**Study Title: Ticagrelor in Methotrexate-Resistant Rheumatoid Arthritis (TIMERA)**

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# 1 Introduction

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

## *1.1 Background*

In addition to significant morbidity from RA morbidity, the risk of myocardial infarction is increased nearly 2-fold in the setting of RA.(Meune et al., 2010; Solomon et al., 2006) Rheumatoid arthritis induced activation of systemic inflammatory pathways and endothelial dysfunction has been implicated in this increased risk.(Sattar et al., 2003) Inflammation mediates many aspects of disease pathogenesis in atherosclerosis, involving diverse cell types and mediating signals.(Hansson, 2005) Platelets have been implicated in atherosclerosis because of their pro-inflammatory and thrombogenic effects.(Gawaz et al., 2005) Moreover, pathological and clinical studies demonstrated the importance of platelet activity in cardiovascular events. It is likely that increased platelet reactivity in patients with RA contributes to the increased risk of myocardial infarction and also contributes to the joint inflammation as well.

## *1.2 Investigational Agent*

This study is looking at the investigational agent ticagrelor. Subjects who are already receiving MTX at stable doses of 10 to 25 mg weekly for at least 12 weeks will receive 90 mg of ticagrelor given orally bid. Ticagrelor is an oral, direct-acting, reversibly binding P2Y12 receptor antagonist,that is approved for the treatment of patients with acute coronary syndrome and prior myocardial infarction. In addition to its antiplatelet effects, ticagrelor can inhibit adenosine cell uptake, likely through inhibition of the equilibrative nucleoside transporter 1. Ticagrelor also significantly increases coronary blood flow velocity via an adenosine mediated mechanism.

## *1.3 Preclinical Data*

Methotrexate (MTX) is the anchor drug in the treatment of rheumatoid arthritis (RA) although many patients will not achieve a complete response to MTX alone. (Weinblatt, 2013) In general, the onset of action of MTX is delayed (onset by 2-3 months) although generally most physicians will not add another agent for the treatment of RA until three months after the patient started MTX therapy and has not achieved a significant clinical response. (Weinblatt, 2013) In prior studies we have shown (Chan and Cronstein, 2013) that many, if not most, of the anti-inflammatory effects of MTX are mediated by an increase in extracellular levels of adenosine, a potent anti-inflammatory agent acting at its receptors (primarily A2A and A3). We postulate that insufficient levels of adenosine to suppress inflammation are reached in many patients not achieving an adequate response to MTX therapy; generally speaking these patients will be prescribed biologic agents (e.g. anti-TNF agents). Because ticagrelor blocks adenosine uptake (Cattaneo et al., 2014) and adenosine contributes to the therapeutic effects of ticagrelor we further hypothesize that ticagrelor will enhance the anti-inflammatory effects of MTX in the treatment of RA. Thus, if addition of ticagrelor enhances MTX response then it may be possible for patients to avoid use of a biologic therapy.

## *1.4 Dose Rationale*

Ticagrelor 90 mg twice daily will be used in this study. This dose was chosen based on ticagrelor's antiplatelet effect at this dose and use in other indications (acute coronary syndrome, prior myocardial infarction). In addition, there is a concentration-dependent response for ticagrelor in vitro in terms of conservation of added adenosine to whole blood. There is also an effect on adenosine induced coronary blood flow of a 180mg loading dose of ticagrelor in healthy subjects (Wittfeldt 2013) and after 90mg in ACS patients (Alexopolous 2013). This effect is mediated by inhibition of the adenosine transporter ENT1 (type 1 equilibrative nucleoside transporter), which provides protection for adenosine from intracellular metabolism, thus increasing its concentration and biological activity. Study medication will be taken orally, twice a day. Safety and tolerability will be monitored closely during the study. The 30-day study duration is considered sufficient to investigate acute safety and efficacy in ticagrelor in RA.

