Prehospital treatment with zalunfiban (RUC-4) in patients with ST- elevation myocardial infarction undergoing primary percutaneous coronary intervention: Rationale and design of the CELEBRATE trial

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Abstract

Background Early and complete restoration of target vessel patency in ST-elevation myocardial infarction (STEMI) is associated with improved outcomes. Oral $P2Y_{12}$ inhibitors have failed to demonstrate either improved patency or reduced mortality when administered in the prehospital setting. Thus, there is a need for antiplatelet agents that achieve prompt and potent platelet inhibition, and that restore patency in the prehospital setting. Zalunfiban, a novel subcutaneously administered glycoprotein IIb/IIIa inhibitor designed for prehospital administration, has shown to achieve rapid, high-grade platelet inhibition that exceeds that of $P2Y_{12}$ inhibitors. Whether prehospital administration of zalunfiban can improve clinical outcome is unknown.

Hypothesis The present study is designed to assess the hypothesis that a single, prehospital injection of zalunfiban given in the ambulance, in addition to standard-of-care in patients with STEMI with intent to undergo primary percutaneous coronary intervention (PCI) will improve clinical outcome compared to standard-of-care with placebo.

Study design The ongoing CELEBRATE trial (NCT04825743) is a phase 3, randomized, double-blinded, placebo-controlled, international trial. Patients with STEMI intended to undergo primary PCI will receive treatment with a single subcutaneous injection containing either zalunfiban dose 1 (0.110 mg/kg), zalunfiban dose 2 (0.130 mg/kg) or placebo, and the study drug will be administered in the ambulance before transportation to the hospital. A target of 2499 patients will be randomly assigned to one of the treatment groups in a 1:1:1 ratio, ie, to have approximately 833 evaluable patients per group. The primary efficacy outcome is a ranked 7-point scale on clinical outcomes. The primary safety outcome is severe or life-threatening bleeding according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) criteria.

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Abbreviations: ADP, Adenosine diphosphate; AE, Adverse Events; BARC, Bleeding Academic Research Consortium; CEC, Clinical Endpoint Committee; CI, Confidence Interval; DSMB, Data Safety Monitoring Board; ECG, Electrocardiogram; GPI, Glycoprotein IIb/IIIA inhibitor; GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; MIDAS, Metal Ion Dependent Adhesion Site; PCI, Percutaneous Coronary Intervention; SAE, Serious Adverse Events; STEMI, ST-elevation Myocardial Infarction; TIMI, Thrombolysis in Myocardial Infarction; TRAP, Thrombin-receptor activating peptide.

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Summary The CELEBRATE trial will assess whether a single prehospital subcutaneous injection of zalunfiban in addition to standard-of-care in patients with STEMI with intent to undergo primary PCI will result in improved clinical outcome. (Am Heart J 2023;258:119–128.)

Background

Early and complete restoration of blood flow in the infarct-related artery improves survival in patients with ST-elevation myocardial infarction (STEMI).[1-4] Primary percutaneous coronary intervention (PCI) is preferred as reperfusion modality and is superior to fibrinolysis in reducing mortality, reinfarction and stroke.[5,6] Nevertheless, crude in-hospital mortality rates after STEMI remain substantial, varying between 4% to 12% and of which approximately 1 of 4 deaths occur before hospital admission.[7,8] Hence, there is an important opportunity to limit infarct size and improve survival by improving prehospital reperfusion.[9-11]

Platelets play a pivotal role in the pathophysiological process leading to coronary artery thrombus formation. Thus, antiplatelet agents – aspirin and an oral $P2Y_{12}$ inhibitor – are important to improve outcomes in patients with STEMI.[12] However, the onset of antiplatelet effects by oral $P2Y_{12}$ inhibitors is delayed up to 6 hours in patients with STEMI due to their need for gastrointestinal absorption, which increases the risk of periprocedural ischemic complications.[13–16] Moreover, prehospital treatment with oral $P2Y_{12}$ inhibitors has not led to improved coronary reperfusion before primary PCI, although early administration was associated with some benefit as shown by the reduction in stent thrombosis in the ATLANTIC trial.[17,18]

