

## PATIENT INFORMATION SHEET

### PART 1

#### Study Title

A multi-centre, randomised controlled study, to evaluate the safety and performance of the DIALIVE device in alcohol related cirrhosis patients with Acute on Chronic Liver Failure (ACLF) versus standard of care (SOC).

#### Introduction

You are being invited to take part in this clinical research study because you have liver cirrhosis and are in need of a treatment for Acute on Chronic Liver Failure (ACLF). Before you make a decision to take part in the study or not, please read this information carefully to find out more about this study. The information below describes the purpose of the study, outlines the visits and procedures, and explains what risks and benefits there are and what would be expected from you.

Please ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

#### Background

The normal liver has many different functions and if it starts to fail, toxins (poisons) can build up to dangerous levels, damaging the liver yet further and affecting other body systems. It is still not clear what causes the rapid progression of ACLF, however the research team believe wide spread Inflammation is thought to play an important role in its progression. Based on this theory, a Liver Dialysis Device (LDD) that can remove endotoxins (poisons that are released by bacteria in the gut that pass into the blood) and dysfunctional (not working) albumin and replace functional (working) albumin may actually slow down the rapid deterioration in liver failure by targeting the immune system.

## What is the purpose of the study?

This study is being sponsored by a company called Yaqrit Limited, who is developing liver disease diagnostics and treatments. The funding for the study is from The European Commission and was awarded as part of a wider programme called ALIVER.

The purposes of this study is to evaluate the safety and performance of a new Liver Dialysis Device (LDD)-DIALIVE. Additionally, data from the study can show if the DIALIVE device improves outcomes for patients with liver failure.

### The Device

The DIALIVE device consists of two types of filters, connected together with standard tubing on a haemofiltration (HF) machine. The combination of the two filters, to remove damaged albumin and endotoxins from your blood, and infusion of fresh albumin at the end of treatment, is the novel (new) approach.

The doctors believe that removal of the endotoxins and replacement of albumin may be beneficial in treating liver failure. The diagram below shows what the device would look like set up.



Prismaflex pump-unit with the DIALIVE device (haemofilters) mounted in front and aside of it.

### ***What will this study do differently?***

The device has been extensively tested in animal models and the results obtained indicate that the device is safe and has potential benefits in liver failure. Both filters (Septex™ Haemodialyser, and oXiris Haemodialyser) are already approved and used separately for kidney dialysis and therefore their safety and performance has already been confirmed. The combination of the two filters is a new approach and as such, has not been tested before for liver patients, which is why you are being asked to take part in this study.

The doctors will use the results of this study to help further guide treatment of patients with your condition. This study will also allow the doctors to check the treatment effect of the DIALIVE device.

## What would taking part involve?

Before deciding if you wish to take part or not in this study your doctor/nurse will explain the purpose of the study to you and provide you with this information sheet, so you can think about the study. If you have any questions, you can call your doctor/nurse or speak to her/him.

It is your choice to take part in this study or not. If you wish to take part, your doctor will first need to check if you are a suitable candidate for the study. Your doctor/nurse will review your medical records to review information about your disease and treatments and to check that you meet the study requirements. If those requirements are met you are happy to take part, and are satisfied with the explanations from your research team, you will be asked to sign a consent form. It is estimated that the consent process will take 15-30 min.

The national local legislation might differ from country to country on the following aspect. For **XXXX** (country) it is mandatory that you, or an appointed member of the family / next of kin, or an appointed physician who is independent from the research group, or a legal representative, decide on your participation in the research OR to stop your participation early. For this study, it is mandatory that you consent to participate in the study by signing the Consent Form; if you decide to involve also another person, then this third person is required to co-sign the Consent Form. If for any reason you would not be able to decide yourself on the continuation or discontinuation of your study participation, then this third person can decide for you. If no third person is identified, then your physician will consider your continued study participation in view of offering at all times the best possible care for you, eventually he will decide on your study discontinuation. If you did lose mental capacity, the research team would approach your appointed consultee to make the decision about your continued involvement in the study or for them to provide agreement to a test or investigation being undertaken.

