Coronary Heart Disease

Intracoronary KAI-9803 as an Adjunct to Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction

Direct Inhibition of δ-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTA MI) Investigators

Background—KAI-9803, a δ-protein kinase C inhibitor, has been shown to ameliorate injury associated with ischemia and reperfusion in animal models of acute myocardial infarction (MI).

Methods and Results—Direct Inhibition of δ-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTA MI) was a “first-in-human,” dose-escalation study that evaluated the safety, tolerability, and activity of KAI-9803 for patients with acute anterior ST-segment elevation MI undergoing primary percutaneous coronary intervention. Patients who presented within 6 hours of symptom onset and had an occluded left anterior descending infarct artery on angiography were randomized in a 2:1 fashion to receive 1 of 4 doses of KAI-9803 (cohort 1, 0.05 mg; cohort 2, 0.5 mg; cohort 3, 1.25 mg; cohort 4, 5.0 mg) versus blinded concurrent placebo delivered in 2 divided doses via intracoronary injection before and after reestablishment of antegrade epicardial flow with percutaneous coronary intervention. Safety and biomarker end points were assessed. Overall, 154 patients were randomized and treated with study drug (37 in cohort 1, 38 in cohort 2, 38 in cohort 3, 41 in cohort 4). The incidence of serious adverse events was similar between patients treated with KAI-9803 versus placebo. Other safety end points, including changes in QT intervals and standard laboratory values after study drug administration, were similar between treatment groups. Although the study was not powered to demonstrate efficacy with the biomarker end points assessed, signs of drug activity with KAI-9803 were suggested by trends for consistent, nonsignificant reductions in creatine kinase–MB area under the curve and ST-recovery area under the curve values across all dosing cohorts with KAI-9803 compared with concurrent placebo, and similar trends were demonstrated for improvements in 99mtechnetium sestamibi infarct size values with active study drug in cohorts 1, 2, and 3.

Conclusions—KAI-9803 had an acceptable safety and tolerability profile when delivered via intracoronary injection during primary percutaneous coronary intervention for ST-segment elevation MI. Signs of potential drug activity were demonstrated with biomarker end points in this small exploratory study, indicating that further testing of KAI-9803 as an adjunctive therapy for ST-segment elevation MI is warranted. (Circulation. 2008;117:886-896.)

Key Words: myocardial infarction ■ angioplasty ■ pharmacology ■ protein kinase inhibitors ■ reperfusion

Protein kinase enzymes play an integral role in cardiac cellular function by transducing signals from the cell membrane to intracellular locations.1 Protein kinase C (PKC) comprises a family of intracellular isozymes that translocate to unique subcellular locations on activation and selectively bind to isozyme-specific receptors for activated C kinase to mediate cellular physiological activities.2,3 KAI-9803 is a novel peptide that inhibits δ-PKC activity by disrupting binding of δ-PKC to its receptor for activated C kinase, thereby preventing localization of δ-PKC to the mitochondria during periods of myocardial ischemia and reperfusion.4,5 δ-PKC inhibition during the reperfusion period leads to restoration of cellular energy stores, enhanced recovery of intracellular acidosis, preservation of mitochondrial function, and, ultimately, reduced damage to myocytes and endothelial cells after an ischemic insult.6 In preclinical studies, when given as a single intracoronary dose just before reperfusion, KAI-9803 (also known as δ-V1-1) reduced infarct size, enhanced early recovery of regional left ventricular contractility, and improved microvascular patency and function in animal models of acute myocardial infarction (MI).6,7 Thus, KAI-9803 appears to be a promising treatment to target the myocardial damage and microvascular dysfunction that occur in patients with acute ST-elevation MI (STEMI) despite restoration of epicardial blood flow in the infarct artery with reperfusion therapy.8

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A complete list of the members of the Direct Inhibition of δ-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTA MI) Investigators appears in the Appendix at the end of this article. All Steering Committee members were part of the Writing Committee.
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We evaluated KAI-9803 as an adjunctive therapy for patients with STEMI in the “first-in-human” Direct Inhibition of δ-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTA MI) trial. The primary objective of the DELTA MI trial was to evaluate the safety, tolerability, and activity of escalating doses of KAI-9803 when administered by intracoronary injection during primary percutaneous coronary intervention (PCI) for STEMI.

Methods

Patient Inclusion Criteria and Consent

Patients with STEMI expected to undergo primary PCI were enrolled if they were >18 years of age, presented with ≥30 minutes of ischemic chest pain and within 6 hours of symptom onset, had persistent ST-segment elevation of ≥0.2 mV in ≥2 contiguous precordial leads indicating anterior MI location (leads V1 to V6), had complete occlusion of the left anterior descending artery (LAD) (Thrombolysis in Myocardial Infarction [TIMI] grade 0 to 1 flow) on the initial diagnostic angiogram, and had a culprit lesion suitable for primary PCI.

Key exclusion criteria included the following: left bundle-branch block (new or old), intraventricular conduction defect, prior documented MI including old Q waves on prior ECGs or a clinical history of definite MI, prior coronary artery bypass grafting, cardiogenic shock at initial hospital presentation, treatment with intravenous fibrinolytic therapy within 24 hours before enrollment, and known shock at initial hospital presentation, treatment with intravenous fibrinolytic therapy within 24 hours before enrollment, and known baseline serum creatinine ≥2.5 mg/dL without renal dialysis/renal replacement therapy within 30 days of randomization.

