over SMT alone with regards to 1-year transplant-free survival. The null hypothesis is that the hazard functions for liver transplantation or 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 liver transplantation or 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 + Albutein 20% / SMT alone) = 1

Alternate Hypothesis Ha: HR (SMT + Albutein 20% / SMT alone) ≠ 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 history of hospitalization for acute decompensation of liver cirrhosis (yes or no) 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 + Albutein 20% compared to the SMT alone group is less than or equal to 0.05 and the hazard ratio is less than 1.

The one -year transplantation-free survival will be summarized by means of Kaplan-Meier survival estimates and curves. The number and percentage of subjects with events of transplantation or death and subjects without events (censored) will be presented by treatment. The median, 25th percentile and 75th percentile for event-free 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 event-free survival for the endpoint at day 31, 61, 91, 181 and 361 for the endpoint and 95% confidence interval (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 history of hospitalization for acute decompensation of liver cirrhosis (yes or no) as recorded in IWRS.

9.1.3 Primary Efficacy Sensitivity Analyses

The primary analysis outlined in Section 9.1.2 will be repeated using the per-protocol population as a sensitivity analysis.
..
An unstratified analysis will be performed as a sensitivity analysis on the ITT population.

In the event that clinically and statistically significant imbalances are observed between treatment groups in any of the subjects' baseline characteristics listed above in section 7.3, a sensitivity analyses will be performed in which treatment effects will be adjusted by those characteristics identified as having imbalances between treatment group by fitting an appropriate Cox PH model stratified by the region (Europe or North America) and history of hospitalization for acute decompensation of liver cirrhosis (yes or no) as recorded in IWRS. This will be performed on the ITT population.

A sensitivity analysis will be used to assess whether the magnitude of treatment effect (i.e., hazard ratio) is consistent between two CLIF-C AD subgroups (CLIF-C AD score >50 vs ≤50) by a stratified Cox model, where the stratification factors include the region (Europe or North America) and history of hospitalization for acute decompensation of

liver cirrhosis (yes or no) as recorded in IWRS. CLIF-C AD category and treatment will be included as fixed effects and treatment by CLIF-C AD category interaction will also be included in the model. This will be performed on the ITT population.

The sensitivity analyses described above based on the ITT population will be repeated for the per-protocol population.

If the IWRS stratification factors region (Europe or North America) and history of hospitalization for acute decompensation of liver cirrhosis (yes or no) 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.

9.1.4 Exploratory Subgroup Analyses (Primary Endpoint)

Subgroup analyses by age group (≤65, >65 years), sex, race (white, other), region (Europe, NA), history of hospitalization for acute decompensation of liver cirrhosis (yes, no), CLIF-C AD group (CLIF-C AD score >50, CLIF-C AD score ≤50), time to randomization from start of screening (≤3 days, >3 days), ethnicity (Hispanic, non-Hispanic), country and European region (East Europe, West Europe, see appendix 3 for details) will be carried out for the primary endpoint based on the ITT population.

In each defined subgroup category, the analysis will be carried out using the same methodology as outlined 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 region or country subgroup, only the history of hospitalization for acute decompensation of liver cirrhosis (yes or no) will be used as the stratification factor in the stratified Cox PH model.

These results will be 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 based on the ITT population will be repeated for the per-protocol population.

9.2 Secondary Endpoints

The analysis of the secondary endpoints will be performed for the ITT population. A fixed-sequence testing method will be used for the analysis of secondary endpoints, as described in Section 6.5. The secondary endpoint definitions are presented in the order in which testing will be performed.

A sensitivity analysis will be performed for each of the secondary endpoints using the PP population.

9.2.1 Time to Death Through 1 Year After Randomization

Time to one-year survival will be calculated as [date of death – randomization date + 1] for those subjects who died within the analysis period. Subjects who did not die within the analysis period will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date 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 Liver Transplantation or Death Through 6 Months After Randomization

Time to 6 Months transplant-free survival will be calculated as the earlier of [(date of liver transplantation or date of death) – randomization date + 1] for those subjects who died or had a liver transplant within the analysis period. Subjects who neither died nor had a liver transplant within the analysis period will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date 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 31, 61, 91, 181 for the endpoint and 95% confidence interval (CI) will be estimated.

9.2.3 Time to Death Through 6 Months After Randomization

Time to 6 Months survival will be calculated as [date of death – randomization date + 1] for those subjects who died within the analysis period. Subjects who did not die within the analysis period will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date 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 31, 61, 91, 181 for the endpoint and 95% confidence interval (CI) will be estimated.

9.2.4 Time to Liver Transplantation or Death Through 3 Months After Randomization

Time to 3 Months transplant-free survival will be calculated as the earlier of [(date of liver transplantation or date of death) – randomization date + 1] for those subjects who died or had a liver transplant within the analysis period. Subjects who neither died nor had a liver transplant within the analysis period will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date 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 31, 61, 91 for the endpoint and 95% confidence interval (CI) will be estimated.

