Safety and Tolerability of Atopaxar in the Treatment of Patients With Acute Coronary Syndromes

The Lessons From Antagonizing the Cellular Effects of Thrombin–Acute Coronary Syndromes Trial

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Background—Atopaxar (E5555) is a reversible protease-activated receptor-1 thrombin receptor antagonist that interferes with platelet signaling. The primary objective of the Lessons From Antagonizing the Cellular Effects of Thrombin–Acute Coronary Syndromes (LANCELOT—ACS) trial was to evaluate the safety and tolerability of atopaxar in patients with ACS.

Methods and Results—Six hundred and three subjects were randomized within 72 hours of non–ST-elevation ACS to 1 of 3 doses of atopaxar (400-mg loading dose followed by 50, 100, or 200 mg daily) or matching placebo. The incidence of Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) major or minor bleeding did not differ significantly between the combined atopaxar and placebo groups (3.08% versus 2.17%, respectively; P=0.63), and there was no dose-related trend (P=0.80). The incidence of CURE major bleeding was numerically higher in the atopaxar group compared with the placebo group (1.8% versus 0%; P=0.12). The incidence of cardiovascular death, myocardial infarction, stroke, or recurrent ischemia was similar between the atopaxar and placebo arms (8.03% versus 7.75%; P=0.93). The incidence of CV death, MI, or stroke was 5.63% in the placebo group and 3.25% in the combined atopaxar group (P=0.20). Dose-dependent trends for efficacy were not seen. Atopaxar significantly reduced ischemia on continuous ECG monitoring (Holter) at 48 hours compared with placebo (relative risk, 0.67; P=0.02). Transient dose-dependent transaminase elevation and relative QTc prolongation were observed with the highest doses of atopaxar.

Conclusion—In patients after ACS, atopaxar significantly reduced early ischemia on Holter monitoring without a significant increase in major or minor bleeding. Larger trials are required to fully establish the efficacy and safety of atopaxar.

Clinical Trial Registration—URL: http://www.ClinicalTrials.gov. Unique identifier: NCT00548587.

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Key Words: acute coronary syndrome ■ clinical trials ■ receptor, PAR-1 ■ therapeutics

Platelet activation plays a central role in the development of atherothrombosis. To that end, therapies that inhibit platelet activation remain the cornerstone of treatment for patients with acute coronary syndromes (ACS). Although such treatments have been shown to reduce the risk of recurrent cardiovascular events, existing antiplatelet drugs have several limitations. In particular, they may increase the risk of bleeding and may exhibit...
significant interindividual variability in pharmacodynamic response.6

Editorial see p 1833
Clinical Perspective on p 1853

Thrombin has been identified as the most potent physiologic platelet agonist,7 and its production is increased after ACS.8 Thrombin can stimulate platelet activation via the protease-activated receptor-1 (PAR-1) receptor on the platelet cell surface. Because aspirin and P2Y12 receptor antagonists do not interfere with PAR-1–dependent platelet activation, patients on standard dual antiplatelet therapy remain at risk of recurrent cardiovascular events because of alternative pathways of platelet activation.

Atopaxar (E5555) is an orally active, reversible, small-molecule inhibitor that selectively inhibits PAR-1 activation by binding at or near the tethered ligand binding site. Because atopaxar selectively interferes with thrombin-mediated platelet activation without disrupting thrombin-dependent fibrin generation or ADP-dependent platelet activation, atopaxar may provide a therapeutic option with diminished risk of bleeding compared with traditional antithrombotic and antiplatelet drugs.

The primary objective of the multicenter, international, phase II Lessons From Antagonizing the Cellular Effects of Thrombin (LANCELOT)—ACS trial was to evaluate the safety and tolerability of atopaxar in patients after ACS. This trial was conducted in parallel with LANCELOT—CAD, a phase II trial of atopaxar in patients with stable coronary artery disease.

Methods
Study Design and Participants
The LANCELOT—ACS trial was a randomized, double-blind, placebo-controlled phase II trial. The study enrolled 603 subjects at 184 sites in 22 countries between March 17, 2008, and June 9, 2009. Subjects were eligible for enrollment if they were between 18 and 80 years of age and had been hospitalized in the past 72 hours with signs and symptoms consistent with non–ST-elevation ACS (unstable angina or myocardial infarction [MI] without persistent ST-segment elevation). All subjects were required to have new onset or a recent history of ischemic stroke or transient ischemic attack (<1 minute and was separated from other episodes by ≥1 minute. The data were combined across active treatment arms because a common loading dose was used in all groups.

