The Swedish study of liver transplantation for non-resectable, non-ablatable colorectal liver metastases (SOULMATE)

A randomized controlled, open-label, multicentre study evaluating if Liver Transplantation with liver grafts, primarily from extended criteria donors, not utilised for approved indications, increases Overall Survival in patients with non-resectable, non-ablatable isolated liver metastases from colorectal cancer, in comparison with Best established treatment.

Protocol for a Phase III Study

Sponsor: Transplant Institute
Sahlgrenska University Hospital
SE-413 45 Gothenburg
Sweden

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1 SIGNATURES

1.1 SPONSOR'S SIGNATURE

1.1.1 Protocol Author

Author:

Signature:..... Date:.....

Per Lindnér, Transplant Institute (YYYY-MM-DD)

Sahlgrenska University Hospital

SE-413 45 Gothenburg, Sweden

1.1.2 Protocol Approved By:

Head of clinic:

Signature:..... Date:.....

Claes Jönsson, Område 5 (YYYY-MM-DD)

Sahlgrenska University Hospital

SE-413 45 Gothenburg, Sweden

1.2 CO-ORDINATING INVESTIGATOR:

Signature:..... Date:.....

Veronica Reivell (YYYY-MM-DD)

Sahlgrenska University Hospital

SE-413 45 Gothenburg, Sweden

1.3 PRINCIPAL INVESTIGATOR'S SIGNATURE

1.3.1 Principal Investigators

1.3.2 Co-Investigators

1.3.3 Investigator's signature

I have read all pages of this clinical study protocol for which Transplant Institute, Sahlgrenska University Hospital, Gothenburg is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH GCP guidelines. I will also ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol, and the ICH GCP guidelines, to enable them to work in accordance with the provisions of these documents.

Signature: .....

Date

Printed Name: .....

2 LIST OF ABBREVIATIONS AND KEY TERMS

2.1 LIST OF ABBREVIATIONS

Abbreviations	Description of abbreviations
AE	Adverse Event
BET	Best established treatment
COPD	Chronic obstructive pulmonary disease
CR	Complete remission
CT	Computed tomography
DCD	Donation after Circulatory Death
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
Ltx	Liver transplantation
MRI	Magnetic resonance imaging
OS	Overall Survival
PLT	Platelet count
QALY	Quality-adjusted life year
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analyses Plan
WBC	White Blood Cell count

2.2 LIST OF KEY STUDY TERMS

Terms	Definition of terms
Baseline	1) Observed values/findings, which are regarded as calibrated zero status in the present study, 2) Time when 'Baseline' is observed.
Investigational period	Period of time where major interests of protocol objectives related to defined endpoints are observed, and usually where the test drug or comparative drug (sometimes without randomization) is given to a subject, and continues until the last observation after completing administration of the test drug or comparative drug.
Investigator	A physician responsible for the conduct of the clinical trial at a trial site. If a team of individuals at a trial site conducts a trial, the investigator is the responsible leader of the team.
Randomization	Action to allocate a subject to the treatment group or treatment cohort. Depending on the type of rules for handling for study drugs, 'Randomization' is usually executed just before entering the 'investigational period'
Randomization/ Treatment number	Number assigned to each subject who has completed ALL screening assessments successfully at baseline and is willing to be included in the study.
Randomized subject/ Subjects given the test drugs	Subjects randomized to the treatment group (test drug group) or control group, and those received open label study treatment.
Source data	All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).
Source documents	Original documents, data, and records including source data.
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Withdrawal	Subject enrolled but did not complete the study for any reason.

