Amendment to Statistical Analysis Plan

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Project	***TITLE:*** A multi-centre, randomised controlled study, to evaluate the safety and performance of the DIALIVE Liver Dialysis Device (LDD) in patients with Acute on Chronic Failure (ACLF) versus standard of care (SOC). ***SHORT TITLE***: DIALIVE in ACLF ***CODE:*** YAQ-002 ***Protocol version/date:*** Final version v6.0, 15th January 2019
Sponsor	*Yaqrit Limited*
Institution	*Medical Statistics Core Facility* *IDIBAPS – Hospital Clínic Barcelona*
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4 LIST OF ABREVIATIONS AND DEFINITION TERMS

ALF	Acute Liver Failure
ACLF	Acute on Chronic Liver Failure
ADE	Adverse Device Effect
ADO	Available Data Only
AE	Adverse Event
AV	Acceptable Value
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organisation
CRP	C-Reactive Protein
CVS	CardioVascular System
DCF	Data Clarification Form
DD	Device Deficiency
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
GCP	Good Clinical Practice
HE	Hepatic Encephalopathy
ICU	Intensive Care Unit
INR	International Normalised Ratio
IWRS	Interactive Wireless Randomization System
LDD	Liver Dialysis Device
LF	Liver Failure
RAE	Related to the treatment Adverse Event
RSAE	Related to the treatment Serious Adverse Event
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	Standard of Care
TV	Target Value
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

5 SCOPE OF AMENDMENT TO THE STATISTICAL ANALYSIS PLAN

This document replaces the Statistical Analysis Plan version of 26th March of 2018.
This amendment includes the application of the changes in version 6.0 of the protocol (15th January 2019) to the Statistical Analysis Plan dated at 26th March of 2018.

6 SCOPE OF ANALYSIS PLAN

This Statistical Analysis Plan (SAP) covers all the statistical analysis of the data collected in the trial YAQ-002, performed by Medical Statistics Core Facility by the assigned project statistician. The SAP will follow the general regulatory recommendations given in the ICHE9[1] guidance, as well as other specific guidance on methodological and statistical issues[2].

7 SOFTWARE METHODS

All tables and listings were produced using SAS System[3](Release 9.4) and were presented in WinWord (Version Microsoft Office 2007) documents.

8 STUDY OBJECTIVES

8.1 Primary objective

To evaluate the safety of the DIALIVE in patients with alcohol related cirrhosis with Acute on Chronic Liver Failure Grades 1,2 and 3a (ACLF) compared with the group treated with standard care.

8.2 Secondary objectives

To evaluate the performance of the DIALIVE in the above mentioned patient group. To evaluate clinical benefit in patients receiving DIALIVE treatment plus Standard of Care (SOC) versus SOC alone.

9 HYPOTHESES AND CLAIMS

The underlying hypothesis is that DIALIVE will significantly improve the prognosis of patients with ACLF by i) exchanging irreversibly damaged native albumin, which accumulates during this disease process and is ineffective in its function, with fresh albumin, and ii) removal of endotoxins, inflammation and endotoxaemia being the central pathogenetic feature of this illness.

This is a first into man study of a novel Liver Dialysis Device. No specific hypothesis is to be statistically assessed in this first feasibility study. Randomization of patients is implemented to obtain unbiased clinical data appropriately balanced between SoC and DIALIVE treated patients to provide fundamental learning data on the outcome of treatment in both study arms, in line with the recommendations of the DSMB (see appendix 7). To this end, safety data, are regularly reviewed (i.e. after each cohort of patient enrollment) but also other clinical parameters are reviewed, to learn and adjust study design when necessary and as appropriate.

Based on this perspective it is the goal to obtain an adequate number of observations in each study arm, with emphasis on the learning from DIALIVE treatment. Future trials will be defined to assess the efficacy of DIALIVE treatment to the appropriate extend.

10 STUDY DESIGN

This is a European, multi-centre, randomised, controlled, open label study to generate data for the evaluation of safety (as measured by the percentage of subjects who experience at least one serious adverse event (SAE)) and performance (as measured by plasma endotoxin concentrations and albumin function) of The DIALIVE in 30 evaluable patients with Acute on Chronic Liver Failure (ACLF) versus standard of care (SOC).
The design is appropriate for the study as the primary outcome is to assess safety of the device on a small group of patients.