Platelet Function Testing
Platelet aggregation was assessed by light transmission aggregometry with the PAP-8 aggregometer (BioData Corp, Hatboro, PA) at selected study sites by a specially trained, independent, blinded technician. Thrombin receptor–activating peptide 15 selected study sites by a specially trained, independent, blinded technician. Thrombin receptor–activating peptide 15

Electrocardiographic Monitoring
A 12-lead ECG was performed at all study visits and reviewed centrally. Continuous 12-lead ECG (Holter) monitoring was to be performed in all subjects for the first 48 hours after randomization or until hospital discharge, whichever came first. The data were forwarded to a core laboratory for analysis (Biomedical Systems, Brussels, Belgium) and then overread by at least 2 independent cardiologists who were blinded to the treatment assignment. Recurrent ischemia by continuous ECG monitoring was defined as horizontal or downsloping ST-segment depression ≥0.1 mV below the baseline or upward ST-segment elevation ≥0.1 mV above the baseline that lasted ≥1 minute and was separated from other episodes by ≥1 minute. The data were combined across active treatment arms because a common loading dose was used in all groups.

Platelet Function Testing
Platelet aggregation was assessed by light transmission aggregometry with the PAP-8 aggregometer (BioData Corp, Hatboro, PA) at selected study sites by a specially trained, independent, blinded technician. Thrombin receptor–activating peptide 15 μmol/L was the primary agonist used at serial time points. Tracings were verified by...
Clinical Outcomes

The primary safety endpoint was the proportion of subjects with major bleeding according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) bleeding classification (defined as significantly disabling bleeding, bleeding requiring ≥2 U of red blood cells or equivalent, intracranial or intraocular hemorrhage, bleeding requiring inotropes or surgical intervention, or bleeding leading to death) up to 12 weeks of treatment. CURE minor bleeding was defined as hemorrhage not meeting the CURE definition for major bleeding and leading to the interruption of study drug.

Bleeding endpoints were also classified according to the Thrombolysis in Myocardial Infarction (TIMI) bleeding definitions (major, minor, or minimal). Secondary objectives included the effects of atopaxar on major adverse cardiovascular events, including cardiovascular death, MI, stroke, or recurrent ischemia; on platelet function; and on Holter-detected ischemia. Recurrent ischemia was defined as discomfort considered to be probable or definite angina lasting at least 10 minutes (ECG changes were not required). All clinical endpoints were adjudicated by a Clinical Endpoints Committee that was blinded to treatment assignment. Assuming a 5.3% incidence of any CURE bleeding, the trial had 80% power to detect a 50% increase in bleeding with the combined atopaxar group compared with placebo.

Statistical Analysis

Baseline characteristics are presented as means (SDs) or counts and percentages. The incidence of safety and efficacy events is reported per subject. No subjects in the placebo or 50 mg dose arms were affected.

Results

Six hundred and three subjects were randomized to 1 of 4 treatment arms, and 593 subjects took at least 1 dose of study drug (Figure 2). The baseline characteristics of the study population were relatively comparable between the placebo and combined active treatment arms (Table 1). Imbalances were observed for the incidence of prior MI and peripheral arterial disease across the individual dose groups, but the incidence rates were similar between the active combined and placebo groups. The mean age of the subjects was 62 years, and 32% were women. The qualifying event was non-ST-elevation MI in 77% of subjects; ~43% of subjects underwent percutaneous coronary intervention, 96% were treated with aspirin, and 82% were treated with clopidogrel or ticlopidine. The use of evidence-based therapies during the course of the trial, including aspirin, thienopyridines, statins, and β-blockers, was similar across the treatment groups (Table 1).