If you agree to take part in the study, the researchers will ensure that you are eligible before you receive any treatment. You will have screening assessments that will include the following:

- a physical examination
- a review of your medical history
- your weight and height measurements
- a 12-lead electrocardiogram (ECG).
- bloods will be taken to screen you for any infections (Hepatitis B and C, and HIV) if you do not have previous results from samples taken within the 8 weeks prior to screening
- bloods to screen for signs of infection

- standard bloods to check your current liver and kidney functions
- If you are female, a pregnancy test will be done
- The medical team will use these results and your clinical status to score the severity of your disease.

This screening will be done up to 3 days (72 hrs) before you are randomised (Day 0).

Researchers randomise trials because they need to be sure that the results are correct and there is no bias that could distort the results. In this study there are two treatments, one group has the new treatment with the device (DIALIVE) and the other has the standard treatment they would receive if they were not in the study. People having the standard treatment are called the control group. A randomised study that has a control group is called a randomised controlled study.

If you are randomised to standard treatment whether you are admitted to the ICU or not, the treatments you receive will be decided by your doctor, on the basis of what he considers to be the best clinical decision for you at this time.

If you are randomised to receive treatment with DIALIVE, treatment will be delivered in a high dependency setting (HDU), Intensive Care Unit (ICU) or Transplant unit (depending on where your hospital normally would do the dialysis). All other treatments that you receive at this time will be as per normal clinical practice and the same as standard treatment.

### DIALIVE Group

During the treatment period you will receive up to a maximum of 3 days treatment over a 10-day window period.

For the study we would ideally like you to have at least 3 consecutive days of treatment (a treatment cycle) during the 10 days. However at least 8 hours per day over 3 consecutive treatments would be considered acceptable (a successful treatment cycle). If you are unable to complete 3 consecutive days of treatment (a treatment cycle) over the 10 day window period you will be withdrawn from the study. Also if you are unable to start treatment by the end of study day 1, you will be considered a screening failure and withdrawn from the study. You may be eligible to be rescreened at a later date.

For the DIALIVE treatment you will need to have venous access if you do not already do so. This involves a small tube (catheter) being inserted into a vein either in your neck or your groin. This will be undertaken by your doctor. You will then be connected to the DIALIVE device for a maximum of 10 hours per day for up to three consecutive days. Routine monitoring of you during these treatment sessions will be undertaken as per normal hospital practice.

Before each treatment the researchers will do a physical examination, check your vital signs, an ECG and repeat the blood tests to make sure that you are still eligible for the treatment.

### Control Group

If you are randomised to the standard of care group you will receive the same treatment and assessments as the DIALIVE group; only you will not have treatment with DIALIVE.

Both groups will be assessed for the purposes of the study on day 1, day 2 (only DIALIVE group), day 3, day 5, day 10, day 14 and day 28.

On day 1 the researchers will assess you during the day for: adverse events, any other medications you may be given, undertake specific liver function scores, kidney function tests, as well as a test of your level of confusion or altered state of consciousness. They will also look for markers of other organ function in your blood and urine. For the DIALIVE patients these tests will be performed before the DIALIVE treatment commences which could be straight after randomisation on day 0. If this occurs the Day 1 assessments will not be repeated.

In total it is anticipated that the volume of blood needed for the laboratory tests will be 15 ml (equivalent to 3 teaspoons) for the screening tests and 15 ml (equivalent to 3 teaspoons) for the test procedures undertaken on day 1, day 2 (only DIALIVE group), day 3, day 5, day 10, day 14 and day 28.

Other than DIALIVE, all the treatments in the study will be part of your care and so will take place whether or not you are randomised to DIALIVE. The routine blood samples collected will be sent and analysed by your local hospital, as per your normal standard of care.

Blood and urine samples for biomarkers, and a sample of dialysate (the fluid used on the dialysis machine) and ultrafiltrate (the waste fluid collected during the dialysis treatment) will be collected by each site and sent to a Central Biobank Laboratory at the Royal Free Hospital in the UK. The laboratory is licenced and strictly controlled under the UK Human Tissue Authority (HTA). Your samples will be labelled with your study ID number. You will not be identified in person. No later than 5 years after the end of the study, the samples will be destroyed in accordance with the standard procedures of the Biobank.

When the laboratory results of the blood samples are available they will be documented in your medical records as normal. Only laboratory results that are part of the study will be collected and the data will be made anonymous i.e. removing any personal information such as name.

If you decide not to continue taking part in this study, any data that has been obtained up to the point of withdrawal as part of the study may be used as part of the research study if you consent for us to do so, however you have the right to ask for any data or samples taken to be destroyed and not used. Withdrawing from the study will not affect your future medical care in any way.

