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Ticagrelor Administered as Standard Tablet or orodispersiblE foRmulation (TASTER) Study

Sponsor: ***Guido Parodi, MD, PhD***

TABLE OF CONTENTS PAGE

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
PPCI	Primary Percutaneous Coronary Intervention
STEMI	ST elevation myocardial infarction
LD	Loading Dose
ODT	OroDispersable Tablets
AE	Adverse Events
OAE	Other Adverse Events
PRO	Patient Reported Outcome

1. INTRODUCTION

1.1 Background

Primary percutaneous coronary intervention (PPCI) is the preferred reperfusion strategy for patients with acute ST-segment elevation myocardial infarction (STEMI). Additional antithrombotic therapy prior or during intervention plays an important role in the short- and long-term outcomes after PPCI (1,2). Oral antiplatelet therapy including a platelet P2Y12 receptor inhibitors is a cornerstone of antithrombotic treatment in patients with STEMI. Prasugrel and Ticagrelor have been shown to be superior to clopidogrel in patients with STEMI in reduction of ischemic complication without any increase in the bleeding risk and with a significant reduction in the stent thrombosis rate (3,4). Current guidelines strongly recommend Prasugrel and Ticagrelor over Clopidogrel in patients with STEMI undergoing PPCI (1,2); nevertheless Prasugrel administration is contraindicated in patients over 75 years of age, weighing less than 60 kg, with history of TIA/stroke, and patients pretreated with clopidogrel. These reasons, together with the need of taking six coated pills to reach 60 mg of prasugrel loading dose, limit prasugrel use in a considerable portion of patients and make ticagrelor more employed than prasugrel in routine clinical practice.

In STEMI patients, pharmacodynamic studies showed prasugrel and ticagrelor loading dose (LD) provided a suboptimal platelet inhibition in the first hours after LD, and at least 4 hours are required to achieve and effective platelet aggregation inhibition in the majority of patients. A several hours vulnerable window of suboptimal antithrombotic therapy exists in which patients are at high risk of thrombotic events (5,6). Increasing ticagrelor loading dose has been shown to be not effective to limit this phenomenon (7, 8).

All P2Y12 receptor antagonists routinely used at the present time in STEMI treatment are only available in the oral form. In absence of liquid dosage form, tablets or pills can be crushed and suspended in a vehicle before administration. Theoretically, Tmax is likely to be shortened since gastric disintegration phase does not occur. The administration of clopidogrel in crushed form resulted in its faster and greater bioavailability and this fact could have widespread clinical implications (9, 10). In a recent pharmacodynamics study in STEMI patients, Parodi et al. demonstrated that crushed ticagrelor tablets provided a faster platelet inhibition as compared with Ticagrelor integral tablets (11). A pharmacokinetic study confermed these findings (12).

Orodispersible tablet (ODT) is a different tablet formulation that disperse upon contact with the moist mucosal surfaces of the oral cavity and quickly release its components before swallowing; thus drug dissolution and absorption as well as onset of clinical effect can be obtained conveniently easily and quickly (13-16). Recently, Ticagrelor 90 mg ODT has become available and bioequivalence studies on healthy volunteers documented its effectiveness with consequent approval by European Medicine Agency of this formulation which is currently available on the market.

In patients with difficulties in swallowing (elderly, previous stroke, sedated and intubated patients) ODTs represent an easy way of drug administration. While, in the clinical settings (ambulance for example) without access to water, ODTs might represent the only way of oral drug administration. Finally, ODT administration might represent the most convenient way of treating lying supine STEMI patients in the ambulance, emergency room or in the cath lab if efficacy data will be provided in real life acute coronary syndrome patients.

Recently, opioids-antiplatelet interaction has been documented (17, 18, 19); in particular in patients with STEMI morphine use is associated with a delayed onset of action of the oral antiplatelet agents. Vomit may frequently occur in STEMI patients, especially in those receiving morphine. Moreover, gastric absorption may be impaired in patients with acute myocardial infarction and/or haemodinamic compromise due to sympathetic nervous activation, nausea, hypotension, and cardiogenic shock. It is unknown whether ODTs might be an effective route of drug administration in STEMI patients.