Bleeding Outcomes

Eight adjudicated major bleeds and 9 adjudicated minor bleeds, according to the CURE bleeding classification, occurred during 12 weeks of treatment. The incidence of CURE major or minor bleeding was similar between the combined atopaxar and placebo groups (3.1% [14 of 455] versus 2.2%
The incidence of CURE major bleeding was numerically higher in the atopaxar group compared with the placebo group (1.8% [8 of 455] versus 0% [0 of 138], respectively; P = 0.12). One hemorrhagic stroke occurred in the 100-mg dose group. The incidence of CURE minor bleeding was comparable between the combined atopaxar and placebo groups (1.3% [6 of 455] versus 2.2% [3 of 138]), respectively; P = 0.58). Although subgroup sizes were small, there was no evidence of heterogeneity for subjects who were elderly (≥75 years of age; n = 70), were women (n = 188), or had a reduced creatinine clearance (<60 mL/min; n = 97).

There were no significant differences between the combined active atopaxar and placebo groups in the individual categories of major, minor, minimal, or instrumented bleeds according to the TIMI bleeding criteria (Table 2). The proportion of subjects who experienced any type of bleeding event according to the TIMI classification did not differ between the combined atopaxar and placebo arms (8.0% [37 of 461] versus 7.8% [11 of 142], respectively; P = 0.93), and there was no dose-dependent trend (P = 0.26; Figure 4). The proportion of subjects who experienced cardiovascular death, MI, stroke, or recurrent ischemia did not differ between the combined atopaxar and placebo arms (8.0% [37 of 461] versus 7.8% [11 of 142], respectively; P = 0.93), and there was no dose-dependent trend (P = 0.26; Figure 3).
cardiovascular death, MI, or stroke was numerically lower in the combined active atopaxar group compared with placebo (3.3% [15 of 461] versus 5.6% [8 of 142]; P=0.20; Figure 4); however, this difference was not statistically significant. Analyses excluding subjects affected by the resupply error and the person-time major adverse cardiovascular events incidence analysis suggested that there was no significant impact of the resupply error on these analyses.

Continuous ECG monitoring by Holter was performed in 561 of randomized subjects (93%). There was a statistically significant 34% reduction in Holter-detected ischemia in the combined active atopaxar treatment groups versus placebo (relative risk, 0.67; 95% confidence interval, 0.48 to 0.94; P=0.02) during the first 48 hours after the 400-mg loading dose.

**Figure 3.** The incidence of bleeding according to the (A) Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) and (B) Thrombolysis in Myocardial Infarction (TIMI) bleeding classifications in the safety population up to week 12. The relative risks (RRs) and 95% confidence intervals (95% CIs) are provided compared with placebo.

**Platelet Function Testing**

A total of 63 patients were enrolled in the platelet function substudy and had an interpretable predose (baseline) aggregation result (Figure 5). Inhibition of platelet aggregation in response to 15 μmol/L thrombin receptor–activating peptide agonist was observed in the first 1 to 3 hours after the loading dose in all active atopaxar treatment groups (mean inhibition of platelet aggregation, 74%). At 3 to 6 hours after the loading dose, 90% to 100% subjects in the atopaxar groups had achieved >80% inhibition of platelet aggregation. During maintenance dosing, a trend toward greater dose-dependent inhibition of platelet aggregation was observed with increasing doses of drug. At week 12, the predose mean inhibition of platelet aggregation was 66.5%, 71.5%, and 88.9% in the 50-, 100-, and 200-mg groups, respectively (P for trend=0.07).
Adverse Effects

A similar percentage of subjects discontinued study drug in the combined active atopaxar treatment group and the placebo group (28.9% and 31.0%, respectively). The proportion of subjects who reported at least 1 adverse event was similar in the combined active atopaxar treatment group and the placebo group (67.3% and 68.1%, respectively). The most commonly reported treatment-related adverse effects were gastrointestinal disorders (6.6% in the combined atopaxar versus 5.8% in the placebo arm), including nausea, constipation, and abdominal pain.

Transient liver function abnormalities were observed in all groups (including placebo) at the time of the qualifying ACS event and resolved by week 2 of treatment. Overall, the incidence of liver function abnormalities did not differ between the combined atopaxar groups and placebo group. Clinically significant alanine aminotransferase elevations (>3 times upper limit of normal) after 2 weeks were recorded more frequently with the highest dose of atopaxar (2.2%, 2.2%, and 5.5% for the 50-, 100-, and 200-mg groups, respectively; P for trend = 0.14) compared with 2.5% in the placebo group (Table 4). Most liver function abnormalities occurred in the 200-mg arm between weeks 4 and 8 and resolved with continued therapy before week 12 (Figure 6).