In contrast, parenteral platelet glycoprotein IIb/IIIa inhibitors (GPI) circumvent the need for gastrointestinal absorption, achieve immediate and higher-grade antiplatelet effects against all platelet activators, and show improved patency of the infarct-related artery before PCI.[19-21] More importantly, prehospital GPI treatment in patients with STEMI led to improved clinical outcomes without an increase in severe bleeding.[20-24] Time from symptom onset to GPI administration was significantly associated with higher patency of the culprit artery and with ST-elevation resolution, with greater improvement in reperfusion in the lowest time quartiles as well as lower occurrence of death.[25,26] This time-related efficacy is consistent with the observation of higher platelet content in freshly formed thrombi, as opposed to more mature thrombi that are rich in fibrin, that makes antiplatelet therapy more effective when administered earlier after symptom onset.[27]

Currently, prehospital GPI administration is not considered standard care for STEMI in North America or Europe, despite evidence of a mortality benefit when used early in patients with STEMI undergoing primary PCI.[25] This may be partly explained by the unfavorable pharmacodynamic and structural profile of currently available intravenous GPIs, which are associated with an increased risk of bleeding complications and thrombocytopenia.[19] Also, the lack of strong evidence supporting prehospital use of GPI may be due to results of studies that randomized patients too late (>150 minutes after symptom onset), used prolonged postbolus drug infusion, and used femoral access that resulted in higher risk of bleeding.[28,29] Another disadvantage of current GPIs is that they require continuous intravenous infusion with an electronic syringe pump, which cannot be universally performed by ambulance services. Thus, there is a need for antiplatelet agents that can be easily administered in the prehospital setting, achieving prompt and potent platelet inhibition, and that can improve coronary reperfusion prior to primary PCI.

Rationale for the development of zalunfiban and mechanism of action

Zalunfiban (RUC-4) is a novel, small molecule inhibitor of the platelet glycoprotein IIb/IIIa receptor, specifically developed to facilitate prehospital antiplatelet therapy at the time of first medical contact, thus maximizing the chance of inducing reperfusion and reducing thrombotic complications. It is a derivative of a compound identified in a high-throughput screen for inhibitors of the glycoprotein IIb/IIIa receptor that has a unique mechanism of action. Zalunfiban displaces the Mg2+ ion in the metal ion dependent adhesion site (MIDAS) of the glycoprotein IIIa subunit that is crucial for the binding of fibrinogen and platelet aggregation.[30,31] The current small molecule GPIs eptifibatide and tirofiban bind to the MIDAS in the glycoprotein IIIa subunit in the same manner as fibrinogen, which triggers a conformational change in the receptor that has been proposed to contribute to the thrombocytopenia associated with these drugs through a mechanism in which preformed antibodies that circulate in the blood of some patients cross-react with the altered drug-induced receptor conformation, resulting of antibody coating of platelets and clearance of the antibody-coated platelets by cells with receptors for immune complexes.[32] Zalunfiban prevents ligand binding by displacing the Mg2+ ion in the MIDAS, thereby locking the receptor in an inactive conformation and not inducing a conformational change, and it is therefore postulated that it may have a lower risk of inducing thrombocytopenia.[31]

Notably, as a GPI, it is much more potent than the $P2Y_{12}$ antagonist ticagrelor in vitro in inhibiting platelet interaction with fibrinogen when platelets are activated by peptides that activate one or both of the thrombin receptors on platelets.[35]