9.2.5 Time to Death Through 3 Months After Randomization

Time to 3 Months survival will be calculated as [date of death – randomization date + 1] for those subjects who died within the analysis period. Subjects who did not die within the analysis period will have their time to event censored at the earlier of the following times:

- Date of last contact.
- Cut-off date 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 31, 61, 91 for the endpoint and 95% confidence interval (CI) will be estimated.

9.2.6 Total Number of Paracenteses

For each subject, the total number of reported paracentesis procedures on treatment will be calculated and summarised by treatment group.

A paracentesis procedure occurring on treatment will be defined as any paracentesis procedure that occurred with a start date/time on or after the subject's date/time of randomization (for SMT alone group) or commencement of Albutein (for SMT+ Albutein treatment group). If time is missing and the procedure occurred on or after the date of randomization (for SMT alone group) or the date of commencement of Albutein

(for SMT+ Albutein treatment group) it will be considered to have occurred while on treatment.

The rate of occurrence of paracenteses will be analyzed using Poisson regression with adjustment for overdispersion using the Pearson statistic to estimate the scale parameter.

- Null hypothesis H_0: The rate of occurrence of paracentesis procedures SMT + Albutein 20% is greater than or equal to the rate of occurrence of paracentesis procedures on SMT alone. [i.e. *Rate ratio (SMT+Albutein 20% vs SMT Alone)* $\geq$ *1*].

- Alternative hypothesis H_a: The rate of occurrence of paracentesis procedures on SMT + Albutein 20% is less than the rate of occurrence of paracentesis procedures on SMT alone. [i.e. *Rate ratio (SMT+Albutein 20% vs SMT Alone)* < *1*].

The rate of occurrence of paracentesis procedures in the SMT + Albutein 20% treatment group will be compared to the rate of occurrence of paracentesis procedures in the SMT alone group. The response variable in the model will be the total number of procedures experienced by a subject while on treatment. The model will include treatment group, IWRS stratification factors of region (Europe of North America) and history of hospitalization for acute decompensation of liver cirrhosis (yes or no) as factors. The logarithm of the subjects' treatment duration will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events could occur. The estimated treatment effect (i.e. the incidence rate ratio of SMT + Albutein 20% versus SMT alone) and corresponding 95% confidence interval (CI) will be presented.

9.2.7 Incidence of Refractory Ascites

The number and percentage of subjects with at least one incidence of refractory ascites on treatment will be presented by treatment. Incidence of refractory ascites occurring on treatment is defined as any incidence that occurred with a start date/time on or after the subjects date/time of randomization (for SMT alone group) or commencement of Albutein (SMT+ Albutein treatment group) treatment. If time is missing and the incidence occurred on or after the date of randomization (for SMT alone group) or the date of commencement of Albutein (for SMT+ Albutein treatment group) treatment it will be considered to have occurred while on treatment.

A chi-square test will be used to assess if there is an association between treatment and incidence of refractory ascites.

Null hypothesis H_o: *P1=P2*
Alternative hypothesis H_a: *P1 ne P2*

where P1 is the proportion of subjects with at least one incidence of refractory ascites in the SMT + Albutein 20% treatment group and P2 is the proportion of subjects with at least one incidence of refractory ascites in the SMT alone treatment group. A two-sided chi-square test at a significance level of significance of 0.05 will be performed.

9.2.7.1 Secondary Efficacy Sensitivity Analyses

The secondary analysis described for each of the secondary endpoints listed above will be repeated using the per-protocol population as a sensitivity analysis.

9.2.8 Exploratory Subgroup Analyses (Secondary Endpoints)

Exploratory subgroup analyses for the subgroup categories outlined in Section 9.1.4 will be performed for the time to death through 1 year after randomization secondary efficacy outcome described in Section 9.2.1. The subgroup analyses will be performed for both the ITT population and the per-protocol population. Because hypothesis testing is not performed and p-values are not reported for subgroup analyses, the fixed-sequence testing methodology does not apply to subgroup analyses.

9.3 Exploratory Endpoints

The analysis of the exploratory endpoints will be performed for the ITT population. Exploratory endpoint scores and sub scores will be derived using clinical parameter results reported in the central laboratory dataset. For the clinical parameters not included as part of the central laboratory tests, results will be taken from the relevant eCRF pages.

9.3.1 Incidence of ACLF at 3, 6 and 12 Months

ACLF is evaluated monthly through Month 12 and will be listed.

The number and percentage of subjects with at least one occurrence of ACLF from Month 1 through Month 3 will be presented by treatment, and treatment differences will be analyzed by the Chi-square test. Month 1 is inclusive of the occurrences reported at the Day 11 and Month 1 scheduled visits.

