A Randomized, Double-Blind, Active-Controlled Phase 2 Trial to Evaluate a Novel Selective and Reversible Intravenous and Oral P2Y12 Inhibitor Elinogrel Versus Clopidogrel in Patients Undergoing Nonurgent Percutaneous Coronary Intervention

The INNOVATE-PCI Trial

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Background—We evaluated the safety, efficacy, and tolerability of elinogrel, a competitive, reversible intravenous and oral P2Y12 inhibitor that does not require metabolic activation, in patients undergoing nonurgent percutaneous coronary intervention.

Methods and Results—In a randomized, double-blind, dose-ranging phase 2b trial, 652 patients received either 300 or 600 mg of clopidogrel pre-percutaneous coronary intervention followed by 75 mg daily or 80 or 120 mg of IV elinogrel followed by 50, 100, or 150 mg oral elinogrel twice daily. Numerous exploratory safety and efficacy end points were assessed and, as such, had no prespecified primary end point, and the study was not powered to conclusively evaluate its objectives. Thrombolysis in myocardial infarction combined bleeding was increased with elinogrel (hazard ratio, 1.98; 95% confidence interval, 1.10 to 3.57), related largely to increased bleeding requiring medical attention (elinogrel 47/408 [11.5%] versus clopidogrel 13/208 [6.3%]) and occurring primarily at the percutaneous coronary intervention access site. Efficacy end points and postprocedure cardiac enzyme were similar, but there was a nonsignificant higher frequency of periprocedural myocardial infarctions in the elinogrel arms (OR, 1.59; 95% confidence interval, 0.79 to 3.48). There was an increased incidence of dyspnea (elinogrel 50/408 [12.3%] versus clopidogrel 8/208 [3.8%]) and transaminase elevation (alanine transferase/aspartate transferase >3× the upper limit of normal; elinogrel 18/408 [4.4%] versus clopidogrel 2/208 [1.0%]) in the elinogrel arms, but there were no cases of heart block, bradycardia, hypotension, or liver failure.

Conclusions—In patients undergoing nonurgent percutaneous coronary intervention and in comparison with clopidogrel, intravenous and oral elinogrel therapy did not significantly increase thrombolysis in myocardial infarction major or minor bleeding, although bleeding requiring medical attention was more common. The significance of these findings will need to be more definitively determined in future Phase 3 studies.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00751231.
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Key Words: chronic ischemic heart disease ■ catheter based coronary interventions ■ cardiovascular pharmacology ■ antiplatelets ■ platelet function inhibitors

Antiplatelet therapy is a fundamental aspect of the management of ischemic heart disease. The addition of a thienopyridine to aspirin is recommended by practice guidelines to reduce the risk of short- and long-term ischemic events in patients with acute coronary syndrome and those undergoing percutaneous coronary intervention (PCI)1-4; however, despite the administration of dual antiplatelet therapy, adverse clinical events continue to accrue in high-risk
The limitations of currently available thienopyridines are well-described and include significant interpatient variability in the pharmacodynamic effect of clopidogrel and increased risk of major and fatal bleeding with the use of prasugrel. Therefore, there exists a substantial need for more effective and safer antiplatelet therapy for patients with coronary artery disease.

The novel antiplatelet agent elinogrel is the only competitive and reversible P2Y₁₂ inhibitor with both intravenous (IV) and oral formulations. Elinogrel is a direct acting P2Y₁₂ inhibitor that, unlike the thienopyridines clopidogrel and prasugrel, does not require metabolic activation and, therefore, may have less interpatient variability and fewer clinically relevant drug-drug interactions. Early clinical data demonstrate that the IV and oral formulations provide rapid and potent platelet inhibition with a terminal half-life of ≈9 to 12 hours. It has balanced clearance through the kidney and liver, and ≈10% of the compound is metabolized to a pharmacologically inactive metabolite. These pharmacokinetic and pharmacodynamic properties suggest that elinogrel may reduce ischemic events, and its competitive adenosine diphosphate (ADP) concentration-dependent, reversible platelet inhibition suggests that it may minimize hemorrhagic risk in clinical situations where endogenous ADP concentrations are high, such as during active bleeding.

To better characterize the safety, efficacy, and tolerability of IV and oral elinogrel compared with standard doses of clopidogrel in patients undergoing nonurgent PCI, the INNOVATE-PCI phase 2b study was performed. We hypothesized that, compared with clopidogrel, a strategy of IV and oral elinogrel administration results in faster and greater platelet inhibition at the time of PCI and that is sustained through the transition to oral therapy.

**WHAT IS KNOWN**

- Dual antiplatelet agents with aspirin and a P2Y₁₂ inhibitor such as clopidogrel or prasugrel are cornerstone therapy in the setting of PCI in stable patients, as well as those with acute coronary syndrome.
- Clopidogrel is limited by significant interpatient variability while prasugrel is associated with an increase risk of bleeding.

**WHAT THE STUDY ADDS**

- Elinogrel is a novel IV and oral competitive and reversible P2Y₁₂ inhibitor.
- In this randomized, double-blind, dose-ranging phase 2b trial, elinogrel was found to have acceptable safety and tolerability compared with clopidogrel in the setting of nonurgent PCI.

**Methods**

The INNOVATE-PCI trial was a multicenter, phase 2b, randomized, double-blind, triple-dummy, active-controlled exploratory study of IV and oral elinogrel compared with clopidogrel in patients undergoing nonurgent PCI (NCT00751231). The study was conducted at 60 sites in Canada, Europe, and the United States.