## **Who is invited to take part?**

To take part in this study you should be aged from 18 to 81 years and diagnosed with ACLF grade 1/ACLF grade 2 or grade 3a on the background of alcoholic cirrhosis. You should be expecting to receive treatment for ACLF. Thirty patients are required to complete the study across different clinics across Europe..

## **What are the possible benefits of taking part?**

It is not known if you will personally benefit from this research but we hope that it will allow us to develop a new way of treating patients with liver failure.

## **Do I have to take part?**

No, it is important to understand that your decision to take part in this research study is completely voluntary. If you do not wish to take part, or if you wish to withdraw your consent after starting the study, this will not affect your medical care in any way. If you decide to take part, you will be asked to sign and date a consent form document and you will be given a copy to keep.

## **Expenses and Payments**

You will not receive any payment for taking part in this study. Arrangements to reimburse you for any travel costs or inconvenience can be made; you should speak to your doctor about this.

## **What are the possible disadvantages and risks of taking part?**

Most of the treatments and assessments you will receive/undergo will be standard of care (i.e. you will receive this anyway). Each centre will provide this standard of care in accordance with their own policies for treating patients with ACLF. Your investigator will determine what is optimal standard of care for you.

If you are randomised to receive treatment with the DIALIVE device, you will receive this on top of your standard of care.

The risks associated with treatment using the DIALIVE device are the same risks associated with standard haemodialysis (HD) and haemofiltration (HF), which are well established and understood.

Similarly the risks associated with intravenous albumin delivery for replacement of blood loss are well known. Both procedures are part of the normal standard of care.

These have been carefully considered by the research team and the following steps have been taken to reduce the risks to a minimum:

Blood loss - dialysis is well established, both types of dialysis filters are approved for their use and have a proven safe track record. The combination of the two filters has been tested in a pre-clinical setting and has been shown to be safe. You will be carefully monitored by the research staff during your dialysis.

Air Embolism (air bubble trapped in a blood vessel) or Thromboembolism (blood clot inside a blood vessel) - The approved dialysis machine control unit (Prismaflex machine) monitors for flow rates that match normal blood flow rates, the machine also checks for air ingress and any blood loss, so these are unlikely.

Risks to your blood (mechanical and chemical breaking of the blood cells, changes in white blood cells, clotting, inflammation) – The DIALIVE devices are compatible with blood and have been approved for other indications than for liver dialysis; the complaint data at the manufacturer’s site do not identify this risk as being a problem for patients.

Hypotension: extra precautions and guidelines were provided to the medical staff to diagnose the potential risk of hypotension and to correct for this situation if present

Contamination or misuse by staff – the DIALIVE devices are sterilized and all packaging is single use only, all staff will be carefully trained staff who are approved for the study. The equipment is to be used only for this study by these trained staff.

The following elements are addressed in the clinical Investigation to mitigate the risk of use:

The liver dialysis device is only being used by a few, selected, qualified and trained investigators who are already very familiar with haemodialysis and filtration techniques.

The study includes further monitoring requirements: liver function, haematology, coagulation factors, platelet count, cardiovascular function, cerebral function, renal function, pulmonary function; albumin function, immune function. So you will be closely monitored at all times.

The study is designed to minimize the risk of making your symptoms worse, and it is in line with standard of care. There are no extra procedures (other than DIALIVE treatment) whilst there are multiple health checks to monitor your condition.

## **What happens when the research study stops?**

When the research study is complete your doctor/nurse will continue to treat you as she/he would if you were not taking part in the study.

## **What if there is a problem?**

Any complaint about the way with which you have been dealt during the study or any possible harm you might have suffered will be addressed. The detailed information relating to this is given in part 2 of this information sheet.

## **Will my taking part in the study be kept confidential?**

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2 of this information sheet.

This completes Part 1

*If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.*

## **PATIENT INFORMATION SHEET**

### **PART 2**

#### **What if relevant new information becomes available?**

If new information is discovered during the course of our research that may affect you in any way the research doctor will discuss with you.

#### **What will happen if I do not want to carry on with the study?**

Taking part in this study is your choice. You can choose to participate in this study and then you can change your mind. Your choice will not influence the medical care that you receive. The study doctor may decide to remove you from this study without your permission for different reasons:

- If you do not follow the procedures required by the study.
- If the study procedures are found to be unsafe.
- If the study procedures are found to be ineffective.
- If the study is closed.

