Pharmacokinetic and Pharmacodynamic Effects of Elinogrel
Results of the Platelet Function Substudy From the Intravenous and Oral Administration of Elinogrel to Evaluate Tolerability and Efficacy in Nonurgent Percutaneous Coronary Intervention Patients (INNOVATE-PCI) Trial

Dominick J. Angiolillo, MD, PhD; Robert C. Welsh, MD; Dietmar Trenk, PhD; Franz-Josef Neumann, MD; Pamela B. Conley, PhD; Matthew W. McClure, MD; Gillian Stephens, PhD; Janusz Kochman, MD; Lisa K. Jennings, PhD; Paul A. Gurbel, MD; Jarosław Wójcik, MD; Marek Dabrowski, MD; Jorge F. Saucedo, MD; Juergen Stumpf, MD; Michael Buerke, MD; Samuel Broderick, PhD; Robert A. Harrington, MD; Sunil V. Rao, MD

Background—Elinogrel is the only selective, competitive and reversible platelet P2Y₁₂ inhibitor available in both intravenous (IV) and oral formulations.

Methods and Results—This substudy of the Intravenous and Oral Administration of Elinogrel to Evaluate Tolerability and Efficacy in Nonurgent Percutaneous Coronary Intervention patients (INNOVATE-PCI) trial evaluated the pharmacokinetic and pharmacodynamic effects of two dosing regimens of IV followed by oral elinogrel (120 mg IV plus 100 mg oral twice daily; 120 mg IV plus 150 mg oral twice daily) versus standard clopidogrel therapy (300–600 mg oral loading dose plus 75 mg oral maintenance dose) in 56 patients undergoing nonurgent PCI. At time of randomization, 71.4% (40/56) of patients were using maintenance clopidogrel therapy. In the acute phase, an IV bolus of elinogrel achieved more rapid and potent antiplatelet effects compared with clopidogrel, which were sustained during the transition from the IV to the oral formulation in the first 24 hours of the peri-PCI period. During chronic therapy, elinogrel achieved similar levels of platelet reactivity compared with clopidogrel before the next oral dose and, although platelet reactivity was lower with elinogrel up to 6 hours after daily oral maintenance dosing, these differences were not statistically significant. These pharmacodynamic effects matched the pharmacokinetic profile of elinogrel. There were no differences in pharmacodynamic and pharmacokinetic effects between the two elinogrel dosing regimens.

Conclusions—Compared with clopidogrel, the combination of IV and oral elinogrel achieves more rapid and enhanced antiplatelet effects that were sustained through the transition to oral elinogrel in the peri-PCI period, but these were not significant during chronic dosing in this pilot investigation.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00751231.

Key Words: elinogrel ■ pharmacodynamics ■ pharmacokinetics

Antiplatelet therapy is of key importance in the management of patients with coronary artery disease. Numerous studies have shown that the addition of a P2Y₁₂ receptor inhibitor to aspirin therapy reduces the incidence of recurrent ischemic events in patients with acute coronary syndrome and in those undergoing percutaneous coronary interventions (PCI). Recently approved P2Y₁₂ inhibitors are characterized by more rapid, potent, and predictable platelet inhibitory effects.
Elinogrel is the only selective, competitive, and reversible P2Y12 inhibitor available in both IV and oral formulations. It is a direct-acting P2Y12 receptor inhibitor that does not require metabolic activation and thus has low potential for drug–drug interactions or genetic modulation. Recently, the dose-ranging Intravenous and Oral Administration of Elinogrel to Evaluate Tolerability and Efficacy in Nonurgent PCI Patients (INNOVATE-PCI) phase 2b trial conducted in patients undergoing nonurgent PCI showed that elinogrel was not associated with increased major or minor bleeding, defined by Thrombolysis In Myocardial Infarction criteria, although there was an increase in bleeding requiring medical attention, primarily at the PCI access site. The present article reports the results of the predefined PK and PD substudy of the INNOVATE-PCI trial.  