The same summary and analysis will be performed for the ACLF evaluations occurring from Month 1 through Month 3, from Month 1 through Month 6, and for all ACLF evaluations occurring from Month 1 through Month 12.

In addition, the ACLF evaluations will be summarized by treatment group for each visit, reporting number and percentage of subjects reporting ACLF and the ACLF grade by visit.

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

CLIF-C OF score is evaluated monthly through Month 12 and 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 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. In addition, the total score change from baseline of scheduled visits for both treatment groups will be analyzed by MMRM, which includes change in total score from baseline as the dependent variable; treatment, visit, region (Europe of North America) and history of hospitalization for acute decompensation of liver cirrhosis (yes or no), treatment-by-visit interaction, region-by-visit interaction, and history of hospitalization for acute decompensation of liver cirrhosis-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. If the model fails to converge, the mixed effects model with a compound symmetry correlation structure will be used.

9.3.3 CLIF-C ACLF Score, CLIF-C AD 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:

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

The CLIF-C Acute Decompensation (AD) score is a continuous numeric value in the range of 0-100 with a higher number representing more severe disease, and is defined as:

$$\text{CLIF-C AD} = 10*[0.03*\text{Age }\{\text{years}\}^{\#} + 0.66*\text{Ln}(\text{Creatinine }\{\text{mg/dl}\}) + 1.71*\text{Ln}(\text{INR}) + 0.88*\text{Ln}(\text{white cell count }\{10^9\text{ cells/L}\}) - 0.05*\text{Sodium }\{\text{mmol/L}\} + 8].$$

The CLIF-C ACLF and AD scores will be included in the listing of CLIF-C OF scores, and each will be summarized as a continuous variable. The total score and change in total

score from baseline to each post-baseline scheduled visit will be summarized by treatment and visit. In addition, the MMRM analysis of CLIF-C OF scores will be repeated for change from baseline total scores

[#] Subject age as collected on the demographics eCRF page

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.

MELD scores are evaluated monthly through Month 12 and will be listed. If any of the individual clinical parameters used to derive the MELD score report results <1, the result is imputed to 1, and then used to generate the MELD score.

The MELD score will be summarized as a continuous variable. The MELD total 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. In addition, the MMRM analysis of CLIF-C OF scores will be repeated for the change from baseline total scores

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 protocol Appendix 3 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 monthly through Month 12 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 generalized linear models implemented in SAS GENMOD procedure, in which each Child-Pugh sub-score is modeled by the proportional odds

cumulative logit model for multinomial data with adjustment for, baseline score, region (Europe of North America), history of hospitalization for acute decompensation of liver cirrhosis (yes or no), 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 Child-Pugh Total Score and change in total score from baseline 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 repeated for the change from baseline total scores.

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

9.3.6 Number and Length of Hospital Readmission for an Acute Complication of Cirrhosis

All occurrences of hospital admissions are collected via eCRF through Month 12 and will be listed.

For each subject, the number of hospital readmissions due to acute complication of cirrhosis will be counted. This endpoint will be presented by treatment as a continuous variable and analyzed by Poisson regression with adjustment for overdispersion using the Pearson statistic to estimate the scale parameter. The total number of hospital admissions in the SMT + Albutein 20% treatment group will be compared to the SMT alone. The response variable in the model will be the total number of hospital admissions experienced by a subject while on treatment. The model will include treatment group, IWRS stratification factors of region (Europe of North America) and history of hospitalization for acute decompensation of liver cirrhosis (yes or no) as factors. The logarithm of the subjects' treatment duration will be used as an offset variable in the model to adjust for subjects having different exposure times during which the events could occur. The estimated treatment effect (ie, the incidence rate ratio of SMT + Albutein 20% versus SMT alone) and corresponding 95% confidence interval (CI) will be presented.

Hospital readmissions occurring on treatment are defined as any hospital admission that occurred with a start date/time on or after the subjects treatment start date/time (treatment start date/time is defined as; date/time of randomization (for SMT alone group) or commencement of Albutein (SMT+ Albutein treatment group) treatment). If time is missing and the incidence occurred on or after the date of randomization (for SMT alone group) or the date of commencement of Albutein (for SMT+ Albutein treatment group) treatment it will be considered to have occurred while on treatment. If the hospital readmission is on-going at the end of the study, it is also considered as occurring on treatment.

In the event a hospital readmission occurs prior to treatment start date and the discharge date is after the treatment start date it will be counted as an occurrence.

For each subject, the total duration (days) of hospital readmission for acute complication of cirrhosis will be calculated as the sum of the durations of each readmission (discharge date – admission date + 1) due to acute complication of cirrhosis. Descriptive statistics will be presented by treatment and analyzed by analysis of covariance (ANCOVA) with adjustment for stratification factors. If a subject's hospital readmission is considered on-going at the end of the study, the end of study completion date will be used to calculate the duration of the hospital readmission.

