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VTL-308 STATISTICAL ANALYSIS PLAN (VERSION 4)

Title A Randomized, Open-label, Multicenter, Controlled, Pivotal Study to Assess Safety and Efficacy of ELAD[®] in Subjects with Alcohol-Induced Liver Decompensation (AILD)

Sponsor Vital Therapies, Incorporated
15010 Avenue of Science, Suite 200
San Diego, CA 92128

Statistician Ciani Sparks, MS

Author Robert A. Ashley, MA

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1 STUDY OBJECTIVES AND SAMPLE SIZE RATIONALE

1.1 INTRODUCTION

The purpose of the VTL-308 Statistical Analysis Plan (SAP) is to provide detailed instruction and guidance for the analysis of the VTL-308 study results. This plan is intended to be inclusive of all planned analyses and to provide the guidelines for additional analyses, should they be necessary, to interpret the pre-specified analyses or to provide further context for the interpretation of the study outcomes.

The plans outlined in the statistical section of the VTL-308 Clinical Protocol are intended to align with this SAP. However, the SAP may be subject to change based on advances in analytical standards and the availability of new information from the literature. In the event that an analysis conflict is observed between the instructions in the protocol and this SAP (other than obvious administrative or typographical errors), the SAP shall supersede the protocol.

There are a number of types of ACLF, including acute flare of chronic hepatitis B and alcohol-induced liver decompensation (AILD). AILD is defined as a progressive inflammatory liver disease leading to an acute form of alcohol-induced liver injury which arises when the proximate cause of the acute decompensation is the consumption of alcohol. A specific, well-defined subset of AILD is severe alcoholic hepatitis (sAH), generally defined as progressive inflammatory liver disease leading to an acute form of alcohol-induced liver injury that occurs with the consumption of large amounts of alcohol in patients with relatively mild, underlying chronic alcoholic liver disease ([Dubuquoy et al. 2015](#), [Shi et al. 2015](#)). Based on current literature and analysis of the VTI-208 ELAD clinical data, it is evident that the diagnosis of all subjects enrolled in VTI-208 fit into the category of sAH. As sAH is the more commonly used clinical term, from this point forward, sAH will be used to refer to the indication, rather than AILD.

1.2 ANALYSIS OBJECTIVES

1.2.1 Primary Objective

The primary objective of the study is to evaluate safety and efficacy of ELAD with respect to overall survival (OS) of subjects with a clinical diagnosis of sAH through at least Study Day 91, with follow-up Protocol VTL-308E providing additional survival data up to a maximum of 5 years, that will be included, as available, through VTL-308 study completion (after the last surviving enrolled subject completes Study Day 91 visit; incorporation of data from VTL-308E is further described in [Section 2](#) and [Section 7.1.1](#)). The primary objective will be assessed using a log-rank analysis of survival data conducted in the Intent-to-Treat (ITT) population.

1.2.2 Secondary Objectives

The secondary objectives are defined as:

- To estimate the effect of ELAD on the proportion of survivors at Study Day 28 and Study Day 91 using a Chi-squared test;
- To estimate the effect of ELAD on the proportion of subjects achieving a 20% reduction in total bilirubin by Day 7 (ECBL20 Yes);

1.2.3 Exploratory Objectives

The exploratory objectives will identify potential differences between treatment groups in factors related to liver transplant, standard demographics, selected baseline characteristics, medical history, and standard of care. These factors are pre-specified in this SAP, and are based on previously identified and medically pertinent influences on treatment outcomes in alcoholic hepatitis, as well as on factors shown to be important in prior studies of ELAD. In addition, the relationship between outcomes and ELAD System performance, therapeutic interventions of interest, and administration of concomitant pharmacotherapies of interest will be assessed in order to help inform product labeling and use. Analyses of post-treatment medical care and behavior will also be carried out to assess whether there are differences between ELAD-treated and Control subjects and whether those differences have an impact on treatment outcomes. Furthermore, the difference between treatment groups at each time point of selected labs and MELD scores with a mixed model repeated measure (MMRM) will be analyzed. Changes in certain biomarkers of interest will also be evaluated (See [Section 7.3](#)).

1.2.4 Safety Assessments

Safety Assessments are discussed in [Section 8](#) and will include analyses of adverse events, changes in medical conditions, changes in vital signs, and changes in clinical laboratory values.

1.3 SAMPLE SIZE RATIONALE

The sample size is based on experience from the VTI-208 study.

The VTL-308 inclusion criteria have been established to reflect a subset of the VTI-208 population, i.e. the VTI-208 population with baseline criteria of MELD <30, age <50, INR \leq 2.5, creatinine <1.3 mg/dL and serum total bilirubin \geq 16 mg/dL.

The key design feature of the VTL-308 Protocol is that the primary analysis of treatment effect on overall survival is based on a log-rank statistic having two-sided significance level of 0.05. This primary analysis will be performed when the last of 150 randomized subjects has been followed for at least 91 days. Sample size adjustments may be made only in the instance in which more than 150 randomized subjects would be needed in order to achieve the minimum threshold of 55 deaths at the time of that analysis.

When the study is nearing completion of enrollment, the total number of deaths occurring through that time will be calculated, along with the mortality rate, based on the enrollment rate per month and the time to death. Based on these calculations a projection will be made of the total number of subjects that will need to be enrolled to achieve the minimum threshold of 55 deaths at the time of study data lock (estimated to be approximately 5 months after last patient enrolled). The total sample size may then be adjusted accordingly.

Analysis of the VTI-208 data suggests that in a group of subjects meeting the inclusion criteria for VTL-308, it might be reasonably anticipated that one-year survival will be in the range from 40% to 48% in the Control group. Under the assumption of a proportional hazards model, if the hazard ratio is 0.4 in favor of the ELAD group, this leads to the anticipation that one-year survival will be in the range from 69.5% to 74.5% in the ELAD subjects.

The rationale for the sample size is based on the following assumptions:

- the analysis of the primary endpoint of overall survival will be conducted in the ITT population;
- the prospectively defined population behaves similarly to the corresponding subgroup of the VTI-208 study;
- the log-rank test will be used to compare two survival curves using a two-sided significance level of 0.05;
- one-year survival will be in the range from 40% to 48% in the Control group and in the range from 69.5% to 74.5% in the ELAD group;
- the accrual distribution will be uniform with an accrual time that will be at least 720 days;
- the rate of missing data will be in the range from 0% to 10%; and
- the primary analysis will be the time when at least 55 deaths have occurred and the time when the last enrolled subject has been followed for at least 91 days. It follows that a sample size for the VTL-308 trial of 75 subjects per group with 1:1 allocation would provide a number of events (i.e., deaths) in the range from 55 to 65, even if we assume average follow-up of only 1 year. With 55 events, the trial will have 90% power if the true hazard ratio is 0.417; with 65 events, the trial will have 90% power if the true hazard ratio is 0.447.

2 STUDY DESIGN

VTL-308 is a randomized, open-label, multicenter, controlled, pivotal study of subjects with sAH. A minimum of 150 subjects meeting the eligibility requirements of the study will be randomly assigned in a 1:1 ratio at site level to receive either standard of care treatment for sAH (as defined in the protocol) plus treatment with the ELAD System (ELAD group) or standard of care treatment for sAH (as defined in the protocol) alone (Control group).

Central randomization will be performed to ensure that neither site nor study personnel will have any foreknowledge of subject treatment assignment.

Because ELAD treatment must take place in an Intensive Care Unit (ICU), or a Step-Down Unit (SDU) with an equivalent standard of care if written pre-approval has been given by VTL, all subjects considered for enrollment must be considered eligible for ICU or SDU placement. Control subjects need not be placed in an ICU or SDU setting unless deemed necessary by the investigator due to the severity of their illness.

Screening evaluations and assessments will be completed for both ELAD and Control subjects and reviewed against inclusion/exclusion criteria prior to Randomization. For both study groups, ELAD-treated and Control, the time of Randomization will define the time of study entry (Hour 0, Study Day 1, study baseline) and inclusion in the ITT population. Laboratory draws for the first post-randomization blood tests required by the protocol will begin with the next standard laboratory draw (typically the following morning).

In addition to the Screening evaluations, because there will be a delay between Randomization and initiation of ELAD treatment, a further assessment to confirm the subject's safety eligibility will be undertaken. This assessment will be conducted in the same manner for both ELAD and Control subjects. Either the principal investigator or sub-investigator trained on the study must have evaluated the safety eligibility results and be immediately available when ELAD treatment begins in order to assess changes in the subject's condition since Randomization. This is especially important when evaluating changes during the 24 hours preceding initiation of ELAD treatment in order to determine whether the subject remains eligible for extracorporeal treatment.

For all subjects randomized, the following key safety factors must be evaluated within 6 hours prior to ELAD treatment initiation, or at End of Study Day 2 (\pm 6 hours) for Control subjects. These include:

- Platelet count;
- International normalized ratio (INR);
- Serum creatinine;
- Evidence of infection unresponsive to antibiotics;
- Hemodynamic instability assessment (blood pressure and MAP);
- Bleeding status;
- Status with respect to ventilation, intubation, or need for hemodialysis.

These factors will be assessed in accord with the pertinent exclusion criteria (2, 3, 4, 7, 9, 10, 15, and 16, relative to the safety evaluation time point) in the VTL-308 Study Protocol (Amendment

1, dated 20 November 2015). Subjects must be assessed within 6 hours prior to ELAD treatment initiation, or at End of Study Day 2 (± 6 hours) for Control subjects, and subjects must continue to be eligible based on these exclusion criteria, at this time point, to remain in the modified intent-to-treat (mITT) population.

In addition, vital signs will be taken, total bilirubin measured and a MELD score will be calculated at this time point.

The standard of care labs may fulfill this requirement provided they are drawn within 6 hours prior to ELAD treatment initiation.

- If an ELAD subject fails to meet these criteria, ELAD treatment will not be initiated, the subject will continue to receive standard of care, and the subject will be excluded from the mITT population;
- If a Control subject fails to meet these criteria, the subject will continue to receive standard of care, and the subject will be excluded from the mITT population.

Subjects randomized to the ELAD group will be treated with ELAD for a minimum of 3 days (72 hours).

ELAD treatment may be interrupted for a period of *less* than 6 hours then restarted with the same set of cartridges provided that, in the opinion of the investigator, the subject remains eligible for treatment. ELAD treatment may be interrupted for a period of *more* than 6 hours but *less* than 72 hours, for example, to allow for the conduct of a diagnostic or therapeutic procedure or for management of an adverse event, or should there be a need to interrupt the use of anticoagulants. Should this circumstance arise, a new set of ELAD cartridges must be used if treatment of the subject will continue, and the subject must meet the same safety eligibility criteria as are required prior to the initiation of treatment.

