FINAL CLINICAL STUDY PROTOCOL

Shaanxi Micot Technology Co. Ltd

Protocol Title: Open-Label, Sequential-Dose Escalation/De-escalation Trial Testing MT1002 in Patients Undergoing PCI Due to Acute Coronary Syndrome with NSTEMI

Protocol Number: MT1002-II-C01

Short Title: MT1002 in PCI

IND Number:	138760
EudraCT Number:	Not Applicable
Name of Investigational Product:	MT1002
Phase of Development:	II
Indication:	Acute coronary syndrome, non-ST-elevation myocardial infarction (NSTEMI)
Sponsor:	Wenfeng Miao, MD, PhD Chief Medical Officer Shaanxi Micot Technology Co. Ltd Building 6, Xietong Innovation Harbour, Fengdong New City Xi'an, China 710116
Protocol Version:	6.0
Protocol Date:	16-Apr-2023

Protocol Historical File

Version	Brief description/summary of changes	Date
1.0	Version submitted to the FDA	27-Nov-2020
2.0	Modifying Exclusion 16	25-Feb-2021
	Clarification of concomitant anticoagulant restrictions	25-Feb-2021
	Clarification of pregnancy reporting	20-Feb-2021
3.0	Modifying inclusion 2. Clarification of timing from patients with onset of symptoms of ACS due to NSTEMI to presenting to the Emergency Room	07-Jun-2021
	Modifying inclusion 3. Clarification of timing from patients presenting to the ER to start of the PCI.	07-Jun-2021
	Modifying exclusion 18. Use of Coumadin derivatives and/or Factor Xa inhibitor drugs within the last 7 days	07-Jun-2021
	Updates to the Table 3 Schedule of Assessments to reflect the changes due to modified inclusion criteria	07-Jun-2021
4.0	Added additional sites in additional countries (Canada, Australia, and New Zealand) Modified secondary endpoints (removal of thrombocytopenia) Adjusted aspirin dosing according to local countries' clinical practice guidance. Allowed more antiplatelet medications (ticagrelor and prasugrel) according to local countries' clinical practice guidance. Added provision for use of ticagrelor and prasugrel. Added provision for femoral access PCI Modified inclusion 1 to increase maximum age to 85 years. Removed "Presenting to the health care facility within 48 hours from the onset of ACS symptoms"	05-Dec-2021

	Modified inclusion requirements around starting PCI time frame. Modifications to exclusion criteria concerning window for prior transient ischemic attack, window for major surgery, window for prior thrombolytics, chronic NSAID treatment definition, allergy to ticagrelor and prasugrel. Clarification that the 200 to 300 sec ACT target is within 30 minutes of initiating infusion. Added additional results from phase 1 healthy volunteer study. Added additional information on the study rationale Removed Day 5 visit. Decreased time points for platelet aggregation, cardiac biomarkers, coagulation parameters, and PK sampling. Changed platelet aggregation assessing device from Verifynow to PFA100 or PFA200. Refined AE intensity classification	

Version 5.0	Changed Inclusion Criteria #3 - increased procedure window from 72 to 96 hours to allow sites have enough time to schedule the PCI and increase eligibility of targeted patients. Updated Exclusion Criteria #5 - removed "new left bundle branch block" since there is no specific safety concern in these patient population with PCI treated with the IP. Removed Exclusion Criteria #7 – removed pre-existing atrial fibrillation or prolonged QTcF since there is no specific safety concern in these patient population with PCI treated with the IP. Updated Exclusion Criteria# 8 - reduced days from Day 30 to 7 post-treatment due to IP short half-life. Updated Exclusion Criteria # 9- updated the exclusion criteria to only limit to those very high bleeding risk patients per investigators' clinical discretion. The rationale is that other exclusion criteria defined for this study are also CRUSADE factors that may limit bleeding risk, such as age>85, eGFR< 30, and SBP more than 180 mmHg. In clinical practice, CRUSADE is only used by some for anticoagulation risk stratification, not used to determine if anticoagulation is needed. In addition, the bleeding risk treated with IP is further reduced by targeting ACT just more than 200 seconds, not more than 250 seconds. Changed Exclusion Criteria #15 – "Severe uncontrolled hypertension, defined as a systolic blood pressure > 180 mmHg and diastolic blood pressure > 100 mmHg despite **up to 24 hours** of adequate treatment." The rationale for this change is that high blood pressure is a common medical condition of the indicated patient population and adequate time should be allowed to treat the patients prior to PCI procedure and IP treatment. Administrative Changes: updated sponsor medical responsible person and protocol signatories.	12-Dec-2022

Version 6.0	Revised dose escalation/de-escalation/stopping /continuation rules based on end of Cohort 1 SMG safety review and recommendation 23Mar2023: • Added "Continue to next higher dose group if 3 or more patients show peak ACT <200 sec in Cohort 2" to avoid inadequate treatment in cohort 2. • Modified "Stop study drug infusion in an individual patient only temporarily and eliminate conditions if ACT <180." The specific dosing adjustment guideline provided, therefore study drug infusion can be resumed to ACT at target level. • Modified the criteria in **Stop the study if:** both more than 3/6 ACT >350 sec **and** more than 2/6 patients experience bleeding events with BARC 3-5. Both ACT as anti-coagulation level biomarker and actual significant bleeding events with BARC 3-5 are needed to justify study to be stopped due to significant risk of bleeding. Proposed new dosing regimen for cohort 3 at 0.75 mg/kg + 1.6 mg/kg/h*4h and dose adjustment guideline for cohort 3 dosing regimen per SMG's recommendation based on the following findings in Cohort 1 and PK/PD modeling results from Phase I study: • MT1002 was safe and well-tolerated in all 6 patients enrolled in the 0.90 mg/kg+1.8mg/kg/h*4h cohort of the study. • None of the patients who received MT1002 experienced serious adverse events, major bleeding events or major adverse cardiovascular events. • At 0.90 mg/kg+1.8mg/kg/h*4h dose-level, MT1002 achieved targeted ACT level resulting in successful PCI in all 6 patients. • 3 patients had one peak ACT >300 after bolus injection at 5 minute, indicated the bolus dosing at 0.9 mg/kg can be reduced. 0.75 mg/kg is recommended by SMG if 0.6 mg/kg shows inadequate anti-coagulate effect. • Only 1 patient had one peak ACT >300 at 30 minutes during infusion period, indicated	16-Apr-2023

	the infusion dose at 1.8 mg/kg/h*4h can be reduced slightly. 1.6 mg/kg/h*4h is recommended by SMG if 1.2 mg/kg/h*4h mg/kg shows inadequate anti-coagulate effect. • Phase I PK /PD modeling results indicate 0.75mg/kg+1.6mg/kg/hr*4h is an effective dose. Dose adjustment guideline for cohort 3 dosing regimen is provided to ensure the **ultimate** dosing regimen can be identified and confirmed for future phase 3 trials. Clarified that patients who are enrolled but do not undergo PCI (e.g., because of PCI contraindication revealed after coronary angiography or due to exclusion criteria) will be evaluated as safety population. Specified a total of **up to** 18 patients on MT1002 (3 cohorts of 6 patients) will be enrolled in the study based on cohort 2 results. Revised content related to aspirin, or clopidogrel or Ticagrelor or Prasugrel use before and at the time of PCI: All patients will receive either aspirin or loading dose of clopidogrel (600 mg) or Ticagrelor or Prasugrel if not already on maintenance dose need to be either before PCI or otherwise at the time of PCI - deleted “on admission”. The rationale is that the investigators may not have contact of the patient “on admission” so prescribing therapy is difficult. Updated Exclusion Criteria #6 - removed “staged PCI” since there is no specific safety concern and not necessary to exclude patients with staged PCI for this study.	

PROTOCOL APPROVAL SIGNATURES

Protocol Title: Open-Label, Sequential-Dose Escalation/De-escalation Trial Testing MT1002 in Patients Undergoing PCI Due to Acute Coronary Syndrome with NSTEMI

Protocol Number: MT1002-II-C01

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements.

Sponsor Signatory

Wenfeng Miao, MD, PhD
Chief Medical Officer
Shaanxi Micot Technology Co. Ltd

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Signer Name: Wenfeng Miao
Signing Reason: I approve this document
Signing Time: 4/21/2023 | 2:50:38 PM PDT
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Tong Salsedo, MBA
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INVESTIGATOR SIGNATURE PAGE

Protocol Title: Open-Label, Sequential-Dose Escalation/De-escalation Trial Testing MT1002 in Patients Undergoing PCI Due to Acute Coronary Syndrome with NSTEMI

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Confidentiality and Current Good Clinical Practice (GCP)/E6(R2 Compliance Statement)

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol, GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Shaanxi Micot Technology Co. Ltd including, but not limited to, the current Investigator's Brochure.
- Once the protocol has been approved by the independent ethics committee (IEC)/institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Shaanxi Micot Technology Co. Ltd and of the IEC/IRB. I will submit the protocol amendments and/or any informed consent form modifications to Shaanxi Micot Technology Co. Ltd and the IEC/IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about Shaanxi Micot Technology Co. Ltd's study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the patients' state of health will be regarded as confidential. No patients' names will be disclosed. All patients will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the patient before disclosure of patient information to a third party.
- Information developed in this clinical study may be disclosed by Shaanxi Micot Technology Co. Ltd to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title> Investigator Signature

Date (DD-MMM-YYYY)

Institution

1 SYNOPSIS

Title of Study:	Open-Label, Sequential-Dose Escalation/De-escalation Trial Testing MT1002 in Patients Undergoing PCI Due to Acute Coronary Syndrome with NSTEMI
Protocol Number:	MT1002-II-C01
Investigators/ Study Sites:	Planned approximately13 sites cross United States (US), Canada, Australia, and New Zealand
Phase of Development:	Phase II
Objectives:	Primary: To determine the safe and well tolerated dose of MT1002 in patients with acute coronary syndrome (ACS) with non-ST-segment elevation myocardial infarction (NSTEMI) and early percutaneous coronary intervention (PCI) Secondary: • Major adverse cardiovascular events (MACE) within 30 days • To evaluate the anticoagulation effect of MT1002 by activated partial thromboplastin time (aPTT) and activated clotting time (ACT) • To evaluate the antiplatelet effect of MT1002 by platelet aggregation (PA)
Study Endpoints:	Co-Primary endpoints: • The number of patients with target ACT (200 - 300 seconds [sec]) achieved on MT1002 (with no switch to standard of care) prior to and during PCI; and PCI success. • Adverse event (AE) of interest: bleeding events major (Bleeding Academic Research Consortium [BARC] Type 3–5) Secondary endpoints: • MACE within 30 days • AEs of interest: bleeding events, infusion reactions, hypersensitivity reactions, thrombotic events (including stent thrombosis), frequency of abrupt vessel closure (AVC), transient ischemic attack, redo of stent procedure (revascularization), or emergency coronary artery bypass grafting (CABG) • Minor bleeding events (BARC Type 2) • General AEs including change from baseline abnormal safety labs • ACT, aPTT, prothrombin time (PT), TT, FIB, INR • PA and correlation with pharmacokinetics (PK) • Thrombolysis in myocardial infarction flow • Percentage of patients who achieve ACT $\geqslant$ 200 sec • PK of MT1002 Exploratory endpoints: creatine kinase (CK)-MB, and troponin I (troponin T can be measured if the local site does not have the troponin I test)
Study Design:	This is an open-label, sequential-dose escalation/de-escalation trial testing 3 dose levels of MT1002 in patients undergoing PCI due to ACS with NSTEMI. MT1002 is a novel bispecific peptide with properties of a direct thrombin inhibitor and a glycoprotein IIb/IIIa inhibitor. Three doses of MT1002 will be sequentially tested in cohorts of 6 patients each to achieve target ACT. Pre-specified dose escalation/de-escalation/stopping/continuation rules for the patient cohorts are shown in the table below:

	Continue to next higher dose group if:	**Stop study drug infusion temporarily in an individual patient if:**	**Stop dose group and de-escalate according to protocol if:**	**Continue the same dose in the next patient cohort (to get more data for initial dose) if:**	**Stop the study if:**
	⩽ 2/6 pts. peak ACT > 300 ⩾ 3 pts. peak ACT<200 (Cohort 2)	Any ACT >350	⩾ 3/6 pts. Peak ACT > 300	⩽ 3/6 pts. Peak ACT > 300	> 3/6 pts. Peak ACT > 350 AND
	⩽ 1/6 pat with BARC 3 to 5	BARC 3 to 5	⩾ 2/6 pat with BARC 3 to 5	⩽ 1/6 pat with BARC 3 to 5	> 2/6 pat with BARC 3 to 5 OR
	No SAE due to study drug	Any AE/SAE due to study drug that requires switching patient to standard of care	⩾ 2/6 SAEs due to study drug	No SAE due to study drug	⩾ 2/6 SAEs due to study drug
	In ⩽ 1/6 pat lab values preventing dose escalation such as LFT up by ⩾ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	Lab values preventing dose continuation such as LFT up by ⩾ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	In ≥2/6 pat lab value preventing dose escalation such as LFT up by ≥ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	In ≤ 1/6 pat lab values preventing dose escalation such as LFT up by ≥ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	In ≥3/6 pat lab values preventing dose escalation such as LFT up by ≥ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes

Abbreviations: AE, adverse event; ACT, activated clotting time; BARC, Bleeding Academic Research Consortium; ECG, electrocardiogram; LFT, liver function test; pat, patient; QTcF, QT interval corrected by Fridericia's formula; SAE, serious AE.

The decision on dose escalation/de-escalation/stopping or continuation for the patient cohort will be taken by the Study Management Group based on data review of each dose group considering safety, efficacy, drug concentration, and in conjunction with the prespecified criteria.

End of Cohort 1 SMG meeting held on March 23, 2023 recommended to proceed to cohort 3 if patients in cohort 2 shows insufficient anticoagulation effect. Insufficient anticoagulation effect is defined when 3 patients or more treated within cohort 2 dosing regimen experienced at least one ACT<200 seconds and confirmed by Ad Hoc SMG meeting.