## *1.5 Research Risks & Benefits*

### 1.5.1 Risk of Study Drug

Ticagrelor can cause bleeding that can be serious and sometimes lead to death. Instances of serious bleeding, including internal bleeding, may require blood transfusions or surgery. Subjects taking ticagrelor may bruise and bleed more easily and be more likely to have nosebleeds. Bleeding will also take longer than usual to stop. Subjects who experience any of these symptoms will be informed to call their study doctor immediately and call 911 in the event of an emergency.

Patients who are taking ticagrelor are also at a greater risk of dyspnea. If ticagrelor must be temporarily discontinued (e.g., to treat bleeding or for significant surgery) it should be restarted as soon as possible. Because the primary route of ticagrelor elimination is hepatic metabolism, patients with severe hepatic impairment should not use ticagrelor.

### 1.5.2 Risks of all study related procedures

Blood draw: Possible side effects from drawing blood include: faintness, inflammation of the vein, pain, bruising, or bleeding at the site of puncture. There is also a slight possibility of infection.

Risk of brachial artery reactivity test: There are no known risks associated with the procedures for measurement of flow- mediated vasodilation. Inflation of a blood pressure cuff for 5 minutes for transient arterial occlusion may be associated with local arm discomfort that is rapidly relieved upon deflation of the cuff. Rarely, cuff inflation can be associated with local bruising.

Nitroglycerin may be associated with transient headache and lightheadedness due to lower blood pressure. Due to its short half-life, side effects would be expected to last < 30 minutes. To minimize risk of hypotension, nitroglycerin will not be administered if resting systolic blood pressure is <100 mmHg.

Loss of privacy and confidentiality: As with participation in any research study, there is always a risk that confidential or private information can be compromised. To minimize this risk, the study team will de-identify your samples and replace your identifying information, such as your name, with a bar code label that will not be associated with any date related to you (for example, your birthday or street address).

Risk of Genetic Testing: Any type of genetic evaluation can generate information about your personal health risks and can cause or increase anxiety, damage family relationships, and/or compromise insurability, employability and can even lead to discrimination. In order to protect against loss of confidentiality, sensitive information will be kept on a secured database and the samples will be de-identified before they are used in research. Your name and identifiers will not be mentioned in publications or reports, thereby greatly reducing the possibility of psychological or social risks that could arise from knowledge of this genetic information, such as risk for your employability or insurability or the risk of discrimination.

### 1.5.3 Potential benefits

The benefits of ticagrelor in patients with RA are currently unknown.

# 2 Study Objectives

We propose to measure platelet activity in subjects with RA and OA and perform a preliminary clinical study in patients with rheumatoid arthritis that have active disease despite MTX therapy. Subjects will receive ticagrelor added to MTX for 30 days. The primary outcome is improvement in the Disease Activity Score for 28-joint counts (DAS28, with scores ranging from 2 to 10 and higher scores indicating more disease activity) at 30 days.

# 3 Study Design

## *3.1 General Design*

This is an open label study to assess the improvement in the Disease Activity Score for 28-joint counts (DAS28) with ticagrelor given at 90 mg twice daily in patients with RA who have active disease despite MTX therapy (as defined by the inclusion/exclusion criteria). There will also be a cross sectional analysis of baseline platelet activity in subjects with rheumatoid arthritis and osteoarthritis. Subjects in the OA cohort will not receive any study medication, and will only have one study visit.

Patients will receive 90 mg ticagrelor orally twice daily. The patients will receive drug for 30-days. Methotrexate will be by prescription as per standard of care and the dose will remain stable throughout the study duration.

A summary of the study design is noted in the Supplemental Figure of Study Design. Briefly, there are 2 major goals: 1) we would like to demonstrate the heightened cardiovascular risk in RA by comparing platelet activity, inflammation and endothelial function in baseline rheumatoid arthritis versus age- and sex-matched patients with osteoarthritis; and 2) we would like to demonstrate the effect of ticagrelor in rheumatoid arthritis by the pre- and post- measures of clinical RA severity, platelet activity, inflammation and endothelial function in rheumatoid arthritis before and after ticagrelor therapy.