It is important that you tell the study doctor if you want to withdraw from the study, so that they can plan an appropriate visit to discuss withdrawal and follow up.

#### **What if there is a problem?**

##### **Complaints**

If you have a concern about any aspect of this study, you should ask to speak with the research staff who will do their best to answer your questions. If you remain unhappy and wish to complain formally, you can do this through the local Complaints Procedure of your hospital. Details can be obtained from your local hospital. The sponsor has insurance in place to cover any possible compensation arrangements if you are harmed by taking part in this research project. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal hospital complaints mechanisms will be available to you.

#### **Involvement of the General Practitioner/Family Doctor/Other Healthcare Practitioner**

Your general practitioner/family doctor will be notified of your involvement in the study and the care you received as part of the standard notification provided by your local hospital.



## How will you keep my information confidential?

During this study your identity will be protected as defined under the new data protection laws that are implemented as of 25 May 2018 in all the European countries (General Data Protection Regulation – GDPR). In the context of the biomedical research in which Yaqrit Ltd is asking you to participate, your personal data will be collected and processed anonymously to allow analysis of the results in order to achieve the objective of the research. Your treating physician does have access to your Medical Dossier.

As added protection to your identity, a study number will be given to you. This number will be used for further study participation and the transfer of information relating to the study.

Data will be recorded onto an electronic case report form (eCRF) that contains all information relevant to the study. Only authorised personnel at each centre may access the eCRF at each site. The eCRFs will be kept securely by the sponsor (Yaqrit Limited) until the end of the study, at which time they will be archived in a secure archiving facility until such time as they can be destroyed (normally at least 5 years after the end of the study, however Yaqrit propose to retain the study information for 20 years in line with the policies of Yaqrit).

Only information needed for this study will be collected and will be sent to sponsor for analysis. All information will be retained for the duration of the study and will be kept strictly confidential.

As part of the Standard of Care and follow-up of your disease your name and personal details will be documented in the medical records, according to the applicable regulations of the health care system.

For the purpose of the study your identity will remain anonymous and neither your name nor personal details will be registered.

All data collected during the study will be anonymous. Any laboratory results will be handled anonymously.

If you consent to take part in the study you also consent to handling of the study data.

If you wish to stop taking part in the study and withdraw, further collection of information about you will be stopped. However, already collected and anonymised data will be used and handled together with the other collected anonymous data.

According to the applicable national laws on data protection you have the right to request and check the existing information about you and have any potential errors corrected. To ensure that the study is conducted properly, authorised representatives from Yaqrit Limited and their collaborators (such as study monitors) may have to access your medical records. Ethics Committees, and applicable national or international European regulatory authorities may also have to access your hospital records and data collected. This is necessary to ensure that the study is carried out according to the approved study plan, and that data are correctly recorded.

Access to your medical records can only be given after your approval has been obtained which will be asked for when you sign the study consent form.

The information about you will be stored and handled in a database and may be transferred to another country within the European Union (EU) (included United Kingdom) to accomplish this. The results from the study may be published in reports, scientific journals or will be used as a basis for future studies and/or marketing purposes. All information will be anonymous, which means that the data about you will never be associated with you as a person in the overview of the results. All handling, processing and transfer of data will be carried out according to national laws listed above.

### **Legal representative**

The clinical trial started in 2016 in UK and was broadened to include different European study centers as of 2017. In the event of UK leaving the European Community (Brexit), the Medical Device Regulation requires non-EU based manufacturers to be represented in a member state. YAQRIT Ltd, sponsor of the DIALIVE trial, has appointed the CRO FAKKEL as the legal representative for the duration of the study.

Contact details:

FAKKEL-bvba  
Groenendael 43/001  
3400 Landen, Belgium  
Contact person : Jaak Minten  
Telephone: +32-475-923-149  
Fax: +32-11-37-53-27

### **What will happen to any samples I give?**

The routine blood samples collected will be processed and analysed by your local hospital, as per your normal standard of care. Samples for endotoxin activity will also be processed locally.