**WHAT IS KNOWN**  
- Elinogrel is the only selective, competitive, and reversible platelet P2Y12 inhibitor available in both intravenous (IV) and oral formulations.  
- Transitioning from IV to oral formulations of other classes of P2Y12 receptor antagonists is associated with drug interactions requiring judicious timing of their administration.

**WHAT THE STUDY ADDS**  
- An IV bolus of elinogrel achieves more rapid and potent platelet inhibitory effects compared with clopidogrel, which are sustained during the transition to its oral formulation reaching lower, but not statistically significant, levels of platelet reactivity compared with clopidogrel during chronic therapy in patients undergoing PCI.  
- The pharmacodynamic effects of elinogrel match its pharmacokinetic profile.
mately 13 and 15 hours, respectively, after the IV dose. Patients were instructed to use oral elinogrel twice daily with meals (ie, breakfast and dinner).

The protocol was approved by the Institutional Review Board at the individual sites and the study was conducted in accordance with regulatory standards and good clinical practice guidelines rooted in the Declaration of Helsinki. Separate written informed consents were provided by all patients to participate in the INNOVATE-PCI trial and the platelet function substudy. The authors had full access to the data and take full responsibility for its integrity. All authors participated in the drafting and review of the manuscript and have agreed to the manuscript as written.

Blood Sampling, Pharmacokinetic, and Pharmacodynamic Assessments

Blood samples for PK and PD assessments were collected at the scheduled time points from an antecubital vein using a loose tourniquet. The first 2 to 4 mL of blood were discarded to avoid spontaneous platelet activation. A vacutainer tube containing ethylenediaminetetraacetic acid (1.8 mg/mL) was used for the PK assessment (elinogrel plasma concentration measurements). Vacutainer tubes containing 3.2% trisodium citrate (TSC) were used for assessment (elinogrel plasma concentration measurements). Vacutainer tubes containing a proprietary anticoagulant (C921-78) (factor Xa inhibitor; Portola Pharmaceuticals) were used for PD assessments using perfusion chamber assay and LTA after 5 and 10 µmol/L ADP and 4 µg/mL collagen stimuli. In addition, vacutainer tubes containing 100% for platelet-poor plasma for each measurement. LTA was performed on addition of 5 µmol/L ADP and 4 µg/mL collagen (Chronolog, Havertown, PA) stimuli from blood anticoagulated with C921-78. Aggregation response was recorded for 6 minutes and on-treatment peak platelet aggregation values were reported.

Pharmacodynamic Assessment

Platelet aggregation was performed with the use of LTA according to standard protocols, as previously described. Briefly, platelet aggregation was assessed using PRP by the turbidimetric method. PRP was the supernatant collected after centrifugation of anticoagulated blood at 250g for 10 minutes. The isolated PRP was kept capped at 37°C before use. Platelet-poor plasma was the supernatant collected after a second centrifugation of the blood fraction at 1,000g for 10 minutes. Light transmission was adjusted to 0% with PRP and to 100% for platelet-poor plasma for each measurement. LTA was performed on addition of 5 µmol/L ADP (Sigma, St. Louis, MO) from blood anticoagulated with citrate and on addition of 5 and 10 µmol/L ADP and 4 µg/mL collagen (Chronolog, Havertown, PA) stimuli from blood anticoagulated with C921-78. Aggregation response was recorded for 6 minutes and on-treatment peak platelet aggregation values were reported.

Pharmacokinetic Assessment

Plasma samples were obtained at selected time points and shipped to a central core laboratory (Cedra Corporation, Austin, TX) for analysis. Sample analysis for study drug concentrations were performed by validated methods using high-performance liquid chromatography with mass spectrometry detection for quantification of elinogrel, as previously described.