**Study Population**

Patients 18 to 75 years of age who were able to provide informed consent, comply with study protocol, and scheduled to undergo nonurgent PCI were enrolled. Detailed inclusion and exclusion criteria were previously published. Key exclusion criteria included low body weight (<55 kg), age >75 years, stroke or transient ischemic attack within the prior 5 years, acute coronary syndrome within 7 days, planned staged PCI, planned glycoprotein IIb/IIIa receptor inhibitor use, glomerular filtration rate <45 mL/min, and planned surgery during the study period. Patients treated with a clopidogrel loading dose of ≥300 mg within 7 days before randomization were excluded, although patients on maintenance clopidogrel therapy (ie, 75 mg/d) were eligible for enrollment.

**Study Protocol and Medications**

The study used a triple-dummy design, with active drugs, including clopidogrel, intravenous elinogrel, and oral elinogrel and their matching placebos with oral therapy encapsulated such that kits were indistinguishable across all arms. After diagnostic angiography, patients were randomized in a 1:1:1:1 fashion to 1 of 4 arms outlined in Figure 1. In arm 1, patients received a 300- or 600-mg loading dose of clopidogrel at the discretion of the local investigator, followed by clopidogrel 75 mg once daily for the duration of the study. The clopidogrel loading dose was to be administered within the 12 hours preceding PCI. An 80-mg IV bolus of elinogrel was given immediately before PCI, followed by twice-daily oral elinogrel administration of 50, 100, or 150 mg for 60 days in arms 2, 3, and 4, respectively. The initial oral dose was administered concurrently with the IV bolus.

Approximately 800 patients were planned with equal distribution among the 4 arms. An independent Data Safety Monitoring Committee (DSMC) monitored the trial for safety and tolerability of the study drug. Per protocol, the DSMC was tasked with assessment for dose escalation for IV elinogrel from 80 to 120 mg, to be determined after the first 80 patients were enrolled. Furthermore the DSMC assessed the safety and tolerability of the oral elinogrel arms, with the possibility of eliminating the low or high dose if deemed appropriate. On April 8, 2009, the DSMC recommended increasing the IV dose from 80 to 120 mg and discontinuation of further enrollment in the 50 mg arm (n=26 treated with this dose), with continuation of enrollment in the 100- and 150-mg oral elinogrel arms based on an acceptable risk-benefit profile in the higher-dose elinogrel arms. The rationale for dropping the 50-mg arm, as relayed by the DSMC after database lock, was based on the perceived lack of need for the 50-mg oral elinogrel dose owing to safety of the 150-mg oral elinogrel dose. Patients randomized to the elinogrel 50-mg arm before April 8, 2009, were allowed to continue blinded therapy until the end of the study. After the 50-mg oral dose was eliminated, a target enrollment of 650 patients was required to achieve a minimum of 200 patients enrolled in the 3 remaining study arms with 1:1:1 randomization. Additionally, the protocol was amended so as to increase the study duration from 60 to 120 days in order to extend the drug exposure period and further examine the clinical profile of oral elinogrel during chronic therapy.

**Concomitant Treatments**

Concomitant thrombin inhibitor therapy during PCI was left to the discretion of the operator, with the exception of fondaparinux, which was specifically excluded by protocol. The number and type of stents was also left to the discretion of the investigator. During the chronic oral therapy phase, investigators were encouraged to follow established guidelines for secondary prevention. The treating physician determined the use of dual antiplatelet therapy beyond the trial follow-up period, and a regimen of open-label clopidogrel reloading at the end of follow-up was recommended in the study protocol.
A number of safety and efficacy end points were assessed. By its very design, however, the study was intended as an exploratory look at numerous clinical (eg, safety, efficacy) and laboratory parameters and, as such, had no prespecified primary end point and was not powered to conclusively evaluate any of its exploratory objectives.

### Safety End Points

Bleeding was assessed using 2 scales: the Thrombolysis In Myocardial Infarction (TIMI) bleeding scale and the clinically relevant/nuisance bleeding scale, which was specifically modified for this study. The following safety end points, occurrence of TIMI bleeding (major, minor, or bleeding requiring medical attention [BRMA]) and occurrence of clinically relevant (major or minor) or nuisance bleeding and their components were assessed at (1) 24 hours or discharge; (2) day 60; and, (3) for patients who signed the amended protocol, day 120. The composite end point event was timed at the occurrence of the first event in the composite. An ad-hoc landmark analysis for the time to the first occurrence of clinically relevant (major or minor) or nuisance bleeding and time to the first occurrence of TIMI (major, minor, or BRMA) was performed (1) after 72 hours and by day 120; and (2) after 24 hours and by day 120.

### Clinical Efficacy End Points

The clinical efficacy endpoints in combination and their individual components (death, myocardial infarction [MI], stroke, urgent target vessel revascularization [UTVR], stent thrombosis, or glycoprotein IIb/IIIa bailout) were examined from the time of treatment to the first event. Efficacy end points were assessed at (1) 24 hours or discharge; (2) day 60; and, (3) for patients who signed the amended protocol, day 120. Markers of myocardial necrosis measured at a central laboratory, including troponin T and creatinine kinase muscle and brain fractionation, both as categorical and continuous variables, were assessed as biological efficacy end points. Blood was drawn pre-PCI and after PCI at approximately 8, 16, and 24 hours (or discharge). Biological efficacy end points were defined as follows: the occurrence of any troponin T elevation; the occurrence of any troponin T elevation above the upper limit of normal (ULN); the occurrence of any creatinine kinase, muscle and brain elevation above ULN, and peak troponin within 24 hours or discharge.