1.2 Research hypothesis

Thus, the aim of the present study is to evaluate the superiority in platelet inhibition with 180 mg Ticagrelor loading dose (LD) administered as ODTs as compared with standard formulation, among patients with STEMI or very high-risk NSTEMI undergoing immediate PCI.

1.3 Rationale for conducting this study

In patients with difficulties in swallowing (elderly, previous stroke, sedated and intubated patients) ODTs represent an easy way of drug administration. In a scenario without access to water the clinical settings (like in ambulance), ODTs might represent the only way of oral drug administration. Finally, ODT administration might represent the most convenient way of treating lying supine STEMI patients in the ambulance, emergency room or in the cath lab if efficacy data will be provided in real life acute coronary syndrome patients.

Moreover, the administration of morphine, used to relieve pain and anxiety in patients with ongoing myocardial infarction, is associated with a delayed onset of action of the oral antiplatelet agents. Furthermore, gastric absorption may be impaired in patients with acute myocardial infarction and/or haemodinamic compromise due to sympathetic nervous

activation, nausea, hypotension, and cardiogenic shock. It is unknown whether ODTs might be an effective route of drug administration in STEMI patients.

1.4 Benefit/risk and ethical assessment

The main risk after antiplatelet drug administration is related to bleeding events. Common measure of good clinical practice will be adopted to minimize this risk, including the limitation to heparin dose during and after procedure, and discouraging drug cross-over. Moreover use of GPI will be not allowed according to the study protocol. Use of transradial access for coronary angiography and PCI will be strongly encouraged according to the most recent recommendations of the European Society of Cardiology.

Of note, ODT administration of ticagrelor loading dose would not lead to an overuse of ticagrelor, which is already the P2Y12 receptor inhibitor most widely employed at our Centre among patients with acute myocardial infarction treated with PCI due to the reasons explained in “Background” paragraph. The most evident advantages of ODT loading dose over coated pills formulation would derive mainly from easier and quicker administering of the drug by the catheter laboratory nurses and by the simpler assumption by the patients, who may find this alternative formulation objectively less complex than swallowing two coated pills, especially if sedated, elderly, or dysphagic.

2. STUDY OUTCOMES

Thus, the aim of the present study is to evaluate the superiority in platelet inhibition with 180 mg Ticagrelor loading dose (LD) administered as ODTs as compared with standard formulation, among patients with STEMI or very high-risk NSTEMI undergoing immediate PCI.

2.1 Primary endpoint

- Platelet reactivity evaluated by Platelet Reactivity Units (PRU) VerifyNow 1 hour after Ticagrelor LD.

2.2 Secondary Efficacy Endpoints

- The percent of patients with a high residual platelet reactivity (PRU > 208) 1 hour after Ticagrelor LD.
- PRU at 2, 4 and 6 hours.
- PRU area-under the curve (AUC) between baseline and 6 hours from LD

