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MONOGRAPH

ELINOGREL POTASSIUM

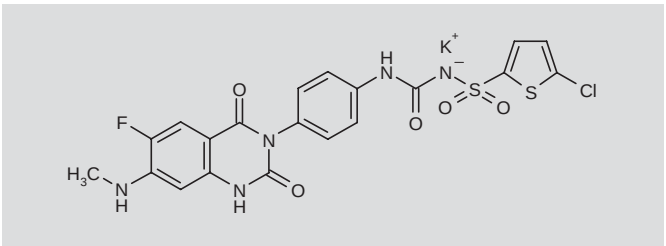
Rec INNM; USAN

$P2Y_{12}$ Receptor Antagonist
Antiplatelet Therapy

PRT-060128
PRT-128

N-[4-[6-Fluoro-7-(methylamino)-2,4-dioxo-1,2,3,4-tetrahydroquinazolin-3-yl]phenyl]-*N*'-(5-chlorothien-2-ylsulfonyl)urea potassium salt

InChI: 1S/C20H15ClFN5O5S2.K/c1-23-15-9-14-12(8-13(15)22)18(28)27(20(30)25-14)11-4-2-10(3-5-11)24-19(29)26-34(31,32)17-7-6-16(21)33-17;/h2-9H,1H3,(H4,23,24,25,26,28,29,30);/q;+1/p-1



$C_{20}H_{14}ClFKN_5O_5S_2$
Mol wt: 562.0350
CAS: 936501-01-8
CAS: 936500-94-6 (free acid)
CAS: 936540-26-0 (sodium salt)
EN: 452678

SUMMARY

The pharmacological management of cardiovascular disease patients with antiplatelet therapy has undergone dramatic changes in recent years with the development of new and more potent $P2Y_{12}$ receptor antagonists. These agents have been developed to address the limitations of the most widely used $P2Y_{12}$ receptor antagonist, clopidogrel. Among the limitations of clopidogrel addressed are response variability and resistance. The latter has been linked to ischemic event occurrence and stent thrombosis in patients treated with percutaneous intervention (PCI). The irreversible effect of clopidogrel is problematic in patients needing urgent surgery. Treatment with the recently approved third-generation thienopyridine prasugrel was associated with less ischemic event occurrence and stent thrombosis compared to clopidogrel therapy in patients with acute coronary artery syndrome (ACS) undergoing PCI. However, greater bleeding, including life-threatening and fatal bleeding, was observed in the prasugrel-treated patients. Ticagrelor is a member of a new class of $P2Y_{12}$ inhibitors, the cyclopentyl-triazolo-pyrimidines (CPTP), the first direct-acting, reversibly-binding, noncompetitive $P2Y_{12}$ receptor antagonist. Ticagrelor therapy resulted in less ischemic event occurrence than clopidogrel in ACS patients. An important potential advantage of ticagrelor is lower mortality and less coronary artery bypass graft-related bleeding than clopidogrel. However, ticagrelor therapy was associated with dyspnea in both phase II and III clinical trials. Cangrelor, an adenosine triphosphate (ATP) analogue, is a parenteral, direct, competitive and reversible $P2Y_{12}$ inhibitor associated with rapid onset and offset of platelet inhibition (within minutes). However, in phase III trials cangrelor was not superior to placebo in reducing ischemic events in patients undergoing PCI who were treated with clopidogrel alone. Elinogrel (PRT-060128) is a novel, direct-acting, competitive and reversible $P2Y_{12}$ receptor antagonist. Elinogrel is a first-in-class sulfonylurea that may be administered intravenously or orally. The latter route of administration may facilitate the transition from immediate to long-term therapy. Results from the INNOVATE-PCI (phase II) trial regarding the safety and antiplatelet efficacy of elinogrel compared to clopidogrel will be published soon.

SYNTHESIS*

Elinogrel potassium is prepared as follows. Condensation of methyl 2-amino-4,5-difluorobenzoate (I) with 4-nitrophenyl chloroformate (II) in refluxing CH_2Cl_2 gives the 4-nitrophenyl carbamate (III), which is condensed with 4-(Boc-amino)aniline (IV) in the presence of Et_3N in THF at 60-70 °C to yield the diaryl urea (V), which, without isolation, is cyclized to the quinazoline-2,4-dione (VI) upon treatment with methanolic NaOMe or DBU. Alternatively, diaryl urea (V) is prepared by treatment of anthranilate (I) with $COCl_2$ in toluene to yield isocyanate (VII) and/or carbamoyl chloride (VIII), which are then condensed with 4-(Boc-amino)aniline (IV) in the presence of Et_3N in DMF (1-4). Deprotection of the amino group in compound (VI) by removal of the Boc group by means of HCl in dioxane provides 3-(4-aminophenyl)-6,7-difluoroquinazoline-2,4(1*H*,3*H*)-dione hydrochloride (IX), which undergoes selective fluoride displacement with methylamine (X) in DMSO at 110 °C to provide 3-(4-aminophenyl)-6-fluoro-7-(methylamino)quinazoline-2,4(1*H*,3*H*)-dione (XI). Subse-