There were no cases of Hy’s law, defined as alanine aminotransferase >3 times above the upper limit of normal and total bilirubin >2 times above the upper limit of normal.

During the treatment phase, there was an overall decrease in the mean QTcF (Fridericia’s formula) interval in both the placebo and atopaxar groups that was likely explained by relative QTcF prolongation at the time of the ACS. The mean decrease in the QTcF interval was greater in the placebo group than in the combined atopaxar group (11.4 versus 6.4 milliseconds, respectively; P = 0.04). This difference was driven mainly by a smaller decrease in the QTcF interval in the 100-mg (4.5 milliseconds) and 200-mg (4.9 milliseconds) groups compared with placebo. There were no known associated cases of syncope or malignant arrhythmias.

Median serum creatinine levels increased slightly throughout the treatment period in all groups, including the placebo group. The incidence of clinically significant abnormal serum creatinine values was similar for the atopaxar and placebo groups. The greatest median increase was observed in the 200-mg group. The median increase from day 4 to week 12 in

Table 2: The Incidence of Bleeding According to Clopidogrel in Unstable Angina to Prevent Recurrent Events and Thrombolysis in Myocardial Infarction Bleeding Classifications

<table>
<thead>
<tr>
<th>Category</th>
<th>Atopaxar (400-mg Loading Dose)</th>
<th>Placebo (N=138), n (%)</th>
<th>50 mg (N=153), n (%)</th>
<th>100 mg (N=156), n (%)</th>
<th>200 mg (N=146), n (%)</th>
<th>Combined Atopaxar (N=455), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any CURE-defined bleed</td>
<td></td>
<td>3 (2.2)</td>
<td>2 (1.3)</td>
<td>9 (5.8)</td>
<td>3 (2.1)</td>
<td>14 (3.1)</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>5 (3.2)</td>
<td>2 (1.4)</td>
<td>8 (1.8)</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
<td>4 (2.6)</td>
<td>1 (0.7)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Any TIMI-defined bleed</td>
<td></td>
<td>14 (10.1)</td>
<td>12 (7.8)</td>
<td>19 (12.2)</td>
<td>11 (7.5)</td>
<td>42 (9.2)</td>
</tr>
<tr>
<td>Major</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>4 (2.6)</td>
<td>2 (1.4)</td>
<td>6 (1.3)</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
<td>2 (1.3)</td>
<td>0 (0.0)</td>
<td>3 (0.7)</td>
</tr>
<tr>
<td>Minimal</td>
<td></td>
<td>13 (9.4)</td>
<td>11 (7.2)</td>
<td>13 (8.3)</td>
<td>9 (6.2)</td>
<td>33 (7.3)</td>
</tr>
<tr>
<td>TIMI instrumented bleed</td>
<td></td>
<td>10 (7.3)</td>
<td>9 (5.9)</td>
<td>9 (5.8)</td>
<td>2 (1.4)</td>
<td>20 (4.4)</td>
</tr>
<tr>
<td>RR vs placebo (95% CI)</td>
<td></td>
<td>0.81 (0.34–1.90)</td>
<td>0.80 (0.34–1.87)</td>
<td>0.19 (0.04–0.76)</td>
<td>0.61 (0.30–1.25)</td>
<td></td>
</tr>
</tbody>
</table>

CURE indicates Clopidogrel in Unstable Angina to Prevent Recurrent Events; TIMI, Thrombolysis in Myocardial Infarction; RR, relative risk; and CI, confidence interval.