3 SYNOPSIS

Title of Study	**The Swedish Study of Liver Transplantation for Non-resectable, Colorectal Liver Metastases** - A randomized, controlled, open-label, multicentre study evaluating if Liver Transplantation with liver grafts, primarily from extended criteria donors, not utilised for approved indications, increases Overall Survival in patients with non-resectable, non-ablatable isolated liver metastases from colorectal cancer, in comparison with Best established treatment.
Planned Study Period	Study period: 2020-02-01----2026-02-01
Study Objective(s)	To evaluate if the addition of liver transplantation, primarily utilizing liver grafts from extended criteria donors, not utilized for approved indications, to conventional treatment of non-resectable CLM increases overall survival compared to Best established treatment. **<u>Primary objective:</u>** • Five-year overall survival from randomisation **<u>Secondary objectives:</u>** • Two-year overall survival from randomisation • Median overall survival • Disease free survival • Hepatic and extrahepatic recurrence • Progression free survival • Health economic evaluation • Quality of Life • Primary graft loss
Planned Total Number of Study Centers and Location	Planned number of centres: 6 Number of performing centres: 2
Design and Methodology	A prospective, multi-centre randomized, open-label study. Active follow-up will be performed for 5 years. Patients will be randomized after diagnoses of liver metastases to one of the following treatment arms: **A. Liver transplantation + Best established treatment** **B. Best established treatment:** The treating physician will together with the patient decide the treatment, but the patient will not undergo liver transplantation
Number of Subjects Planned	45 patients will be included in the study. Enrolment will continue until the required sample size has been randomized. An enrolment time of 60 months is expected.

Main Selection Criteria	**Inclusion Criteria:** • Patients with non-resectable, non-ablatable liver metastases from colorectal adenocarcinoma. • Male or female 18 years or above. • Primary tumour removed with a standard oncological resection. Histologically verified adenocarcinoma from colon or rectum, with safe margins. Adequate TNM-staging. • Liver metastases measurable by MRI or CT according to RECIST version 1.1 Imaging within 4 weeks prior to inclusion. • No present or previous signs of extrahepatic metastatic disease or local recurrence according to o MRI or CT of abdomen o CT of thorax o whole body PET/CT scan. Previous resection of local relapse or non-hepatic metastasis more than 2 years ago can be accepted. • A colonoscopy performed within the last 12 months in order to exclude existing CRC tumours. • ECOG performance status of 0 or 1. • Satisfactory blood tests: Hb ≥ 90 g/L (transfusions are permitted to achieve baseline hemoglobin level),WBC>3,0x10^9/L, Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, PLT >75, Bilirubin<2 x upper normal level, ASAT, ALAT<5 x upper normal level, Calculated Creatinine clearance ≥ 50 mL/min(MDRD). • At least 2 months of first or second line chemotherapy for liver metastatic disease with PR or CR according to RECIST 1.1, or SD with a minimum of 10% relative decrease in sum of diameter of target lesions at any evaluation scan (taking as reference the baseline evaluation of the ongoing treatment line)(SD-10%). If the response is SD-10% at the first line, then it is necessary with SD-10% also at second line. • One year or more from the initial CRC diagnosis to the date of inclusion in the study. • Patient accepted for transplantation by a national study board. • Signed and dated written informed consent before the start of specific protocol procedures. Exclusion Criteria: • Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within seven days prior to the start of study.

	• Weight loss >10% the last 6 months. • Other malignancies within the last 5 years, except CRC and low risk tumours such as basaliomas. • If a patient has pathological lymphatic nodules in the abdomen, a staging operation with PAD from the nodules with no signs of tumour cell involvement has to be performed before inclusion. • B-RAF mutation in primary tumour. • MSI-H in primary tumour. • Progressive disease PD at ongoing treatment line defined by RECIST 1.1. • Previous organ transplantation. • Liver metastases larger than 10 cm.
Discontinuation Criteria	Subjects must be discontinued from the study for the following reasons: 1. Inappropriate enrolment (violation of Inclusion / Exclusion Criteria) 2. Withdrawal of consent

4 INTRODUCTION

4.1 BACKGROUND

Surgical treatment of liver metastases from colorectal cancer is the only treatment option with curative potential; however, only about 15% to 20% of the patients seen at major hospitals are candidates for surgical resection. The majority of patients undergoing liver resection relapse and 5-year survival is about 30% to 40% in most studies, but can be as high as 58% (Abdalla, 2004). Most patients with colorectal liver metastases (CLM) have non-resectable disease and these patients have poor prognosis and only about 10% survive up to 5 years. Standard treatment for patients with non-resectable liver-only metastases is palliative chemotherapy.

In a prospective study of liver transplantation (Ltx) for non-resectable CLM a 5-year overall survival rate of 60 % have been shown. (Hagness, 2013). Compared with chemotherapy in a similar cohort of CRC patients with liver-only disease included in a first-line chemotherapy study, the NORDIC VII study, liver transplantation resulted in a marked increased OS (Dueland, 2015) even though disease-free survival were similar in both groups. Liver transplantation is therefore considered as a potential new treatment option for this patient category, but no randomized study has so far been performed (Gorgen, 2018).

