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| Sponsor  | Asian Institute of Gastroenterology  |
| Reference /protocol Number (If any) | AHF- AIG-ICSCRT 001  |
| Study Title: | Autologous transfusion of mobilized peripheral blood CD 34+ve Cells in patients with liver cirrhosis.  |
| Language: | English |

**Patient Identification**

Subject / Patient full name in BLOCK LETTERS: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Subject / Patient initials:\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Date of Birth / Age : \_\_\_\_\_\_\_\_\_\_\_\_\_\_

**Study Doctor Identification**

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| --- | --- |
| Principal investigators name in:  | Co- Investigators  |
| Dr. Mithun Sharma, Consultant Hepatologist, drmithunsharma@gmail.com  | Dr.P.N.Rao, Consultant Hepatologist, npadaki@yahoo.com  |
|  | Dr M. Sasikala, Senior Scientist, aigres.mit@gmail.commailto:aigres.mit@gmail.com |
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Address : Asian Institute of Gastroenterology, Asian Healthcare foundation, somajiguda, hyderabad

6-3-661, Somajiguda, **Email Address** for receipts of regulatory documents

Hyderabad – 082 aigres.mit@gmail.com

Tel/ Fax: +91 040 23378888/ 91-40-23324255

1. **Participation**

You are being considered for participation in a research study. Your eligibility to participate in the study is subject to the screening procedures described below and other eligibility criteria. Before you can take part in this study, it is important that you understand what the study involves. Please read this information carefully and ask any questions that you might have.

1. **Purpose of the Study**

The purpose of this study to **“Evaluate efficacy and clinical improvement by infusing mobilized peripheral blood CD 34 +ve cells in patients with liver cirrhosis”**. A healthy liver has a remarkable ability to regenerate itself however a diseased liver as in liver cirrhosis / acute or chronic liver failure cannot regenerate on its own but when this ability is compromised. An important challenge of modern medicine is to find a way to supplement the natural process of regeneration, and thereby restore liver function. Liver transplantation is the standard treatment of end-stage liver diseases. However, it has several limitations such as shortage of organ donors, high cost, and complications. Over the past 3 decades, a significant body of scientific literature has shown that in animals and human studies, infused primary, fetal liver hepatocytes and bone marrow stem cells engraft into host tissue, survive, proliferate, function, and participate in the regenerative process Adult stem cell therapy could solve the problem of degenerative disorders, including liver disease. Hematopoietic stem cells (CD 34+ve) cells in bone marrow have the ability to develop into hepatocytes. The efficacy and safety of transplantation these cells have been demonstrated in animals and humans previously and clinical improvement was recorded in patients with liver disease.

**3) Approximate Number of Participants and the Expected Duration of Your Participation in the Study**

About 100 patients in total are expected to participate in the study. Before being enrolled in the study, which is entirely voluntary, you have to meet the inclusion criteria listed in our protocol. If you are enrolled in the study, you can remain on study treatment until you have any side effect, health status worsens your doctor thinks it is the best interest to stop study treatment or study is closed. The entire procedure from pre test investigation to infusion of CD34 positive cells will be around 1 week. You may also have choice to stop participating in the study at any time. Which ever study group you are included is need to follow up with us every week / 2 months, then every monthly once for one year.

You may be discontinued from the study treatment if you do not follow the treatment schedule or if you are female and become pregnant.

**4)** **Study Treatments**

Based on your preference, you can either opt for receiving autologous CD34 positive cell infusion where or you will be administered Granulocyte colony – Stimulating factor (G-CSF) via subcutaneous route to mobilize stem cells from the bone marrow into the peripheral circulation and the blood cells will be collected by leukapheresis. The entire procedure from pre test investigation to infusion of CD34 positive cells will be around 1 week.

Alternatively you can choose to receive only G-CSF injection for 5 consecutive days. In this group, recent studies have shown that G-CSF can mobilize CD34 positive cells from bone marrow, which goes to the liver and help in regeneration process. Many researchers have claimed it to be of equal efficacy as CD34 autologous infusion.

Lastly, you may opt out of receiving either CD34 positive cells / G-CSF alone and continue with standard of care for liver cirrhosis. Which ever study group you are included is need to follow up with us every week / 2 months, then every monthly once for one year.