Rationale for dose selection and clinical experience with zalunfiban

The rationale for the dose selection is based on the pharmacodynamic results of the phase 2a study.[34] In the phase 2a study platelet inhibition was measured for 3 escalating doses (0.075 mg/kg [$n = 8$], 0.090 mg/kg [$n = 9$], or 0.110 mg/kg [$n = 10$]) with the VerifyNow $P2Y_{12}$ assay employing the thrombin-receptor activating peptide (iso-TRAP) channel. The VerifyNow $P2Y_{12}$ cartridge has channels with different activators to initiate platelet activation, including adenosine diphosphate (ADP) + prostaglandin E1, and iso-TRAP. Because ticagrelor, which was routinely given in STEMI subjects in the prehospital settingin the phase 2a study, has a major effect on the ADP-based assay, but minimal effect on the iso-TRAP-based assays, the iso-TRAP assay was used to assess the pharmacodynamic effects of zalunfiban. The primary pharmacodynamic end point of high-grade inhibition (77% or greater inhibition with the iso-TRAP channel, which corresponds to 80% inhibition of light transmission aggregometry stimulated by 20 μM ADP) at 15 minutes after administration was met in 3/8, 7/8, and 7/8 patients in the 3 cohorts with a dose-response relationship.[35] The offset of platelet inhibition at 1 to 2 hours after administration provides optimal cardiac protection until PCI can be performed and the orally administered $P2Y_{12}$ antagonist reaches therapeutic levels, thus diminishing the hemorrhagic risk and allowing for emergency cardiac surgery when indicated.[34,36,37] Zalunfiban did not produce thrombocytopenia in the phase 1 and 2 trials, the majority of bleeding complications were mild and resolved before discharge, and no patients died during the studies.[33,34] Finally, zalunfiban was designed to have high solubility so that an entire dose could be contained in less than 2 mL, facilitating prehospital use by (para)medics and making it possible to develop it for auto-injector administration, opening the potential for self-administration.

Modification from phase 2b to phase 3 trial

The CELEBRATE trial (CELEcor Blinded RAndomized trial in sTE-elevation myocardial infarction) was originally designed as a phase 2b trial to assess the restoration of coronary artery blood flow at initial angiography and to assess resolution of ST-segment deviation at 1 hour after PCI in STEMI patients treated in the ambulance with zalunfiban or placebo. After discussion with regulatory agencies, the steering committee modified the primary surrogate end points to a composite, ranked, 7-point clinical scale to assess the efficacy of a prehospital subcutaneous injection of zalunfiban in patients with STEMI anticipated to undergo primary PCI. Following modification of the primary end points the trial changed into a phase 3 clinical trial.

Methods

Objectives

The primary efficacy objective of the CELEBRATE trial is to test the hypothesis that a single prehospital subcutaneous injection of zalunfiban in addition to standard care improves clinical outcome at 30 days in patients with STEMI with intent to undergo primary PCI, as assessed on a ranked 7-point scale, compared to placebo. The primary safety objective is to assess bleeding events according to the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) severe or life-threatening criterion for safety assessment after a single subcutaneous injection of zalunfiban versus placebo at 30 days follow-up. Bleeding academic research consortium (BARC) 3C and 5 bleeding will also be reported.

Study design and population

The CELEBRATE trial (NCT04825743, EudraCT 2020-003320-16) is a phase 3, randomized, double-blinded, placebo-controlled, international trial. The study will be conducted in multiple countries in Europe and North America. Patients with STEMI presenting with persistent ischemic chest pain (>10 minutes) and ≥2 mm ST-segment elevation in 2 adjacent electrocardiogram (ECG) leads, in whom the total duration of symptoms is 4 hours maximum will be randomized and treated accordingly in the ambulance if they meet all eligibility criteria. The key in- and exclusion criteria are summarized in Table I. Patients will be evaluated by experienced (para)medics who transport the patients to the interventional centers.

A total of 2499 patients will be randomized to 1 of the 3 treatment groups in a 1:1:1 ratio. Each subject will receive a single subcutaneous injection containing either zalunfiban dose 1 (0.110 mg/kg) or zalunfiban dose 2 (0.130 mg/kg) or placebo.

This study is being conducted in accordance with the Declaration of Helsinki and is consistent with the International Conference on Harmonization/Good Clinical Practice. The study protocol and study procedures were approved by the local medical ethics committees.