ELAD treatment will be discontinued and will not be restarted if any of the following discontinuation criteria are met. If ELAD treatment is discontinued, subjects will receive standard of care therapy alone and be followed through Study Day 91. Discontinuation criteria include the following:

- Continued ELAD treatment is judged to be futile, defined as an increase of more than 25% in total bilirubin at 72 (+6) hours (includes clinical consideration of impact of artifactual hyperbilirubinemia) compared to the most temporal measurement of total bilirubin taken within 6 hours prior to ELAD initiation. Bilirubin measurements must be taken at least 12 hours after any procedure known to artificially alter serum bilirubin (e.g., administration of packed red blood cells, plasma exchange);
- Subject has been off treatment for more than 72 hours;
- Subject has suffered an adverse event that, in the investigator's opinion, requires ELAD treatment to be discontinued, and which cannot be resolved within a period of 72 hours;
- Subject has suffered a disseminated intravascular coagulopathy (DIC) event;
- Subject develops an indication for hemodialysis;

- Subject requires an extracorporeal procedure that takes precedence over ELAD treatment;
- Subject has been treated for a maximum of 120 hours within five (5) 24-hour periods regardless of treatment interruption;
- Subject undergoes orthotopic liver transplantation;
- Subject is discharged from the hospital;
- The first set of ELAD cartridges has been replaced for any reason and the second set also requires replacement, or the subject fails safety eligibility checks for the second set;
- Subject or legally authorized representative withdraws consent for further ELAD treatment;
- Investigator decides to stop ELAD treatment;
- ELAD System performance issues arise that cannot be resolved within a period of 72 hours;
- Subject experiences catheter-related issues that cannot be resolved within a period of 72 hours.

Subjects in both groups will be evaluated throughout the 91-day study period.

Subjects undergoing orthotopic liver transplantation during ELAD treatment will be evaluated exactly the same as any other subject who completed treatment early. The evaluation mandated for the first day after treatment will be carried out 24 hours post-transplantation. All subjects (ELAD and Control) receiving a liver transplant will be followed through Study Day 91 and also in Study VTL-308E in an identical manner to subjects who did not receive a liver transplant.

If standard of care treatment as defined by the institution is consistent with discharging the subject home, then the subject should be discharged. Prior to discharge, the subject will be advised to attend all protocol-required visits. Instructions for home visits will also be reviewed.

An extension of this study, VTL-308E, will provide extended follow-up of subjects enrolled in VTL-308 over a period of 5 years to determine survival, incidence of cancer, liver transplant, and quality of life. Data obtained from the extension study will provide additional survival data up to a maximum of 5 years that will be included, as available, through VTL-308 study termination (after the last surviving enrolled subject completes Study Day 91).

3 STATISTICAL ANALYSIS POPULATIONS

3.1 INTENT-TO-TREAT (ITT)

The ITT population is defined as all subjects who are randomized; analyses of this population will be based on assigned randomized treatment. This population will include all randomized subjects assigned to the group to which they were randomized irrespective of actual treatment administered. The ITT population will be the primary analysis population.

3.2 MODIFIED INTENT-TO-TREAT (MITT)

The mITT population is defined as all subjects who are randomized to the ELAD treatment group that subsequently became eligible for treatment initiation and received ELAD treatment, and all subjects who are randomized to the Control group that also remained eligible for treatment in accord with end-of-study-day (EOSD) 2 evaluations. If a subject in the Control group does not have a EOSD 2 evaluation, they will remain in the mITT population. Treatment assignment will be based on the treatment group to which the subject was randomized.

3.3 PER-PROTOCOL (PP)

The PP population will include all randomized subjects based on assigned treatment group (ELAD or Control) excluding subjects:

- That received <72 hours of treatment (ELAD or Control), as defined by the period from initiation of treatment to treatment stopping, irrespective of periods of treatment interruption <6 hrs. Note: initiation of treatment for ELAD subjects is defined by the time at which the ultrafiltrate pump is first switched on. Control subjects who died or withdrew consent within 72 hours from Randomization will be excluded from the PP population. Control subjects who were discharged within 72 hours from Randomization according to hospital standard of care will be included in the PP population;
- That failed to meet all of the inclusion criteria or had at least one of the exclusion criteria;
- That incorrectly received a treatment regimen that differs from the treatment specified by the randomization schema;
- In whom
 - treatment was initiated with ELAD C3A cell cartridges that started recirculation (centrifugal pump start at 2LPM) in the ELAD System more than 60 hours after being removed from the bioreactor;
 - treatment was carried out with more than two different sets of cell cartridges;
- That were ineligible for ELAD treatment initiation but treated anyway;
- In whom ELAD treatment was continued for more than 3 days despite an increase in bilirubin exceeding 25%;
- That were off treatment (ultrafiltrate pump switched off) for longer than 6 hours in one interruption with the same set of cell cartridges;

- In whom treatment with the first set of cell cartridges had been stopped and a period of 72 hours or more had passed before treatment with a second set of cell cartridges could be initiated.

It should be noted that those subjects deemed an “ELAD-treatment initiation failure” that received no ELAD treatment but received standard of care for at least 72 hours from Randomization will be included in this population. Control subjects who failed EOSD 2 evaluation but received standard of care for at least 72 hours from Randomization will also be included in the this population. In both cases this is because the protocol mandated treatment is being administered in accord with the protocol.

3.4 SAFETY

The safety population is defined as all subjects who are randomized based on actual treatment received.

As a practical matter this means that a subject deemed an “ELAD-treatment initiation failure” that received no ELAD treatment will be assigned to the Control group. A subject that was randomized to the Control group yet received ELAD treatment will be assigned to the ELAD group.

4 STUDY POPULATION PARAMETERS

4.1 DISPOSITION

VTI-308 End of Study Disposition and VTL-308E Disposition at time of cut-off of all subjects will be presented in a table by treatment group for ITT population. These presentations will include the number of subjects who completed their Study Day 91 visit and the number who discontinued, as well as the reason for study discontinuation. The disposition for subjects who entered VTL-308E when the database locks will also be provided. Survival status at time of Day 91, Day 180, Day 365 and time of cut-off will be summarized using ITT populations. Additionally, subjects who received a liver transplant and/or were diagnosed with cancer will be summarized using the ITT population.

4.2 PROTOCOL DEVIATIONS

Protocol deviations will be divided into two distinct groups.

- Major deviations will include:
 - Subjects who were randomized but had failed to meet all of the inclusion criteria or have at least one of the exclusion criterion;
 - Subjects who incorrectly received a treatment regimen that differs from the treatment specified by the randomization schema;
 - Subjects in whom
 - treatment was initiated with ELAD C3A cell cartridges that started recirculation (centrifugal pump start at 2LPM) in the ELAD System more than 60 hours after being removed from the bioreactor;
 - treatment was carried out with more than two different sets of cell cartridges.
- All deviations not categorized as major will be deemed minor.

All protocol deviations will be reviewed by the medical monitor, and/or a member of the clinical operations team to verify that the major and minor protocol deviation classifications are correct.

4.3 STANDARD OF CARE COMPLIANCE

Compliance to the Standards of Care (SOC) will be assessed for each subject after Randomization up to Study Day 91.

A method will be developed and employed to assess compliance with all categories of SOC. The specific questions that will be asked in order to determine compliance with each SOC are provided in [Appendix A](#). These data will be used to determine whether there is a difference in SOC between treatment groups and to conduct further analyses on SOC compliance.

Subject compliance with SOC will be established by first determining whether or not the subject should have received the SOC (i.e. had the condition requiring the SOC to be administered). If a subject has the condition and is appropriately administered SOC, the subject will be considered to be compliant. If a subject does not have the condition and is not administered the SOC, the subject will also be considered to be compliant. If a subject has the condition and is not administered SOC, the subject will be considered non-compliant with that SOC. The proportion of subjects who were compliant will be assessed by dividing the number of subjects considered

compliant with each SOC (whether or not they have the condition requiring that SOC) by the total number of subjects in each SOC for each treatment group.

4.4 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Baseline comparability of the treatment groups will be assessed with respect to demographic variables, screening vital signs, and medical history. Summary statistics (N, mean, standard deviation (SD), median, minimum, maximum and proportions, as appropriate) will be presented by treatment group for the ITT population. If more than one screening value is recorded, the last record before the randomization date will be used for analysis.

4.4.1 Demographics

Demographic variables to be summarized for the ITT population include:

- Age;
- Sex;
- Ethnicity;
- Race;
- Height;
- Weight.

4.4.2 Severe Alcoholic Hepatitis

Baseline sAH characteristics to be summarized for the ITT population include:

- Steroids >6 weeks prior to baseline (Yes/No); response to steroid treatment (Yes/No/Unknown);
- Steroids during the 6 weeks prior to baseline (Yes/No); response to steroid treatment (Yes/No); and method used to assess response;
- Selected medical treatments at baseline (steroids, pentoxifylline, N-acetyl-cysteine);
- MELD score with corresponding components (creatinine, total bilirubin, and INR);
- Maddrey score with corresponding components (prothrombin time [PT], laboratory control PT, and total bilirubin);
- Subjects that had dialysis at least twice in the past week
- Time from last alcohol consumption to hospital admission (weeks); and
- Time from hospital admission to Randomization (days).

4.4.3 Liver Disease Characteristics

Baseline liver disease characteristics to be summarized for the ITT population include:

- Presence of ascites;
- Liver size;
- Liver volume;
- White blood cell count;

- Child-Pugh Score.

4.4.3.1 Child-Pugh Score

The Child-Pugh score is based on total bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy; each of these variables is scored from 1 to 3, with 3 indicating the most severe derangement. Details for how to calculate the Child-Pugh score are displayed in Table 1.

Table 1. Child-Pugh Score

| Measure | 1 point | 2 points | 3 points |
|---|---------------------------|--|---------------------------|
| Total bilirubin, mg/dL | <2 mg/dL | 2 to 3 mg/dL | >3 mg/dL |
| Serum albumin ^[1] , g/dL | >3.5 g/dL | 2.8 to 3.5 g/dL | <2.8 g/dL |
| Prothrombin time, prolongation ^[2] , seconds or INR | < 4.0 seconds or < 1.7 | 4.0 to 6.0 seconds or 1.7 – 2.3 (inclusive) | > 6.0 seconds or > 2.3 |
| Ascites ^[3] | none | mild | moderate to severe |
| Hepatic encephalopathy | none | Grade I to II | Grade III to IV |

^[1] If subjects are missing albumin values before Randomization, then use the first available value after Randomization.

^[2] Prothrombin time (PT) prolongation = PT – Control PT. If subjects are missing PT values before Randomization, INR values will be used.

^[3] If ascites is recorded as having more than one severity per subject, choose the more severe category. Only include medical records that are ongoing at Randomization.