Blood and urine for biomarkers (including endotoxin and albumin),, and a sample of dialysate and ultrafiltrate will be collected in each participating hospital for central analysis in the Biobank Laboratory held at the Royal Free Hospital in the UK. Once there, they will be analysed, some may be analysed in a batch with other research study samples and stored in a freezer until the end of the study. This means that if there are any problems with the analysis of a blood sample the analysis can be repeated. All laboratory results will be recorded on a properly validated computer system and entered onto a secure database.

At all times you and the samples will only be referred to by their unique research study number and their initials. They will never be referred to by your name or hospital number.

Once the study is completed and the results have been reported any remaining blood samples will be destroyed after maximum 5 years by the laboratory in accordance with the standard procedure of the Biobank.

## **What will happen to the results of the research study?**

The results of this study will be analysed and submitted to the regulatory authorities for the purpose of obtaining a CE mark for the device. The results of this research will be published in a journal once the study is completed. The results from all of the patients who take part will be pooled together so that you and your results will not be identifiable in the final report/publication.

## **Who is organising and funding the research?**

The funding for this study will be via the ALIVER project (EU-grant number 733057). ALIVER is funded by the European Commission's Horizon 2020 programme.

The sponsor of this study is:

Yaqrit Ltd, Labs Triangle, 3rd Floor, Triangle Building Stables Market,

Chalk Farm Road, London NW1 8AB United Kingdom

## **Who has reviewed the study?**

All research is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has received formal approval from specific Ethics Committees and national medical authorities before the study commenced in each respective country. Any amendment made to the study will also require country specific approvals in accordance with national legislation.

## **FURTHER INFORMATION AND CONTACT DETAILS**

If you have any questions about the study, your rights as a participant, study-related procedures or if you need to seek medical help for any other complaint, please contact:

*Responsible Doctor: Dr xx*

*Phone: xx*

*Responsible Nurse: Xx*

*Phone: xx*

**Thank you for taking the time to read this information sheet. Please ask the research doctor or nurse any further questions if you need further information.**

[HOSPITAL HEADED PAPER]

<b>Study Title:</b> A multi-centre, randomised controlled study, to evaluate the safety and performance of DIALIVE in alcohol related cirrhosis patients with Acute on Chronic Liver Failure (ACLF) versus standard of care (SOC).
<b>Protocol No.:</b> YAQ-002 V6.0 15 January 2019
<b>Sponsor Details:</b> Yaqrit Ltd, Labs Triangle, 3rd Floor, Triangle Building Stables Market, Chalk Farm Road, London NW1 8AB United Kingdom
<b>Investigator Name:</b> Dr <b>xx</b>
<b>Patient Identification Number:</b> .....

**CONSENT FORM**

*Please initial in each box below*

I confirm that I have <u>read</u> and understand the information given orally and in writing on the Patient information Sheet Version 6.0 dated 10 October 2019 for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.	Pt initials
I understand that my taking part is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected.	Pt initials
I have appointed a representative to act in my best interest should I loose mental capacity during my involvement in the study. My representative may agree to my withdrawal from the study following discussion with the research team.	Pt initials <input type="checkbox"/> N.A.
I understand that relevant sections of my medical notes and data collected during the study, may be looked at by responsible individuals from Yaqrit Ltd or other workers on behalf of Yaqrit Ltd, from ethics committees or regulatory authorities or from the local hospital, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records for as long as the Sponsor requires it for the study.	Pt initials
I understand that specific blood, urine, dialysate and ultrafiltrate samples will be transferred to the central Biobank in the UK for analysis. I agree to such transfer of samples.	Pt initials
I understand that the data from this study may be used for publications or presentations which may be for marketing purposes. I also understand that I will not be identified through any material used in such instances.	Pt initials

[HOSPITAL HEADED PAPER]

I confirm that I have received a copy of the entire Patient information Sheet and this signed consent form.	Pt initials
I agree to take part in the above study.	Pt initials

\_\_\_\_\_  
Print Name of Participant                      Date                      Signature of Participant

If applicable:

\_\_\_\_\_  
Print Name of Representative                      Date                      Signature of Representative

I hereby declare that I have informed the above study participant verbally and in writing about the nature, significance, implications and risks of the study named above and that **the individual has not been coerced into giving consent**. A copy of the Information Sheet and this signed Consent Form has been provided to the participant and one original has been filed in the site file.

\_\_\_\_\_  
Print Name of person                      Date                      Signature of person  
obtaining Consent                      obtaining consent