RESEARCH SUBJECT INFORMATION, CONSENT FORM, AND HIPAA AUTHORIZATION FOR RESEARCH

TITLE OF PROJECT: A single center, prospective study to compare the quality and quantity of the cellular content of M-PRP harvested after peripheral mobilization of progenitor cells using filgrastim versus pegfilgrastim.

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SITE(S): Andrews Research & Education Foundation (AREF)

SPONSOR: State Grant

INVESTIGATOR CONTACT INFORMATION:

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Informed Consent Form

A single center, prospective study to compare the quality and quantity of the cellular content of M-PRP harvested after peripheral mobilization of progenitor cells using filgrastim versus pegfilgrastim

INTRODUCTION:

To decide whether you wish to participate in this research study, you should understand why the study is being done, how the study will be run, the types of study procedures involved, your time commitments, and the possible risks and/or benefits associated with your participation to enable you to make an informed decision. This process is known as "informed consent."

This written consent form and HIPAA Authorization provides detailed information about the research study. This consent form and HIPAA Authorization may contain words that you do not understand. Please ask the study doctor ("Investigator" or "Researcher") or the study staff to explain any words or information that you do not clearly understand. Before you decide to take part in this study, you may want to think about it more, or discuss it with family or friends. You can take a copy of this form home with you before making your decision. Your participation in this study is voluntary. You should not join this research study until all of your questions are answered to your satisfaction.

If you wish to participate in this research study, you will be asked to sign this consent form and HIPAA Authorization. You must sign before any study procedures are done. You will be given a copy of this consent form and HIPAA Authorization to keep for your records.

PURPOSE OF THE RESEARCH STUDY:

Doctors are using treatments which involve taking something from your body from one location to help injuries and diseases in another location of your body. One example is taking blood from your body and making an injection to treat an injury at another location. The blood product prepared through spinning it in a centrifuge is the basis for platelet rich plasma (PRP), often referred to as a biologic product. PRP has been studied for the treatment of injuries of bone, muscle, and joints. It has been established that repair cells move toward PRP when it is injected. Some repair cells begin in bone marrow and move to areas of injury through your blood stream when an injury occurs. Mobilization agents are drugs which have been developed by drug companies to increase the production of cells in the bone marrow and release to the peripheral blood circulation. We believe that using mobilizing agents and PRP techniques can make a better biologic product to treat injuries of the bone, muscle, and joints.

WHAT ARE FILGRASTIM AND PEGFILGRASTIM?

Filgrastim and Pegfilgrastim are leukocyte growth factors which increases the circulation of stem/repair cells in the blood which might be useful for the treatment of injuries of bone, muscle, and joints. Granix® (tbo-filgrastim), an FDA-approved biosimilar of filgrastim, will be used for the filgrastim mobilization. Fulphila® (pegfilgrastim-jmdb), an FDA-approved biosimilar of pegfilgrastim, will be used for the pegfilgrastim mobilization. Biosimilars are biological products that have no clinically meaningful differences from a reference product. Biosimilars are approved by the FDA after rigorous evaluation and testing by the applicant. The above biosimilars were selected by the study investigator and a consulting board-certified oncologist based on the similarity of indication, risk/benefit ratio, previous clinical testing, and general availability.

WHAT WILL HAPPEN DURING THIS STUDY?

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After consenting to the study, the physician will complete a health screening and provide you with information on Granix® (tbo-filgrastim) and Fulphila® (pegfilgrastim-jmdb). During this initial screening visit, the physician will obtain your medical history and perform a physical exam. If you pass the screening, an initial blood draw will occur. Your results will be evaluated, and you will be informed about your eligibility in the study.

Once you are eligible for the study, you will begin the filgrastim and pegfilgrastim treatment series separated by 8 weeks in the specified order or reverse.

During the filgrastim treatment, four serial days of filgrastim will be administered with a blood draw on the first and a day after last administration. During the pegfilgrastim treatment, you will receive one dose of pegfilgrastim with a blood draw on the first day and a week after pegfilgrastim administration.

SELECTION OF SUBJECTS:

If you decide to be in this study, you will be one of ten males in this research study. You must be between the ages of 19 and 39. You must consent to come for four serial days for filgrastim treatment and two additional visits for pegfilgrastim treatment with blood draw at before and after each treatment.

HOW LONG WILL I PARTICIPATE IN THIS STUDY?

The approximate duration of this study will be 10 weeks.

WHAT AM I RESPONSIBLE FOR?