9.3.7 Number and Length of ICU Admission

For each subject, the number of hospital readmissions in which the subject was admitted to the ICU will be counted. This endpoint will be presented by treatment as a continuous variable and analyzed in the same way as hospital readmissions using Poisson regression with adjustment for over dispersion using the Pearson statistic to estimate the scale parameter.

ICU admission occurring on treatment are defined as any ICU admission that occurred with a start date/time on or after the subjects date/time of randomization (for SMT alone group) or commencement of Albutein (SMT+ Albutein treatment group) treatment. If time is missing and the incidence occurred on or after the date of randomization (for SMT alone group) or the date of commencement of Albutein (for SMT+ Albutein treatment group) treatment it will be considered to have occurred while on treatment.

In the event a ICU admission occurs prior to treatment start date, and the discharge date is after the treatment start date, it will be counted as an occurrence and the duration of this ICU admission will be calculated as [(discharge date – treatment start date) + 1].

For each subject, the total duration (days) of hospital readmission to the ICU will be calculated as the sum of the durations of each ICU admission (ICU discharge date – ICU admission date + 1). Descriptive statistics will be presented by treatment and analyzed by ANCOVA with adjustment for stratification factors. If a subject's ICU admission is considered on-going at the end of the study, the end of study completion date will be used to calculate the duration of the ICU readmission.

9.3.8 Incidence of Disease-Related Complications

All disease-related complications will be collected via a eCRF through Month 12 and will be listed.

The number and percentage of subjects with at least one occurrence of each of the following disease-related complications from the list below on or after treatment start date will be presented by treatment, and compared using the generalized linear models implemented in SAS GENMOD procedure, in which the odds ratio and corresponding 95% Confidence Interval (CI) will be determined from a logistic model, with the incidence of disease related complication (Yes/No) as the dependent variable and treatment, stratification factors of region (Europe of North America) and history of hospitalization for acute decompensation of liver cirrhosis (yes or no) as factors. The robust variance estimate for the treatment effect will be estimated based on the compound symmetry working correlation structure. If the model does not converge, first-order autoregressive (AR (1)) working correlation structure will be used. If it fails to converge, the independent working correlation structure will be used.

Anticipated disease related complications will include:

- HE – including HE I, HE II, HE III, and HE IV
- GI Bleeding – including lower GI bleeding and upper GI bleeding
- Portal Hypertension
- Ascites
- Spontaneous Bacterial Peritonitis
- Hyponatremia
- HRS – including Type 1 and Type 2
- Other (includes disease related complications not captured in the types listed above)

In addition, the number of each type of disease-related complications 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.

9.3.9 Serum Albumin Concentration and Albumin Functional Capacity in Serum (Albumin Binding Capacity)

Serum albumin concentration and albumin binding capacity are analyzed by a central laboratory, with all results and normal ranges reported in SI units. Serum albumin concentration is measured before and after each infusion at each visit during the treatment period; albumin binding capacity is measured once per visit.

Serum albumin concentration and albumin binding capacity will be listed for each subject, and summarized by visit. A summary table will present descriptive statistics for original values and change from baseline by treatment, parameter and visit. For the SMT + Albutein 20% group and serum albumin concentration parameter, change from baseline to the pre-infusion timepoint will be summarized. Moreover, the difference between pre-infusion and post-infusion within each visit will also be summarized.

In addition, change from baseline at each visit will be analyzed for visits with data collected for both treatment groups, in the same way as CLIF-C OF scores. Figures will be presented for means over time including the baseline visit for both albumin concentration and functional capacity.

9.3.10 Incidence of Insertion of TIPS for Refractory Ascites

All occurrences of TIPS insertion are collected via a log through Month 12 and will be listed.

The number and percentage of subjects with at least one occurrence of TIPS insertion on or after treatment start date will be presented by treatment, and treatment differences will be analyzed using the same method as that for Incidence of disease-related complications. If a subject had at least one occurrence between screening and before the treatment start date it will be considered as a baseline occurrence The odds ratio and corresponding 95% Confidence Interval (CI) will be determined from a logistic model, with the incidence of insertion of TIPS for Refractory Ascites (Yes/No) as the dependent variable and treatment, baseline occurrence, stratification factors of region (Europe of North America) as factors. Pre-hospitalization will not be included in the model as the subjects would be required to have been hospitalized to have an insertion of TIPS for refractory Ascites and this is considered as an exclusion criterion for the study.

9.3.11 Quality of Life: EQ-5D-5L Health Questionnaire

The EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) questionnaire is assessed monthly through Month 12; all data will be listed.

The EQ-5D-5L health questionnaire consists of five-dimension scores for mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension score has values of 1-5 with a higher number representing worse quality of life. Refer to protocol Appendix 5 for more details. Each EQ-5D-5L domain score will be summarized as a categorical variable by treatment for each visit.

