The Swedish Randomized Controlled Trial of Isolated Hepatic Perfusion for Uveal Melanoma Liver Metastases

the SCANDIUM trial

A randomized controlled, open-label, multicenter study evaluating if Isolated Hepatic Perfusion increases Overall Survival, in comparison with Best Alternative Care in patients with isolated liver metastases from uveal melanoma

Protocol for a Phase III Study

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

ClinicalTrials number: NCT01785316
EudraCT number: 2013-000564-29

This confidential document is the property of the sponsor. No unpublished information contained in this document may be disclosed without prior written approval of the sponsor.
# Table of Contents

1. **SIGNATURES** ................................................................................................................. 4  
   1.1 Sponsor’s Signature ................................................................................................. 4  
      1.1.1 Protocol Author .............................................................................................. 4  
      1.1.2 Protocol Approved By: .................................................................................... 4  
   1.2 Co-ordinating Investigator: ..................................................................................... 4  
   1.3 Principal Investigator’s signature ............................................................................ 5  
      1.3.1 Principal Investigators ....................................................................................... 5  
      1.3.2 Principal Investigator’s signature .................................................................... 5  
2. **LIST OF ABBREVIATIONS AND KEY TERMS** ....................................................... 6  
   2.1 List of Abbreviations ............................................................................................... 6  
   2.2 List of Key Study Terms .......................................................................................... 7  
3. **SYNOPSIS** .................................................................................................................... 8  
4. **INTRODUCTION** ......................................................................................................... 10  
   4.1 Background ............................................................................................................. 10  
5. **STUDY OBJECTIVES AND DESIGN** ....................................................................... 11  
   5.1 Study Objectives ...................................................................................................... 11  
   5.2 Study Design .......................................................................................................... 11  
6. **STUDY POPULATION** .............................................................................................. 11  
   6.1 Selection of Study Population .................................................................................. 11  
   6.2 Inclusion Criteria ..................................................................................................... 11  
   6.3 Exclusion Criteria .................................................................................................... 12  
   6.4 Discontinuation Criteria for Individual Subjects ..................................................... 12  
   6.5 Premature Termination of the Study ...................................................................... 12  
7. **STUDY TREATMENTS** .............................................................................................. 13  
   7.1 Description of Study Treatments .......................................................................... 13  
   7.2 Concomitant Medications ...................................................................................... 14  
8. **TREATMENTS AND EVALUATION** ...................................................................... 14  
   8.1 Efficacy Assessments .............................................................................................. 14  
   8.2 Safety and Tolerability ............................................................................................ 14  
      8.2.1 Adverse Events (AEs) ........................................................................................ 15  
      8.2.2 Serious Adverse Events (SAEs) ........................................................................ 15  
      8.2.3 Reference Safety Information (RSI) ................................................................. 15  
9. **RISK-BENEFIT EVALUATION** ................................................................................ 16
1 SIGNATURES

1.1 SPONSOR’S SIGNATURE

1.1.1 Protocol Author

Author:

Signature:................................................................. Date:.................................
Per Lindnér, Transplant Institute
Sahlgrenska University Hospital
SE-413 45 Gothenburg, Sweden

1.1.2 Protocol Approved By:

Head of clinic:

Signature:................................................................. Date:.................................
Per Karlsson, Område 5
Sahlgrenska University Hospital
SE-413 45 Gothenburg, Sweden

1.2 CO-ORDINATING INVESTIGATOR:

Signature:................................................................. Date:.................................
Roger Olofsson, Department of Surgery
Sahlgrenska University Hospital
SE-413 45 Gothenburg, Sweden
1.3 PRINCIPAL INVESTIGATOR’S SIGNATURE

1.3.1 Principal Investigators
Roger Olofsson  
Sahlgrenska University Hospital, Gothenburg
Ingrid Ljuslinder  
Norrlands University Hospital, Umeå
Johan Hansson  
Karolinska University Hospital, Stockholm
Gunnar Adell  
Linköping University Hospital, Linköping
Gustav Ullenåag  
Uppsala University Hospital, Uppsala
Lotta Lundgren  
Skåne University Hospital, Lund