5 STUDY OBJECTIVES AND DESIGN

5.1 STUDY OBJECTIVES

To evaluate if the addition of liver transplantation primarily utilizing liver grafts from extended criteria donors not utilized for approved indications to conventional treatment of non-resectable, non-ablatable CLM increases overall survival compared to Best established treatment.

Primary objective:

- Five-year overall survival from randomization

Secondary objectives:

- Two-year overall survival from randomization
- Median overall survival
- Progression-free survival
- Hepatic progression-free survival
- Extrahepatic recurrence-free survival
- Quality of Life
- Health economic evaluation
- Rate of primary non-function liver grafts
- Rate of donor-derived malignancies

Study Design

A prospective, multi-centre, randomized controlled, open-label study. Patients will be followed actively according to this protocol for five years at each study centre.

6 STUDY POPULATION

6.1 SELECTION OF STUDY POPULATION

It is expected that the percentage of subjects who reach the endpoint of overall survival after 5 years will be 55 % in the study group and 10 % in the control group. Based on this assumption, 45 subjects are planned to be randomized to the two treatment groups in a 5:4 ratio (Ltx:BAC) to achieve 80% power for the superiority comparison (Fisher´s exact test) of the primary endpoint between the two treatment groups, with a 2-sided type I error of 5% and allowing for a 20 % drop-out rate in the Ltx-group. An enrolment time of 60 months is expected.

6.2 INCLUSION CRITERIA

Inclusion Criteria:

- Patients with non-resectable, non-ablatable liver metastases from colorectal adenocarcinoma.
- Male or female 18 years or above.
- Primary tumour removed with a standard oncological resection. Histologically verified adenocarcinoma from colon or rectum, with safe margins. TNM adequate staging.
- Liver metastases measurable by MRI or CT according to RECIST version 1.1 Imaging within 4 weeks prior to inclusion.
- No present or previous signs of extrahepatic metastatic disease or local recurrence according to
    - MRI or CT of abdomen
    - CT of thorax
    - whole body PET/CT scan.

  Previous resection of local relapse or non-hepatic metastasis more than 2 years ago can be accepted.
- A colonoscopy performed within the last 12 months in order to exclude existing CRC tumours.
- ECOG performance status of 0 or 1.
- Satisfactory blood tests: Hb ≥ 90 g/L (transfusions are permitted to achieve baseline hemoglobin level),WBC>3,0x10^9/L, Absolute neutrophil count (ANC) ≥ 1.5 × 10^9/L, PLT >75, Bilirubin<2 x upper normal level, ASAT, ALAT<5 x upper normal level, Calculated Creatinine clearance ≥ 50 mL/min(MDRD).
- At least 2 months of first or second line chemotherapy for liver metastatic disease with PR or CR according to RECIST 1.1, or SD with a minimum of 10% relative decrease in sum of diameter of target lesions at any evaluation scan (taking as reference the baseline evaluation of the ongoing treatment line)(SD-10%). If the response is SD-10% at the first line, then it is necessary with SD-10% also at second line.
- One year or more from the initial CRC diagnosis to the date of inclusion in the study.
- Patient accepted for transplantation by a national study board.

- Signed and dated written informed consent before the start of specific protocol procedures.

6.3 EXCLUSION CRITERIA

SUBJECT WILL BE EXCLUDED FROM PARTICIPATION IF ANY OF THE FOLLOWING APPLY:

- Pregnant or breast-feeding patients. Women of childbearing potential must have a negative pregnancy test performed within seven days prior to the start of study.
- Weight loss >10% the last 6 months.
- Other malignancies within the last 5 years, except CRC and low risk tumours such as basaliomas.
- If a patient has pathological lymphatic nodules in the abdomen, a staging operation with PAD from the nodules with no signs of tumour cell involvement has to be performed before inclusion.
- B-RAF mutation in primary tumour.
- MSI-H in primary tumour.
- Progressive disease PD at ongoing treatment line defined by RECIST 1.1.
- Previous organ transplantation.
- Liver metastases larger than 10 cm.

6.4 DISCONTINUATION CRITERIA FOR INDIVIDUAL SUBJECTS

The subject is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a subject's involvement in the study at any time if the subject's clinical condition warrants it.