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quent carbamoylation of the primary amino group of quinazoline (XI) with ethyl *N*-(5-chlorothien-2-ylsulfonyl)carbamate (XII) in refluxing DMSO or acetonitrile yields elinogrel (XIII) (1-4), which is finally converted to its potassium salt by treatment with KOH in acetonitrile/H_2O at 45-55 °C (2-4). Scheme 1.

Key intermediate (XII) is prepared by chlorosulfonation of 2-chlorothiophene (XIV) with $ClSO_3H$ and PCl_5 to give 5-chlorothien-2-ylsulfonyl chloride (XV), which by treatment with NH_4OH in H_2O/THF yields sulfonamide derivative (XVI). Finally, sulfonamide (XVI) is condensed with ethyl chloroformate (XVII) by means of Cs_2CO_3 in THF (1-4). Scheme 2.

BACKGROUND

Platelet activation and aggregation play pivotal roles in the development of ischemic events in patients with coronary artery diseases (CAD). Adenosine diphosphate (ADP), an important secondary agonist released from dense granules upon activation by various agonists, is pivotal in the amplification of platelet activation and aggregation. In addition, the $P2Y_{12}$ receptor-mediated pathway is responsible for sustained activation of the GPIIb/IIIa receptor and the subsequent generation of a stable thrombus at the site of plaque rupture (5-7). Furthermore, platelet activation results in the expression of surface adhesion molecules, especially P-selectin and CD40 ligand, leading to heterotypic aggregation of platelets with leukocytes. Such heterotypic interactions promote both inflammation and amplification of thrombin generation. Finally, platelet activation also results in membrane exposure of phosphatidyl serine, which provides binding sites for coagulation factors. The coagulation process results in the generation of thrombin and subsequent platelet–fibrin clot formation (7). Therefore, the $P2Y_{12}$ receptor pathway is a central target in the treatment of patients with atherothrombotic disease. In support of this premise, it has been demonstrated that dual antiplatelet therapy that targets the $P2Y_{12}$ receptor pathway by thienopyridines and the cyclooxygenase COX-1 pathway by aspirin has improved clinical outcomes in a wide range of patients with CAD (8). However, despite dual antiplatelet therapy, recurrent thrombotic events are not uncommon and stent thrombosis remains a major concern. Treatment failure has been attributed, in part, to the specific limitation of clopidogrel therapy in effectively inhibiting platelet function in many patients (9).

Clopidogrel is a prodrug that undergoes two-step hepatic conversion to an active metabolite that irreversibly inhibits the $P2Y_{12}$ receptor. ADP-induced activation and aggregation are subsequently inhibited for the lifetime of the platelet. The pharmacodynamic effects of clopidogrel are characterized by a delayed onset of action, wide response variability and an overall modest degree of platelet inhibition. Moreover, a substantial percentage of patients exhibit either limited or no platelet inhibition, and consequently have high on-treatment platelet reactivity (HPR) to ADP, as measured by ex vivo assays. This phenomenon has been described as "clopidogrel resistance" or "nonresponsiveness" (10). Multiple studies have repeatedly demonstrated the relationship between HPR to ADP and the occurrence of ischemic events in patients undergoing percutaneous intervention (PCI). Nonuniform and limited hepatic active metabolite generation are considered to be the primary reasons for clopidogrel response variability and nonresponsiveness, respectively. The level of active metabolite generation may also be influenced by variability in intestinal absorption (due to drug–drug interactions or single nucleotide polymorphisms [SNPs] of the *ABCB1* gene). Variability in hepatic cytochrome (CYP) P450 isoenzyme activity is also due to drug–drug interactions and SNPs of genes encoding CYP P450 isoenzymes (11).