All patients provided written informed consent, and the protocol was approved by the institutional review board of each participating institution. Patients provided consent before the start of the diagnostic angiogram.

Treatment and Randomization Procedures

Patients were recommended to receive aspirin (162 to 325 mg orally), a thienopyridine loading dose (clopidogrel 300 to 600 mg or ticlopidine 500 mg), unfractionated heparin, and glycoprotein IIb/IIIa inhibitors during PCI. Within each dosing cohort, patients were randomly assigned 2:1 to receive active study drug (KAI-9803) or saline placebo. After the final angiographic inclusion criteria were verified during diagnostic angiography, randomization and study drug preparation occurred in the catheterization laboratory before the beginning of the PCI procedure.

Each study drug kit contained either a blinded 20-mL glass vial containing 5 mg of KAI-9803 or a blinded empty 20-mL vial. KAI-9803 was formulated as a sterile powder containing 5 mg of KAI-9803 and 40 mg of mannitol in a lyophilized formulation. Study drug was reconstituted into a clear solution at 1 of 4 concentrations with the use of serial dilutions with 0.9% sodium chloride solution. Study drug was administered during PCI in the following sequence. First, the guidewire was passed across the obstruction in the LAD infarct vessel, and an over-the-wire balloon catheter was positioned at the level of the obstruction. Second, the guidewire was removed, and dilute contrast was injected to confirm positioning of the catheter tip downstream from the obstruction and to assess patency of the distal vessel. The contrast injection was followed by a saline flush, and the guidewire was reinserted. Third, the balloon was inflated, and, after the guidewire was removed, 2 mL of blinded study drug was hand-injected slowly into the distal vascular bed over at least 1 minute. Fourth, the guidewire was readvanced through the catheter into the distal vessel, and the balloon was deflated. Finally, after antegrade epicardial coronary flow was reestablished following initial balloon inflations, 3 mL of blinded study drug was injected through the guide catheter positioned at the ostium of the left main coronary artery. The PCI procedure was then completed according to standard technique.

Ascending dosing cohorts were designed to sequentially evaluate progressively higher doses of KAI-9803. The total dose of KAI-9803 administered in cohort 1 was 0.05 mg (0.02 mg with first dose, 0.03 mg with second dose), and, subsequently, total doses of 0.5 mg (0.2 mg with first dose, 0.3 mg with second dose), 1.25 mg (0.5 mg with first dose, 0.75 mg with second dose), and 5.0 mg (2.0 mg with first dose, 3.0 mg with second dose) were studied in cohorts 2, 3, and 4, respectively. The first dose delivered via balloon catheter in cohort 1 (0.02 mg) corresponds to the lowest efficacious dose tested in preclinical studies when adjusted for the increased cardiac mass in humans.6

Collection of Biomarker End Points

After initial informed consent was obtained and before diagnostic angiography was performed, a continuous digital 12-lead ECG monitor (NEMON 180+, Nardini Medical, Natick, Mass) was applied, and baseline serum samples were obtained for analyses of cardiac markers including creatinine kinase (CK and CK-MB), troponin T, and N-terminal pro-brain natriuretic peptide. These data were destroyed for patients who had provided consent but were not randomized.

After completion of the PCI procedure, angiography was performed a minimum of 10 minutes after the final balloon inflation and a minimum of 30 minutes after antegrade epicardial flow was reestablished to measure TIMI flow grade, corrected TIMI frame count, and TIMI myocardial perfusion grade. TIMI myocardial perfusion grade was assessed approximately 30 minutes after administration of study drug and before intracoronary administration of adenosine. Coronary flow reserve was determined by measuring corrected TIMI frame count before and after administration of 18 to 24 μg of intracoronary adenosine. A left ventriculogram was performed to assess ejection fraction.

The continuous ECG monitor was removed after 24 hours of data collection. Continuous ST-segment recovery analysis was performed in a blinded core laboratory. End points assessed from measurements of continuous 12-lead ECGs included time to stable ST recovery, percent ST-segment resolution at serial static time points, and ST recovery time-trend curve area defined by summated ST-segment resolution and reelevation integrated over the first 3 hours after PCI.

Blood collection for CK-MB levels was performed at 3 to 6 hours, 6 to 12 hours, 18 to 24 hours, and 36 hours after randomization. CK-MB end points assessed included infarct size by CK-MB area under the curve (AUC) and estimated peak CK-MB values as determined through curve-fitting techniques.7 Additionally, N-terminal pro-brain natriuretic peptide levels were drawn at 24 hours and on the day of discharge.

Patients were scheduled for a follow-up visit 14 days after randomization for blood collection for N-terminal pro-brain natriuretic peptide levels, myocardial single photon emission computed tomographic imaging with the use of 99m Technetium sestamibi for final infarct size measurement, and transthoracic echocardiography for assessment of left ventricular ejection fraction and regional wall motion contractile function. All core laboratories for the biomarker analyses were blinded to treatment assignment.