Table 3: The Incidence of Major Adverse Cardiovascular Events by Treatment Arm up to Week 12

<table>
<thead>
<tr>
<th>Category</th>
<th>Atopaxar (400-mg Loading Dose)</th>
<th>Placebo (N=142), n (%)</th>
<th>50 mg (N=156), n (%)</th>
<th>100 mg (N=157), n (%)</th>
<th>200 mg (N=148), n (%)</th>
<th>Combined Atopaxar (N=461), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, MI, stroke, or recurrent ischemia</td>
<td></td>
<td>11 (7.8)</td>
<td>6 (3.9)</td>
<td>17 (10.8)</td>
<td>14 (9.5)</td>
<td>37 (8.0)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td></td>
<td>8 (5.6)</td>
<td>3 (1.9)</td>
<td>9 (5.7)</td>
<td>3 (2.0)</td>
<td>15 (3.3)</td>
</tr>
<tr>
<td>CV death</td>
<td></td>
<td>2 (1.4)</td>
<td>2 (1.3)</td>
<td>2 (1.3)</td>
<td>1 (0.7)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>MI</td>
<td></td>
<td>6 (4.2)</td>
<td>1 (0.6)</td>
<td>6 (3.8)</td>
<td>1 (0.7)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Recurrent ischemia</td>
<td></td>
<td>3 (2.1)</td>
<td>3 (1.9)</td>
<td>8 (5.1)</td>
<td>11 (7.4)</td>
<td>22 (4.8)</td>
</tr>
<tr>
<td>Recurrent ischemia requiring revascularization</td>
<td></td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>2 (1.3)</td>
<td>3 (2.0)</td>
<td>5 (1.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>1 (0.7)</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td></td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.6)</td>
<td>0 (0.0)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

CV indicates cardiovascular; MI, myocardial infarction. Subjects are counted only once per treatment in each category.
the placebo group ranged between 2 and 4 μmol/L; in the 50-mg arm, between 7 and 10 μmol/L; in the 100-mg arm, between 7 and 9 μmol/L; and in the 200-mg arm, between 9 and 13 μmol/L.

**Discussion**

The LANCELOT—ACS trial assessed the safety and tolerability of the novel PAR-1 inhibitor atopaxar (E5555) at 3 dose levels (50, 100, and 200 mg daily) after a 400-mg loading dose in patients after ACS. The results of this phase II trial demonstrated that atopaxar significantly reduced Holter-detected ischemia without a clear increase in bleeding compared with placebo. In a focused platelet function substudy, atopaxar achieved rapid and sustained platelet inhibition via the PAR-1 receptor. Although the drug was generally well tolerated, liver transaminase elevation and relative QTc prolongation were observed with the highest doses of atopaxar.

Atopaxar is a reversible and orally active small-molecule inhibitor that interferes with thrombin-mediated platelet activation via the PAR-1 receptor. In preclinical animal models, atopaxar significantly prolonged time to occlusion in injured arterial vessels and significantly inhibited neointimal hyperplasia in a balloon-injured carotid artery. It is hypothesized that PAR-1-mediated platelet activation might contribute to the formation of pathological thrombosis but may not be required for formation of the early platelet monolayer in appropriate hemostasis. Thus, it is plausible that PAR-1 antagonists might offer clinical benefit without significantly increasing the risk of bleeding. To that end, atopaxar has demonstrated potent antplatelet effects without increasing bleeding times in preclinical studies. Furthermore, atopaxar has previously been shown to inhibit the thrombin-mediated release of soluble CD40 ligand from the platelet while allowing ADP-mediated pathways to remain intact.

Vorapaxar (SCH 530348), another oral PAR-1 receptor antagonist, is being evaluated in 2 phase III trials, the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Atherosclerosis (TRA 2°P-TIMI 50; NCT00526474) and the Trial to Assess the Effects of SCH 530348 in Preventing Heart Attack and Stroke in Patients With Acute Coronary Syndrome (TRA-CER; NCT00527943). In January 2011, the joint Data and Safety Monitoring Board for the 2 trials reported an excess of intracranial hemorrhage in patients with a history of stroke. As a consequence, study drug was discontinued in the TRA 2°P-TIMI 50 trial for subjects with a history of stroke, but remains ongoing for subjects with a history of MI or peripheral arterial disease. The TRACER trial was stopped prematurely after reaching its prespecified number of primary endpoints. Although vorapaxar and atopaxar share similarities, vorapaxar exhibits a much longer half-life (165 to 311 hours) and achieves 50% recovery of platelet function at 4 weeks after treatment discontinuation. In contrast, atopaxar has an approximate plasma half-life of 22 to 26 hours. Although future evaluation is required, the shorter half-life for atopaxar could offer a theoretical advantage for patients requiring urgent surgery or for those who are actively bleeding. The current phase II trial is underpowered for safety events, including intracranial hemorrhage. A large clinical outcomes study will be required before the safety of atopaxar can be adequately ascertained.