## *3.2 Secondary Study Endpoints*

The primary outcomes of this study are: (1) investigate the heightened platelet profile in subjects with RA versus those with osteoarthritis, and (2) demonstrate the improvement in the Disease Activity Score for 28-joint counts (DAS28, with scores ranging from 2 to 10 and higher scores indicating more disease activity) at 30 days. The DAS28 is a composite index of the number of swollen and tender joints, the erythrocyte sedimentation rate, and a patient-reported disease activity.(Prevoo et al., 1995) A decrease in the DAS28 of 1.2 or more is considered to be a clinically meaningful improvement.(van Gestel et al., 1996)

## *3.3 Secondary Study Endpoints*

<u>Rheumatoid Arthritis Severity</u>
To assess whether ticagrelor 90 mg twice daily for 30 days improves:

- American College of Radiology (ACR) 20, 50, and 70 responses, indicating 20%, 50%, and 70% reductions, respectively, in the number of both tender and swollen joints and equivalent improvement in at least three of five other criteria
- Responses on the Clinical Disease Activity Index (CDAI), which is a composite score of the sum of tender and swollen joints (28 joints) and the patient and physician global assessments (each scored with the use of a scale ranging from 0 to 10), and
- Responses on the Routine Assessment of Patient Index Data 3 (RAPID3), which is a composite score of the sum of physical function, pain and patient global estimate
- Functional outcomes, as measured with the use of the Multi-dimensional Health Assessment Questionnaire (MDHAQ)

<u>Adenosine Activity</u>
To assess whether ticagrelor for 30 days improves:

- Vascular endothelial dysfunction
- Endothelial function will be measured by brachial artery reactivity testing (BART) before and after 30 days of therapy because a) this measure has been shown to improve in response to short-term therapy in other inflammatory conditions,(Flammer et al., 2008; Gupta et al., 2008; Patti et al., 2011; Warnholtz et al., 2009) b) it is a validated noninvasive and minimal risk measure of cardiovascular health,(Liang et al., 1998; Sorensen et al., 1995) and c) it is predictive of incident cardiovascular events and mortality.(Celermajer et al., 1992)
- Adenosine receptor expression on PBMCs

Platelet Activity
To assess whether ticagrelor for 30 days causes a greater decline in platelet activity than baseline using the following markers:

- ADP-induced platelet aggregation
- Vasodilator-stimulated phosphoprotein (VASP) index
- Monocyte – platelet aggregation

### *3.4 Primary Safety Endpoints*

A safety objective of this study will be to assess the safety and tolerability of ticagrelor in participants with active RA despite MTX therapy. Bleeding events will be analyzed using accepted bleeding definitions (PLATO, ISTH and BARC). Other adverse events will be reviewed within the context of the earlier safety experience with the drug.

### *3.5 Exploratory Endpoints*

To determine the effect(s) of adding ticagrelor for 30-days to participants with active RA after MTX failure on the following exploratory objectives:

- Soluble markers of inflammation, platelet and immune activation: IL-6, sCD14, hs-CRP, sCD40L, and sP-selectin, sCD163, and CXCL10/IP10.
- Intracellular cytokine concentration (TNF∝ and IL-6 from PBMCs)
- Contingent upon significant improvement in the primary objective and additional funding, measurements of inflammatory transcripts may be performed upon stored frozen PBMCs by measuring cell associated RNA and DNA.

## 4 Subject Selection and Withdrawal

### *4.1 Inclusion Criteria*

**Inclusion Criteria (RA cohort)**:

- Receiving MTX at stable doses of 10 to 25 mg weekly for at least 12 weeks
- Have a DAS28 of 3.2 or higher (The level of disease activity is considered to be low if the DAS28 is 3.2 or less) (Prevoo et al., 1995)
- Written informed consent prior to any study specific procedures
- Over 18 years of age at time of enrollment.

**Inclusion Criteria (OA cohort)**:

- Age- and Sex- Matched to RA cohort. Subjects will not be selected based on grade of OA.
- Diagnosis of osteoarthritis made by physician.