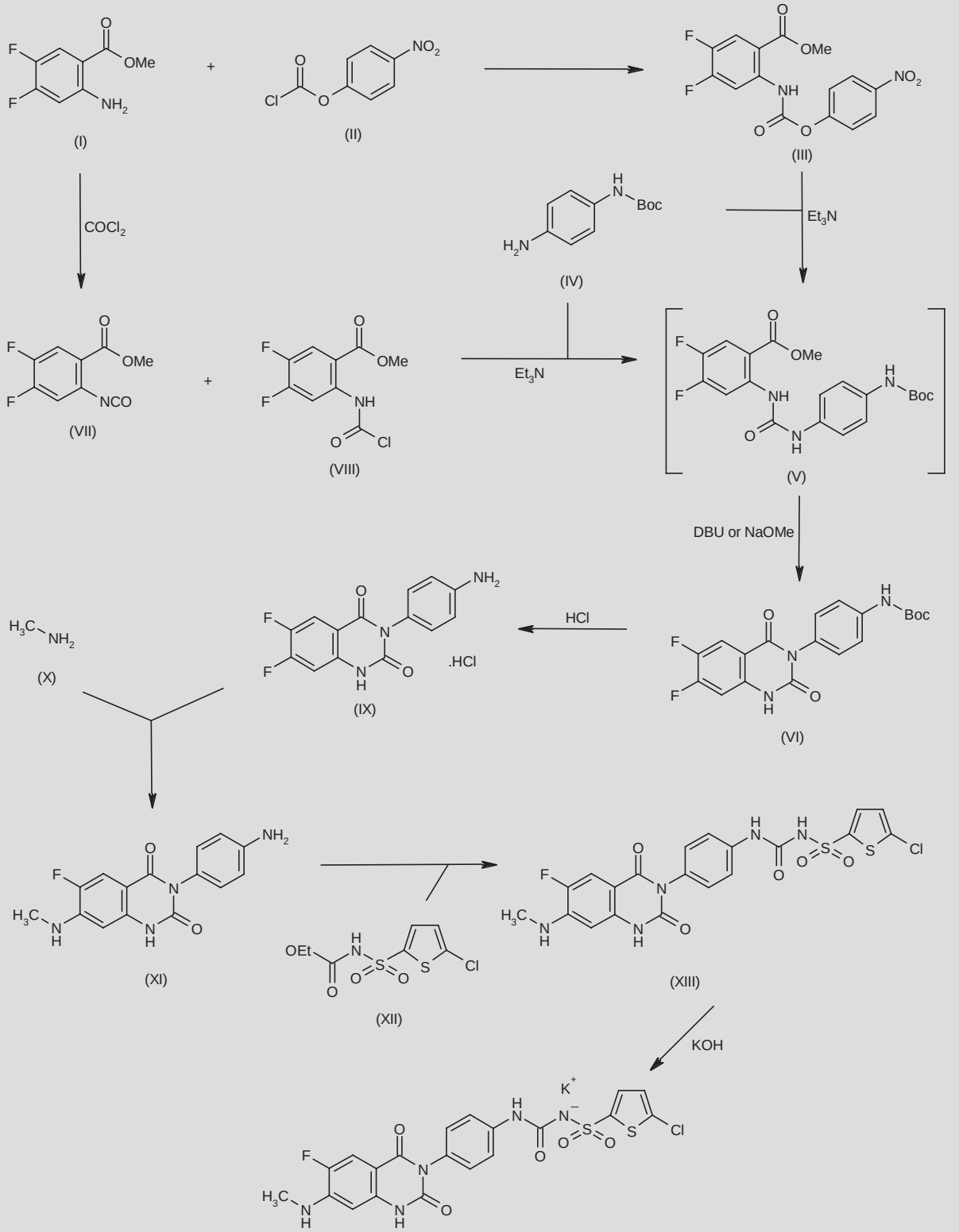
The third-generation thienopyridine, prasugrel, was developed to address the limitations of clopidogrel therapy. Prasugrel has a faster onset of action and provides greater and more consistent platelet inhibition than clopidogrel. Thus far, prasugrel metabolism has not been reported to be affected by SNPs or have significant drug–drug interactions involving the hepatic CYP P450 system (12). Compared with the combination therapy of clopidogrel and aspirin, the combination therapy of prasugrel and aspirin was associated with significantly improved clinical outcomes (20% relative decrease in major cardiovascular events) among acute coronary syndrome (ACS) patients undergoing PCI in the TRITON-TIMI 38 trial. However, the higher level of irreversible platelet inhibition achieved by prasugrel (versus clopidogrel) may have accounted for an increased incidence of both coronary artery bypass graft (CABG)- and non-CABG-related major bleeding events. Because of this increased bleeding risk, prasugrel is contraindicated in patients with active pathological bleeding, and also in patients with a history of transient ischemic attack or stroke, and should be used with caution in selected patients who weigh < 60 kg or are ≥ 75 years old. Prasugrel should be discontinued at least 7 days prior to any surgical procedure if possible (13). Although an increased occurrence of solid tumors was observed among prasugrel-treated patients in the TRITON-TIMI 38 study, the potential mechanisms underlying this observation and its significance are unclear and a subject of debate (14).