All patients will be administered a loading dose of aspirin approximately 325 mg (not exceeding 400 mg, if not already on maintenance ASA dose) and will stay on 75-100 mg/day

	(according to local countries clinical practice guidance) as maintenance therapy. All patients will receive a loading dose of clopidogrel (600 mg) if not already on maintenance dose either before PCI or otherwise at the time of PCI, and then maintain a maintenance dose of 75 mg/day. If the local clinical guidance recommends use of Ticagrelor or Prasugrel, the recommended doses will be: Either before PCI or otherwise at the time of PCI, all patients will receive a loading dose of Ticagrelor 180 mg if not already on a maintenance dose, and then stay on a maintenance dose of 90 mg twice daily. Or either before PCI or otherwise at the time of PCI, all patients will receive a loading dose of Prasugrel 60 mg if not already on a maintenance dose, and then stay on a maintenance dose of 5-10 mg daily. Patients with symptoms of ACS due to NSTEMI who are being triaged in the Emergency Room/hospital and who are selected for early PCI will be screened for the study. Enrollment should occur once the patient has completed screening and satisfied all the I/E criteria. Initiation of the MT1002 intravenous injection would then only start just before the PCI procedure. All patients will be given routine care for ACS according to applicable guidelines including analgesics, nitrates, beta-blockers, and potentially additional drugs as needed (anti-arrhythmic drugs, statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, calcium-channel blockers, proton pump inhibitors, etc.). If a patient meets all the admission criteria and all the eligibility criteria, he/she can be enrolled to MT1002 (1 of 3 dose levels) and undergo early PCI (including diagnostic coronary angiography procedure). Procedure: either radial access/distal radial access PCI or femoral access PCI will be used in this study. It is up to the discretion of the Principal Investigator what type of stent(s), if indicated, will be used. Follow-up: At completion of PCI, subjects will be continued on IV MT1002 for 4 hours from infusion start. All patients will stay on clopidogrel 75 mg/day. If the local clinical guidance recommends use of Ticagrelor or Prasugrel, the recommended maintenance doses will be: Ticagrelor 90 mg twice daily or Prasugrel 5-10 mg daily and aspirin 75-100 mg/day (according to local countries clinical practice guidance) and be followed up for 30 days. Longer-term follow-on treatment will be done according to local treatment guidelines outside of this protocol. Rescue: Patients who fail to achieve an ACT target of 200 to 300 sec with MT1002 (within 30 minutes after MT1002 infusion initiation) will be switched to standard of care (unfractionated heparin or bivalirudin) and discontinued from the study drug.
Selection of Patients:	Inclusion Criteria: 1. Males and females ≥ 18 to 85 years of age. **2.** Diagnosed with NSTEMI defined as new or presumably new ST-segment depression of at least 1 mm in 2 contiguous leads, T-wave inversion more than 3 mm, or any dynamic ST shifts, or elevated troponin I (or troponin T if the local site does not have the troponin I test) higher than upper limit of normal (ULN), or CK-MB consistent with the universal definition of MI. 3. Patients who will undergo PCI during the index hospitalization for an NSTEMI (ideally start of PCI within 96 hours of presenting to the emergency room/ hospital). 4. Ability to understand and willing to give written informed consent. Signed informed consent form before any study related activities. 5. Women of childbearing potential must have a negative pregnancy test or be post-menopausal for at least 1 year before enrollment or be permanently sterilized since ≥6 weeks (i.e., documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). Females of childbearing potential and males with partners of childbearing potential must be using effective contraception if they become sexually active from the time of consent to 90 days after the MT1002 infusion day (i.e., any double combination of male or female condom with spermicidal gel, diaphragm,

	sponge, or cervical cap with spermicidal gel). Women who are breastfeeding are excluded. Exclusion Criteria: 1. Cardiogenic shock or prolonged cardiopulmonary resuscitation (CPR). 2. Active bleeding, bleeding diathesis, coagulopathy. 3. Any history of intracranial bleeding or structural abnormalities (intracerebral mass, aneurysm, arteriovenous malformation [AVM]). 4. Prior transient ischemic attack, prior stroke within 6 months. 5. Index MI is STEMI (ST elevation Myocardial Infraction),. 6. The following planned procedures within 30 days after enrollment: CABG, valve surgery, or additional invasive procedures. 7. Requirement for oral anticoagulants before Day 7 post IP treatment. 8. Based on investigator's discretion, subject is at high bleeding risk, i.e., CRUSADE (**C**an **R**apid risk stratification of **U**nstable angina patients **S**uppress **AD**verse outcomes with **E**arly implementation of the American College of Cardiology/ American Heart Association [ACC/AHA] Guidelines) bleeding risk score >60. 9. Suspected aortic dissection. 10. History of gastrointestinal or genitourinary bleeding within the previous 3 months. 11. Refusal to receive blood transfusion if needed during the study. 12. Major surgery in the last month. 13. History of heparin-induced thrombocytopenia and bleeding diathesis. 14. Severe uncontrolled hypertension, defined as a systolic blood pressure > 180 mmHg and diastolic blood pressure > 100 mmHg despite up to 24 hours of adequate treatment. 15. Prior (within 30 days prior to enrollment) or planned administration of thrombolytics, glycoprotein IIb/IIIa inhibitors, bivalirudin, or fondaparinux for the index MI. Subcutaneous injections of unfractionated heparin and low molecular weight heparin are allowed up to 4 hours and 8 hours, respectively, before study drug. Use of intravenous unfractionated heparin may be continued up until the time of enrollment (just prior to PCI) if ACT is < 200 seconds. 16. Known relevant hematological deviations: hemoglobin (male) < 11 g/dL, hemoglobin (female) < 10 g/dL, hematocrit < 35%, platelet count < 100,000 cells/μL. 17. Use of Coumadin derivatives and/or Factor Xa inhibitor drugs within the last 7 days. 18. Chronic therapy with non-steroidal anti-inflammatory drugs (NSAIDs; except aspirin) (NSAID use is defined as chronic if these medications are taken more than 3 times a week for more than 3 months), cyclooxygenase (COX)-2 inhibitors within 1 month before screening. 19. Known malignancies or other comorbid conditions with life expectancy < 1 year that may result in protocol noncompliance. 20. Known severe liver disease (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT] > 3 × ULN). 21. Known positive serology for hepatitis B & C, HIV screen. 22. Known chronic kidney disease with estimated glomerular filtration rate (eGFR) <30 mL/min and/or dialysis. 23. Known allergy or intolerance to aspirin, clopidogrel, ticagrelor, prasugrel, bivalirudin, unfractionated heparin, P2Y12 antagonists, or contrast. 24. Previous enrollment in this trial. 25. Inability to fully cooperate with the study protocol. 26. Any other medical or psychiatric condition that in the Investigator's judgment precludes participation in the study.
Planned Sample Size:	A total of up to 18 patients on MT1002 (3 cohorts of 6 patients) will be enrolled. Approximately 30 patients will need to be screened. The number of patients screened is based on a screen failure rate of 40%.

Investigational Therapy:

Monotherapy of MT1002, 3 doses via intravenous (IV) + infusion:

Sequence	N	MT1002: Initial loading dose and maintenance dose	Expected peak ACT based on Phase 1 results in healthy volunteers	Expected peak aPTT based on Phase 1 results in healthy volunteers	Expected ACT in 5 min after MT1002 start	Expected aPTT in 5 min after MT1002 start	Expected ACT in 30 min after MT1002 start	Expected aPTT in 30 min after MT1002 start
First dose cohort	6	0.90 mg/kg + 1.8 mg/kg/h* 4h	234.3±26.1 sec – at 4 hours	74.4±6.2 sec – at 4 hours	209.7±19.2	63±4.8	212.3±29.5	65.6±7.5
Second cohort if dose escalate	6	1.2 mg/kg + 2.3mg/kg/h* 4h	253.8±9.6 sec – at 2 hours	83.6±5.4 sec – at 4 hours	234.3±6.9	74.5±7.3	240.3±4.1	78.3±9
Second cohort if dose de-escalated	3 - 6	0.60 mg/kg + 1.2 mg/kg/h* 4h	221.7±11.1 sec – at 2 hours	65.9±2.5 sec – at 4 hours	194.5±28.6	56.5±7.4	216.2±15.7	60.6±4.4
Third *expansion* cohort	6 - 8	0.75 mg/kg + 1.6 mg/kg/h* 4h based on results from initial cohort(s)	220.7 sec at 4 hours	67.7 sec at 4 hours	217.5	66.5	216.5	66.1

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; h, hours; min, minutes; N, number of patients; sec, seconds; Tbd, to be determined.

The goal is to achieve a target ACT of 200 to 300 sec (within 30 minutes after infusion initiation) during the continuous infusion period of MT1002.

MT1002 should be started as close to the start of PCI as possible. MT1002 should be initiated during diagnostics angiography when indication for PCI is confirmed, provided the early PCI is indicated right after the coronary angiography.

Patients who are enrolled but do not undergo PCI (e.g., because of PCI contraindication revealed after coronary angiography or due to exclusion criteria) will be replaced for the study. However, the patients will be evaluated as safety population.

Dose adjustment guideline for cohort 3 dosing regimen, all adjustment will be documented in the patient's source document in detail:

- Bolus dosing

  All patients will receive 0.75 mg/kg as an IV bolus dose, followed immediately by 1.6 mg/kg/hr*4h IV for the duration of the PCI. Five minutes after the bolus dose, ACT should be performed and an additional bolus of 0.3 mg/kg IV may be given if needed (i.e., ACT <200 sec).

- Dosing during infusion period

  10 minutes after initiation of 1.6 mg/kg/hr IV for the duration of the PCI, or 5 minutes after additional bolus if it is given, additional ACT can be monitored, and IP infusion rate can be adjusted. An incremental 10% additional infusion rate can be titrated up until ACT >200 sec. If ACT >300 sec during that period of time, IP infusion can be stopped for 5 minutes, and/or the rate of infusion can be adjusted until ACT maintains between 200 sec and 300 sec. Duration of IP infusion can be 4 hours +-30 minutes in order to accommodate potential infusion rate adjustments.

Reference Therapy:	None
Treatment Duration:	Treatment in preparation for PCI, during PCI, and until approximately 4 hours after enrollment. Patients will receive MT1002 IV followed by MT1002 infusion for 4 hours. This regimen was found safe and well tolerated in Phase 1. MT1002 will be initiated as close to the start of PCI as possible. PCI can start after MT1002 initiation as soon as ACT is confirmed to be ⩾200 sec or within 30 min after MT1002 starts, whichever occurs first. Patients will be discharged from the hospital when they are stable, as defined by the Investigator's judgment. Patients will be followed for 30 days from study drug dosing.
Key Efficacy:	The numbers of patients who achieve ACT target 200 to 300 sec, and measurement of Platelet Aggregation (PA)
Key Safety:	General safety (including vital signs, physical examination, electrocardiogram [ECG], laboratory assessments), AEs, MACE within 30 days, and major bleeding events
Pharmacokinetics:	PK levels of MT1002
Pharmacodynamics:	ACT, aPTT, PT, TT, FIB, INR
Other Assessments:	Thrombolysis in myocardial infarction (TIMI) flow assessments; creatine kinase (CK)-MB, and troponin I (troponin T can be measured if the local site does not have the troponin I test)
Statistical Methods and Planned Analyses:	The efficacy, safety, PK, and pharmacodynamics endpoints will be summarized descriptively. Descriptive summaries of data will be presented (number of observations [n], means, standard deviation, median, minimum and maximum) for continuous parameters, and numbers and percentages will be provided for categorical data. The numbers of patients with target ACT achieved prior/during PCI and PCI success, or failed to finish PCI, or achieved ACT ⩾ 200 sec, and PA measurement will be summarized by cohort and overall. All AEs including bleeding events, MACE, and AEs of interest will be coded using Medical Dictionary for Regulatory Activities (MedDRA), and summarized by MedDRA system organ class, preferred term, and by cohort and overall. The laboratory data, vital signs, and ECG (including category of noteworthy values) will be summarized by visit and by cohort and overall. ACT, aPTT, PT, TT, FIB, and INR and other exploratory endpoints will be summarized descriptively by visit, cohort, and overall.

2 TABLE OF CONTENTS

Page

2.1 List of In-text Tables

Page

3 LIST OF ABBREVIATIONS

Abbreviation	Definition
^{125}I-MT1002	^{125}I-labelled MT1002
ACC/AHA	American College of Cardiology/American Heart Association
ACE	angiotensin-converting enzyme
ACS	acute coronary syndrome
ACT	activated clotting time
ADP	adenosine diphosphate
AE	adverse event
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
BARC	Bleeding Academic Research Consortium
CABG	coronary artery bypass graft
CFR	Code of Federal Regulations
CK	creatine kinase
COX	cyclooxygenase
CRUSADE	**C**an **R**apid risk stratification of **U**nstable angina patients **S**uppress **AD**verse outcomes with **E**arly implementation of the ACC/AHA Guidelines
eCRF	electronic case report form
ECG	electrocardiogram
EDC	electronic data capture
$FeCl_3$	iron chloride
eGFR	estimated glomerular filtration rate
GCP	good clinical practice
HbA1c	glycosylated hemoglobin
hERG	human ether-a-go-go-related gene
HIPAA	Health Insurance Portability Accountability Act
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
IND	Investigational New Drug
IPA	inhibition of platelet aggregation
IRB	institutional review board
IV	intravenous
LFT	Liver function test
MACE	major adverse cardiovascular event(s)
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effect level

Abbreviation	Definition
NSAID	non-steroidal anti-inflammatory drug
MI	myocardial infarction
MTD	maximum tolerated dose
NSTEMI	non-ST-elevation myocardial infarction
PA	platelet aggregation
PAU	platelet-aggregation units
PCI	percutaneous coronary intervention
PK	pharmacokinetic(s)
PT	prothrombin time
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
sec	seconds
STEMI	ST-elevation myocardial infarction
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TIMI	thrombolysis in myocardial infarction
TRAP	thrombin receptor activator peptide
TT	thrombin time
WOCBP	women of childbearing potential
UFH	unfractionated heparin
ULN	upper limit of normal
US	United States
WBC	white blood cell

4 INTRODUCTION

4.1 Background on Acute Coronary Syndrome and Non-ST-Elevation Myocardial Infarction

Acute coronary syndrome (ACS) refers to a spectrum of clinical presentations associated with sudden, reduced blood flow to the heart. There are 3 types of ACS: non-ST-elevation myocardial infarction (NSTEMI), ST-elevation myocardial infarction (STEMI), and unstable angina. The cause of the reduced blood flow to the heart in STEMI is usually coronary plaque rupture causing thrombosis formation occluding a coronary artery. In NSTEMI, the causes of the reduced blood flow to the heart and/or the inability to meet the oxygen demand include flow-limiting conditions such as a stable plaque, vasospasm, coronary embolism, or coronary arteritis; noncoronary injury to the heart such as cardiac contusion, myocarditis, or presence of cardiotoxic substances; and conditions that are relatively unrelated to the coronary arteries or myocardium, such as hypotension, hypertension, tachycardia, aortic stenosis, and pulmonary embolism. NSTEMI and unstable angina are very similar, with NSTEMI having positive cardiac biomarkers. There are several potential causes of NSTEMI, including tobacco abuse, lack of physical activity, high cholesterol, diabetes, obesity, and family history. NSTEMI typically presents as a pressure-like substernal pain, occurring at rest or with minimal exertion. The pain generally lasts more than 10 minutes and may radiate to either arm, neck, or jaw. The pain may also be associated with dyspnea, nausea or vomiting, syncope, fatigue, or diaphoresis. The median age at the time of presentation of ACS in the United States is 68 years, with males outnumbering females by a ratio of 3:2. The incidence of ACS in the United States is over 780,000 of whom approximately 70% will have NSTEMI.[1]

Treatment for NSTEMI depends on the amount of blockage and the severity of the condition. Patients are categorized into low, medium, or high risk, taking into consideration the following factors: age, heart rate, systolic blood pressure, physical examination, serum creatinine, cardiac arrest at hospital admission, ST-segment deviation in electrocardiogram (ECG), and cardiac marker level. Those who are determined to be at low risk will be given drug treatment such as anticoagulants, antiplatelets, beta-blockers, nitrates, statins, angiotensin-converting-enzyme (ACE) inhibitors, or angiotensin receptor blockers. Those with a medium to high risk will have a percutaneous coronary intervention (PCI) or a coronary artery bypass graft (CABG) performed.