### Independent Clinical Endpoint Committee

The Duke Clinical Research Institute Clinical Endpoint Committee remained blinded to treatment groups and adjudicated myocardial infarction (MI), UTVR, stroke, and stent thrombosis, as well as TIMI major/minor and clinically relevant major bleeding events.

### Randomization and Ethical Considerations

Randomization was generated using random permuted blocks of 5 and 10 within region (United States, Canada, European Union [EU] non-substudy, EU substudy) stratified by whether or not the patient entered the trial on maintenance clopidogrel therapy, as well as the intended loading dose (300 or 600 mg) of clopidogrel or matching placebo. The study adhered to the principles outlined in the Declaration of Helsinki. All sites obtained approval from their respective Institutional Review Boards and all patients gave verbal and written informed consent.

### Statistical Analysis

INNOVATE-PCI was not powered to determine superiority or noninferiority of elinogrel compared with clopidogrel but rather to evaluate the clinical safety, efficacy, and tolerability of IV and oral elinogrel therapy in patients undergoing nonurgent PCI as a prelude to a more definitive phase 3 trial. Consequently, a number of statistical hypotheses were addressed in order to accomplish that. The sample size was not based on a prespecified power calculation.
but was estimated based on a planned enrollment, which was expected to provide an acceptable qualitative assessment of elinogrel’s impact on study end points: 200 patients per arm. Analysis was conducted on an intent-to-treat basis of all randomized patients. An efficacy analysis was conducted based on all patients who underwent PCI and received at least 1 dose of study medication, and a safety analysis was performed on all patients treated with at least 1 dose of study medication. Since the 50-mg oral elinogrel dose was terminated after very few (n = 26) patients were randomized into this arm, descriptive data from the 50-mg arm are provided but are not included in any of the analyses.

The biological efficacy end points are presented at 24 hours after treatment start or hospital discharge, whichever occurred first. The clinical efficacy and safety end points are presented as 2 time periods: the periprocedural phase (24 hours after treatment start or hospital discharge, whichever occurred first), which reflects the loading doses of the study drugs, and the total study phase (from treatment to 60 and 120 days), which reflects both the IV elinogrel doses and the oral maintenance doses of the study drugs.

Hazard ratios (HRs) and their 95% confidence intervals (CIs) were computed using a Cox proportional hazards model, with the treatment group as the only predictor variable for each of the composite safety and efficacy end points comparing clopidogrel and elinogrel event rates during the chronic phase. For each composite efficacy and safety end point described in the previous section, a 2-sided test of the null hypothesis was performed to compare risks for patients in the clopidogrel and elinogrel oral arms (pooled 100- and 150-mg oral doses) using a log-rank test. Statistical significance was set at the 0.05 alpha level, with no adjustment for multiple comparisons, given the exploratory nature of this phase 2 trial. To address the IV elinogrel therapy, data are presented with pooled IV data and comparison of the 80- and 120-mg doses where appropriate. Using landmark analysis, the follow-up period was divided into the periprocedural phase (ie, from time of treatment to 24 hours after treatment start or hospital discharge, whichever occurred first), reflecting largely the effects of IV elinogrel versus clopidogrel loading dose, and the time period from 24 hours after treatment start or hospital discharge to 120 days, reflecting the effects of oral elinogrel versus clopidogrel. Odds ratios (from a logistic regression model, with only treatment in the model) and their 95% CIs were computed by dose to compare clopidogrel (reference group) and elinogrel event rates during the periprocedural phase. A 2-sided test of the null hypothesis was performed using a Fisher exact test, with a midp correction at the a = 0.05 significance level for each of the safety, efficacy, and biological end points during the acute phase.15 For peak troponin, a 95% CI for the treatment difference was computed by dose to compare clopidogrel (reference group) and elinogrel event rates during the periprocedural phase. A 2-sided test of the null hypothesis of no difference between the clopidogrel and pooled 100 mg and 150 mg elinogrel groups was performed at the a = 0.05 significance level using a log-rank test. Twenty five tests were carried out (5 for the composite clinical efficacy end points during the periprocedural phase and 3 for each day 60 and day 120; 2 tests for the composite safety end points at each the periprocedural phase, day 60 and day 120; and 8 tests for the biological end points at the periprocedural phase) in order to explore the clinical efficacy and biological and safety endpoints described above.

In order to enable sponsor decision-making for a phase 3 trial, an unplanned interim analysis of both efficacy and safety data were generated by the Duke Clinical Research Institute. Selected study personnel, at the coordinating center and the sponsor, had knowledge of the results, but the sites, patients, and study coprincipal investigators remained blinded, and the analysis did not influence the INNOVATE-PCI trial design. No adjustments were made to the final significance level. The data were held and analysis conducted by the Duke Clinical Research Institute using SAS version 9.2 (SAS Institute).

**Results**

**Patient Population**

Between December 8, 2008, and November 17, 2009, 652 patients were enrolled in 60 sites, encompassing Austria (n = 28), Canada (n = 132), Germany (n = 126), Poland (n = 74), and the United States (n = 292). Figure 1 demonstrates the patient flow through the study.