### *4.2 Exclusion Criteria*

**Exclusion Criteria (RA cohort)**:

- History of sensitivity to study medications or any of their excipients
- Previous intolerance to MTX
- Current treatment with antiplatelet therapy
- Absolute indication for anti-platelet therapy
- Need for chronic oral anticoagulant therapy
- Severe hepatic impairment (eg, ascites and/or clinical signs of coagulopathy)
- Renal failure (eGFR <30 or requiring dialysis) by history
- A known bleeding diathesis, hemostatic or coagulation disorder, or prior major bleeding
- Prior stroke
- Active pathological bleeding
- History of intracranial haemorrhage

- Life expectancy <12 months based on investigator's judgement
- Patients considered to be at risk of bradycardic events (e.g., known sick sinus syndrome or second or third degree atrioventricular [AV)] block) unless already treated with a permanent pacemaker
- Anemia (hematocrit < 27%) by history
- Platelet count < 100,000/ml by history
- Concomitant use of strong CYP 3A inhibitors or inducers
- History of thrombocytopenia or neutropenia
- Pregnant or nursing women, or females with a positive urine and/or serum pregnancy test at screening/baseline
- Females of child bearing potential not using acceptable method of birth control prior to or during study
- Concern for inability of the patient to comply with study procedures and/or follow-up (eg, alcohol or drug abuse)

**Exclusion Criteria (OA cohort)**:

- History of sensitivity to study medications or any of their excipients
- Current treatment with antiplatelet therapy
- Absolute indication for anti-platelet therapy
- Need for chronic oral anticoagulant therapy
- Severe hepatic impairment (eg, ascites and/or clinical signs of coagulopathy)
- Renal failure (eGFR <30 or requiring dialysis) by history
- A known bleeding diathesis, hemostatic or coagulation disorder, or prior major bleeding
- Prior stroke
- Active pathological bleeding
- History of intracranial haemorrhage
- Life expectancy <12 months based on investigator's judgement
- Anemia (hematocrit < 27%) by history
- Platelet count < 100,000/ml by history
- History of thrombocytopenia or neutropenia
- Pregnant or nursing women, or females with a positive urine and/or serum pregnancy test at screening/baseline
- Females of child bearing potential not using acceptable method of birth control prior to or during study
- Concern for inability of the patient to comply with study procedures and/or follow-up (eg, alcohol or drug abuse)

## *4.3 Subject Recruitment and Screening*

Recruitment of patients will come mainly through routine clinical care visits by rheumatologists in the faculty practice at the Center for Musculoskeletal Care. NYU is home to the Center for Musculoskeletal Care and has a special emphasis on Arthritis and Autoimmunity. Over 20,000 rheumatology visits a year are captured at NYU Hospital for Joint Diseases. Approximately 70 new patients are seen each week in rheumatology clinics and practices which can provide 4 to 5 new RA patients a week. Subjects will be recruited by study physicians. Recruitment of patients will come mainly through routine clinical care visits by rheumatologists in the faculty practice at the Center for Musculoskeletal Care and other rheumatology clinics. Physicians at clinical sites will be aware of the current protocol and will be encouraged to speak with their patients. If there is a need for additional patient materials, a separate advertisement will be placed with prior IRB approval. Letters to affiliate physicians may also be written that also would be submitted for IRB approval. Management of DataCore will also be mining the database for our specific recruitment needs.

### Target patient population

The target study population is male and female participants over the age of 18 who meet the 1987 American College of Rheumatology (ACR) classification criteria for RA (Arnett et al., 1988) or OA (Altman et al., 1991; Altman et al., 1990; Altman et al., 1986) fulfilling all of the inclusion and none of the exclusion criteria. This study aims to have 25 subjects in the RA cohort complete all study activities, and 10 subjects with OA to

match with the RA cohort. To achieve 35 subjects completing the entirety of the study, there will be a maximum total accrual of 60.

## *4.4 Informed Consent*

Investigators must ensure that subjects are clearly and fully informed about the purpose, potential risks, and other critical issues regarding clinical studies in which they volunteer to participate. Freely given written informed consent must be obtained from every subject before clinical study participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study. Written informed consent will be obtained by the research staff member designated by the PI. All written informed consent originals will be maintained for study purposes and review if needed.