For the randomization an Interactive Wireless Randomization System (IWRS) is used, which is linked to the study data base. Randomization is automatically assigned through the IWRS system. Patients are randomised to either the DIALIVE or SOC arm in a 1:1 ratio. P The randomization list was generated using the software: proc Plan of SAS System (Release 9.4), which assigns random numbers and treatments to patient.

Patients will be assigned into five (5) Cohorts. Each cohort will consist of six (6) patients (3 DIALIVE: 3 SOC). If there are dropouts in any of the following cohorts during the study period, patients will be replaced in each of the cohorts described below to reach the appropriate number of 6 evaluable patients in each cohort.

Cohort 1: including 3 control and 3 DIALIVE treated patients.
Cohort 2: including 3 control and 3 DIALIVE treated patients.
Cohort 3: including 3 control and 3 DIALIVE treated patients.
Cohort 4: including 3 control and 3 DIALIVE treated patients.
Cohort 5: including 3 control and 3 DIALIVE treated patients.

A DIALIVE treatment session = A minimum, cumulative duration of 8 to 10 hrs (+ 30 min) of the DIALIVE treatment, thus allowing for breaks which may be planned (for example patients needing to go for imaging) or unplanned (device clotting, issues with vascular access or other any other unplanned reasons). A break within a treatment session (consisting of a cumulative time longer than 4hrs), or a cumulative duration of less than 8 hrs of dialysis during one day constitutes a session failure for that day. A session failure will require to restart the dialysis session within 24 hrs after the end of the previous session and will reset the start of the dialysis cycle.
A DIALIVE treatment cycle= Consists of 3 consecutive days of 8-10 hrs of DIALIVE treatment sessions on each day within the 10 day window period. A break of more than 24hrs between each treatment session will require a new baseline (i.e. a new treatment cycle commenced). A second failed treatment session within the 10 day window period would result in patient exlusion.The patient must have completed one successful treatment cycle within the 10 day window period to be considered evaluable.

11 FLOW CHART OF TRIAL PROCEDURES

See Schedule of assessments below for Standard of Care and DIALIVE Patients:

SOC Patients	Pre-Screening	Screening	Study Days							
Study Procedures		**0-72hrs**	**Day 0**	**Day 1**	**Day 3**	**Day 5**	**Day 10**	**Day 14 +/- 2 days**	**Day 28 +/- 5 days**	**Day 90 +/- 5 days**
Informed consent[1]	X									
Inclusion/exclusion criteria		X	X[2]							
Demographics		X								
Medical history		X								
Complete physical examination		X		X	X	X	X	X	X	
Weight (kg) and height (cm)		X		X	X	X	X	X	X	
Vital signs		X		X	X	X	X	X	X	
12-lead ECG		X		X						
Viral screen (local laboratory)[3]		X								
Clinical laboratory (local laboratory)[4]		X		X	X	X	X	X	X	
Full infection screen (local laboratory)		X		X		X	X			
Pregnancy test (women only)		X								
Coagulation (local laboratory)[5]		X		X	X	X	X	X	X	
Randomisation			X							
AE assessments				X	X	X	X	X	X	
Concomitant medications				X	X	X	X	X	X	X[6]
CLIF-C OF Score, CLIF-C ACLF score, ACLF grade		X		X	X	X	X	X	X	

1 Informed consent must occur before ANY studyspecific procedures commence. Thorough clinical examination and assessment of FBC, U&Es, LFTs, Coagulation must be repeated even if the test have been undertaken > 24 hours before randomization. Microbiology results obtained within the previous 72 hrs prior to screening maybe used and samples not repeated. Viral serology results obtained within 8weeks prior to screening maybe used and samples not repeated. Liver imaging results obtained 6 weeks prior to screening maybe usedand tests not repeated unless there has been a significant change in clinical status

2 Confirmation only. Document in medical notes.

3 Tests performed: HBsAg, anti-HCV, and anti-HIV.Viral serology results obtained within 8 weeks prior to screening maybe usedand samples not repeated.