The data reported for each of these five variables are collected at baseline and will be the data that will be used to calculate each subject’s baseline Child-Pugh Score. Subjects with a total score of 5 to 6 points will be assigned to Child-Pugh Class A, subjects with a total score of 7 to 9 will be assigned to Child-Pugh Class B, and subjects with a total score of 10 to 15 will be assigned to Child-Pugh Class C. The number of subjects with Child-Pugh Class A, B, and C cirrhosis will be summarized for each treatment group. Difference between treatments will be analyzed using a Chi-squared test.

4.4.4 Clinical Profile

Baseline clinical profile characteristics to be summarized for the ITT population include:

- Kidney (creatinine);
- Cerebral (HE grade);
- Coagulation (INR);
- Circulation (MAP);
- Lungs (pulse oximetry and FiO₂);
- CLIF-SOFA score;
- Systemic Inflammatory Response Syndrome (SIRS).

4.4.4.1 *CLIF-SOFA Score*

The sequential organ failure assessment (SOFA) was modified to take into account specific features of cirrhosis and is called the CLIF-SOFA score (Moreau et al. 2013). The CLIF-SOFA Score consists of subscores ranging from 0 to 4 for each of six components (liver, kidneys, brain, coagulation, circulation and lungs) with higher scores indicating more severe organ impairment (Table 2). If subjects were administered any medications relating to dopamine, dobutamine, terlipressin, epinephrine or norepinephrine at the time of the calculation of the CLIF-SOFA score, then the reason for the administration of the medication will be reviewed by the Medical Monitor in order to establish whether the administration of the medication is pertinent to the determination of the subject’s CLIF-SOFA score for circulation.

The CLIF-SOFA score will be summarized for each treatment group.

Table 2. CLIF-SOFA Score

| Organ System | 0 | 1 | 2 | 3 | 4 |
|--|-------|---------------|---|--|--|
| Liver (bilirubin, mg/dL) | <1.2 | ≥1.2 to <2.0 | ≥2.0 to <6.0 | ≥6.0 to <12.0 | ≥12.0 |
| Kidney (creatinine, mg /dL) | <1.2 | ≥1.2 to <2.0 | ≥2.0 to <3.5 | ≥3.5 to <5.0 | ≥5.0 |
| Cerebral (HE grade) | No HE | I | II | III | IV |
| Coagulation (INR) | <1.1 | ≥1.1 to <1.25 | ≥1.25 to <1.5 | ≥1.5 to <2.5 | ≥2.5 |
| Circulation (MAP, mm Hg) | ≥70 | <70 | Dopamine ≤5* or dobutamine or terlipressin | Dopamine >5 or E≤0.1 or NE ≤0.1* | Dopamine >15 or E>0.1 or NE>0.1* |
| Lungs SpO ₂ /FiO ₂ ¹ | >512 | >357 to ≤512 | >214 to ≤357 | >89 to ≤214 | ≤89 |

Abbreviations: E, epinephrine; FiO₂, fraction of inspired oxygen; HE, hepatic encephalopathy; NE, norepinephrine; and SpO₂, pulse oximetric saturation.

Note: Aggregated scores range from 0 to 24 and provide information on overall severity. Text in bold indicates the diagnostic criteria for organ failures.

*Adrenergic agents administered for at least 1 h (doses are given in µg/kg/min).

¹ If baseline FiO₂ scores are missing, the value 0.21 will be used.

4.4.4.2 *Systemic Inflammatory Response*

Systemic inflammatory response syndrome (SIRS) is defined as two or more of the following variables being present concurrently:

- Fever of more than 38°C (100.4°F) or less than 36°C (96.8°F);
- Heart rate of more than 90 beats per minute;
- Respiratory rate of more than 20 breaths per minute;
- Abnormal white blood cell count (>12,000/µL or <4,000/µL).

The numbers of subjects with SIRS at baseline will be summarized for each treatment group.

4.4.5 Past Medical History

Liver medical history and general medical history will be captured and the terms will be coded using MedDRA, version 18.1. Medical history will be summarized by system organ class and preferred term by treatment group in the ITT population. Subjects with more than one medical history term in the same system organ class or preferred term will only be counted once.

5 DATABASES

Data will be collected in the Electronic Data Capture (EDC) system and other databases for the statistical analyses presented in this plan. The following table lists these databases and provides a description of the type of data being captured in each:

| Data Source | Primary Utility |
|-------------------------------|--|
| VTL-308 clinical database | Primary database for establishment of outcomes. Primary source of screening information, baseline characteristics, laboratory values, concomitant medications, adverse events (AEs), PEth lab results, ELAD Specialist data, and Home Health Care visit data. |
| VTL-308E interim data | Extension data documenting survival (at 6, 9, 12, and 24 months), transplant, incidence of cancer, and quality of life. Survival data earlier than 6 months may also be available for subjects who do not complete their Day 91 visit. Note: a snapshot of the VTL-308E database will be conducted at the time of the VTL-308 database lock to provide the updated information for the analysis of the primary endpoint of overall survival. |
| ELAD System performance files | Information recorded automatically by the ELAD System (Sorin S3/S5) documenting multiple system performance parameters during subject treatment. These data are stored in CSV format (one file per subject/cartridge set). |
| Manufacturing data | Files documenting ELAD cartridge performance and product release parameters such as albumin, transferrin, glucose consumption, and oxygen utilization, along with date of manufacture, and date of shipping. |

6 GENERAL ANALYSIS CONSIDERATIONS

If significant OS differences are identified between populations, then subgroup analyses of OS will be summarized for additional populations.

6.1 EFFICACY

- Log-rank analysis of the effect of ELAD on OS will be used;
- Chi-squared test of the effect of ELAD on proportions of survivors will be used at Study Days 28 and 91.

6.2 SAFETY

- A t-test or ANOVA test will be used for selected continuous variables;
- Fisher's exact test or Chi-squared test will be used for categorical variables.

7 EFFICACY ANALYSIS

Unless otherwise specified, all analyses will be of randomized subjects by treatment group.

No data imputation will be used, except for the ECBL and Lille analyses. For the primary log-rank analyses of the effect of ELAD on OS, the subject's last available study evaluation through Day 91 after the calendar date at which the last subject was randomized will be used. This OS follow-up will draw from data generated by VTL-308 and VTL-308E follow-up data. Every effort will be made to capture the survival status of each randomized subject through Day 91 after the calendar date at which the last subject was randomized.

For the log-rank analysis of the effect of ELAD on OS, the null hypothesis will be that the true survival curves do not differ and will be tested at the two-sided 0.05 level of significance. The primary efficacy analysis will be carried out on the ITT population, and sensitivity analyses will be performed using the mITT, PP and Safety populations. Kaplan-Meier estimates of survival will be generated for both treatment groups, and estimates will be obtained for median survival, 25th and 75th quartiles. A Cox regression analysis will be performed to obtain an estimate of the hazard ratio and corresponding confidence limits. Exploratory analyses of treatment effect within subgroups will be performed.

7.1 PRIMARY EFFICACY ANALYSIS

7.1.1 Overall Survival (OS) of Subjects with sAH through at least Study Day 91

OS will be assessed using a log-rank analysis of survival data in the intent-to-treat (ITT) population. Protocol VTL-308E will provide additional survival data up to a maximum of 5 years. Kaplan-Meier estimates of survival will be provided, along with estimates of median survival, 25th and 75th quartiles, by treatment group, while a Cox regression analysis will be used to provide estimates of the hazard ratio and its confidence limits. These analyses will also be carried out on the mITT, Per-Protocol (PP) and Safety populations as sensitivity analyses.

In addition, a similar sensitivity analysis for 91-day overall survival will be carried out using overall survival data through Day 91. Subjects who survived at Day 91 are censored at Day 91. Subjects who were lost to follow-up prior to Day 91 are censored at their last contact Study Day.

Although every effort will be made to determine each subject's survival status through the calendar date for the primary analysis of OS, it is possible that some subjects will be lost to follow-up. In the primary OS analysis, such observations will be censored as of the last date when the subject's survival status was known.

7.1.2 Subgroup Analyses of OS

Descriptive summaries will be provided to give evidence regarding estimates of treatment effect across subgroups defined by standard demographics, selected baseline characteristics, medical history, regional and geographical site-related factors and baseline standard of care (SOC). These descriptive summaries will provide evidence regarding the generalizability of the primary analyses of treatment effect. The ITT population will be used in these descriptive summaries, which are listed below.

- Demographics and baseline characteristics:
 - Age (<Median and ≥Median);

- Gender;
- Baseline MELD score (<Median and ≥Median);
- Hepatic encephalopathy grade (0 vs 1 or 2 vs 3 or 4);
- Baseline total bilirubin level (<Median and ≥Median);
- Baseline creatinine (<Median and ≥Median);
- Baseline INR;
- Region (US vs. Non-US).
- Medical history characteristics:
 - Time from hospital admission for this episode of sAH to Randomization (<Median and ≥Median).
- Other Baseline measures:
 - Site size:
 - This will be evaluated based on defining high-enrolling sites as those that enroll 4 or more subjects, and low-enrolling sites as those that enroll fewer than 4 subjects, and presenting summary statistics for OS within each of these subgroups;
 - The same analysis will be done with 8 or more subjects as a cut-off.
 - All sites with only one subject enrolled will be combined together and compared to all sites;
 - Any site with more than 10% of the total number of subjects will be analyzed separately and compared to all sites.
 - Enrollment order within a site. This will be evaluated based on defining early-enrolled subjects as those subjects who were the first or second subject enrolled within a site compared to later-enrolled subjects who will be defined as those subjects who were at least the third or later subject enrolled within a site; summary statistics for OS within each of these subgroups will be presented.

The above factors were identified as potential effect modifiers for the effect of ELAD, based on scientific considerations including the outcomes of the VTI-208 Study, the STOPAH study (Thursz et al. 2015) and the findings of the EASL-CLIF consortium (Arroyo et al. 2015, Moreau et al. 2013).

7.1.3 Cox Regression Analyses of OS

In exploratory analyses, the estimated effect of treatment on OS will be adjusted for baseline factors that are strongly prognostic for OS and that could be imbalanced across treatment groups in spite of randomization. In the first step of these exploratory analyses, each covariate will be assessed in a univariate analysis to assess its prognostic influence. In the second step, the 5 most prognostic covariates will be entered into a Cox multivariate regression model along with treatment to obtain an estimated effect of treatment on OS, adjusted for these covariates.

The following factors will be included in these analyses:

- Age (continuous; dichotomized based on median);
- Baseline MELD score (continuous; dichotomized based on median);
- Baseline total bilirubin level (continuous; dichotomized based on median);
- Baseline PT ratio (continuous);
- Baseline white blood cells (continuous);
- Baseline blood urea nitrogen (BUN) (continuous);
- Baseline creatinine (continuous);
- Hepatic encephalopathy (0, 1/2, 3/4);
- Steroids use (Yes/No);
- Baseline weight (continuous; dichotomized based on median);
- Baseline height (continuous; dichotomized based on median);
- Region (USA vs. Europe).

Other baseline factors may also be identified and included in exploratory analyses related to OS.