Safety End Points

Adverse events were assessed through hospital discharge or 7 days, whichever occurred first. Serious adverse events were assessed through 30 days after treatment. All adverse events were coded to a common dictionary (MedDRA). Investigators were asked to monitor for unexpected cardiopulmonary symptoms, arrhythmias, hemodynamic deterioration, and allergic symptoms during the initial PCI procedure and administration of study drug; arrhythmias (other than those that occur during reperfusion) requiring intervention; clinical end points as detailed below; ECG abnormalities such as QT interval prolongation, atrioventricular block, or symptomatic bradycardia requiring intervention; and ischemic or hemorrhagic stroke. Continuous ECG monitoring was used to assess QT intervals before, during, and after study drug administration during PCI. Standard laboratory values were assessed at baseline and at 24 and 48 hours after randomization.
Clinical End Points
Investigator-reported clinical outcomes were assessed through 6 months and were not adjudicated by an independent clinical events committee. End points included all-cause mortality, reinfarction, congestive heart failure (CHF), and infarct artery revascularization procedures (PCI and coronary artery bypass grafting). Reinfarction within 18 hours of randomization was defined as recurrent ischemic discomfort at rest persisting for ≥30 minutes accompanied by new or recurrent ST-segment elevation of ≥0.1 mV in ≥2 contiguous leads. Reinfarction >18 hours after randomization was defined by a similar recurrence of ischemic discomfort with new Q waves in ≥2 leads or new left bundle-branch block associated with reelevation of CK-MB levels above the upper limit of normal and increased by ≥50% over the most recent value before the recurrent ischemic event. CHF at any time point after randomization was defined as any 1 of the following 3 scenarios: (1) cardiogenic shock with systolic blood pressure <90 mm Hg for >1 hour and signs of hypoperfusion; (2) physician’s decision to treat signs or symptoms of CHF with an intravenous diuretic, intravenous inotropic agent, or intravenous vasodilator; or (3) evidence of CHF, including pulmonary edema on chest x-ray, rales >1/3 up lung fields, or pulmonary capillary wedge pressure >18 mm Hg measured with a pulmonary artery catheter.

Study Design and Statistical Considerations
This first-in-human study was designed primarily to assess the safety of escalating doses of KAI-9803. This study was not designed or specifically powered to assess safety or efficacy by clinical or biomarker end points but included a large enough sample of patients to provide an exploratory assessment of the safety and activity of KAI-9803 compared with saline placebo. A primary biomarker end point was not prespecified, but an array of biomarkers was evaluated to assess potential drug activity.

An independent data monitoring committee reviewed safety data through hospital discharge for the first 10 patients receiving a given dose of the active study drug (KAI-9803) before deciding to allow advancement to the next dosing cohort in the dose-escalation schedule. If no safety concerns were found, each dosing cohort was continued until the target enrollment of 37 to 38 patients was reached, and then the next dosing cohort was started. Each of the 4 dosing cohorts was designed to target enrollment of ~37 to 38 patients (25 randomized to active drug and 12 to 13 randomized to placebo). The data monitoring committee also reviewed safety data through hospital discharge after enrollment was completed in each dosing cohort.

The primary analysis population was prespecified to be the modified intent-to-treat population based on randomized patients who received any quantity of study drug. All data analyses were performed independently by the trial coordinating center (Duke Clinical Research Institute, Durham, NC). Statistical comparisons were performed across dosing groups to explore whether a dose–response relationship exists among each dose of study drug compared with the respective concurrent placebo group. Furthermore, comparisons were also performed between pooled KAI-9803 dosing cohorts and pooled placebo cohorts to explore the potential activity of KAI-9803. For continuous end points, dose trends were assessed with the Jonckheere-Terpstra test. For dichotomous end points, dose trends were assessed with the Cochran-Mantel-Haenszel χ² test of trend with the use of ridit scores. Pairwise contrasts were used to evaluate pooled KAI-9803 dosing cohorts versus pooled placebo with an ANOVA orthogonal test or the nonparametric Wilcoxon rank sum test. For categorical end points, the Fisher exact test or χ² test was used to compare the KAI-9803 dose levels with pooled placebo.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Consent and Randomization
From September 2004 through May 2006, a total of 262 patients provided consent for inclusion in the study, and 159 patients were randomized (Figure 1). The most common reasons for patients not being eligible for randomization after informed consent was obtained included TIMI grade 2 to 3 flow in the LAD on the initial diagnostic angiogram (n=85), failure to meet nonangiographic inclusion criteria (n=9), and need for urgent bypass surgery (n=2). Of the 159 randomized patients, 5 patients were not treated with study drug because of inability to cross the culprit lesion during PCI (n=2) or other technical reasons related to drug preparation (n=3). Thus, the modified intent-to-treat population (which formed the primary analysis population) included 154 patients who were randomized and treated with some amount of study drug. Among these patients, 37 were treated in cohort 1, 38 in cohort 2, 38 in cohort 3, and 41 in cohort 4.