4 Standard haematology and biochemistry as per local practice (Including CRP).

5 Tests performed: Platelets, PT, INR, PTT, Fibrinogen

6 Suvival data only via a telephone call.

SOC Patients	Screening	Study Days							
Study Procedures	**0-72hrs**	**Day 0**	**Day 1**	**Day 3**	**Day 5**	**Day 10**	**Day 14 +/- 2 days**	**Day 28 +/- 5 days**	**Day 90 +/- 5 days**
MELD, MELD-Na	X		X	X	X	X	X	X	
Pugh and Lille Scores	X		X	X	X	X	X	X	
eGFR	X		X	X	X	X	X	X	
West Haven grade	X		X	X	X	X	X	X	
Blood sample for biomarkers including Albumin (HNA2) and Endotoxin Plasma Concentration (initial processing locally, samples are transferred to Biobank Royal Free Hospital for analysis)[7]			X	X	X	X			
Urine sample for biomarkers (initial processing locally, samples are transferred to Biobank Royal Free Hospital for analysis)[8]			X	X	X	X			
PBMCs (initial processing locally, sample are transferred to Biobank Royal Free Hospital for analysis)[9]			X	X	X	X			
Endotoxin Activity Assay (local processing and analysis)			X	X	X	X			

7 Blood Biomarker tests : cCK18/M30, flCK18/M65, Caspase 3, Caspase 7, IL-18, soluble CD163, cytokines (TNF-α, IL-6, IL-8, IL-10), chemokines (CX3CL1, CXCL3, CCL2, CCL5)
8 Urine Biomarker tests: NGAL, TLR4, IL-18
9Peripheralbloodmononuclearcells (PBMC) Royal Free Hospital London only.

DIALIVE Patients	Pre-screening	Screening	Treatment Period								
Study Procedures		**0-72hrs**	**Day 0**	**Day 1[1]**	**Day 2**	**Day 3**	**Day 5**	**Day 10**	**Day 14 +/- 2 days**	**Day 28 +/- 5 days**	**Day 90 +/- 5 days**
Informed consent[2]	X										
Inclusion/exclusion criteria		X	X[3]								
Demographics		X									
Medical history		X									
Complete physical examination		X		X	X	X	X	X	X	X	
Weight (kg) and height (cm)		X		X			X	X	X	X	
Vital signs[4]		X		X	X	X	X	X	X	X	
12-lead ECG		X		X							
Viral screen (local laboratory)[5]		X									
Clinical laboratory (local laboratory)[6]		X		X	X	X	X	X	X	X	
Full infection screen (local laboratory)		X		X			X	X			
Pregnancy test (women only)		X									
Coagulation (local laboratory)[7]		X		X	X	X	X	X	X	X	
Randomisation			X								

1 DIALIVE treatment must commence before end of day 1. DIALIVE treatment may commence on day 0 at the discretion of the investigator. If DIALIVE treatment commences on Day 0, then Day 1 tests must be perfomed before treatment commences on Day 0 and therefore does not need repeating again on Day 1.

2 Informed consent must occur before ANY study specific procedures commence. Thorough clinical examination and assessment of FBC, U&Es, LFTs, Coagulation must berepeated ifthe test have been undertaken >24 hours before randomization. Microbiology results obtained within the previous 72 hrs prior to screening maybe used and samples not repeated. Viral serology results obtained within 8 weeks prior to screening maybe usedand samples not repeated. Liver imaging results obtained 6 weeks prior to screening maybe usedand tests not repeated unless there has been a significant change in clinical status.

3 Confirmation only. Record in medical notes.

4 Blood pressure (supine), respiratory rate, body temperature will be recorded throughout DIALIVE treatment (as per Standard of Care)

5 Tests performed: HBsAg, anti-HCV, and anti-HIV.Viral serology results obtained within 4 weeks prior to screening maybe usedand samples not repeated

6 *S*tandard haematology and biochemistry as per local practice (including CRP). Performed throughout DIALIVE treatment as per local practices.