The goals of pharmacotherapy in PCI are to reduce morbidity and prevent complications. Patients receiving PCI are treated with a combination of aspirin and a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor). Glycoprotein IIb/IIIa receptor (abciximab, eptifibatide, tirofiban) can be used as adjunctive therapy at the time of PCI, on an individual bispecific basis, for large thrombus burden or inadequate P2Y12 receptor antagonist loading.

Heparin has been the mainstay of anticoagulation during PCI in patients with angina and ACS for decades. However, the choice of anticoagulation for PCI remains a hotly-debated issue.

The introduction of bivalirudin in the management of patients undergoing PCI was welcomed by interventional cardiologists because, compared with heparin plus glycoprotein inhibitor, it was associated with better clinical outcomes, mainly driven by the lower rates of bleeding. Treatment with bivalirudin compared with heparin plus glycoprotein inhibitor reduced bleeding complications but resulted in higher rates of ischemic events, including acute stent thrombosis in patients with STEMI.

The Sponsor, Shaanxi Micot Technology Limited Company (hereafter, referred to as Shaanxi Micot), hypothesized that the increased incidence of acute stent thrombosis with bivalirudin was due to the lack of or weak synchronized anti-platelet effect. Based on this hypothesis, Shaanxi Micot aims to design new compounds to have both thrombin inhibitory activity as well as anti-platelet aggregation effect and other characteristic of ideal parenteral anticoagulant, i.e., to be immediately effective, easily dosed so as not to require frequent monitoring, free of dose adjustment in renally or hepatically impaired patients, and predictably reversible.

4.2 Background on MT1002

MT1002 is a novel 32-amino acid synthetic peptide that Shaanxi Micot is developing as a direct thrombin inhibitor and glycoprotein IIb/IIIa inhibitor, indicated for use as an antithrombotic and anticoagulant in patients with ACS and in patients undergoing PCI. Subsequent indications will be developed for use as an antithrombotic agent and anticoagulant in perioperative patients.

4.2.1 Nonclinical Studies

In vitro and in vivo pharmacology studies of MT1002 were conducted to demonstrate that MT1002 had molecular functions of both a direct thrombin inhibitor and a platelet glycoprotein IIb/IIIa receptor antagonist.

4.2.1.1 In Vitro Pharmacology Studies

The results of the in vitro assay to determine MT1002's thrombin-inhibiting activity showed that MT1002 is a direct thrombin inhibitor and can absolutely inhibit the activity of human thrombin at 10 μM. The half maximal inhibitory concentration (IC_{50}) is 0.046 μM.

The in vitro anticoagulant activity of MT1002 was evaluated using platelet poor plasma samples from Sprague Dawley rats, Beagle dogs, cynomolgus monkeys, and humans. MT1002 was shown to have significant in vitro anticoagulant activity in rat, dog, monkey, and human plasma, which was equivalent to that of bivalirudin.

The in vitro platelet aggregation effect of MT1002 was evaluated using Beagle dog plasma (adenosine diphosphate [ADP]-induced platelet aggregation) and human plasma (ADP, arachidonic acid, and Thrombin Receptor Activator Peptide [TRAP] induced platelet aggregation). The data showed that MT1002 can significantly inhibit the ADP-induced aggregation function of platelets in Beagle dogs and human platelets in vitro; MT1002 can also

significantly inhibit arachidonic acid-induced and TRAP-induced platelet aggregation in human plasma.

4.2.1.2 In Vivo Pharmacology Studies

- The effect of MT1002 was investigated in rats (arteriovenous-shunt thrombosis rat model). Six groups of rats (57 in total) were administered normal saline, bivalirudin 6 mg/kg, enoxaparin 300 IU/kg, low dose MT1002 4.5 mg/kg, middle dose MT1002 9 mg/kg, and high dose MT1002 18 mg/kg. The study demonstrated that thrombosis was inhibited with the administration of MT1002 at high dose in rats but with no obvious evidence of a dose-dependent relationship. Prothrombin time (PT), thromboplastin time (TT), and activated partial thromboplastin time (aPTT) were significantly increased 20 min after the administration of MT1002; there was a dose-dependent relationship between the dose and the increase in PT and aPTT. MT1002 had a lower prolongation of aPTT compared with bivalirudin and enoxaparin with similar antithrombotic effects, indicating that MT1002 would have a lower bleeding risk.
- The effect of MT1002 on iron chloride (FeCl3)-induced thrombosis in rats was investigated. A total of 160 rats were divided into the model control group (normal saline), positive control enoxaparin groups (5 groups of doses: 60 U/kg+240 U/kg/h, 90 U/kg+120 U/kg/h, 30 U/kg+120 U/kg/h, 60 U/kg+60 U/kg/h, and 30 U/kg+45 U/kg/h), positive control bivalirudin groups (6 groups of doses: 0.7 mg/kg+2.8 mg/kg/h, 0.5 mg/kg+2 mg/kg/h, 0.35 mg/kg+1.3 mg/kg/h, 0.17 mg/kg+0.65 mg/kg/h, 0.08 mg/kg+0.325 mg/kg/h, and 0.04 mg/kg+0.163 mg/kg/h), and MT1002 groups (6 groups of doses: 1.5 mg/kg+3.75 mg/kg/h, 1 mg/kg+2.5 mg/kg/h, 0.5 mg/kg+1.25 mg/kg/h, 0.25 mg/kg+0.75 mg/kg/h, 0.125 mg/kg+0.375 mg/kg/h, and 0.041 mg/kg+0.125 mg/kg/h). Compared with the control group, thrombi weight of the inferior vena cava was significantly reduced in the groups of MT1002 at the dose of 1.5 mg/kg+3.75 mg/kg/h, 1 mg/kg+2.5 mg/kg/h, and 0.5 mg/kg+1.25 mg/kg/h, suggesting that MT1002 is capable of reducing the $FeCl_3$- induced thrombus weight in a dose-independent manner. Compared with the control group, the time required for occlusion in the common carotid artery was significantly increased in animals in the MT1002 groups, suggesting that MT 1002 is capable of increasing the time required for occlusion in the common carotid artery in a dose-independent manner. Study results also showed that MT1002 was capable of increasing aPTT and PT in rats in a dose-dependent manner. Compared with the bivalirudin and enoxaparin groups, MT1002 had a lower prolongation of aPTT (5.71, 4.06, and 3.07 times) with similar antithrombotic effects. The inhibitory potency of MT1002 indicated that MT1002 has a lower bleeding risk than bivalirudin and enoxaparin.
- The effect of MT1002 on thrombosis and platelet aggregation was evaluated in rabbits. A total of 53 rabbits were randomly divided into 7 groups: control group (normal saline), bivalirudin 6.0 mg/kg, enoxaparin 200 IU/kg, MT1002 3.0 mg/kg, MT1002 6.0 mg/kg, MT1002 12.0 mg/kg, and MT1002 24.0 mg/kg. The results suggested that MT1002

administration at various doses is capable of decreasing the dry and wet weight of arteriovenous shunt thrombi and inhibiting arteriovenous shunt thrombosis in rabbits. Compared with those in saline group, the dry and wet weight of arteriovenous shunt thrombi was significantly reduced in the MT1002 groups at doses of 6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg. Average inhibition rate of arteriovenous shunt thrombosis was also greater in the MT1002 groups than in the bivalirudin and enoxaparin groups. Results also suggested that platelet aggregation was inhibited to some extent in animals in the MT1002 groups. Compared with those in the saline, enoxaparin, and bivalirudin groups, platelet aggregation was significantly inhibited in the MT1002 groups when administered for 5 minutes at doses of 6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg. When administered for 15 minutes, the MT1002 doses of 12.0 mg/kg and 24.0 mg/kg significantly inhibited platelet aggregation compared with that in the saline, enoxaparin, and bivalirudin groups. Coagulation was also affected:

- The enoxaparin, bivalirudin, and MT1002 groups (6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg) showed significant increase in aPTT compared with that in the saline group when administered for 5 minutes. When administered for 15 minutes, the enoxaparin and MT1002 groups (6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg) showed significant increase in aPTT compared with that in the saline group.
- The bivalirudin and MT1002 groups (6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg) showed significant increase in PT compared to saline when administered for 5 minutes and 15 minutes.
- The analysis on the relationship between the MT1002 dose of 3.0 mg/kg, 6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg for 5 min and 15 min and the increase in aPTT and PT showed that there was a dose-response relationship between the MT1002 dose and the increase in aPTT and PT.
- Thromboplastin time in rabbits was increased to the point exceeding the upper limit of detection in groups of MT1002 administration for 5 minutes and 15 minutes.
- The enoxaparin, bivalirudin, and MT1002 groups (6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg) showed significant increase in activated clotting time (ACT) compared with that in the saline group when administered for 5 minutes. When administered for 15 minutes, the bivalirudin, enoxaparin, and MT1002 groups (3.0 mg/kg, 6.0 mg/kg, 12.0 mg/kg, and 24.0 mg/kg) showed significant increase in ACT compared with that in the saline group. It was suggested that ACT was increased to some extent in the MT1002 groups, and the increase in ACT decreased over time during the period of 15 min after administration. The analysis on the relationship between MT1002 administration at the doses of 3.0, 6.0, 12.0, and 24.0 mg/kg for 5 minutes and 15 minutes and the increase in ACT showed

that there was no dose-response relationship between MT1002 dose and the increase in ACT.

- The effect of MT1002 on coagulation and platelet aggregation was investigated in Beagle dogs. The platelet aggregation was rapidly inhibited after the administration of MT1002 at doses of 3.0, 1.5, and 0.75 mg/kg. The degree of inhibition decreased over time, and the inhibition of platelet aggregation (IPA) of each group was 97.6%, 94.2%, and 80.9% for the groups of 3.0 mg/kg, 1.5 mg/kg, and 0.75 mg/kg, respectively. Based on the analysis of correlation between MT1002 dose and IPA, there was no dose-effect relationship observed. Coagulation was also inhibited to some extent by a single-dose of an intravenous (IV) administration of MT1002 at doses of 3.0, 1.5, and 0.75 mg/kg.
- The effect of MT1002 at a maintenance dose on coagulation and platelet aggregation was investigated in Beagle dogs. The data showed that MT1002 dose-dependently inhibits platelet aggregation, thrombin activity, platelet aggregation, and antithrombin function, while the control substance bivalirudin only has antithrombin activity.
- The exploration of non-effect and minimum effective dose of MT1002 on coagulation and platelet aggregation was investigated in Beagle dogs via continuous administration of MT1002. The results of the early experiment showed that MT1002 at 0.375 mg/kg + 1 mg/kg/h was a minimum effective dose. The data showed that the ineffective dose was 0.09 mg/kg + 0.25 mg/kg/h for which the cumulative dose was 1.09 mg/kg for MT1002 IV maintenance dosing, and this served as a reference on dose selection in clinical trials.

4.2.1.3 Secondary Pharmacology

The potential off-target effects of MT1002 were investigated to evaluate whether MT1002 would interact with other related targets including similar clotting and coagulation factors, serine proteases other than thrombin, and integrins other than glycoprotein IIb/IIIa. Two off-target assays were developed: the adhesion inhibition assay and de-adhesion assay on human umbilical vein cells (HUVEC) were performed to test the affinity for the vitronectin receptor (αVβ3) which has the same β3 subunit as platelet glycoprotein IIb/IIIa receptor. In addition, the binding activity of MT1002 to 53 receptors was evaluated by enzyme and radioligand binding assays.

MT1002 has high selectivity for platelet glycoprotein II (αIIbβ3) receptor and thrombin and has no significant effect on other related targets.

4.2.1.4 Safety Pharmacology

A human ether-a-go-go-related gene (hERG) assay and a battery of safety pharmacology studies, including a behavioral/central nervous system function study in Sprague Dawley rats using the functional observational battery and a respiratory and cardiovascular function study in Beagle dogs using a telemetry system, have been conducted in compliance with Title 21 of the Code of Federal Regulations (CFR), Part 58 of the US Food and Drug Administration (FDA) Good Laboratory Practice (GLP) regulations.

The hERG potassium channel assay demonstrated that MT1002 inhibited hERG-mediated potassium current in a HEK293 cell line with an IC_{50}> 100.67 μmol/L, suggesting little potential for QT prolongation at clinically relevant concentrations.

MT1002 had no significant effects on the central nervous system functions in Sprague-Dawley rats after a single subcutaneous injection at dosages of 3, 10, or 30 mg/kg.

MT1002 at doses of 2.5, 7.5, and 25.0 mg/kg/day had no effect on cardiovascular functions or respiratory functions in conscious Beagle dogs after IV infusion.

4.2.1.5 Pharmacokinetics, Absorption, Distribution, Metabolism, and Excretion in Animals

Nonclinical pharmacokinetics (PK) of MT1002 was evaluated in Sprague-Dawley rats and Beagle dogs after IV administration. PK profiles with moderate clearance and relative short half-life were observed following IV administration of MT1002 in Sprague Dawley rats and Beagle dogs.

A tissue distribution and excretion study of MT1002 in Sprague-Dawley rats indicated that MT1002 was mainly observed in the stomach, kidney, and bladder after IV administration. MT1002 was less distributed to other tissues. The peak time of ^{125}I-labelled MT1002 (^{125}I-MT1002) in most tissues was at 0.25 hour after dosing. The peak time of ^{125}I-MT1002 in liver, lipid, bladder, gonad, and brain were at 1 hour after dosing. The peak time of ^{125}I-MT1002 in the stomach was 2 hours after dosing.

After IV administration with ^{125}I-MT1002, radioactivity was mainly excreted by the kidneys in rats. More than 90% of ^{125}I-MT1002 was excreted by the kidneys in the first 11 days after administration. Less radioactivity was excreted in bile.

4.2.1.6 Nonclinical Toxicology

Nonclinical toxicology studies included the following: a behavioral/central nervous system function study in rats using the functional observational battery, an hERG assay; a cardiovascular and respiratory telemetry study in the unrestrained conscious Beagle dogs; an acute IV toxicity study in Sprague Dawley rats, an acute IV toxicity study in Beagle dogs, a 4-week repeat dose IV toxicity and toxicokinetics study in Sprague Dawley rats with a 4-week recovery, a 4-week repeat dose IV toxicity and toxicokinetics study in Beagle dogs with a 4-week recovery; a bacterial reverse mutation assay (Ames); an in vitro chromosome aberration assay in Chinese hamster lung cells; an in vivo bone marrow micronucleus assay in mice; and an in vitro hemolysis assessment using human blood cells. The results from these are briefly summarized below:

- The maximum tolerated dose (MTD) was considered to be 400 mg/kg in Sprague-Dawley rats after single IV infusion of MT1002 for injection. The MTD for Beagle dogs was considered to be ⩾ 250 mg/kg.