After consenting to the study, you will be responsible for attending the scheduled filgrastim/pegfilgrastim administration and subsequent blood draw appointments. It will also be your responsibility to communicate openly with the research team during follow up phone calls.

RESEARCH PROCEDURES:

If you agree to be in the study, we will ask you to do the following things:

Visit 1: Screening Visit (Day 1)

1. The Research Team will complete the screening process along with the screening form (Consenting, Review Medical History and of Inclusion/Exclusion Criteria).
2. The subject will be provided the Granix® (tbo-filgrastim) and Fulphila® (pegfilgrastim-jmdb) handouts to continue best practices.
3. If not excluded, the study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
4. Standard vitals will be taken.
5. A blood draw will be completed (CBC, CMP) and sent to the lab.
6. Next visit will be scheduled if all screening procedures are within acceptable limits. Next visit may occur on the same day as screening.

Visit 2: 130 mL blood draw, 1st Dose of Filgrastim

1. The Research Team will discuss any adverse events, changes to medications, or concerns.

7. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
8. Standard vitals will be taken.
2. A standard venipuncture will be performed on the left or right upper extremity.
3. Before the treatment 130.0 ml of blood will be drawn and processed with the Arthrex Angel® System (Arthrex, Inc, Naples, FL USA).
4. The 10 mcg/kg dose of filgrastim will be administered to the participants subcutaneously
5. Granix® (tbo-filgrastim) information handout will be given after administration.
6. Compensation will be dispensed; next visit will be scheduled.

Visit 3: 2nd Dose of Filgrastim (1 day from Visit 2)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.
2. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
3. Standard vitals will be taken.
4. The 10 mcg/kg dose of filgrastim will be administered to the participants subcutaneously.
5. Compensation will be dispensed, next visit will be scheduled.

Visit 4: 3rd Dose of Filgrastim (1 day from Visit 3)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.
2. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
3. Standard vitals will be taken.
4. The 10 mcg/kg dose of filgrastim will be administered to the participants subcutaneously.
5. Compensation will be dispensed; next visit will be scheduled.

Visit 5: 4th Dose of Filgrastim (1 day from Visit 4)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.
2. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
3. Standard vitals will be taken.
4. The 10 mcg/kg dose of filgrastim will be administered to the participants subcutaneously.
5. Compensation will be dispensed; next visit will be scheduled.

Visit 6: 130 mL blood Draw (1 day from Visit 5)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.
2. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
3. Standard vitals will be taken.

4. A standard venipuncture will be performed on the left or right upper extremity.
5. Before the treatment 130.0 ml of blood will be drawn and processed with the Arthrex Angel® System (Arthrex, Inc, Naples, FL USA).
6. Compensation will be dispensed; next visit will be scheduled.

Safety Follow-Up: Phone Call (7 days from Visit 6, +/- 5 days)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.

Safety Follow-Up: Phone Call (28 days from Visit 6, +/- 5 days)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.

Visit 7 (42 days after Visit 6, +/- 5 days): 130 mL blood draw, 1st Dose of Pegfilgrastim

1. The Research Team will discuss any adverse events, changes to medications, or concerns.
2. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
3. Standard vitals will be taken.
4. A standard venipuncture will be performed on the left or right upper extremity.
5. Before the treatment 130.0 ml of blood will be drawn and processed with the Arthrex Angel® System (Arthrex, Inc, Naples, FL USA).
6. The 6 mg dose of pegfilgrastim will be administered to the participants subcutaneously.
7. Fulphila® (pegfilgrastim-jmdb) information handout will be given after administration.
8. Compensation will be dispensed, next visit will be scheduled.

Visit 8 (7 days after Visit 7): 130 mL blood draw

1. The Research Team will discuss any adverse events, changes to medications, or concerns.
2. The study Physician will perform the physical exam including height/weight, head/neck, cardiovascular, lung, and abdominal examinations.
3. Standard vitals will be taken.
4. A standard venipuncture will be performed on the left or right upper extremity.
5. Before the treatment 130.0 ml of blood will be drawn and processed with the Arthrex Angel® System (Arthrex, Inc, Naples, FL USA).
6. Compensation will be dispensed, next visit will be scheduled.

Safety Follow-Up : Phone Call (7 days from Visit 8, +/- 5 days)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.

Safety Follow-Up : Phone Call (28 days from Visit 8, +/- 5 days)

1. The Research Team will discuss any adverse events, changes to medications, or concerns.

Depending on the group to which you are assigned you may receive the above schedule of events or the same events in the reverse order.