Study site characteristics will also be examined to see if region, site size, or enrollment order have an effect on OS between treatment groups. Hazard ratios will be displayed as well as p-values from univariate cox regression models including the study site characteristic, treatment group, and site characteristic by treatment group interaction.

7.1.4 Assessment of Potential Bias due to Treatment Group Assignment

VTL-308 is an open-label study. While every effort has been made in the study protocol to minimize the effects of post-treatment differences in investigator evaluation, medical care and subject behavior, there is a potential that differences in these factors may be associated with treatment group assignment, and that these differences might influence outcomes. An evaluation of the proportion of survivors at Study Days 28 and 91 will be carried out to determine whether these differences had any impact on study outcome. Parameters assessed will include, but not be limited to, the following:

- Alcohol use post-discharge. This will be evaluated based on either a PEth result of >20 ng/mL (evidence of moderate or heavy alcohol consumption) or any self-report of alcohol use post-discharge (note: a positive PEth result will supersede a self-report of no alcohol use);
- Length of Initial ICU Stay (<Median and ≥Median), defined as the first ICU discharge date minus ICU admission date plus 1, if the admission date is after randomization. If the admission date is before randomization, then the length of stay will be the discharge date minus randomization date plus 1. If the discharge date is missing and the subject died, the death date will be used;
- Length of Initial Hospital Stay (<Median and ≥Median), defined as the hospital discharge date minus randomization date plus 1. If discharge date is missing and the subject died, the death date will be used;
- Steroids Use Post-randomization (Yes/No);
- Steroids Use Post-randomization for <7 days (Yes/No);

- Steroids Use Post-randomization for ≥ 7 to < 14 days (Yes/No);
- Steroids Use Post-randomization for ≥ 14 to < 28 days (Yes/No);
- Steroids Use Post-randomization for at least 28 days (Yes/No);
- Concomitant heparin use within the first 10 days of the study (Yes/No);
- For the ELAD group only, ELAD treatment duration dichotomized based on < 72 hours vs. ≥ 72 hours. This analysis will be based on total ELAD treatment duration inclusive of any time off treatment (i.e., final stop date/time of treatment, defined as the time at which the ultrafiltrate pump is switched off for the last time – initial start date/time of treatment, defined as the time at which the ultrafiltrate pump is switched on for the first time). Additional analyses of ELAD treatment duration are described in [Section 8.2](#) and [8.10.1](#).

Post-randomization is defined as the steroid starting within one day after Randomization. If start dates are partial/missing for steroid use, the following imputation will be followed:

- If the entire set of steroid dates are partial, and only the year and month are reported, and they are the same year and month as the Randomization date, then the day will be imputed to be the same as the randomization day. If the first steroid date is a complete start date, and the following steroid records have partial dates that are in the same month and year, then all subsequent partial dates will be imputed to be the same as the first steroid date. Otherwise, the day will be imputed to the first day of the month;
- If the entire set of steroid dates are partial, and only the year is reported, and it is the same year as the randomization date, then the day and month will be imputed to be the same as the randomization day and month. If the first steroid date is a complete start date, and the following steroid records have partial dates in the same year, then all subsequent partial dates will be imputed to be the same as the first steroid date. Otherwise, the day and month will be imputed to January 1st;
- If the entire set of steroid dates are completely missing, then the start dates will be imputed to be the same as the randomization date.

The same logic will be applied for steroid end dates, using discontinuation dates instead of randomization dates. If the steroid is ongoing, the last visit date for the subject will be used.

7.2 SECONDARY EFFICACY ANALYSIS

7.2.1 Proportion of Survivors at Study Days 28 and 91

The effect of ELAD on the proportion of subjects who survived at End of Study Days 28 and 91 will be estimated with 95% confidence intervals for the ITT, mITT, PP and Safety population. Analyses will be presented using the last date known alive, leaving subjects who are not known to be dead, in both the numerator and the denominator. Additional analysis will be done for subjects whose Study Day 28 and/or 91 survival status is unknown at the time of database lock. These subjects will not be included in either the numerator or the denominator of the calculation.

7.2.2 Early Change in Bilirubin Level (ECBL) at Study Day 7

There is a strong correlation between ECBL and response to therapy, as demonstrated by the prior studies evaluating the effects of corticosteroids in AH (Mathurin et al. 2003). Post-hoc analysis of the VTI-208 Safety population suggested that there were more ECBL20 Yes subjects in the ELAD-treated group, and the survival of ECBL20 Yes subjects was significantly higher than the survival in ECBL20 No subjects.

A secondary endpoint for the VTL-308 study will be the proportion of subjects who achieve ECBL20 at Study Day 7 in the ITT population. The 20% or greater threshold for the reduction in ECBL, and the 7-day time point, were chosen as this is consistent with prior literature (Lee et al. 2014, Li et al. 2016, López-Velázquez et al. 2014, Louvet et al. 2007, Mathurin et al. 2003, Morris and Forrest 2005) and in the findings from the VTI-208 study. Differences between treatment groups will be analyzed using a Chi-squared test. The same analysis will also be carried out on the safety population as an exploratory sensitivity analysis.

Definition of Early Change in (total) Bilirubin (tBili) Level (ECBL)

Subjects who died within 7 days (including Day 7) will be excluded from the analysis. ECBL (End point minus start point) will be expressed as a percentage of start point.

- For the start point value, “Within 6 hours prior to ELAD start” tBili value and “Day 2” tBili value will be used for ELAD-treated subjects and Control subjects, respectively;
- For the end point value, “Day 7” tBili value (if the subject was not on treatment when the lab test took place and the value was collected greater than 6 hours after treatment ended) will be used for ELAD-treated subjects. If the value was collected within 6 hours of treatment ending, use “24 hours Post-ELAD Stop” tBili value. “Day 7” tBili value will be used for Control subjects.

Missing Data for Calculations of ECBL

- For the start point value, if End of Study Day Results were used, then start point should be the corresponding Study Day value. Otherwise, if the value is truly missing, Last Observation Carried Forward (LOCF) will be used for both ELAD-treated and Control subjects;
- For the end point value, if End of Study Day Results were used, then end point should be the corresponding Study Day value. Otherwise, if the value is truly missing, “24 hours Post-ELAD Stop” tBili value will be used, and if “24 hours Post-ELAD Stop” tBili value is not available, LOCF will be used.

There are three sets of tBili measurements collected on the CRF (MELD tBili – used to calculate MELD scores at various times during the study; lab tBili – measurements taken as part of laboratory analyses collected at various times during the study; and MADD tBili – used to calculate Maddrey scores at various times during the study). MELD tBili should be prioritized over lab tBili and MADD tBili. If MELD tBili is missing then use lab tBili then MADD tBili.

7.3 EXPLORATORY EFFICACY ANALYSIS

Exploratory efficacy analyses may include, but not be limited to, analyses of efficacy outcomes based on any subgroups, such as those defined by medical history, and baseline demographics and other baseline characteristics, along with region (USA vs. Europe).

Additional exploratory analyses that may lead to a better understanding of what other factors may or may not influence efficacy outcomes will be conducted. These analyses will be performed on the ITT population and are summarized below. Pending the results of these analyses, further analyses may be conducted.

7.3.1 Transplant-Free Survival

Typically, orthotopic liver transplantation would not take place in patients diagnosed with sAH until the patient has demonstrated at least 6 months of abstinence. However, recent data ([Burra et al. 2010](#)) has suggested that outcomes from liver transplant in sAH patients are at least as good, and in some analyses better, than outcomes for subjects with viral hepatitis or other conditions associated with liver transplantation. In order to accommodate any potential imbalance between transplant rates in the ELAD-treated and Control subjects in the VTL-308 study, transplant-free survival (TFS) will be assessed as an exploratory efficacy analysis.

TFS will be assessed using a log-rank analysis of survival as with the primary efficacy endpoint, using the ITT population. However, unlike the primary efficacy analysis, subjects receiving a transplant will be treated as follows:

- Censored in the analysis at the time of transplant and be dealt with as though they had dropped out of the study following transplant;
- Included in the analysis as an event at the date/time of the transplant (i.e., transplant-free survival).

In addition an analysis will be carried out of the proportion of transplant-free survivors at Study Day 91 using the ITT population. For this analysis, subjects receiving a transplant will either:

- Not be included in either the denominator or the numerator of the calculation of the proportion of survivors (i.e. they will be dealt with as though they had dropped out of the study prior to Study Day 91);
- Counted in the analysis as an event.

7.3.2 Proportion of Survivors at Study Day 28 and 91

The proportion of survivors at Study Day 28 and at Study Day 91 for ELAD-treated subjects will be provided for the following subgroups:

- ELAD treatment duration based on PERF data, defined as total hours during which the ultrafiltrate pump is on (<72 hours vs. ≥72 hours);
- Total amount of ultrafiltrate delivered (dichotomized based on median value);
- Total amount of oxygen utilization by the cell cartridges (dichotomized based on median value);

- Total number of ELAD components exchanged and total number of exchanges for specific components (e.g. UFGs, bubble traps, etc.) (dichotomized based on median value);
- Total blood loss estimated for each subject based on component exchange (dichotomized based on median value).

7.3.3 Outcome Relative to Selected Screening Factors

In addition, exploratory analyses of outcome relative to selected screening factors will be conducted. The overall survival rates at Study Day 28 and Study Day 91 for the ELAD treatment group and the Control group will be provided for the following subgroups:

- Steroid / pentoxifylline / NAC use at Randomization (Yes/No);
- Steroid / pentoxifylline / NAC use during treatment period (Yes/No);
- Steroid / pentoxifylline / NAC use after treatment (Yes/No).

For the ELAD subjects, treatment period is defined as the period from initiation of ELAD treatment to ELAD treatment stopping. For the Control subjects, treatment period is defined as the period from Study Day 2 to Day 7.

7.3.4 Early Change Bilirubin at Different Levels at Study Day 7

In order to further explore the change in bilirubin as a potential surrogate endpoint for studies of new therapeutic approaches to the treatment of sAH, together with findings from VTI-208 that significant differences were observed for all ECBL values between ECBL 10% and ECBL 40% in the Safety population in the VTI-208 study (VTL data on file), additional exploratory analyses will be carried out. The proportion of subjects will be presented by treatment group and by the following bilirubin categories for the Safety and ITT Populations. Differences between treatment groups at each cutoff will be evaluated using a Chi-squared test.

- 0% reduction from baseline in bilirubin (ECBL0);
- 10% reduction from baseline in bilirubin; (ECBL10);
- 15% reduction from baseline in bilirubin; (ECBL15);
- 25% reduction from baseline in bilirubin. (ECBL25);
- 30% reduction from baseline in bilirubin. (ECBL30);
- ECBL as a continuous variable (use median as cutoff).