7 Tests performed: Platelets, PT, INR, PTT, Fibrinogen. Performed throughout DIALIVE treatment as per local practices.

DIALIVE Patients	Screening	Treatment Period								
Study Procedures	**0-72hrs**	**Day 0**	**Day 1**	**Day 2**	**Day 3**	**Day 5**	**Day 10**	**Day 14 +/- 2 days**	**Day 28 +/- 5 days**	**Day 90 +/- 5 days**
AE assessments			X	X	X	X	X	X	X	X[8]
Concomitant medications			X	X	X	X	X	X	X	
CLIF-C OF Score, CLIF-C ACLF score, ACLF grade	X		X	X	X	X	X	X	X	
CLIF-AD Score (if relevant)	X		X	X	X	X	X	X	X	
MELD, MELD-Na	X		X	X	X	X	X	X	X	
Pugh and Lille Scores	X		X	X	X	X	X	X	X	
eGFR	X		X	X	X	X	X	X	X	
West Haven grade	X		X	X	X	X	X	X	X	

1 DIALIVE treatment must commencebefore end of day 1. DIALIVE treatment maycommence at day 0 at thediscretion of the investigator. If DIALIVE treatment commences on Day 0, then Day 1 tests must be perfomed before treatment commences on Day 0 and therefore does not need repeating on Day 1.
8 Suvivial only via telephone call

12 STATISTICAL ANALYSIS

12.1 Study populations and handing of missing values.

There is only one population for this study, the safety population, defined as the subset of randomised patients who receive at least one treatment (in the DIALIVE arm when the first session started).

No formal imputation will be performed for any of the variables and the analyses will be based on the available data only (ADO) approach.

A modified Safety population with only the evaluable patients will be also considered for all analyses (as a sensitivity), defined as all those patients who received standard of care or those who received the correct dialysis treatment cycle (see section 10 for the definition of evaluable patient) of DIALIVE.

12.2 Variables

12.2.1 Demographic characteristics, pre-randomization and baseline

The following pre-treatment characteristics will be analysed:

- Informed consent.
- Demographics (age, sex and race/ethnicity).
- Subject characteristics (Height, Weight and BMI).
- Diagnostic of cirrhosis, previous decompensations and previous liver treatments.
- Medical/Surgical history.
- Viral parameters (HNsAg, Anti-HCV, anti-HIV, EBV and CMV).
- Urine Drug.
- Pregnancy test (if applicable).
- Inclusion and exclusion criteria.
- Randomization.

12.2.2 Primary, secondary and exploratory variables

The primary, secondary and exploratory variables (or group of variables) are listed below:

- Adverse Events Characteristics.
- Endotoxin levels.
- Albumin Sample: HNA-2 and HMA.
- CLIF-C OF and CLIF-C ACLF Score parameters.
- CLIF-C AD Score and parameters included.
- MELD, MELD-Na Score and parameters included.
- Immune functions by markers.
- Coagulation by parameter.
- Control Status: presence of changes in concomitant medication, any adverse event and control of visits and final evaluation.
- DIALIVE treatment: treatment yes/no and treatment characteristics (albumin return of 20% and 5% concentrations).
- DIALIVE sessions: prismaflex settings and anticoagulation.
- Physical examination by system organ class.

- Vital signs.
- ECG.
- Haematology by parameter.
- Full Infection by kind of infection, CRP and WCC.
- Biochemistry by parameter.
- West Haven grade.
- Pugh Score and Lille Score and parameters included.
- eGFR.
- Sample for biobank.
- Dic (D-dimer value or Fibrin degradation products).
- Blood Gasses.
- Device deficiency characteristics.
- Medication record.
- Blood products and IV fluid administration.
- Parecentesis characteristics and parameters.
- Continuous Renal Replacement Therapy (CRRT).
- End of study.
- Protocol deviation.
- 90 day follow up (survival status)

12.3 Main and Secondary Outcomes

The following sections shows the primary, secondary and exploratory outcomes related to the study objectives. Other analyses performed with previous list of variables will be considered as a secondary.

12.3.1 Primary outcome

To evaluate the safety of the DIALIVE in patients with alcohol related cirrhosis with Acute on Chronic Liver Failure Grades 1,2 and 3a (ACLF) compared with the group treated with standard care.
The primary endpoint related to the main objective (to evaluate the safety of the DIALIVE in patients with alcohol cirrhosis with Acute on chronic failure grades 1, 2 and 3a (ACLF) compared with the group of treated with standard care) is the evaluation of the following outcomes:

- The percentage of subjects who experience at least one SAE between Day 1 to Day 10.
- The percentage of subjects who discontinued DIALIVE treatment due to a serious adverse device event (SADE) between Day 1 (first day of treatment) and Day 10 (DIALIVE arm only).