## *4.5 Early Withdrawal of Subjects*

### 4.5.1 Patient Withdrawal

Patients may withdraw from the study at any time and for any reason. Reason for study withdrawal will be documented and may include the following reasons:

- Patient choice;
- At the discretion of the Investigator;
- Development of a contraindication to ticagrelor or MTX;
- Development of a bleeding diathesis, hemostatic or coagulation disorder, or major bleeding;
- Pregnancy;
- Death.

### 4.5.2 Early Withdrawal Procedures

Patients who withdraw due to an AE or SAE require additional follow-up.

- If a patient is early terminated from the study due to an AE, he/she will be followed until resolution of the event or for 30 days after discontinuation of study medication (whichever occurs first).
- For SAE follow-up, please refer to Section 8.

Patients who are discontinued from study medication for any reason other than an SAE will be encouraged to remain on the study (not be officially withdrawn from the study) and complete all study visits.

# 5 Study Drug

## *5.1 Administration of Study Drug*

Patients will self-administer study medication twice daily, orally for 30 days.

## *5.2 Subject Compliance Monitoring*

Patients will be trained on study medication dosing prior to beginning treatment. Compliance will be discussed over the phone as needed and during the post dose visit (Day 30).

## *5.3 Concomitant Medications*

Concomitant medications will be reviewed at all study visits.

## *5.4 Receiving, Storage, Dispensing and Return*

### 5.4.1 Storage and dispensing of Study drug

The following will be supplied by the Sponsor:

- 90 mg Ticagrelor tablets

Records will be maintained indicating the receipt and dispensation of all medication supplies.

The Study drug will be stored between 15° to 30° C. The study drug will be labeled according to local regulatory requirements.

### 5.4.2 Return or Destruction of Study Drug

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

# 6 Study Procedures

Study participation includes a 30-day treatment period. Screening and baseline visits may be done on the same day if the subject is able to give fasting blood and does not meet any exclusion criteria.

**Table 1: Schedule of Assessments.**

| | **Screening** | **Baseline** | **1 and 2 Week Phone call** | **Day 30** |
|---|---|---|---|---|
| **Visit #** | **1** | **1 or 2** | | **2 or 3** |
| **Day#** | **− 30 − 3** | **0** | | **30 ± 5** |
| Informed consent | X | | | |
| Medical history | X | X | | |
| Medications | X | X | | X |
| Vital signs/physical exam | | X | | X |
| DAS28/CDAI/RAPID3/MDHAQ | X | X | | X |
| ACR responses | | X | | X |
| Blood (fasting) collection | | X | | X |
| Urine and/or serum pregnancy test for WOCBP only | X | X | | |
| Platelet Activity | | X | | X |
| Brachial Artery Reactivity Testing (fasting) | | X | | X |
| Dispense study drug | | X | | |
| Adverse events | X | X | X | X |
| Medication compliance/diary | | | X | X |

## *6.1 Screening (Visit 1, Days -30 to -3)*

- Patients will sign a written informed consent form prior to undergoing any study-specific activities;
- Patients will be assessed for inclusion/exclusion criteria;
- Demographics, medical history, review of medications will be performed;

- DAS28, CDAI, RAPID3 and MDHAQ will be performed and records;
- Adverse events will be collected.

### *6.2 Baseline (Visit 1 or 2, Day 0)*

- Medical history and review of medications will be performed;
- Vitals will be recorded and the patient will have a physical exam;
- DAS28, CDAI, RAPID3 and MDHAQ will be performed and recorded;
- ACR responses will be measured by the physician using patient questionnaires and joint counts;
- Fasting blood will be collected;
- For each subject, no more than 75 cc of blood will be collected in red (no anticoagulant) top, Pax gene tube for genomics, lavender (EDTA anticoagulant) top, green (heparin) and blue (sodium citrate anticoagulant) top tubes. Approximately 40 cc of blood will be used for the different measurements of platelet function, inflammation, immune activation, and other markers of cardiovascular risk, and approximately 30 cc of blood will be used to purify cells, RNA and DNA and then stored in -80C/liquid nitrogen for genetic and functional profiling. The results of the genetic testing will not be shared with the subjects.
    - The drawing of a maximum of 75 cc of blood is justified by the need for the above referenced tests, measurements and purification. These tubes will be drawn at the time of the standard of care blood draws for routine patient care monitoring. This amount of blood is medically safe to draw. The physician will always ensure the safety of drawing this volume of blood.
- Fasting brachial artery reactivity testing including one time dose of 0.4 mg of nitroglycerin given sublingual. To minimize risk of hypotension, nitroglycerin will not be administered if resting systolic blood pressure is <100 mmHg;
- Study medication will be dispensed;
- Adverse events will be collected.