Furthermore, exploratory analyses will be carried out and the proportion of survivors at Study Days 28 and 91 will be presented by achieving bilirubin reduction (Yes vs No for ECBL0, ECBL10, ECBL15, ECBL20, ECBL25, ECBL30) for overall, ELAD treatment group and Control group using the ITT Population.

7.3.5 Lille Score

The Lille score ([Louvet et al. 2007](#)) is a composite score developed in order to help in the decision making about continued steroid administration to patients with sAH – i.e., a Maddrey Discriminant Function score of ≥ 32 . The score is measured over a 7-day period of therapy and

has been shown to have good prognostic value in predicting 90-day and 6-month survival. There are also data in the literature for measuring Lille after a 4-day period ([Garcia-Saenz-de-Sicilia et al. 2017](#)). Where the components for calculating the Lille score are available, the Lille score will be derived at Study Days 3, 4 and 7 (± 24 hours) as an exploratory composite biomarker.

The proportion of subjects who have Lille score <0.45 vs ≥ 0.45 at Study Days 3, 4 and 7 will be presented by treatment group for the ITT and Safety Populations. Differences between treatment groups will be analyzed based on a Chi-squared test. Additionally, the proportion of survivors at Study Day 28 and at Study Day 91 will be presented by treatment group and by the Lille score (<0.45 vs ≥ 0.45) at Study Days 3, 4 and 7 for the ITT Population. Lille scores at Study Days 3, 4, and 7 will be presented in a listing for the ITT and Safety Populations.

In order to avoid the effect of ELAD treatment on factors used in the calculation of Day 0 bilirubin for the Lille score, and to best align the 3, 4 or 7-day treatment period between the groups, baseline values will be taken immediately prior to the initiation of ELAD treatment for the ELAD treatment group, while the last evaluation prior to Randomization will be used for the Control group. For the post-baseline bilirubin, the measurement collected 24 hours after the last ELAD treatment is ended or the measurement at Study Days 3, 4 or 7, whichever is later, will be used for the ELAD treatment group, and the measurement at Study Days 3, 4 or 7 will be used for the respective Control group.

For both ELAD and Control groups, see [Section 0](#) for missing bilirubin values at Day 0 and applicable evaluation day (Study Days 3, 4 or 7). Use LOCF for missing albumin, creatinine and INR/PT at Day 0. If a lab test was not done before Randomization or initiation of ELAD treatment for Control or ELAD treatment groups, respectively, the first lab value after Randomization or initiation of ELAD treatment will be used. Subjects who die on or before the applicable evaluation day (Study Days 3, 4 or 7) will be excluded from the analysis.

7.3.6 Selected Labs and MELD Scores Summarized by Visit

Changes in selected lab values and disease severity scores that have been demonstrated to correlate with survival will be presented for the ITT population. Differences between treatment groups at each time point will be analyzed based on a mixed model repeated measure (MMRM) with fixed effects of treatment group, visit and the treatment group by visit interaction, and a covariate of baseline value for the corresponding treatment. An unstructured covariance matrix will be used. If the model does not converge with an unstructured covariance matrix due to insufficient data at some visits, the spatial power covariance structure will be used. In addition, one sample t-test will be used to test if change from baseline value is zero at each time point within treatment group. All changes will be calculated relative to randomization date/time (as all subjects are on standard of care treatment as of the randomization date/time). Additional summaries of changes relative to ELAD start date/time will be provided for selected analyses. For comparative purpose, the Control group will be summarized by changes relative to End of Study Day 2, as this most closely mimics the time of initiation of ELAD treatment in those subjects randomized to ELAD. If Study Day 2 is missing for Control subjects, the last non-missing visit before Study Day 2 will be used for analysis.

As a sensitivity analysis, the analyses will be repeated after the missing data is imputed using the last observation carried forward (LOCF) approach. These will include:

- MELD;
- Total Bilirubin;
- Creatinine;
- INR;
- Sodium.

The values for MELD, Total Bilirubin, Creatinine, INR and Sodium will be displayed in a listing.

7.3.7 Outcome relative to Infection, Fluid Overload/Fluid Loss and Bleeding

Proportion of survivor tables at Study Day 28 and at Study Day 91 will be presented by treatment group and by infection. Ongoing infection at Randomization, infection which emerged as a TESAE between Randomization and Day 7, between Day 8 and Day 14 and between Day 15 and Day 28, will be summarized separately. Proportion of survivors at Study Day 91 will be summarized by treatment group by subjects who developed an infection TESAE between Day 29 and Day 91. Differences between treatment groups within each infection group will be analyzed based on a Chi-squared test. Additionally, differences between infection group, regardless of treatment, will be analyzed based on a Chi-square test.

Proportion of survivor tables at Study Day 28 and at Study Day 91 will be presented by treatment group and by occurrence of fluid overload or loss events. Fluid overload or loss events which emerged as a TESAE between Randomization and Day 7, between Day 8 and Day 14, and between Day 15 and Day 28, will be summarized separately. Proportion of survivors at Study Day 91 will be summarized by treatment group by subjects who developed a fluid overload or loss event TESAE between Day 29 and Day 91. Differences between treatment groups within each fluid overload or loss group will be analyzed based on a Chi-squared test. Additionally, differences between fluid overload or loss group, regardless of treatment, will be analyzed based on a Chi-square test.

Proportion of survivor tables at Study Day 28 and at Study Day 91 will be presented by treatment group and by occurrence of bleeding. Bleeding which emerged as a TESAE between Randomization and Day 7, between Day 8 and Day 14, and between Day 15 and Day 28, will be summarized separately. Proportion of survivors at Study Day 91 will be summarized by treatment group by subjects who developed a bleeding TESAE between Day 29 and Day 91. Differences between treatment groups within each bleeding group will be analyzed based on a Chi-squared test. Additionally, differences between bleeding group, regardless of treatment, will be analyzed based on a Chi-square test.

Subjects that die, are lost to follow up or withdraw from the study during one of these periods will not be included in the summaries covering subsequent periods for the above analyses.

8 SAFETY ANALYSIS

All safety analyses will use the Safety population, unless otherwise specified. All safety assessments will be summarized by treatment group. There may, in addition, be separate analyses of groupings of adverse events, laboratory values, or procedures of special interest.

Safety analyses will be summarized by treatment group (e.g., N, mean, median, SD and proportions, as appropriate). All analyses will be summarized by Study Day, as appropriate. Analyses will also be provided for the time periods during the treatment period and also for the time periods after the treatment ends. Factors related to post-treatment care and activities will be included in summaries of post-baseline distributions. All changes will be calculated relative to randomization date/time (as all subjects are on standard of care treatment as of the randomization date/time). Additional summaries of changes relative to ELAD start date/time will be provided for selected analyses. For comparative purpose, the Control group will be summarized by changes relative to End of Study Day 2, as this most closely mimics the time of initiation of ELAD treatment in those subjects randomized to ELAD. If Study Day 2 is missing for Control subjects, the last non-missing visit before Study Day 2 will be used for analysis.

Summaries of quantitative variables will include distributions by a clinically relevant discretization of each of the variables, along with computation of the mean, median, SD, minimum, and maximum. All data captured on the CRF will be presented in individual listings.

If a data point is collected more than once at the same visit, the last measurement will be used for analysis.

8.1 HANDLING MISSING DATA

Summaries will be based on observed data only, except for the following:

- Treatment-emergent derivation: If an AE start date is incomplete or completely missing, the following imputation rules apply to determine if an AE is treatment-emergent:
 - If only the year and month are reported, and they are the same year and month as the randomization date, then the day will be imputed to be the same as the randomization day, and the AE start time will be imputed to be the randomization time. Otherwise, the day will be imputed to the first day of the month;
 - If only the year is reported, and it is the same year as the randomization date, then the day and month will be imputed to be the same as the randomization day and month, and the AE start time will be imputed to be the randomization time. Otherwise, the day and month will be imputed to January 1st;
 - If the date is completely missing, then the start date/time will be imputed to be the same as the randomization date/time;
 - If only the AE start time is missing, and the AE start date is the same as the randomization start date, then the AE start time will be imputed to be the same as the randomization time. Otherwise, the AE start time will not be imputed.

For analyses of AE onset relative to ELAD treatment, the same imputation rules will be applied for analysis using ELAD start date/time instead of randomization start date/time.

8.2 EXTENT OF EXPOSURE

For subjects who receive ELAD treatment, the duration of ELAD treatment will be calculated based on the start date/time of ELAD treatment (defined as the time at which the ultrafiltrate pump is switched on for the first time) to the end date/time of ELAD treatment (defined as the time at which the Ultrafiltrate pump is switched off for the last time). A second analysis will exclude any off-time gaps >6 hours (e.g., for cartridge exchange). The duration of ELAD treatment will be summarized by descriptive statistics and by proportions of subjects receiving <72 hours, 72 to <96 hours, and ≥96 hours of treatment. The mean time from Randomization to ELAD treatment initiation will also be presented using descriptive statistics.

For subjects who receive SOC treatment, the treatment start date will be the same as the randomization date.

Additionally, the proportions of subjects who completed at least 72 hours and 120 hours on ELAD treatment will be presented, along with the reason for discontinuation of ELAD treatment.

8.3 ADVERSE EVENTS

The number and percent of subjects with treatment-emergent adverse events (TEAEs), TEAEs leading to ELAD discontinuation, TEAEs leading to ELAD treatment interruptions, TEAEs classified by their highest relationship to study drug, and TEAEs classified by their maximum severity, will be summarized by treatment group and by MedDRA System Organ Class and Preferred Term. Individual listings of all TESAEs, all deaths, and all TEAEs leading to ELAD discontinuation/interruption will be prepared.

Treatment-emergent adverse events are defined as those AEs with an onset date/time on or after the randomization date/time. The rationale for this is that subjects in both treatment groups are receiving standard of care at the time of Randomization. In addition summary tables of TEAEs and TESAEs will be presented based on treatment and post-treatment study periods. The study periods used in analysis for ELAD-treated subjects will be defined as Pre-ELAD (Randomization date/time to ELAD start date/time), ELAD Treatment (ELAD start date/time to Study Day 7), D8-D14 (Study Day 8 to Study Day 14) and D15-D91 (Study Day 15 to Study Day 91); and for Control subjects, Rand-D2 (Randomization date/time to Study Day 2), D3-D7 (Study Day 3 to Study Day 7), D8-D14 (Study Day 8 to Study Day 14) and D15-D91 (Study Day 15 to Study Day 91). Additional summaries of TEAEs that started between Randomization and ELAD treatment start, and TEAEs/TESAEs that started after ELAD treatment start will be presented by MedDRA System Organ Class and Preferred Term for subjects in the ELAD treatment group. For comparison purposes within these summary tables, TEAEs that started between Randomization and Study Day 2, and TEAEs/TESAEs that started after Study Day 2 will be presented for subjects in the Control treatment group.

Treatment-emergent adverse events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (Version 18.1) and incidences will be compared between treatment groups using MedDRA Preferred Terms within System Organ Classes. Subjects will only be counted once within each level of summarization.