Any additional analyses performed with the Adverse Events will be considered as a secondary.

12.3.2 Secondary outcomes

The secondary endpoints related to the secondary objectives (see section 8.2) are the evaluation of the following outcomes:

- Change in Plasma endotoxin level (endotoxin activity and concentration):
  - D1, D3, D5 and D10 across SOC arm.
  - D1, D3, D5 and D10 across DIALIVE arm.

  - Start and end of treatment session (on D3, D4, D5) with DIALIVE
  - D1, D5 and D10 between SOC and DIALIVE arms for patients presenting with the same grades of ACLF at the time of the inclusion in the study (i.e. Grade 1 ALCF compared with Grade 1 ACLF).
  - Target-Value (TV): 40% reduction.
  - Acceptable-Value (AV): 20% reduction.
- Change in Albumin function (Human non-mercapt albumin -2 (HNA-2) / Human marcapt albumin (HMA) ratio:
  - D1, D3, D5 and D10 across SOC arm.
  - D1, D3, D5 and D10 across DIALIVE arm.
  - Start and end of treatment session (on D3, D4, D5) with DIALIVE
  - D1, D5 and D10 between SOC and DIALIVE arms for patients presenting with the same grades of ACLF at the time of the inclusion in the study (i.e. Grade 1 ALCF compared with Grade 1 ACLF).
  - Target-Value (TV): 40% reduction.
  - Acceptable-Value (AV): 20% reduction.
- Mortality at Day 28 and 3 months
- Change in ACLF Grade
- Change in CLIF-ACLF score
- Improvement in individual organ function: Brain (HE), Kidney (creatinine), CVS (mean arterial pressure), Pulmonary (P/F ratio, or S/F if patient is not intubated), Liver (serum bilirubin) and coagulation (INR and platelets).
- Status at ICU and Hospital Discharge (including discharge to a hospice for palliative care).
- Lengths of stay in ICU and Hospital at D28 and D90
- ICU and Hospital re-admissions with another episode of ACLF up to 3 months after randomisation.

Any other analysis performed with these variables will be considered additional analysis.

12.3.3 Exploratory outcomes

The exploratory endpoints related to the secondary objectives (see section 8.2) are the evaluation of the following outcomes:

- Liver: Changes in MELD score, plasma/serum cCK18/M30 and flCK18/M65 (markers of liver cell death) in DIALIVE patients with ACLF and SOC patients.
- Kidney: Changes in serum creatinine and urinary NGAL (marker of kidney injury).
- Brain: West Haven Criteria to assess changes in severity of hepatic encephalopathy.
- Immune function: Incidence of Infection. Changes in white cell count and plasma-induced neutrophil function (Phagoburst and Phagotest), serum CRP and cytokines (TNF-α, IL-6, IL-8, IL-10, IL1RA).
- Assessment of Coagulation and haemostasis: Incidence of thrombotic or bleeding complications, assessment of pro- and anti-coagulant clotting factors and complement activation.

Any other analysis performed with these variables will be considered additional analysis..

12.4 Statistical Methods

All statistical analysis will be performed using ADO approach on Safety set and modified Safety set (with only evaluable patients).
All analyses performed with modified Safety set will be considered sensitivity analyses.

12.4.1 Descriptive Analysis

Results will be presented by study group with descriptive statistics appropriate to the nature of the variables:

- Continuous variables: Mean, 95%CI of Mean (95% mean confidence interval), SD (standard deviation), minimum, P25 (percentile 25), Median, P75 (percentile 75), maximum and N. Per group and globally.
- Categorical variables: total column %, each category N. Per group and globally.
- Ordinal variables with few categories (less than 10) will be described using two tables: one including continuous variables descriptive parameters (as long as the interpretation is reasonable) and the other including categorical variables descriptive parameters. For ordinal variables with >10 categories, the same approximation used for continuous variables will be applied.