- After IV infusion administration of MT1002 for injection to Sprague-Dawley rats once daily at 10, 30, and 100 mg/kg/day for 4 weeks, no apparent systematic toxicity was observed except the prolongation of PT, aPTT, and TT as well as the decrease of fibrinogen related to the test article's pharmacologic effect. The no observed adverse effect level (NOAEL) in Sprague Dawley rats was considered to be ⩾ 100 mg/kg/day.
- After the IV administration at doses of 0.72, 3.6, or 7.2 mg/kg followed by IV infusion at a dose of 0.072, 0.36, or 0.72 mg/kg/min for approximately 4 hours once daily for 4 consecutive weeks (the daily cumulative dose was 18, 90, and 180 mg/kg/day, respectively), no mortality was noted in any animal throughout the study. Treatment-related pharmacologic action and dose-dependent increases in PT, aPTT, and TT, and decreases in fibrinogen were noted compared with those in the concurrent control group. The NOAEL was considered to be 90 mg/kg/day associated with the clinical responses of animals in the high dose group.
- Hemorrhage and subacute inflammation in the adventitia of the injection site were noted in animals given an IV injection of MT1002 for injection at the concentration range of 2 to 20 mg/mL. These changes resolved during the 4-week recovery period. No test article-related irritation reaction of the injection site was noted in animals given slow IV infusions.
- The genotoxic potential of MT1002 was evaluated in the Ames test, chromosomal aberration study, and micronucleus assay, and negative results were obtained from all 3 tests, strongly suggesting that MT1002 is not mutagenic at clinically relevant concentrations.
- MT1002 for injection at the concentration of 20 mg/mL had no hemolytic or aggregative effect using the hemolysis test with red blood cells of New Zealand rabbits under the current study condition.

4.2.2 Clinical Studies

A Phase 1 study in healthy volunteers has been completed. The study was a randomized, open-label, sequential parallel group, single ascending doses study to evaluate the safety, tolerability, PK, and pharmacodynamics of MT1002 in healthy subjects. Five cohorts of 6 subjects each (total of 30 subjects) were administered MT1002 at the following doses: 0.15 mg/kg+0.3 mg/kg/h*4h, 0.30 mg/kg+0.6 mg/kg/h*4h, 0.60 mg/kg+1.2 mg/kg/h*4h, 0.90 mg/kg+1.8 mg/kg/h*4h, and 1.2 mg/kg+2.3 mg/kg/h*4h. Based on a 70 kg body weight, the starting dose (based on 0.15 mg/kg+0.3 mg/kg/h*4h) was determined to be 94.5 mg. This starting dose represents an approximate 10-fold safety margin based on body surface area-adjusted dose at the NOAEL dose of 100 mg/kg/day (equivalent to 968 mg/day in the human) after MT1002 was intravenously administered to Sprague Dawley rats for 28 days, and an approximate 30-fold safety margin based on body surface area-adjusted dose at the NOAEL dose of 90 mg/kg/day (equivalent to 3000 mg/day in the human) after MT1002 was intravenously administered to Beagle dogs for 28 days.

After a single dose of MT1002 following IV bolus/infusion ascending dose administration, exposures of MT1002 (C_{max} and AUC), increased in a slightly greater than dose proportional manner. Clearance and volume of distribution at were similar across the 5 doses studied. The amount of MT1002 excreted in urine increased with increasing dose and less than 5% of the doses studied was excreted in urine.

Study drug administration resulted in changes in the levels of clotting (ACT, aPTT, PT, INR, TT, fibrinogen) and platelet aggregation parameters post-dose consistent with reduced clotting and platelet aggregation activity. For clotting parameters other than fibrinogen, the maximal change after the MTD approximated the time to maximum plasma concentration (T_{max}) of study drug. The post-dose change in platelet aggregation occurred more rapidly than the changes in the clotting endpoints with maximal change from baseline at 5 minutes post-dose. Day 2 values of all parameters approximated baseline values. These effects were more prominent after the 0.60 mg/kg+1.2 mg/kg/h*4h and 0.90 mg/kg+1.8 mg/kg/h*4h doses than in the lower dose levels.

There were no deaths, serious adverse events (SAEs), discontinuations of study drug due to a TEAE or withdrawals due to a TEAE. Of the 13 adverse events (AEs), nervous system disorders, the most commonly reported SOC, were reported by 1 subject in Cohort 3 (headache) and 2 in Cohort 5 (headache and dizziness). Gastrointestinal disorders were reported by 1 subject in Cohort 4 (discolored feces) and 1 in Cohort 5 (mouth hemorrhage). General disorders and administration site conditions were reported by 1 subject in Cohort 3 (injection site bruising and injection site nodule) and 1 in Cohort 5 (injection site hemorrhage). Each treatment-related TEAE was reported by a single subject. All TEAEs were Grade 1 in severity, and all patients recovered.

The results of the study showed that continuous IV infusion for 4 hours was safe and well tolerated in healthy subjects and had significant effect on coagulation function. The MTD in healthy subjects was 1.2 mg/kg + 2.3 mg/kg/h*4h. MT1002 had a fast elimination rate in the human body and was positively correlated with dose.

4.3 Clinical Risks/Benefits of MT1002

Based on the observations from the nonclinical studies and the clinical study noted in the previous sections, MT1002 is expected to be safe for the patients in this study with no anticipated risks.

COVID-19 Related Risk/Benefit Assessment

The COVID-19 pandemic is a globally evolving and dynamic situation. The risk of infection is highly variable and dependent on factors such as country, type of hematological facility, patient characteristics, and continues to vary over time. Treating physicians are aware of the status of the COVID-19 pandemic in their area at a specific time. In order to ensure positive risk/benefit for patients treated in this study, site interest and Investigator assessment of positive local risk/benefit will be established in advance of initiating enrollment.

4.4 Study Rationale

Therapies for ACS includes antithrombotic therapy and glycoprotein IIb/IIIa receptor antagonists (GPI) as well as anticoagulant therapy. Additional therapeutic measures that may be indicated include thrombolysis and PCI. The goals of pharmacotherapy in PCI are to reduce morbidity and prevent complications. Heparin has been the mainstay of anticoagulation during PCI in patients with angina and ACS for decades. However, the choice of anticoagulation for PCI remains a hotly debated issue. MT1002 is a novel 32-amino acid synthetic peptide aimed to combine molecular functions of both a direct thrombin inhibitor and a platelet glycoprotein IIb/IIIa receptor antagonist, and other characteristics of an ideal parenteral anticoagulant, i.e., to be immediately effective, easily dosed so as not to require frequent monitoring, free of dose adjustment in renally or hepatically impaired patients, and predictably reversible, indicated for use as an antithrombotic and anticoagulant in patients with ACS and in patients undergoing PCI. This study is to investigate the safety, tolerability, and efficacy of MT1002 in patients undergoing PCI due to ACS with NSTEMI.

Three doses of MT1002 (IV loading + continuous IV infusion) will be sequentially tested. The first dose level is 0.90 mg/kg initial loading dose (bolus intravenous injection) + 1.8 mg/kg/h (infusion) for 4 hours. The second dose level will be based on the results from the first cohort (If the dose is escalated, then the second dose level is 1.2 mg/kg initial loading dose (bolus intravenous injection) + 2.3 mg/kg/h (infusion) for 4 hours; if the dose is de-escalated, then the second dose level is 0.6 mg/kg initial loading dose (bolus intravenous injection) + 1.2 mg/kg/h (infusion) for 4 hours). The third dose will be determined based on the results from the first 2 cohorts. The doses of 0.90 mg/kg+ 1.8 mg/kg/h*4h, and 1.2 mg/kg+2.3 mg/kg/h*4h were tested in the Phase 1 healthy volunteer study and were considered to be safe and well tolerated, with the 1.2 mg/kg+2.3 mg/kg/h*4h dose declared the MTD.

5 STUDY OBJECTIVES AND ENDPOINTS

5.1 Study Objectives

5.1.1 Primary Objective

The primary objective of the study is to determine the safe and well tolerated dose of MT1002 in patients with ACS patients NSTEMI and early PCI.

5.1.2 Secondary Objectives

The secondary objectives of the study are:

- Major adverse cardiovascular events (MACE) within 30 days
- To evaluate the anti-coagulation effect of MT1002 by aPTT and ACT
- To evaluate the anti-platelet effect of MT1002 by PA

5.2 Study Endpoints

5.2.1 Co-Primary Endpoints

The co-primary endpoints of this study are:

- The number of patients with target ACT (200 to 300 seconds [sec]) achieved on MT1002 (with no switch to standard of care) prior to and during PCI and PCI success. PCI success is defined as achievement of < 30% residual diameter stenosis of all treated lesions as assessed by visual inspection or Quantitative Coronary Analysis (QCA), without an in-hospital major adverse cardiac event (death, myocardial infarction [MI], or repeat coronary revascularization of the target lesion)
- AE of interest: bleeding events major (Bleeding Academic Research Consortium [BARC] Type 3–5)

5.2.2 Secondary Endpoints

The secondary endpoints are as follows:

- MACE within 30 days
- AEs of interest: bleeding events, infusion reactions, hypersensitivity reactions, thrombotic events (including stent thrombosis), frequency of abrupt vessel closure (AVC), transient ischemic attack, redo of stent procedure (revascularization), or emergency coronary artery bypass grafting (CABG)
- Minor bleeding events (BARC Type 2)
- General AEs including change from baseline abnormal safety laboratory test results
- ACT, aPTT, PT, TT, FIB, INR
- PA and correlation with PK

- Thrombolysis in myocardial infarction (TIMI) flow
- Percentage of patients who achieve ACT ⩾ 200 sec
- PK of MT1002

5.2.3 Exploratory Endpoints

The exploratory endpoint of this study is: creatine kinase (CK)-MB and troponin I (troponin T can be measured if the local site does not have the troponin I test).

6 INVESTIGATIONAL PLAN

6.1 Description of Overall Study Design and Plan

This is an open-label, sequential-dose escalation/de-escalation trial testing 3 dose levels of MT1002 in patients undergoing PCI due to ACS with NSTEMI. Three doses of MT1002 will be sequentially tested in cohorts of 6 patients each to achieve target ACT.

Pre-specified dose escalation/de-escalation/stopping/continuation rules for the patient cohorts are shown in Table 1 below.

Table 1 Rules for Dose Escalation/De-Escalation/Stopping/Continuation

Continue to next higher dose group if:	**Stop study drug infusion temporarily in an individual patient if:**	**Stop dose group and de-escalate according to protocol if:**	**Continue the same dose in the next patient cohort (to get more data for initial dose) if:**	**Stop the study if:**
⩽ 2/6 pat peak ACT > 300	Any ACT > 350 or < 180	⩾ 3/6 pat peak ACT > 300	⩽ 3/6 pat peak ACT > 300	> 3/6 pat peak ACT > 350
≥ 3 pts. peak ACT<200 (Cohort 2)				AND
⩽ 1/6 pat with BARC 3 to 5	BARC 3 to 5	⩾ 2/6 pat with BARC 3 to 5	⩽ 1/6 pat with BARC 3 to 5	> 2/6 pat with BARC 3 to 5
				OR
No SAE due to study drug	Any AE/SAE due to study drug that requires switching patient to standard of care	⩾ 2/6 SAEs due to study drug	No SAE due to study drug	⩾ 2/6 SAEs due to study drug
In ⩽ 1/6 pat lab values preventing dose escalation such as LFT up by ⩾ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	Lab values preventing dose continuation such as LFT up by ⩾ 2 ×from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	In ≥ 2/6 pat lab value preventing dose escalation such as LFT up by ≥ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	In ≤ 1/6 pat lab values preventing dose escalation such as LFT up by ≥ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes	In ≥ 3/6 pat lab values preventing dose escalation such as LFT up by ≥ 2 × from baseline; platelet count < 50,000; QTcF interval > 500 ms or > 60 ms change from baseline, based on ECGs; or study drug related vital sign changes that require stabilization of hemodynamics with positive inotropes

Abbreviations: AE, adverse event; ACT, activated clotting time; BARC, Bleeding Academic Research Consortium; ECG, electrocardiogram; LFT, liver function test; pat, patient; QTcF, QT interval corrected by Fridericia's formula; SAE, serious AE.

The decision on dose escalation/de-escalation/stopping or continuation for the patient cohort will be taken by the Study Management Group based on data review of each dose group considering safety, efficacy, drug concentration, and in conjunction with the prespecified criteria.

End of Cohort 1 SMG meeting held on March 23, 2023 recommended to proceed to cohort 3 if patients in cohort 2 shows insufficient anticoagulation effect. Insufficient anticoagulation effect is defined when 3 patients or more treated within cohort 2 dosing regimen experienced at least one ACT<200 seconds and confirmed by Ad Hoc SMG meeting.

All patients will be administered a loading dose of aspirin approximately 325 mg (not exceeding 400mg, if not already on maintenance ASA dose) and will stay on 75-100 mg/day (according to local countries clinical practice guidance) as maintenance therapy. All patients will receive a loading dose of clopidogrel (600 mg) if not already on maintenance dose either before PCI or otherwise at the time of PCI, and then maintain a maintenance dose of 75 mg/day. If the local clinical guidance recommends use of Ticagrelor or Prasugrel, the recommended doses will be: Either before PCI or otherwise at the time of PCI, all patients will receive a loading dose of Ticagrelor 180 mg if not already on a maintenance dose, and then stay on a maintenance dose of 90 mg twice daily. Or either before PCI or otherwise at the time of PCI, all patients will receive a loading dose of Prasugrel 60 mg if not already on a maintenance dose, and then stay on a maintenance dose of 5-10 mg daily.

Patients with symptoms of ACS due to NSTEMI who are being triaged in the Emergency Room/hospital and who are selected for early PCI will be screened for the study. Enrollment should occur be as close to the actual start of PCI as possible. All patients will be given routine care for ACS according to applicable guidelines including analgesics, nitrates, beta-blockers, and potentially additional drugs as needed (anti-arrhythmic drugs, statins, ACE inhibitors/angiotensin II receptor blockers, calcium-channel blockers, proton pump inhibitors, etc).

If a patient meets all the admission criteria and all the eligibility criteria, he/she can be enrolled to receive MT1002 treatment (1 of 3 dose levels) and undergo early PCI (including diagnostic coronary angiography procedure).

Procedure: either radial access/distal radial access PCI or femoral access PCI will be used in this study. It is up to the discretion of the Principal Investigator what type of stent(s), if indicated, will be used.

Follow-up: At completion of PCI, subjects will be continued on IV MT1002 for 4 hours from infusion start. All patients will stay on clopidogrel 75 mg/day. If the local clinical guidance recommends use of Ticagrelor or Prasugrel, the recommended maintenance doses will be: Ticagrelor 90 mg twice daily or Prasugrel 5-10 mg daily and aspirin 75-100 mg/day (according to local countries clinical practice guidance) and be followed up for 30 days. Longer-term follow-on treatment will be done according to local treatment guidelines outside of this protocol.

Rescue: Patients who fail to achieve an ACT target of 200 to 300 sec with MT1002 (within 30 minutes after MT1002 infusion initiation) will be switched to standard of care (unfractionated heparin [UFH] or bivalirudin) and discontinued from the study drug.