In the LANCELOT—ACS trial, the overall rate of bleeding was lower than anticipated. No major bleeding events occurred in the placebo group despite the use of standard antithrombotic and antiplatelet therapy for patients with ACS. This result notwithstanding, the overall incidence of bleeding was similar between the placebo and combined atopaxar treatment groups. The frequency of CURE major bleeds was numerically higher in the combined atopaxar group compared with placebo, but the frequency of minor or instrumented bleeds was lower for patients on atopaxar than in the placebo arm; these differences did not achieve statistical significance.

Because the LANCELOT—ACS trial was not powered to assess clinical efficacy, the efficacy data should be inter-
preted with caution. The overall incidence of cardiovascular death, MI, stroke, or recurrent ischemia was similar for patients treated with atopaxar and placebo. The incidence of CV death, MI, or stroke was 5.63% in the placebo group and 3.25% in the combined atopaxar group ($P = 0.20$). Although underpowered to achieve statistical significance, this possible signal of clinical efficacy was supported mechanistically by a significant 33% reduction in the incidence of ischemia by Holter monitoring in the first 48 hours after a 400-mg loading dose of atopaxar. To the best of our knowledge, this is the first time that an oral antiplatelet drug has been shown to significantly reduce ischemia as detected by Holter monitor, a surrogate endpoint for clinical events. Importantly, these findings were observed on a background of guideline-recommended therapies, including $\beta$-blockers, aspirin, and thienopyridines. These results may also suggest that Holter monitoring could be an important means to detect efficacy signals in future phase II studies of novel compounds.

A clear dose-dependent trend for either efficacy or bleeding was not observed with increasing doses of atopaxar. In particular, subjects randomized to the 100-mg dose experienced the highest incidence of both major adverse cardiovascular events and bleeding. It is plausible that these findings are explained by play of chance or possibly by differences in baseline characteristics between randomized treatment arms. To that end, a larger percentage of subjects in the 100-mg group had a history of peripheral artery disease, carotid artery disease, and previous transient ischemic attack or nonhemorrhagic stroke. In addition, the majority of bleeding and major adverse cardiovascular events occurred early after randomization; therefore, the use of a common loading dose in all active groups may have attenuated a dose-dependent signal.
The present study has limitations that warrant consideration. Because the bleeding rates for the trial were lower than anticipated, we cannot exclude a small or moderate increase in bleeding with atopaxar compared with placebo. Although atopaxar did not increase the incidence of instrumented bleeding, the overall rate of percutaneous coronary intervention for an ACS trial was relatively low. In addition, as a result of a programming error in the interactive voice response system, some subjects were erroneously dispensed the 50-mg dose of drug in the 100- and 200-mg dosing arms at the 1-month visit. Thus, the relationship between escalating doses and safety or efficacy signals could have been partly attenuated. However, all analyses were verified in a population that excluded those subjects affected by the resupply error. Furthermore, all major bleeding events occurred during the first month after randomization and before the incorrect drug dispensation. Treatment duration was relatively short, and further information on longer-term tolerability is needed.

**Conclusions**

This study demonstrated that atopaxar was generally well tolerated, especially at the 50-mg treatment dose. However, relative QTcF prolongation and liver function abnormalities were observed more frequently with the highest doses of atopaxar, a finding that is consistent with the results of the smaller phase II studies conducted in Japan.\(^\text{17}\)

The LANCELOT—ACS trial is the first international phase II trial to evaluate a PAR-1 receptor antagonist in patients after ACS. Potential signals of efficacy without a clear increase in evident bleeding support a possible role for atopaxar in the treatment of patients after ACS and support