Blinding

Sites participating in the platelet function substudy used an unblinded technician to perform and report aggregometry results. Technicians, however, were blinded to treatment assignment and were instructed to keep all results confidential to ensure that personnel involved in the clinical treatment or assessment of patients enrolled in the trial remained blinded. Substudy sites remained...
Statistical Analysis

Pharmacodynamic Assessment
The analysis population for this assessment included subjects who enrolled in the platelet function substudy and received any study drug. There was not a sample size calculation for this substudy because this analysis was the first to evaluate both IV and oral dosing of elinogrel in humans. Therefore, this substudy served to provide pilot data for future investigations. Our objective was to achieve at least 15 patients per group to have meaningful PK/PD information.

Pharmacokinetic Assessment
The analysis population for the PK assessment included subjects who enrolled in the platelet function substudy and received elinogrel. For each PK sampling time point, medians of elinogrel concentrations were calculated for each of the two elinogrel treatment groups in the substudy. Plots of the medians over time were constructed for both the acute and chronic phases.

Results

Study Population
A total of 56 patients (20 treated with clopidogrel and 36 with elinogrel) of the overall trial population (n=652) agreed to participate in the platelet function substudy of the INNOVATE-PCI trial. The clinical characteristics of these subjects are shown in Table. There were no significant differences between groups except for a higher prevalence of patients with previous coronary artery bypass surgery in the clopidogrel arm (P=0.01). Patient characteristics did not differ significantly from those of the overall cohort enrolled in the INNOVATE-PCI study (data not shown). At time of randomization, 71.4% (40/56) of substudy patients were using maintenance clopidogrel therapy with approximately equal distribution across treatment groups (Table).
In the acute phase of treatment, there were no differences in baseline levels of platelet reactivity between groups (Figure 2A–C). Patients randomized to treatment with elinogrel achieved more rapid and potent antiplatelet effects than clopidogrel, as assessed with LTA after 5 and 10 μmol/L ADP stimuli in C921–78–anticoagulated PRP and after 5 μmol/L ADP stimuli in citrate-anticoagulated PRP. For both elinogrel and clopidogrel, the overall extent of aggregation was greater at each time point when 10 μmol/L ADP was used as an agonist (Figure 2B), compared with 5 μmol/L ADP (Figure 2A). The antiplatelet effect observed with 5 μmol/L ADP in citrate-anticoagulated PRP and 5 μmol/L ADP stimuli in PRP anticoagulated was similar to that using 5 μmol/L ADP in PRP anticoagulated with C921-78 (Figure 2A). In particular, near-maximal levels of antiplatelet activity were achieved within 15 to 30 minutes with elinogrel and between 2 and 6 hours with clopidogrel irrespective of ADP concentration or anticoagulant. The absolute difference in extent of platelet aggregation between clopidogrel and elinogrel doses during the acute peri-PCI period was approximately 6% to 24% based on LTA using 5 μmol/L ADP stimuli in C921-78. The observed PD effects were sustained during the transition from the IV to the oral formulation of elinogrel, suggesting there is no interruption in platelet inhibition when transitioning from IV to oral elinogrel. PD profiles were similar among patients treated with elinogrel 120 mg IV plus 100 mg oral dose compared with elinogrel 120 mg IV plus 150 mg oral without any differences in on-treatment platelet reactivity between groups. Parallel findings during the dosing cycle, albeit less enhanced, were observed with LTA after collagen stimuli (data not shown). In contrast, PD results from the perfusion chamber assay were not easily interpretable, because all three dosing arms showed full inhibition at most time points (data not shown), indicating that the assay was fully saturated.