Demographics were comparable between treatment arms and typical of a nonurgent PCI population (Table 1). The majority (66%) of patients received a 600-mg loading dose of clopidogrel/placebo, and many patients (46%) were already being treated with clopidogrel therapy at the time of randomization. The median time from diagnostic catheterization until randomization was approximately 35 minutes. The median time from oral clopidogrel/placebo to PCI was 9 minutes (interquartile range, 5 to 24 minutes). The median times from IV elinogrel/placebo to PCI was 5 minutes (interquartile range, 2 to 9 minutes), and oral elinogrel/placebo to PCI was 5 minutes (interquartile range, 2 to 10 minutes).

**Clinical Outcomes: Safety**

Bleeding events using TIMI and clinically relevant definitions from treatment until 24 hours or discharge and 120 days are presented in Table 2.

There were no TIMI major bleeding events and few differences in TIMI minor bleeding at 24 hours or discharge (periprocedural period) (Table 2). There was a higher rate of combined TIMI bleeding (odds ratio, 2.42; 95% CI, 1.16 to 5.69) mainly due to a higher rate of TIMI BRMA during the 24 hours after IV elinogrel therapy. The majority (89%) of bleeding events in the first 24 hours after treatment onset were related to the vascular access site. Similarly, there were no clinically relevant major bleeding events during the periprocedural period (Table 2). There was a higher rate of combined clinically relevant/nuisance bleeding (odds ratio, 1.47; 95% CI, 0.92 to 2.43).

There was overall increased combined TIMI bleeding over the duration of follow-up with elinogrel (HR, 1.98; 95% CI, 1.10 to 3.57). Specifically, overall study TIMI major and minor bleeding rates were similar between elinogrel and clopidogrel arms, but there was increased frequency of TIMI BRMA with elinogrel, primarily due to the increase in events observed in the first 24 hours after initiating IV elinogrel therapy (clopidogrel, 3.8%, 1.67 to 7.44; elinogrel, 100 mg oral, 8.46%, 5.00 to 13.20; elinogrel, 150 mg oral, 9.18%, 5.62 to 13.96) (Figure 2A). A possible dose-response relationship between combined TIMI bleeding and elinogrel dose compared with clopidogrel was demonstrated: 100 mg oral elinogrel HR, 1.66 (0.85 to 3.25) and 150 mg oral elinogrel, HR, 2.30 (1.22 to 4.31).

A landmark analysis conducted at 24 hours further demonstrated that there were no statistical differences in TIMI major, TIMI minor, or TIMI BRMA across the arms during chronic (oral) phase of treatment (ie, between 24 hours and 120 days of follow-up) (Figure 2B).

**Clinical Outcomes: Biological Efficacy**

The measures of myocardial necrosis obtained at 24 hours or hospital discharge are presented in Table 3. There was no statistical difference in cardiac enzyme elevations between the pooled oral elinogrel arms or the 2 IV doses of elinogrel compared with the clopidogrel arm.
Clinical Outcomes: Clinical Efficacy
Clinical end points at 24 hours or discharge and 120 days are presented in Table 4. The majority of clinical events were periprocedural MIs that were numerically more frequent in the elinogrel arms. The Kaplan-Meier analysis of the combined clinical efficacy end points (death, MI, stroke, UTVR, or stent thrombosis; HR, 1.82 [0.96 to 3.45], P=0.058) from treatment to 120 days is shown in Figure 3.

Adverse Events
The reported adverse events and selected laboratory results comparing the clopidogrel with pooled elinogrel arms are shown in Table 5. The median duration of study drug exposure for clopidogrel was 118.5 days (62 to 124) and elinogrel, 117 days (62 to 124). Study drug discontinuation occurred in 30/208 (14.4%) in the clopidogrel arm and 73/408 (17.9%) in the patients treated with elinogrel. Discontinuation due to adverse events was similar between groups: clopidogrel, 15/208 (7.2%), and elinogrel, 30/408 (7.4%). Overall, the incidence of adverse events was similar between clopidogrel and elinogrel. Elinogrel therapy was associated with an increased incidence of dyspnea, which was generally mild (elinogrel, 44/56 mild and 12/56 moderate, versus clopidogrel, 6/8 mild and 2/8 moderate), transient, and infrequently led to study drug discontinuation (elinogrel, 4/408 patients).

Elinogrel was associated with increased incidence of elevated liver transaminases, most of which occurred within 60 days of treatment onset and were asymptomatic. All cases resolved even when study medication was continued (approximately 50% of cases). Specifically, per protocol, alanine transferase, aspartate transferase, alkaline phosphatase and bilirubin were checked at hospital discharge, day 30, day 60, and day 120. From the time of signing the informed consent to end of treatment in INNOVATE-PCI, a total of 22 patients (19 elinogrel, 3 clopidogrel) developed alanine transferase,
aspartate transferase, or alkaline phosphatase elevations >3× ULN. Of these 22 cases, 1 case (which received elinogrel) was elevated before dosing at baseline and resolved, despite receiving a full course of elinogrel. Of the 21 remaining, 3 cases (2 elinogrel, 1 clopidogrel) developed elevations at discharge, 11 cases (9 elinogrel, 2 clopidogrel) occurred at day 30, 6 cases (6 elinogrel) occurred at day 60, and 1 case occurred at day 120. In 2 cases, both of which received elinogrel 100 mg, an alternative explanation for the elevation was apparent: in 1 case, cholecystitis requiring cholecystectomy, and, in the other case, aspartate transferase but not alanine transferase was elevated in the setting of a large periprocedural MI. There were no cases of Hy’s law, a pattern of transaminase/bilirubin elevation highly suggestive of drug-induced hepatic necrosis that may often lead to liver failure and death.