Figure 1. Patient flow diagram detailing the composition of the modified intent-to-treat population and patients lost to follow-up (LFU) through 6 months.
Patient Characteristics
The majority of patients enrolled in cohorts 1 and 2 were from the United States and Canada, whereas the majority of patients enrolled in cohorts 3 and 4 were from Europe and Brazil (Table 1). The median patient age ranged from 55 to 64 years, 70% to 80% of the patients were male, and the proportion of patients with cardiac risk factors such as diabetes mellitus varied across dosing cohorts. In all dosing cohorts, a higher proportion of patients receiving active study drug presented in Killip class II or III compared with concurrent placebo. The median time from symptom onset to randomization increased progressively across dosing cohorts and was 171 to 174 minutes in cohort 1 compared with 234 to 256 minutes in cohort 4. The maximum degree of ST elevation before PCI also increased progressively across dosing cohorts, ranging from 584 (20851 481, 900) to 700 (900 456, 900).

Procedural Characteristics and Results
The median total ischemia time (time from symptom onset to reestablishment of flow with PCI) increased progressively across dosing cohorts (Table 2). Median total ischemia times were longer in the active study drug groups compared with concurrent placebo groups in cohorts 3 (299 versus 211 minutes) and 4 (286 versus 248 minutes), respectively. The culprit lesion was located in the proximal LAD in approximately one third of patients, and the proportion of patients with significant visible collaterals to the LAD distribution varied from 23% to 62%. Glycoprotein IIb/IIIa inhibitors were administered to the majority of patients during PCI. Antegrade flow was successfully reestablished in all patients according to the investigators’ reports, and all patients received both doses of study drug. Post-PCI corrected TIMI frame count results were similar across dosing cohorts, whereas the proportion of patients with normal TIMI myocardial perfusion grade 3 was nonsignificantly higher with active study drug compared with placebo in cohorts 2 and 3. Coronary flow reserve measurements were similar among patients treated with active study drug versus those treated with concurrent placebo in each dosing cohort.

Safety Results
No serious adverse events occurred that required early termination of study drug during the PCI procedure for any given patient or modification of the protocol on the basis of ongoing adverse events.
Among the pooled populations, the median maximum change in the QT interval from baseline until after the second dose of study drug was 16.9 ms for patients treated with active study drug versus 15.3 ms for those treated with placebo ($P=0.83$). Assessment of changes in clinical laboratory values, including complete blood counts, white blood cell count differentials, electrolytes, blood urea nitrogen, creatinine, and liver hepatic function tests, yielded no significant findings.

### Table 2. Procedural Characteristics by Concurrent Placebo*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (0.05 mg)</th>
<th>Cohort 2 (0.5 mg)</th>
<th>Cohort 3 (1.25 mg)</th>
<th>Cohort 4 (5.0 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active Drug (n=23)</td>
<td>Placebo (n=14)</td>
<td>Active Drug (n=25)</td>
<td>Placebo (n=13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active Drug (n=26)</td>
<td>Placebo (n=12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Active Drug (n=28)</td>
<td>Placebo (n=13)</td>
</tr>
<tr>
<td>Procedural timing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital arrival to flow reestablished, min†</td>
<td>134 (108, 144)</td>
<td>102 (85, 120)</td>
<td>97 (66, 129)</td>
<td>90 (67, 129)</td>
</tr>
<tr>
<td>Symptom onset to flow reestablished, min†</td>
<td>194 (165, 252)</td>
<td>192 (158, 224)</td>
<td>220 (156, 245)</td>
<td>202 (142, 260)</td>
</tr>
<tr>
<td>Procedural features‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal LAD lesion, %</td>
<td>39.1</td>
<td>21.4</td>
<td>28.0</td>
<td>23.1</td>
</tr>
<tr>
<td>LAD Rentrop collateral score 2/3, %</td>
<td>43.5</td>
<td>23.1</td>
<td>52.0</td>
<td>61.5</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor used during PCI, %</td>
<td>87.0</td>
<td>92.9</td>
<td>92.0</td>
<td>84.6</td>
</tr>
<tr>
<td>Thrombectomy device used during PCI, %</td>
<td>0</td>
<td>7.1</td>
<td>12.0</td>
<td>0</td>
</tr>
<tr>
<td>IABP inserted, %</td>
<td>8.7</td>
<td>0</td>
<td>8.0</td>
<td>0</td>
</tr>
<tr>
<td>DES used during PCI, %</td>
<td>78.3</td>
<td>85.7</td>
<td>76.0</td>
<td>61.5</td>
</tr>
<tr>
<td>Post-PCI angiography§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TIMI flow grade, %</td>
<td>0–1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>27.3</td>
<td>18.2</td>
<td>30.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>72.7</td>
<td>91.7</td>
<td>81.8</td>
</tr>
<tr>
<td>cTFC, frames/min‡</td>
<td>21.8 (17.7, 27.7)</td>
<td>21.8 (13.5, 27.1)</td>
<td>20.3 (15.9, 24.1)</td>
<td>20.9 (12.9, 56.5)</td>
</tr>
<tr>
<td>TMPG, %</td>
<td>0–1</td>
<td>40.0</td>
<td>27.3</td>
<td>27.8</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>60.0</td>
<td>72.7</td>
<td>72.2</td>
</tr>
<tr>
<td>Coronary flow reserve†</td>
<td>1.2 (1.0, 1.5)</td>
<td>1.3 (1.1, 1.3)</td>
<td>1.1 (1.0, 1.5)</td>
<td>1.0 (1.0, 1.1)</td>
</tr>
</tbody>
</table>

GP indicates glycoprotein; IABP, intraaortic balloon pump; DES, drug-eluting stent; cTFC, corrected TIMI frame count; and TMPG, TIMI myocardial perfusion grade.