Irreversible inhibition of the $P2Y_{12}$ receptor by thienopyridines is associated with a delayed recovery of platelet function and a narrow therapeutic window for the occurrence of ischemic and bleeding events. Since the usual life span of a platelet is up to 10 days, delayed or slow recovery of platelet function following discontinuation of a thienopyridine is an important potential limitation for patients who require urgent surgery. This limitation provides a rationale for the development of reversible $P2Y_{12}$ receptor blockers (15).

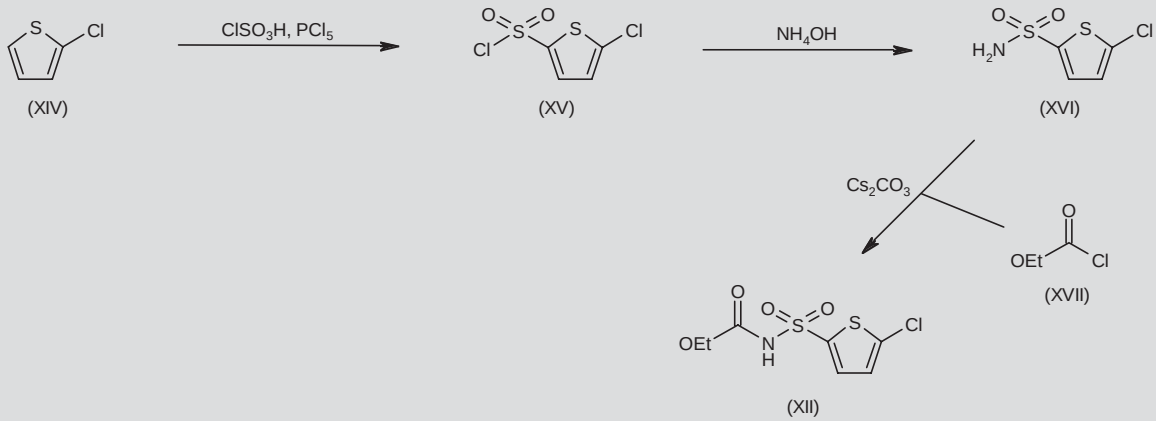
Ticagrelor (AstraZeneca) was the first oral, reversibly-binding and direct-acting $P2Y_{12}$ receptor blocker. Ticagrelor belongs to the cyclopentyl-triazolo-pyrimidine (CPTP) class of antiplatelet agents. It has been reported that ticagrelor does not prevent ADP binding, but reversibly inhibits receptor conformational changes and G-protein activation induced by ADP by binding to a site distinct from the ADP binding site (15).

In the Platelet Inhibition and Patient Outcomes (PLATO) trial, ticagrelor was compared to clopidogrel and significantly reduced the rate of the combined endpoint of cardiovascular death, nonfatal myocardial infarction or nonfatal stroke in patients with ACS who were treated with aspirin (1.87% absolute and 16% relative risk reduction; $P = 0.0003$). Other important observations from the PLATO trial included the relative benefit of ticagrelor for reductions in both stent thrombosis and mortality, as well as a lower prevalence of CABG-related bleeding. Dyspnea was more common following ticagrelor (13.8% vs. 7.8%; $P < 0.001$), but infrequently (0.9%) required discontinuation of therapy. A higher frequency of ventricu-

Scheme 1. Synthesis of Elinogrel Potassium



Scheme 2. Synthesis of Intermediate (XII)



lar pause (≥ 3 s) determined by Holter monitoring was observed during ticagrelor treatment during the first week of therapy (5.8% vs. 3.8%; *P* = 0.01), but was no longer evident at 30 days (16).

In the ONSET/OFFSET study, which compared the onset of platelet inhibition and recovery following ticagrelor or clopidogrel therapy in ACS patients, ticagrelor was associated with a more rapid onset of action (evident within 30 min), a superior level of inhibition that persisted during maintenance therapy, and a more rapid offset of action (recovery of platelet aggregation) (17).

In the RESPOND study, ticagrelor was associated with a greater level of platelet inhibition compared to clopidogrel in both clopidogrel responders and nonresponders. Furthermore, ticagrelor significantly reduced the prevalence of HPR that was evident within 30 min of therapy (18). Recently, the FDA Cardiovascular and Renal Drugs Advisory Committee voted to recommend approval of ticagrelor for patients with either ST-segment elevation myocardial infarction (STEMI) or non-STEMI who will be treated with PCI or with medical management.