2.3 Secondary Safety Endpoints

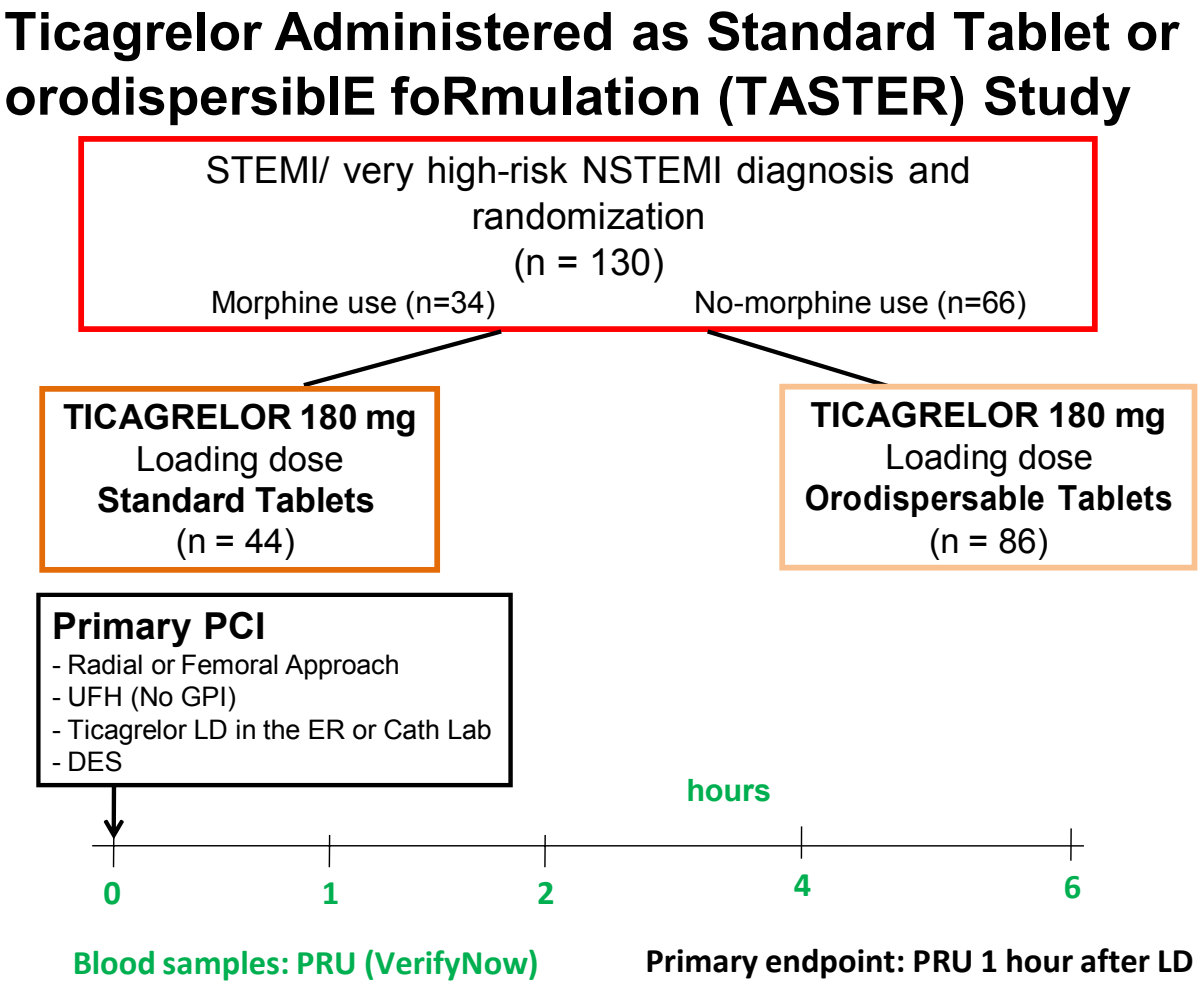
Safety objective will be major bleeding events across the two different regimens of Ticagrelor administration.

2.4 Exploratory objectives

- Potential morphine-ticagrelor interaction will be assessed by stratified randomization according to morphine use.
- Combined ticagrelor administration-related adverse events defined as in-hospital ≥2 BARC bleedings, dyspnea, ventricular pauses, allergic reactions, or vomit
- Comparison of time necessary for preparation and administering of either formulation of ticagrelor loading dose by the catheter laboratory nursing personnel.

3. STUDY PLAN AND PROCEDURES

3.1 Overall study design and flow chart



3.2 Rationale for study design, doses and control groups

See the Background section

4. SUBJECT SELECTION CRITERIA

All patients enrolled in the study will have to strictly respect the following inclusion and exclusion criteria.

