Participant Informed Consent Form

Protocol Title: A Prospective, Single- Center, Phase IV Interventional, Single Arm Trial for the Evaluation of subcutaneous recombinant Hirudin 15 mg (RB variant) in prophylaxis of Deep Vein Thrombosis (DVT) post major orthopedic operations.

Protocol No.: Sub-Thromb-001

Principal Investigator's Name: Prof. Dr. Ayman Soliman

Sub Investigator's Name: Dr. Abdallah Hammad

Dear Participant,

You are invited to participate in a research study performed for a registered & marketed medication. You are kindly asked to take time to carefully read this document, which will address and explain all the important information, which will help you take your decision in whether you would participate in this study or not. You can also take this document home with you to discuss it with your family members, friends or someone you feel comfortable with. If anything is unclear or there are words that you do not understand, please feel free to ask questions at any time, and the study doctor will take time to answer them & explain to you until you are comfortable and understand the study procedures, risks, benefits and also what will be required of you as participant. If you have questions later, feel free to ask me or any study doctor available.

The study will be conducted according to the declaration of Helsinki (last updated October 2013) and Guidelines for good practice in the conduct of clinical trials with a human participant, which deals with your rights as a research participant and which guide the study doctor (investigator) in biomedical research involving human participants. The study doctor will be paid by Minapharm Pharmaceuticals to conduct this study.

Why have you been invited to take part in this study?

The reason you have been invited to take part in this research study is because your doctor has given you the study drug as a prophylaxis of Deep Vein Thrombosis (DVT) post major orthopedic operations. Thus, you have been invited to take part in the study to determine if the medicine is effective in preventing Deep Vein Thrombosis (DVT) post major orthopedic operations.

What are your rights as a participant?

Your participation in this study is voluntary. You may choose not to be in the study or to leave the study at any time by telling the study doctor. If you decide not to participate in the study or to withdraw your consent, you will not lose any benefits to which you are otherwise entitled and you will not be treated any differently by the doctor or staff members due to your decision. The study doctor has the right to withdraw you from the study if it is considered to be in your best interests, in which event, the reasons will be given to you.

Purpose of the study:

The primary objective of this study is to evaluate the efficacy of r-Hirudin RB variant 15 mg in DVT prophylaxis post major orthopedic operations. And, the secondary objective of this study is to evaluate the safety of r-Hirudin RB variant 15 mg in DVT prophylaxis post major orthopedic operations in terms of serious bleeding.

The study population consists of 200 patients, which are post major orthopedic operations.

The expected period of your participation is approximately 15 days, from the day of the screening visit.

Who can take part?

✓ You or your doctor must be able to answer **YES** to all of these requirements to be suitable to take part in this study:

1- Subject is 18 years of age or older

2- Subject's Body Weight >60 kg

3- Subject is undergoing major orthopedic operations

4- Subject is ready to sign the informed consent form (ICF)

5- Subject is ready to discontinue any agents that affect haemostasis prior to the study medication use unless strictly indicated. These agents include medications such as: anticoagulants, thrombolytics, non-steroidal antiinflammatory agents (including Ketorolac tromethamine), preparations containing aspirin, systemic salicylates, ticlopidine, dextran 40, clopidogrel, other anti-platelet agents including glycoprotein IIb/IIIa antagonists or systemic glucocorticoids.

X You or your doctor must be able to answer **NO** to all of these requirements to be suitable to take part in this study. If you have or have had any of the following, you will not be allowed to take part in the study:

1- Subject has significant bleeding injury such as solid organ laceration or intracranial bleed at discretion of attending physician.
2- Subject has Hypersensitivity to Hirudin or prior documented Allergy to its components.
3- Subject is pregnant or breast feeding.
4- Subject has encountered a hemorrhagic stroke in the preceding 3 months.
5- Subject with abnormal baseline coagulation characterized by an INR >1.4, obtained at the discretion of the treating clinician.
6- Subject requires therapeutic anticoagulation for atrial fibrillation, prior VTE, or mechanical heart valve.
7- Subject with a history of coagulation disorder.

8- Subject is treated with concomitant anti-platelet agent other than aspirin 326 mg or more, daily
(Platelet count< 100 X109 /dl).
9- Subject with active bleeding.
10- Subject with a life expectancy less than 1 month

Study Design:

This study has been designed to assess the efficacy & safety of subcutaneous recombinant Hirudin 15 mg (RB variant) in patients undergoing major orthopedic operations such as Total knee & hip Arthroplasty. The treatment duration is approximately 15 days. A total of 100 participants will be included in the study. There are 3 study phases. During Phase 1 (Preoperative Phase) subject will be screened for fulfillment of the eligibility criteria. During the second phase (Operative Phase/ Day 0), subject will undergo surgery and treatment will be initiated. Finally, the Postoperative Phase which consists of 3 follow- up visits which are scheduled on days 1, 8, and 15.