During chronic therapy, elinogrel achieved similar platelet inhibition to clopidogrel before the next oral dose (trough levels), as shown in Figure 3A, 3B, and 3C. After daily oral

**Figure 2.** Pharmacodynamic assessment during the acute peri-percutaneous coronary intervention (PCI) period. Pharmacodynamic effects of two dosing regimens of elinogrel (120 mg intravenous [IV] plus 100 mg oral dose and 120 mg IV plus 150 mg oral dose) compared with clopidogrel (300–600 mg loading dose plus 75 mg maintenance dose) using light transmittance aggregometry after 5 μmol/L adenosine diphosphate (ADP) stimuli in C921–78 (A), 10 μmol/L ADP stimuli in C921–78 (B), and 5 μmol/L ADP stimuli in citrate (C). Platelet aggregation data are expressed as median and interquartile ranges of percentage of maximal (peak) platelet aggregation. LD, loading dose; MD, maintenance dose; IV, intravenous; PO, oral.
maintenance dose administration, although elinogrel was associated with lower levels of platelet reactivity (absolute difference in extent of platelet aggregation between clopidogrel and elinogrel doses was approximately 10% to 18% based on LTA using 5 \(\mu\)mol/L ADP stimuli in C921-78) approximately 2 to 6 hours after dosing (Figure 3A–C), this difference was not statistically significant. The PD profiles were similar among patients treated with elinogrel 100 mg dose compared with elinogrel 150 mg dose without any differences in on-treatment platelet reactivity between groups.

**Pharmacokinetic Assessments**

The PK data were available in 36 elinogrel-treated patients (120 mg IV plus 100 mg oral dose \([n=15]\) and 120 mg IV plus 150 mg oral dose \([n=21]\)). In the acute phase of treatment, PK assessments after IV administration showed the highest plasma drug levels at approximately 15 to 30 minutes, which was the earliest time point measured, followed by a decline that reached steady-state levels (ie, day 30 levels) after approximately 20 hours post-PCI. The median elinogrel Cmax during the acute phase was 30,600 ng/mL and 20,700 ng/mL for the 120 mg IV plus 100 mg oral dose and 120 mg IV plus 150 mg oral dose, respectively \((P=0.0079)\). The area under the curve levels for the first 24 hours after IV administration (153,088 versus 163,091 ng.hr/mL; \(P=0.73\)) were similar between patients treated with 120 mg IV plus 100 mg oral dose and 120 mg IV plus 150 mg oral dose, respectively (Figure 4A). In the chronic phase of treatment, plasma levels of elinogrel were similar to those observed after 20 hours in the acute phase of treatment, with small differences between groups and substantial overlap in plasma concentrations between the 100 mg and 150 mg elinogrel doses (Figure 4B). The time course of the PD effect parallels the PK of elinogrel, as expected for a direct-acting reversible drug.

**Discussion**

Elinogrel is a quinazolinedione with selective, competitive, and reversible inhibitory effects on the platelet P2Y\(_{12}\) receptor.\(^8\) It is the only P2Y\(_{12}\) receptor antagonist available in both IV and oral formulations and, therefore, presents the advantages of having immediate platelet inhibitory effects after parenteral administration and a seamless transition to oral

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**Figure 3.** Pharmacodynamic assessment during the chronic (day 30) period. Pharmacodynamic effects of two dosing regimens of elinogrel (100 mg and 150 mg oral doses) compared with clopidogrel (75 mg maintenance dose) using light transmittance aggregometry after 5 \(\mu\)mol/L adenosine diphosphate (ADP) stimuli in C921-78 (A), 10 \(\mu\)mol/L ADP stimuli in C921-78 (B), and 5 \(\mu\)mol/L ADP stimuli in citrate (C). Platelet aggregation data are expressed as median and interquartile ranges of percentage of maximal (peak) platelet aggregation.