**Elinogrel 50-mg Oral Dose**

Twenty-six patients received the elinogrel 50-mg oral twice-daily dose before the termination of this study arm. These patients were similar to the overall study population, with a median age of 61 years of age (55 to 70), and 77% were male (20/26). None of these subjects were treated in the trial extension. Combined TIMI bleeding from treatment until 24 hours or discharge occurred in 3 patients (11.5%) (TIMI minor bleeding \(n = 1\) or TIMI BRMA \(n = 2\)). Combined TIMI bleeding from treatment until day 60 occurred in 5 patients (19.2%) (TIMI major bleeding \(n = 0\), or TIMI minor bleeding \(n = 1\), or TIMI BRMA \(n = 4\)). From treatment until 24 hours or discharge, 3 patients (11.5%) suffered the composite endpoint of death, MI, stroke, UTVR, stent thrombosis, or glycoprotein IIb/IIIa receptor bailout. All 3 events were related to periprocedural MI. From treatment to day 60, there was 1 additional nonprocedural MI.

**Discussion**

The results of the exploratory phase 2b INNOVATE-PCI trial demonstrate that IV and oral elinogrel compared with standard loading doses of clopidogrel had greater peri-PCI TIMI BRMA but no significant difference in TIMI major or minor bleeding. It is not known if the greater TIMI BRMA will predict increased risk of TIMI major or TIMI minor bleeding in a larger study, which needs to be addressed in phase 3 investigations. Also, during chronic maintenance therapy, elinogrel was not associated with increased bleeding risk, as shown in the 24-hour landmark analysis.

The study was not powered to show any differences in end points, including bleeding and efficacy. As with all the end points explored, the somewhat conflicting patterns of clinical and biological efficacy measures should be interpreted with caution.

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**Table 2. Bleeding Complications From Treatment Onset to 24 Hours or Discharge and 120 Days (Safety Population)**

<table>
<thead>
<tr>
<th></th>
<th>Clopidogrel ((N = 208))</th>
<th>Oral Elinogrel Pooled ((N = 408))</th>
<th>Elinogrel 80 mg IV + 100 mg Oral ((N = 49))</th>
<th>Elinogrel 80 mg IV + 150 mg Oral ((N = 47))</th>
<th>Elinogrel 120 mg IV + 100 mg Oral ((N = 152))</th>
<th>Elinogrel 120 mg IV + 150 mg Oral ((N = 160))</th>
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<tr>
<td><strong>TIMI bleeding at 24 hours or discharge</strong></td>
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<tr>
<td>TIMI major/minor/BRMA</td>
<td>8 (3.8%)</td>
<td>36 (8.8%)</td>
<td>4 (8.2%)</td>
<td>3 (6.4%)</td>
<td>13 (6.6%)</td>
<td>16 (10.0%)</td>
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<tr>
<td>TIMI major</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<td>TIMI minor</td>
<td>0 (0%)</td>
<td>2 (0.5%)</td>
<td>1 (2.0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
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<tr>
<td>TIMI BRMA</td>
<td>8 (3.8%)</td>
<td>34 (8.3%)</td>
<td>3 (6.1%)</td>
<td>3 (6.4%)</td>
<td>13 (8.6%)</td>
<td>15 (9.4%)</td>
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<td><strong>Clinically relevant/nuisance bleeding at 24 hours or discharge</strong></td>
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<tr>
<td>Major/minor/nuisance</td>
<td>26 (12.5%)</td>
<td>71 (17.4%)</td>
<td>9 (18.4%)</td>
<td>7 (14.9%)</td>
<td>23 (15.1%)</td>
<td>32 (20.0%)</td>
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<tr>
<td>Major</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
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<td>Minor</td>
<td>5 (2.4%)</td>
<td>32 (7.8%)</td>
<td>5 (10.2%)</td>
<td>2 (4.3%)</td>
<td>13 (8.6%)</td>
<td>12 (7.5%)</td>
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<tr>
<td>Nuisance</td>
<td>24 (11.5%)</td>
<td>40 (9.8%)</td>
<td>5 (10.2%)</td>
<td>5 (10.6%)</td>
<td>10 (6.6%)</td>
<td>20 (12.5%)</td>
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<td><strong>TIMI bleeding at 120 days</strong></td>
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<tr>
<td>TIMI major/minor/BRMA</td>
<td>14 (6.7%)</td>
<td>53 (13.0%)</td>
<td>22 (10.9%)</td>
<td>31 (15.0%)</td>
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<tr>
<td>TIMI major</td>
<td>0 (0%)</td>
<td>4 (1.0%)</td>
<td>2 (1.0%)</td>
<td>2 (1.0%)</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
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<tr>
<td>TIMI minor</td>
<td>1 (0.5%)</td>
<td>2 (0.5%)</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
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<tr>
<td>TIMI BRMA</td>
<td>13 (6.3%)</td>
<td>47 (11.5%)</td>
<td>19 (9.5%)</td>
<td>28 (13.5%)</td>
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<td><strong>Clinically relevant/nuisance bleeding at 120 days</strong></td>
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<tr>
<td>Major/minor/nuisance</td>
<td>50 (24%)</td>
<td>120 (29.4%)</td>
<td>54 (26.4%)</td>
<td>66 (31.9%)</td>
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<tr>
<td>Major</td>
<td>1 (0.5%)</td>
<td>4 (1.0%)</td>
<td>2 (1.0%)</td>
<td>2 (1.0%)</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
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<tr>
<td>Minor</td>
<td>19 (9.1%)</td>
<td>50 (12.3%)</td>
<td>25 (12.4%)</td>
<td>25 (12.1%)</td>
<td></td>
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<tr>
<td>Nuisance</td>
<td>38 (18.3)</td>
<td>72 (17.6%)</td>
<td>29 (14.4%)</td>
<td>43 (20.8%)</td>
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</tbody>
</table>