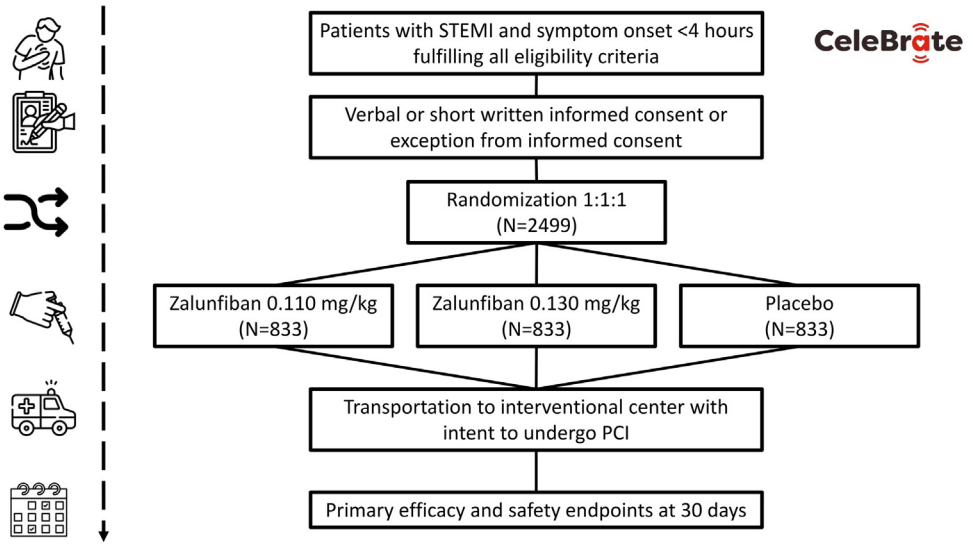
Study procedures, randomization, and treatment

The overall study flow chart is summarized in Figure 1. In brief, patients will be screened at first medical contact based on the information available by (para)medics before transport to interventional centers. Those fulfilling the eligibility criteria and for whom the exception

Table I. Study inclusion and exclusion criteria

Inclusion criteria
1. Males aged ≥18 y or postmenopausal or surgically sterile females ≥50 y or ≥55 y (for Czech Republic study sites only)
2. Weight (by history) between 52 and 130 kg
3. Patients with STEMI, presenting with persistent ischemic chest pain (>10 min) and ≥2 mm ST-segment elevation in 2 adjacent ECG leads, in whom the total duration of symptoms is 4 h maximum. If time of symptom onset is uncertain, the cardiologist may be contacted to confirm inclusion criteria
4. Exception from Informed Consent Requirements (EFIC) process, verbal witnessed/short written informed consent, or written informed consent signed by subject or legally authorized representative/independent witness, will be obtained in the acute phase by paramedics, according to local applicable legal regulations. Subject is willing and able to give informed consent. Written informed consent will be obtained as soon as the subject's clinical condition allows it
Exclusion criteria
1. Cardiopulmonary Resuscitation (CPR) for current Out of Hospital Cardiac Arrest (OHCA).
2. Presenting with systolic blood pressure <90 mm Hg (confirmed on repeat assessment) and heart rate >100 beats per minute (bpm)
3. Current known active coronavirus disease 2019 (COVID-19) infection (criteria according to local guidelines)
4. Currently treated with renal dialysis
5. Current treatment with oral anticoagulation
6. Major surgery, or trauma or bleeding leading to hospitalization, within the past month
7. Known history of ischemic or hemorrhagic stroke
8. Known severe anemia (regular blood transfusion needed)
9. Previously enrolled in this study
10. Participation in another clinical study with an investigational product or device within the past month
11. Life expectancy less than 1 y

Figure 1



Study flow chart. *PCI*, percutaneous coronary intervention; *STEMI*, ST elevation myocardial infarction.

from informed consent process applies or who have provided verbal witnessed/short written informed consent, or for whom or their legally authorized representative/independent witness have provided written informed consent, according to local applicable legal regulations, can be enrolled in the study. The diagnostic 12-lead ECG will later be used for evaluation of STEMI (inclusion criterion #3) by the ECG Core Laboratory. Full written informed consent will be obtained, when possible, after the patient's medical conditions have been stabilized.

Once they are enrolled, participants will be randomly assigned to receive 1 of 3 study treatments in a 1:1:1 fashion. Each ambulance will have a single, prerandomized, blinded study drug kit available on board, containing 1 of the 3 study drugs: zalunfiban dose 1 (0.110 mg/kg) or za-

lunfiban dose 2 (0.130 mg/kg) or placebo. The randomization schedule is computer-generated with random permuted blocks with stratification by country. The dose of zalunfiban or placebo will be based on the weight of the subject. Single subcutaneous injection of study drug will take place in the ambulance by the (para)medics either before or during transport to an interventional center, within 15 minutes after STEMI diagnosis in the upper arm, or if neither upper arm is suitable, via the lateral thigh or abdomen. Treatment assignment will be blinded to sponsor, (para)medics, subject, and investigator. A replacement study drug kit will be dispensed by the pharmacy unit of the interventional center to resupply ambulance stock. In the event that emergency unblinding is necessary the investigator can immediately break the blind via the pharmacist to provide adequate medical treatment.