Study Procedures:

1. **The Preoperative Phase: Screening Visit (Visit 1)/ Eligibility**

   During this visit, you will be asked to sign the Informed Consent Form, after being introduced to the study, its procedures & being assured of your rights. Then, you will be screened for fulfillment of the inclusion and exclusion criteria. Moreover, the following data will be recorded: your demography, history of diseases, Vital signs (Blood pressure, Pulse rate, Respiratory rate & Temperature), & any concomitant medication. Also, if you are a female in the child-bearing age, you will be asked to perform a urine pregnancy test. Finally, the following lab tests will be performed: Hemoglobin count, Platelets count, APTT, INR, SGPT, SGOT, Serum albumin, serum Bilirubin, serum creatinine and random blood glucose. If you were found eligible, you will be considered to be included as a study subject.

2. The Operative Phase: Day 0 (Visit 2)

   During this visit, patient's registries for the type of surgery done, Type of anesthesia, patient position and type of prosthesis, & blood transfusion during surgery should be recorded. APTT should be done before IMP administration, in addition to the patient's data of Thrombexx® administration regimen decided by the treating investigator according to the standard clinical practice or as prescribed in the usual manner in accordance with the terms of the local marketing authorization with regards to dose, population and indication (and within the

approved label). And IMP dispensing starts 6 hours after surgery or upon adequate hemostasis will be done. APTT will also be done 4 & 8 hours after the first dose.

3. The Postoperative/ Follow up Phase: Days 1, 8 & 15.

During those visits, which are done on Day1 in the hospital, Day8 & Day 15 in outpatient clinic, a spiral chest CT will be performed to detect signs of Pulmonary Embolism, Doppler ultrasound will be performed to detect any DVT, Bleeding assessment will be done, & APTT blood test will be performed. Moreover, any concomitant medications, Hospital stay or adverse event data will all be recorded if present.

Summary of the study procedures for all the visits:

Activity	Pre-operative phase (Screening)	Operative phase (Day 0)	Follow -up 1 (Day 1)	Follow -up 2 (Day 8)	Follow-up 3/ End of Study (Day15)
ICF Signature	×				
Inclusion/Exclusion Criteria	×				
Demographic Data	×				
Medical History	×				
Vital signs	×	×	×	×	×
Concomitant Medication	×	×	×	×	×
Physical Examination	×	×	×	×	×
Laboratory investigation	×		×	×	×
Type of surgery		×			
Assessment of bleeding		×	×	×	×
IMP Administration		×	×	×	×
Assessment of DVT			×	×	×
Assessment of PE			×	×	×
Assessment of therapeutic response					×
APTT	×	×	×	×	×

Adverse Event		×	×	×	×
Study completion					×

What is expected from you as a study participant?

For this study to be successful, it is important that you co-operate fully with the study doctor and follow his or her instructions precisely. Please inform the study doctor of all the medication that you are currently taking. Do not take any other medication, including over the counter, prescription, herbal or traditional, without first informing the study doctor. You will be asked to return the blisters of the medication you received for the study.

What are the possible risks or side-effects of being in the study?

Thrombexx common side effects are bleeding manifestations, hypersensitivity reaction including rash and urticaria, injection site reactions, very rarely anti-hirudin antibodies detected on re-exposure.

What are the possible benefits of being in the study?

It is not guaranteed that you would benefit from your participation in the study.

The information gained during the study can benefit society by gaining useful information on the future treatment of seasonal allergic rhinitis accompanied with mild asthma, which may improve the patterns of care of this disease.

Compensation in the event of a trial-related injury

You will get medical treatment if you are injured as a result of taking part in this study. You will not be charged for this treatment. The Sponsor will pay for the reasonable costs of your medical treatment and compensation will be provided to the extent permitted by the law if:

1. The study medication was taken as directed by the Study Doctor.
2. The injury was not intended.
3. Study Doctor was immediately notified about your injury.
4. The medical advice of the Your Study Doctor was followed.