Discontinuation Criteria for Individual Subjects:

1. Inappropriate enrolment (violation of Inclusion / Exclusion Criteria)
2. Withdrawal of consent

The reasons for discontinuation should be recorded in the eCRF (Electronic Case Report Form).

Patients discontinued from the study will be taken care of and followed at the discretion of the treating physician. After the 60 months of planned follow-up, patients will be taken care of and followed at the discretion of the treating physician.

6.5 PREMATURE TERMINATION OF THE STUDY

The sponsor has the right to terminate or change the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer feasible. If such action is taken, the reasons for terminating the trial must be documented in detail.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subjects changes markedly.
- The sponsor considers that the trial must be discontinued for safety reasons
- An interim analysis or results of other research show that one of the trial treatments arms is superior or inferior to another.
- Due to futility

The trial will be temporarily stopped if two post-operative deaths within 30 days of liver transplantation occur. The causes of death will then be analysed in detail and discussed within the study group, before any final decision about continuing or stopping the trial. In the case of a prematurely stopped trial, the patients will be taken care of and will be followed at the discretion of the treating physician.

7 STUDY TREATMENTS

7.1 DESCRIPTION OF STUDY TREATMENTS

Patients will be randomized to one of the following treatment arms:

A. Liver transplantation

Patients subjected to Ltx will during the waiting time receive individualized chemotherapy, with the aim to avoid progressive disease and side effects that make them not transplantable.

Patients will be treated with Ltx at Sahlgrenska University Hospital, Gothenburg or Karolinska University Hospital, Huddinge.

If possible, patients randomized to Ltx should be treated within 12 weeks after randomization.

If the patients tumour recurs outside the liver before Ltx, they will be treated with Best established treatment and not undergo Ltx.

If they progress only within liver they continue to be transplantable until they are deemed technically not transplantable by the transplant surgeon.

Choice of donor livers

As Ltx for CRC is not an established indication, study patients will primarily receive liver grafts from extended donors, not used on the ordinary waiting list, so the waiting time for patients with already established indications isn´t prolonged.

The following livers could be accepted within the study:

- Donors with a history of malignancy with an intermediate to high risk of transmission.
- Donors with a present malignancy with a low to intermediate risk of transmission.
- Donors with recent drug use.

- Donors with active hepatitis C and with preserved liver function that are not utilized for patients on the general waiting list. Donors with core-positive and HBsAg-positive hepatitis B with preserved liver function
- Donor livers, including DCD-donors with no suitable recipient on the ordinary waiting list within the Scandiatransplant area.

In case of an early technical complication or delayed graft function in a study patient, with a need for an early retransplantation, a similar procedure as for patients on the ordinary waiting list with a kind request for liver could be applied. If such a complication occurs in this study, a thorough analysis of the causes is warranted immediately.

Choice of donors with a history of malignancy
The acceptance of donors with a history of malignancy is based on the risk assessment that is made in Guide to the quality and safety of organs for Transplantation (EDQM 2016).

Donors with a history of cancer that is considered minimal to intermediate risk for transmission are accepted as donors.

Donors with a high risk for transmission can be accepted by the transplant surgeon in the individual case.

Example of high-risk donors that could be accepted:

- Breast cancer with CR and more than 5 years follow-up with a favourable initial stage.
- Colo-rectal cancer with a CR and more than 5 years follow-up.
- Intraprostatic tumours with Gleason score of 7 or less at donation
- Brain tumours WHO class IV (glioblastoma, gliosarcoma) at donation

Donors with an unacceptable risk for transmission defined according to EDQM should never be accepted.

B. Best established treatment

The treating physician will together with the patient decide the treatment. All available treatments as well as other experimental treatments are tolerated, however no cross-over to Arm A will be allowed.

7.2 CONCOMITANT MEDICATIONS

Immunosuppression
After liver transplantation patients will receive the standard immunosuppressive protocol at the institution.
The protocol consists of:

- Basiliximab
- Tacrolimus, aiming at a concentration of 5-8 ng/ml.
- Mycophenolate mofetil.
- Steroids will be used in the perioperative phase but will after that be withdrawn.

Tacrolimus and/or Mycophenolate mofetil should after at least 4-6 weeks be replaced with Everolimus.
The dosing will be individualized.

