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**A Pilot Study to Evaluate the Safety and Tolerability and potential Efficacy of using a Bone Marrow Derived Mesenchymal Stem Cell Extracellular Vesicle Isolate Product (EVIP) in patients with Non-Alcoholic Fatty Liver Disease (NAFLD)**

PRINCIPLE INVESTIGATOR: James Howton D.O.

STUDY LOCATION: 3553 Clydesdale Parkway. Suite 230. Loveland, CO 80538

PHONE: 970-278-0900

STUDY NUMBER:

SUBJECT NAME:_____DATE:_____

Please read this form carefully. The following information describes a study that you are being asked to participate in and describes your rights and obligations as a participant in the study. This is a subject consent form for you to participate in the study and to authorize limited disclosure of your health information. If you agree to take part in the study, you need to sign this form. If there is anything you do not understand, or anything you may have a question about, you mayask the principal investigator.

You are being asked to take part in a research study carried out by James Howton, D.O. This form explains the research study and your part in it should you decide to join the study. Please read the form carefully, taking as much time as you need. Ask the researcher to explain anything you don't understand. You can decide not to join the study. If you join the study, you can change your mind later or quit at any time. There will be no penalty or loss of services or benefits if you decide to not take part in the study or quit later. This study has been approved for humansubject participation by the American Academy of Stem Cell Physicians Institutional Review Board.

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There are no approved medications for the treatments of NAFLD. The current Standard of Care is to address factors associated with NAFLD such as obesity, insulin resistance and lipid abnormalities with the goal of decreasing the likelihood of developing NASH and progressing towards liver fibrosis.

**What is this study about?**

This research study is being done to evaluate the SAFETY and Tolerability and Potential Efficacy of using a single 10cc IV treatment of an Extracellular Vesicle Isolate Product (EVIP) in patients with NAFLD.

*You are being asked to take part because you suffer from NAFLD and desire to improve your function.*

**The IV infusion will take 30 minutes to perform. You will be required to undergo a physical exam and obtain blood work before and after the treatments and fill out some forms to monitor your progress. You will also be required to undergo a liver ultrasound before the study and 6 weeks, 3 months and six months after the EVIP IV infusion**

You cannot take part in this study if: Candidates who meet **ANY** of the following Exclusion Criteria at the time of the study procedure are **NOT** eligible for enrollment in the study:

1. The subject is unable to conform to the study protocol follow-up procedures and visits.
2. The subject has major risk factors such as a history of narcotic abuse, paucity of family support, unemployed, history of previous physical or mental abuse or severe medical comorbidities beyond NAFLD.
3. Any patient with a previous history of alcohol abuse.
4. Patients with a history of steroid use within 3 months.
5. Any patient with a history of any Cancer within the last 5 years.

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6. Any patient with a history of cardiac or renal disease.
7. Any patient positive for HIV.
8. Patients who have received any other investigational drugs for treatment.
9. Any patient felt not to be a suitable study patient by the principal Investigator.

**What will I be asked to do if I am in this study?**

If you take part in the study, you will be asked to: 1) Submit to a medical history and physical examination and have your imaging studies and outside pertinent medical records reviewed. 2) Be evaluated to see if you meet all the inclusion/exclusion criteria. 3) Have a liver ultrasound and liver function blood tests before then again 6 weeks and 3 months after the treatment. 4) Undergo one 10cc IV treatment of the EVIP. This will be performed under the direction of Dr. James Howton. Each IV infusion procedure will typically take around thirty minutes.

**Are there any benefits to me if I am in this study?**

- Unfortunately, there are no guarantees for personal improvement with the injection.
- The potential benefits to you for taking part in this study are: Participation in the study will provide ageneral benefit to better guide the use of the EVIP in patients with NAFLD by establishing a record of patient SAFETY as per the study protocol. Additionally, subjects participating in the study may receive a direct benefit as follows:
- Evidence for improved patient outcomes following the IV EVIP.
- Potential for stabilization or improved liver health.
- Potential for enhanced recovery and better long-term outcomes compared to no treatment

**Are there any risks to me if I am in this study?**

The potential risks from taking part in this study are: This is considered a high-risk study because the EVIP is a non-FDA approved biologic.
As with any IV infusion there is a risk of discomfort, bruising, infection and vein damage.

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**Will my information be kept private?**

The data for this study will be kept confidential to the extent allowed by federal and state law. The data may be shared with both the FDA and the IRB. Under certain circumstances, information that identifies you may be released for internal and external reviews of this project. Any adverse reactions will be communicated to the Institute of Regenerative and Cellular Medicine (IRCM) within 48 hours. No published results will identify you, and your name will not be associated with the findings. All data for this study will be kept for 5 years.

The results of this study may be published or presented at professional meetings, but the identities of all research participants will remain anonymous.

**Are there any costs or payments for being in this study?**

You will not receive money or any other form of compensation for taking part in this study and there is not any cost to you to participate in the study.

**What are my rights as a research study volunteer?**

Your participation in this research is completely voluntary. You may choose not to be a part of this study. There will be no penalty to you if you choose not to take part. You may choose not to answer specific questions or to stop participating at any time.

**Who Should I Contact if I have further questions or concerns?**

You may contact the principal investigator. Dr. James Howton at 970-278-0900.

This study was reviewed by the IRCM Institutional Review Board (IRB). An IRB reviews research to protect the rights and welfare of study participants. Should subjects wish to contact an impartial third party not associated with this study they may contact J.P. Faber, Secretary of theIRB of the Institute of Regenerative and Cellular Medicine (IRCM) at jpfaber@ircm.org or (786) 271-2156.

**What does my signature on this consent form mean?**

Your signature on this form means that:

- You understand the information given to you in this form.
- You have been able to ask the researcher questions and state any concerns.

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- The researcher has responded to your questions and concerns.
- You believe you understand the research study and the potential benefits and risks that are involved.
- You are at least 18 years of age.

**Statement of Consent**

I give my voluntary consent to take part in this study. I have read the above information about this study and have had a chance to ask questions. My questions have been answered to my satisfaction. I have been told that I can change my mind later if I want to. By signing this consent form, I am not giving up any of my legal rights. I will be given a copy of this consent document for my records.

| Signature of Participant | Date |
|---|---|
| Printed Name of Participant | |

**Statement of Person Obtaining Informed Consent**

I have carefully explained to the person taking part in the study what he or she can expect.
I certify that when this person signs this form, to the best of my knowledge, he or she understands the purpose, procedures, potential benefits, and potential risks of participation.I also certify that he or she:

- Speaks the language used to explain this research.
- Reads well enough to understand this form or, if not, this person is able to hear and understand when the form is read to him or her.
- Does not have any problems that could make it hard to understand what it means to take part in this research.

| Signature of Person Obtaining Consent | Date |
|---|---|
| Printed Name of Person Obtaining Consent | Role in Research Study |

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