**5) Study Procedures:**

If you have opted for CD34 positive cell autologous infusion then you will be admitted in the hospital and your base line laboratory tests will be done. If your reports are fine, you will receive daily subcutaneous injection of G-CSF @ 520ug/day for 5 days and your blood samples and clinical parameters will be closely monitored daily. After completion of G-CSF, you will be shifted to the leukapheresis room where the doctor will insert a catheter through the jugular vein and blood will be collected and separated. This is called leukapheresis and the procedure will be between 3 to 4 hours and will start at 8 am. After this your collected sample will be sent to the stem cell lab in our hospital and the CD34 positive cells will be isolated. This procedures takes another 3 to 4 hours. Once the CD34 cells are ready, you will be shifted to the cath lab, where our interventional radiologist will insert a catheter through the femoral artery in the thigh and the CD34 positive cells will be infused under fluoroscopic guidance in to the hepatic artery. You may feel some pain at the catheter site which we will take care. You have to be in the hospital for next 24 to 48 hours for monitoring.

If you opt for only G-CSF infusion then you will be admitted in the hospital and your base line laboratory tests will be done. If your reports are fine, you will receive daily subcutaneous injection of G-CSF @ 520ug/day for 5 days and your blood samples and clinical parameters will be closely monitored daily. You will be monitored for next 24 to 48 hours in hospital.

If you opt to receive standard of care, your monitoring doctor will outline the treatment protocol. (Which is the standard of care for liver cirrhosis)

**The following procedures will be done at Day 1 of study treatment:**

* Medical history including previous treatment and current medications.
* Physical examination
* Vital signs including heart rate and blood pressure
* Blood samples to be sent to research lab prior to G-CSF injection.
* Physical measurements including height and weight
* Review of medications you may have taken and any side effects you may have experienced.
* Administration of G-CSF subcutaneous route of 520µg/day.

**The following procedures will be done at (Day 2):**

* Review of medical history including previous treatment and current medications, enquiry obtaining any specific standard of care
* Physical examination
* Vital signs including heart rate and blood pressure
* Blood samples to be sent in the morning to research lab.
* Physical measurements including height and weight
* Review of medications you may have taken and any side effects you may have experienced.
* Administration of G-CSF subcutaneous route of 520µg/day.

**The following procedures will be done at (Day 3):**

* Review of medical history including previous treatment and current medications, enquiry obtaining any specific standard of care
* Physical examination
* Vital signs including heart rate and blood pressure
* Blood samples to be sent in the morning to research lab.
* Physical measurements including height and weight
* Review of medications you may have taken and any side effects you may have experienced.
* Administration of G-CSF subcutaneous route of 520µg/day.

**The following procedures will be done at (Day 4):**

* Review of medical history including previous treatment and current medications, enquiry obtaining any specific standard of care
* Physical examination
* Vital signs including heart rate and blood pressure
* Blood samples to be sent in the morning to research lab.
* Physical measurements including height and weight
* Review of medications you may have taken and any side effects you may have experienced.
* Administration of G-CSF subcutaneous route of 520µg/day.

**The following procedures will be done at (Day 5):**

* Review of medical history including previous treatment and current medications, enquiry obtaining any specific standard of care
* Physical examination
* Vital signs including heart rate and blood pressure
* Blood samples to be sent in the morning to research lab.
* Physical measurements including height and weight
* Review of medications you may have taken and any side effects you may have experienced.
* Administration of G-CSF subcutaneous route of 520µg/day.

**The following procedures will be done at (Day 6):**

* Review of medical history including previous treatment and current medications, enquiry obtaining any specific standard of care
* Physical examination
* Vital signs including heart rate and blood pressure
* Blood samples to be sent in the morning to research lab.
* Physical measurements including height and weight
* Review of medications you may have taken and any side effects you may have experienced.
* You will be shifted to the leukapheresis room and the doctor will insert a catheter through the jugular vein and blood will be collected and separated. This is called leukapheresis and the procedure will be between 3 to 4 hours and will start at 8 am. After this your collected sample will be sent to the stem cell lab in our hospital and the CD34 positive cells will be isolated. This procedures takes another 3 to 4 hours. Once the CD34 cells are ready, You will be shifted to the cath lab, where our interventional radiologist will insert a catheter through the femoral artery in the thigh and the CD34 positive cells will be infused under fluoroscopic guidance in to the hepatic artery. You may feel some pain at the catheter site which we will take care. You have to be in the hospital for next 24 to 48 hours for monitoring.