RISKS AND DISCOMFORTS:

Risks of Blood Draw:

- Pain
- Bruising
- Redness, swelling near draw site
- Infection

Common Risks of Filgrastim:

- bones pain
- pain in the extremities

Common Risks of Pegfilgrastim:

- bones pain
- pain in the extremities
- Musculoskeletal and connective tissue disorders

Other severe adverse effect has been reported following the administration of Filgrastim and Pegfilgrastim:

- Splenic Rupture and splenomegaly (enlarged spleen)
- Acute Respiratory Distress Syndrome (ARDS): It is an acute lung condition where organs have inadequate oxygen supply due to fluid build-up in the lungs.
- Serious Allergic Reactions/hypersensitivity, including anaphylaxis, skin rash, urticaria, generalized
- erythema, and flushing
- Sickle Cell Disorders/Crisis: A sickle cell crisis occurs when sickle-shaped red blood cells clump together and block small blood vessels that carry blood to certain organs, muscles, and bones.
- Glomerulonephritis: It is a group of diseases that injure the part of the kidney that filters blood (called glomeruli).
- Alveolar Hemorrhage and Hemoptysis where blood tends to fill alveolar spaces at multiple sites.
- Aortitis refers to inflammation of the aorta
- Capillary Leak Syndrome is characterized by massive leakage of plasma from blood vessels into neighboring body cavities and muscles. This results in a sharp drop in blood pressure that, if not treated, can lead to organ failure and death. As the fluid leaks out from the bloodstream, blood volume and blood pressure drop. This can starve tissues in the kidneys, brain and liver of the oxygen and nutrients they need for normal function.
- Thrombocytopenia is a condition in which platelet level decrease.

- Leukocytosis, it is a condition in which the white cell (leukocyte count) is above the normal range in the blood.
- Cutaneous Vasculitis is a group of disorders resulting from inflamed blood vessels in the skin.
- Contact dermatitis and local skin reactions such as rash, pruritus, and urticaria have been reported with the use of the on-body injector for Pegfilgrastim, possibly indicating a hypersensitivity reaction to the adhesive.
- Application site reactions (including events such as application site hemorrhage, application site pain, application site discomfort, application site bruise, and application site erythema) have been reported with the use of the on-body injector for Pegfilgrastim.

What if I am injured because of this study?

In the unlikely event of an emergency, AREF will provide basic first aid medical treatment. However, if you were to require additional medical care because of participating in this study, you would need to contact your personal physician at your own expense.

The Investigators, the employers of the Investigators, and the Research Site do not have programs for compensating subjects for injury or complications related to human subjects research. Any treatment will be at your expense.

With any research involving patients there is the inherent risk of a breach in patient confidentiality though this will be minimized using participant code numbers and adherence to all HIPAA guidelines.

There is a small risk of disclosure of your protected health information, which will be minimized where possible, including the removal of all identifiable information from data collection sheets and storing study information in secure locations as described in more detail below.

ALTERNATIVES:

You do not have to take part in this study and can choose to proceed without receiving any treatment from filgrastim and/or pegfilgrastim.

BENEFITS:

What are the health benefits of participating in this study?

No benefits to subject health may be obtained from participation in this study, but it is also believed that the information obtained in this study will help improve regenerative orthobiologic product development for point-of-care application.

Will it cost me anything to be in this study?

There will be no cost to you for the filgrastim and/or pegfilgrastim injections, blood draws, or physical exams.

Will I be paid for participating in this study?

Compensation will be provided to participants on a pre-set schedule. A $50.00 dollar stipend will be provided to participants on the first day of receiving the mobilization agents. Each subsequent scheduled study treatment visit will award the participant a $75.00 stipend until the total of $500.00 is met.

Who is funding this study?

This study is being funded by the State of Florida Grant awarded to the Andrews Research & Education Foundation.

CONFIDENTIALITY:

All personal information is strictly confidential, and no names will be disclosed except as required by law. Your individual performance or results will not be reported; when/if this study is published, only the results of all participants as a group will be reported. During this study, your information will be de-identified and identified only by a subject number.

All information and data collected during this research will be recorded in a spreadsheet. This spreadsheet will not contain protected health information. The spreadsheet will be stored in a secure password protected folder on a laptop that only the study Investigators will have access to and will be permanently deleted following publication of all manuscripts, if any, written because of this research. Records related to this study will be securely retained in a secure location for a period of 3 years after the completion of the study or longer as required by law. At that time, all records will be properly destroyed.