6.2 Discussion of Study Design

This study is a single dose, sequential-dose escalation study in patients undergoing PCI due to ACS with NSTEMI. The first 2 doses were considered safe and well tolerated in the Phase 1 healthy subject study. The third dose to be given will be determined based on the safety and efficacy results from the first 2 doses. Dose escalation/de-escalation and stopping rules have been put in place to ensure the safety of the patients in this study (see Section 6.1).

The patients in this study will receive a single MT1002 close to the initiation of PCI (Day 1) followed by 4 hours of IV infusion and follow-up at Day 2, Day 14, and Day 30. This period is considered adequate for the collection of PK, efficacy, and safety data.

6.3 End of Study

A patient will have fulfilled the requirements for study completion if/when the patient has completed all study periods, including the end of study (EOS) visit or the last scheduled visit as indicated in the Schedule of Assessments (Table 4).

The end of the study will be the last patient's last visit as indicated in the Schedule of Assessments (Table 4).

7 SELECTION OF STUDY POPULATION

7.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Males and females ⩾ 18 to 85 years of age.
2. Diagnosed with NSTEMI defined as new or presumably new ST-segment depression of at least 1 mm in 2 contiguous leads, T-wave inversion more than 3 mm, or any dynamic ST shifts, or elevated troponin I (or troponin T if the local site does not have the troponin I test) higher than upper limit of normal (ULN), or CK-MB consistent with the universal definition of MI.
3. Patients who will undergo PCI during the index hospitalization for an NSTEMI (ideally patients start of PCI within 96 hours of presenting to the emergency room/ hospital).
4. Ability to understand and willing to give written informed consent. Signed informed consent form before any study related activities.
5. Women of childbearing potential (WOCBP) must have a negative pregnancy test or be post-menopausal for at least 1 year before enrollment or be permanently sterilized since ⩾ 6 weeks (i.e., documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). Females of childbearing potential and males with partners of childbearing potential must be using effective contraception if they become sexually active from the time of consent to 90 days after the MT1002 infusion day (i.e., any double combination of male or female condom with spermicidal gel, diaphragm, sponge, or cervical cap with spermicidal gel). Women who are breastfeeding are excluded. For the definition and list of allowed highly effective methods of contraception, see APPENDIX 1.

7.2 Exclusion Criteria

Individuals meeting any of the following criteria at Screening are ineligible to participate in this study:

1. Cardiogenic shock or prolonged cardiopulmonary resuscitation (CPR).
2. Active bleeding, bleeding diathesis, coagulopathy.
3. Any history of intracranial bleeding or structural abnormalities (intracerebral mass, aneurysm, arteriovenous malformation [AVM]).
4. Prior transient ischemic attack, prior stroke within 6 months.
5. Index MI is STEMI (ST elevation Myocardial Infraction).
6. The following planned procedures within 30 days after enrollment: CABG, valve surgery, or additional invasive procedures.
7. Requirement for oral anticoagulants before Day 7 post IP treatment.
8. Based on investigator's discretion, subject is at high bleeding risk, i.e., CRUSADE (**C**an **R**apid risk stratification of **U**nstable angina patients **S**uppress **AD**verse outcomes with **E**arly implementation of the American College of Cardiology/American Heart Association [ACC/AHA] Guidelines) bleeding risk score >60.
9. Suspected aortic dissection.
10. History of gastrointestinal or genitourinary bleeding within the previous 3 months.
11. Refusal to receive blood transfusion if needed during the study.
12. Major surgery in the last month.
13. History of heparin-induced thrombocytopenia and bleeding diathesis.
14. Severe uncontrolled hypertension, defined as a systolic blood pressure > 180 mmHg and diastolic blood pressure > 100 mmHg up to 24 hours of adequate treatment.
15. Prior (within 30 days prior to enrollment) or planned administration of thrombolytics, glycoprotein IIb/IIIa inhibitors, bivalirudin, or fondaparinux for the index MI. Subcutaneous injections of unfractionated heparin and low molecular weight heparin are allowed up to 4 hours and 8 hours, respectively, before study drug. Use of intravenous unfractionated heparin may be continued up until the time of enrollment (just prior to PCI), if ACT is < 200 seconds.
16. Known relevant hematological deviations: hemoglobin (male) < 11 g/dL hemoglobin (female) < 10 g/dL, hematocrit < 35%, platelet count < 100,000 cells/μL.
17. Use of Coumadin derivatives and/or Factor Xa inhibitor drugs within the last 7 days.

18. Chronic therapy with non-steroidal anti-inflammatory drugs (NSAIDs; except aspirin) (NSAID use is defined as chronic if these medications are taken more than three times a week for more than three months), cyclooxygenase (COX)-2 inhibitors within 1 month before screening.
19. Known malignancies or other comorbid conditions with life expectancy < 1 year that may result in protocol noncompliance.
20. Known severe liver disease (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT] > 3 × ULN).
21. Known positive serology for hepatitis B & C, HIV screen.
22. Known chronic kidney disease with estimated glomerular filtration rate (eGFR) < 30 mL/min and/or dialysis.
23. Known allergy or intolerance to aspirin, clopidogrel, ticagrelor, prasugrel, bivalirudin, UFH, P2Y12 antagonists, or contrast.
24. Previous enrollment in this trial.
25. Inability to fully cooperate with the study protocol.
26. Any other medical or psychiatric condition that in the Investigator's judgment precludes participation in the study.

7.3 Study Withdrawal, Removal, and Replacement of Patients

If a patient discontinues study treatment and/or is withdrawn from the study for any reason, the study site must immediately notify the Medical Monitor. The date and the reason for treatment/study discontinuation must be recorded on the electronic case report form (eCRF). Patients who complete or discontinue early from the study will be asked to return to the study site within 30 days of completion of PCI to complete assessments as indicated in the Schedule of Assessments (Table 4).

In the event that a patient discontinues prematurely from the study because of a treatment-emergent AE (TEAE) or serious TEAE, the TEAE or serious TEAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the Investigator to no longer be clinically significant.

Patients who are enrolled but do not undergo PCI (e.g., because of PCI contraindication or exclusion criteria revealed after coronary angiography) will be replaced for the study.

- Patients who drop out during the screening phase before enrollment with MT1002 dose allocation will be considered a screen failure. They are to be recorded as screen failures in the eCRFs, along with the reason for failing screening, and no further follow-up is required.
- Patients who discontinue treatment prematurely, and/or discontinue or withdraw from the study after enrollment with MT1002 dose allocation will be considered as "early

discontinuations" and the reason for premature discontinuation must be recorded in the eCRFs. The data will be included in the trial database and will be reported.

Once a patient is withdrawn from the study, the patient cannot reenter the study.

A patient may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- unacceptable toxicity or AE
- patient withdrawal of consent: at any time, a patient's participation in the study may be terminated at his/her request or on the basis of the Investigator's clinical judgment. The reason for patient/subject withdrawal will be noted on the eCRF.
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that becomes apparent during treatment and necessitates the patient's termination from the study
- general or specific changes in the patient's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- patient fails to adhere to the protocol requirements (e.g., failure to return for defined number of visits)
- lost to follow-up: the patient stops coming for visits, and study personnel are unable to contact the patient

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An Investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

As this is a single-dose study in which the treatment period starts before PCI and continuation in the study consists of standard of care collection of medical outcomes, the Investigators are encouraged to continue collection of medical information to ensure patient safety, and all patients will be asked to allow information from their medical records (including non-study-related records) to continue to be collected through 30 days post-dose.

8 TREATMENTS

8.1 Details of MT1002

MT1002 is a white or off-white amorphous powder that is highly soluble in water. The MT1002 dosage form was designed based on the physical and chemical properties of MT1002. Because MT1002 is a peptide, it is not stable in solution. Therefore, a lyophilized product for injection is developed. Mannitol is used as an excipient. The compatibility study of the active pharmaceutical ingredient and excipient shows that mannitol has no impact on the stability of the active pharmaceutical ingredient.

MT1002 is provided as a solution for injection filled in a transparent tubing borosilicate glass vial (Type 1, US Pharmacopeia) stopped with a brominate butyl rubber stopper and capped with a combined aluminum-plastic cap. Each vial contains 50 mg of MT1002. The composition of a MT1002 50 mg/vial is provided in Table 2.

Table 2 Composition of MT1002 for Injection, 50 mg/vial

Components	Unit Formula (50 mg)	Quality Reference	Function
MT1002	50.0 mg	In-house	Active pharmaceutical ingredient
Mannitol	90 mg	USP/NF	Excipient
Sodium hydroxide	Sufficient quantity	USP/NF	Adjust pH
Water for injection	Add to 2 mL	USP	Solvent

Abbreviations: NF, National Formulary; USP, United States Pharmacopeia.

Results from stability studies demonstrate that MT1002 for injection remained chemically and physically stable during 6 months of storage at accelerated condition (25±2°C/60%±10% relative humidity) and 12 months at long-term stability conditions (5±3°C).

All drug supplies will be provided by the Sponsor.

8.2 Dosage Schedule

Patients will receive MT1002 IV followed by MT1002 infusion for 4 hours. This regimen was found safe and well tolerated in Phase 1. MT1002 will be initiated as close to the start of PCI as possible. MT1002 should be initiated during diagnostics angiography when indication for PCI is confirmed, provided the early PCI is indicated right after the coronary angiography. PCI can start after MT1002 initiation as soon as ACT is confirmed to be ≥ 200 sec or within 30 min after MT1002 starts, whichever occurs first. MT1002 will be administered by an intravenous injection of 0.90 mg/kg, 1.2 mg/kg, 0.75 mg/kg or 0.6 mg/kg (depending on the dose selected for the cohort) via IV access prior to the PCI procedure, immediately followed by an IV infusion of 1.8 mg/kg/hour, 2.3 mg/kg/hour, 1.6 mg/kg/hour or 1.2 mg/kg/hour (depending on the dose selected for the cohort) until completion of the procedure.

Patients will be discharged from the hospital when they are stable, as defined by the Investigator's judgment. Patients will be followed for 30 days from study drug dosing.

Three doses of MT1002 will be evaluated in this study as noted in the table below. The first dose level is 0.90 mg/kg initial loading dose (bolus intravenous injection) + 1.8 mg/kg/h (infusion) for 4 hours. The second dose level will be based on the results from the first cohort (If the dose is escalated, then the second dose level is 1.2 mg/kg initial loading dose (bolus intravenous injection) + 2.3 mg/kg/h (infusion) for 4 hours; if the dose is de-escalated, then the second dose level is 0.6 mg/kg initial loading dose (bolus intravenous injection) + 1.2 mg/kg/h (infusion) for 4 hours). The third dose will be based on the results from the initial 2 cohorts (Table 3). The goal is to achieve a target ACT of 200 to 300 sec (within 30 minutes after infusion initiation) during the continuous infusion period of MT1002.

Patients who are enrolled but do not undergo PCI (e.g., because of PCI contraindication revealed after coronary angiography or due to exclusion criteria) will be replaced for the study. However, the patients will be evaluated as safety population.

Dose adjustment guideline for cohort 3 dosing regimen is below. All adjustment will be documented in the patient's source document in detail:

- Bolus and maintenance dosing

  All patients will receive 0.75 mg/kg as an IV bolus dose, followed immediately by 1.6 mg/kg/hr*4h IV for the duration of the PCI. Five minutes after the bolus dose, ACT should be performed and an additional bolus of 0.3 mg/kg IV may be given if needed (i.e., ACT <200 sec).

- Dosing during infusion period

  10 minutes after initiation of 1.6 mg/kg/hr IV for the duration of the PCI, or 5 minutes after additional bolus if it is given, additional ACT can be monitored, and IP infusion rate can be adjusted. An incremental 10% additional infusion rate can be titrated up until ACT >200 sec. If ACT >300 sec during that period of time, IP infusion can be stopped for 5 minutes, and/or the rate of infusion can be adjusted until ACT maintains between 200 sec and 300 sec. Duration of IP infusion can be 4 hours +-30 minutes in order to accommodate potential infusion rate adjustments.

Table 3 Planned Dose Regimen of MT1002 for Injection and Expected ACT and aPTT Values

Sequence	N	MT1002: Initial loading dose and maintenance dose	Expected peak ACT based on Phase 1 results in healthy volunteers	Expected peak aPTT based on Phase 1 results in healthy volunteers	Expected ACT in 5 min after MT1002 start	Expected aPTT in 5 min after MT1002 start	Expected ACT in 30 min after MT1002 start	Expected aPTT in 30 min after MT1002 start
First dose cohort	6	0.90 mg/kg + 1.8 mg/kg/h*4h	234.3±26.1 sec – at 4 hours	74.4±6.2 sec – at 4 hours	209.7±19.2	63±4.8	212.3±29.5	65.6±7.5
Second cohort if dose escalated	6	1.2 mg/kg + 2.3mg/kg/h*4h	253.8±9.6 sec – at 2 hours	83.6±5.4 sec – at 4 hours	234.3±6.9	74.5±7.3	240.3±4.1	78.3±9
Second cohort if dose de-escalated	6	0.60 mg/kg + 1.2 mg/kg/h*4h	221.7±11.1 sec – at 2 hours	65.9±2.5 sec – at 4 hours	194.5±28.6	56.5±7.4	216.2±15.7	60.6±4.4
Third *expansion* cohort	6-8	0.75 mg/kg + 1.6 mg/kg/h*4h based on results from initial 2 cohorts	220.7 sec at 4 hours	67.7 sec at 4 hours	217.5	66.5	216.5	66.1

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; h, hours; min, minutes; N, number of patients; sec, seconds; Tbd, to be determined.

8.3 Measures to Minimize Bias: Study Treatment Assignment

8.3.1 Method of Study Treatment Assignment

This is an open-label, sequential-dose escalation/de-escalation study testing 3 dose levels of MT1002. The decision on dose escalation/de-escalation/stopping or continuation for the patient cohort will be made by the Study Management Group based on data review of each dose group considering safety, efficacy, PK, and in conjunction with the prespecified criteria in Section 6.1.

8.3.2 Blinding

This is an open-label study; therefore, blinding is not applicable.

8.4 Treatment Accountability and Compliance

The pharmacist or other designated individual will be responsible for: maintaining records of study drug delivered to the study site, the inventory at the study site, the distribution to and use by each patient, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature log, and unique code numbers assigned to the product and study patients.

The study drug will only be applied by the Investigator on Day 1 (prior, during, and after PCI). The timing and duration of the loading dose followed by infusion as well as the dose calculation depending on the patient's weight will be noted in the patient's medical file. Early termination of infusion and reason for termination will also be recorded in the eCRF.

Administration of study drug will be performed by study site personnel, and the date, time, and dose information will be recorded in the eCRF.

8.5 Prior and Concomitant Therapy

8.5.1 Prior and Concomitant Medications

Restricted prior therapies that exclude patients from the study are provided in Section 7.2.

All cardiovascular, antiplatelet, anticoagulant, and diabetic medications and other treatments taken by the patient during the study, including those treatments initiated or ongoing within 48 hours before the start of the study, must be recorded on the eCRF (based on patient/caregiver report and/or medical records).