Anti-infective medication
After liver transplantation patients will receive standard anti-infective prophylaxis including Sulfametoxazole-trimetoprim and Valgancyklovir.

8 TREATMENTS AND EVALUATION

8.1 EFFICACY ASSESSMENTS

The subjects will be followed for five years. Study visits will be at each centre and performed at baseline and after 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 42, 48, 54 and 60 months. The visit window is +/- 2 weeks up to 36 months and +/- one month after that.

At the above-mentioned visits the following mandatory tests will be performed:

1. MRI of the liver and CT of the thorax or CT of the thorax and abdomen.
2. EQ5D-3L
3. Blood samples (Hb, WBC, CEA, PLT, PK-INR, ASAT, ALAT, ALP, Bilirubin, and Creatinine)
4. Tacrolimus and/or everolimus concentrations if they are liver transplanted
5. Plasma samples for liquid biopsies.
6. Any further examinations at the discretion of the treating doctor

EORTC QLQ-C30 and QLQ-LMC21 will be filled in at baseline and at 3, 6, 12, 18, 24, 36 and 60 months.

Participating study sites will store tissue samples at the time of transplantation as well as blood samples before and after the transplantation from patients to enable future translational studies regarding metastatic growth patterns in liver metastasis, resistance to chemotherapy, targeted therapies and pattern of cfDNA in plasma. Samples will only be stored in existing biobanks and no new biobank will be created specifically for this study.

8.2 SAFETY AND TOLERABILITY

The subjects will be followed for 5 years. Study visits will be at each centre and performed according to the schedule described in 8.1

8.2.1 Adverse Events (AEs)

AEs are defined as any undesirable experience, including abnormal laboratory results, occurring to a subject during the study, whether or not considered related to the experimental intervention. **AEs will not be reported.**

8.2.2 Serious Adverse Events (SAEs)

A SAE is any medical occurrence that:

- Results in death
- Is life threatening (an event in which the subject is at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe)
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly, or birth defect
- Requires inpatient hospitalization or leads to prolongation of hospitalization
- Other medically important events

8.2.2.1 Recording of SAEs

SAEs will be reported for both treatment arms.

- Primary non-function of liver grafts and donor-derived malignancies could be attributed to the utilization of marginal liver grafts and should be reported as SAEs.

Events that are commonly related to cancer disease are exempted from SAE reporting. For this reason, the following events should not be reported:

- Death, if due to progression of the cancer
- Progression of disease
- Inpatient hospitalization if due to expected cancer morbidity, for example:
    - Weight loss
    - Fatigue
    - Electrolyte disturbances
    - Pain management
    - Anxiety
    - Admission for palliative care
    - Planned surgical procedures

8.2.2.2 Reporting of SAEs

The Investigator should complete and submit a SAE Worksheet to the principal investigator of the study by fax (031-413440), KPE Transplantationscentrum SU/Sahlgrenska) immediately (within 24 hours of awareness or at the earliest possible time point). Full details of the SAE should also be recorded in the subject's medical records and in the eCRF.

The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the treatment
- Identifiable details of reporter/Investigator

The Data Monitoring Committee (DMC) will perform efficacy and safety analyses during the study and can recommend discontinued inclusion in the study to the steering group.

9 RISK-BENEFIT EVALUATION

Liver transplantation is a major surgical procedure with associated risks. In Stockholm and Gothenburg the procedure was implemented in the 1980s. At our institutions the overall 5-year survival is 80-85% (Fosby 2015).

In this study we hope to reach a 5-year survival that is above 50% based on the results from the Norwegian study where most patients recurred in their disease but the 5- year survival was almost 60%.

A higher risk for transmission of cancer can be accepted in this study as all patients have metastatic cancer at inclusion and a poor prognosis with conventional treatment. We estimate the 5-year-survival to be not higher than 10 % with Best established treatment.

10 TERMINATION OF THE CLINICAL STUDY

Study end is defined as date of the last visit of the last subject participating in the study.

11 STATISTICAL METHODOLOGY

The Transplant Institute, Gothenburg will be responsible for all statistical programming and analysis, as well as quality control and validation of programming and statistical analysis. The responsible biostatistician will coordinate the statistical analysis.
A detailed description of all the statistical analyses of all efficacy and safety variables together with an overview of tables and figures will be given in a separate Statistical Analysis Plan (SAP). The SAP will be finalized before the database of the study is locked. Any deviations from the SAP will be justified in the clinical study report.