Where applicable, these summaries will be provided by visit/time point, including the absolute differences between visit and baseline results.

All text variables will be listed.

12.4.2 Inferential analysis

No inferential analysis will be performed in this study (no statistical test will be applied), all statistical analysis will be descriptive only.

12.4.3 Demographic characteristics, pre-randomization and baseline

Descriptive statistics and listings for each variable per study product group and visit (Prior Screening, Screening Visit or Baseline Visit) will be performed.

Results are presented by means of individual tables and listings for each of the variables described in section12.2.1.

12.4.4 Primary, secondary and exploratory analyses

12.4.4.1 Analysis related to the primary outcome

The primary analyses will be conducted to evaluate the safety of the DIALIVE device compared with the standard care group. For this primary endpoint, the following variables will be summarized by means of appropriate descriptive statistics (see section 12.4.1) and listings:

- Number of subjects with at least one SAE, by study arm and overall.
- Number of subjects who discontinued DIALIVE due to SADE between Day 1 and Day 10, only for the DIALIVE arm.

Additionally complete descriptive analysis of adverse events will be performed as follow:

- Number of subjects with at least one: Adverse Event (AE), Related to the treatment Adverse Event (RAE), Serious Adverse Event (SAE), Related to the treatment Serious Adverse Event (RSAE), Adverse Device Event (ADE) and Serious Adverse Device Event

(SADE), Unanticipated Serious Adverse Device Event (USADE) and Device Deficiency (DD) will be summarized in an descriptive table as n (%).

- The number and percentage of patients who experience one or more treatment-emergent AEs as well as the number of AE episodes will be tabulated by body system, preferred term (according to MedDRA v20),seriousness, severity, action taken with study treatment and causality.

12.4.4.2 Analysis related to the secondary and exploratory outcomes

The appropriate descriptive statistics (see section 12.4.1) and listing will be generated for the following variables to assess the secondary outcomes (see sections 12.3.2 and 12.3.3 per study product group and visit where applicable:

- Endotoxin level (endotoxin activity and concentration):
  - D1, D3, D5 and D10 per arm and global.
  - Start and end of session for DIALIVE arm (D3, D5 and D5).
  - D1, D3, D5 and D10 per arm and global separately by ACLF grade at the time of the inclusion in the study.
  - Target-Value (TV): 40% reduction.
  - Acceptable-Value (AV): 20% reduction.
- Albumin function (Human non-mercapt albumin -2 (HNA-2) / Human marcapt albumin (HMA) ratio:
  - D1, D5 and D10 per arm and global.
  - Start and end of session for DIALIVE arm (D3, D5 and D5).
  - D1, D5 and D10 per arm and global separately by ACLF grade at the time of the inclusion in the study.
  - Target-Value (TV): 40% reduction.
  - Acceptable-Value (AV): 20% reduction.
- Mortality at Day 28.
- ACLF Grade (grade per day and improvement Yes/No per day).
- CLIF-ACLF score.
- Evaluation of improvement organ function by means of:
  - Brain (Hepatic Encephalopathy)
  - Kidney (creatinine).
  - CVS (mean arterial pressure).
  - Pulmonary (P/F ratio, or S/F if patient is not intubated)
  - Liver (serum bilirubin)
  - Coagulation (INR and platelets).
- Liver: MELD score, plasma/serum cCK18/M30 and flCK18/M65 (markers of liver cell death) in DIALIVE patients with ACLF and SOC patients.
- Kidney: serum creatinine and urinary NGAL (marker of kidney injury).
- Brain: West Haven Criteria.
- Immune function: Incidence of Infection. White cell count and plasma-induced neutrophil function (Phagoburst and Phagotest), serum CRP and cytokines (TNF-α, IL-6, IL-8, IL-10, IL1RA).
- Coagulation: Incidence of thrombotic or bleeding complications, assessment of pro- and anti-coagulant clotting factors and complement activation.

Furthermore, all variables collected in the data groups indicated in section 12.2.2 will be described by means of appropriate descriptive statistics (see section 12.4.1) and listings per group and time point when applicable.