IV indicates intravenously; TIMI, thrombolysis in myocardial infarction; BRMA, bleeding requiring medical attention.
caution. Additionally, more definitive characterization of the safety and efficacy profile of elinogrel are warranted in future phase 3 studies.

Elinogrel is the only IV and oral direct-acting, reversible and competitive inhibitor of the P2Y<sub>12</sub> receptor. These properties may provide specific theoretical advantages related to safety and efficacy. In the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel (TRITON-TIMI 38), prasugrel reduced the composite end point of death, MI, or stroke by 19% (HR, 0.81; 95% CI, 0.73 to 0.90) compared with clopidogrel but was associated with increased non-coronary artery bypass graft TIMI major bleeding by 32% (HR, 1.32; 95% CI, 1.03 to 1.68), life-threatening bleeding (1.4% versus 0.9%, \(P = 0.01\)), and fatal bleeding (0.4% versus 0.1%, \(P = 0.002\)). Similarly, in the PLATelet inhibition and patient Outcomes (PLATO) trial, the nonthienopyridine platelet inhibitor ticagrelor resulted in a 16% (HR, 0.84; 95% CI, 0.77 to 0.92) reduction in

Table 3. Biological Efficacy End Points at 24 Hours or Discharge (Efficacy Population)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Clopidogrel N=208</th>
<th>Elinogrel N=404</th>
<th>Elinogrel 80 mg IV N=118</th>
<th>Elinogrel 120 mg IV N=312</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any troponin elevation</td>
<td>40/200 (20.0%)</td>
<td>82/394 (20.8%)</td>
<td>22/110 (20.0%)</td>
<td>68/309 (22.0%)</td>
</tr>
<tr>
<td>Troponin elevation &gt;2× ULN</td>
<td>26/200 (13.0%)</td>
<td>51/394 (12.9%)</td>
<td>15/110 (13.6%)</td>
<td>40/309 (12.9%)</td>
</tr>
<tr>
<td>Peak troponin mean (SD)</td>
<td>0.137 (0.971)</td>
<td>0.096 (0.209)</td>
<td>0.103 (0.229)</td>
<td>0.094 (0.194)</td>
</tr>
<tr>
<td>Any CK-MB elevation</td>
<td>49/201 (24.4%)</td>
<td>104/395 (26.3%)</td>
<td>26/113 (23.0%)</td>
<td>86/307 (28.0%)</td>
</tr>
<tr>
<td>CK-MB elevation &gt;2× ULN</td>
<td>26/201 (12.9%)</td>
<td>52/395 (13.2%)</td>
<td>15/113 (13.3%)</td>
<td>42/307 (13.7%)</td>
</tr>
<tr>
<td>CK-MB elevation &gt;3× ULN</td>
<td>10/201 (5.0%)</td>
<td>29/395 (7.3%)</td>
<td>10/113 (8.8%)</td>
<td>23/307 (7.5%)</td>
</tr>
<tr>
<td>CK-MB elevation &gt;5× ULN</td>
<td>5/201 (2.5%)</td>
<td>14/395 (3.5%)</td>
<td>9/113 (8.0%)</td>
<td>9/307 (2.9%)</td>
</tr>
<tr>
<td>CK-MB elevation &gt;10× ULN</td>
<td>3/201 (1.5%)</td>
<td>3/395 (0.8%)</td>
<td>0/113 (0%)</td>
<td>3/307 (1.0%)</td>
</tr>
</tbody>
</table>

IV indicates intravenously; ULN, upper limit or normal; SD, standard deviation; CK-MB, creatine kinase, muscle and brain.
vascular death, MI, or stroke over clopidogrel but was associated with an increased risk of TIMI non-coronary artery bypass graft-related major bleeding by 25% (HR, 1.25; 95% CI, 1.03 to 1.53); however, there was no difference in overall major bleeding between ticagrelor and clopidogrel, likely driven by the patients who underwent coronary artery bypass graft where the reversible (noncompetitive) platelet inhibition of ticagrelor provided a safety advantage.