Standard care will be given to all randomized patients, including prehospital administration of aspirin, unfractionated heparin, and oral $P2Y_{12}$ loading doses according to local standards. If unfractionated heparin is administered in the prehospital phase, an activated clotting time measurement will be performed in the cardiac catheterization lab. Additional heparin is only recommended if the activated clotting time is <200 seconds. During or after primary PCI, bail-out use of a currently available GPI or cangrelor is permitted in case of a prespecified indication. Coronary angiography will be performed according to standard procedures, and the choice for revascularization and postprocedural antithrombotic therapy is left to the discretion of the operator.

Data collection, data management and follow-up

Prehospital patient data including body weight, vital signs, diagnostic ECG, and adverse events will be recorded by ambulance personnel and provided to the research personnel at the receiving hospital. Blood samples will be collected before and directly after the end of the procedure. Twelve-lead ECGs will be obtained before and after primary PCI and analyzed by the ECG core laboratory. Throughout the admission, adverse events (AEs), serious adverse events (SAEs) and bleeding events will be collected by research personnel from the participating sites. Follow-up phone calls will take place at approximately 30 days and 12 months after randomization. In case a subject cannot be contacted, the subject's primary care physician will be contacted. All data will be captured and stored via an electronic data capture system.

Study end points

The primary efficacy outcome will be assessed using a ranked 7-point scale of clinical outcomes at 30-day follow-up, ranked from worst to least bad:

1) All-cause death through 30 days
2) Hemorrhagic or ischemic stroke through 30 days
3) Recurrent myocardial infarction (type 1 to type 4) through 30 days
4) Acute stent thrombosis at 24 hours post-PCI
5) New onset heart failure or rehospitalization for heart failure through 30 days
6) Myocardial infarction with high sensitivity cardiac troponin levels $\geq$10x upper limit of normal at 24 hours post-PCI/angiography
7) none of the above

The key secondary outcomes include:

- Corrected Thrombolysis In Myocardial Infarction (TIMI) frame count in the infarct-related artery before PCI[38]
- ST-segment deviation resolution 1 hour post-PCI, measured at the J-point in all leads, except aVR[39]

The primary safety outcome is the incidence of severe or life-threatening bleeding according to the GUSTO criteria at 30 days follow-up. GUSTO severe or life-threatening bleeding is defined as either intracranial hemorrhage or bleeding that causes hemodynamic compromise and requires intervention. Other key secondary safety outcomes include:

- Recording of AE or SAE up to 30 days follow-up; SAE will be followed-up until resolution/stabilization, mortality, hospitalization for heart failure and atrial fibrillation up to 12-months follow-up
- Platelet count at multiple time points (baseline, 6 and 24 hours after angiography, and at discharge or at 72 hours)
- Major bleeding events according International Society on Thrombosis and Hemostasis (ISTH) criteria to at 30 days follow-up[40]
- Bleeding events according to GUSTO mild and moderate criteria, Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 criteria, ISTH minor and or major bleeding, TIMI minor and major criteria at 30 days follow-up[40,41]
- Injection site reactions

An independent clinical end point committee (CEC), blinded to treatment groups, will provide independent central adjudication of all major safety and efficacy events. The members of the CEC will not directly participate in this study, nor will any participate as a member of the data safety monitoring board (DSMB). An unblinded, independent, international DSMB committee oversees trial conduct and quality, as well as the safety of study participants. A blinded review of angiographic data and ECG recordings will be conducted by 2 independent Core Laboratories, (Boston Clinical Research Institute, Boston, MA, United States of America and Diagram Research, Zwolle, The Netherlands), respectively.