8.3.1 Adverse Events of Special Interest

8.3.1.1 Infections

8.3.1.1.1 Infections prior to Randomization

Infections that occur prior to Randomization are listed in the Liver Medical History or the General Medical History, and will be identified by the terms listed in **Appendix B**. Each of these infections has an onset date and a stop date. If the stop date is prior to the date of Randomization, the infection will be considered resolved at Randomization, and if the stop date is after Randomization the infection will be considered ongoing at Randomization. In order for a subject to be eligible for the study all infections ongoing at time of Randomization had to be controlled.

A listing of infections occurring prior to Randomization will be generated. It will be split into two sections. The first will include all infections resolved by Randomization, i.e. those with a stop date prior to Randomization. The second will include all infections listed as ongoing at Randomization (i.e. those with a start date prior to randomization and a stop date after randomization).

The number of subjects with at least one ongoing infection at Randomization will be summarized by treatment group, and the number of subjects with one ongoing infection, two ongoing infections and three or more ongoing infections at Randomization will be summarized by treatment group and Preferred Term.

8.3.1.1.2 Infections post-randomization

A listing of all TESAEs of infection post-randomization by subject using the terms included in **Appendix B** will be generated. The TESAEs of infection will include the following parameters: treatment group, subject ID, AE ID, SOC/Investigator term/MEDRA Preferred Term, start date/time, and stop date/time; outcome; relationship to any of the ELAD components (VTL C3A cells, System, and Procedure); whether concomitant medications (Yes/No) were administered to treat the infection; whether steroids were administered (Yes/No) to treat the alcoholic hepatitis based on a start date between Post-randomization up to Study Day 28 (to assess risk for infection); and any action taken with ELAD (i.e., prompted discontinuation). This listing will be sorted into two sections; one section will list those subjects who have an ongoing infection at randomization and the other section will list those subjects who do not have an ongoing infection at randomization.

The total number of TESAEs of infection emerging post-randomization will be summarized by Preferred Term and treatment group.

The number of subjects with at least one TESA of infection post-randomization, the number of subjects that also had an ongoing infection at baseline or no ongoing infection at baseline, and the number of subjects with at least one TESA of infection that also had a positive blood culture that occurred during the same time period as the infection, will also be summarized in separate tables for the periods between Randomization and Study Day 7, between Study Day 8 and Study Day 14, between Study Day 15 and Study Day 28 and between Study Day 29 and Study Day 91.

8.3.1.2 *Fluid Overload/Fluid Loss*

All TESAEs of fluid overload and fluid loss that emerged following randomization up to Study Day 91 for each subject will be identified by the terms listed in [Appendix C](#).

The total number of TESAEs of fluid overload/fluid loss emerging post-randomization will be summarized by Preferred Term and treatment group.

The number of subjects with at least one TESAЕ of fluid overload/fluid loss post-randomization, will also be summarized in separate tables for the periods between Randomization and Study Day 7, between Study Day 8 and Study Day 14, between Study Day 15 and Study Day 28 and between Study Day 29 and Study Day 91.

8.3.1.3 *Bleeding*

All TEAEs and TESAEs of bleeding that emerged following randomization up to Study Day 91 for each subject will be identified by the terms listed in [Appendix D](#).

Two series of separate tables will be generated for the periods between Randomization and Study Day 7, between Study Day 8 and Study Day 14, between Study Day 15 and Study Day 28 and between Study Day 29 and Study Day 91. The first series will summarize the total number of TEAEs of bleeding emerging post-randomization by Preferred Term and treatment group, and the number of subjects with at least one bleeding TEAE, with more than one bleeding TEAE, along with the number of subjects administered heparin for ELAD treatment or for DVT prophylaxis. The second series will summarize the total number of TESAEs of bleeding emerging post-randomization by Preferred Term and treatment group, and the number of subjects with at least one bleeding TESAЕ, with more than one bleeding TESAЕ, along with the number of subjects administered heparin for ELAD treatment or for DVT prophylaxis.

In addition the number of subjects reporting at least one TEAE and also the number of subjects reporting at least one TESAЕ will be summarized by Preferred Term and treatment group.

8.4 CONCOMITANT MEDICATIONS AND BLOOD PRODUCTS

Concomitant medications and blood products are those administered at any time between Randomization and through Study Day 91. Concomitant medications and blood products will be summarized by treatment group. Additionally, the following medications and blood products will be summarized by treatment group and study period:

Medications of interest

- Steroids;
- Pentoxifylline;
- N-acetyl cysteine;

Additional medications of interest

- Antibiotics;
- Beta-blockers;
- Diuretics;
- Heparin;

- H₂ receptor antagonists;
- Proton pump inhibitors;
- Lactulose;
- Midodrine;
- Octreotide;
- Rifaximin;
- Vasopressors;

Blood products

- Albumin;

Selected medications will be evaluated based on proportions of subjects using each of the above classifications by treatment group and study period.

A summary of blood products administered during treatment and post-treatment periods will be presented by treatment group: descriptive statistics will be displayed by type of blood product, treatment group and the amount of blood product administered. In addition the number and proportion of subjects receiving certain accumulated amounts of blood products within defined treatment and post-treatment periods will be presented by treatment group.

Verbatim medication terms will be mapped to the Anatomical Therapeutic Chemical (ATC) classification system and Preferred Drug Names using the September 1st, 2015 version of the World Health Organization (WHO) dictionary. All concomitant medications and blood products will be summarized by ATC Level 3 and Preferred Name for proportions of subjects in each treatment group using each concomitant medication/blood product. Subjects will only be counted once within each level of summarization.

Concomitant medication and blood product use for medications of interest will be summarized in a similar manner based on proportions of subjects by treatment group, based on medications taken within treatment and post-treatment periods. The study periods used in analysis will be the same as described in the adverse event section ([Section 8.3](#)). The use of steroids, pentoxifylline and N-acetyl cysteine ([Singh et al. 2015](#)) will be of particular interest.

8.5 CHEMISTRY, HEMATOLOGY, COAGULATION, DISEASE-SPECIFIC EVALUATIONS

Data will be summarized by treatment group based on means by study visit, and mean (both absolute and %) changes from baseline by study visit. The baseline evaluation of a laboratory parameter is defined as the last evaluation of that parameter prior to randomization date/time. Additional summaries of changes relative to ELAD start date/time will be provided for subjects in the ELAD treatment group. For comparison purpose, changes relative to End of Study Day 2 will be summarized for the Control treatment group. Laboratory data will be prioritized over MELD/Maddrey data, if more than one measurement is recorded on the same study day.

For the following lab tests, proportion of subjects meeting the specified criteria will be presented by treatment group at each study visit:

- Bilirubin: <12 mg/dL vs. ≥12 mg/dL;
- Bilirubin: <16 mg/dL vs. ≥16 mg/dL;
- Hemoglobin: <7 g/dL;
- Platelet count: ≤20,000/mL;
- INR: >2.5 and >3.5;
- Calcium: ≤0.88 mmol/L;
- Glucose: >350 mg/dL or <50 mg/dL;
- Lactate: >4 mmol/L;
- Magnesium: <1.0 mEq/L;
- Phosphorus: <0.3 mmol/L;
- Potassium: >7.0 mEq/L or <2.0 mEq/L;
- Creatinine: Change <0.3 mg/dL vs. Change ≥0.3 mg/dL;
- Sodium: <130 mEq/L vs. ≥130 mEq/L;
- Sodium: <120 mEq/L.

No inferential statistical analyses will be performed for the summaries of laboratory data.

8.6 VITAL SIGNS AND PULSE OXIMETRY

Vital sign data [systolic blood pressure, diastolic blood pressure, pulse, respiration rate, temperature, mean arterial pressure (MAP)] will be collected at each study time point, and pulse oximetry/FiO₂ data will be collected through Study Day 7. Summaries will be prepared for each time point as well as the changes from baseline (i.e., last observation prior to Randomization). Additional summaries of changes relative to ELAD start date/time will be provided for subjects in the ELAD treatment group. For comparison purposes, changes relative to End of Study Day 2 (± 6 hours) will be summarized for the Control treatment group. Proportion of subjects with MAP <60 mmHg vs. ≥60 mmHg will be presented by study group. No inferential statistical analyses will be performed for the summaries of vital sign data.

8.7 CONCOMITANT PROCEDURES

Concomitant procedures will be coded using MedDRA version 18.1, similar to the approach for coding adverse events. Concomitant procedures including concomitant therapies (e.g., intubation, tracheostomy, CVVH/CVVHD, arterial line) are those administered any time between Randomization and through Study Day 91. Proportions of subjects by coded procedure administered during treatment and post-treatment periods will be presented by treatment group. No inferential statistical analyses will be performed.

8.8 HOSPITALIZATION SUMMARY

The number of days alive and out of the hospital during the first 90 days post-randomization will be summarized by treatment group. This will be based on the date of initial hospital admission (including referral hospital where applicable) and the date of hospital discharge for this hospital admission. Mean period of hospitalization will be compared between ELAD and Control.

Additionally, the proportion of subjects by initial discharge location out of the hospital will be summarized by treatment group.

8.9 HOME HEALTH CARE SUMMARY

After hospital discharge, home visits are conducted on a weekly basis up to Study Day 91 for all subjects to administer questionnaires on self-reported alcohol use and treatment services utilization, along with collection of an alcohol biomarker (PEth test). The proportion of subjects consuming alcohol post-discharge will be summarized by treatment group based on the following criteria:

- Subjects who reported any standard drink taken at any time post-hospital discharge;
- Subjects with a PEth lab results >20 ng at any time post-hospital discharge.

In order to evaluate differences between the treatment groups on the above recidivism variables, a Chi-squared test will be performed.

All home health care summary data will be listed.

8.10 EXPLORATORY ANALYSIS

Exploratory safety analyses will be based on ELAD System performance, therapeutic interventions of interest and administration of concomitant pharmacotherapies of interest.

For ELAD-treated subjects, analyses specific to ELAD treatment will be conducted based on the ELAD System performance files (PERF), the ELAD Specialist CRF, and the ELAD cartridge manufacturing data. These analyses will include summary statistics (e.g., N, mean, median, SD, proportions, as appropriate) for average fluid administration per day, glucose administration per hour and overall, number of component exchanges per subject per treatment, number of subjects with component exchanges by component along with reason for exchange and number of total exchanges for components of interest, estimated blood loss per subject due to component exchange and non-component exchange, and ELAD cartridge parameters including oxygen utilization rate (OUR) per minute, albumin production rate (mg/day), transferrin production rate (mg/day), glucose consumption per hour, age of cartridge, time to flush the cartridge, and time from cartridge shipping to treatment start.

A listing of subjects who were not on steroids at randomization will be presented along with the reason why steroid administration was not initiated. Listings will also be presented for blood cultures, sputum cultures, peritoneal fluid cultures and lab test results, and urine cultures.