The Albumin function and endotoxin levels will be analyzed in order to evaluate the following (according to the definition of secondary end point):

- Absolute values by time/point (pre and post) per day.
- Absolute differences between pre and post per day.
- Absolute differences between pre-value at D1 and the final post-value.

All continuous variable will be described as an absolute value and as an absolute difference from baseline when applicable.
These analyses also will be performed separately by grade of ACLF at the time of the inclusion in the study.

13 DSMB STATISTICAL ANALYSIS

This section describes the information provided by IDIBAPS to the Data Safety Monitoring Board (DSMB) members at least 5 business days prior to the each DSMB meeting (open and closed session).
According to the DSMB charter final version (version 1.0, 25May 2017), five DSMB analyses are planned, one after each cohort of 6 patients (see section 10) and the following safety data will be presented in a blinded manner to the members of DSMB.
The descriptive tables will be presented blinded and grouped in 2 groups identified as "α" and "Ω" but without any link to the "control" or "treatment arm" of the study.

The following summary tables/listings will be generated for the open session DSMB meeting:

- Study status.
  - Overall enrolment
  - Patients disposition
  - Screen failures
  - Withdrawals and discontinuations
- Major protocol violations
- Adverse events and serious adverse events

For the closed session DSMB meeting the following tables and listings will be generated:

- **Table 1: Enrolment status:** number of patients who signed the Informed Consent Form, number of screen failures, number of withdrawals, number of randomized patients, number of patients in each arm of the study, number of patients with 7, 14, and 28 days of follow up and the number of patient who completed the study (28 days of follow up) and number of patients who discontinued the study and theirs reasons.

- **Table 2**: Subject disposition presented per the different analytical groups – presentation of results as “partially blinded data”.
  A. All randomized patients;
  B. All patients receiving any treatment session (control or treatment) (safety population);

C. Number of patients receiving a correct treatment cycle, i.e. a minimum of 3 consecutive days and a maximum of 5 days of DIALIVE treatment sessions – each of min 8 and max 12 hrs - over a period of 10 days.

- **Table 3. Major protocol deviations.**
- **Table 4. Adverse Events and emergency treatments:**
  - Patient deaths
  - SAE and USAE
  - Serious adverse device effects (ADE, SADE, USADE and DD's), including clinical procedure related events
  - All other reported adverse events

14 FINAL ANALYSIS TABLES

All tables will be descriptive and the results will be presented by group and time-point when applicable. Also, all continuous variables will be analysed as absolute values by visit and absolute change from baseline.
The following tables may contain one or more sub-tables depending on the type of summarized data.

14.1 Demographic characteristics, pre-randomization and baseline

Table 1. Subjects disposition.
Table 2. Informed consent.
Table 3. Demographics. Age, sex and race(ethnicity).
Table 4. Subjects characteristics. Height, weight and BMI.
Table 5. Cirrhosis diagnostic, previous decompensations and previous liver treatments.
Table 6. Medical/Surgical history.
Table 7. Viral Parameters (HNsAg, Anti-HCV, anti-HIV, EBV and CMV).
Table 8. Urine Drug by drug type.
Table 9. Pregnancy test.
Table 10. Inclusion and exclusion criteria.

14.2 Primary, secondary and exploratory variables.

Table 11. AEs. **Main outcome**. Number (%) of subjects with at least one SAE between Day 1 and Day 10.
Table 12. AEs. **Main outcome**. Number (%) of subject who discontinued DIALIVE due to a SADE between Day 1 and Day 10.
Table 13. AEs. **Secondary outcome**. Number (%) of died subject at Day 28.
Table 14. AEs. Number (%) of subjects with at least AE, RAE, SAE, RSAE, ADE, SADE, USADE and DD.
Table 15. AEs. Number (%) of subjects reporting one or more treatment-emergent AE by body system.
Table 16. AEs. Number (%) of subjects reporting one or more treatment-emergent AE and number of AE occurrences by body system and treatment group.
Table 17. AEs. Number (%) of subjects reporting one or more treatment-emergent AE and number of AE occurrences by body system, preferred term, and treatment group.
Table 18. AEs. Number (%) of subjects reporting one or more treatment-emergent AE and number of AE occurrences by body system, preferred term, seriousness and treatment group.
Table 19. AEs. Number (%) of subjects reporting one or more treatment-emergent AE and number of AE occurrences by body system, preferred term, intensity and treatment group.
Table 20. AEs. Number (%) of subjects reporting one or more treatment-emergent AE and number of AE occurrences by body system, preferred term, relationship to the treatment and treatment group.
Table 21. AEs. Number (%) of subjects reporting one or more treatment-emergent AE and number of AE occurrences by body system, preferred term, seriousness, intensity, relationship to the treatment and treatment group.
Table 22. Endotoxin levels. **Secondary outcome**.
Table 22.1 Endotoxin levels. **Secondary outcome**. D1, D3, D5 and D10 by arm and global.