Table II. Percentage of patients hypothesized to be in each stage (*based on results from The Ongoing Tirofiban in Myocardial Evaluation (On-TIME 2) study.[19]

Status	Placebo*	Cumulative placebo (%)	Pooled doses*	Cumulative zalunfiban (%)
Death (all cause) at 30 d follow-up	4.0% of patients, or 4.0%	4.0	2.4% of patients, or 2.4%	2.4
Stroke at 30 d follow-up	0.9% of remaining, or 0.9%	4.9	0.2% of remaining, or 0.2%	2.6
Recurrent myocardial infarction at 30 d follow-up	2.8% of remaining, or 2.6%	7.5	2.7% of remaining, or 2.7%	5.3
Acute Stent Thrombosis at 24 h post-PCI/angiography	1.2% of remaining, or 1.1%	8.6	0.2% of remaining, or 0.2%	5.5
New onset heart failure or rehospitalization for heart failure at 30 d follow-up	4.9% of remaining, or 4.5%	13.1	4.3% of remaining, or 4.0%	9.8
Myocardial infarction with high sensitivity cardiac troponin levels ≥10x upper limit of normal at 24 h post-PCI/angiography	94.2% of remaining, or 81.9%	95.0	91.8% of remaining, or 83.1%	92.6
None of the above	All of remaining, or 5.0%		All of remaining, or 7.4%	

Sample size determination

The sample size required to detect potential beneficial effects in the clinical ordinal scale by comparing the pooled dose groups against placebo was derived from the On-TIME 2 (The Ongoing Tirofiban in Myocardial Evaluation) trial.[20] Using end point component proportions derived or estimated from the On-TIME 2 trial, a sample size calculation for a Wilcoxon-Mann-Whitney test for ordinal data was determined. Table II shows the percentage of patients expected to be in each state.

The sample size of the study is calculated to give 90% power for the comparison of the pooled doses tested against placebo, which requires 2334 patients, 778 patients per treatment group. The attrition rate is assumed to be 6.6%. Therefore, a target of 2499 patients (833 patients per treatment group) will be randomized.

Statistical analysis and analysis populations

The primary efficacy analysis will use a modified intention to treat population, which includes all consented and randomized patients who had confirmed prehospital STEMI diagnosis based on ST-elevation on the enrollment ECG (see Figure 2 for all analysis sets). The primary efficacy analysis will compare pooled doses 1 and 2 vs placebo. The primary outcome measure will be analyzed using a proportional odds model with treatment group fitted as covariate and adjusting for age, heart rate, blood pressure, and infarct location (anterior, nonanterior). The adjusted treatment odds ratio estimated from the model and 95% confidence interval (CI) will be presented along with the 2-sided *P*-value for superiority. A frequency distribution bar graph will be provided for the number of patients in each of the 7 categories by treatment group.

Adjustment for multiple comparisons will be performed using a fixed sequence closed testing procedure:

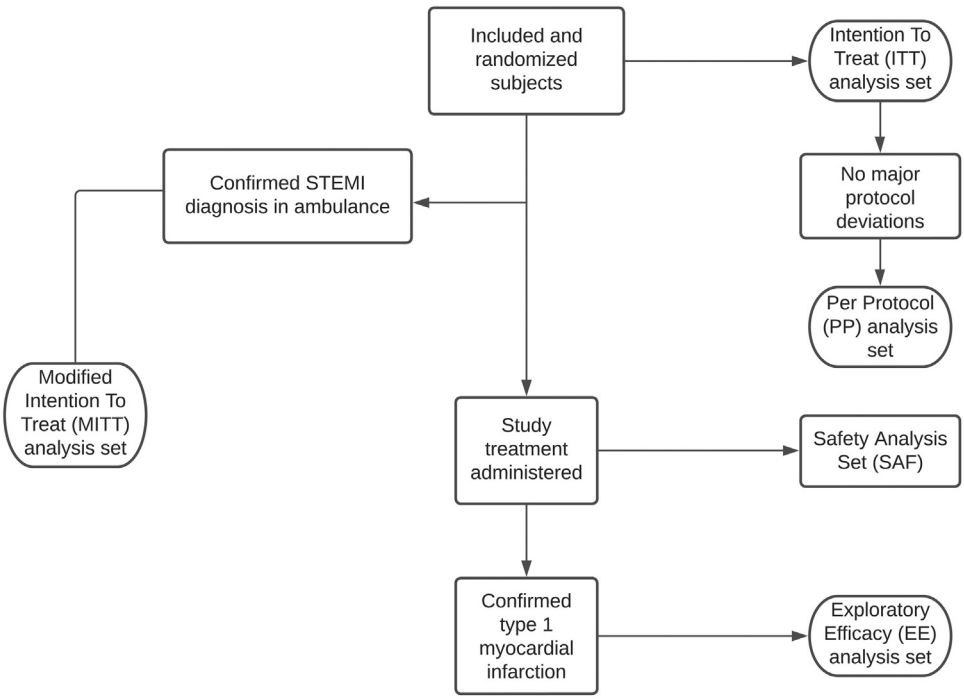
- The pooled high and low doses versus placebo on the clinical ordinal scale will be tested at 2-sided 0.05 significance level
- If the previous comparison is significant, both doses will simultaneously be tested individually at a 2-sided 0.05 significance level

