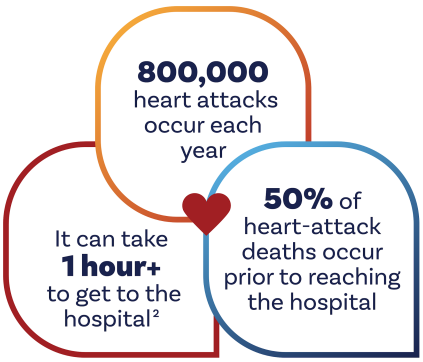
Zalunfiban, a novel GPIIb/IIIa platelet inhibitor for rapid pre-hospital treatment of heart attack

The problem

Each year, 800,000 people in the United States have an acute myocardial infarction (AMI), or heart attack, a life-threatening condition in which blood flow to the heart muscle is suddenly decreased or blocked by a blood clot in one or more of the coronary vessels.



When a heart attack occurs, time is muscle. But while in-hospital management of heart attacks has greatly improved over the past 30 years, treatment at the scene of a heart attack and during transport has stagnated. It often takes more than an hour to transport a heart-attack patient to a referral center—and at least 50% of heart-attack deaths occur before the patient reaches the hospital.[1]

For patients who survive, the extent of irreversible heart-muscle damage increases with every minute the blood vessel remains closed. This heart-muscle damage can later result in heart failure, one of the most common causes of hospitalization and death in the United States.

To significantly reduce deaths, we need a therapy that restores blood flow rapidly and can be administered in the critical time before a patient reaches the hospital.

A potential solution

In the initial stages of a heart attack, platelet aggregation and subsequent blood-clot formation occurs when there is inflammation or injury in a coronary artery—such as when a plaque ruptures. The platelet GPIIb/IIIa receptor plays a key role in this clot-formation process, suggesting that a fast-acting GPIIb/IIIa receptor antagonist could reduce blood-clot formation in the coronary artery or re-open the artery.

Zalunfiban is a next-generation investigational GPIIb/IIIa inhibitor that was specifically designed for medical first responders and emergency department staff to administer by subcutaneous injection using an auto-injector, allowing a full dose to be contained in a volume of less than 1 milliliter (less than ¼ teaspoon). It reaches maximal effect within 15 minutes and its antiplatelet effect wears off in less than two hours.[3] It also was designed to minimize the risk of thrombocytopenia, a rare but serious side effect of other GPIIb/IIIa inhibitors.

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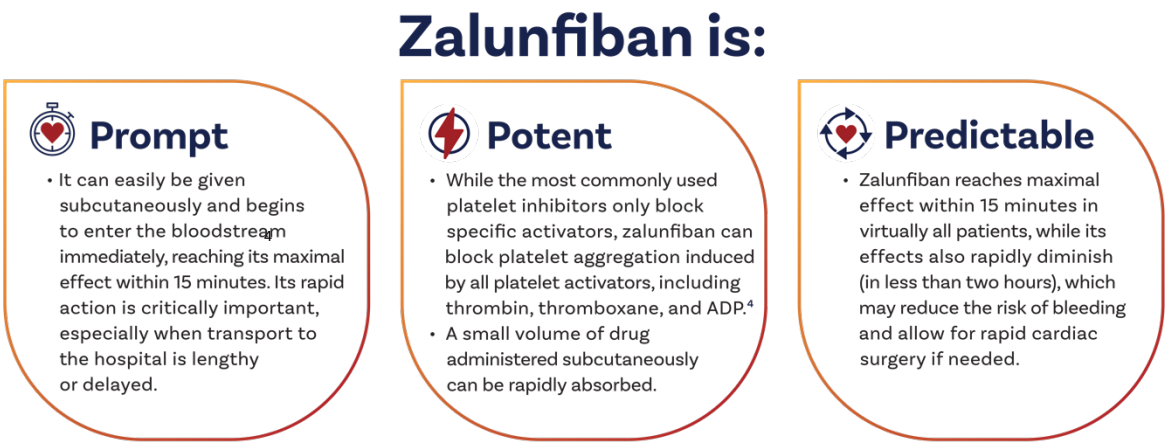
1 Dudas et al, Trends in Out-of-Hospital Deaths Due to Coronary Heart Disease in Sweden (1991 to 2006). Circulation. 2011;123:46-52.