Cangrelor, an ATP analogue, is a parenteral, competitive, direct-acting, reversible $P2Y_{12}$ inhibitor with very rapid onset and offset pharmacodynamics (within minutes). However, a major challenge facing cangrelor is the ability to safely and effectively sequence this agent with the irreversible oral thienopyridine agents. For example, in a study involving healthy volunteers, the degree of platelet inhibition observed following oral clopidogrel loading was affected by the concomitant administration of cangrelor. When clopidogrel was administered simultaneously with a cangrelor bolus the level of sustained platelet inhibition for the clopidogrel load was less than expected (19). It appears that the active metabolite of clopidogrel (or prasugrel) is precluded access to the $P2Y_{12}$ receptor by the presence of cangrelor. As thienopyridine active metabolites appear transiently, the concomitant presence of cangrelor can effectively "block" their effect on platelets (20). In the recently published phase II clinical trials of patients undergoing PCI who were randomly assigned to therapy with either cangrelor or placebo, cangrelor was not superior to placebo for reducing the composite occurrence of death, myocardial infarction or ischemia-driven revascularization at 48 h, which comprised the study's primary endpoint (21, 22).

A novel, direct-acting, competitive and reversible $P2Y_{12}$ receptor antagonist, elinogrel (PRT-060128), has been developed by Portola Pharmaceuticals. Elinogrel is a first-in-class sulfonylurea that may be administered either intravenously (i.v.) or orally (p.o.). This dual route of administration may facilitate achievement of a smooth transition from short- to long-term platelet inhibitor therapy (23).

PRECLINICAL PHARMACOLOGY

The in vitro antithrombotic effects (anti-initiation, -propagation, -stabilization of thrombosis) of aspirin, elinogrel and a GPIIb/IIIa inhibitor (eptifibatide) were evaluated in anticoagulated human whole blood by real-time perfusion chamber technology (RTTP). In this assay, the rate of deposition of fluorescently labeled platelets on a collagen-coated perfusion tube is monitored continuously. In this experiment, eptifibatide at clinically relevant concentrations was associated with significant attenuation of thrombus growth. Aspirin alone did not affect the rate of thrombus formation but destabilized the thrombus. Adding elinogrel to aspirin further decreased the rate of thrombus formation compared to aspirin alone (1.80 FU/s vs. 2.70 FU/s; $P < 0.01$) (24).

A significant increase in the surface expression of $P2Y_{12}$ receptors derived from the internal platelet pool was demonstrated following thrombin stimulation using saturation binding experiments in both nonfixed (from 894 to 1069 [^{3}H]-2-MeS-ADP molecules/platelet) and fixed (to limit the internalization; from 109 to 283 [^{3}H]-2-MeS-ADP molecules/platelet) mouse platelets in an in vitro study by Haberstock-Debic et al. (25). The increased surface expression of $P2Y_{12}$ receptors was observed in platelets from clopidogrel-treated mice in this study. Furthermore, the differential $P2Y_{12}$ receptor antagonist properties of clopidogrel and elinogrel were evaluated in mice treated with 0.5-50 mg/kg clopidogrel for 3 days. Clopidogrel was associated with a dose-dependent inhibition of ex vivo platelet aggregation in response to 10 µM ADP, reaching maximum inhibi-

tion (98%) at a dose of 50 mg/kg. Clopidogrel treatment was also associated with inhibition of ex vivo binding of [^{3}H]-2-MeS-ADP to unstimulated platelets in both washed platelets and platelet-rich plasma (65-100% inhibition). However, despite superior inhibition of surface $P2Y_{12}$ receptors, ex vivo platelet aggregation was similar in both clopidogrel- (50 µg/kg) and vehicle-treated mice following both thrombin receptor activator peptide (TRAP) and collagen stimulation. Elinogrel (added in vitro) was associated with further dose-dependent inhibition of ex vivo platelet aggregation in clopidogrel-treated mice. Finally, in an in vivo $FeCl_3$ mesenteric artery injury thrombosis model, fewer platelets were recruited at the site of vascular injury in either elinogrel (60 mg/kg)-treated mice or $P2Y_{12}$ receptor knockout mice when compared to clopidogrel (50 µg/kg)-treated mice. Moreover, the i.v. administration of elinogrel (1 mg/kg) completely blocked residual thrombotic activity in mice that were orally gavaged with 50 µg/kg clopidogrel. These experiments demonstrate that strong agonists (collagen and TRAP) are capable of inducing the internal pool of $P2Y_{12}$ receptors to be expressed on the platelet surface and that these receptors are relatively insensitive to clopidogrel but can be effectively inhibited by elinogrel.