4.1 Inclusion criteria

1. Patients presenting within 12 hours from the onset of symptoms with STEMI or very high-risk NSTEMI referred for immediate (< 2 hours) angiography. Very high-risk NSTEMI patients include patients with haemodynamic instability or cardiogenic shock, heart failure, life-threatening arrhythmias or resuscitated cardiac arrest, intermittent ST-segment elevation, or ongoing chest pain.
2. Informed, written consent
3. Male or female patients, aged ≥ 18 years old

4.2 Exclusion criteria

Subjects should not enter the study if any of the following exclusion criteria are fulfilled:

1. Age < 18 years
2. Active bleeding; bleeding diathesis; coagulopathy
3. History of gastrointestinal or genitourinary bleeding <2 months
4. Major surgery in the last 6 weeks
5. History of intracranial bleeding or structural abnormalities
6. Suspected aortic dissection
7. Administration in the week before the index event of clopidogrel, ticlopidine, prasugrel, ticagrelor, thrombolytics, bivalirudin, low-molecular weight heparin or fondaparinux.

8. Concomitant oral or IV therapy with strong CYP3A inhibitors or strong CYP3A inducers, CYP3A with narrow therapeutic window
9. Known relevant hematological deviations: Hb <10 g/dl, Thromb. <100x10^9/l
10. Use of warfarin or new oral anticoagulant derivatives within the last 7 days
11. Known severe liver disease, severe renal failure
12. Allergy or hypersensitivity to ticagrelor or any of the excipients.
13. Pregnancy or lactation

5. STUDY CONDUCT

5.1 Restrictions during the study

It is mandatory that the patients enrolled in the present study have not to simultaneously participate to other studies.

5.2 Subject enrollment <<and randomization>> <<and initiation of investigational product>>

5.2.1 Procedures for randomization

Allocation to treatment will be made by means of sealed opaque envelopes containing a computer-generated sequence; this will be done immediately after establishing the indication for PCI. Patients who meet all of the inclusion criteria and none of the exclusion criteria will be randomized in the order that they qualify. Patients will be allocated to each of the two treatment groups in equal proportions. Randomization will be stratified according to morphine use. We plan to enrol 44 patients with and 86 patients without morphine treatment. The two treatment groups will be studied concurrently. Patients will be considered enrolled in the study and eligible for the final intention to treat analysis at the time of PCI.

5.3 Procedures for handling subjects incorrectly enrolled<< or randomized>> <<or initiated on investigational product>>

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

Site investigators performing platelet function tests will be blinded regarding patient randomization arm and the blood samples will be fully anonymized.

5.5 Treatments

5.5.1 Identity of investigational product(s)

Investigational product	Dosage form and strength	Manufacturer
Ticagrelor	90 mg standard tablets	AstraZeneca
Ticagrelor	90 mg orodispersable tablets	AstraZeneca

5.5.2 Doses and treatment regimens

Ticagrelor 180 mg loading dose standard (coated) tablets

Ticagrelor 180 mg loading dose orodispersable tablets

5.5.3 Additional study drug

1) Aspirin: 500 mg LD followed by 100 mg daily maintenance dose
2) UFH 80-100 U/Kg endovenous bolus during PCI, additional intraprocedural bolus depending on ACT values
3) Morphine: from 0 to 10 mg according to the attending physician preference in the ambulance, emergency room or cath lab. Once the patient will be allocated to study arm (stratified according to morphine use) opioids will be no more allowed
4) B-blockers, ACE-Inhibitors or Angiotensin II receptor blockers, Statins, Proton Pump Inhibitors and other drugs according to the current guidelines of patients with STEMI and NSTEMI

5) Glycoprotein IIb/IIIa inhibitors are not allowed. In the case of bail out use of glycoprotein IIb/IIIa inhibitors the patient will be excluded by the final primary end-point analysis.

5.5.4 Labeling

The label will include the following information: patient's initials, date of birth, identification code of the patient.

5.5.5 Storage

Standard storage protocol will be followed for study drugs.

5.6 Concomitant and post-study treatment(s)

After the Ticagrelor loading dose administration in orodispersable vs. standard coated tablets all patients in both study arms will receive maintenance dose of 90 mg b.i.d. given as standard coated tablets. After the 30-days follow-up the patients will continue DAPT regimen (aspirin and standard ticagrelor) according to international guidelines. Associated drugs will be prescribed following current international guidelines.