1.3.2 Co-Investigators
Per Lindnér  
Sahlgrenska University Hospital, Gothenburg
Magnus Rizell  
Sahlgrenska University Hospital, Gothenburg
Christian Cahlin  
Sahlgrenska University Hospital, Gothenburg
Lars Ny  
Sahlgrenska University Hospital, Gothenburg
Ulrika Stierner  
Sahlgrenska University Hospital, Gothenburg

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:  

Printed Name:  

Date
## 2 LIST OF ABBREVIATIONS AND KEY TERMS

### 2.1 LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviations</th>
<th>Description of abbreviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALAT</td>
<td>Alanine aminotransferase</td>
</tr>
<tr>
<td>ALP</td>
<td>Alkalic phosphatase</td>
</tr>
<tr>
<td>ASAT</td>
<td>Aspartate aminotransferase</td>
</tr>
<tr>
<td>BAC</td>
<td>Best Alternative Care</td>
</tr>
<tr>
<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>ECOG</td>
<td>Eastern Cooperative Oncology Group</td>
</tr>
<tr>
<td>eCRF</td>
<td>Electronical Case Report Form</td>
</tr>
<tr>
<td>ET</td>
<td>Early Termination</td>
</tr>
<tr>
<td>FEV</td>
<td>Forced Expiratory Volume</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>IHP</td>
<td>Isolated Hepatic Perfusion</td>
</tr>
<tr>
<td>LPK</td>
<td>Leukocyte concentration</td>
</tr>
<tr>
<td>LVEF</td>
<td>Left Ventricular Ejection Fraction</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OS</td>
<td>Overall Survival</td>
</tr>
<tr>
<td>PFT</td>
<td>Pulmonary Function Tests</td>
</tr>
<tr>
<td>PHP</td>
<td>Percutaneous Hepatic Perfusion</td>
</tr>
<tr>
<td>PK-INR</td>
<td>Prothrombin complex-International Normalized Ratio</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-adjusted life year</td>
</tr>
<tr>
<td>RECIST</td>
<td>Response Evaluation Criteria In Solid Tumors</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical Analyses Plan</td>
</tr>
<tr>
<td>TPK</td>
<td>Trombocyte concentration</td>
</tr>
<tr>
<td>ULN</td>
<td>Upper limit normal</td>
</tr>
</tbody>
</table>
## 2.2 List of Key Study Terms

<table>
<thead>
<tr>
<th>Terms</th>
<th>Definition of terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>1) Observed values/findings, which are regarded as calibrated zero status in the present study, 2) Time when ‘Baseline’ is observed.</td>
</tr>
<tr>
<td>Investigational period</td>
<td>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.</td>
</tr>
<tr>
<td>Investigator</td>
<td>A physician or dentist 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.</td>
</tr>
<tr>
<td>Randomization</td>
<td>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’</td>
</tr>
<tr>
<td>Randomization/Treatment number</td>
<td>Number assigned to each subject who has completed ALL screening assessments successfully at baseline and is willing to be included in the study.</td>
</tr>
<tr>
<td>Randomized subject/Subjects given the test drugs</td>
<td>Subjects randomized to the treatment group (test drug group) or control group, and those received open label study treatment.</td>
</tr>
<tr>
<td>Source data</td>
<td>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).</td>
</tr>
<tr>
<td>Source documents</td>
<td>Original documents, data, and records including source data.</td>
</tr>
<tr>
<td>Subject</td>
<td>An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>Subject enrolled but did not complete the study for any reason.</td>
</tr>
</tbody>
</table>
3 SYNOPSIS