Concomitant anticoagulant medications before enrollment:

Unfractionated heparin: UFH administered to patients before enrollment will be discontinued at the time of enrollment with MT1002 allocation (if not already discontinued). MT1002 can be administered after discontinuation of intravenous UFH or 4 hours after subcutaneous UFH discontinuation provided ACT is <200 seconds. The wash-out period for UFH should help to

ensure complete UFH elimination[5] to avoid initial ACT increase due to residual heparin effect that could confound the analysis of MT1002's effect on the indices of coagulation.

Low molecular weight heparin: LMWH administered to patients before enrollment will be discontinued at the time of enrollment with MT1002 allocation (if not already discontinued). MT1002 can be administered 8 hours after subcutaneous low molecular weight heparin discontinuation provided ACT is <200 seconds.

Patients receiving fondaparinux for the index admission before enrollment with MT1002 allocation should not be included in the study.

Background therapy:

Acetylsalicylic acid: On admission, all patients will be administered a loading dose of aspirin approximately 325 mg (not exceeding 400 mg, if not already on a maintenance dose) and will stay on 75-100 mg/day (according to local countries clinical practice guidance) as maintenance therapy. Patients should continue aspirin for the remainder of the study period (i.e., through 30 days post-dose) or longer per local standard of care. This background medication will not be provided as part of the clinical trial supplies, unless required by local laws and regulations.

Clopidogrel: On admission, all patients will receive a loading dose of clopidogrel (600 mg) if not already on a maintenance dose, and then stay on a maintenance dose of 75 mg/day. Patients should continue this ADP/P2Y12 inhibitor for the remainder of the study period (i.e., through 30 days post-dose) or longer per local standard of care, as outlined by the current ACCF/AHA and European Society of Cardiology Guidelines.

Ticagrelor or Prasugrel: if the local clinical guidance recommends use of Ticagrelor or Prasugrel, the recommended doses will be: On admission, all patients will receive a loading dose of Ticagrelor 180 mg if not already on a maintenance dose, and then stay on a maintenance dose of 90 mg twice daily. Or on admission, all patients will receive a loading dose of Prasugrel 60 mg if not already on a maintenance dose, and then stay on a maintenance dose of 5-10 mg daily. Patients should continue this ADP/P2Y12 inhibitor for the remainder of the study period (i.e., through 30 days post-dose) or longer per local standard of care, as outlined by the current ACCF/AHA and European Society of Cardiology Guidelines.

In this study, clopidogrel (or Ticagrelor or Prasugrel) and acetylsalicylic acid are considered non-investigational medicinal products. This means that in the event of an SAE, the Investigator will assess the causal relationship of the SAE to the non-investigational medicinal product.

Bivalirudin: Patients receiving bivalirudin before enrollment into the study for the index MI should not be included in the study. Patients who fail to achieve the ACT target of 200 to 300 sec with MT1002 (within 30 minutes after MT1002 infusion initiation) can be switched to bivalirudin before PCI as a standard of care. Bivalidurin cannot be administered simultaneously with MT1002; MT1002 treatment should be discontinued at least 30 mins before switching to bivalirudin (dosing per local standard of care).

Glycoprotein IIb/IIIa inhibitors: Upstream use of glycoprotein IIb/IIIa inhibitors (i.e., within 24 hours before enrollment) is an exclusion criterion. After enrollment, glycoprotein IIb/IIIa inhibitors may be used as bail out for procedural or angiographic complications or clinical instability (dosing per local standard of care). Glycoprotein IIb/IIIa inhibitors cannot be administered simultaneously with MT1002; MT1002 treatment should be discontinued 30 minutes before switching to glycoprotein IIb/IIIa inhibitors.

Aspirin, clopidogrel (or Ticagrelor or Prasugrel), bivalirudin as a rescue therapy, and glycoprotein IIb/IIIa inhibitor as bail out for PCI is standard practice and not exclusive to this study. Therefore, these agents will be supplied by the hospital pharmacy or other local qualified pharmacy source as part of the local standard of care.

Concomitant anticoagulant therapy:

All patients should receive evidence-based medications for coronary artery disease (e.g., beta-blockers, ACE-inhibitors, statins, diabetic medications, etc.) as recommended in practice guidelines and/or per local standard of care. Concomitant medications through Day 30 will be recorded in the source documents and eCRF. In addition:

- Heparin is not permitted from enrollment through 7 hours post-MT1002 infusion completion except for the following situations (per local standard of care):
    - After enrollment, patients who fail to achieve ACT target of 200 to 300 sec with MT1002 (within 30 minutes after MT1002 infusion initiation) can be switched to UFH as a standard of care. UFH cannot be administered simultaneously with MT1002; MT1002 treatment should be discontinued 30 minutes before switching to UFH (dosing per local standard of care).
    - In the case of intracoronary or stent thrombosis during the procedure or within 24 hours after the procedure, heparin may be administered as a bail out therapy if it is deemed that inadequate anticoagulation has been achieved with MT1002 based on clinical or angiographic findings.
      Monitoring of ACT levels and administration and dosing of UFH should be performed per local standard of care and should be continued to maintain a therapeutic level of anticoagulation.
    - In patients undergoing emergent or urgent open-heart surgery after the PCI
    - In patients undergoing urgent device placement that requires continuous anticoagulation (e.g., intra-aortic balloon pump)
    - For routine flushing of catheters and IV lines, including radial or femoral access catheters.
- Heparin is permitted after 4 hours post sheath removal (per local standard of care).

The concomitant administration of proton pump inhibitors is strongly recommended in patients without clinical contraindications for those agents, to reduce the risk of gastrointestinal bleeding. Proton pump inhibitors that do not interact with CYP2C19 (lansoprazole, pantoprazole, etc.) should be used.

The Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies that may occur during the study.

Medications taken by or administered to the patient for the time period before Screening will be recorded in the eCRF. After the baseline visit, medication to treat minor treatment-emergent illness(es) is generally permitted.

Any medication or therapy that is taken by or administered to the patient during the course of the study must be recorded in the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

8.5.2 Prohibited Medications

The following drugs are not permitted during the course of the study:

- Anticoagulants or antiplatelet agents other than those described above for per-protocol assignment or as rescue or bail-out treatment, by any route (with the exception of parenteral agents used to treat a new clinical event);
- Fibrinolytic agents, unless required to treat a new clinical event, such as acute MI, pulmonary embolism, or stroke, in which case the risks and benefits of such treatment should be considered and, if given, the assigned study drug should be stopped;
- Chronic use (i.e., more than 3 times a week for more than 3 months) of oral or parenteral NSAIDs including both COX-1 and COX-2 inhibitors other than aspirin. Aspirin is permitted in the regimen predefined in the above section on background therapy only. Use of NSAIDs via other routes (e.g., topical, inhaled, intranasal, intraocular, etc.) is not restricted;
- Hormonal contraception;
- Investigational drugs (other than in the study treatment regimen).

Patients on these drugs at the time of enrollment will be excluded from the study.

9 STUDY PROCEDURES

Table 4 outlines the timing of procedures and assessments to be performed throughout the study. Section 11.5 specifies laboratory assessment samples to be obtained. See Sections 100 and 111 for additional details regarding efficacy/pharmacodynamic assessments and safety assessments, respectively.

Table 4 Schedule of Assessments

Assessment	Screening	Day of Procedure, Day 1			Follow-up		
Study Day	On admission	Pre PCI (Baseline)	During PCI[a] (≤ 72 hours from admission depending on the risk criteria)	Post PCI	Day 2[b]	Day 14±1	End of Study Day 30±2
Informed consent	X						
Inclusion/exclusion criteria	X	X					
Significant medical and surgical history	X						
Demographics	X						
Cardiac and noncardiac medication on	X						
Physical examination[c]	X			X	X	X	X
Weight, height, body mass index	X						
Vital signs	X[l]		X	X	X	X	X
12-lead electrocardiogram	X[l]			X	X	X	X
CK-MB, cardiac troponin I (or troponin T) [d]	X[l] X		X	X	X	X	X
ACT, aPTT, PT, TT, FIB, INR	X[l]		X[k]	X	X	X	X
PA (by PFA100 or PFA200)[e]	X[l]		X	X	X	X	X
Hematocrit, hemoglobin, platelet count, RBC and WBC counts	X[l]		X	X	X	X	X
Serum chemistry including lipid panel and HbA1c[f]	X				X	X	X
Serum or urine pregnancy test (women of childbearing potential only)	X						X
Percutaneous coronary intervention			X				
Aspirin[g]	X	(X)			◄----------		----------►
Clopidogrel (or Ticagrelor or Prasugrel)[h]	X	(X)			◄----------		----------►
Enrollment to MT1002		X					
Administration of MT1002[i]		X	X	X			
TIMI flow grade		X	X				
Pharmacokinetic blood sampling[j]		X	X	X	X		
Concomitant medication review	X	X	X	X	X	X	X
Bleeding adverse events (BARC)		X	X	X	X	X	X
Other adverse events	X						

Assessment	Screening	Day of Procedure, Day 1			Follow-up		
Study Day	**On admission**	**Pre PCI (Baseline)**	**During PCI[a] (⩽ 72 hours from admission depending on the risk criteria)**	**Post PCI**	**Day 2[b]**	**Day 14±1**	**End of Study Day 30±2**
Discharge					X		
Study close out							X

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; BARC, Bleeding Academic Research Consortium; CK, creatine kinase; HbA1c, glycosylated hemoglobin; min, minutes; PA, platelet aggregation; PCI, percutaneous coronary intervention; PT, prothrombin time; RBC, red blood cell; sec, seconds; TIMI, thrombolysis in myocardial infarction; WBC, white blood cell.

[a] PCI should start after MT1002 initiation as soon as ACT is confirmed to be ⩾ 200 sec or within 30 min after MT1002 start, whichever occurs first.

[b] Day 2 lasts until 24 hours ± 1 hour after the MT1002 intravenous injection start on Day 1 and until study-related procedures are complete. Patients will be discharged from the hospital when they are stable according to local standard of care.

[c] Physical examination is to be performed on Admission Day 1 and includes general appearance, head, eyes, ears, nose, and throat; and cardiovascular, respiratory, gastrointestinal, dermatological, neurological, musculoskeletal, lymphatic, and other systems at the discretion of the Investigator. Brief physical examination should be performed on all other visits from Post-PCI Day 1 onwards and includes general appearance, cardiovascular, respiratory, gastrointestinal, and other at the discretion of the Investigator.

[d] CK-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test) to be collected at Screening; immediately before PCI (Day 1 predose); and 0.5 (±5 mins), 4 (-5 to 10 mins, 5-10 min before the infusion completion), 6 (±15 mins), 8 (±15 mins), and 24 (±15 mins) hours post dose initiation.

[e] The PA (by PFA100 or PFA200) test should be conducted within 15 min of sample collection. Platelet aggregation sampling to be done at Screening; at 5 (±1) min after MT1002 intravenous injection; and 0.5 (±5 mins), 4 (-5 to 10 mins, 5-10 min before the infusion completion), 6 (±15 mins), 8 (±15 mins), and 24 (±15 mins) hours post dose initiation.

[f] Lipid panel only assessed at Screening and Day 30; HbA1c assessed at Screening only. For the other chemistry parameters, see Section 11.5.

[g] Aspirin approximately 325 mg (not exceeding 400mg) loading dose on admission, followed by 75-100 mg/day (according to local countries clinical practice guidance). No loading dose if patient is already on chronic treatment with aspirin.

[h] Clopidogrel 600 mg loading dose on admission, followed by 75 mg/day. If the local clinical guidance recommends use of Ticagrelor or Prasugrel, the recommended doses will be: Ticagrelor 180 mg loading dose on admission, followed by a maintenance dose of 90 mg twice daily. Or Prasugrel 60 mg loading dose on admission, followed by a maintenance dose of 5-10 mg daily. No loading dose if patient is already on chronic treatment with clopidogrel or Ticagrelor or Prasugrel.

[i] MT1002 will be initiated as close to the start of PCI as possible. MT1002 should be initiated during diagnostics angiography when indication for PCI is confirmed, provided the early PCI is indicated right after the coronary angiography. PCI can start after MT1002 initiation as soon as ACT is confirmed to be ⩾ 200 sec or within 30 min after start of MT1002, whichever occurs first.

[j] Pharmacokinetic samples will be taken at Day 1 pre-dose; at 5 (±1) min after MT1002 intravenous injection; and 0.5 (±5 min), 4 (-5 to 10 mins, 5-10 min before the infusion completion), 6 (±15 min), 8 (±15 min), and 24 (±15 min) hours post-dose initiation.

[k] ACT, aPTT, and PT, TT, FIB, INR will be taken at Screening; on Day 1 pre-dose; at 5 (±1) min after MT1002 intravenous injection; and 0.5 (±5 min), 4 (-5 to 10 mins, 5-10 min before the infusion completion), 6 (±5 min), 8 (±15 min), and 24 (±15 min) hours post-dose initiation.

l Between screening and Pre-PCI within 48 hours, Vital signs, 12-lead ECG, CK-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test), ACT, aPTT, PT, TT, FIB, INR, PA (PFA100 or PFA 200), Hematocrit, hemoglobin, platelet count, RBC and WBC counts take once; screening and Pre-PCI beyond 48 hours, should take twice before PCI.

Table 5 Time Points for Platelet Aggregation, Cardiac Biomarkers, Coagulogram, and Pharmacokinetics

Time points/ blood tests	Screening	Day1 pre-dose	5 min (±1 min) post-dose initiation	0.5 h (± 5 min) post-dose initiation	4h (-5 to10 min) post-dose initiation, 5-10 min before the infusion completion)	6h (± 15 min) post-dose initiation	8 h (± 15 min) post-dose initiation	24 h (±15 min) post-dose initiation
PA	X		X	X	X	X	X	X
Cardiac biomarkers[a]	X	X		X	X	X	X	X
ACT, aPTT, PT, TT, FIB, INR	X	X	X	X	X	X	X	X
PK		X	X	X	X	X	X	X

Abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; h, hours; PA, platelet aggregation; min, minutes; PK, pharmacokinetics; PT, prothrombin time; TT, Thrombin time; FIB, Fibrinogen; INR, International Normalized Ratio.

[a] Creatine kinase-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test).

9.1 Informed Consent

Before performing any study-related procedures, the Investigator (or designee) will obtain written informed consent from the patient.

9.2 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 4). Section 11.5 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at the visit where study drug is administered should be performed before administration of treatment unless otherwise indicated in the Schedule of Assessments (Table 4).

Efficacy/pharmacodynamic assessments are described in Section 100 and include evaluation of anti-coagulation effect via assessment of ACT and aPTT; and anti-platelet effect via assessment of PA.

Safety assessments are described in Section 111 and include vital signs, physical examinations, ECGs, laboratory assessments, AEs, MACE, and major bleeding events.

The Investigator may, at his/her discretion, arrange for a patient to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the Investigator to be possibly related to the use of study drug. The unscheduled visit page in the eCRF must be completed.

Study discontinuation procedures are described in Section 7.3.

9.2.1 Screening on Admission

Screening procedures will follow the normal pre-PCI evaluation per local standard of care, providing that all protocol-specific testing and procedures are completed before the administration of MT1002. All standard of care laboratory assessments and ECGs will be performed at the study site.

Unless specifically noted otherwise (or required by regulation), all study assessment time points are relative to initial intravenous injection of MT1002.