In preclinical studies, elinogrel has demonstrated a broader therapeutic window (less bleeding for equivalent antithrombotic activity) than thienopyridines, likely owing to its competitive, reversible mechanism of action. In preclinical

| Table 4. Adjudicated Clinical End Points at 24 Hours or Discharge and 120 Days (Efficacy Population) |
|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
|  | 24 Hour or Discharge |  | 120 Days |  |
|  | Clopidogrel N=208 | Oral Elinogrel Pooled N=404 | Oral Elinogrel N=200 | Oral Elinogrel N=204 |
| Death/MI/stroke, n (%) | 10 (4.8) | 30 (7.4) | 15 (7.5) | 15 (7.4) |
| Death/MI/stroke/UTVR, n (%) | 10 (4.8) | 31 (7.7) | 16 (8.0) | 15 (7.4) |
| Death/MI/stroke/UTVR/stent thrombosis, n (%) | 10 (4.8) | 31 (7.7) | 16 (8.0) | 15 (7.4) |
| Death/MI/stroke/UTVR/GP IIb/IIIa thrombotic bailout, n (%) | 12 (5.8) | 35 (8.7) | 19 (9.5) | 16 (7.8) |
| Death/MI/stroke/UTVR/stent thrombosis/GP IIb/IIIa thrombotic bailout, n (%) | 12 (5.8) | 35 (8.7) | 19 (9.5) | 16 (7.8) |
| Death, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| MI, n (%) | 10 (4.8) | 30 (7.4) | 15 (7.5) | 15 (7.4) |
| Peri-PCI, n (%) | 10 (4.8) | 30 (7.4) | 15 (7.5) | 15 (7.4) |
| Stroke, n (%) | 0 | 0 | 0 | 0 |
| UTVR, n (%) | 0 | 0 | 0 | 0 |
| Stent thrombosis | 0 | 0 | 0 | 0 |
| GP IIb/IIIa bailout, n (%) | 3 (1.4%) | 7 (1.7%) | 4 (2.0%) | 3 (1.5%) |

Death/MI/stroke, MI indicate myocardial infarction; UTVR, urgent target vessel revascularization; GP, glycoprotein.

Figure 3. Adjudicated clinical efficacy end points from treatment to day 120. Kaplan-Meier curves of time to death/myocardial infarction (MI)/stroke/urgent target vessel revascularization (UTVR)/stent thrombosis.
models, elinogrel prevents thrombus formation under high shear conditions where ADP concentrations are low (<1 μmol/L), but, in conditions where concentrations of ADP are higher (5 to 10 μmol/L range), platelet inhibition during elinogrel treatment was less pronounced, mostly likely owing to its competition with ADP for the P2Y12 receptor. Although speculative and not supported by this phase 2b study, a competitive inhibitor such as elinogrel may exhibit more separation between antithrombotic activity (ie, low ADP concentration) and major bleeding risk (ie, high ADP concentration) than other P2Y12 receptor inhibitors, which remains to be demonstrated in an adequately powered study.

Elinogrel therapy was associated with similar adverse events compared with clopidogrel, with the exception of increased dyspnea and laboratory-documented elevated liver transaminases. Dyspnea was mild in nature and infrequently required drug discontinuation. Given that dyspnea has now been reported with 3 novel reversible P2Y12 receptor inhibitors (cangrelor, ticagrelor, and elinogrel), there may be some, as yet, undefined effect of these agents. Elinogrel does not share structural similarities with the other agents, and the mechanism(s) underlying increased dyspnea compared with clopidogrel are unknown. Close follow-up and assessment of this symptom is warranted in the phase 3 program. There was also an increased incidence of liver transaminase elevation with elinogrel that were largely asymptomatic, and all resolved even in the 50% of cases when treatment was continued. Importantly, there were no reported cases of Hy’s Law. Future investigations will require vigilance to ensure safety of this agent for acute and chronic therapy.

This phase 2b study has provided important information that will help inform additional investigation for this novel IV and oral, direct-acting, competitive and reversible antiplatelet agent elinogrel. Prior investigation has demonstrated the rapid and potent antiplatelet effect of IV elinogrel, which was not associated with evidence of increased risk of TIMI major or minor bleeding in this study and warrants further investigation in patients with acute coronary syndrome.
there were no statistical differences between the 100-mg and 150-mg oral doses, there were numerically more ischemic events and bleeding events in the 2 doses, respectively. It is possible that eliningrel offers no efficacy advantage compared with existing therapiess. This information combined with pharmacodynamic and pharmacokinetic results, as well as the liver transaminase elevations, must be taken into careful consideration while determining the appropriate chronic dosing strategy to be tested in phase 3 investigations.

Limitations
The INNOVATE-PCI trial was a phase 2b study and, as such, had limited statistical power to show meaningful differences in clinical outcomes between the treatment arms. The interpretation of the comparisons performed without adjustment for multiplicity, along with HRs and probability values should be viewed with caution owing to the limited number of events and the possible time-varying hazards. Although we would have anticipated that the properties of eliningrel would be associated with a more consistent and favorable effect on clinical and biological efficacy end points, this was not observed, likely related to the low ischemic event rate in this nonurgent PCI population and small sample size of the study. Eliningrel was evaluated in the setting of nonurgent PCI, a relatively low-risk population where ischemic outcomes occur with relatively low frequency. Nonurgent PCI provides a favorable setting to examine the safety and tolerability of novel antithrombotic drugs. There is an easily defined time during which there is a risk of ischemic events and a context in which bleeding is expected to occur (ie, owing to the vascular puncture). There was a high prevalence of enrolled patients on clopidogrel maintenance therapy at the time of enrollment, which may have affected the clinical events. Additionally, although the investigators had a 12-hour window before PCI to administer the clopidogrel oral loading dose, the median time was brief (ie, 9 minutes), which could influence efficacy and safety outcomes. Patients were not systematically followed after study drug termination and, therefore, we are unable to assess medication transition from eliningrel to standard of care. Finally, we did not compare eliningrel with more potent antiplatelet agents such as prasugrel or ticagrelor. Neither of these agents is indicated for nonurgent PCI, and ticagrelor was not commercially available during the conduct of the study.