The EQ-5D-5L health profile, defined by the EQ-5D-5L descriptive system, may be converted into a single index score on the basis of the US set of weights using the EuroQol value level dataset which contains the values of the EQ-5D-5L crosswalk index values (19). The US EQ-5D-5L index score is a numeric value in the range of -0.109 to 1.00 with a higher number generally representing a better quality of life. The EQ-5D-5L index score will be summarized as a continuous variable. The index score and change from baseline will be summarized by treatment for each visit. In addition, the change from baseline will be compared at visits with data collected for both treatment groups using the same method as that for CLIF-C OF scores.

The EQ-5D-5L Visual Analog Scale (EQ VAS) rates the subject's health on a scale of 0 to 100, with a higher number representing better health. The EQ VAS score will be summarized as a continuous variable. The VAS score and change from baseline will be summarized by treatment for each scheduled visit. In addition, the change from baseline will be compared for scheduled visits with data collected for both treatment groups in the same way as CLIF-C OF scores.

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. A suspected 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.

A temporally associated (i.e., infusional) AE is an AE that is temporally associated with the infusion of Albutein 20%, and is identified as an AE that occurs during an Albutein infusion (as recorded by the investigator), or within 72 hours following an Albutein infusion (determined by calculating the time from infusion end to AE start). These definitions only apply to subjects in the SMT + Albutein 20% group.

All adverse events, both treatment-emergent and non-treatment emergent, will be included in a listing, with a flag to distinguish whether or not 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:

- AE with Onset Prior to Treatment
- TEAE
- Suspected ADR
- AR
- TEAE Leading to Death
- Serious TEAE
- Serious Suspected ADR
- 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
- PT – summary of number of TEAEs and number/percentage of subjects with at least one TEAE by treatment 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 number of infusions, number of adverse events, rate of adverse events per infusion, and rate of adverse events per exposure week by preferred term. Rate per infusion is defined as total number of events divided by total number of infusions received. Rate per exposure week is defined as total number of events divided by total duration of exposure in weeks. This summary applies to the SMT + Albutein 20% 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 + Albutein 20% 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**
AE with Onset Prior to Treatment	□					
TEAEs	□	□	□	□	□	□
Suspected ADR	□		□		□	□
AR	□		□		□	
TE SAEs	□	□		□		□
Non-serious TEAEs	□#					
TEAEs leading to Study Withdrawal	□					□
TEAEs leading to Death	□					□
Temporally associated TEAEs*	□				□	

* This subset applies only to the SMT + Albutein 20% group.
# This summary will include number of events by SOC / PT.

10.2 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 with available data will be included in the laboratory listings and summaries.

Test Panel	Planned tests
Hematology	Hemoglobin, hematocrit, platelets, red blood cell count, WBC count with differential
Chemistry	Sodium, potassium, creatinine, BUN, calcium, magnesium, LDH, AST, ALT, GGT, ALP, glucose, total bilirubin, direct and indirect bilirubin, CRP, lactate, serum albumin
Coagulation	International normalized ratio (INR), fibrinogen, prothrombin time
Albumin functional capacity assessment	Albumin binding capacity
Systemic inflammation assessment	Procalcitonin, WBC (hematology panel), CRP (chemistry panel)

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.

Summary tables for all continuous/quantitative laboratory parameters (including hematology, chemistry, coagulation and systemic inflammation assessment) will present descriptive statistics for original values and change from baseline by treatment and visit. 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

The above imputation for laboratory values does not apply to the central laboratory values used for all the exploratory endpoint scores. For these exploratory endpoint scores the original result collected will be used with no imputation applied. Shifts from baseline

(with categories L/N/H for low/normal/high) will be presented by parameter, 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.

Pregnancy tests will be listed for each subject.

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.

10.3 Vital Signs

Vital signs including systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), 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 treatment and visit. For SMT+ Albutein 20% group, change from baseline to the pre-infusion timepoint will be summarized. Moreover, the difference between pre-infusion and post-infusion within each visit will also be summarized.

10.4 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

During the conduct of the study, protocol amendments and varying recruitment rates between countries introduced potential variables to the study that will be analyzed for relevance to interpreting the outcomes on the efficacy endpoints. Specifically, the following variables will be analyzed as described further in the subsections below:

- Addition of CLIF-C AD > 50 as an inclusion criterion

- Number of subjects recruited per country and region in Europe (East and West Europe) as a subgroup analysis. Time from start of screening to randomization with first dose of IP as a subgroup analysis.
- Changes in the analysis of longitudinal outcomes.