**The following procedures will be done at end of the study treatment :**

Follow up visits and telephonic calls / Emails for 1 week and every week visit to the hospital for 2 month to collect information regarding additional treatment and disease status. If you seeks emergency, or if hospitalization is required, please inform the treating doctor that you are participating in the clinical study**.**

**6)** **Your Responsibilities**

At each visit:

* You will be asked how you feel and possible side effects will be discussed.
* You must inform your study doctor of any medication that you take while you are in the study..
* Keep the doctor informed of any new or changes in your current medication you may be taking, including daily supplements, vitamins, natural products, over the counter medication. You may not take any medications prescribed by other doctors until you speak with your study doctor because they may effect how you react to the study medication.
* Tell the doctor about the problems or side effects you experience. At each visit you will be asked how you feel and possible side effects will be discussed.
* For women of childbearing potential:

1. Use adequate birth control to avoid becoming pregnant while you are on study and for at least 12 weeks after stopping study medication. You must tell your study doctor if you changed your method of birth control, you think you may be pregnant, you missed your menstrual period, or your menstrual period is late.

2. No breast feeding while you are on study for at least 12 weeks after stopping the medication.

Fathering a child while you take study medication and for at least 12 weeks after stopping this medication. You must tell your study doctor if you think your partner is pregnant.

* Record the dose of medication or missed doses in the drug diary, and bring the drug diary with you to every visit.

**7) Risks / Possible Adverse Drug Reactions:**

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**Possible Side Effects of G-CSF**

1.The side effects of G-CSF may include nausea, vomiting and stomach pain along with headache and flu-like symptoms. In addition, there may be weakness and muscle aches and joint pain or bone pain or pain in the arms and legs. Other side effects may include an itchy skin rash.

**Other Side Effects**

2. Contact your doctor if you experience persistent or severe sensations of burning or itching, redness, swelling or pain at the site of the injection. Be aware that G-CSF may cause mild pain in the lower back or in the pelvis; this will occur as the production of white blood cells begin in the bone marrow. Talk with your doctor if the pain persists. Your doctor will usually prescribe a mild painkiller for this condition.

**Serious Side Effects**

3. These side effects should be reported immediately to your doctor: loss of appetite, night-time sweating and feeling full very quickly while eating. Seek immediate emergency medical care if you should experience a skin rash, fever or chills and shaking or rapid heartbeat, wheezing or difficulty breathing.

**Adult Respiratory Distress Syndrome**

4. Adult Respiratory Distress Syndrome (ARDS) is a serious lung condition. Symptoms may include shortness of breath, tightness in the chest, or wheezing along with difficulty in breathing. Seek immediate emergency medical treatment if you experience any of these symptoms.

**Possible Side Effects of Leukapheresis**

Leukapheresis is well tolerated and occasional fever with chills may be expected

Hepatic artery pain at the site of injection is tolerable.

**Other Risks:**

(8) Risk to reproduction, unborn babies and nursing infants

**8A. General Statement:**

You must not be pregnant are breast feeding, and you should become pregnant or breast feed while you are taking the study treatment an upto 12 weeks after the last dose of study medication. You must use and adequate method to avoid pregnancy for the duration of the study. You should immediately contact your study doctor if there is a change in your method to avoid pregnancy or if you start any prescription drug or other medication (including over-the-counter drugs and herbal supplements) not prescribed by the study doctor.

**8B. Unforeseeable risks**:

 Their may be unknown risks to you, your unborn baby or nursing infant if you are become pregnant during this study or breast feeding during this study.

**8C. Laboratory and Animal reproductive toxicology findings**:

While laboratory and animal studies have been conducted to determine possible risks, the result do not necessarily show that will happen when the drug is used in humans.

**8D. Human pregnancy outcomes**:

There is no information on human pregnancy outcomes available for granulocyte colony- stimulating factors (G-CSF).

**8E. Requirements for pregnancy testing**:

During this study you will have serum (blood) pregnancy test (beta-HCG) at the baseline visit, with in 72 hours of your first dose of study medication and then every 6 weeks.

**8F. Occurrence of pregnancy or suspected pregnancy**:

If you become pregnant, suspected pregnancy or if your missed your period or it is late, or if you have any change in your menstrual cycle (e.g. heavier bleeding during your period or bleeding between periods), you should immediately contact your study doctor.

**8G. Discontinuation from the study**:

Should you become pregnant during the study, you will be immediately withdraw from the trial and referred for obstetrical care. The sponsor has not said aside any funds to pay for any aspects of obstetric, child or relative care and does not plan to pay for them.

**8H. Pregnancy Reporting**:

In case of a pregnancy, your pregnancy and its outcome will be reported to the study sponsor.