5.7 Treatment compliance

All interventions during hospitalization are administrated and monitored directly by caregivers. After discharge, daily assumption of therapy will be recommended, patients will be educated on the potential catastrophic consequences of premature interruption especially of antiplatelet drugs.

5.8 Discontinuation of investigational product

Study drug should be discontinued in case of:

1. serious uncontrolled bleeding

2. need for emergency surgery

3. anaphylaxis to study drug

4. serious drug-related side effects

The reason for discontinuation of the study treatment and the exact duration of the infusion of study drug should be reported on the Case Report Forms (CRF). These complications should be treated according to local standards and the type of treatment and should also be reported on the Adverse Event Form (AEF).

5.9 Withdrawal from study

Patients can be withdrawn from the study at every time from the enrolment if any of the following criteria occurs: withdrawal of informed consent, non-compliance, safety issue (i.e. unexpected risk related to study procedure), premature interruption of the study, presence of any exclusion criteria that was not known at the time of enrolment.

6. COLLECTION OF STUDY VARIABLES

6.1 Recording of data

Source data must be available at the site to document the existence of the study participants. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Source documents include demographic data, visit dates, participation in study and Informed Consent Forms, randomization number, SAEs, AEs and concomitant medication, and results of relevant examinations. The investigator assures that source documents are appropriately stored and completed. The patient's file will reveal that this patient is a study participant by entering the following details: study name, protocol number, date of enrolment, informed consent obtained prior to any study specific procedure. Each follow up visit will be reported in the source data and should at least contain the information required according the protocol. The investigator assures that medical files

and Case Record Forms are accessible for inspection by authorities and monitoring visits. All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. All data will be stored at the main site at Sassari University Hospital.

6.2 Data collection at enrolment and follow-up

6.2.1 Enrollment procedures

Enrollment procedures will last for 12 months.

6.2.2 Follow-up procedures

After enrollment, follow-up visit is scheduled at 1 month. This visit will include detailed anamnesis (comprehensive of questions about eventual bleeding events), physical examination, electrocardiogram and transthoracic echocardiogram.

6.3 EFFICACY

6.3.1 Efficacy variable

The platelet reactivity test reports at each time point (as reported on the table at paragraph 9.3) will be collected in the patient's medical records.

6.4 SAFETY

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. For what concerns the main safety issues related to ticagrelor administration, during the hospital stay and at 30-days follow-up visit detailed anamnesis will focus on eventual bleeding events referred by the patients. Routine blood samples comprehensive of hemoglobin will be drawn at various time points (as reported on the table at paragraph 9.3). In addition, all the patients will receive continuous vital signs monitoring and ECG telemetric recording during the first 48h after myocardial infarction; this

will allow assessing eventual ventricular pauses. Moreover, 12-leads ECG will be recorded also at discharge and at 30-days follow-up visit.

6.4.1 Definition of adverse events

An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event (SAE)

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, wash-out, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

6.4.3 Recording of adverse events

Time period for collection of adverse events

Serious Adverse event occurrence should be reported to Principal Investigator and to AstraZeneca as soon as possible, ideally within 24 hours.

Follow-up of unresolved serious adverse events

SAEs will be followed until resolution or stabilisation. Participants with ongoing SAEs at study termination will be further followed up until recovery or until stabilisation of the disease after termination.

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to

- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Causality assessment in relation to Additional Study Drug
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE.

Adverse Events based on signs and symptoms

When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

Deterioration as compared to baseline in protocol-mandated, e.g. laboratory values or vital signs, should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

Reporting of serious adverse events

Investigators and other site personnel must inform the Competent Authorities, via appropriate form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of CT-3, and will concurrently forward all such reports to AZ. A copy of the report must be faxed to AstraZeneca at the time the event is reported to the Competent Authorities. It is the responsibility of the investigator to compile all necessary information and ensure that the Competent Authorities receive a report according to the reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time, at the following contacts:

fax number: +46 31 776 37 34 / +1 302 886 4114;

e-mail: AEMailboxClinicalTrialTCS@astrazeneca.com (to be used if a secure e-mail is available).