2 Bates ER et.al. Time to treatment in patients with STEMI. N Engl J Med 2013; 369:889-892.

3 Bentur OS, et al. Assessing the Pharmacodynamics of RUC-4 (Zalunfiban), a Novel αIIbβ3 Antagonist, Using VerifyNow Assays in

This novel formulation addresses the three factors that are crucial to AMI treatment stakeholders, from first responders to ED staff to PCI experts. It is prompt, potent, and predictable:



Approximately 40% of AMI patients have an ST-segment elevation myocardial infarction (STEMI). This is the most severe form of AMI, where blood flow to a portion of the heart is almost always cut off by a blood clot. The clot consists of platelets, fibrin, and red blood cells and solidifies over time, blocking or reducing blood flow to the heart.

In more than 30,000 STEMI patients in over 40 studies, early therapy with a GPIIb/IIIa inhibitor plus aspirin compared with aspirin alone demonstrated numerous clinical benefits, including reduced short-term and long-term risk of death. The central role of thrombin in clot formation likely accounts for the greater benefit with GPIIb/IIIa inhibitors than with other antiplatelet agents.

The priority in treating STEMI is opening the coronary artery quickly, as soon as possible after the onset of symptoms, to help prevent irreversible heart damage. Thus, there is an urgent need for an antiplatelet agent that can be easily administered to STEMI patients before they reach the hospital. The ideal agent should be potent and rapidly and predictably absorbed to quickly inhibit clot formation at the early stages. To reduce the risk of bleeding and to avoid interfering with later patient management, inhibition should not persist more than two hours.

Aspirin is a relatively weak antiplatelet drug because it only interferes with the thromboxane pathway, but it is nevertheless beneficial in treating AMI patients. The oral P2Y12 inhibitors only block one of the ADP receptors, so although they are more potent than aspirin, their delayed onset of action in STEMI patients provides only marginal benefit when used as a pre-hospital therapy.[5]

GPIIb/IIIa inhibitors are the most potent antiplatelet drugs[6] because they can block platelet aggregation induced by all platelet activators, including thrombin, thromboxane A2, and ADP. However, the currently FDA-approved GPIIb/IIIa inhibitors Aggrastat®, and Integrilin® are not appropriate for pre-hospital administration, as they must be given by an intravenous (IV) injection followed by continuous IV delivery using an infusion pump.

Patients with ST-Segment Elevation Myocardial Infarction (STEMI) Treated with Aspirin and Ticagrelor [abstract]. Res Pract Thromb Haemost. 2021; 5 (Suppl 1).

4 Orzalkiewicz M., et al. Comparison of Routine Versus Selective Glycoprotein IIb/IIIa Inhibitors Usage in Primary Percutaneous Coronary Intervention (from the British Cardiovascular Interventional Society). American Journal of Cardiology. 124(2019) P373-380.

5 Orzalkiewicz M., et al. Comparison of Routine Versus Selective Glycoprotein IIb/IIIa Inhibitors Usage in Primary Percutaneous Coronary Intervention (from the British Cardiovascular Interventional Society). *American Journal of Cardiology*. 124(2019) P373-380.

6 Ibid.

Competitive Landscape

	Aspirin	Ticagrelor (Brillinta®) Prasugrel (Effient®)	Tirofiban (Aggrastat®) Eptifibatide (Integrilin®)	Cangrelor (Kengreal®)	Selatogrel	Zalunfiban CeleCor THERAPEUTICS
Rapid onset of action			●	●	●	♥
Easy to adminster in pre-hospital setting	●	●			●	♥
Inhibits all platelet aggregation pathways			●			♥
Can open a closed coronary artery			●			♥
Predictable response	●		●	●		♥
Absorption independent of opioid administration			●	●		♥
Low risk of thrombocytopenia	●	●		●	●	♥

Data supporting zalunfiban use in STEMI patients

A Phase 1 randomized study of 14 healthy volunteers and 30 patients with stable coronary artery disease taking aspirin showed that zalunfiban administered subcutaneously provided rapid, high-grade, limited-duration platelet inhibition while being well tolerated.[7]

A Phase 2A, open-label, randomized study assessed the onset of platelet aggregation inhibition after a single subcutaneous injection in 27 adults with STEMI, administered just before they underwent percutaneous coronary intervention (PCI). The primary endpoint was the number of patients with at least 77% inhibition of thrombin-induced platelet aggregation within 15 minutes. This threshold was achieved by three of eight patients at the lowest dose and seven of eight patients in the other two dose groups. Maximal platelet inhibition was achieved within 15 minutes and the antiplatelet effects decreased quickly, with a return to 50% of platelet function by about two hours.[8]

Zalunfiban is now being studied in **CeleBrate**, a pivotal Phase 3 prospective, blinded, randomized, placebo-controlled, international multicenter study designed to assess the safety and efficacy of a single subcutaneous injection of zalunfiban in STEMI patients in the pre-hospital setting.