**8I. Information for men with partners of childbearing potential**:

Most study drugs do not pose a risk to a woman who becomes pregnant while her male partner is a study subject. It is not unknown if Granulocyte colony- Stimulating factor (G-CSF) passes in the semen or if it affects a man’s ability to father a child or the development of sperm. If you are partner is pregnant or breast feeding, use of a condom is recommended. If your partner is of childbearing potential, it is advised the adequate birth control be used during the study and for 12 weeks after stopping study medication to avoid pregnancy. However you are asked to inform your study doctor, if your partner becomes pregnant while you are enrolled in this clinical trial, and you and your partner will be asked to provide information about the pregnancy outcome. The sponsor has not set aside any funds to pay for any aspects of obstetric, child or related care and does not plan to pay for them.

**9) Benefits**

You may or may not benefit from participating in this study, but the knowledge gained may benefit others. The study treatment, office/clinic fees, and diagnostic and laboratory tests will be provided free of charge.

You may benefited in improve in LFT levels in acute liver failure**.** The cost of any other treatments for (disease), other medications, and any other tests your doctor may recommend will not be covered by this study.

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| **Print name of the participant** |  | **Date to be entered by the participant** |  | **Signature. Thumb impression** |

 **10) Alternative treatment available:** The standard treatment that is currently available will be provided to you.

**11) Insurance or Compensation:**

* **Compensation for injury:**

In the event that you experience a severe side effect during the study related to the study protocol, immediately contact Dr. Mithun Sharma at 040-23378888 or any doctor on emergency duty in the hospital. The patient has to be immediately bought to the Emergency room of our hospital or any nearby hospital for immediate evaluation by a doctor and provide medical care accordingly.

If you suffer a physical injury as a result of the research treatment or medical procedures required by the study plan (protocol), you will be reimbursed for customary fees and medical expenses actually incurred to treat such injury (to the extent not paid by your insurance or governmental coverage), provided that medical expenses will not be reimbursed if the injury is attributable to your failure to follow instructions contained in this informed consent or otherwise communicated to you by the study personnel, or to your underlying disease or medical condition. No other provision has been made for financial payments or other forms of compensation (such as lost wages, lost time from work or discomfort), with respect to such injuries. You do not give up any legal rights as a research subject by you signing this consent form.

**12) Voluntary Participation / Withdrawal from the Study**

Your participation in this study is entirely voluntary. It is up to you to decide whether to take part or not. Even if you do decide to take part, you are free to leave the study at any time without giving a reason. This will not affect your future medical care in any way. Furthermore, your study doctor may withdraw you from the study if he/she feels this is in your best interest, or in case of stopping the study early. If you decide to withdraw your consent to participate in the study, your study doctor will ask your agreement to perform the final evaluation and to collect the data through a report form. If you do not agree, no new data on you will be added to the database.

Your doctor, the Sponsor of the study or designee may end your participation in this study at any time without your consent. Possible reasons for ending your participation are if the study treatment offers you little or no future benefits or if you develop severe or life-threatening side effects. You will be discontinued from the study if you fail to follow directions for participating in the study.

**13) Sponsoring Company :**

Asian Institute of Gastroenterology

6-3-661, Somajiguda, Hyderabad - 500082

**14) Permission for Review of Records, Confidentiality and Access to Records**

The study doctor or research staff will collect information about you. This information called data, will be entered without your name, on a report form. In all of these report forms a code will replace your name. All the data collected will be kept confidential. Authorized personnel will enter the data into the sponsors computer data base. The data might be transferred to other sponsor location within the European union, The United States or other countries for review or analysis by the authorized personnel.

The data collected will be used for the evaluation of the study, and may be used in the future in related or other studies. The data may be submitted to health authorities for registration purposes, Member of the health authorities, ICMR and like independent Ethics Committee (IEC) / Institutional Review Board (IRB) or other persons required by law may review the data provided. This data may also used in publication about the study drug.

Your identity, including your name, for identity will not be revealed in any compilation, study report or publication at any time. Your study doctor will maintain a confidential list linking your name to the code and only authorized persons will have access to this list.

Your study doctor has collected laboratory specimen and will store the sample as a back-up at the study site unless required by a central laboratory for processing or long term storage. Some samples may be sent to laboratories that do specialized hepatitis B testing or measure the study drug in your blood. Regardless of where they are stored, the samples will be retained for a maximum of 10 years, then subsequently destroyed at the study site or at the centralized or specialized laboratory, You can contact your study doctor for results of these blood tests. Any specimens collected for this study are labeled with a code and are not specifically linked to your identity.