15 FINAL ANALYSIS LISTINGS

16 REFERENCES

1. CPMP/ICH/363/96. ICH E9 Statistical Principles for Clinical Trials. URL: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500002928, last access: 16-Jun-2014.

2. EMEA Scientific Guidelines for Human Medicinal Products, Clinical Efficacy and Safety Guidelines, General Guidelines. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000085.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027549&jsenabled=true, last access: 16-Jun-2014.

3. SAS version 9.2 software, SAS Institute Inc., Cary, NC, URL: http://www.sas.com/, last access, 21Feb2014.

17 TEMPLATE TABLES

Template Table 1. Categorical variables.

	DIALIVE (n=XX) n (%)	SOC (n=XX) n (%)	TOTAL (n=XX) n (%)
Variable 1			
Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Variable 2			
Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)

.....

Source: Path\Tables.sas (Date-time)

Statistical Report PROTOCOL NUMBER: YAQ-002

Template Table 2. Categorical variables by parameter.

Parameter	DIALIVE (n=XX) n (%)	SOC (n=XX) n (%)	TOTAL (n=XX) n (%)
Parameter 1			
Variable 1			
Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Variable 2			
Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....			
Parameter 2			
Variable 1			
Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Variable 2			
Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
.....			
.....			

Source: Path\Tables.sas (Date-time)

Statistical Report PROTOCOL NUMBER: YAQ-002

Template Table 3. Categorical variables by parameter and time-point.

Parameter	Time-point		DIALIVE (n=XX) n (%)	SOC (n=XX) n (%)	TOTAL (n=XX) n (%)
Parameter 1	Time-point 1				
		Variable 1			
		Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Variable 2			
		Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....			
	Time-point 2				
		Variable 1			
		Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Variable 2			
		Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....			
	.....				
Parameter 2	Time-point				
		Variable 1			
		Category 1	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		Category 2	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		TOTAL	XX (XX.XX%)	XX (XX.XX%)	XX (XX.XX%)
		.....			
.....					

Source: Path\Tables.sas (Date-time)

Template Table 4. Continous variables.

			DIALIVE (n=XX)	SOC (n=XX)	TOTAL (n=XX)
Variable 1	Result				
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX
Variable 2	Result				
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX

.....

Source: Path\Tables.sas (Date-time)

Template Table 5. Continous variables by parameter.

Parameter			DIALIVE (n=XX)	SCC (n=XX)	TOTAL (n=XX)
Parameter 1	Result				
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX
	.....				
Parameter 2	Result				
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX
	.....				

Source: Path\Tables.sas (Date-time)

Template Table 6. Continous variables by parameter and time-point.

Parameter	Time-Point		DIALIVE (n=XX)	SCC (n=XX)	TOTAL (n=XX)
Parameter 1	Time-Point 1	Result			
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX
	Time-Point 2	Result			
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX
	.....				
Parameter 2	Time-Point 1	Result			
		N	XX	XX	XX
		Mean	XX.XX	XX.XX	XX.XX
		SD	XX.XX	XX.XX	XX.XX
		SEM	XX.XX	XX.XX	XX.XX
		95% CI Lower	XX.XX	XX.XX	XX.XX
		95% CI Upper	XX.XX	XX.XX	XX.XX
		Minimum	XX.XX	XX.XX	XX.XX
		P25	XX.XX	XX.XX	XX.XX
		Median	XX.XX	XX.XX	XX.XX
		P75	XX.XX	XX.XX	XX.XX
		Maximum	XX.XX	XX.XX	XX.XX
	.....				

Source: Path\Tables.sas (Date-time)