The sponsor will not be liable for any loss, injuries and/or damages which you may sustain to the extent that such loss is caused by:

1. The use of any other medicine during the study.
2. Any injury as a result of you not following protocol requirements, instructions or indications given to you by the study doctor.
3. Any injury arising from any action or lack of action on your part in dealing adequately with a side-effect or reaction to the study medication.
4. An injury arising from negligence on your part.

By signing this document, you are not giving up any of your legal rights. Specifically, your legal

right to claim compensation for injury where you can prove negligence is not affected.

Confidentiality

All records identifying you will be kept confidential, and to the extent permitted by applicable laws and regulations, will not be made publicly available. The study doctor and research team will use personal information about you to conduct this study. This may include your name, address, medical history and information from your study visits. However, this personal information is not included in the study data that will be forwarded to the sponsor or sponsor representatives. You will be identified by a coded number in any reports or publications produced from this study (study data).
To confirm that the study data collected about you is correct and relates to you, selected people who work for the sponsor (such as monitors and auditors), as well as representatives of the government regulatory authorities and ethics committees will have access to your personal information at the study site. These persons are required to maintain the confidentiality of your information. By signing this document, you are authorising such access.

The sponsor or representatives may use the study data sent to them for the following purposes:

1. To see if the study medication works and is safe.
2. To compare the study medication to other medications.
3. For other activities relating to the study medication.

You have the right to ask the study doctor about the data being collected on you and to see your personal health information, as well as have access to any necessary corrections that are made to the data.

When conducting this study, the study sponsor or his representative as well as the principal investigator are subject to the provisions of the Egyptian laws.

Payment, expenses and costs

You will not receive payment for participating in this study.

Any study-related costs, such as study medication, treatment, tests, examinations and procedures specified in the protocol will be paid for by the sponsor-neither you, your medical scheme nor your healthcare provider will be responsible for these expenses.

Termination of participation

Your participation in the study may be stopped for the following reasons:

1. If you don't follow the study doctor's instructions.

2. If you do not take the study medication as prescribed.

3. If the study doctor decides that it is in your best interests.

4. If there aren't enough participants in the study, or the study has acquired the required number of participants.

5. If the sponsor stops the study or closes the study site for unknown reasons.

Withdrawal

You are free to withdraw at any time.

At the discretion of the investigator, if he/she believes that continuation in the trial would be detrimental to your well-being in any way;

At the discretion of the monitor if he/she believes that continuation in the trial would be detrimental to your well-being in any way; or Any protocol non-conformance that results in a significant risk to the participant's safety

Study results

A description of this clinical trial will be available on http://www.ClinicalTrials.gov , as required by the Egyptian Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Contacts for answers related to the research, and your rights as a research participant

In case you have questions about the study, please contact:

Name: _____(PI and/or Sub-I) Phone no.: _____

Name: _____(PI and/or Sub-I) Phone no.: _____

If you have any questions about your rights as participant in this research study, you may also contact your Ethics Committee/Institutional Review Board:

Name: _____(EC/IRB Contact Name)

Address: _____

Telephone number: _____

If you have questions about this trial, you should first discuss them with your doctor or the ethics committee (contact details as provided on this form).

Consent Statement

By signing below, I agree that:

1. I have read or had been read to me the informed consent form.
2. The purpose, treatment and procedures of this trial have been explained to me and I understand them.
3. I understand my responsibilities as a trial participant.
4. I understand that participation in the trial is voluntary and that I can refuse to participate or withdraw at any time, without it affecting my ongoing care.
5. I have been informed of the possible risks, harm and inconvenience of participating.
6. For women: I am not pregnant, breastfeeding or trying to fall pregnant.
7. I have been informed of the expected benefits of the trial.
8. I have been informed of the compensation and treatment that would be available to me in the event of a trial-related injury.
9. I have had sufficient time to ask questions and they were answered to my satisfaction.
10. I have been given time to discuss the trial with others and to decide whether or not to take part.
11. I am aware that the results of the trial, including personal details about me and my health information may be reasonably disclosed to the sponsor, regulatory authorities and research ethics committees, if required by law.
12. I will receive a signed and dated copy of this informed consent form.
13. I agree to participate in this trial.

_____ _____

Printed Name of participant Signature or Finger print of Participant

_____

Date of Signature

_____ _____

Printed Name of PI or person obtaining

the Consent Signature

_____

Date of Signature

I hereby verify that verbal consent was obtained from the above participant. The participant has been informed about the risks and the benefits of the research, understands such risks and benefits and is able to give consent to participate, without coercion, undue influence or inappropriate incentives.

Printed name of witness*	Signature of witness*
Date	Patient Name (Printed by Impartial Witness*)

*: Where applicable