*All comparisons for active study drug vs concurrent placebo within each dosing cohort were not significant ($P>0.05$).

†Median values with 25th, 75th percentiles.

‡Angiographic characteristics, such as proximal lesion location and collateral score, assessed from the baseline angiogram performed before PCI. According to the treating physician, antegrade flow was successfully reestablished in all patients, and all patients received both doses of study drug.

§Angiographic results obtained during post-PCI angiography performed 30 minutes after reestablishment of antegrade flow in the LAD before the protocol-designated intracoronary administration of adenosine to estimate coronary flow reserve. Coronary flow reserve was determined after assessment of the other angiographic parameters by measuring cTFC before and after administration of 18 to 24 μg of intracoronary adenosine. All results are reported for the LAD only.

‖No patients were found to have TMPG 2 during post-PCI angiography.
function tests from baseline through 48 hours, demonstrated no differences between active study drug versus placebo. The incidence of serious adverse events through 30 days was 15.4% for pooled placebo and varied across active study drug cohorts (cohort 1, 30.4%; cohort 2, 16.0%; cohort 3, 19.2%; and cohort 4, 35.7%), but no significant differences were demonstrated ($P < 0.13$ for trends across the active study drug groups compared with placebo). The majority of serious adverse events were cardiac disorders that were also captured as clinical events such as CHF, reinfarction, and cardiogenic shock.

### Table 3. Serious Adverse Events by Pooled Placebo

<table>
<thead>
<tr>
<th>System Organ Class*</th>
<th>Placebo (n=52)</th>
<th>Cohort 1 (0.05 mg; n=23)</th>
<th>Cohort 2 (0.5 mg; n=25)</th>
<th>Cohort 3 (1.25 mg; n=26)</th>
<th>Cohort 4 (5.0 mg; n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any serious adverse event</td>
<td>8 (15.4)</td>
<td>7 (30.4)</td>
<td>4 (16.0)</td>
<td>5 (19.2)</td>
<td>10 (35.7)</td>
</tr>
<tr>
<td>Blood and lymphatic disorders</td>
<td>0</td>
<td>1 (4.3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>4 (7.7)</td>
<td>6 (26.1)</td>
<td>2 (8.0)</td>
<td>2 (7.7)</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>1 (1.9)</td>
<td>1 (4.3)</td>
<td>1 (4.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>1 (1.9)</td>
<td>0</td>
<td>0</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>0</td>
<td>1 (4.3)</td>
<td>1 (4.0)</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3.8)</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>1 (1.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>0</td>
<td>0</td>
<td>1 (4.0)</td>
<td>1 (3.8)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>0</td>
<td>0</td>
<td>1 (4.0)</td>
<td>1 (3.8)</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>1 (1.9)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (3.6)</td>
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<tr>
<td>Vascular disorders</td>
<td>0</td>
<td>1 (4.3)</td>
<td>0</td>
<td>0</td>
<td>1 (3.6)</td>
</tr>
</tbody>
</table>

*Data are displayed as n (%).

*All serious adverse events were coded to a common dictionary (MedDRA). All comparisons between each dose of active study drug vs pooled placebo were nonsignificant ($P > 0.05$).

### Biomarkers of Cellular Recovery and Myocardial Necrosis

The median percentage of ST resolution at 60 minutes varied from 59% to 71% and was nonsignificantly higher with active study drug compared with concurrent placebo in each cohort, whereas the time to stable ST recovery was nonsignificantly more rapid with active study drug in cohorts 2 and 3 (Table 4). When both the extent and speed of ST recovery were integrated, ST-segment AUC values were nonsignificantly lower with active study drug in each cohort, except for the

### Table 4. Biomarkers of Cellular Recovery and Myocardial Necrosis by Concurrent Placebo*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (0.05 mg)</th>
<th>Cohort 2 (0.5 mg)</th>
<th>Cohort 3 (1.25 mg)</th>
<th>Cohort 4 (5.0 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST recovery at 60 min, %‡</td>
<td>65.8 (51.0, 80.7)</td>
<td>66.6 (51.9, 82.1)</td>
<td>62.2 (51.7, 75.8)</td>
<td>71.4 (49.4, 84.5)</td>
</tr>
<tr>
<td>Time to stable ST recovery, min‡</td>
<td>60.0 (41.0, 91.5)</td>
<td>51.5 (28.0, 105.0)</td>
<td>45.5 (21.0, 89.0)</td>
<td>88.5 (49.5, 111.5)</td>
</tr>
<tr>
<td>ST recovery AUC–3 h, V/min‡</td>
<td>5549 (4193, 8003)</td>
<td>6956 (4635, 8930)</td>
<td>6459 (4642, 8813)</td>
<td>8540 (5677, 11991)</td>
</tr>
<tr>
<td>Cardiac markers§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated peak CK-MB, ng/mL‡</td>
<td>261 (149, 422)</td>
<td>345 (181, 544)</td>
<td>289 (183, 445)</td>
<td>386 (200, 488)</td>
</tr>
<tr>
<td>CK-MB AUC, ng/ml·h‡</td>
<td>4001 (2597, 6921)</td>
<td>4858 (3677, 7328)</td>
<td>5226 (3420, 7416)</td>
<td>6934 (3446, 9394)</td>
</tr>
</tbody>
</table>

*All comparisons for active study drug vs concurrent placebo within each dosing cohort were not significant ($P > 0.05$) except for ST recovery AUC–3 h in cohort 4, in which the difference between active study drug vs concurrent placebo was significant ($P = 0.04$).