Inhibition of ex vivo 10 µM ADP- and 4 µg/mL collagen-induced platelet aggregation was evaluated in 20 healthy volunteers following treatment with clopidogrel (75 mg/day for 14 days) with or without aspirin (325 mg/day for 7 days), and was similar to platelet inhibition observed following the in vitro addition of elinogrel (0.5-3.0 mM). In the same experiment, higher concentrations of elinogrel resulted in greater inhibition of platelet aggregation. Similarly, the inhibition of thrombus formation by 1.25 mM elinogrel was similar to that observed following clopidogrel with or without aspirin, and higher concentrations of elinogrel (2.5 and 5 mM) resulted in even greater inhibition in the RTTP assay. In the same study, two of the five diabetic patients undergoing stenting were demonstrated to be nonresponders to clopidogrel where no destabilization of thrombus was observed in the RTTP assay. A clear antithrombotic effect with the destabilization of thrombus was observed when elinogrel (2.5 or 5 nM) was added in vitro to the blood samples collected from these nonresponders (26).

The effects of i.v. elinogrel (2.5, 7.5, 20 and 60 mg/kg) administered with or without the specific factor Xa inhibitor betrixaban (2, 10, 40 and 400 mg/kg) were evaluated in a mouse model of arterial thrombosis induced by $FeCl_3$ and monitored in real time using intravital microscopy. Both agents administered alone provided a dose-dependent prolongation of the time to appearance of first thrombus, as well as the time to vascular occlusion. Maximum effects were observed at plasma concentrations ≥ 1 g/mL for both antagonists. A strong synergistic inhibitory effect was observed when both compounds were administered together (2.5 mg/kg elinogrel and 2 mg/kg betrixaban) (27).

The differential effect of $P2Y_{12}$ receptor inhibition by clopidogrel (50 µg/kg), prasugrel (10 mg/kg) or elinogrel (60 mg/kg) on thrombosis was studied in the mouse mesenteric $FeCl_3$-induced injury model and relative effects on hemostasis were evaluated in the mouse tail vein blood loss model, as well as by micropuncture-induced hemorrhage of mesenteric veins. These doses were chosen based on the maximal inhibition of arterial thrombosis determined by mesenteric intravital microscopy. The experiments were repeated in $P2Y_{12}$ knockout mice as well. Blood loss was significantly greater in clopidogrel- or prasugrel- compared to elinogrel-treated mice (vehicle control: 43.9 ± 19 µL; clopidogrel: 551 ± 43 µL; prasugrel: 561 ± 73 µL; elinogrel: 152 ± 62 µL; $P2Y_{12}$ knockout mice: 293 ± 38 µL; $P < 0.001$). Thienopyridine treatment was associated with less platelet deposition (measured by mean AUC fluorescence at 390 s) in the micropuncture hemorrhage model compared to elinogrel (vehicle: 16,818; elinogrel: 13,866; clopidogrel: 7,909; prasugrel: 8,845; $P2Y_{12}$ knockout mice: 11,884). Furthermore, in $P2Y_{12}$ knockout mice, blood loss was significantly greater in mice treated with clopidogrel or prasugrel (612 ± 71 µL and 802 ± 49 µL, respectively) compared to controls (328 ± 53 µL; $P < 0.0002$) and was not significantly different between control and elinogrel-treated mice (441 ± 66 µL). Based on these observations, it was suggested that the increased blood loss following thienopyridine treatment might be attributed to off-target effects and was not completely explained by $P2Y_{12}$ receptor inhibition (28).

SAFETY

In phase I studies involving healthy volunteers elinogrel therapy alone was safe and well tolerated, without any serious or clinically significant adverse events. Moreover, elinogrel was well tolerated in healthy volunteers treated with aspirin and also in patients with stable CAD treated with clopidogrel and aspirin (29, 30).

CLINICAL STUDIES

In the "first in human" experience with elinogrel, the pharmacokinetic and pharmacodynamic properties of a single oral dose were studied in healthy volunteers. In this double-blind, randomized, placebo-controlled, dose-escalation phase I study, single oral doses of elinogrel (10 and 30 mg with or without aspirin pretreatment, and 100, 200, 400 and 800 mg) were administered to 48 healthy volunteers (6 active and 2 placebo in each group). The perfusion chamber assay, collagen- and ADP-induced platelet aggregation, as well as plasma elinogrel concentrations, were measured. Plasma elinogrel concentrations were elevated in a dose-proportionate manner up to 100 mg and the terminal half-life was 12 h. Dose-dependent inhibition of ADP-induced platelet aggregation was observed with IC_{50} values of 980 ng/mL based on maximal aggregation and 450 ng/mL based on aggregation measured at 6 min. Thrombus destabilization and inhibition of thrombus growth were observed with doses ≥ 30 mg in the perfusion chamber assay. A synergistic effect for aspirin and elinogrel was observed for collagen-induced platelet aggregation only and complete destabilization of thrombus, which prevented the formation of large platelet aggregates, was observed in the perfusion chamber assay following elinogrel in conjunction with aspirin treatment (31).