You have the right to obtain any initial and updated information about what data are recoded as well as the right to require corrections of errors according to local law and procedures. This information can also be forwarded to your primary physician if you so wish. You can discuss this further with your study doctor.

In order to make sure that the data collected from you is correct. It is necessary for the sponsor or national / International authorities to directly compare them with your medical record. Such checks will only be done by qualified and authorized personnel. While all reasonable efforts will be made to keep the data confidential, absolute confidentiality cannot be guaranteed.

If you agree, your personal doctor will be informed of your participation in the study.

1. **Questions/Information**

If you or your representative(s) have any questions regarding the study or in case of study related injuries, you should contact your study doctor at this telephone no. +91 040 23378888

* If you or your representative(s) have any questions regarding your patient rights as they relate to the study, you should contact the following personnel as allowed by local regulation and IRB/IEC policy,

Name of the IRB Personnel: \_\_\_\_Dr.P. N Rao\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Tel no. \_\_+91 040 23378888

Name of the IEC Personnel: \_\_\_\_Dr.M.Padmaja\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Tel no. \_\_+91 040 23378888

* If you seek emergency care, or if hospitalization is required, please inform the treating doctor that you are participating in a clinical trial.
* If any new information becomes available during the course of the study that may affect your willingness to participate, you will be informed.
1. **Consent Signatures**

Please read this section carefully an if in agreement please sign and date at the bottom of the page:

* I have been provided the details of the known or foreseeable side effects and risks of the research medication and study procedures that I may receive.
* I understand I am free to accept or refuse my participation at any time without giving a reason. My decision to accept or refuse my participation will have no effect on my continuing treatment. I understand that I am free to discontinue my participation at any time without giving a reason. My decision to discontinue my participation will have no effect on my continuing in treatment. I will keep all my rights to treatment and alternative therapy.
* I agree that data collected for the study will be used for the purpose described above, including transferring data to the\_\_\_\_\_\_ and processing and archiving by AIG in a coded form with respect to confidentiality of my data.
* I agree that direct access to my medical records may be given to authorized persons representing as well as national and international authorities. These authorities may include the US Food and Drug Administration or Independent Ethics Committee (IEC)/Institutional Review Boards (IRB’s).
* I understand that my study records can be forwarded to my primary physician if I request my study doctor to do so.
* I will not lose any rights that I have under law by signing and dating this form.
* I have read and understand the information presented in this informed Consent Form. I have been given the opportunity to ask questions have been answered.
* I will receive a signed and dated copy of this Informed Consent Form.
1. **For Women of Childbearing Potential, If applicable:**

The information on pregnancy prevention for women of childbearing potential has been reviewed with me

1. **Signature:**

I freely accept to participate in this study

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|  |  | Please initial box (Subject/ Patient) |
| (i) | I confirm that I have read and understood the information mentioned in this Informed Consent Form dated --------------(DATE) for the above study and have had the opportunity to ask questions. I have been informed of the nature, purpose procedures, duration and foreseeable effects and risk of the study, of its possible advantages and inconveniences and what I will be expected to do. My questions have been answered satisfactorily.  | [ ] |
| (ii) | I understand that my participation in the study 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. | [ ] |
| (iii) | I understand that the Sponsor of the clinical trial, others working on the Sponsor’s behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published.  | [ ] |
| (iv) | I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) | [ ] |
| (v) | I agree to take part in the above study. I agree to co-operate and inform unexpected or unusual symptoms experienced during the study. For the duration of the study, I will notify the investigator of any other medical treatments that may be necessary to undergo.   | [ ] |

To be signed simultaneously, (i.e. same date), by all parties:

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| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Print Name of < Subject / Patient > | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date (to be entered by Subject) | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature / Thumb Impression |
| (When consent of the subject/patient cannot be obtained the following signature should be added*:)* |
| Name of <subject’s/patient’s> legally acceptable representative\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_State relationship to the subject | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date (to be entered by legally acceptable representative) | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature / Thumb Impression |
| I have explained the study protocol and research involved, to the subject and answered all of his/her questions. I believe that he/she understands information described in this document and freely gives permission for his/her to participate. |
| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Name of Study Investigator or (Designee) obtaining consent | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date  | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature  |

(If the subject/patient / legally acceptable representative cannot read:

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| \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Name of Impartial Witness | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Date (to be entered by witness) | \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_Signature |

Distribution: original for study doctor, copy to Subject/ Patient