A sensitivity analysis will be performed for the primary efficacy end point based on the intention to treat analysis set, per protocol analysis set, and exploratory efficacy analysis set (Figure 2).

All secondary efficacy analyses will compare dose 1 and dose 2 pooled to placebo. The secondary efficacy analyses will be performed using a linear mixed model analysis. The model will include a fixed categorical effect for treatment and infarct location (anterior, nonanterior). From this model, least squares means, standard errors, treatment differences in least square mean and 95% CIs will be estimated.

Primary safety and all secondary safety analyses will compare Dose 1 and Dose 2 pooled to placebo as well as individual doses against placebo. All safety analyses will be performed on the safety analysis set, which includes all patients who were administered the study treatment (Figure 2). Categorical outcomes will be sta-

Figure 2



Study Analysis sets. *STEMI*, ST-elevation myocardial infarction. All consented and randomized patients will go in ITT analysis set. All patients in the ITT with confirmed STEMI diagnosis will go in the mITT. All primary efficacy analyses will be performed on the mITT analysis set. A sensitivity analysis will be performed for the primary efficacy end point based on the ITT, PP, and EE analysis set. All safety analyses will be performed on the SAF.

tistically tested between groups using Fisher exact test. Two-sided 95% CIs of the difference in percentages between groups will be calculated using exact methods. Continuous outcomes will be analyzed using *t* tests. Kaplan-Meier estimates will be used to summarize time-to-event data along with survival distributions, and the log rank test will be used to test treatment differences. A semiparametric Cox proportional hazards regression model will be used to evaluate the magnitude of effect based on the hazard ratio.

A full statistical analysis plan, including approach to addressing missing data, will be finalized before unblinding of the trial results. All statistical calculations will be performed by a statistician, unless otherwise specified.

Evaluation of subgroups

Prespecified subgroup analyses and interaction tests of the primary efficacy outcome will be performed for: Diabetes mellitus [including new diabetes based on HbA1c 6.5% or higher]; duration of symptoms prior to study drug administration (0-≤2 hours and >2-4 hours); $P2Y_{12}$ pretreatment ($P2Y_{12}$ vs no pretreatment with $P2Y_{12}$ (clopidogrel, ticagrelor or prasugrel); age (<65 year vs ≥65 year, <75 year vs ≥75 year); sex (male vs female); location of myocardial infarction (anterior vs nonanterior); access site (radial vs femoral); heparin and $P2Y_{12}$ pretreatment (aspirin vs aspirin plus heparin vs aspirin plus heparin plus $P2Y_{12}$ blocker); morphine or fentanyl pretreatment (yes or no for each drug); body mass index. While not a subgroup based on baseline data, results will be analyzed according to duration of time from study drug administration to angiography (pretreatment time, 0-60 min and >60 minutes).

Planned pharmacodynamic substudy

The aim of this substudy is to investigate the measure of platelet inhibition before primary PCI after a single prehospital administered injection of zalunfiban in patients with STEMI. The pharmacodynamic effects of zalunfiban have only been investigated while zalunfiban was administered at the cardiac catheterization lab, as opposed to its intended prehospital use.[34] The primary outcome of this pharmacodynamic substudy is platelet reactivity reported as platelet aggregation units with the iso-TRAP channel and as percent inhibition of platelet function inhibition with the BASE channel measured by

the VerifyNow $P2Y_{12}$ assay (Accumetrics, San Diego, CA). Secondary objectives include the evaluation of clot strength expressed as maximal amplitude measured with the TEG 6s device (Haemonetics Corporation, Braintree, MA). Blood samples will be collected upon arrival at the cardiac catheterization lab, before angiography. All pharmacodynamic assays will be performed immediately after blood sample collection.