<table>
<thead>
<tr>
<th>Title of Study</th>
<th>A randomized controlled, open-label, multi-center study evaluating if Isolated Hepatic Perfusion (IHP) increases Overall Survival compared with Best Alternative Care (BAC) in patients with isolated liver metastases from uveal melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Objective(s)</td>
<td>To evaluate if IHP increases the Overall survival compared to BAC.</td>
</tr>
<tr>
<td><strong>Primary objective:</strong></td>
<td>• Overall survival defined as the frequency of individuals alive at 24 months</td>
</tr>
</tbody>
</table>
| **Secondary objectives:** | • Median overall survival  
| | • Hepatic progression-free survival  
| | • Response  
| | • Health economic evaluation  
| | • SAE |
| Planned Total Number of Study Centers and Location | Planned number of centers: 6-10 centers primarily in Sweden, however all Nordic countries will be invited to participate in the study. Randomization and treatment in Arm B will occur at each center. Patients randomized to Arm A will be treated with IHP at Sahlgrenska University Hospital, Göteborg, Sweden. |
| Design and Methodology | Prospective, multi-centre controlled, randomized, parallel group, open-label study. Active follow-up will be performed for 2 years. Patients will be randomized after diagnoses of liver metastases to one of the following treatment arms:  
| | **A. Isolated Hepatic Perfusion:** Patients will be treated with IHP. If the patients progress systemically or in the liver, they will be treated with BAC.  
| | **B. Best Alternative Care:** The treating physician will together with the patient decide the treatment. No cross-over to Arm A will be allowed. |
| Number of Subjects Planned | 78 patients will be included in the study. Subjects will be randomized after signing informed consent. Enrolment will continue until the required sample size has been randomized. An enrolment time of 60 months is expected. |
| Main Selection Criteria | **Inclusion Criteria**  
| | 1. Male or female aged above 18 years.  
| | 2. Signed and dated written informed consent before the start of specific protocol procedures.  
| | 3. Histologically or cytologically proven liver metastases of uveal melanoma.  
| | 4. Liver metastases measurable by CT/MRI (thorax and abdomen) according to RECIST version 1.1 with at least one unidimensional measurable lesion ≥ 10 mm.
| 5. ECOG performance status of 0 or 1. |
| 6. No previous chemotherapy, radiotherapy, or biologic therapy for uveal melanoma metastases (ie first-line therapy) |
| 7. Adequate hepatic function (defined as ASAT, ALAT, bilirubin <= 3*ULN and PK-INR <= 1.5) and no medical history of liver cirrhosis or portal hypertension |

**Exclusion Criteria**

1. More than 50% of the liver volume (measured by CT or MRI) replaced by tumour.
2. Evidence of extrahepatic disease by PET-CT
3. Life expectancy of less than 4 months
4. Pregnant or breast-feeding. Women of childbearing potential must have a negative pregnancy test performed within seven days prior to the start of study.
5. Active infection.
6. Ischemic cardiac disease or history of congestive heart failure with an LVEF < 40%.
7. COPD or other chronic pulmonary disease with PFT's indicating an FEV< 50% predicted for age.
8. Reduced renal function defined as S-Creatinine >=1.5xULN or Creatinine Clearance < 40 mL/min, calculated using the Cockcroft and Gault formula.
9. Reduced blood leukocytes or platelets defined as LPK < 2.0x10^9/L and TPK <100x10^9/L
10. Use of live vaccines four weeks before or after the start of study.
11. Body mass index above 35.

**Discontinuation Criteria**

Subjects must be discontinued from the study for the following reasons:

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


4 INTRODUCTION

4.1 BACKGROUND

Uveal melanoma is the most common primary intraocular malignancy in adults. Despite successful control of the primary tumour, metastatic disease will develop in approximately 35%-50% of the patients within 10 years. The liver is the most common site for metastases, and about 50% of the patients will have isolated liver metastases. These metastases are generally refractory to systemic chemotherapy and the median survival for patients with liver metastases is about 6 months. Regardless of treatment, the mortality rate is approximately 90% at 2 years with only about 1% of the patients surviving more than 5 years (Diener-West, Reynolds et al. 2005).

For patients with uveal melanoma liver metastases few therapeutic options exist. Liver resection was analysed in a retrospective study by Mariani et al including a material of 3873 patients with uveal melanoma (Mariani, Piperno-Neumann et al. 2009). Of these patients, 798 developed liver metastases and 255 of them later underwent surgical resection with an OS of 14 months, radical resection (R0) was possible in 76 patients resulting in an OS of 27 months.

Recently, a randomized phase III trial evaluated percutaneous hepatic perfusion (PHP), a less invasive procedure, for unresectable liver metastases from both uveal and cutaneous melanoma (Pingpank, Hughes et al. 2010). In this study, 4-6 sessions of PHP was compared with BAC. There was a high proportion of patients crossing over from BAC to PHP making any conclusive results concerning overall survival difficult to assess in this study. The median survival after IHP is numerically longer than what was observed after PHP (24 vs. 10 months), however no direct comparison has been made between the two strategies.