In another randomized, double-blind phase I study to determine tolerability, pharmacokinetic and pharmacodynamic characteristics, single i.v. doses of elinogrel (1, 3, 10, 20 and 40 mg for 20 min) or placebo were administered to 40 healthy volunteers (6 elinogrel and 2 placebo in each group). Maximum platelet inhibition was achieved at 20 min (first assessment) following the i.v. bolus dose, indicating a very rapid onset of action. Following 20 mg i.v., inhibition of platelet aggregation (10 µM ADP-induced) was 99% and 81%, respectively, based on final aggregation (6 min after the addition of

an agonist) and maximum platelet aggregation measurements, indicating a high level of platelet inhibition. In the perfusion chamber assay, inhibition of platelet thrombosis was evaluated after 20 min of infusion and was 75% following 20 mg and 87% following 40 mg compared to baseline. Higher doses of elinogrel (20 and 40 mg) were also associated with an increased duration of inhibition. The dose-proportional increase in elinogrel plasma concentrations was correlated with pharmacodynamic measurements and the average terminal half-life for the 40-mg dose was ~11 h (32).

Platelet inhibition was evaluated following 7 days of orally administered elinogrel (immediate-release tablet 100 mg b.i.d.) or clopidogrel (75 mg q.d.) in healthy aspirin (325 mg/day)-treated volunteers using the perfusion chamber assay and variable concentrations of ADP for light transmittance aggregometry measurements in a phase I study by Conley et al. (27). A distinct concentration-dependent inhibition of ADP-induced platelet aggregation following elinogrel (55% with 5 μM ADP vs. 33% with 20 μM ADP), which was more pronounced than following clopidogrel (66% with 5 μM ADP vs. 52% with 20 μM ADP), was observed. Moreover, in the perfusion chamber assay, inhibition of thrombus generation (triggered by shear and collagen and amplified by endogenously released ADP) was more pronounced with elinogrel compared to clopidogrel (83% vs. 75% inhibition, respectively). The investigators further reported that 300 nM ADP was the optimal concentration required to stabilize the thrombi under shear conditions in the RTTP assay. Finally, these investigators suggested that high levels of exogenously added ADP may compete with elinogrel for the $P2Y_{12}$ receptor binding site during ex vivo light transmittance aggregometry and underestimate the actual antithrombotic effect of elinogrel when compared to irreversible inhibitors such as thienopyridines (29).

In the "first in patient" single-center phase II study, the pharmacodynamic and pharmacokinetic effects of a single 60-mg oral dose of elinogrel were evaluated in 20 previously stented patients with HPR during chronic administration of clopidogrel (75 mg q.d.) and aspirin (325 mg q.d.) (30). The definition of HPR was based on a prior study of patients on maintenance clopidogrel plus aspirin therapy that identified those individuals in the upper tertile of platelet aggregation (≥ 43% in response to 5 μM ADP) to be at increased risk for post-PCI ischemic events (33). Patients received a single oral dose of elinogrel (60 mg) 12-16 h following their last dose of clopidogrel. Serial pharmacokinetic and pharmacodynamic measurements (4, 6 and 24 h and 7-10 days post-dosing) were performed. Pharmacodynamic measurements included 5 and 20 μM ADP-induced platelet aggregation in citrate anticoagulant, as well as 10 μM ADP-induced aggregation in the betrixiban anticoagulant VerifyNow P2Y12 assay, vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) assay (a specific marker of $P2Y_{12}$ receptor activity), thrombelastography with the Platelet Mapping assay and the perfusion chamber assay. Platelet reactivity decreased within 4-6 h, as measured by all assays, and returned to baseline levels within 24 h. The time course for platelet inhibition as reflected by the various pharmacodynamic assays paralleled the pharmacokinetic profile of elinogrel. The IC_{50} increased with each increase in ADP concentration (IC_{50} for 5, 10 and 20 μM ADP-induced aggregation was 2230, 2412 and 5852 ng/mL, respectively), as would be expected for a competitive, reversible $P2Y_{12}$ antagonist such as elinogrel. This study demonstrated that elinogrel effectively overcame HPR in the majority of clopidogrel- and aspirin-treated patients within 4 h of an oral dose and was fully reversible within 24 h. In addition, the influence of single nucleotide polymorphisms of CYP2C19 (*2, *3, *5 [loss-of-function alleles] and *17 [gain-of-function allele]) on platelet function was evaluated. As expected, the presence of CYP2C19*2 was more frequent in clopidogrel-treated patients with HPR compared with those without HPR (77% vs. 16%; $P = 0.0004$). Finally, a single 60-mg oral dose of elinogrel was effective in overcoming HPR even in patients who had at least one CYP2C19*2 allele (30).