Funding

The CELEBRATE trial and the pharmacodynamic substudy are funded by CeleCor Therapeutics Inc.

Author contribution

The Steering Committee for the CELEBRATE trial comprises Arnoud W.J. van 't Hof (chair), C. Michael Gibson, Christopher B. Granger, Jurriën M. ten Berg, Barry S. Coller (nonvoting advisor) and Gilles Montalescot. The steering committee is responsible for the design and conduct of the study and all study analyses. The first draft of the manuscript was developed by Sem A.O.F. Rikken and Abi Selvarajah, and all co-authors subsequently contributed to its development and finalization. CeleCor Therapeutics Inc. reviewed the manuscript during its development and was allowed to propose suggestions, but the final content was determined by the first and the last author.

Summary

The CELEBRATE trial is being conducted to determine whether a single prehospital subcutaneous injection of zalunfiban in addition to standard-of-care in patients with STEMI results in improved clinical outcome, measured on a ranked 7-point scale, compared to placebo.

Disclosures

Sem A.O.F. Rikken has nothing to declare. Abi Selvarajah has nothing to declare. Renicus S. Hermanides has nothing to declare. Barry S. Coller is an inventor of abciximab and in accord with U.S. federal law and the policies of the Research Foundation of the State University of New York, shared in payments for the sales of abciximab. He is also an inventor of the VerifyNow assays and receives royalties based on sales of the P2Y12 cartridge. He is also an inventor of zalunfiban and in accord with U.S. federal law and the policies of Rockefeller University, has a royalty interest in any future sales of zalunfiban. He also is a founder of CeleCor Therapeutics, Inc., which is developing zalunfiban for human use, and is an equity owner in CeleCor and serves as a scientific advisory to CeleCor. Dr Coller participated in the design of the CeleBrate trial and serves as a scientific advisor to the Steering committee, but has no role in assessing safety or efficacy end points. C. Michael Gibson Dr Gibson has received research grant support from Angel Medical Corporation, Bayer Corp, CSL Behring, Janssen Pharmaceuticals, Johnson & Johnson Corporation, and Portola Pharmaceuticals; and has received modest consulting monies from Amarin Pharma, Amgen, Arena Pharmaceuticals, Bayer Corporation, Boehringer Ingelheim, Boston Clinical Research Institute, Cardiovascular Research Foundation, Chiesi, CSL Behring, Eli Lilly, Gilead Sciences, Inc, Janssen Pharmaceuticals, Johnson & Johnson Corporation, The Medicines Company, Merk & Co, Inc, Novo Nordisk, Pfizer, Pharma Mar, Portola Pharmaceuticals, Sanofi, Somahlution, St Francis Hospital, Verson Corporation, and Web MD. He serves as a scientific advisory to CeleCor. Christopher B. Granger reports consulting fees from Medtronic, Inc, and Boston Scientific, as well as consulting fees and research grants from Philips. He serves as a scientific advisory to CeleCor. Frédéric Lapostolle has nothing to declare Sonja Postma has nothing to declare. Henri van de Wetering has nothing to declare. Risco C.W. van Vliet has nothing to declare. Gilles Montalescot has received research grants from Abbott, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cell Prothera, CSL Behring, Europa, Idorsia, IRIS-Servier, Medtronic, Merck Sharp and Dohme, Novartis, Pfizer, Quantum Genomics, and Sanofi. He serves as a scientific advisory to CeleCor. J.M. ten Berg reports grants from the Netherlands Organization for Health Research and Development, a Dutch government institution called ZonMw. He reports speaker fees from AstraZeneca, Daiichi Sankyo, Eli Lilly, the Medicines Company, Accumetrics, Boehringer-Ingelheim, Bayer, BMS, Pfizer and Ferrer. He serves as a scientific advisory to CeleCor. A.W.J. van 't Hof reports unrestricted grants from AstraZeneca, Medtronic, Boehringer Ingelheim, Abbott vascular and Ferrer. He serves as a scientific advisor to CeleCor.

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*** These lists are updated monthly and therefore might need revision upon time of acceptance.

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