### *6.3 Visit 2 or 3 (Day 30 +/-5): RA cohort only*

- Review of medications will be performed;
- Vitals will be recorded and the patient will have a physical exam;
- DAS28, CDAI, RAPID3 and MDHAQ will be performed and recorded;
- ACR responses will be measured;
- Fasting blood will be collected;
- For each subject, no more than 75 cc of blood will be collected in red (no anticoagulant) top, Pax gene tube for genomics, lavender (EDTA anticoagulant) top, green (heparin) and blue (sodium citrate anticoagulant) top tubes. Approximately 40 cc of blood will be used for the different measurements of platelet function, inflammation, immune activation, and other markers of cardiovascular risk, and approximately 30 cc of blood will be used to purify cells, RNA and DNA and then stored in -80C/liquid nitrogen for genetic and functional profiling. The results of the genetic testing will not be shared with the subjects.
- Fasting brachial artery reactivity testing including one time dose of 0.4 mg of nitroglycerin given sublingual. To minimize risk of hypotension, nitroglycerin will not be administered if resting systolic blood pressure is <100 mmHg;
- Adverse events will be reviewed and recorded;
- Medication compliance will be reviewed with the subject.

## 7 Sample storage for future research

The samples will be stored in the PI's lab without any identifying information other than a code number. The code number will not be based on any information that could be used to identify the subject (for example, social security number, initials, birth date, etc). The master list linking names to code numbers will be kept in a locked file cabinet, separate from all research information. All specimen handling, collection, processing, and storage, will be performed as per regulations and Tisch Laboratory and NYU policy. Specimens will be

collected at CMC and transferred to Tisch Laboratory for analysis. Samples will be stored for 10 years after the end of the study, if subjects give permission in their consent form.

### *7.1 Optional permission to store samples for future use*

Subjects have the option to allow researchers to store their blood samples for future research, either for new research studies or in order to run additional tests on blood collected as part of this study. The consent form has a section that will allow subjects to explicitly grant permission for this by checking a box and initialing. This permission to store samples for future use is completely optional and voluntary. Samples kept for future research after the duration of this study will be stored in the same manner as they were stored during the course of the study. The samples will be stored in the lab of the PI, Dr. Jeffery Berger, located at New York University Langone Health, New Science Building, 435 East 30th Street, 7th floor, Lab # 723, New York, NY 10016. Samples would be stored for 10 years after the end of the study and then destroyed. Subjects may request, in writing, for their samples to be destroyed if they change their mind or for any other reason. The purpose of this possible future research is unknown, but will have the purpose of contributing to medical knowledge and understanding of human health. Genetic testing will not be performed on stored samples. The stored samples will be available to the PI of this study and all co-investigators. Any new information derived from stored samples will be kept in a secure database matching all of the confidentiality requirements of any database use in this study. Samples will not be shared with other researchers outside the scope of this study.

## 8 Statistical Plan

The primary end point of the trial is the Disease Activity Score for 28-joint counts (DAS28) at 30 days after randomization. The DAS28 is a composite index of the number of swollen and tender joints, the erythrocyte sedimentation rate, and a visual-analogue scale of patient-reported disease activity.(Prevoo et al., 1995) A decrease in the DAS28 of 1.2 or more is considered to be a clinically meaningful improvement.(van Gestel et al., 1996; Ward et al., 2014) A total of 25 subjects with RA would have 90% power to detect a before- and after difference of 1.2 in the DAS28 at 30 days (assuming a SD of 1.5), with a two-sided type I error of 5%, and a 20% attrition rate.