11.1 SAMPLE SIZE

It is expected that the percentage of subjects who reach the endpoint of overall survival after 5 years will be 55 % in the study group and 10 % in the control group. Based on this assumption, 45 subjects are planned to be randomized to the two treatment groups in a 5:4 ratio (Ltx:BET) to achieve 80% power for the superiority comparison (Fisher´s exact test) of the primary endpoint between the two treatment groups, with a 2-sided type I error of 5% and allowing for a 20 % drop-out rate in the Ltx-group. An enrolment time of 60 months is expected.

11.2 POPULATIONS OF ANALYSIS

The primary analysis of efficacy data will be based on the Intention To Treat (ITT) population. Patients will be analysed for efficacy according to their randomized treatment. The per protocol (PP) population will be used to assess the robustness of the primary analysis result.

11.3 DEMOGRAPHICS AND OTHER BASELINE CHARACTERISTICS

Subject demographics and baseline characteristics will be analysed and summarized using descriptive statistics on a group base according to randomization.

11.4 EFFICACY ANALYSIS

11.4.1 Primary Objective

Five-year overall survival from randomization.

11.4.2 Secondary Objectives:

1. Two-year overall survival from randomization.

2. Median overall survival

Defined as time from randomization to death and analysed using Kaplan-Meier and the log-rank test.

3. Progression-free survival

Defined as time from randomization to progress of existing lesions, or appearance of new lesions, within the liver according to RECIST criteria (version 1.1) using CT or MRI and analysed using Kaplan-Meier and the log-rank test.

4. Hepatic progression-free survival

Defined as time from randomization to progress of existing lesions in the liver, or appearance of new lesions in the liver, according to RECIST criteria (version 1.1) using CT or MRI and analysed using Kaplan-Meier and the log-rank test.

5. Extrahepatic recurrence-free survival

Defined as time from randomization to appearance of new extra-hepatic lesions, using CT or MRI and analysed using Kaplan-Meier and the log-rank test.

6. Quality of Life

EQ5D-3L will be filled in at each study visit.
EORTC QLQ-C30 and QLQ-LMC21 will be filled in at baseline and at 3, 6, 12, 18, 24, 36 and 60 months.

7. Health economic evaluation

QALY will be estimated using EQ5D-3L at baseline and at 3, 6, 12, 18 and 24, 36 and 60 months.

A detailed description of all secondary efficacy variables will be given in a separate Statistical Analysis Plan (SAP)

11.5 DATA MONITORING COMMITTEE (DMC)

A Data Monitoring Committee (DMC) will be appointed. This will be done by an independent group outside sponsor and steering group. The DMC will consist of one or two physicians and one statistician, neither with any other involvement in the study. The DMC should also look for safety and at conditional power when giving advice regarding continuation of the study. The DMC should start to look at the data after 40% of the subjects have been followed for 2 years in the study. The work of DMC will be defined in a Data Monitoring Committee Charter. This document should be signed off by sponsor and DMC members preferably before the start of the study but at the latest before the first look at the data.

12 OPERATIONAL AND ADMINISTRATIVE CONSIDERATIONS

12.1 PROCEDURE FOR CLINICAL STUDY QUALITY CONTROL

12.1.1 Data Collection

All data on each subject generated according to the protocol must be recorded continuously in the eCRF.

12.1.2 Data Management

Data management will be coordinated by the sponsor. The study database will be soft-locked when all data that are specified in the study protocol to be collected, have been received and cleaned. It will be hard-locked when a (blind) data review meeting has been held, and all data related decisions have been made and reflected in the database.

12.1.3 Specification of Source Documents

The following documents are considered source, including but not limited to: Medical records, medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if subject visited any during the study period.

Source data must be available at the centre to document the existence of the study subjects and substantiate the integrity of study data collected. The following information (at least but not limited to) should be included in the source medical records:

- Demographic data (age, sex, weight, and height)
- Participation in the study and signed and dated Informed Consent Form
- Visit dates
- Key efficacy and safety data (as specified in the protocol)
- Reason for premature discontinuation
- Randomization number

12.1.4 Clinical Study Monitoring

The sponsor is responsible for monitoring the clinical study to ensure that subjects' human rights, safety, and well-being are protected, that the study is properly conducted in adherence to the current protocol, and study data reported by the investigator/sub-investigator are accurate and complete and that they are verifiable with study-related records such as source documents. The sponsor is responsible for assigning study monitor(s) to this study for proper monitoring. They will monitor the study in accordance with monitoring procedures.