- Obtain informed consent before any protocol-specific procedures.
- Record demographic data, such as date of birth or age (according to applicable regulations), ethnic origin, and sex.
- Collect relevant medical and surgical history, including a detailed allergy history, concomitant illnesses/diseases, and concomitant medications (including cardiac and noncardiac medications) at the time of admission.
- Perform a full physical examination; record body weight and height, and body mass index (BMI).
- Record vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure).
- Perform a 12-lead ECG.
- Collect blood samples for hematology, coagulation, and clinical chemistry (refer to the Schedule of Assessments [Table 4] and Section 11.5 for parameters included)
    - CK-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test)
    - ACT, aPTT, PT, TT, FIB, INR
    - Hematocrit, hemoglobin, platelet count, red blood cell (RBC) and white blood cell (WBC) counts
    - Serum chemistry including lipid panel and glycosylated hemoglobin (HbA1c)
- Perform a PA (by PFA100 or PFA200)

- Locally perform serum or urine pregnancy test on all WOCPB who have not been postmenopausal for at least 1 year or sterilized.
- Assign or confirm, if already assigned, dual antiplatelet therapy. If not already given, administer a loading dose of the dual antiplatelet therapy of aspirin and clopidogrel (or Ticagrelor or Prasugrel) as indicated in the Schedule of Assessments (Table 4).
- Record any AEs that have occurred and any changes in concomitant medication since signing of the informed consent.
- Obtain CRUSADE bleeding risk score.
- Assess for eligibility (against the inclusion and exclusion criteria). Indication for early PCI should be confirmed in accordance with latest international or local guidelines[3,4]
    - Established diagnosis of NSTEMI based on elevated cardiac biomarkers
    - Dynamic ST/T-changes (symptomatic or silent)
    - Global Registry of Acute Coronary Events (GRACE) score >140

9.2.2 Pre-percutaneous Coronary Intervention Day 1 (Baseline)

Enrollment should occur as close to the planned start of PCI as possible, and MT1002 dosing should be started as close to the actual start of PCI as possible. MT1002 should be initiated during diagnostics angiography when indication for PCI is confirmed, provided the early PCI is indicated right after the coronary angiography. Study drug should be administered in the catheterization lab.

Either radial access/distal radial access PCI or femoral access PCI will be used in this study. It is up to the discretion of the Principal Investigator what type of stent(s) will be used.

- Confirm that diagnostic catheterization indicates the need for PCI. The Investigator's interpretation of the diagnostic angiogram, TIMI flow grade, the treatment plan, and if the patient remains eligible to continue the study should be recorded.
- Record vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure).
- Perform a 12-lead ECG.
- Confirm all screening procedures have been completed and that the patient meets all other eligibility requirements and record patient enrollment with identification of allocated study drug vial.
- Record all changes in concomitant medications including cardiovascular, antiplatelet, anticoagulant and diabetic medications administered since screening.
- Obtain pre-dose baseline central cardiac biomarkers (troponin I [troponin T can be measured if the local site does not have the troponin I test], and CK-MB) immediately before PCI; and hemoglobin, hematocrit, platelet count, and RBC and WBC counts; coagulogram (ACT, aPTT, PT, TT, FIB, INR according to the time points in the Schedule of Assessments [Table 4] and Table 5), Pharmacokinetic blood sampling (according to the time points in the Schedule of Assessments [Table 4] and Table 5).

Additional ACT test can be performed if MT 1002 dose is adjusted. The ACT test value and time of test will be recorded in eCRF. These blood samples may be obtained either peripherally or through the arterial sheath.

- Collect PK plasma samples according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Perform a PA (by PFA100 or PFA200) according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Administer study drug via IV access before the PCI and record time of dosing in the eCRF. Study drug should be administered in catheterization lab as close to randomization and the start of the PCI procedure as possible.
- Conduct a visual bleeding inspection and assess bleeding AEs according to the BARC criteria; record any patient-reported bleeding.
- Record any other AEs that have occurred.

9.2.3 During Percutaneous Coronary Intervention, Day 1

Either radial access/distal radial access PCI or femoral access PCI will be used in this study. It is up to the discretion of the Principal Investigator what type of stent(s) will be used.

- Conduct the PCI procedure per local standard of care.
- Record TIMI flow grade post PCI.
- Patients who fail to achieve ACT target of 200 to 300 sec with MT1002 (within 30 minutes after MT1002 infusion initiation) before PCI will be switched to standard of care (UFH or bivalirudin, see Section 8.5.1).
- Patients who achieve ACT target of 200 to 300 sec with MT1002 (within 30 minutes after MT1002 infusion initiation) before PCI should continue the study drug infusion for 4 ±0.5 hours after infusion start.
- Monitor patients for potential AEs, including allergic reactions during the MT1002 administration.
- Record vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure).
- Record any procedural complications, as well as any other AEs
    - Glycoprotein IIb/IIIa inhibitors may be used for procedural or angiographic complications only (dosing per local standard of care, see Section 8.5.1)
    - In those patients who experience significant intracoronary thrombosis during the procedure, or experience acute thrombosis after the procedure, heparin bail out may be administered (see Section 8.5.1).
- Perform a PA (by PFA100 or PFA200) according to the time points in the Schedule of Assessments (Table 4) and Table 5.

- Obtain central cardiac biomarkers (troponin I [troponin T can be measured if the local site does not have the troponin I test], and CK-MB) according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Obtain coagulogram (ACT, aPTT, PT, TT, FIB, INR according to the time points in the Schedule of Assessments [Table 4]and Table 5), hemoglobin, hematocrit, platelet count, RBC, and WBC counts.
- Obtain PK samples according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Conduct a visual bleeding inspection and assess bleeding AEs according to the BARC criteria; record any patient-reported bleeding.
- Record all changes in concomitant medications.
- Obtain a copy of the PCI procedure report and record information about index-procedure (e.g., but not limited to vascular access, lesions treated, stents used, procedure result). Successful treatment with PCI is defined as achievement of < 30% residual diameter stenosis of all treated lesions assessed by visual inspection or quantitative coronary angiography, without an in-hospital major adverse cardiac event (death, MI or repeat coronary revascularization of the target lesion).

9.2.4 Post Percutaneous Coronary Intervention, Day 1

- Record end of PCI time in the eCRF. End of procedure is defined as the date/time when the last coronary catheter (all catheters other than arterial sheath or intra-aortic balloon positioning) is removed from the body.
- Continue MT1002 infusion for 4 hours after infusion start (including post-PCI).
- Remove the sheath approximately 3 hours after MT1002 infusion is complete. Record sheath removal time in the eCRF.
- Perform a brief physical examination.
- Record vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure).
- Perform a 12-lead ECG.
- Perform a PA (by PFA100 or PFA200) according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Collect blood samples for hematology, coagulogram, and cardiac biomarkers (refer to Section 11.5 for parameters included)
    - CK-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test) according to the time points in the Schedule of Assessments (Table 4) and Table 5
    - ACT, aPTT, PT, TT, FIB, INR as per time points in the Schedule of Assessments (Table 4) and Table 5
    - Hematocrit, hemoglobin, platelet count, RBC and WBC counts according to the time points in the Schedule of Assessments (Table 4)

- Obtain PK samples according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Record all changes in concomitant medications.
- Conduct a visual bleeding inspection and assess bleeding AEs according to the BARC criteria; record any patient-reported bleeding
    - Immediately upon achievement of hemostasis, with time of complete hemostasis recorded on the eCRF;
    - Thereafter, per local standard of care
- Record any other AEs that have occurred.

9.2.5 Day 2

- Perform a brief physical examination.
- Record vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure).
- Perform a 12-lead ECG.
- Collect blood samples for hematology, serum chemistry, coagulogram, and cardiac biomarkers (refer to the Schedule of Assessments [Table 4] and Table 5;and Section 11.5 for parameters included)
    - CK-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test)
    - ACT, aPTT, PT, TT, FIB, INR
    - Hematocrit, hemoglobin, platelet count, RBC and WBC counts
    - Serum chemistry
- Perform a PA (by PFA100 or PFA200) according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Obtain PK samples according to the time points in the Schedule of Assessments (Table 4) and Table 5.
- Record all changes in concomitant medications.
- Continue dual antiplatelet therapy with aspirin and clopidogrel (or Ticagrelor or Prasugrel).
- Conduct a visual bleeding inspection and assess bleeding AEs according to the BARC criteria; record any patient-reported bleeding.
- Record any other AEs that have occurred.

Patients will be discharged from the hospital when they are stable according to local standard of care.

9.2.6 Day 14±1, Day 30±2 (End of Study)

- Perform a brief physical examination.

- Record vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure).
- Perform a 12-lead ECG.
- Collect blood samples for hematology, serum chemistry, coagulogram, and cardiac biomarkers (refer to the Schedule of Assessments [Table 4] and Table 5; and Section 11.5 for parameters included)
    - CK-MB, cardiac troponin I (troponin T can be measured if the local site does not have the troponin I test)
    - ACT, aPTT, PT, FIB, TT, INR
    - Hematocrit, hemoglobin, platelet count, RBC and WBC counts
    - Serum chemistry including lipid panel (lipid panel on Day 30 only)
- Perform a PA (by PFA100 or PFA200).
- Locally perform serum or urine pregnancy test (only Day 30) on all WOCPB who have not been postmenopausal for at least 1 year or sterilized.
- Record all changes in concomitant medications.
- Continue dual antiplatelet therapy with aspirin and clopidogrel (or Ticagrelor or Prasugrel) (Day 30: confirm continuation of dual antiplatelet therapy with aspirin and clopidogrel (or Ticagrelor or Prasugrel).
- Conduct a visual bleeding inspection and assess bleeding AEs according to the BARC criteria; record any patient-reported bleeding.
- Record any other AEs that have occurred.

10 EFFICACY/PHARMACODYNAMIC ASSESSMENTS

The Schedule of Assessments (Table 4) outlines the efficacy assessments to be performed throughout the study and their timing.

10.1 Anti-coagulation effect and anti-platelet effect

Anti-coagulation effect and anti-platelet effect will be evaluated using standard local lab equipment and PFA100 or PFA200 (PA).

11 SAFETY ASSESSMENTS

Safety assessments (vital signs, physical examinations, ECG recording, AEs, MACE, major bleeding events, clinical laboratory results [serum chemistry; hematocrit, hemoglobin, platelet count, RBC and WBC counts]) are to be performed at protocol-specified visits, as noted in the Schedule of Assessments (Table 4).

11.1 Medical History

Significant medical history will be recorded at Screening (upon admission on Day 1). Investigators should document the occurrence, signs, and symptoms of the patient's relevant preexisting conditions, including all relevant prior significant illnesses and surgery; the focus should be on coronary artery disease. Additional preexisting conditions present at the time when informed consent is given and up to the time of dosing are to be regarded as concomitant. Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 11.6. All changes not present at Screening/Baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all patients and include date of birth or age according to applicable regulations, sex, race, and ethnicity.

11.2 Vital Signs

Vital signs (body temperature, respiration rate, heart rate, and systolic and diastolic blood pressure measurements) will be evaluated at the visits indicated in the Schedule of Assessments (Table 4). All vital signs will be measured after the patient has been resting in a semi-supine position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight and height (without shoes) and body mass index will be recorded at Screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure, respiratory rate, or heart rate measurements will be repeated at the Investigator's discretion. Any confirmed clinically significant vital sign measurements must be recorded as AEs.

11.3 Physical Examination

A complete physical examination (general appearance, head, eyes, ears, nose and throat; and cardiovascular, respiratory, gastrointestinal, dermatological, neurological, musculoskeletal, lymphatic, and other systems at the discretion of the Investigator) will be performed by a physician on Admission Day 1. Brief physical examination should be performed on all other visits from Post-PCI Day 1 onwards and includes general appearance, as well as cardiovascular, respiratory, gastrointestinal, and other systems at the discretion of the Investigator.

11.4 Electrocardiograms

A 12-lead, resting ECG will be obtained at the visits indicated in the Schedule of Assessments (Table 4).

At Screening, the Investigator will examine the ECG traces for signs of cardiac disease that could exclude the patient from the study. An assessment of normal or abnormal will be recorded; if the ECG is considered abnormal, the abnormality will be documented on the eCRF. ECGs will be repeated if clinically significant abnormalities are observed or artifacts are present. All ECGs will be read locally.

11.5 Laboratory Assessments

The hematology and clinical chemistry laboratory analyses will be performed at local laboratories. Reference ranges will be supplied by local laboratories and used by the Investigator to assess the laboratory data for clinical significance and pathological changes.

Laboratory assessment samples (Table 6) are to be obtained at designated visits as detailed in the Schedule of Assessments (Table 4).

Table 6 Laboratory Assessments

Hematology	**Serum Chemistry**
Hct Hb Platelet count RBC count WBC count with differential	ALT AST BUN or urea Creatinine Creatine kinase and subtypes Electrolytes (sodium, potassium) Glucose LDH Total bilirubin Direct bilirubin Total protein Lipid panel eGFR HbA1c
Coagulation	**Others**
PT Activated PTT ACT TT FIB INR PA (by PFA100 or PFA200)	CK-MB Cardiac troponin I or troponin T (troponin T can be measured if the local site does not have the troponin I test)
Pregnancy test: A pregnancy test (serum or urine) will be performed on all women of childbearing potential at Screening and at End of Study (Day 30±2).	

Abbreviations: ACT, activated clotting time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HbA1c, glycosylated hemoglobin; Hct, hematocrit; LDH, lactate dehydrogenase; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; WBC, white blood cell.

Blood samples will be analyzed at a local laboratory facility. All laboratory reports must be reviewed, signed, and dated by the Investigator. A legible copy of all reports must be filed with both the patient's eCRF and medical record (source document) for that visit. Any laboratory test result considered by the Investigator to be clinically significant should be considered an AE (clinically significant AEs include those that require an intervention). Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

11.6 Adverse Events

11.6.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at Screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study)

present at Screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study. Clinically significant laboratory abnormalities should also be recorded as AEs.

Anticipated AEs

Anticipated AEs for this study population based on the results from the completed Phase 1 healthy volunteer study include bleeding (see also Section 11.6.3), allergic reactions, and headache.

Drug-related AEs which occurred in the completed Phase 1 study included headache, dizziness, discolored feces, mouth hemorrhage, injection site bruising and injection site nodule, and injection site hemorrhage.

Reporting of AEs

Patients will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the patient gives informed consent until the end of study visit. Follow-up of the AE, even after the date of study drug completion, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the Investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 7 and Table 8.

Table 7 Classification of Adverse Events by Intensity

Severity	Description
Mild	Awareness of signs and symptoms, but are easily tolerated; are of minor irritant type; causing no limitations of usual activities. Signs or symptoms may require minor action.
Moderate	Discomfort severe enough to cause some limitations of usual activities and may require action.

Severity	Description
Severe	Incapacitating with inability to carry out usual activities or significantly affects clinical status, and requires specific action and/or medical attention.