Rationale and plan for subgroup analysis based on CLIF-C AD score

CLIF-C AD, a specific prognostic score for hospitalized cirrhotic patients with acute decompensation (18), was not an entry criterion in the study until Protocol Amendment 4, Version 5. In this amendment, the enrollment criteria that subjects needed a CLIF-C AD score >50 at screening was added to increase event rates for the primary efficacy endpoint. A subgroup analysis on the primary and secondary efficacy endpoints will be conducted comparing "CLIF-C AD score >50" vs "CLIF-C AD ≤50". This subgroup analysis is incorporated into the appropriate sections above (See Section 9.1.4). This subgroup analysis is intended to address whether the study intervention demonstrates any differential effect on endpoints based on CLIF-C AD scores at enrollment.

Rationale and plan for subgroup analysis based on country recruitment

Since this study is a large multinational study with varying rates of recruitment between countries, a subgroup analysis will be conducted for countries with reasonably large number of patients (30 patients). The objective of these analyses is to examine whether the patients in different countries benefit differently from the treatment possibly due to different standard medical treatment This subgroup analysis is incorporated in the appropriate sections above (See Section 9.1.4). We do not conduct this subgroup analysis for countries with fewer patients because the model may not converge due to the fact that uncertainties in the parameter estimates become larger due to small sample size. For European countries an additional grouping based on the region in Europe the countries are located will be applied and subgroup analyses will be performed.

Rationale and plan for subgroup analysis based on time from start of screening to randomization with first treatment with IP

The time window from screening to first administration of Albutein 20% in the treatment arm has varied with protocol amendments. The final protocol amendment under which most of the patients were enrolled dictates that patients are randomized and receive first dose of IP within 3 days (72 hours) of start of screening, whereas earlier versions allow for the first dose of IP to occur more than 3 days (72 hours) after start of screening. To account for any possible differential treatment effect based on time to treatment with IP, a subgroup analysis will be done comparing subjects with time to randomization from start of screening ≤3 days vs time to randomization from start of screening >3 days. This subgroup analysis is incorporated in the appropriate sections above (See Section 9.1.4).

Discussion of the definition of TEAE in the SAP

In the protocol, a TEAE is defined as an AE which occurs between the start of study treatment and the final visit of the clinical study. In this SAP, TEAEs are defined as AE

with onset date/time on or after the subject's randomization date/time for SMT arm, and with onset date/time during or after the first dose administration for the SMT + Albutein 20% arm. For subjects in the SMT + Albutein 20% arm, the first dose is scheduled on the same day as randomization. The definition is modified because the treatment time after randomization entered in the EDC for subjects in the SMT arm may not be on day 1, which may cause bias in the comparison of TEAE between the two groups. The new definition assumes that subjects in the SMT group had been on the SMT treatment before entering the trial. The new definition intends to remove bias in the comparison of TEAE between two treatment groups.

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, CLIF-C AD score, MELD score, EQ-5D-5L index score, EQ-5D-5L VAS score], and general linear model implemented in SAS Proc GENMOD will be used to analyze the longitudinal binary or ordinal outcomes [Child-Pugh Score, Incidence of disease-related complications, Incidence of insertion of TIPS for refractory ascites]. However, as stated in Section 9.1.2.3 of the protocol, exploratory endpoints would be analyzed by means of ANCOVA or Student's t tests (for normally-distributed variables), non-parametric Mann-Whitney U test (for non-parametric variables), and Fisher's exact test or Chi-square test (for binomial variables). The methods specified in the protocol are not suitable for longitudinal outcomes with missing data.

Adding Ethnicity as a new subgroup analysis

The Ethnicity is collected in EDC. To account for any possible differential treatment effect based on ethnicity, a subgroup analysis will be done comparing Hispanic subjects vs non-Hispanic subjects. This subgroup analysis is incorporated in the appropriate sections above (see Section 9.1.4).

13 References

1. Arroyo V, García-Martinez R, Salvatella X. Human serum albumin, systemic inflammation, and cirrhosis. J Hepatol 2014; 61: 396-407.
2. García-Martinez R, Caraceni P, Bernardi M, et al. Albumin: Pathophysiological basis and its role in the treatment of cirrhosis and its complications. Hepatology 2013; 58: 1836-46.
3. Romanelli RG, La Villa G, Barletta G, et al. Long-term albumin infusion improves survival in patients with cirrhosis and ascites: an unblinded randomized trial. World J Gastroenterol 2006; 12: 1403-1407.
4. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. Gut 2007;56:1310-1308.
5. Luca A, García-Pagán JC, Bosch J, et al. Beneficial effects of intravenous albumin infusion on the hemodynamic and humoral changes after total paracentesis. Hepatology 1995;22:753-758.
6. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med 1999; 341: 403-9.
7. Angeli P, Albino G, Carraro P, , et al. Cirrhosis and muscle cramps: evidence of a causal relationship. Hepatology 1996;23:264-273.
8. Era S, Kuwata K, Imai H, et al. Age-related change in redox state of human serum albumin. Biochim Biophys Acta. 1995;1247(1):12-16.
9. Oettl K and Marsche G. Redox state of human serum albumin in terms of cysteine-34 in heath and disease. Methods Enzymol 2010;474:181-195.
10. Moeller S, Henriksen JH. Cardiovascular complications of cirrhosis. Postgrad Med J 2009; 85: 44-54.
11. Murray J, Ezzati M, Flaxman A, et al. The global burden of disease study 2010: a multi-investigator collaboration for global comparative descriptive epidemiology. Lancet 2012;380: 2055-2058.
12. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. Gut 2015;64:531-537.
13. Gluud LL, Christensen K, Christensen E, et al. Terlipressin for hepatorenal syndrome. Cochrane Database Syst Rev 2012. doi:10.1002/14651858.CD005162.pub3.
14. Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases. Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology 2013; 57: 1651-3
15. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol 2010; 53: 397-417
16. Bernal W, Jalan R, Quaglia A, et al. Acute-on-chronic liver failure. Lancet 2015; 386:1576–87.