Power and sample size analysis was performed to investigate appropriate sample size for evaluating platelet activity markers in subjects with RA versus age- and sex matched OA controls. Since patients with RA have a heightened inflammatory phenotype and at higher cardiovascular risk than osteoarthritis, we hypothesize that the mean measurement of platelet markers for RA is 35% greater (similar to previously demonstrated differences in high risk phenotypes) than age- and sex matched OA controls for each measurement. Based on two-sided two-sample t-tests with 25 patients in the RA group and 10 patients in the OA group, our power is listed in the table for each measure of platelet measure at the 0.05 significance level using mean/SDs from preliminary data in healthy controls.

| **Measurement** | **Power** |
|---|---|
| Platelet Aggregation* | 91% |
| PAC-1 | 87% |
| Monocyte platelet aggregates | 94% |
| Leukocyte platelet aggregates | 93% |

**Powered for low-dose epinephrine based on preliminary data (as described above)*

*If patients with RA do not have an increased platelet (and inflammatory) phenotype compared with OA – that would be an important finding we will report in this study.*

# 9 Safety and Adverse Events

## *9.1 Definitions*

**Unanticipated Problems Involving Risk to Subjects or Others**
Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (i.e. not described in study-related documents such as the IRB-approved protocol or consent form, package insert, etc)
- Related or possibly related to participation in the research (i.e. possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

**Adverse Event**
An ***adverse event*** (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

**Serious Adverse Event**
Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- immediately life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.
All adverse events that do not meet any of the criteria for serious should be regarded as ***non-serious adverse events***.

**Adverse Event Reporting Period**
The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures to the end of the study treatment follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment.

**Preexisting Condition**
A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

**General Physical Examination Findings**
At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

**Post-study Adverse Event**
All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator should notify the study sponsor of any death or adverse event occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The sponsor should also be notified if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

**Abnormal Laboratory Values**
A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.

**Hospitalization, Prolonged Hospitalization or Surgery**
Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for and adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

## *9.2 Recording of Adverse Events*

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

## *9.3 Reporting of Serious Adverse Events and Unanticipated Problems*

Investigators and the protocol sponsor must conform to the adverse event reporting timelines, formats and requirements of the various entities to which they are responsible, but at a minimum those events that must be reported are those that are:

- related to study participation,
- unexpected, and
- serious or involve risks to subjects or others
  (see definitions, section 8.1).

At the time an SAE is reported to the FDA via MedWatch, a copy of the report must be concurrently faxed to AstraZeneca at the time the event is reported to the FDA. Use the cover page provided by AstraZeneca with a copy of the MedWatch form. The cover page will contain the following:

- External Sponsored Research (ESR)
- The investigator's name and address
- The trial name/title and AstraZeneca ESR reference number

Investigative site must also indicate, either in the SAE report or the cover page, the causality of events in relation to all study medications and if the SAE is related to disease progression, as determined by the principal investigator. Send SAE report and accompanying cover page by way of fax to AstraZeneca's designated fax line: +1 302 886 4114. Serious adverse events that do not require expedited reporting to the FDA need to be reported to AstraZeneca at least monthly.

**For Narrative Reports of Safety Events**

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Concomitant medications
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment
- Outcome of the event

### 9.3.1 Investigator reporting: notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

**Report Promptly, but no later than 5 working days:**

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- ***Unanticipated problems including adverse events*** **that are unexpected and related**
  - *Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.*
  - *Related to the research procedures: An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.*
  - *Harmful: either caused harm to subjects or others, or placed them at increased risk*

**Other Reportable events:**

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
  - *one or more participants were placed at increased risk of harm*
  - *the event has the potential to occur again*
  - *the deviation was necessary to protect a subject from immediate harm*
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New Information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

**Reporting Process**
The reportable events noted above will be reported to the IRB using the : “Reportable New Information” function or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory study file.