\[ * = p<0.05 \text{ for E100 vs. clopidogrel} \]
administration without concerns of drug interactions. The combination of the two formulations of oral and IV dosing was tested for the first time in the INNOVATE-PCI trial, a phase 2b dose-ranging study conducted in patients undergoing nonurgent PCI. The present analysis describes the results of the predefined substudy of the INNOVATE-PCI trial assessing the PK and PD effects of elinogrel in the acute and chronic phases of therapy. In particular, in the acute phase of treatment, an IV bolus of elinogrel achieved more rapid and potent antiplatelet effects compared with clopidogrel, which were sustained during the transition from the IV to the oral formulation in the first 24 hours of the peri-PCI period. During chronic therapy, elinogrel achieved similar platelet inhibition to clopidogrel before the next oral dose (trough levels) and, although elinogrel was associated with lower levels of platelet reactivity up to 6 hours after daily oral maintenance dose administration, these differences were not statistically significant. The PK assessments showed a rapid increase in plasma drug levels, with a maximum measured concentration at approximately 15 to 30 minutes after IV administration, followed by a decline that reached steady-state (ie, day 30) levels after approximately 20 hours.
hours. There were no important differences in PD and PK effects between the two dosing regimens of elinogrel tested in this substudy.

The findings of the present pilot substudy provide important insights that may be pivotal for the future clinical development of elinogrel. The PD effects of IV elinogrel demonstrate very rapid and potent platelet inhibitory activity. In particular, near-maximal platelet inhibitory effects were observed within 15 to 30 minutes after IV bolus administration. However, because this evaluation is the earliest measured PD time point, it cannot be excluded that even more immediate antplatelet effects may be observed if earlier functional determinations had been performed, consistent with the Cmax levels occurring nearly instantaneously after IV bolus administration. Importantly, these observed PD effects were predictable, leading to near-complete blockade of ADP-induced aggregation. Further, these platelet inhibitory effects were additive, as demonstrated by increased platelet inhibition in the elinogrel arms, relative to baseline measurements, in which most patients were already using clopidogrel maintenance therapy. In fact, IV elinogrel provided increased antplatelet effects in addition to clopidogrel and aspirin therapy, a finding that is in line with previous investigations conducted in clopidogrel-treated patients with high platelet reactivity. Overall, these increased antplatelet effects are desirable properties, particularly in the peri-PCI period, and may overcome the limitations of oral P2Y12 inhibiting agents, which have a longer time to onset of platelet inhibition. In fact, although novel oral P2Y12 platelet inhibitors such as prasugrel and ticagrelor also achieve high levels of platelet inhibition and have additive inhibitory effects in patients already using clopidogrel treatment, they require more time (approximately 1–2 hours) than an IV bolus of elinogrel to reach their maximal effects. Furthermore, on the basis of PK principles, it is expected that an IV formulation of a given drug, especially if administered as an infusion, will deliver a more consistent, predictable, and titratable exposure over time than an oral formulation, which is a desirable property in the peri-PCI period. Of note, elinogrel does not have concerns of drug interaction during transition from its IV to oral formulation, a phenomenon that affects cangrelor, an investigational P2Y12 receptor antagonist available in an IV formulation that requires judicious timing of administration of oral P2Y12 agents after discontinuation of cangrelor.

Intersubject response variability to antplatelet therapy, particularly in clopidogrel-treated patients, has emerged as a concern given its association with adverse outcomes. In particular, genetic and environmental factors interfering with clopidogrel metabolism have been associated with limited drug response and an increased risk of atherothrombotic events. These factors are not known or expected to impact elinogrel because it does not require metabolic activation and is direct acting; therefore, it represents a potentially promising antplatelet agent in the acute coronary syndrome/PCI setting. Equally important, the PD results from this substudy suggest that chronic orally administered elinogrel is at least as pharmacodynamically effective as clopidogrel throughout the dosing cycle.

In this investigation, the observation that the peak and trough PK effects were paralleled by PD effects during both the acute phase and chronic phase is also a desired property, particularly for those patients who need to undergo surgery. Although this study was not designed to assess pharmacological washout of elinogrel as patients underwent PCI and thus needed to maintain P2Y12 inhibiting therapy, previous studies have shown a return to baseline PD effects within 36 to 48 hours of last oral administration of elinogrel (Portola, data on file). This return of function is more rapid than that observed with the other available oral reversible P2Y12 receptor inhibitor, ticagrelor, for which approximately 5 days are needed to return to baseline response after withdrawal and for which drug-regulating authorities in the United States and Europe recommend 5 or 7 days, respectively, of washout before surgery to reduce bleeding complications. However, it needs to be acknowledged that this PK–PD property of elinogrel may raise concerns for subjects with poor compliance because they may be exposed to subtherapeutic antplatelet effects when they miss doses. Dedicated studies are warranted to fully understand the washout properties of elinogrel when used at therapeutic doses.