The Early Rapid rEversAl of platelet thromboSis with intravenous elinogrel before PCI to optimize reperfusion in acute Myocardial Infarction (ERASE MI) pilot study was the first phase IIa study conducted to evaluate the safety and tolerability of escalating doses of elinogrel. In this study, patients with STEMI were randomly assigned to treatment with 10, 20, 40 or 60 mg of elinogrel or placebo administered as a single i.v. bolus at the start of the diagnostic angiogram preceding primary PCI. All patients received a 600-mg clopidogrel oral loading dose followed by an additional 300-mg dose 4 h after PCI. The additional clopidogrel dose was administered given the potential competitive interaction between high concentrations of elinogrel and the clopidogrel active metabolite for the $P2Y_{12}$ receptor binding site. In-hospital bleeding events, the study's primary endpoint, were infrequent and similar between the treatment and placebo groups; there were no intracranial hemorrhages. Finally, no differences were observed in serious adverse events or corrected Thrombolysis in Myocardial Infarction (TIMI) frame counts between active treatment and placebo arms. The study was terminated prematurely due to administrative reasons and the results have been taken into account in the design of the phase II INNOVATE (Novel Intravenous and Oral $P2Y_{12}$ Inhibitor, in Non-Urgent) PCI trial (34, 35).

INNOVATE PCI was a randomized, double-blind, active-controlled trial designed to evaluate elinogrel (80 mg i.v. prior to PCI, followed by 50 or 100 mg p.o. b.i.d. for 60 days) versus clopidogrel (300/600-mg oral loading dose followed by 75 mg p.o. q.d. for 60 days) in patients (N = 800) undergoing nonemergent PCI. The study was not powered to examine a prespecified endpoint; rather, a number of analyses will be undertaken to understand the clinical efficacy, biological activity, tolerability and safety of elinogrel at 24 h, hospital discharge and 60 days in patients undergoing nonurgent PCI.

The results of the INNOVATE PCI were recently presented at the European Society of Cardiology Meeting at Stockholm (35). The INNOVATE-PCI trial demonstrated that i.v. administration of elinogrel is associated with more rapid and more potent platelet inhibition compared with standard doses of clopidogrel in patients undergoing elective PCI. There was a smooth transition from i.v. to p.o. administration, with sustained platelet inhibition. It was demonstrated that 120 mg elinogrel administered i.v. was associated with no major or minor bleeding within 24 h or at discharge, but more bleeding requiring medical attention was observed at the vascular access site with elinogrel. At 24 h to 120 days, there was no difference in major or minor bleeding or bleeding requiring medical attention with elinogrel or clopidogrel administration. The study was not powered to observe any ischemic endpoint. There was no significant difference in ischemic endpoints between clopidogrel or elinogrel treatment. However, more dyspnea and elevated liver enzymes

were observed in patients treated with elinogrel. The pharmacodynamic and safety profile of elinogrel support the further development of the drug. A large phase III trial involving approximately 24,000 patients with a previous myocardial infarction has been planned. It will compare low- and high-dose elinogrel with placebo for the prevention of cardiovascular death, myocardial infarction and stroke.

CONCLUSIONS

The newly developed potent $P2Y_{12}$ receptor blockers offer credible alternatives to clopidogrel for the acute and long-term treatment of patients with ACS and patients undergoing stenting. Elinogrel assumes an important place in this arena due to its novel properties, including: 1) direct action; 2) superior platelet inhibition irrespective of clopidogrel response status and genotype; 3) fast onset (with i.v. administration) and offset of action; and 4) choice of both i.v. and p.o. administration to facilitate a smooth transition from short- to long-term therapy. The direct action of elinogrel may also provide a wider therapeutic window than thienopyridine therapy. Results from the INNOVATE PCI trial will provide more insight into the efficacy, tolerability, safety and pharmacodynamic properties of elinogrel compared to clopidogrel.

SOURCES

Portola Pharmaceuticals, Inc. (US); licensed to Novartis Pharma AG (DE).

DISCLOSURES

Dr. Gurbel has received research grants from AstraZeneca, Portola, Pozen and sanofi-aventis, and has acted as a consultant or received honoraria from AstraZeneca, Portola, Pozen, sanofi-aventis, Bayer, Lilly, Daiichi Sankyo and Schering-Plough (now Merck & Co.). Dr. Kereiakes has received research grants from Daiichi Sankyo and has acted as a consultant or received honoraria from Lilly. Dr. Tantry states no conflicts of interest.

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