Table 8 Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the study drug/procedure but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug/procedure if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the test drug/study procedure; (2) it could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it does not follow a known pattern of response to the test drug/study procedure; or (4) it does not reappear or worsen when the study drug/procedure is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the test drug/study procedure administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the test drug/study procedure; (2) it could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; or (3) it follows a known pattern of response to the test drug/study procedure.
PROBABLY: This category applies to those AEs that the Investigator feels with a high degree of certainty are related to the test drug/study procedure. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study drug/ procedure; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the study drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the test drug/study procedure.
DEFINITELY: This category applies to those AEs that the Investigator feels are incontrovertibly related to test drug/study procedure. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the study drug/ procedure; (2) it could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient; (3) it disappears or decreases on cessation or reduction in dose and recurs with re-exposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the test drug/study procedure.

Abbreviation: AE, adverse event.

11.6.2 Major Adverse Cardiovascular Events

MACE is defined as nonfatal MI, unplanned revascularization (PCI or CABG) of the ischemic target vessel including intraprocedural stent thrombosis, re-hospitalization for a CV-related condition, nonfatal stroke, CV death, and all-cause mortality.

11.6.3 Bleeding Events

Bleeding events are classified as major or minor based on BARC classification. Minor bleeding events are those that meet the criteria for BARC Type 2, and major bleeding events are those meeting the criteria for BARC Types 3 to 5.

BARC definitions are provided in Table 9.

Table 9 Bleeding Academic Research Consortium Definitions

Type	Definition
0	No bleeding
1	Bleeding that is not actionable and does not cause the patient to seek treatment
2	Any clinically overt sign of hemorrhage that "is actionable" and requires diagnostic studies, hospitalization, or treatment by a health care professional
3	a. Overt bleeding plus hemoglobin drop of 3 to < 5 g/dL (provided hemoglobin drop is related to bleed); transfusion with overt bleeding b. Overt bleeding plus hemoglobin drop < 5 g/dL (provided hemoglobin drop is related to bleed); cardiac tamponade; bleeding requiring surgical intervention for control; bleeding requiring intravenous vasoactive agents c. Intracranial hemorrhage confirmed by autopsy, imaging, or lumbar puncture; intraocular bleed compromising vision
4	Coronary artery bypass grafting-related bleeding within 48 hours
5	a. Probable fatal bleeding b. Definite fatal bleeding (overt or autopsy or imaging confirmation)

11.6.4 Adverse Events of Special Interest

The AEs of interest include major bleeding events (BARC Type 3 to 5; see also Section 11.6.3), infusion reactions, hypersensitivity reactions, thrombotic events (including stent thrombosis), frequency of abrupt vessel closure, transient ischemic attack, redo of stent procedure (revascularization), or emergency CABG.

11.6.5 Serious Adverse Events

An SAE is any untoward medical occurrence, in the view of either the Investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect

Other important medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the patient and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the Investigator's and the Sponsor's assessment. If either the Sponsor or the Investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

11.6.6 Serious Adverse Event Reporting

An SAE occurring from the time informed consent is obtained, during the study, or within 30 days of stopping the treatment must be reported to the Zhejiang Taimei Medical Technology Co., Ltd. (Taimei) Safety and Pharmacovigilance group and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the Investigator becomes aware of the event. Notification can be made using the dedicated fax line or email for the Taimei pharmacovigilance group:

Taimei Safety and Pharmacovigilance fax numbers:

- 0086-21-68825798 (primary)
- 0086-18358381225 (alternative)

Taimei Safety and Pharmacovigilance email address: pv-qa@mobilemd.cn

If the Investigator contacts the Taimei pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the Investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The Investigator must report all additional follow-up evaluations to the Taimei Safety and Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the Investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the patient's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

11.6.7 Suspected Unexpected Serious Adverse Reactions

AEs that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (i.e., the event is not consistent with the safety information in the Investigator's Brochure)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The Investigator will assess whether an event is causally related to study treatment. The Sponsor (or Taimei Medical Technology) will consider the Investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are fatal or life-threatening must be reported to the regulatory authorities and the independent ethics committee (IEC)/institutional review boards (IRBs) (where required) within 7 days after the Sponsor (or Taimei Medical Technology) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IEC/IRBs within 15 calendar days after the Sponsor (or Taimei Medical Technology) first has knowledge of them.

The Sponsor (or Taimei Medical Technology) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing Investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IEC/IRBs of reportable events within the applicable timeframes.

11.6.8 Pregnancy

Women of childbearing potential (WOCBP) must have a negative pregnancy test at Screening. An additional pregnancy test will be performed on Day 30, at the End of Study Visit.

After administration of study drug, any known cases of pregnancy in female patients or female partners of male patients will be reported up until 90 days after the date of MT1002 administration. Patients will be instructed to inform the investigator of any such pregnancies occurring during the study or for up to 90 days after MT1002 administration. The pregnancy will be reported immediately by the investigator by faxing/emailing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow up with the patient until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected

in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the Investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or designee) within 24 hours of knowledge of the event.

If the Investigator becomes aware of a pregnancy occurring in the partner of a patient participating in the study, the pregnancy should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The Investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the patient to undue risk will be performed. The Investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a patient is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

11.6.9 **Overdose**

The Investigator must immediately notify the Sponsor of any occurrence of overdose with study drug.

Overdose after administration of MT1002 may lead to hemorrhagic complications due to its pharmacodynamic properties. In cases of suspected overdose, it may be advisable to assess the anticoagulation status to assist in determining an excess of anticoagulant activity with a higher risk of bleeding.

12 PHARMACOKINETICS

12.1 Pharmacokinetic Sampling

12.1.1 Blood Samples

Blood samples for PK analysis of MT1002 levels will be collected at the time points indicated in the Schedule of Assessments (Table 4) and Table 5. The actual date and time of each blood sample collection will be recorded. The timing of PK samples may be altered, and/or PK samples may be obtained at additional time points to ensure thorough PK monitoring.

Details of PK blood sample collection, processing, storage, and shipping procedures are provided in a separate laboratory manual.

12.2 Pharmacokinetic Analytical Methodology

The concentration of study drug will be determined from the plasma samples using a validated analytical method. Details of the method validation and sample analysis will be included with the final clinical study report.

13 OTHER ASSESSMENTS

13.1 Biomarkers

Blood samples for analysis of PA will be collected at the visits indicated in the Schedule of Assessments (Table 4). The actual date and time of each collection will be recorded. The timing of the samples may be altered, and/or samples may be obtained at additional time points to ensure thorough monitoring.

13.2 Thrombolysis in Myocardial Infarction Flow

The TIMI flow is a scoring system assessing levels of coronary blood flow during PCI. The score ranges from 0 (no perfusion) to 3 (full perfusion) as shown in Table 10.

Table 10 Thrombolysis in Myocardial Infarction Flow Grading System

Grade	Description
0	Complete occlusion of the infarct-related artery
1	Some penetration of contrast material beyond the point of obstruction but without perfusion of the distal coronary bed
2	Perfusion of the entire infarct vessel into the distal bed but with delayed flow compared with a normal artery
3	Full perfusion of the infarct vessel with normal flow

Source: See Reference 2.

13.3 CRUSADE Bleeding Risk Score

The CRUSADE bleeding risk score ranges from 1 to 100 points with higher score indicating higher risk of bleeding: very low risk = ≤ 20, low risk = 21 to 30, moderate risk = 31 to 40, high risk = 41 to 50, very high risk = > 50. Patients with a CRUSADE score > 40 will be excluded from the study. Scoring will be based on the following variables: baseline hematocrit, creatinine clearance, heart rate, gender, signs of congestive heart failure, prior vascular disease, diabetes mellitus, and systolic blood pressure.

14 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a compliment to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by dose cohort. For continuous variables, data will be summarized with the number of patients (N), mean, standard deviation, median, minimum, and maximum by dose group. For categorical variables, data will be tabulated with the number and proportion of patients for each category by dose group.

14.1 Determination of Sample Size

Based on clinical experience, a total of up to 18 patients will be enrolled to achieve the study objectives in this study. Approximately 30 patients will need to be screened. The number of patients screened is based on a screen failure rate of 40%.

14.2 Analysis Populations

As-Treated Population

The as-treated population will include all patients who receive at least 1 dose of MT1002. All efficacy, safety, and pharmacodynamics data will be summarized in this population.

Pharmacokinetics Population

The PK population will include those patients in the as-treated population who have valid PK concentration data. PK concentrations and PK parameters will be summarized in this population.

14.3 Efficacy and Pharmacodynamics Analyses

14.3.1 Analysis of Efficacy Endpoints

The numbers of patients with target ACT achieved before/during PCI and PCI success, or failed to finish PCI, or achieved ACT $\geqslant$ 200 sec will be summarized by cohort and overall. The PA measurement will also be summarized descriptively by visit, cohort, and overall.

14.3.2 Analysis of Pharmacodynamic Endpoints

The ACT, aPTT, PT, TT, FIB, INR will be summarized descriptively by visit, cohort, and overall.

14.4 Safety Analysis

All reported AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), version used will be the current one at the time of analysis. The incidence of TEAEs

(events with onset dates on or after the start of the study drug) will be included in incidence summary tables. Events with missing onset dates will be included as treatment-emergent. If a patient experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. The major bleeding events, minor bleeding events, MACE within 30 days, and AEs of interest will be summarized by MedDRA system organ class and preferred term, and by cohort and overall; SAEs and AEs causing study discontinuation will also be summarized. All AEs will be listed by patient, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome.

Clinical laboratory data and vital signs will be summarized using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of patients with values outside limits of the normal range at each time point.

12-lead ECGs will be summarized descriptively. The noteworthy QTcF interval (>450, >480, >500 mec) and noteworthy change from baseline (>30 and >60 msec) will also be summarized.

Summary tables will be provided for concomitant medications initiated during the study period.

Physical examination results will be listed.

14.5 Pharmacokinetic Analysis

The standard PK parameters of peak plasma concentration, area under the curve, elimination half-life, elimination rate constant, volume of distribution, and clearance will be estimated by standard noncompartmental methods.

PK plasma concentrations and PK parameters will be summarized descriptively by cohort.

14.6 Other Analyses

Other endpoints will be summarized descriptively if appropriate. Further analyses will be specified in the SAP.

14.7 Interim Analysis

The study data review after each cohort will be performed by the Study Management Group for decisions on dose escalation, de-escalation, stopping, or continuing for each patient cohort.

The interim analysis is planned in this study. It will be safety, PK. PD and efficacy analyses after getting the clinical data of 9-12 patients.

Further details may be found in the SAP.

14.8 Study Management Group

The Study Management Group (consisting of the Sponsor representatives, the Medical Monitor, one of the principal investigators and an independent cardiologist) will meet to review accumulating safety data after each cohort throughout the study, monitor overall study conduct,

and make decisions regarding the recommended dose for the next patient cohort. A charter will be established to provide decisions of study next step.

15 STUDY MANAGEMENT

15.1 Approval and Consent

15.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and/or all relevant regulations as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the US CFR, in compliance with International Council for Harmonisation (ICH) and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

15.1.2 Institutional Review Board/Independent Ethics Committee

Conduct of the study must be approved by an appropriately constituted IEC/IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and patient information sheets, and other patient/subject-facing material.

15.1.3 Informed Consent

For each study patient, written informed consent will be obtained before any protocol-related activities. As part of this procedure, the Principal Investigator or designee must explain orally and in writing the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation. The patient should be informed that he/she may withdraw from the study at any time, and the patient will receive all information that is required by local regulations and guidelines for ICH. The Principal Investigator will provide the Sponsor or its representative with a copy of the IEC-/IRB-approved ICF before the start of the study.

15.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained. See also Section 15.3.

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have procedures in place to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly-identifying personal information is not transmitted. The primary method of data transmittal is via the secure, internet-based electronic data capture (EDC) system maintained by

Premier Research. Access to the EDC system is available only to authorized users via the study's internet web site, where a user-unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

15.3 Source Documents

Source documents are considered to be all information in original records and certified copies of original records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The Investigator will provide direct access to source documents and/or source data in the facilitation of trial-related monitoring, audits, review by IECs/IRBs, and regulatory inspections.

The Investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

15.4 Record Retention

Study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The Investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of patient health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The Investigator shall ensure that study patients authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

15.5 Monitoring

The study will be monitored to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Monitoring visits and contacts will be made at appropriate times during the study. The Principal Investigator will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to source documentation in order to check the completeness, clarity, and consistency of the data recorded in the eCRFs for each patient.

The Investigator will make available to the clinical monitor all source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the Investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

15.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the Investigator generating the data.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed at study sites and during data management to assure that safety and efficacy data are adequate and well documented.

15.7 Protocol Amendment and Protocol Deviation

15.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of patients or the conduct of the study will be classed as administrative amendments and will be submitted to the IEC/IRB for information only. The Sponsor will ensure that acknowledgement is received and filed. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IECs/IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

15.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Protocol deviations will be reported to the IRB/IEC in accordance with applicable regulatory authority.

15.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

IECs/IRBs will review and approve this protocol and the ICF. All patients are required to give written informed consent before participation in the study.

15.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the Investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the Investigator (or the institution signatory) and the Sponsor (or its designee).

The Investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

15.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the Investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by Investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, Investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

16 REFERENCES

1. Basit H, Malik A, Huecker MR. Non ST Segment Elevation (NSTEMI) Myocardial Infarction. StatPearls Publishing; 2020.
2. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, Phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation. 1987;76:142–154. doi: 10.1161/01.cir.76.1.142.
3. Patel MR, Dehmer GJ, Hirshfeld JW, Smith PK, Spertus JA. ACCF/SCAI/STS/AATS/AHA/ASNC/HFSA/SCCT 2012 Appropriate Use Criteria for Coronary Revascularization Focused Update: A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Society for Cardiovascular Angiography and Interventions, Society of Thoracic Surgeons, American Association for Thoracic Surgery, American Heart Association, American Society of Nuclear Cardiology, and the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol 2012; 59(9):857–881. doi: 10.1016/j.jacc.2011.12.001.
4. Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS); European Association for Percutaneous Cardiovascular Interventions (EAPCI); Wijns W, et al. Guidelines on myocardial revascularization. Eur Heart J 2010; 31(20):2501 – 2555. doi: 10.1093/eurheartj/ehq277.
5. Douketis J D, Berger P B, Dunn A S, et al. American College of Chest Physicians The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition) Chest. 2008;133(6, Suppl):299S–339S.

17 APPENDICES

APPENDIX 1 describes the contraception guidelines applicable for this study.

APPENDIX 1. CONTRACEPTION GUIDELINES

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception during the study and for 90 days after the last dose of study treatment.

A woman is considered to be a WOCBP (fertile) after menarche and until becoming postmenopausal, unless she is permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and for this study include:

intrauterine device

intrauterine hormone-releasing system

bilateral tubal ligation or occlusion

vasectomy (provided that the male has a medical assessment of surgical success)

sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical trial, in line with the preferred and usual lifestyle of the patient)

Any double combination of male or female condom with spermicidal gel, diaphragm, sponge or cervical cap with spermicidal gel is also acceptable for the study.

All patients will be strongly advised that they (or the female partners of male patients) should not become pregnant while on study treatment or for 90 days after the last dose. A female patient will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

Reference

1. [HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 19-Aug-2020.