* A ***cover page*** should accompany the form indicating the following:

- Investigator Sponsored Study esr)
- CT number
- 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***.

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the Competent Authorities.

Serious adverse events that do not require expedited reporting to the Competent Authorities need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

In the case of blinded trials, AstraZeneca will request that the Sponsor either provide a copy of the randomization code/ code break information or unblind those SAEs which require expedited reporting.

All SAEs have to be reported to AstraZeneca, whether or not considered causally related to the investigational product. All SAEs will be documented. The investigator is responsible for informing the IRB and/or the Regulatory Authority of the SAE as per local requirements.

Non-serious adverse events and SAEs will be collected from the time consent is given, throughout the treatment period and up to and including the *30 day follow-up* period. After withdrawal from treatment, subjects must be followed-up for all existing and new AEs for *30 calendar days after the last dose of trial drug and/or until event resolution.* All new AEs occurring during that period must be recorded (if SAEs, then they must be reported to the Competent Authorities and AstraZeneca). All study-related toxicities/ SAEs must be followed until resolution, unless in the Investigator's opinion, the condition is unlikely to resolve due to the patient's underlying disease.

Non serious adverse event should be communicated to AstraZeneca periodically (quarterly) by line-listing.

7. BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

For each patient participating to the study 25 ml of blood samples will be collected.

7.2 Handling, storage and destruction of biological samples

7.2.1 Pharmacokinetic and/or pharmacodynamic samples

Pharmacodynamic samples will be analyzed shortly after withdrawal and will be destructed after use. Due to economic reason, pharmacokinetic samples will be not obtained.

7.3 Labeling of biohazard samples

Biological samples will be labeled using the identification code of the patient.

7.4 Chain of custody of biological samples

Biological samples will be strictly shield in a dedicated room and destructed after analysis.

7.5 Withdrawal of informed consent for donated biological samples

The patients will be able to retire their consent for the donated biological sample to the study in every moment.

8. ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study adhered to the ethical principles of the Declaration of Helsinki, specifications of the International Conference of Harmonisation, and Good Clinical Practice.

8.2 Ethics and regulatory review

The ethics of the study protocol will be submitted for approval by an independent ethics committee and by local ethics committee.

8.3 Informed consent

Patients provided written informed consent before they were randomly assigned to treatment.

8.4 Changes to the protocol and informed consent form

Substantial amendments are only implemented after approval of the CEC.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible. All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

8.5 Audits and inspections

The study site may be subject to audits and inspections to verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and ISO14155, and that the protocol is followed. The study documentation and the source data/documents should be accessible to auditors/inspectors (also CEC) and questions should

be answered during inspections. All involved parties must keep the participant data strictly confidential.

9. STUDY MANAGEMENT

9.1 Training of study site personnel

Principal investigator is responsible for the training of the study site personnel.

9.2 Monitoring of the study

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. Monitoring will verify that the rights and well-being of the patients are protected, the trial is conducted according to Good Clinical Practices (GCP) and ISO14155, and that the protocol is followed. The dates of the visits will be recorded by the monitor in a log kept at the site. The source data/documents should be accessible to monitors and questions should be answered during monitoring. The Local Investigator and their relevant personnel should be available during monitoring visit and possible audits and sufficient time should be devoted to the process. The progress of the study will be monitored by:

- Informed Consent Forms for each study participant;

- Ensuring completed eCRFs match source documents, and resolution of any discrepancies. Direct access to complete source documents must be made available during monitoring visits for verification of eCRF data.
- Periodic on-site visits and, if necessary, remote monitoring of data.