Previous investigations have shown dose-responsive effects with lower doses of elinogrel than studied in INNOVATE-PCI. By contrast, there were no significant differences in PD measures between the elinogrel dosing regimens in this study. This observation may be attributable to the fact that the PD assay was saturated and thus unable to detect greater levels of platelet inhibition. The similar levels of antplatelet effect observed at the 15 to 30 minutes after IV administration time point, when maximal P2Y12 inhibition was observed, and at the 6 hours after day 30 oral dose time point are consistent with this hypothesis. Additionally, the PD findings are in line with the PK assessments, which show only modest differences in plasma levels of elinogrel with the 100 mg and 150 mg maintenance dosing regimens. Although the impact of elinogrel dosing on efficacy and safety measures warrants further investigation, this small substudy does not suggest that the 150 mg oral dose regimen of elinogrel has substantially different PK or PD effects over a 100 mg dose.

Study Limitations

This was a small sample study in which no formal sample size calculations or statistical adjustments for the multiplicity of the tests were performed. However, this is justified in small proof-of-concept studies that serve to provide pilot data for large-scale investigations. Numerous assays are currently available to test for P2Y12-mediated effects. In the present study, we limited our PD assessments to LTA and perfusion chamber assay. Whereas other currently available tests such as vasodilator-stimulated phosphoprotein phosphorylation measurements and VerifyNow P2Y12 would have been of additive value, these tests were not performed because of the ethical restrictions on the total blood volume permitted to be sampled. In fact, the present substudy included numerous time points during which multiple LTA assessments were conducted, in addition to the PK analysis and other laboratory measures conducted as part of the main trial. Further, the use of higher concentrations of ADP in citrated blood in the PD
assessments would have allowed a better comparison of the results with other novel P2Y12 inhibitors. However, during platelet stimulation with high ADP concentrations, elinogrel effects are less pronounced because of its direct competition with ADP for the P2Y12 receptor. Therefore, this property also may imply limitations of PD assays to fully define the platelet inhibitory effects of elinogrel. Nevertheless, the competitive effects of elinogrel for ADP binding have been suggested to be a beneficial property of elinogrel, because this may mitigate the bleeding potential of this compound as higher ADP levels are encountered in active major bleeding than in ischemic/thrombotic events. The differences in PK this may mitigate the bleeding potential of this compound as higher ADP levels are encountered in active major bleeding than in ischemic/thrombotic events. The differences in PK/PD profile as well as the safety and efficacy of elinogrel. Nevertheless, the platelet inhibitory effects of elinogrel. Nevertheless, the platelet inhibitory effects of elinogrel. Nevertheless, the platelet inhibitory effects of elinogrel.

Conclusions

In summary, in the acute phase of treatment, an IV bolus of elinogrel achieved more rapid and potent antiplatelet effects compared with clopidogrel, as assessed by multiple determinations using light transmission aggregometry, which were sustained during the transition from the IV to the oral formulation in the first 24 hours of the peri-PCI period. During chronic therapy, elinogrel achieved similar platelet inhibition to clopidogrel before the next oral dose (trough levels), and although elinogrel was associated with lower levels of platelet reactivity up to 6 hours after daily oral maintenance dose administration, these differences were not statistically significant. As expected for a direct-acting reversible inhibitor, the observed PD effects closely matched the observed PK profile of elinogrel throughout the dosing cycle. Additional studies are warranted to further define the PK/PD profile as well as the safety and efficacy of elinogrel.

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Disclosures

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