Another randomized trial (the EORTC 18021 study) compared hepatic intra-arterial chemotherapy (HIA) with systemic chemotherapy. The study showed a modest rise in overall response rate (14% versus 2%) but without improvement in overall survival (Leyvraz, Suciu et al. 2012).

The introduction of ipilimumab in the therapeutic arsenal for cutaneous melanoma also creates hope for patients with uveal melanoma metastases. Still, very limited data are available and a small study of 13 patients reported no objective responses, but three patients experienced stable disease (Danielli, Ridolfi et al. 2012).

Isolated hepatic perfusion (IHP) is a regional treatment that was first performed more than 40 years ago (Aust and Ausman 1960). During IHP, the liver is completely isolated from the systemic circulation, allowing a high concentration of chemotherapy to be perfused through the liver with minimal systemic exposure. In a previous study from our institution, IHP was analysed based on improvements in the procedure and the results showed an improved outcome together with minimized morbidity and mortality over time (Rizzell, Mattson et al. 2008).
A phase II follow-up study confirms that IHP is a promising technique with tolerable morbidity. There are yet no randomized trials comparing overall survival in IHP, but in an attempt to answer this question we did a register study showing a 14 months increased survival when comparing the patients treated with IHP with the longest surviving patients in Sweden during the same time period (Olofsson et al Manuscript).

5 STUDY OBJECTIVES AND DESIGN

5.1 STUDY OBJECTIVES
To evaluate if IHP increases OS compared to BAC.

Primary objective:
• OS defined as the frequency of individuals alive at 24 months

Secondary objectives:
• Median overall survival
• Hepatic progression-free survival
• Response
• Health economic evaluation
• Serious Adverse Events

5.2 STUDY DESIGN
Prospective, multi center, controlled, randomized, parallel group, open-label study. Patients will be followed actively according to this protocol for 2 years at each study center.

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 24 months will be 50 % in the study group and 20 % in the control group. Based on this assumption, 78 subjects are planned to be randomized to the two treatment groups in a 1:1 ratio (IHP: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 5 % drop-out rate. Subjects will be randomized after signing informed consent. Enrolment will continue until the required sample size has been randomized. An enrolment time of 60 months is expected.

6.2 INCLUSION CRITERIA
1. Male or female aged above 18 years.
2. Signed and dated written informed consent before the start of specific protocol procedures.
3. Histologically or cytologically proven liver metastases of uveal melanoma.
4. Liver metastases measurable by CT/MRI (thorax and abdomen) according to RECIST version 1.1 with at least one unidimensional measurable lesion ≥ 10 mm.
5. ECOG performance status of 0 or 1.
6. No previous chemotherapy, radiotherapy, or biologic therapy for uveal melanoma metastases (ie first-line therapy)  
7. Adequate hepatic function (defined as ASAT, ALAT, bilirubin <= 3*ULN and PK-INR <=1.5) and no medical history of liver cirrhosis or portal hypertension

6.3 Exclusion Criteria
Subject will be excluded from participation if any of the following apply:
1. More than 50% of the liver volume (measured by CT or MRI) replaced by tumour.  
2. Evidence of extrahepatic disease by PET-CT  
3. Life expectancy of less than 4 months  
4. 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.  
5. Active infection.  
6. Ischemic cardiac disease or history of congestive heart failure with an LVEF < 40%.  
7. COPD or other chronic pulmonary disease with PFT's indicating an FEV< 50% predicted for age.  
8. Reduced renal function defined as S-Creatinine >=1.5xULN or Creatinine Clearance < 40 mL/min, calculated using the Cockroft and Gault formula.  
9. Reduced blood leukocytes or platelets defined as LPK < 2.0x10^9/L and TPK <100x10^9/L  
10. Use of live vaccines four weeks before or after the start of study.  
11. Body mass index above 35.