Conclusions
The INNOVATE-PCI trial demonstrates that, in patients undergoing nonurgent PCI, a strategy of IV and oral eliningrel compared with standard doses of clopidogrel was associated with increased TIMI combined bleeding, although not associated with any appreciable increase in TIMI major or minor bleeding during the acute (IV) or chronic (oral) phases of the study. No difference in clinical efficacy was found, although the trial was not powered for efficacy. These safety and tolerability data support the further development of this novel antiplatelet agent for the treatment of ischemic heart disease.

Disclosures
Dr Welsh has received research funding from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, Portola Pharmaceuticals Inc, and Sanofi-aventis; has received honoraria from AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, and Sanofi-aventis; and has served on consultant/advisory boards of AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Roche, and Sanofi-aventis. Dr Rao has received research funding from Portola Pharmaceuticals Inc; honoraria: AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, Sanofi-aventis, and Terumo; has served on speakers bureaus for Bristol-Myers Squibb and Sanofi-aventis; and has served on the consultant/advisory boards of Bristol-Myers Squibb and The Medicines Company. Dr Zeymer has received research funding from Eli Lilly and Company and Portola Pharmaceuticals Inc; has received honoraria from AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, Novartis, and Sanofi-aventis; and has served on the consultant/advisory boards of AstraZeneca, Bristol-Myers Squibb, Daiichi Sankyo, Eli Lilly and Company, Novartis, and Sanofi-aventis. V. Thompson has no conflicts to disclose. Dr Huber has no conflicts to disclose. Dr Kochman received research funding from Portola Pharmaceuticals Inc. Dr McClure is employed by Portola Pharmaceuticals Inc. Dr Greter is employed by Portola Pharmaceuticals Inc. Dr Bhatt has served on the advisory board of Medscap Cardiology; has served on the board of directors of Boston VA Research Institute and the Society of Chest Pain Centers; has served as chair of the American Heart Association Get With The Guidelines Science Subcommittee; has received honoraria from the American College of Cardiology (Editor, Clinical Trials, CardioSource), Duke Clinical Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today: Intervention), WebMD (CME steering committees); has received research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai Co Ltd, Ethicon, Medtronic, Sanofi-aventis, The Medicines Company; and has conducted unfunded research for PLx Pharma and Takeda. Dr Gibson has received research funding from AstraZeneca, Bayer AG, Genentech, Johnson & Johnson, and Sanofi-aventis; has served on speakers bureaus for Daiichi Sankyo, Eli Lilly and Company, Schering-Plough, and The Medicines Company; and has served on consultant/advisory boards of Bayer AG, Johnson & Johnson, Portola Pharmaceuticals Inc, Sanofi-aventis, Schering-Plough, and The Medicines Company. Dr Angiolillo has received research funding from Accumetrics, AstraZeneca, Bristol-Myers Squibb, Boston Scientific, Daiichi Sankyo, Eisai Co Ltd, Eli Lilly and Company, GlaxoSmithKline, Johnson & Johnson, Otsuka, Portola Pharmaceuticals Inc, Sanofi-aventis, and Schering-Plough; and has received honoraria from Accumetrics, Arena Pharmaceuticals, AstraZeneca, Bristol-Myers Squibb, Eli Lilly and Company, Evolva, Novartis, Medicure, Portola Pharmaceuticals Inc, Roche, and The Medicines Company. Dr Gurbe has received research funding from AstraZeneca, Bayer AG, Bo, Daiichi Sankyo, Eli Lilly and Company, and Haimonetics, Nanosphere, Novartis, Portola Pharmaceuticals Inc, and Sanofi-aventis; has served on speakers bureaus for Accumetrics, AstraZeneca, Daiichi Sankyo, Eli Lilly and Company, Merck, Novartis, Portola Pharmaceuticals Inc, and Sanofi-aventis; has received honoraria from Accumetrics, AstraZeneca, Bayer AG, Daiichi Sankyo, Novartis, Portola Pharmaceuticals Inc, and The Medicines Company; and has served on consultant/advisory boards of AstraZeneca, Bayer AG, Bo, Daiichi Sankyo, Eli Lilly and Company, and Novartis. L. Berdan has no conflicts to disclose. G. Paynter has no conflicts to disclose. Dr Leonard has no conflicts to disclose. Dr Madan MD has received research funding from AstraZeneca and Portola Pharmaceuticals Inc; has served on consultant/advisory boards of AstraZeneca and Eli Lilly and Company; and has received honoraria from AstraZeneca, Eli Lilly and Company, and Portola Pharmaceuticals Inc. Dr French has received research funding from Portola Pharmaceuticals Inc; has served on a speakers bureau for Eli Lilly and Company; and has fulfilled various speaking engagements. Dr Harrington has received research funding from AstraZeneca, Bristol-Myers Squibb, Novartis, Merck, Portola Pharmaceuticals Inc, Sanofi-aventis, and The Medicines Company; and has served on consultant/advisory boards of AstraZeneca, Bristol-Myers Squibb, Merck, Novartis, and Sanofi-aventis.
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A Randomized, Double-Blind, Active-Controlled Phase 2 Trial to Evaluate a Novel Selective and Reversible Intravenous and Oral P2Y\(_{12}\) Inhibitor Elinogrel Versus Clopidogrel in Patients Undergoing Nonurgent Percutaneous Coronary Intervention: The INNOVATE-PCI Trial


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