HIPAA and PROTECTED HEALTH INFORMATION:

We are dedicated to protecting the privacy of that information. Because of this promise, we must get your written authorization (permission) before we may use or disclose your protected health information, also called "PHI," or share it with others for research purposes.

You are being asked to sign this authorization allowing us to share your PHI for purposes of this research study. If you sign this authorization, you give permission to the Investigators to use or disclose your PHI for the research study described here. You can decide to sign or not to sign this authorization. However, if you choose not to sign this authorization, you will not be able to take part in the research study. Any choice made will not affect your access to medical care.

The United States government has issued a privacy rule to protect the privacy rights of patients ("Privacy Rule"). This rule was issued under a law called the Health Insurance Portability and Accountability Act of 1996 (HIPAA). The Privacy Rule is designed to protect the confidentiality of your health information. Andrews Research and Education Foundation is required by law to protect your health information. By signing this document, you authorize Andrews Research and Education Foundation to use and/or disclose your health information for this research. Those persons who receive your PHI may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your information with others without your permission, if permitted by laws governing them.

During this study, the Investigators will need to use your PHI. PHI is information about you that could be used to identify you, such as your name, address, telephone number, date of birth, new and existing medical records, or the types, dates, and results of various tests and procedures. This may also include information in your medical record and information created or collected during the study. We may also ask other health care providers to give us any information about your health status or your health care. If you sign this authorization, you are agreeing to allow the Researchers to use your PHI to carry out this study.

By signing this authorization, and solely for the purposes of completing this research, you allow the research staff to disclose your PHI to outside entities involved in completing the research project, such as people who review the research study, their staff, lawyers, government groups (such as the Food and Drug Administration), or safety monitors. The study data that the Researchers send to these entities will not include your name, address,

or social security number, but instead, will be designated with a code number. However, your medical records can be reviewed or copied at the study site by regulatory authorities or other oversight bodies, including the Institutional Review Board. The purpose of these reviews is to make sure the study is being conducted properly and that the data is being collected correctly, or for other purposes allowed by law.

Your PHI may no longer be protected by the privacy rule once it is disclosed. Your PHI will be kept as confidential as possible under the law; however, absolute confidentiality cannot be guaranteed.

You may cancel this authorization at any time by writing to the Investigator at the Contact Information provided above. If you cancel this authorization, the Researchers will no longer use or disclose your PHI under this authorization for this study, unless it is needed to preserve the scientific integrity of the study. Information obtained before you cancel the authorization may still be used by the Researchers. If you do not cancel this authorization, it will automatically expire at the conclusion of the research study.

CONFLICT OF INTEREST:

There are no conflicts of interest to disclose for the investigator and this study.

VOLUNTARY PARTICIPATION/WITHDRAWAL:

Taking part in this study is **voluntary.** Your medical treatment, costs of treatment and eligibility for benefits will not be affected if you decide not to sign this Consent Form or participate in the study. If you agree to participate, in the event new information becomes available that may affect your willingness to participate in this study, this information will be given to you so that you can make an informed decision about whether to continue your participation.

QUESTIONS:

It is your right, as a research participant, to ask questions at any time regarding the procedures involved and any aspects of this study including the potential benefits or risks. For any questions you may have for the Investigators, you may contact them at (850) 916-8796. For any questions you may have for the Research Team, you may contact them at (850)916-8590.

If you have questions about your rights as a research subject or if you have questions, concerns or complaints about the research, you may contact the Baptist Hospital Institutional Review Board* at (850) 469-2227. The IRB will not be able to answer some types of questions, such as questions about appointment times.
*The IRB is a group of individuals who independently review research

STATEMENT OF CONSENT TO PARTICIPATE IN THIS RESEARCH STUDY:

By signing this consent form, I agree to and acknowledge the following statements:

I agree to participate as a subject with the understanding that my participation is completely voluntary, and that I may withdraw at any time without prejudice by sending a written request to the Investigator at the Sports Medicine Research Lab, Andrews Research and Education Foundation, 1020 Gulf Breeze Pkwy, Gulf Breeze, FL 32561.

I have read and understand the above information and have been given the opportunity to discuss it and ask questions.

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I understand that this authorization does not have an expiration date.

I have received a copy of this authorization form for my records.

I have been informed that I may contact the Investigators by phone at (850) 916-8796 in order to answer any questions that I may have at any time during my participation.

_____
Printed Name of Participant

_____ _____
Signature of Participant Date

_____
Printed Name of Person Conducting Informed Consent

_____ _____
Signature of Person Conducting Informed Consent Date