†Timing for ST-segment recovery analyses began at the time of last contrast injection after post-PCI angiography and was determined with the Kaplan–Meier method.

‡Median values with 25th, 75th percentiles.

§Cardiac markers sampled 5 times during the first 36 hours after randomization.
fourth dosing cohort, in which the difference was significant ($P=0.04$). Among the pooled active study drug and placebo populations, the median ST recovery AUC values were 8727 μV/min for placebo versus 5735 μV/min for active study drug ($P=0.005$), whereas the cumulative distribution frequencies demonstrated a separation of ST-recovery AUC curves among patients with higher values (Figure 2B).

Estimated peak CK-MB values and CK-MB (AUC) values were nonsignificantly lower with active study drug in each dosing cohort. Among the pooled active study drug and placebo populations, the median CK-MB AUC values were 6463 ng/mL×h for placebo versus 5571 ng/mL×h for active study drug ($P=0.27$), whereas the cumulative distribution frequencies demonstrated a separation of CK-MB AUC curves among patients with values between 5000 and 10 000 ng/mL×h (Figure 2A).

**Biomarkers of Residual Infarct Size and Left Ventricular Contractility**

Infarct size values determined with 99mtechnetium sestamibi were nonsignificantly lower with active study drug compared with concurrent placebo for cohorts 1, 2, and 3 and nonsignificantly higher with active study drug in cohort 4 (Table 5). Ejection fraction and LAD-specific wall motion score values were similar between active study drug versus concurrent placebo within each cohort. Among the pooled active study drug and placebo populations, the median infarct size values were 31.5% for placebo versus 30.0% for active study drug ($P=0.96$) when all available infarct size data were analyzed. When infarct size values collected only during the protocol-specified time window (10 to 35 days) were analyzed, the median infarct size values were 33% for pooled placebo versus 26% for pooled active study drug populations.

**Clinical End Points**

Among the entire population, 6 deaths and 28 investigator-reported CHF events occurred through 6 months (Table 6). A total of 4 deaths and 24 CHF events occurred during the initial hospitalization. A total of 9 of the 21 CHF events in the active study drug group occurred in patients who had CHF on presentation (Killip class II or III), whereas no patients with CHF events in the placebo group had CHF on presentation. However, 12% of the pooled active study drug patients presented in Killip class II or III versus 4% in the pooled placebo group. The 6-month mortality rates in the pooled active study drug and placebo groups were 3% versus 6%, respectively.

**Discussion**

We have demonstrated in this first-in-human study that, when administered via intracoronary injection during primary PCI for STEMI, KAI-9803, a δ-PKC inhibitor, had an acceptable safety and tolerability profile. Despite significant differences in patient clinical and presentation characteristics across dosing cohorts in this small, exploratory study, consistent but nonsignificant improvements in CK-MB AUC, ST-recovery AUC, and 99mtechnetium sestamibi infarct size values with active study drug compared with concurrent placebo (except for infarct size values with the 5.0-mg dose) suggest signs of potential drug activity that warrant further exploration (Figure 3).

**Use of Biomarkers of Reperfusion Success**

Studies that have used multiple simultaneous biomarkers of reperfusion success suggest that biomarker arrays provide a more comprehensive approach for the initial evaluation of adjunctive therapies for STEMI, both by enhancing information content and retrieval and by overcoming the loss of data that occurs when individual biomarkers are used. We used multiple biomarkers of reperfusion success in the DELTA MI trial to evaluate the potential drug activity of KAI-9803, but we did not demonstrate consistent signs of drug activity across the array of biomarkers evaluated for this study, a finding that serves to highlight several important points for designing clinical trials that use biomarkers of reperfusion success. First, despite inclusion and exclusion criteria in DELTA MI that were designed to define a very specific, homogeneous patient population, factors that significantly influence biomarker end points (including total ischemia time before reperfusion, diabetes mellitus, prodromal angina before presentation, and collaterals to the LAD distribution) varied substantially among active study drug versus concurrent placebo across dosing cohorts and influenced the evaluation of drug activity with the biomarker results.
All available data were analyzed. Patients with missing data were not included in these analyses, and no data imputations were performed.