9.2.1 Source data

The study participant's contact information will be securely stored at the clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

9.3 Study timetable and end of study

Study Periods	*Enrollment*	*Treatment, Intervention Period*				*In-hospital*				*Follow-up*
Time point	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*	*10*
Time	*0*	*Ticagrelor LD*	*1 h*	*2 h*	*4 h*	*6h*	*24 hrs*	*48 hrs*	*Discharge*	*30 days*
Patient Information and Informed Consent	*x*									
Demographics	*x*									
Medical History	*x*									
In- /Exclusion Criteria	*x*									
Physical Examination	*x*						*x*	*x*	*x*	*x*
Vital Signs	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Randomisation	*x*									
12-leads ECG/ telemetry ECG monitoring	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Transthoracic echocardiogram	*x*						*x*		*x*	*x*
Administer Study Medication		*x*								
Variables for primary endpoint	*x*		*x*							

Variables for secondary efficacy endpoints	x		x	x	x	x				
Routine laboratory tests (complete blood count with haemoglobin, creatinine, cardiac troponin)	x					x	x	x	x	
Concomitant Therapy, Intervention	x	x								
Adverse Events	X	x	x	x	x	x	x	x	x	x

10. DATA MANAGEMENT

11. EVALUATION AND CALCULATION OF VARIABLES

11.1 Calculation or derivation of pharmacodynamic variable(s)

Calculation and/or derivation of pharmacodynamic variables, including PRU AUC will be performed off-line during data analysis.

11.1.1 Population analysis of pharmacokinetic/pharmacodynamic variables

One-hundred and 30 patients will be used for pharmacodynamic analyses.

12. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

12.1.1 Efficacy analysis set

This evaluation is designed on the basis of the superiority principle.

12.1.2 Safety analysis set

Not performed.

12.2 Methods of statistical analyses

Categorical variables such as demographics and medical history data will be summarized using frequencies and proportions and will be compared using the chi-square test or Fisher's exact test, as appropriate. Continuous data will be summarized using mean ± standard

deviation or median [25th, 75th percentiles] and will be compared using Student t test or nonparametric Wilcoxon rank-sum test. All tests will be two-sided and an alpha level of 0.05 will be considered statistically significant. All analyses will be performed in a blinded manner regarding the randomly assigned treatment and on an intention-to-treat basis. Unblinding of the study groups will be done after completion of the statistical analyses regarding the primary endpoint.

12.2.1 Interim analyses

Interim analysis is planned after the enrollment of 50% of the entire study population (n=65 patients).

12.3 Determination of sample size

The study will comprise a sample size of 130 patients. This evaluation is designed on the basis of the superiority principle. We hypothesized that OTD Ticagrelor would be superior as compared with standard ticagrelor tablets. Based on the result of the MOJITO study (11), and considering a) the inclusion of only 44 morphine-treated patients, b) the inclusion of high-risk NSTEMI patients, and c) the expected lower PRU standard deviation with Ticagrelor OTD, as compared with hand-crushed ticagrelor, we assumed a PRU of 230±90 in the Ticagrelor standard tablet group and of 185±90 in the Ticagrelor OTD group. The enrollment of 126 patients provides 80% power. We planned to enroll 130 patients in order to account for potential missing values.

12.4 Data monitoring committee

Data monitoring committee will include 3 physicians and will be activated before the beginning of study patient enrolment.

13. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Pregnancy

Pregnancy and lactation will be study exclusion criteria. All outcomes of pregnancy will be reported to AstraZeneca using contacts listed at Par.6.4.3.

13.2 Overdose

An overdose of study medication is defined as intake of more than 360 mg ticagrelor/ticagrelor placebo per day.

In the event of an overdose of study medication ascertain the time and extent of the overdose regardless of severity. Determine the causative circumstance and whether haemorrhagic or toxic complications have occurred or are likely to do so. Depending on these facts it has to be decided if the patient should be hospitalised for observation or not. Bleeding is one of the most likely pharmacological effects of excessive ticagrelor dosing, and appropriate supportive measures such as volume replacement, local haemostatic measures (eg, compression), and decompression or drainage may be required depending on the localisation, extent of bleeding or volume of blood lost. Patients with overdose-related bleeding should be cautioned to avoid unnecessary activity, mechanical tissue stress, and minor trauma for at least 24 hours after the bleeding has stopped. The IB documents other symptoms that can be expected after an overdose of ticagrelor.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

- An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it.

For overdoses associated with SAE, standard procedure.

14. LIST OF REFERENCES

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