A Randomized, Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Intravenous MCC-135 as an Adjunct to Primary Percutaneous Coronary Intervention in Patients with Acute Myocardial Infarction: Rationale and Design of the Evaluation of MCC-135 for Left Ventricular Salvage in Acute MI (EVOLVE) Study

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Abstract. As a consequence of acute ischemia and reperfusion in patients with acute ST elevation myocardial infarction, calcium overload inside myocytes not only affects myocardial contraction, relaxation, and myocyte recovery following reperfusion, but also may be related to myocyte necrosis and fatal arrhythmia. MCC-135 is the first in a new class of agents that reduce intracellular calcium overload. Pre-clinical and early clinical studies yielded promising results for patients with ST elevation myocardial infarction. The Evaluation of MCC-135 for Left Ventricular Salvage in Acute MI (EVOLVE) study is a Phase 2a, multicenter, randomized, double-blind, placebo-controlled clinical trial of 2 new doses of MCC-135 (4.5 mg/kg/48 hours and 9.0 mg/kg/48 hours) as adjunct therapy for preservation of left ventricular function and reduction of infarct size in patients undergoing primary percutaneous coronary intervention (PCI) for electrocardiographically moderate-large ST elevation myocardial infarction. The primary endpoint will be left ventricular ejection fraction on Day 5 post myocardial infarction as determined by single photon emission computed tomography (SPECT). Secondary endpoints will include SPECT and echocardiographic assessments, serum cardiac markers, clinical outcomes, and safety measures at specific time points through Day 30 post myocardial infarction. Follow-up clinical and safety assessments will be continued until Day 180. The rationale, design, and methods of the EVOLVE study are described in this paper, along with 2 sub-studies, involving a comparison of pre- and post-PCI measurements with either SPECT or echocardiography, to examine myocardial salvage and the time course of changes in myocardial infarction size and left ventricular function.

Miniabstract. The Evaluation of MCC-135 for Left Ventricular Salvage in Acute MI (EVOLVE) study is a Phase 2, multicenter, randomized, double-blind, placebo-controlled clinical trial of two doses of MCC-135, first in a new class of agents that reduce intracellular calcium overload, as adjunct therapy for preservation of left ventricular function and reduction of infarct size in patients with moderate-large STEMI undergoing primary PCI. The rationale, design, and methods of the EVOLVE study, along with two sub-studies, are described in this paper.

Key Words. left ventricular function, percutaneous coronary intervention, single photon emission computed tomography, ST elevation myocardial infarction

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Introduction

The treatment of patients with acute ST elevation myocardial infarction has changed considerably over the last several decades. Initial treatment involved passive management of the complications of ST elevation myocardial infarction, namely arrhythmia and hemodynamic instability. With a better understanding of the pathophysiology of ST elevation myocardial infarction, reperfusion therapy using thrombolysis became the main mode of therapy to restore antegrade epicardial blood flow. Due to its limitations in efficacy and its potential bleeding risk, especially intracranial hemorrhage, this pharmacologic therapy was gradually replaced by primary percutaneous coronary intervention (PCI) when available. The introduction of coronary stents to maintain vessel patency and the recent advances in anti-thrombotic therapy by glycoprotein IIb/IIIa antagonists have made the mechanical approach to reperfusion even more effective. Thrombolysis in Myocardial Infarction flow of the culprit vessel can routinely be achieved in up to 90 to 95% of all cases [1,2]. However, despite these approaches, significant morbidity and mortality still persist in patients treated with PCI and glycoprotein IIb/IIIa antagonists, approximately 5 to 6% at 30 days and 17 to 20% at 1 year [3–6].

Recent investigations have focused attention on improvements in the microcirculation distal to the epicardial lesion. It is now common practice in cardiac catheterization laboratories to administer intracoronary adenosine, verapamil, or nitroprusside in the setting of primary PCI to protect distal microcirculation. Other approaches such as glucose-insulin-potassium therapy [7], a distal embolic protection device [8], and complement blocking antibody [9,10] have failed to demonstrate any significant benefit in reducing infarct size among patients undergoing primary PCI.

Protection of myocytes has recently been the focus of new research. Intravenous adenosine [11,12] and Na+/H+ exchange inhibitors [13,14] have shown promise for reduction of infarct size in some patient subgroups, but ultimately failed to improve clinical outcomes in larger scale studies [12,13]. A recent study designed to cool the body core temperature as an adjunct to primary PCI demonstrated no benefit on reduction of infarct size [15]. Another study designed to deliver supersaturated oxygen to targeted ischemic myocardium as an adjunct to PCI yielded disappointing results with respect to ST segment resolution [16]. These data indicate that future effective therapies might focus on the mechanism of ischemia-induced myocyte damage or on reperfusion injury.

Various mechanisms have been proposed for reperfusion injury and cell death following ST elevation myocardial infarction. One such mechanism involves alterations in myocardial calcium handling, which leads to intracellular calcium overload [17]. Calcium overload not only affects myocardial contractility, but this imbalance of ions also alters myocyte recovery following reperfusion and may be related to fatal arrhythmia [18]. Any successful interventions in reducing the infarct size are likely to be related, in part, to restoring the intracellular calcium balance due to ischemia at the myocyte level. Therapies that can protect the myocardium (limit infarct size) before reperfusion can be restored and also reduce secondary reperfusion injury may theoretically improve morbidity and mortality.

MCC-135 (5-methyl-2-[piperazin-1-yl] benzene sulfonic acid monohydrate), developed by Mitsubishi Pharma Corporation, targets intracellular calcium homeostasis as a mechanism for reducing the extent of myocardial injury. It is the first in a new class of agents that is distinct from calcium ion channel blockers, angiotensin-converting enzyme inhibitors, beta adrenergic antagonists, phosphodiesterase inhibitors, and cardiac glycosides. Its proposed mechanism of action is to reduce intracellular calcium overload by inhibiting the sodium-calcium exchanger on the cell membrane or enhancing the ability of the sarcoplasmic reticulum to uptake extra calcium [19,20]. Hence, subsequent pathologic processes set in motion by ischemic or post-reperfusion calcium overload may be reduced or terminated.

Pre-clinical studies of MCC-135 have demonstrated benefit in models of myocardial ischemia and heart failure. In a canine model of myocardial stunning, MCC-135 significantly improved regional contractile dysfunction, as measured by percent (%) segmental shortening of the left ventricular endocardium, in a dose-dependent manner (data on file, Mitsubishi Pharma Corporation) [21]. In rat models of myocardial infarction, MCC-135 was shown to significantly reduce infarct size when given 1 hour before or within 2 minutes after ligation of the left coronary artery (data on file, Mitsubishi Pharma Corporation). In canine models of ischemia-reperfusion where intravenous MCC-135 was initiated prior to reperfusion and continued during reperfusion, subsequent infarct size was significantly reduced in comparison to controls (data on file, Mitsubishi Pharma Corporation) [21]. Also, MCC-135 given 15 minutes prior to reperfusion in a porcine model of prolonged ischemia-perfusion was found to improve myocardial contractility and reduce myocardial necrosis assessed through peak plasma levels of serum cardiac markers released from damaged cells [22].

In each of the experimental canine models, where hemodynamic parameters were also measured, MCC-135 was found to have no significant effects on blood pressure or heart rate. Together with findings from studies in normal dogs, which showed that oral and intravenous doses of MCC-135 had no significant effects on hemodynamics (data on file, Mitsubishi Pharma Corporation), the pre-clinical