In January 2022, after discussion with FDA, CeleCor modified CeleBrate's primary endpoints to a seven-point clinical scale and increased the trial size to 2,499 STEMI patients. The FDA agreed that a statistically significant effect on this primary endpoint in

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7 KereiakesDJ, et al. First Human Use of RUC-4: A Nonactivating Second-Generation Small-Molecule Platelet Glycoprotein IIb/IIIa (Integrin αIIbβ3) Inhibitor Designed for Subcutaneous Point-of-Care Treatment of ST-Segment Elevation Myocardial Infarction. *J Am Heart Assoc*. 2020;9:e016552. DOI: 10.1161/JAHA.120.016552

8 Bor WL, et. al. Pharmacokinetics, pharmacodynamics, and tolerability of subcutaneous administration of a novel glycoprotein IIb/IIIa inhibitor, RUC-4, in patients with ST-segment elevation myocardial infarction. *EuroIntervention* 2021;17-online publish-ahead-of-print May 2021

the CeleBrate trial alone could be sufficient to provide evidence of effectiveness to support an NDA filing. CeleBrate is estimated to complete in Q4 2024.

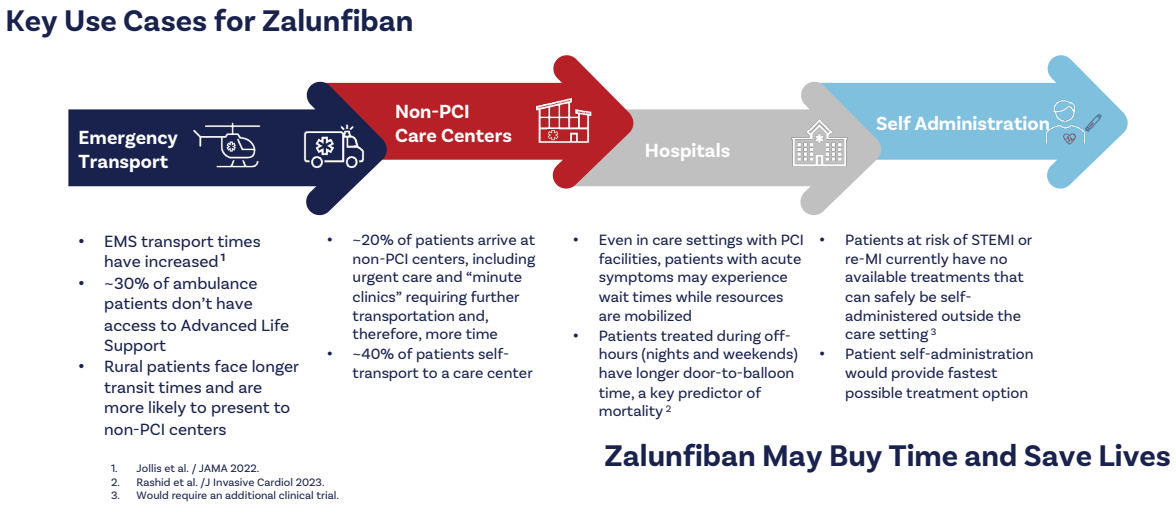
The primary endpoints, ranked from worst to best, are:

1. Death
2. Stroke
3. Recurrent MI
4. Acute stent thrombosis
5. New-onset heart failure or rehospitalization for heart failure
6. MI with hs-cTnT levels >10x ULN
7. None of the above

CeleBrate is focusing on STEMI patients rather than all AMI patients, because STEMI AMIs are usually more serious and are almost always caused by a blood clot. All patients will be evaluated by ECG to establish the diagnosis of STEMI before being entered into the study. This is crucial because fewer than 20% of patients with chest pain or other symptoms suggestive of an AMI actually have an AMI.[9]

The CeleBrate study design also streamlines the consenting process—an important operational benefit in critical care settings. The study has exception from informed consent (EFIC) in the U.S. and similar agreements in other countries through ambulance companies.

There are many care settings in which zalunfiban can be used, comprising a large market and umet medical need.



If zalunfiban is successful in its first indication, there is potential for additional use beyond the medical first-responder environment. For example, the one-dose injectable applicator and subcutaneous administration of zalunfiban (combined with an easy-to-administer ECG) potentially make it an ideal solution for patient self-administration, particularly among people at high risk of STEMI and those who have experienced a first heart attack. This would allow treatment even before a medical first responder arrives—with the goal of preserving as much heart muscle as possible during the critical pre-hospital time window.

[9] JH Pope et al., *N Engl J Med* 2000 Apr 20;342(16):1163-70. Missed diagnoses of acute cardiac ischemia in the emergency department.