**Echocardiography**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (0.05 mg)</th>
<th>Cohort 2 (0.5 mg)</th>
<th>Cohort 3 (1.25 mg)</th>
<th>Cohort 4 (5.0 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>22</td>
<td>22</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Infarct size, %</td>
<td>25.5 (15.0, 43.0)</td>
<td>21.0 (11.0, 35.0)</td>
<td>33.0 (18.0, 39.0)</td>
<td>47.0 (8.0, 58.0)</td>
</tr>
<tr>
<td>of left ventricle</td>
<td>33.5 (7.0, 56.0)</td>
<td>26.0 (7.0, 38.0)</td>
<td>43.0 (7.0, 55.0)</td>
<td>30.0 (17.5, 41.0)</td>
</tr>
</tbody>
</table>

**Dose–Response Relationship**

Although KAI-9803 showed signs of potential drug activity in this early-phase trial, we did not demonstrate a dose–response relationship with escalating doses. Several explanations for this observation are possible. First, significant changes in patient recruitment, patient clinical characteristics, and presentation characteristics across the dosing cohorts limited comparisons among dose levels. Second, the initial dose tested (0.02 mg) during the first of the 2 injections in cohort 1 was equivalent to the dose used in the preclinical experiments that led to a substantial reduction in infarct size, and therefore higher doses may not have led to incremental benefit but were tested to ensure safety and tolerability with dose escalation. Finally, the prolonged total ischemia times in the later dosing cohorts were associated with progressively worse biomarker results in the placebo-treated patients across dosing cohorts (Tables 4 and 5, Figure 3). Because myocardial salvage and mortality reduction have been shown to be maximized when reperfusion occurs within the first 4 hours after symptom onset, there may be a “window of therapeutic opportunity” for an adjunctive therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Active Drug</th>
<th>Placebo</th>
<th>Active Drug</th>
<th>Placebo</th>
<th>Active Drug</th>
<th>Placebo</th>
<th>Active Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK-MB AUC</td>
<td>(2.0, 2.3)</td>
<td>(1.9, 2.3)</td>
<td>(2.0, 2.3)</td>
<td>(1.9, 2.3)</td>
<td>(2.0, 2.3)</td>
<td>(1.9, 2.3)</td>
<td>(2.0, 2.3)</td>
<td>(1.9, 2.3)</td>
</tr>
</tbody>
</table>

**Table 6. Six-Month Status and Clinical Outcomes by Concurrent Placebo***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (0.05 mg)</th>
<th>Cohort 2 (0.5 mg)</th>
<th>Cohort 3 (1.25 mg)</th>
<th>Cohort 4 (5.0 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost to follow-up</td>
<td>1 (4.3)</td>
<td>1 (4.0)</td>
<td>0</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>1 (4.3)</td>
<td>0</td>
<td>1 (5.8)</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (7.1)</td>
<td>1 (4.2)</td>
<td>0</td>
</tr>
<tr>
<td>CHF</td>
<td>8 (34.8)</td>
<td>2 (14.3)</td>
<td>4 (16.2)</td>
<td>2 (15.4)</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (7.7)</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>1 (4.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

Dose–Response Relationship

Although KAI-9803 showed signs of potential drug activity in this early-phase trial, we did not demonstrate a dose–response relationship with escalating doses. Several explanations for this observation are possible. First, significant changes in patient recruitment, patient clinical characteristics, and presentation characteristics across the dosing cohorts limited comparisons among dose levels. Second, the initial dose tested (0.02 mg) during the first of the 2 injections in cohort 1 was equivalent to the dose used in the preclinical experiments that led to a substantial reduction in infarct size, and therefore higher doses may not have led to incremental benefit but were tested to ensure safety and tolerability with dose escalation. Finally, the prolonged total ischemia times in the later dosing cohorts were associated with progressively worse biomarker results in the placebo-treated patients across dosing cohorts (Tables 4 and 5, Figure 3). Because myocardial salvage and mortality reduction have been shown to be maximized when reperfusion occurs within the first 4 hours after symptom onset, there may be a “window of therapeutic opportunity” for an adjunctive therapy

**Table 5. Biomarkers of Residual Infarct Size and Left Ventricular Contractility by Concurrent Placebo***

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (0.05 mg)</th>
<th>Cohort 2 (0.5 mg)</th>
<th>Cohort 3 (1.25 mg)</th>
<th>Cohort 4 (5.0 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>22</td>
<td>22</td>
<td>25</td>
<td>22</td>
</tr>
<tr>
<td>Ejection fraction, %†</td>
<td>45.3 (42.4, 48.2)</td>
<td>38.9 (34.3, 45.2)</td>
<td>34.2 (32.4, 38.2)</td>
<td>33.3 (29.2, 37.5)</td>
</tr>
<tr>
<td>LAD-specific wall motion score†</td>
<td>2.1 (1.7, 2.2)</td>
<td>2.0 (1.7, 2.3)</td>
<td>2.2 (1.8, 2.3)</td>
<td>2.0 (2.0, 2.3)</td>
</tr>
</tbody>
</table>

SPECT indicates single photon emission computed tomography.

*All comparisons for active study drug vs concurrent placebo within each dosing cohort were not significant (P>0.05). Number of patients with analyzable data during the follow-up period is listed above each section. Patients with missing data were not included in these analyses, and no data imputations were performed. All available data were analyzed.

†Median values with 25th, 75th percentiles.

Data are displayed as n (event rate percentage). Percentages were determined by the Kaplan–Meier method. TVR indicates target vessel revascularization.