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 enrollment (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 24 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 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

Since there have been mortality associated with previous IHP treatment protocols, the trial will be temporarily stopped if two post-operative deaths within 30 days of IHP occur. The causes of death will then be analyzed in detail and discussed within the study group, the DMC and with Läkemedelsverket (MPA), 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. IHP

Patients will be treated with IHP at Sahlgrenska University Hospital, Göteborg, Sweden. The procedure is performed under general anesthesia. A bilateral subcostal incision is made and the intrahepatic tumor volume as well as signs of extra hepatic spread is evaluated. Wire reinforced catheters are inserted into the iliac vein and the axillary vein and connected to an external centrifugal pump to allow for shunting of blood from the lower extremity during the procedure when the caval vein is clamped. The caval vein is isolated infrahepatically above the renal veins and suprarehepatically between the diaphragm and the pericardium. Tributaries from the lumbal veins, the diaphragmatic veins and the right adrenal veins are ligated. Using the right gonadal vein, a catheter is placed in the retrohepatic portion of the caval vein for perfusion outflow. The portal vein is clamped and the proper hepatic artery is cannulated via the gastroduodenal artery. The catheters are then connected to the perfusion system. The liver perfusion is performed at a rate of 8–9 ml/kg/min with a target liver temperature of 40 degrees Celsius. The temperatures are continuously registered with thermistor probes placed in the inflow catheter and in the liver parenchyma. The leakage from the system was continuously recorded using Technetium labelled albumin (Vasculosis) injected into the perfusion circuit and measured using scintillation detector placed over the veno-venous bypass pump. All the measurements are recorded and stored via the MedicView (Systemdata, Gothenburg, Sweden) computerized system. When steady-state conditions in the perfusion circuit are established, melphalan (1 mg/kg bodyweight divided into two doses, given 30min apart) is added to the perfusion system. The perfusion is then continued for 60 minutes, after which the perfusion was discontinued and the liver is irrigated with Ringer-
Acetate. The shunts and the perfusion circuit are disconnected and the catheters are removed.

If the patients progress systemically or in the liver, they will be treated with Best Alternative Care (cross-over to treatment arm B).

**B. Best Alternative Care-arm**

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

According to FASS there are no applicable drug interactions with melphalan. Also considering that the principle of the procedure is to isolate the liver from the systemic circulation, the systemic effects of the melphalan used are considered being small. Taken together, IHP with melphalan does not render any specific prohibitions in the use of other medications.

### 8 Treatments and Evaluation

#### 8.1 Efficacy Assessments

The subjects will be followed for 2 years. Study visits will be at each center and performed at baseline, and after 3, 6, 12, 18 and 24 months.

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

1. CT or MRI of liver (same modality as baseline examination) according to specified protocol (addendum)
2. EQ5D-3L Quality of Life questionnaire
3. Any further examinations at the discretion of the treating doctor

#### 8.2 Safety and Tolerability

The subjects will be followed for 2 years. Study visits will be at each center and performed at baseline, and after 3, 6, 12, 18 and 24 months. For patients randomized to IHP, an additional study visit will be performed at day 10±5 to allow for early detection of SAE/SUSAR (the patient will stay approximately one week at the hospital after IHP, and this study visit will be performed the same day as the patient leave the hospital).

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

a. Blood samples (Hb, LPK, TPK, PK, ASAT, ALAT, ALP, Bilirubin, Creatinine).

b. Any further examinations at the discretion of the treating doctor
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.

For patients randomized to the IHP group, all AEs reported spontaneously by the subject or observed by the investigator or his staff will be recorded in the eCRF according to the MedDRA classification for manifestation site, and in the subject’s medical record. Information to be collected includes assessment of severity (mild, moderate, severe) and the relationship to the study treatment. AEs occurring in the BAC group will not be recorded, however SAE and SUSARs will 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 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 Sponsor will notify all other investigators in the study of the SAE.

For Suspected Unexpected Serious Adverse Reactions (SUSARs) a report will be submitted to the EudraVigilance-database, the Ethics committee and the DMC.

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.

8.2.3 Reference Safety Information (RSI)
FASS is the reference for safety information about the use of melphalan. Except from liver insufficiency, no known safety issue have been correlated to the specific use of melphalan and IHP together. Since the principle of the procedure is to isolate the liver
from the systemic circulation, the systemic effects of the melphalan dose used are considered being small.