## *9.4 Cases of Pregnancy and Overdose*

In case of pregnancy the patient should discontinue study medication and the study team notify AstraZeneca. The patient should be followed by the Investigator until completion of the pregnancy. If the pregnancy ends for any reason before the anticipated date, the Investigator should notify AstraZeneca. At the completion of the pregnancy, the Investigator will document the outcome of the pregnancy. If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e, postpartum complication, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting a SAE.

## *9.5 Medical Monitoring*

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see section 9 Auditing, Monitoring and Inspecting). Medical monitoring will include a regular assessment of the number and type of serious adverse events.

### 9.5.1 Data and Safety Monitoring

The monitoring plan includes the number and severity of adverse events as well as the overall dropouts and dropouts per group. The frequency and severity of the adverse events will continually be monitoring to determine if modifications to the protocol or consent form are required. In addition, a review of all potential safety data will be performed by the PI at least annually or as needed. Since the study is relatively small with only 35 subjects, there are no statistical measures for suspending enrollment. In the case of any severe adverse event, the PI will suspend enrollment till discussions can be made in conjunction with the NYU IRB on how (or if) to proceed. Efficacy will be assessed at the end of the study, after all subjects have completed all study-related events.

# 10 Data Handling and Record Keeping

## *10.1 Confidentiality and Data storage*

Primary research data will be stored at the NYU Center for Musculoskeletal Care, where study visits take place. Source documents will be stored in study binders, which will remain in a locked room/cabinet at the study facility.

## *10.2 Record keeping*

Records of patients, source documents, monitoring visit logs, CRFs, inventory of study product, regulatory documents, and other sponsor correspondence pertaining to the study must be kept in the appropriate study files at the site. Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the evaluation and reconstruction of the clinical study. Source data are contained in source documents (original records or certified copies). These records will be retained in a secure file for the period as set forth in the Clinical Study Agreement.

## *10.3 Confidentiality and HIPAA*

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e. that the subject is alive) at the end of their scheduled study period.

# 11 Ethical Considerations

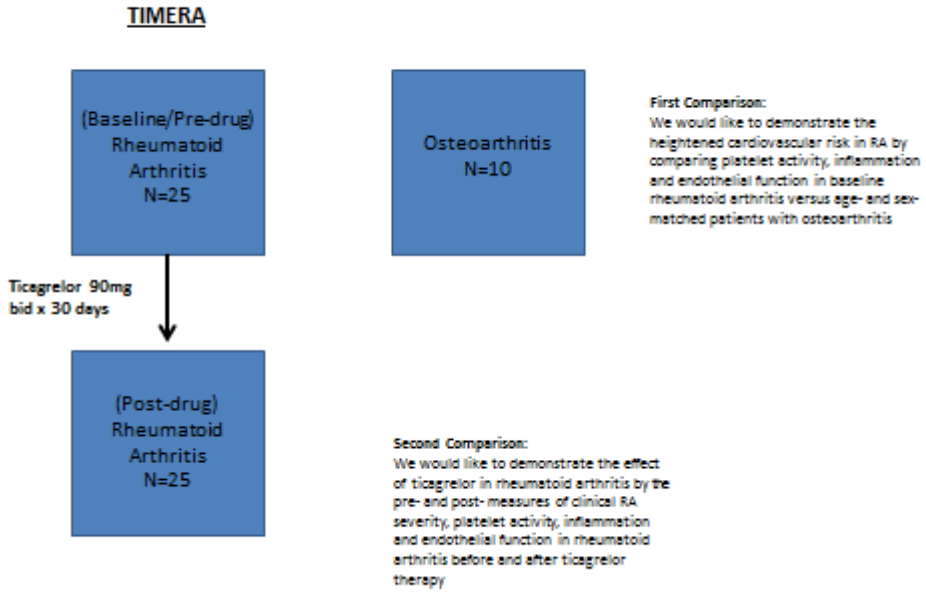
This study is to be conducted accordance with applicable US government regulations and international standards of Good Clinical Practice, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted Institutional Review Board (IRB).

# 12 Cost and payment to the subjects

Subjects will not have to pay for anything to be in this study. AstraZeneca will provide the study medication. Subjects will be reimbursed $50 per study visit that they complete.

# 13 Supplemental Figure of Study Design

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