8.10.1 ELAD Treatment Duration

ELAD treatment duration based on PERF data will be summarized. The duration is defined as total number of hours during which the ultrafiltrate pump is on. It will also be categorized into 3 groups: <72 hours, 72 hours to <96 hours, ≥96 hours. The counts of subjects in each category will be reported.

8.10.2 Total Amount of Ultrafiltrate

The total amount of ultrafiltrate (L) generated for each subject per day and overall by treatment, which is defined as the sum of the volume of ultrafiltrate delivered for each minute of perfusion (based on PERF data) will be summarized.

8.10.3 Blood Loss Associated with Blood Circuit Line Component Exchanges

A listing of subjects with a total blood loss volume ≥ 250 mL associated with blood circuit line component exchanges during ELAD treatment will be provided.

The total blood loss volume ≥ 250 mL associated with component exchanges during ELAD treatment was selected since this blood volume is equivalent to approximately one-half unit of packed red blood cells and this blood loss volume was deemed to be clinically significant.

8.10.4 Total Amount of Oxygen Utilization by Cell Cartridges

The total amount of oxygen utilization by the cell cartridges (mmHg·L) will be calculated by multiplying the amount of ultrafiltrate delivered each minute by the difference in oxygen partial pressure for each minute and then by calculating the sum of these values for each subject per day and overall by treatment. This will be summarized using descriptive statistics.

8.10.5 Fluid Administration Associated with Component Exchanges

A listing of subjects with a fluid volume that is \geq the median volume of fluid administered with component exchanges during ELAD treatment will be provided.

8.10.6 Correlation Analyses

Correlational analyses will look at the relationship between the age of the ELAD cartridge vs. oxygen and glucose consumption during treatment, as well as total blood loss and the total number of component exchanges.

9 DATA QUALITY ASSURANCE

Training was provided for the investigators and study coordinators at an investigator meeting held prior to initiation of the study. Site initiation visits for training and orientation of site personnel will be held at all sites prior to opening the site for enrollment. These meetings and visits will include training on completion of the eCRFs. Manuals will be provided to describe handling of laboratory samples, collection of the PEth alcohol test, study site responsibilities regarding home visits, and responsibilities of the home nurse.

The conduct of the study will be closely monitored by representatives of the Sponsor to verify adherence to ICH GCP guidelines and applicable standard operating procedures. Site monitoring visits will occur periodically during the course of the study, generally every 6 weeks or more frequently as needed.

Data management activities for this study will be performed by VTL and Axiom Real-Time Metrics (Axiom). Edit checks and review processes will be performed until all data clarifications are resolved. The data will be exported as SAS datasets. After all data clarifications are resolved and subject evaluability determined, the database will be locked. Synteract HCR will use the final SAS data for statistical analysis.

All SAEs will be reported directly by sites to the Axiom Pharmacovigilance team using a CRF designed to capture all SAE information. Axiom will be responsible for following up to ensure completeness of information. Axiom and VTL's medical monitor will work together to confirm that the event qualifies as an SAE, and to determine-if the SAE is a suspected unexpected serious adverse reaction (SUSAR). All information will be maintained in the Axiom Electronic Data Capture (EDC) database.

Narratives will be written for each randomized subject. All clinical details that are summarized in the narratives will be cross-checked against the final tables and listings to make sure that the clinical data reported in the clinical database are in agreement with the same clinical data presented in the narratives.

10 SOFTWARE AND VERSIONS

All analyses, data listings, tables, and graphs will be produced using SAS®, Version 9.2 or higher. MedDRA Version 18.1 will be used to code all adverse events.

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Appendix A Standards of Care Compliance Assessment

The questions to assess compliance to the standards of care (SOC) for nutrition, steroids, ascites, gastroesophageal varices, hepatic encephalopathy, hepatorenal syndrome, hyponatremia, spontaneous bacterial peritonitis and hepatic hydrothorax are listed for each medical problem (ascites, gastroesophageal varices, hepatic encephalopathy, hepatorenal syndrome, hyponatremia, spontaneous bacterial peritonitis and hepatic hydrothorax) and both treatment regimens (nutrition and steroids). An overall assessment on subject compliance with each SOC will also be listed.

- Nutrition
 - Did subject have at least one Dietary Consult?
 - Was subject diagnosed with malnutrition?
 - Did subject receive nutritional supplements?
 - Did subject have hypocalcemia, hypomagnesemia, or hypophosphatemia?
 - Did subject receive metal supplements?
 - Did subject have any vitamin deficiencies?
 - Did subject receive vitamin supplements?
 - Overall assessment: was this subject compliant with Nutrition SOC?
- Steroids
 - Did subject receive Prednisone/ Prednisolone for at least 7 days?
 - Was treatment with steroids contraindicated?
 - Overall assessment: was this subject compliant with Steroids SOC?
- Ascites
 - Was subject diagnosed with ascites?
 - Subject underwent a paracentesis if clinically indicated either during screening or after randomization.
 - Ascitic fluid analysis, if clinically indicated, included relevant lab tests (e.g., cell count and differential and if indicated, ascitic fluid cultures)?
 - Diuretics were administered if clinically indicated?
 - Subjects with tense ascites (as assessed by investigator) underwent a paracentesis?
 - Subjects with refractory ascites (as assessed by investigator) underwent a paracentesis followed by oral diuretics?
 - Subjects who had >5 liters of ascitic fluid removed received albumin?

- Overall assessment: was this subject compliant with Ascites SOC?
- Gastroesophageal Varices
 - Was subject diagnosed with gastroesophageal varices?
 - Was the subject diagnosed to have gastroesophageal varices who had no previous history of gastroesophageal bleeding treated with either non-selective beta-blockers, endoscopic venous ligation, endoscopic sclerotherapy, or TIPS?
 - Were subjects who had active bleeding within 2 weeks prior to randomization given an antibiotic?
 - Did subjects who had a variceal bleed during screening or after randomization receive blood transfusions, antibiotics, and pharmacologic therapy (e.g., vasopressin, terlipressin) if clinically indicated?
 - Did subjects who had persistent or recurring gastroesophageal bleeding undergo an endoscopic variceal ligation (EVL)/sclerotherapy or a transjugular intrahepatic portosystemic shunt (TIPS)?
 - Were subjects who had a recurrent variceal bleed after randomization despite EVL or non-selective β -blockers treated with both EVL and non-selective β -blockers?
 - Overall assessment: was this subject compliant with Gastroesophageal Varices SOC?
- Hepatic Encephalopathy (HE)
 - Was subject diagnosed with HE?
 - If subject was diagnosed with HE, was subject treated with Lactulose and/or Rifaximin?
 - Overall assessment: was this subject compliant with Hepatic Encephalopathy SOC?
- Hepatorenal Syndrome (HRS)
 - Was subject diagnosed with HRS?
 - If subject had Type I HRS, was subject treated with a regimen consisting of at least one of the following medications: albumin, octreotide, and/or midodrine, or a regimen of at least one of the following medications: terlipressin and albumin?
 - Overall assessment: was this subject compliant with HRS SOC?
- Hyponatremia
 - Did subject have hypovolemic hyponatremia after Randomization?

- If subject had hypovolemic hyponatremia, was subject treated with fluids, and were diuretics discontinued?
- Did subject have hypervolemic hyponatremia after Randomization?
- If subject had hypervolemic hyponatremia, was subject treated with fluid restriction (if clinically indicated)?
- Overall assessment: was this subject compliant with Hyponatremia SOC?
- Spontaneous Bacterial Peritonitis (SBP)
 - Was subject diagnosed with SBP, culture-negative neutrocytic ascites, or monomicrobial nonneutrocytic bacterascites after Randomization?
 - If subject was diagnosed with SBP, etc., was subject treated with antibiotics?
 - Did subject have a prior episode of SBP?
 - If subject had a prior episode of SBP, was subject treated with long-term antibiotic prophylaxis?
 - Overall assessment: was this subject compliant with SBP SOC?
- Hepatic Hydrothorax
 - Did the subject have hepatic hydrothorax?
 - Was treatment administered if clinically indicated to treat hepatic hydrothorax?
 - Overall assessment: was this subject compliant with hepatic hydrothorax SOC?

Appendix B Infection Search Terms

Abdominal abscess
Abdominal infection
Abdominal sepsis
Abdominal wall abscess
Abdominal wall infection
Abscess
Abscess bacterial
Abscess fungal
Abscess intestinal
Abscess jaw
Abscess limb
Abscess neck
Abscess oral
Abscess rupture
Abscess soft tissue
Abscess sweat gland
Acid fast bacilli infection
Acne pustular
Acquired immunodeficiency syndrome
Acrodermatitis chronica atrophicans
Acute endocarditis
Adenopathy syphilitic
Administration site abscess
Administration site cellulitis
Administration site infection
Administration site joint infection
Adrenal gland abscess
Adrenal gland tuberculosis
Anal abscess
Anorectal infection
Anorectal infection bacterial
Appendiceal abscess
Appendicitis
Appendicitis perforated
Application site abscess
Application site cellulitis
Application site infection
Application site pustules
Arboviral infection
Asymptomatic bacteriuria
Atypical mycobacterial infection
Atypical mycobacterial lower respiratory tract infection
Atypical mycobacterial pneumonia
Atypical mycobacterium pericarditis
Atypical pneumonia

Bacillus bacteraemia
Bacillus infection
Bacteraemia
Bacterascites
Bacterial colitis
Bacterial dacryocystitis
Bacterial diarrhoea
Bacterial infection
Bacterial pericarditis
Bacterial pyelonephritis
Bacterial rhinitis
Bacterial sepsis
Bacterial toxemia
Bacterial translocation
Bacteriuria
Bacteriuria in pregnancy
Bacteroides bacteraemia
Bacteroides infection
Beta haemolytic streptococcal infection
Bifidobacterium infection
Biliary abscess
Biliary sepsis
Biliary tract infection
Biliary tract infection bacterial
Bladder candidiasis
Blister infected
Bone abscess
Bone tuberculosis
Bovine tuberculosis
Brain abscess
Brain empyema
Breast abscess
Breast cellulitis
Bronchitis bacterial
Bronchitis fungal
Bursitis infective
Campylobacter colitis
Campylobacter gastroenteritis
Campylobacter infection
Campylobacter sepsis
Candida infection
Candida sepsis
Candiduria
Carbuncle
Cardiac infection
Catheter site abscess

Catheter site cellulitis
Catheter site infection
Catheter site pustule
Cellulitis
Cellulitis enterococcal
Cellulitis gangrenous
Cellulitis pasteurella
Cellulitis pharyngeal
Cellulitis staphylococcal
Cellulitis streptococcal
Chagoma
Chest wall abscess
Chlamydial infection
Chlamydial pelvic inflammatory disease
Cholecystitis infective
Clonorchiasis
Clostridial infection
Clostridium bacteraemia
Clostridium colitis
Clostridium difficile colitis
Clostridium difficile infection
Clostridium difficile sepsis
Colon gangrene
Colonic abscess
Community acquired infection
Corneal infection
Cystitis bacterial
Dental gangrene
Dermatitis infected
Device related infection
Device related sepsis
Diarrhoea infectious
Ear infection bacterial
Ear infection staphylococcal
Ear lobe infection
Empyema
Endocarditis
Endometritis bacterial
Enterobacter bacteraemia
Enterobacter infection
Enterobacter pneumonia
Enterobacter sepsis
Enterococcal bacteraemia
Enterococcal infection
Enterococcal sepsis
Enterocolitis bacterial

Enterocolitis fungal
Erysipelas
Escherichia bacteraemia
Escherichia infection
Escherichia sepsis
Escherichia urinary tract infection
Escherichia vaginitis
Eubacterium infection
Exserohilum infection
Fungaemia
Fungal infection
Fungal sepsis
Gallbladder abscess
Gallbladder empyema
Gastritis bacterial
Gastritis fungal
Gastroenteritis Escherichia coli
Gastroenteritis bacterial
Gastroenteritis caliciviral
Gastroenteritis clostridial
Gastroenteritis pseudomonas
Gastroenteritis rotavirus
Gastroenteritis salmonella
Gastroenteritis sapovirus
Gastroenteritis shigella
Gastroenteritis staphylococcal
Gastrointestinal bacterial infection
Gastrointestinal candidiasis
Gastrointestinal fungal infection
Gastrointestinal gangrene
Gastrointestinal infection
Genital abscess
Genital infection
Genital infection bacterial
Genital infection fungal
Genital infection male
Genitourinary tract infection
Geotrichum infection
Gingival abscess
Gingivitis
Groin abscess
Groin infection
Haematoma infection
Haemophilus bacteraemia
Haemophilus infection
Haemophilus sepsis

Haemorrhoid infection
Helicobacter gastritis
Helicobacter infection
Helicobacter sepsis
Herpes dermatitis
Herpes oesophagitis
Herpes pharyngitis
Herpes sepsis
Histoplasmosis
Histoplasmosis cutaneous
Iatrogenic infection
Incision site abscess
Incision site cellulitis
Incision site infection
Infection
Infective aortitis
Infusion site abscess
Infusion site cellulitis
Infusion site infection
Infusion site joint infection
Infusion site pustule
Injection site abscess
Injection site cellulitis
Injection site infection
Injection site pustule
Intestinal fistula infection
Intestinal gangrene
Intestinal sepsis
Kidney infection
Klebsiella bacteraemia
Klebsiella infection
Klebsiella sepsis
Laryngitis
Laryngitis bacterial
Lip infection
Liver abscess
Localised infection
Lower respiratory tract infection
Lower respiratory tract infection bacterial
Lower respiratory tract infection fungal
Lower respiratory tract infection viral
Ludwig angina
Lung infection
Mastitis
Mastitis bacterial
Mastitis fungal

Mastoid abscess
Mastoid empyema
Mastoiditis
Medical device site abscess
Medical device site cellulitis
Medical device site infection
Medical device site joint infection
Medical device site pustule
Myocarditis mycotic
Nail bed infection
Nail bed infection bacterial
Nail bed infection viral
Nail infection
Neutropenic infection
Neutropenic sepsis
Oesophageal candidiasis
Oesophageal infection
Oesophagitis bacterial
Oral bacterial infection
Oral candidiasis
Oral fungal infection
Oral hairy leukoplakia
Oral helminthic infection
Oral herpes
Oral infection
Oral pustule
Oral tuberculosis
Oropharyngeal candidiasis
Oropharyngeal gonococcal infection
Oropharyngitis fungal
Overgrowth bacterial
Pancreas infection
Pancreatic abscess
Pancreatitis bacterial
Pancreatitis fungal
Paronychia
Parotid abscess
Parotitis
Pelvic abscess
Pelvic infection
Perihepatic abscess
Perineal abscess
Perineal infection
Perinephric abscess
Periodontitis
Periorbital abscess

Perirectal abscess
Peritoneal abscess
Peritonitis
Peritonitis bacterial
Peritonitis gonococcal
Peritonitis pneumococcal
Pharyngeal abscess
Pharyngitis bacterial
Pharyngolaryngeal abscess
Pharyngotonsillitis
Phlebitis infective
Pleural infection
Pleural infection bacterial
Pneumococcal bacteraemia
Pneumococcal infection
Pneumococcal sepsis
Pneumonia
Pneumonia adenoviral
Pneumonia bacterial
Pneumonia escherichia
Pneumonia fungal
Pneumonia haemophilus
Pneumonia klebsiella
Pneumonia legionella
Pneumonia pseudomonal
Pneumonia salmonella
Pneumonia staphylococcal
Pneumonia streptococcal
Post abortion infection
Post procedural cellulitis
Post procedural infection
Post procedural pneumonia
Post procedural sepsis
Post vaccination autoinoculation
Post viral fatigue syndrome
Postoperative abscess
Postoperative wound infection
Postpartum sepsis
Presumed ocular histoplasmosis syndrome
Primary syphilis
Primary transmission
Proctitis bacterial
Proctitis chlamydial
Proctitis fungal
Proctitis gonococcal
Proctitis herpes

Proctitis infectious
Pseudomonal bacteraemia
Pseudomonal sepsis
Pseudomonas infection
Puncture site abscess
Puncture site infection
Pyoderma
Rectal abscess
Renal abscess
Renal cyst infection
Respiratory tract infection
Respiratory tract infection bacterial
Respiratory tract infection fungal
Retroperitoneal abscess
Retroperitoneal infection
Salmonella bacteraemia
Salmonella sepsis
Scrotal abscess
Scrotal gangrene
Scrotal infection
Sepsis
Sepsis pasteurella
Sepsis syndrome
Septic shock
Septic vasculitis
Serratia bacteraemia
Serratia infection
Serratia sepsis
Severe acute respiratory syndrome
Severe invasive streptococcal infection
Shigella infection
Shigella sepsis
Shunt infection
Skin bacterial infection
Skin candida
Skin infection
Splenic infection bacterial
Splenic infection fungal
Splenic infection helminthic
Staphylococcal abscess
Staphylococcal bacteraemia
Staphylococcal infection
Staphylococcal sepsis
Staphylococcal skin infection
Staphylococcal toxemia
Streptobacillus infection

Streptococcal abscess
Streptococcal bacteraemia
Streptococcal endocarditis
Streptococcal impetigo
Streptococcal infection
Streptococcal sepsis
Streptococcal urinary tract infection
Subacute endocarditis
Systemic candida
Systemic infection
Testicular abscess
Tetanus
Tongue abscess
Tongue fungal infection
Tonsillitis bacterial
Tonsillitis streptococcal
Tooth abscess
Tooth infection
Toxic shock syndrome
Toxic shock syndrome staphylococcal
Toxic shock syndrome streptococcal
Tracheobronchitis
Tracheobronchitis mycoplasmal
Upper respiratory tract infection
Upper respiratory tract infection bacterial
Urinary tract abscess
Urinary tract infection
Urinary tract infection bacterial
Urinary tract infection enterococcal
Urinary tract infection pseudomonas
Urinary tract infection staphylococcal
Vaginal abscess
Vaginal cellulitis
Vaginal infection
Vaginitis bacterial
Vessel puncture site infection
Vestibular neuritis
Wound abscess
Wound infection
Wound infection bacterial
Wound infection fungal
Wound infection pseudomonas
Wound infection staphylococcal
Wound sepsis
Yersinia bacteraemia
Yersinia infection

Yersinia sepsis

Appendix C Fluid Overload/Fluid Loss Symptoms Search Terms

Ascites

Oesophageal varices haemorrhage

Upper gastrointestinal haemorrhage

Generalised oedema

Oedema peripheral

Edema without specification

Acute respiratory distress syndrome

Acute respiratory failure

Hypoxia

Pleural effusion

Pulmonary oedema

Respiratory arrest

Respiratory failure

Renal failure (any type)

Hypotension (any type)

Shock (any type)

Appendix D Bleeding Search Terms

Aggravated bleeding tendency
Bleeding tendency
Haemorrhagic diathesis
Hemorrhagic diathesis
Haemorrhage abnormal
Haemorrhagic disorder
Haemorrhagic disorder due to circulating anticoagulants
Hemorrhage abnormal
Hemorrhagic disorder due to circulating anticoagulants
Spontaneous haematoma
Spontaneous hematoma
Spontaneous haemorrhage
Spontaneous hemorrhage
Gastric haemorrhage
Gastric varices haemorrhage
Gastroduodenal haemorrhage
Mallory-Weiss syndrome
Oesophageal haemorrhage
Oesophageal varices haemorrhage
Portal hypertensive gastropathy
Anal haemorrhage
Colonic haematoma
Intestinal haematoma
Large intestinal haemorrhage
Mesenteric haematoma
Mesenteric haemorrhage
Portal hypertensive enteropathy
Rectal haemorrhage
Small intestinal haemorrhage
Chronic gastrointestinal bleeding
Gastrointestinal haemorrhage
Haematemesis
Haematochezia
Intra-abdominal haematoma
Intra-abdominal haemorrhage
Lower gastrointestinal haemorrhage
Melaena
Upper gastrointestinal haemorrhage
Application site haematoma
Application site haemorrhage
Catheter site haematoma
Catheter site haemorrhage
Infusion site haematoma
Infusion site haemorrhage
Injection site haematoma

Injection site haemorrhage
Abnormal withdrawal bleeding
Anovulatory cycle
Bleeding anovulatory
Delayed menarche
Dysfunctional uterine bleeding
Dysmenorrhoea
Early menarche
Menometrorrhagia
Menorrhagia
Menstrual discomfort
Menstrual disorder
Menstruation irregular
Metrorrhagia
Polymenorrhagia
Polymenorrhoea
Premenstrual cramps
Premenstrual dysphoric disorder
Premenstrual headache
Premenstrual pain
Premenstrual syndrome
Retrograde menstruation
Withdrawal bleed
Scrotal haematoma
Testicular haemorrhage
Deep dissecting haematoma
Haemorrhage subcutaneous
Haemorrhage subepidermal
Mucocutaneous haemorrhage
Skin haemorrhage
Subcutaneous haematoma
Arterial haemorrhage
Arterial perforation
Bloody discharge
Exsanguination
Extravasation blood
Haematoma
Haemorrhage
Internal haemorrhage
Shock haemorrhagic
Venous haemorrhage

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|---------|--|
| Approve | Andrew Henry Clinical Operations 24-Aug-2018 21:20:02 GMT+0000 |
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|---------|--|
| Approve | Rob Ashley Executive 25-Aug-2018 07:20:20 GMT+0000 |
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| | |
|---------|--|
| Approve | Jan Stange Medical 26-Aug-2018 02:27:43 GMT+0000 |
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