Other complications are to refer to the surgery in itself, with infections (wound infections, pneumonia, urinary tract infections, septicemia), thromboembolic events (DVT, PE) and respiratory problems being the most common events.

9 RISK-BENEFIT EVALUATION

IHP using melphalan is a major surgical procedure with associated risks. At Sahlgrenska the procedure was implemented in the 1980s. A study from our institution (Rizell et al 2008) reports how the IHP procedure has improved by sequential changes in the treatment protocol. Before 2005 there was a high frequency of post-operative mortality, however after excluding patients with high tumor burden and by lowering the melphalan dose to 1mg/kg bodyweight, there has been no mortality in more than 50 patients treated since 2005.

Liver insufficiency has most predominantly been reported in patients with large tumour burden (above 50% of the liver volume), and these patients are excluded from this study. The liver insufficiency is due to an acute toxicity, and will be found during the immediate post-operative period (within 5 days) by daily control of LFTs.

The current morbidity related to the procedure has all been attributed to the surgical intervention itself, mostly complications related to post-operative infections and thromboembolic events. To reduce this risk, patients receive preoperative prophylaxis with antibiotics, as well as a 10-day prophylactic regimen of low-molecular weight heparin (Fragmin 5000 IE) postoperatively.

Two patients have also developed respiratory failures associated with a prolonged stay at the ICU, both these patients were obese, and the respiratory failure was considered related to this. Therefore, patients with obesity are excluded from the trial.

This group of patients, with liver metastases of ocular melanoma origin, has a dismissal prognosis and there exists no proven therapy that prolongs survival. The median survival is between 6-12 months and there are very few patients that can be considered long-term survivors (3-5 years). IHP has in a retrospective study (Olofsson et al, submitted manuscript) shown a prolongation in overall survival of 14 months in median compared to the longest surviving patients in Sweden during the same time period.

Taken together, there is a risk of undergoing IHP that could be compared to other major surgery (eg. liver resections) with associated complications and a small risk of post-operative mortality. However, for this group of patients with a short expected survival and no standard treatment option, the possible advantages of improved survival are considered to outweigh the risks.

10 TERMINATION OF THE CLINICAL STUDY

The 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 statistical 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 24 months will be 50% in the study group and 20% in the control group. Based on this assumption, 78 subjects are planned to be randomized to the two treatment groups in a 1:1 ratio (IHP: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 5% drop-out rate.

11.2 POPULATIONS OF ANALYSIS
The primary analysis of efficacy data will be based on the Intention To Treat (ITT) population. Patients will be analyzed 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 analyzed and summarized using descriptive statistics on a group base according to randomization.

11.4 EFFICACY ANALYSIS

11.4.1 Primary Objective
- Overall survival defined as the frequency of individuals alive at 24 months.

11.4.2 Secondary Objectives:

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

2 Hepatic 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.

3 Response
   Defined as best response according to RECIST criteria (version 1.1) using CT or MRI. For the BAC-group, during the whole follow-up of 24 months. For the IHP-group, until hepatic progression (the time point when cross-over to the BAC-group is allowed).
4 Health economic evaluation
QALY will be estimated using EQ5D-3L at baseline and at 3, 6, 12, 18 and 24 months.

5 Serious Adverse Events
Any SAE/SUSAR that occurs in either of the two groups will be reported.

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. For efficacy the DMC should use O’Brien-Flemming group sequential boundaries. 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 completed 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 when 40% of the subjects have completed the study.

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 GCP, 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 favorable opinion must be obtained in writing. No subject must be included in the study before the relevant Independent Ethics Committee has issued a favorable 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, Good Clinical Practice (GCP), ICH Guidelines 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 in accordance with the principles of Good Clinical Practice (GCP). 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 PUL (the Swedish Data Protection Law) will be followed to ensure protection of sensitive personal information. No patient identifiable data will be obtained.

12.3 **ADMINISTRATIVE MATTERS**
Each study center 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, GCP, and applicable regulatory requirement(s).
14 STUDY ORGANIZATION
Planned number of centers: 6-10 centers primarily in Sweden, however all Nordic countries will be invited to participate in the study. Randomization and treatment in Arm B will occur at each center. Patients randomized to Arm A will be treated with IHP at Sahlgrenska University Hospital and then followed at each participating center.

15 REFERENCES