12.1.5 Direct Access to Source Data/Documents

The investigator and the study site must accept monitoring and auditing by the sponsor as well as inspections from the IEC and relevant regulatory authorities. The confidentiality of the subjects' identities shall be well protected consistent with local and national regulations when the source documents are subject to direct access.

12.2 Ethics and Protection of Subject Confidentiality

12.2.1 Independent Ethics Committee (IEC)

This protocol and the Subject Information Sheet and Informed Consent Form will be submitted to the relevant Independent Ethics Committee (IEC) according to the national laws and regulations. Prior to starting the study favourable opinion must be obtained in writing. No subject must be included in the study before the relevant Independent Ethics Committee has issued a favourable opinion.

12.2.2 Ethical Conduct of Study

The investigator(s) and all parties involved in this study should conduct the study in adherence to the ethical principles based on the Declaration of Helsinki and the applicable laws and regulations.

12.2.3 Informed Consent of Subjects

Verbal and written informed consent must take place before any specific procedure related to the study is started. Signed and dated informed consent will be obtained from each patient. Documentation that the informed consent was signed and dated prior to study inclusion must be entered into the medical records at the time the informed consent is obtained.

12.2.4 Subject Confidentiality

All patient data collected and processed for the purposes of this study will be managed by the sponsor with adequate precautions to ensure the confidentiality of those data, and in accordance with applicable national and/local laws and regulations on personal data protection. No patient identifiable data will be obtained. In any presentations of the results of this study at meetings or in publications, the patients' identity will remain confidential. The sponsor will be collecting the data for the study. In all activities the GDPR(General Data Protection Regulation) will be followed to ensure protection of sensitive personal information. No patient identifiable data will be obtained.

12.2.5 Insurance

The study patients are insured by the care provider according to Patientskadelagen

12.3 Administrative Matters

Each study centre will enter all study data into an eCRF. The sponsor will be responsible for all data registrations, statistical programming and analysis as well as statistical quality control and validation of programming and statistical analysis. The sponsor will be responsible for the collected data in the study.

12.3.1 Arrangement for Use of Information and Publication of the Clinical Study

The study will be considered for publication or presentation at scientific symposia and congresses.

12.3.2 Documents and Records Related to the Clinical Study

The investigator will archive all study data (e.g., Subject Identification Code List, source data, CRFs, and Investigator's File) and relevant correspondence. These documents are to be kept on file for the appropriate term determined by local regulation. It is recommended however that records be retained for at least 10 years in the event follow-up is necessary to help determine any potential hazard to subjects who took part in the study. The investigator agrees to obtain the sponsor's agreement prior to disposal, moving, or transferring of any study-related records. The sponsor will archive and retain all documents pertaining to the study according to local regulations.

12.3.3 Protocol Amendment and/or Revision

Any changes to the study, which arise after approval of the protocol, must be documented as protocol amendment or administrative amendments. Depending on the nature of the amendment and/or revision, either IEC and regulatory authority approval or notification is required. The changes will become effective only after the approval of the sponsor, the regulatory authority and the IEC (if applicable). Written verification of IEC and regulatory authority approval will be obtained before any amendment is implemented. Modifications to the protocol that are administrative in nature do not require IEC and regulatory authority approval, but will be submitted to the IEC and the regulatory authority for their information.

13 QUALITY ASSURANCE

The sponsor is maintaining quality assurance to ensure that the study is conducted and data are generated, documented (record), and reported in compliance with the protocol and applicable regulatory requirement(s).

14 STUDY ORGANIZATION

Planned number of centres: 6 centres, one in each Health care region will identify patients. The study work-up will be performed at these centres.
Patients, eligibility for the study, will be reviewed by a transplant hepatologist in Gothenburg or Huddinge and discussed in a multi-disciplinary board.
Inclusion and randomization will be performed when the patient has been accepted at the multi-disciplinary board
Patients randomized to Arm A will be treated with Ltx at Sahlgrenska University Hospital or Karolinska University Hospital and then followed at each participating centre.
Treatment in Arm B will occur at each centre.

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