*A total of 5 patients were lost to follow-up, and 2 patients withdrew consent.
such as KAI-9803, beyond which irreversible myocardial damage may have occurred that cannot be ameliorated.19,21,22 As a result, the potential impact of larger doses of KAI-9803 tested in the later dosing cohorts may have been confounded by longer total ischemia times observed among patients treated with active study drug in cohorts 3 and 4 compared with the respective concurrent placebo patients in these cohorts (Table 2).

**Limitations**

The present study has many limitations. First, this study was not powered to detect a difference in safety, biomarker, or clinical end points, and therefore the small sample sizes in each dosing cohort prevented definitive conclusions on the safety, tolerability, and signs of drug activity of KAI-9803 in this exploratory study. Second, nonfatal clinical end points were investigator reported and not independently adjudicated, and therefore CHF and reinfarction event rates are not comparable with prior studies in which event rates were rigorously adjudicated. Because most of the CHF events occurred during the initial hospitalization, signs of CHF on presentation and fluid shifts related to the initial PCI procedure may have influenced reporting of CHF events by investigators. Finally, because of inadequate images in some patients, ≈11% of patients treated with study drug did not have 99mtechnetium sestamibi infarct size data that could be evaluated, and because of early deaths and patients lost to follow-up, 7 patients could not be fully accounted for in the 6-month clinical end-point analyses.

**Future Directions**

By targeting a precise molecular pathway involved in the myocardial and endothelial intracellular response to ischemia and reperfusion for patients with STEMI, δ-PKC inhibition with KAI-9803 represents a novel myocardial protection approach designed to optimize the results of reperfusion therapy with primary PCI.23,24 On the basis of the favorable safety and tolerability profile and potential signs of drug activity of KAI-9803 observed in this small, exploratory study, further testing in an adequately powered clinical trial is warranted to accurately determine the safety and therapeutic potential of this agent. Experiences gained from this first-in-human study will help to identify the preferred inclusion criteria, study drug dose and route of administration, safety end points, and biomarker end points for use in a definitive clinical trial.

**Appendix**

**DELTA MI Trial Participants**

**Steering and Writing Committee**

Eric Bates, Christoph Bode, Marco Costa, C. Michael Gibson, Christopher Granger, Cindy Green, Kevin Grimes (sponsor representative), Robert Harrington, Kurt Huber, Neal Kleiman, Daria Mochly-Rosen (sponsor representative), Matthew Roe (principal investigator), Zygmunt Sadowski, Scott Solomon, Petr Widimsky.

**Data Monitoring Committee**

Thomas Fleming, Mark Hlatky, Spencer King (chairman).

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ST Monitoring
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Single Photon Emission Computed Tomography Nuclear Imaging
SPECT Mayo Core Laboratory, Rochester, Minn: Ray Gibbons (director).

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Disclosures
The following disclosures have been reported: M.T. Roe, research grants and consultant (KAI Pharmaceuticals); K. Grimes: employee and stock options (KAI Pharmaceuticals); C. Green: research grants (KAI Pharmaceuticals); C.B. Granger: research grants (KAI Pharmaceuticals); C.M. Gibson: research grants (KAI Pharmaceuticals); S. Solomon: research grants (KAI Pharmaceuticals); D. Mochly-Rosen: member of board of directors, stock options (KAI Pharmaceuticals); R.A. Harrington: research grants (KAI Pharmaceuticals); E. Bates, N. Kleiman, C. Bode, K. Huber, M. Costa, P. Widimsky, and Z. Sadowski report no conflicts.

References


**CLINICAL PERSPECTIVE**

KAI-9803, a δ-protein kinase C inhibitor, reduced infarct size, enhanced early recovery of regional left ventricular contractility, and improved microvascular function in animal models of acute myocardial infarction. The safety, tolerability, and activity of escalating intracoronary doses of KAI-9803 were evaluated among patients with acute ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention in the “first-in-human” Direct Inhibition of δ-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTAM) trial. A total of 154 patients who had an occluded left anterior descending infarct artery on angiography were randomized in a 2:1 fashion and received 1 of 4 doses of KAI-9803 (cohort 1, 0.05 mg; cohort 2, 0.5 mg; cohort 3, 1.25 mg; cohort 4, 5.0 mg) versus blinded concurrent placebo delivered in 2 divided doses via intracoronary injection before and after reestablishment of antegrade epicardial flow with percutaneous coronary intervention. The incidence of serious adverse events and other safety end points was similar between patients treated with KAI-9803 versus placebo. Although the study was not powered to demonstrate efficacy with the biomarker end points assessed, signs of drug activity with KAI-9803 were suggested by trends for consistent, nonsignificant reductions in cardiac marker elevations, ST-segment recovery, and technetium sestamibi infarct size values across dosing cohorts with KAI-9803. Thus, KAI-9803 had an acceptable safety and tolerability profile when delivered via intracoronary injection during primary percutaneous coronary intervention for ST-segment elevation myocardial infarction, and signs of potential drug activity were demonstrated with biomarker end points in this small exploratory study.
Intracoronary KAI-9803 as an Adjunct to Primary Percutaneous Coronary Intervention for Acute ST-Segment Elevation Myocardial Infarction
Direct Inhibition of d-Protein Kinase C Enzyme to Limit Total Infarct Size in Acute Myocardial Infarction (DELTA MI) Investigators

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