17. Bernardi M, Riggio O, Angeli P, et al. Long-Term Use of Human Albumin for the Treatment of Ascites in Patients With Hepatic Cirrhosis: The Interim Analysis of the ANSWER Study.
18. Jalan R, Pavesi M, Saliba F, Amorós A, et al. CANONIC Study Investigators; EASL-CLIF Consortium. The CLIF Consortium Acute Decompensation score (CLIF-C ADs) for prognosis of hospitalised cirrhotic patients without acute-on-chronic liver failure. J Hepatol. 2015 Apr;62(4):831-40.
19. https://euroqol.org/wp-content/uploads/2024/01/US_crosswalk_SAS.txt

14 Appendices

Appendix 1 – Schedule of Study Procedures and Events

		Treatment Period[a]					
	Screening	Day 1	Day 11, Months 1-11[b]	Treatment Days[c]	Month 12 / Early Discontinuation	End of Study: Completed	Follow-up: Discontinued[d]
Inclusion/exclusion criteria	X	X					
Medical history & demographics	X						
Abdominal ultrasound	X[k]						
Endoscopic procedures	X[l]						
Urine pregnancy test	X						
Physical exam	X[m]		X[n]		X		
Randomization		X					
Vital signs [e]		X	X	X	X		
Ascites assessment	X	X	X		X		
Hepatic encephalopathy evaluation	X		X		X		
Hemodynamics assessment (MAP)	X		X		X		
Peripheral capillary oxygen saturation (SpO2)	X		X		X		
Weight		X	X	X	X		
Clinical laboratory assessments [f]	X	X	X		X		
Serum albumin concentration [g]		X	X		X[r]		
Record ACLF grade	X		X		X		
Systemic inflammation assessment [h]		X	X		X		
Illness severity scores evaluation [i]	X		X		X		
Quality of life assessment (EQ-5D-5L health questionnaire)		X	X[o]		X		
Prior and concomitant medications	X	X	X	X	X	X	
Albumin infusion		X[c]	X[c]	X[c]	X[r]		
Assess TIPS insertion			X		X		
Albumin functional capacity assessment (albumin binding capacity)		X	X[p]		X		
Adverse events	X	X	X	X	X	X	
Biomarker retains [j]		X	X[o]		X		
Liver transplantation, survival, cause of death data			X[q]		X		X

Abbreviations: ACLF = Acute-on-chronic liver failure; EQ-5D-5L = EuroQol 5 Dimensions 5 Levels; MAP = Mean arterial pressure; TIPS = Transjugular intrahepatic portosystemic shunt.

[a] The treatment period will be up to 12 months.

[b] Subjects will have assessments on Day 11 (±2 days), Month 1 (±2 days), and then monthly (±2 days) for up to 12 months.

[c] Subjects will be randomized (Day 1) within 3 days (72 hours) of Screening. Following randomizations, subjects in the SMT + Albutein 20% treatment group will receive the first infusion on the same day at the dose of 1.5 g/kg body weight (maximum 100 grams per subject). Thereafter, subjects will receive Albutein 20% infusions at the dose of 1.5 g/kg body weight (maximum 100 grams per subject) every 10 ± 2 days for the rest of the study.

[d] Subjects who discontinue from the study early will have follow-up vital status assessments performed at Months 3, 6, and 12.

[e] Vital signs include systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate. Vital signs will be measured immediately prior to and immediately after the end of the Albutein 20% administration in the SMT + Albutein 20% treatment group.

[f] Clinical laboratory assessments will include hematology, chemistry, and coagulation performed by the central lab. At the Screening visit only, local laboratory tests will be performed in order to determine subject eligibility. Screening local laboratory test results will be kept in subjects' source documents but will not be entered into the eCRF.

[g] Serum albumin concentration will be measured immediately prior to treatment. In the SMT + Albutein 20% treatment group, serum albumin concentration will also be measured immediately after the end of the Albutein 20% administration.