**Table 4. Incidence of Liver Function Abnormalities at or After Week 2**

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (N=138), n (%)</th>
<th>50 mg (N=153), n (%)</th>
<th>100 mg (N=156), n (%)</th>
<th>200 mg (N=146), n (%)</th>
<th>Combined Atopaxar (N=455), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AST ≥3×ULN</td>
<td>3 (2.5)</td>
<td>3 (2.2)</td>
<td>2 (1.5)</td>
<td>3 (2.3)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td>&gt;5×ULN</td>
<td>0</td>
<td>2 (1.5)</td>
<td>0</td>
<td>1 (0.8)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>&gt;8×ULN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>ALT ≥3×ULN</td>
<td>3 (2.5)</td>
<td>3 (2.2)</td>
<td>3 (2.2)</td>
<td>7 (5.5)</td>
<td>13 (3.2)</td>
</tr>
<tr>
<td>&gt;5×ULN</td>
<td>0</td>
<td>3 (2.2)</td>
<td>1 (0.7)</td>
<td>4 (3.1)</td>
<td>8 (2.0)</td>
</tr>
<tr>
<td>&gt;8×ULN</td>
<td>0</td>
<td>2 (1.5)</td>
<td>0</td>
<td>3 (2.3)</td>
<td>5 (1.2)</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>121</td>
<td>137</td>
<td>139</td>
<td>129</td>
<td>405</td>
</tr>
<tr>
<td>&gt;1.5×ULN</td>
<td>2 (1.7)</td>
<td>2 (1.5)</td>
<td>1 (0.7)</td>
<td>1 (0.8)</td>
<td>4 (1.0)</td>
</tr>
<tr>
<td>≥2×ULN</td>
<td>2 (1.7)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>121</td>
<td>137</td>
<td>139</td>
<td>129</td>
<td>405</td>
</tr>
<tr>
<td>&gt;1.5×ULN</td>
<td>1 (0.8)</td>
<td>3 (2.2)</td>
<td>5 (3.6)</td>
<td>1 (0.8)</td>
<td>9 (2.2)</td>
</tr>
<tr>
<td>≥3×ULN</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

AST indicates aspartate aminotransferase; ULN, upper limit of normal; and ALT, alanine aminotransferase.

The incidence of alanine aminotransferase (ALT) elevations (3 times or above the upper limit of normal [ULN]) at serial time points during the treatment phase at or beyond 2 weeks. Three subjects discontinued the study drug because of liver function abnormalities. An ALT elevation was seen more frequently in the 200-mg dose group between weeks 4 and 8 but returned to within normal limits on continued therapy by week 12. There were no cases of Hy’s law.
the concept of the PAR-1 receptor as a possible key target for inhibition.

Appendix

The members of the Operations Committee and Steering Committee of the LANCELOT—ACS trial were as follows (with principal investigators and participating centers listed separately in the Appendix in the online-only Data Supplement): M.D. Flather (principal investigator), D.L. Bhatt (coprincipal investigator), M.L. O’Donoghue (investigator), S.D. Vivioti (investigator). Steering Committee: Argentina: F. Cura; Australia, P. Aylward; Belgium, D. Schoors; Canada, S. Goodman; Czech Republic, P. Jansky; France, G. Montalescot; Germany, U. Zeymer; Hungary, M. Keltai; Italy, M. Valgimigli; Israel, V. Guetta; Netherlands, A. Withagen; Poland, D. Dudek; South Africa, L. Burgess; Sweden, O. Hansen; United Kingdom, M. Flather; United States, D. Bhatt. ECG Core Laboratory: S. Goodman. Platelet Function Core Laboratory: D. Fitzgerald. Data Safety Monitoring Board: R. Becker (chair), F. Spencer, K. Lee, F. Verheugt, J. Weitz, C.P. Cannon (first meeting only). Clinical Events Committee: A. Askari (director), V. Menon (director), I. Ahmad, M. Akhtar, B. Austin, E. Gorodeski, C. Silla, N. Pasca (manager), K. Brown (project manager), L. Schultz (project specialist).