[h] Systemic inflammation assessment includes testing for procalcitonin, WBC, and CRP.

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

[j] Biomarker retains will be drawn for potential analysis of cytokines (IL-6, IL-8, IL-10, and TNFα) found in the blood which are significantly correlated with disease activity. All clinical blood samples will need to be drawn first before biomarker retains are drawn.

[k] Findings from abdominal ultrasounds performed in the last 6 months will be recorded.

[l] Findings from endoscopic procedures performed in the last 6 months will be recorded.

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

[n] Physical examination performed on Month 6 only.

[o] EQ-5D-5L health questionnaire and optional collection for blood biomarker retains on Months 1, 3, 6, and 9. All clinical blood samples will need to be drawn first.

[p] Assessed on Day 11 and Months 1, 3, 6, and 9.

[q] Assessed on Months 3 and 6.

[r] Month 12 Visit only.

Appendix 2 – 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 + Albutein 20% 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 + Albutein 20% treatment group

1a. If the AE end year value is less than the treatment start 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 start 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 start month value, and the AE is a TEAE if the AE start month value is larger than the treatment start 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 start day value, and the AE is a TEAE if the AE start day value is larger than the treatment start day value
2g. otherwise, if the AE start day value is larger than the treatment start 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 start hour value, and the AE is a TEAE if the AE start hour value is larger than the treatment start 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 start minute value, and the AE is a TEAE if the AE start minute value is equal to or larger than the treatment start 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 3 – Region in Europe Categories

Region in Europe	Countries
West Europe	Belgium, France, Germany, Denmark, Spain, Italy, United Kingdom
East Europe	Bulgaria, Bosnia - Herzegovina, Hungary, Poland, Serbia

Appendix 4 – Visit Mapping for early discontinuation visit

Table 1: Scheduled Visits and Analysis Visit Windows for ALCF, CLIF-C OF Score and Sub Scores, CLIF-C ACLF Score, CLIF-C AD Score, MELD Score, Child Pugh Score, Child Pugh Sub Score, Child Pugh Class, Serum Albumin Concentration

Analysis Period	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day)*
Baseline	Day 1	Baseline	1	<=1
	Day 11	Day 11	11	[2 to 21]
	Day 31 (Month 1)	Day 31 (Month 1)	31	[22 to 46]
	Day 61 (Month 2)	Day 61 (Month 2)	61	[47 to 76]
	Day 91 (Month 3)	Day 91 (Month 3)	91	[77 to 106]
	Day 121 (Month 4)	Day 121 (Month 4)	121	[107 to 136]
	Day 151 (Month 5)	Day 151 (Month 5)	151	[137 to 166]
	Day 181 (Month 6)	Day 181 (Month 6)	181	[167 to 196]
	Day 211 (Month 7)	Day 211 (Month 7)	211	[197 to 226]
	Day 241 (Month 8)	Day 241 (Month 8)	241	[227 to 256]

	Day 271 ((Month 9)	Day 271 ((Month 9)	271	[257 to 286]
	Day 301 (Month 10)	Day 301 (Month 10)	301	[287 to 316]
	Day 331 (Month 11)	Day 331 (Month 11)	331	[317 to 346]
	Day 361 (Month 12)	Day 361 (Month 12)	361	[347 to 376]

*Relative to Study Day 1.
Note: For Serum Albumin Concentration this is the Day 1 pre-dose visit

Table 2: Scheduled Visits and Analysis Visit Windows for Albumin Functional Capacity in Serum (Albumin Binding Capacity)

Analysis Period	Scheduled Time Point	Analysis Visit (label on output)	Target Time Point (Day*)	Analysis Visit Window (Day)*
Baseline	Day 1	Baseline	1	<=1
	Day 11	Day 11	11	[2 to 21]
	Day 31 (Month 1)	Day 31 (Month 1)	31	[22 to 46]
	Day 61 (Month 2)	Day 61 (Month 2)	61	[47 to 76]
	Day 91 (Month 3)	Day 91 (Month 3)	91	[77 to 106]
	Day 121 (Month 4)	Day 121 (Month 4)	121	[107 to 136]
	Day 151 (Month 5)	Day 151 (Month 5)	151	[137 to 166]
	Day 181 (Month 6)	Day 181 (Month 6)	181	[167 to 196]
	Day 211 (Month 7)	Day 211 (Month 7)	211	[197 to 226]
	Day 241 (Month 8)	Day 241 (Month 8)	241	[227 to 256]
	Day 271 ((Month 9)	Day 271 ((Month 9)	271	[257 to 286]
	Day 301 (Month 10)	Day 301 (Month 10)	301	[287 to 316]
	Day 331 (Month 11)	Day 331 (Month 11)	331	[317 to 346]
	Day 361 (Month 12)	Day 361 (Month 12)	361	[347 to 376]