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Disclosures

Dr O’Donoghue receives research grants from GlaxoSmithKline and Eisai and honoraria from Eli Lilly and Daiichi Sankyo (continuing medical education only). Dr Bhatt receives research grants from Astra Zeneca, Bristol-Myers Squibb, Eisai, Sanofi-aventis, and The Medicines Company. Dr Goto has received research grants and honoraria from Sanofi-aventis, Eisai, and Otsuka and consulting fees from Merck and Eisai. Dr Vivioti has received grants from Eli Lilly, Daiichi Sankyo, and Schering-Plough and consulting fees from Bristol Myers Squibb, Sanofi-aventis, AstraZeneca, ARENA, and Medco. Dr Angiolillo reports honoraria for lectures from Bristol Myers Squibb, Sanofi-aventis, Eli Lilly, and Daiichi Sankyo; consulting fees from Bristol-Myers Squibb, Sanofi-aventis, Eli Lilly, Daiichi Sankyo, The Medicines Company, Portola, Novartis, Medicure, Accumetrics, Arena Pharmaceuticals, Merck, and AstraZeneca; and research grants from GlaxoSmithKline, Otsuka, Boston Scientific, Eli Lilly, Daiichi Sankyo, The Medicines Company, Portola, Accumetrics, Schering-Plough, Astra Zeneca, Eisai, Bristol-Myers Squibb, Sanofi Aventis, and Johnson & Johnson. Dr Goodman has received research grant support and/or speaking/consulting/advisory board honoraria from Eisai, Sanofi-aventis, Bristol Myers Squibb, Eli Lilly, Daiichi Sankyo, AstraZeneca, and Merck. Dr Montalescot has received grants, consulting fees, and/or lecture fees from Abbott Vascular, BMS, Boston Scientific, Centocor, Eli Lilly, INSERM, ITC Edison, Guerbet, Servier, Europa, Lead-Up, Nanospheres, Medtronic, Pfizer, Sanofi-aventis, Stago, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, Eisai, Menarini, Novartis, Portola, The Medicines Company, Accumetrics, Cordis, GSK, and Merck. Dr Zeymer has received honoraria for his participation at meetings related to the development of atopaxar; research grants and honoraria for speaker meetings and advisory boards from Sanofi-aventis, Bristol Myers Squibb, Eli Lilly, Daiichi Sankyo, and AstraZeneca; and consulting fees from Eli Lilly, AstraZeneca, and Sanofi-aventis. Dr Aylward has received grants from Eisai, Merck, and AstraZeneca; speaking fees and/or honoraria from Astra Zeneca, Sanofi-aventis, Boehringer Ingelheim, and Merck; and consulting fees from Astra Zeneca, Pfizer, and Boehringer Ingelheim. Dr Zieczina is an employee of Eisai. Dr Flather has received honoraria for his participation at meetings related to the development of atopaxar and receives research grants and honoraria for speaker meetings and advisory boards from Sanofi-aventis, Bristol Myers Squibb, Eli Lilly, Daiichi Sankyo, Novartis, and GlaxoSmithKline. The other authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

Atopaxar (E5555) is a reversible protease-activated receptor-1 thrombin receptor antagonist that interferes with platelet signaling. The primary objective of the phase II Lessons From Antagonizing the Cellular Effects of Thrombin–Acute Coronary Syndromes (LANCELOT—ACS) trial was to evaluate the safety and tolerability of atopaxar in patients with an acute coronary syndrome. A total of 603 subjects were randomly assigned to 1 of 3 doses of atopaxar (400-mg loading dose followed by 50, 100, or 200 mg daily) or matching placebo for 12 weeks. At the end of the follow-up, the incidence of bleeding (according to the Clopidogrel in Unstable Angina to Prevent Recurrent Events and Thrombolysis in Myocardial Infarction bleeding definitions) did not differ significantly between the combined atopaxar and placebo groups. Atopaxar significantly reduced ischemia on continuous ECG monitoring (Holter) at 48 hours compared with placebo. Transient dose-dependent transaminase elevation and relative QTc prolongation were observed with the highest doses of atopaxar. Overall, the study demonstrated that atopaxar was generally well tolerated, especially at the 50-mg treatment dose. Potential signals of efficacy without a clear increase in bleeding support the concept of the protease-activated receptor-1 receptor as a possible key target for inhibition. Larger trials are required to fully establish the efficacy and safety of atopaxar.
Safety and Tolerability of Atopaxar in the Treatment of Patients With Acute Coronary Syndromes: The Lessons From Antagonizing the Cellular Effects of Thrombin—Acute Coronary Syndromes Trial


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Supplementary Material

Principal Investigators (who enrolled at least 1 subject) and Numbers of Enrolled Subjects by Participating Country: