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CLINICAL RESEARCH
Thrombosis and antithrombotic therapy

Pharmacodynamics, pharmacokinetics, and safety of single-dose subcutaneous administration of selatogrel, a novel $P2Y_{12}$ receptor antagonist, in patients with chronic coronary syndromes

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Aims To study the pharmacodynamics and pharmacokinetics of selatogrel, a novel $P2Y_{12}$ receptor antagonist for subcutaneous administration, in patients with chronic coronary syndromes (CCS).

Methods and results In this double-blind, randomized study of 345 patients with CCS on background oral antiplatelet therapy, subcutaneous selatogrel (8 mg, $n = 114$; or 16 mg, $n = 115$) was compared with placebo ($n = 116$) (ClinicalTrials.gov: NCT03384966). Platelet aggregation was assessed over 24 h (VerifyNow assay) and 8 h (light transmittance aggregometry; LTA). Pharmacodynamic responders were defined as patients having $P2Y_{12}$ reaction units (PRU) <100 at 30 min post-dose and lasting ≥3 h. At 30 min post-dose, 89% of patients were responders to selatogrel 8 mg, 90% to selatogrel 16 mg, and 16% to placebo ($P < 0.0001$). PRU values (mean ± standard deviation) were 10 ± 25 (8 mg), 4 ± 10 (16 mg), and 163 ± 73 (placebo) at 15 min and remained <100 up to 8 h for both doses, returning to pre-dose or near pre-dose levels by 24 h post-dose. LTA data showed similarly rapid and potent inhibition of platelet aggregation. Selatogrel plasma concentrations peaked ∼30 min post-dose. Selatogrel was safe and well-tolerated with transient dyspnoea occurring overall in 7% (16/229) of patients (95% confidence interval: 4–11%).

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Conclusions Selatogrel was rapidly absorbed following subcutaneous administration in CCS patients, providing prompt, potent, and consistent platelet $P2Y_{12}$ inhibition sustained for ≥8 h and reversible within 24 h. Further studies of subcutaneous selatogrel are warranted in clinical scenarios where rapid platelet inhibition is desirable.

Keywords Selatogrel • Platelet aggregation • Coronary artery disease • $P2Y_{12}$ receptor antagonist • Pharmacodynamics • Pharmacokinetics

Introduction

The activation of platelets at sites of vascular injury is a key step in thrombus formation, mediated in part by adenosine diphosphate (ADP)-induced activation of platelet $P2Y_{12}$ receptors.[1] Current treatment guidelines recommend the use of dual oral antiplatelet therapy consisting of aspirin and a platelet $P2Y_{12}$ receptor antagonist ('$P2Y_{12}$ inhibitor') for the management of patients with acute coronary syndromes (ACS) and/or patients undergoing percutaneous coronary intervention (PCI) in order to prevent stent thrombosis and future atherothrombotic events.[2–5] In the absence of contraindications, ticagrelor and prasugrel are recommended as the oral $P2Y_{12}$ inhibitors for most ACS patients in preference to clopidogrel, in view of their more potent and consistent antiplatelet effects and superior net clinical benefits.[2,3]

However, the onset of action of all oral $P2Y_{12}$ inhibitors may be delayed by up to 6 h or more in the setting of acute myocardial infarction (AMI), and the only non-oral $P2Y_{12}$ inhibitor available is cangrelor, which is administered intravenously in patients undergoing PCI when oral $P2Y_{12}$ inhibitors are not indicated or not yet administered. Therefore, there is a need for a $P2Y_{12}$ inhibitor that achieves consistently fast and effective platelet inhibition in the acute phase of a myocardial infarction.[6,7]

Selatogrel (ACT-246475) is a 2-phenylpyrimidine-4-carboxamide analogue that represents a novel class of reversibly-binding $P2Y_{12}$ inhibitor, distinct from the two classes represented by ticagrelor and cangrelor. Selatogrel is being developed for subcutaneous (s.c.) administration for early, pre-hospital treatment of AMI.[8,9] Preclinical data from a rodent ferric chloride model suggest that selatogrel has a potentially lower risk of bleeding and Phase 1 data from healthy subjects indicate selatogrel is well tolerated at doses up to 32 mg, with a favourable pharmacodynamic (PD) and pharmacokinetic (PK) profile.[9,10]

To investigate the PD and PK properties of selatogrel in patients with atherosclerotic disease, the present study was conducted in patients with stable chronic coronary syndromes (CCS). Patients with CCS represent a population that permits more frequent blood sampling without increasing the risk to patient safety, while avoiding interference with standard of care required in an emergency setting such as AMI. Furthermore, assessment in a population of patients with CCS allows better control and stability of concomitant treatments, and therefore more accurate characterization of the PD and PK profiles of selatogrel in the presence of background antiplatelet therapies. The main objective of this study was to characterize the inhibition of platelet aggregation relative to placebo after a single s.c. injection of selatogrel in patients with CCS receiving conventional background oral antiplatelet therapy.

Methods

Study population

Patients with CCS were identified by either (i) history of coronary artery disease with coronary artery stenosis on angiography ≥ 50% or (ii) previously documented AMI occurring more than 3 months prior to randomization.

Eligible male and female patients were aged 18–85 years, inclusive, and females of childbearing potential were required to have a negative urine pregnancy test both at screening and immediately before randomization. Patients were required to have a body weight of ≥40.0 kg and have had no changes to their current antiplatelet medication in the prior 1 month. Patients were excluded if they had conditions associated with increased bleeding risk or likely to impair study procedures or safety, or if they were treated with inhibitors of organic anion-transporting polypeptide (OATP)1B1 or OATP1B3 of which selatogrel is a substrate. Additional exclusion criteria were ACS, PCI, any intervention for peripheral artery disease, acute ischaemic stroke, or transient ischaemic attack within 3 months prior to randomization. Detailed inclusion and exclusion criteria are presented in the Supplementary material online.

Study design

This was a prospective, multi-national, double-blind, randomized, placebo-controlled, parallel-group, Phase-2 study (ClinicalTrials.gov registration number NCT03384966) of a single s.c. administration of selatogrel at two dose levels in CCS patients receiving conventional background antiplatelet therapy. All study procedures were performed according to protocols approved by local regulatory authorities and all patients provided written informed consent prior to any study-mandated procedure.

Eligible patients were randomized to one of eight groups based on treatment (selatogrel or matching placebo), dose (8 or 16 mg), and s.c. injection site (thigh or abdomen) (*Figure 1*). The 8 and 16 mg doses of selatogrel were selected based on data from the single ascending dose study[9] and on modelling to achieve at least 85% inhibition of ADP-induced platelet aggregation that was sustained for at least 3 up to 8 h. Patients and investigators were both blinded to the study treatment (selatogrel or placebo). Selatogrel and placebo were not distinguishable and were provided as lyophilizate for reconstitution prior to s.c. administration. Investigators reconstituted selatogrel/placebo to the same volume for 8 and 16 mg out of sight of the patients and so only patients were blinded to the dose. Blood samples for PD and PK measurements were collected pre-dose and then 15 min, 30 min, and 1, 2, 4, 8, and 24 h following the single dose of s.c. study medication.

The treatment period was defined as lasting 2 days after study medication administration, representing ~5 half-lives of selatogrel. Patients were followed up by telephone call or a visit at 1 month (28–35 days).

Blood samples

Venous blood for PD assessment was collected into Monovette tubes containing the direct thrombin inhibitor phenylalanine-proline-arginine-

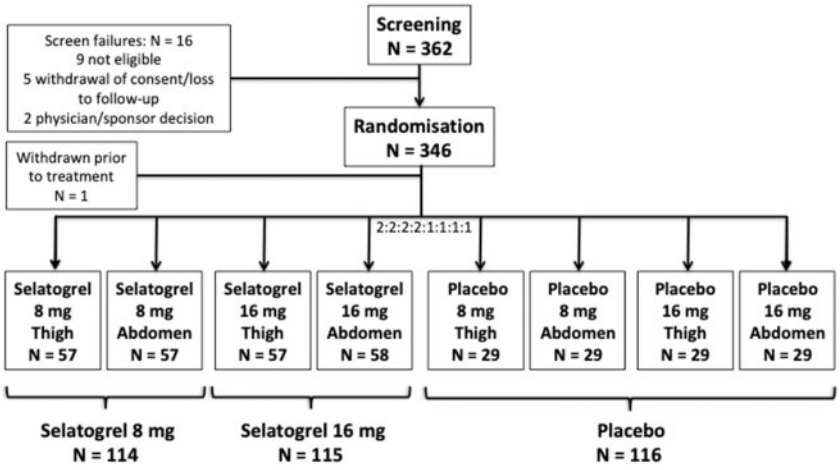


Figure 1 Patient screening and randomization schedule.

chloromethyl ketone (PPACK) as anticoagulant and assessments were made within 2 h of blood collection. PPACK was used as the anticoagulant since the conventional anticoagulant for platelet function studies, trisodium citrate dihydrate ('citrate'), is recognized to affect the potency of some antiplatelet drugs,[11,12] as has been found for selatogrel (unpublished data on file, Idorsia Pharmaceuticals Ltd). Venous blood for PK assessment was collected into Monovette tubes containing ethylenediaminetetraacetic acid and plasma derived within 30 min of collection for storage at or below -20°C prior to analysis.

Pharmacodynamic assessments

Pharmacodynamic assessments were performed by laboratory staff who were blinded to both treatment and dose. The investigators remained blinded to the results for the duration of the study. The principal measurement of platelet reactivity was the VerifyNow PRUTest (Accriva Diagnostics, San Diego, CA, USA), assessing platelet aggregation in response to ADP in the presence of prostaglandin E_1. Tubes containing PPACK-anticoagulated whole blood were inserted into the VerifyNow PRUTest cartridge within the VerifyNow analyser, according to the manufacturer's instructions, and $P2Y_{12}$ reaction units (PRU) were recorded.

Platelet-rich plasma (PRP) was prepared by centrifugation of PPACK-anticoagulated blood at 200 *g* for 7 min, then platelet-poor plasma was prepared by centrifugation at 1800 *g* for 10 min for use as calibration only. Light transmittance aggregometry (LTA) was performed pre-dose and 30 min, 1, 2, and 8 h post-dose using the available aggregometer at each site (see Supplementary material online) with aggregation recorded as maximum percentage platelet aggregation over 6 min after addition of ADP 20 μmol/L as agonist.[13]

All laboratory consumables for platelet function studies were provided to sites by CirQuest Labs (Memphis, TN, USA).

Pharmacokinetic assessments

Plasma concentrations of selatogrel were measured by Idorsia Pharmaceuticals Ltd (Allschwil, Switzerland) using a validated high-performance liquid chromatography-tandem mass spectrometry assay, as previously described.[14]

Safety assessments

Adverse events (AEs) were recorded up to 1 month. Treatment-emergent AEs were defined as occurring within 48 h of administration of study medication. All bleeding events were recorded, regardless of severity. Safety assessments included treatment-emergent changes in heart rate, blood pressure, electrocardiographic parameters, and clinical laboratory measurements (including full blood count, electrolytes, liver and renal function, and urate).

A Safety Event Committee consisting of two independent clinical experts reviewed unblinded safety data independently from the sponsor during the study.

Statistical analyses

Data are presented on all randomized patients who were administered study treatment. Continuous variables are presented as mean and standard deviation (SD), mean and 95% confidence interval (CI), or median and interquartile range, as indicated, and categorical variables as number of patients and percentage.

The primary PD endpoint was the proportion of patients responding to selatogrel, with 'responders' pre-defined as having PRU <100 at 30 min after injection and lasting ≥3 h. This PRU threshold was chosen in order to reflect the typical levels of platelet reactivity achieved by ticagrelor or prasugrel loading in ACS patients.[13,15,16]

The study aimed at assessing the efficacy of each selatogrel dose vs. placebo using a hierarchical two-step approach. A *P*-value significance level was set to 0.025 for each of the two steps, based on an overall Type-I error rate of 0.05 adjusted for multiple comparisons using a Bonferroni approach (two comparisons within each sequential step). For the first step, the proportion of responders for each of the two doses of selatogrel was compared to placebo (assuming 50% responders with placebo). In step two, for doses superior to placebo it was tested if the proportion of responders was >70%. Assuming 10% drop-out or non-evaluable data, each arm was intended to include at least 108 patients to achieve 90% power.

Platelet aggregation was compared using a mixed-effects model with treatment group (selatogrel 8 mg, selatogrel 16 mg, placebo), injection site (abdomen, thigh), PRU level at baseline (stratification levels), age (continuous), and sex (male and female) as fixed factors. The model also included (treatment*injection site) as an interaction term to assess

consistency of treatment effect across injection sites. Additional exploratory comparisons of PD data were performed at each time point, comparing each selatogrel dose with placebo using the Student's *t*-test, and *P* values are presented descriptively.

Plasma selatogrel concentrations are presented as arithmetic mean and SD. Peak plasma concentrations (C_{max}) and the time to C_{max} (T_{max}) were estimated using non-compartmental methods.

Results

Study population

The study was conducted between January and September 2018. A total of 346 patients with CCS were randomized, of whom 345 received study medication [selatogrel 8 mg ($n = 114$), selatogrel 16 mg ($n = 115$), or placebo ($n = 116$)]: one patient in the selatogrel 8-mg group did not proceed to treatment with study medication and was excluded from the presented analyses (*Figure 1*). All treated patients completed the study except for one patient who died before the 1-month follow-up. Demographics, baseline characteristics, and concomitant antiplatelet medications were well balanced across the treatment groups (*Table 1*).

Pharmacodynamic responses

One hundred and two out of 114 patients (89%; 95% CI 82–94%) were responders to selatogrel 8 mg, 103 out of 115 patients (90%; 95% CI 82–94%) were responders to selatogrel 16 mg, and 18 out of 116 patients (16%; 95% CI 9–23%) were responders to placebo ($P < 0.0001$ for each selatogrel dose vs. placebo). There was no statistically significant interaction for injection site, age, or sex on PRU change from baseline (repeated-measures mixed model). Response by subgroup is presented in the Supplementary material online, *Figure S1*. At baseline, mean PRU levels were similar across all groups (selatogrel 8 mg: 156 ± 71; selatogrel 16 mg: 156 ± 77; placebo: 155 ± 73). At 15 min post-dose, PRU values (mean ± SD) were 10 ± 25 with selatogrel 8 mg, 4 ± 10 with selatogrel 16 mg, and 163 ± 73 with placebo. PRU levels were maintained below 100 for up to 8 h for both selatogrel doses, returning to pre-dose or near pre-dose levels by 24 h post-dose [(24 h vs. pre-dose PRU level) selatogrel 8 mg: 144 ± 74 vs. 156 ± 72; selatogrel 16 mg: 129 ± 66 vs. 157 ± 76; placebo: 153 ± 74 vs. 153 ± 73](*Figure 2A*).

Absolute PRU values for each treatment were not different between injection sites (Supplementary material online, *Figure S2*).

LTA showed similar findings to VerifyNow, with rapid onset of antiplatelet effect (*Figure 2B*).

A consistent PD profile for both doses of selatogrel was noted in patients regardless of baseline oral $P2Y_{12}$ inhibitor therapy (*Figure 3*).

Pharmacokinetics

Selatogrel was rapidly absorbed as indicated by the achievement of C_{max} shortly after the 30-min time point (t_{max}, mean ± SD, selatogrel 8 mg: 40 ± 14 min; selatogrel 16 mg: 44 ± 18 min) (*Figure 4*). The C_{max} (mean ± SD) following administration of selatogrel 8 and 16 mg was 316 ± 117 and 513 ± 171 ng/mL, respectively. Plasma selatogrel concentrations declined steadily over the 24-h post-dose period with estimated mean ± SD levels of 0.4 ± 0.6 and 2.1 ± 0.9 ng/mL at 24 h following 8 and 16 mg doses, respectively. There was no difference in plasma selatogrel concentration according to the site of injection, i.e. thigh or abdomen (Supplementary material online, *Figure S3*).

Adverse events

Bleeding events occurred in 9.6% (95% CI: 4.9–16.6%) and 4.3% (95% CI: 1.4–9.9%) with selatogrel 8 and 16 mg, respectively, vs. 6.9% (95% CI: 3.0–13.1%) with placebo. Transient dyspnoea (mild in all but one patient who had moderate dyspnoea on selatogrel 16 mg) occurred in 5.3% (95% CI: 2.0–11.1%) and 8.7% (95% CI: 4.3–15.4%) with selatogrel 8 and 16 mg, respectively, vs. none with placebo; median (min–max) duration of dyspnoea was 2.4 (0.1–8.4) h and 0.8 (0.0–22.1) h for the 8 and 16 mg selatogrel doses, respectively. Dizziness occurred in 4.4% (95% CI: 1.4–9.9%) and 3.5% (95% CI: 1.0–8.7%) vs. 0.9% (95% CI: 0.02–4.7%), respectively, without significant haemodynamic or electrocardiographic changes (*Table 2*).

There were no treatment-emergent deaths or other serious AEs. One patient in the selatogrel 8 mg group died 17 days after selatogrel administration as a result of cardiac arrest and this was not considered by the investigator to be related to study drug administration.

No marked treatment-emergent differences in heart rate, blood pressure or electrocardiographic findings, including bradycardia, atrioventricular block, and QT interval, were observed with either dose of selatogrel, compared with placebo (Supplementary material online, *Table S1* and *Figure S4*). There were no notable treatment-related changes in biochemistry or haematology parameters (Supplementary material online, *Table S2*).

Discussion

The present study is the first to characterize the antiplatelet effect of selatogrel (8 and 16 mg) in CCS patients. Both doses of selatogrel produced similar PD and PK profiles, with no difference between thigh and abdomen injection sites. Selatogrel was rapidly absorbed following single-dose s.c. administration, translating into a fast onset of a high level of platelet inhibition that was maintained for ≥8 h and reversible within 24 h. A high level of platelet inhibition was rapidly achieved in patients who were not receiving an oral $P2Y_{12}$ inhibitor. Both doses of selatogrel also rapidly achieved additional platelet inhibition in patients established on an oral $P2Y_{12}$ inhibitor with, as expected, greater incremental platelet inhibition in patients on clopidogrel compared with prasugrel or ticagrelor (*Figure 3B–D*). This is particularly relevant in the case of patients who sustain thrombotic events in the context of poor PD response to clopidogrel or as a result of poor adherence to oral therapy.

The potent oral $P2Y_{12}$ inhibitors ticagrelor and prasugrel have been shown to have onset of action within 1–2 h in CCS patients.[17–19] However, it was subsequently discovered that their onset of action is more variable and often delayed by several hours in patients with AMI.[20,21] Part of this phenomenon has been attributed to the use of parenteral opiates, which delay gastric emptying and, therefore, may slow the onset of action of orally administered drugs, including $P2Y_{12}$ inhibitors.[19,22] Based on data obtained from CCS patients, the fast onset of platelet aggregation inhibition within 15 min of single-dose s.c. selatogrel injection makes it a potential candidate to address the need for reliably rapid platelet inhibition in patients with AMI, which is not provided by current oral $P2Y_{12}$ inhibitors. This hypothesis was

Table 1 Patient characteristics

	Selatogrel 8 mg (*n* = 114)	Selatogrel 16 mg (*n* = 115)	Placebo (*n* = 116)
Age, years, mean (SD)	64.8 (9.4)	65.2 (8.5)	64.9 (9.1)
Female sex, *n* (%)	20 (18)	26 (23)	23 (20)
Body weight, kg, median (IQR)	87 (76–102)	85 (76–99)	90 (82–101)
Body mass index, mean (SD)	29 (5)	29 (6)	31 (5)
Race, *n*, (%)			
White	97 (85)	96 (83)	103 (89)
Black	10 (9)	13 (11)	9 (8)
Asian	7 (6)	6 (5)	4 (3)
Prior medical history, *n* (%)			
PCI	89 (78)	94 (82)	100 (86)
CABG surgery	36 (32)	19 (17)	23 (20)
Myocardial infarction	73 (64)	68 (59)	78 (67)
Stroke	4 (4)	5 (4)	3 (3)
Transient ischaemic attack	3 (3)	2 (2)	1 (1)
Peripheral vascular surgery	3 (3)	3 (3)	4 (3)
Congestive cardiac failure	8 (7)	7 (6)	4 (3)
Diabetes mellitus	34 (30)	35 (30)	39 (34)
Hypertension	88 (77)	85 (74)	78 (67)
Dyslipidaemia	80 (70)	81 (70)	77 (66)
Peripheral arterial disease	5 (4)	2 (2)	3 (3)
Chronic kidney disease	9 (8)	5 (4)	4 (3)
Concomitant antiplatelet medication, *n* (%)			
Aspirin[a]	109 (96)	111 (97)	114 (98)
Any oral $P2Y_{12}$ inhibitor	35 (31)	41 (36)	43 (37)
Clopidogrel	25 (22)	23 (20)	30 (26)
Ticagrelor	7 (6)	11 (10)	10 (9)
Prasugrel	3 (3)	7 (6)	3 (3)
No aspirin[a] or $P2Y_{12}$ inhibitor	2 (2)	0 (0)	0 (0)
Aspirin[a] + clopidogrel	22 (19)	19 (17)	28 (24)
Aspirin[a] + ticagrelor	7 (6)	11 (10)	10 (9)
Aspirin[a] + prasugrel	3 (3)	7 (6)	3 (3)
Other medication, *n* (%)			
Proton-pump inhibitors	41 (36)	42 (37)	49 (42)
Nitrates	41 (36)	42 (37)	50 (43)
Beta-blockers	75 (66)	80 (70)	76 (66)
Statins	106 (93)	108 (94)	104 (90)
ACE inhibitors	54 (47)	63 (55)	58 (50)
Angiotensin receptor blockers	27 (24)	20 (17)	26 (22)

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass graft; IQR, interquartile range; PCI, percutaneous coronary intervention.
[a]Including carbasalate calcium.

tested, as part of the development programme of selatogrel, in a complementary study investigating PK and PD properties of selatogrel in AMI patients (ClinicalTrials.gov NCT03487445).

The reported treatment-emergent AEs suggest that selatogrel is safe and well tolerated in this patient population. An excess of dyspnoea AEs was noted with both doses of selatogrel compared with placebo, with all the events being mild apart from one that was moderate in severity. This is similar to findings with other reversibly-binding $P2Y_{12}$ inhibitors, including ticagrelor,[23,24] elinogrel,[25] and cangrelor,[26] as compared with the irreversible inhibitor clopidogrel.[27] However, the aetiology of dyspnoea following $P2Y_{12}$ inhibition is not yet fully understood. Non-dyspnoea AEs that occurred in numerically more selatogrel-treated patients require further assessment in a larger trial to further explore the AE profile. In particular, bleeding events need further assessment since such events in this study were mostly trivial, related to venepuncture and s.c. injection of study drug.

A limitation of this study was that patients were stable and it is possible that some patients with acute conditions have reduced skin

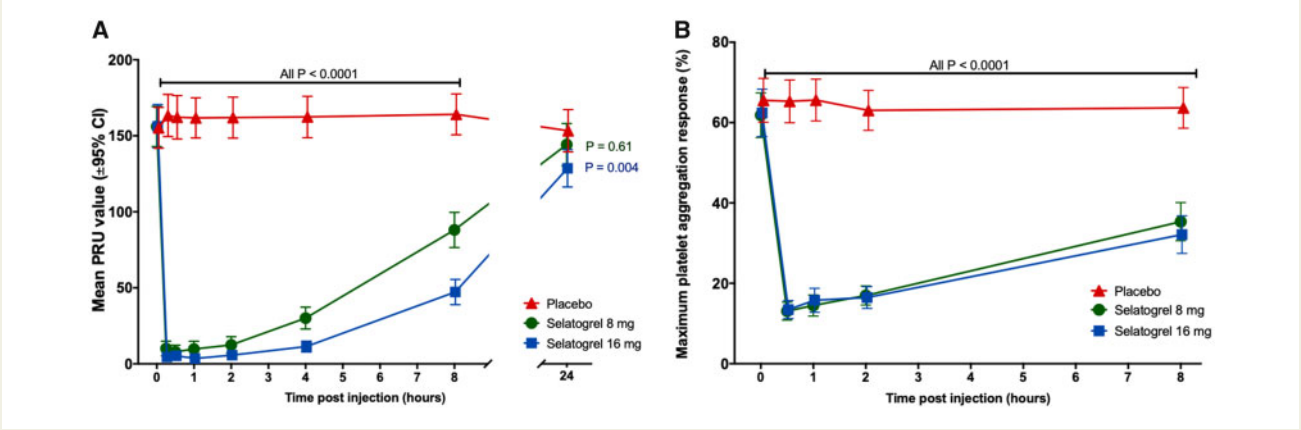


Figure 2 Effects of selatogrel on adenosine diphosphate-induced platelet aggregation. (*A*) $P2Y_{12}$ reaction units assessed by VerifyNow PRUTest assay and (*B*) maximum platelet aggregation response to adenosine diphosphate 20 µmol/L determined by LTA at the indicated time points before and after administration of subcutaneous selatogrel 8 mg ($n = 114$), selatogrel 16 mg ($n = 115$), or placebo ($n = 116$). Data are mean and error bars indicate 95% confidence interval. Exploratory *P* values comparing each dose of selatogrel with placebo at each time point are derived from the Student's *t*-test.

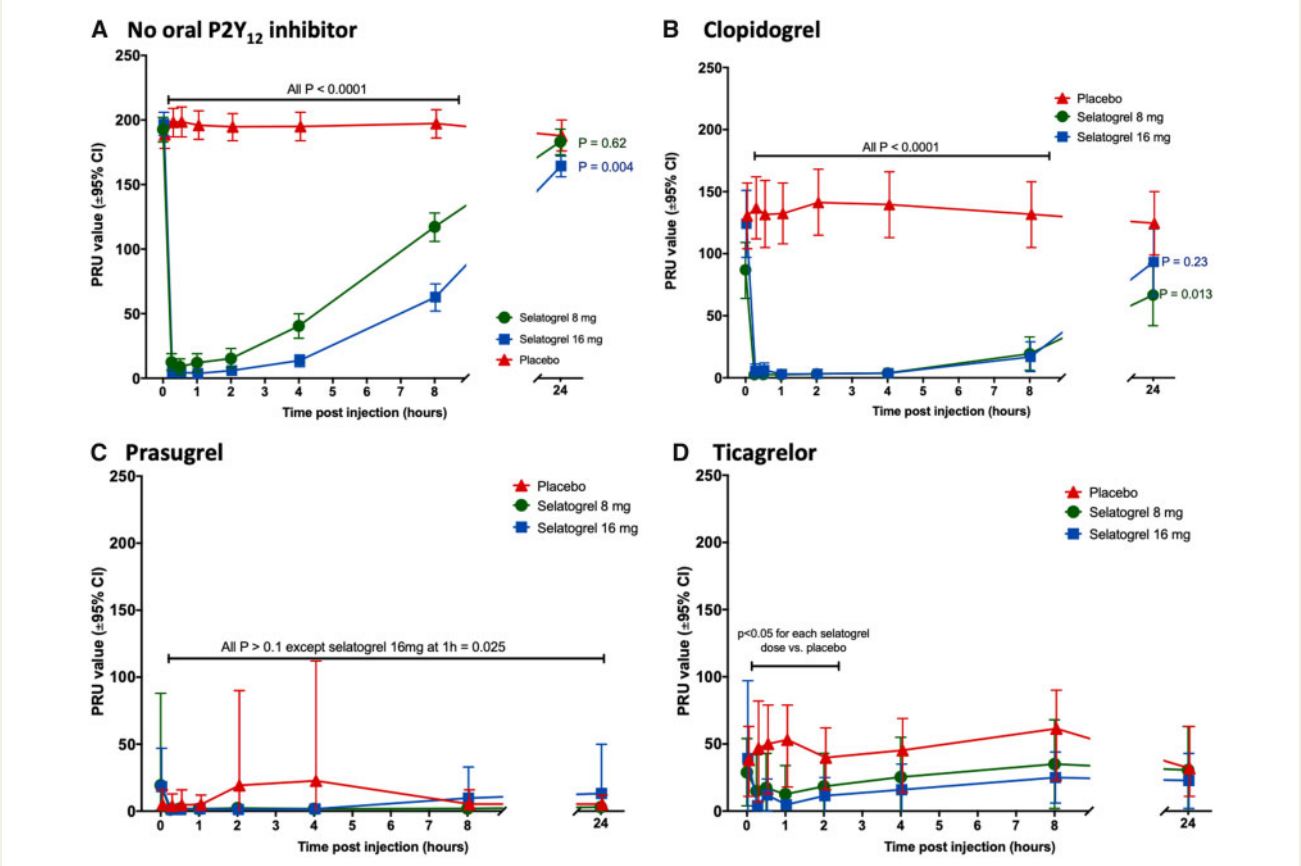


Figure 3 Effects of selatogrel on platelet reactivity assessed as $P2Y_{12}$ reaction units by VerifyNow PRUTest assay according to treatment with (*A*) no oral $P2Y_{12}$ inhibitor ($n = 30$–35 per group), (*B*) clopidogrel ($n = 18$–21 per group), (*C*) prasugrel ($n = 3$–6 per group), or (*D*) ticagrelor ($n = 7$–11 per group). Data are mean and error bars indicate 95% confidence interval. Exploratory *P* values comparing each dose of selatogrel with placebo at each time point are derived from the Student's *t*-test.

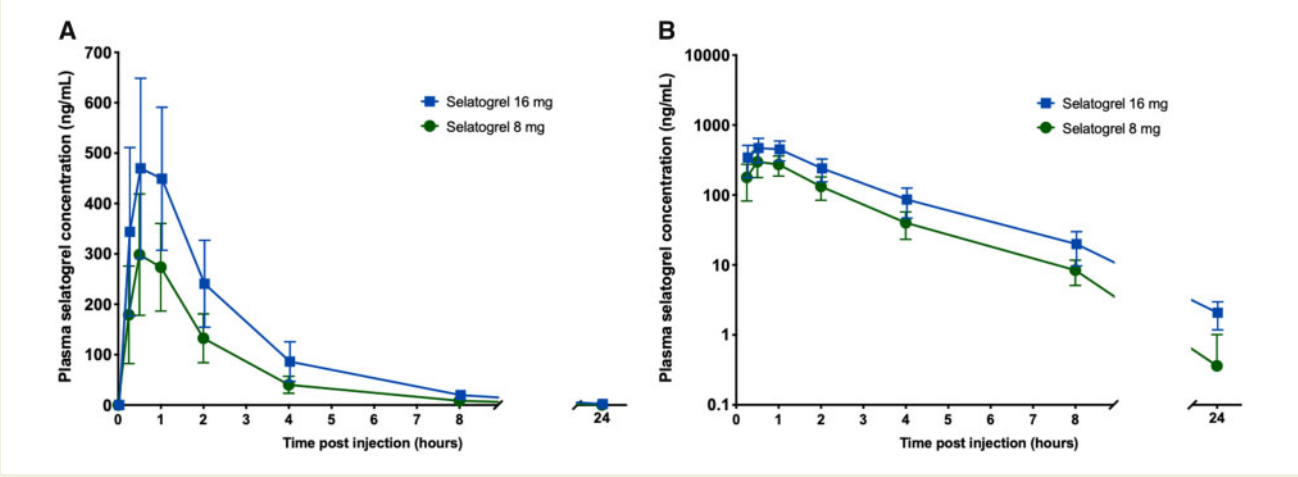
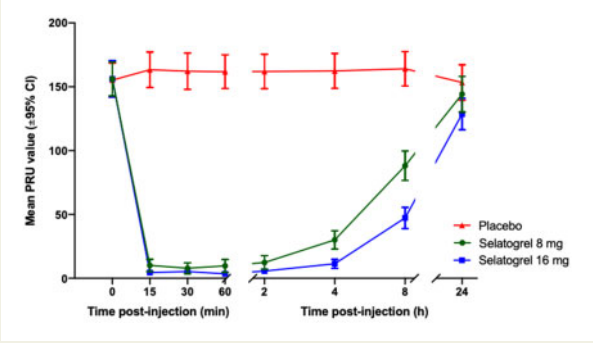


Figure 4 Selatogrel concentrations in plasma over time and by dose. Plasma concentrations (ng/mL) of selatogrel following single doses of either 8 mg or 16 mg, shown on (*A*) linear scale and (*B*) semi-logarithmic scale, measured using a validated liquid chromatography-tandem mass spectrometry assay. Data are mean and error bars indicate standard deviation.



Take home figure Effect of selatogrel on platelet reactivity assessed by VerifyNow $P2Y_{12}$ reaction units test showing response to subcutaneous administration of selatogrel 8 mg, selatogrel 16 mg, or placebo within 60 min, between 2 and 8 h, and at 24 h. Data are mean and error bars indicate 95% confidence interval.

and organ perfusion that delays the absorption of selatogrel. Consequently, it is important that the onset of action of s.c. selatogrel is also assessed in acute conditions, as has been performed in a separate study in AMI patients (ClinicalTrials.gov NCT03487445). We also did not assess the transition between selatogrel administration and loading with oral $P2Y_{12}$ inhibitors. It is recognized that cangrelor impedes the binding of clopidogrel and prasugrel active metabolites to the $P2Y_{12}$ receptor leading to drug–drug interactions[28] and further work is required to identify optimal strategies for transitioning from selatogrel to oral therapy. A further limitation of this study was the method of blood sample collection. The potency of selatogrel is lower in citrated PRP as compared with PRP anticoagulated with a direct thrombin inhibitor.[14] Further investigations (data on file) to profile the influence of various methods of anticoagulation confirmed that physiological ionized calcium concentrations are important for determination of potency of selatogrel. Accordingly, to perform the platelet aggregation assays, blood was collected with PPACK as anticoagulant. PRU levels tend to be slightly lower with blood anticoagulated with a direct thrombin inhibitor compared to citrate-anticoagulated blood.[11,12] For this reason, any direct comparison of absolute PRU values obtained in this study with those published from studies of other $P2Y_{12}$ inhibitors should be avoided.

Conclusions

In patients with CCS, selatogrel (8 and 16 mg) was rapidly absorbed following single-dose s.c. injection resulting in strong inhibition of platelet reactivity as early as 15 min that was maintained for ≥8 h and reversible within 24 h. The PD and PK profiles characterized in this study suggest s.c. selatogrel may be a promising treatment in the pre-hospital setting and in clinical scenarios where early, rapid, potent and reversible platelet inhibition is desirable, such as patients presenting with AMI or undergoing PCI. Further clinical investigation of selatogrel in these patient populations is required, and will further inform selection of the optimal dose for Phase 3 clinical studies.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Table 2 Treatment-emergent adverse events

n (%)	Selatogrel 8 mg (*n* = 114)	Selatogrel 16 mg (*n* = 115)	Placebo (*n* = 116)
Any AE	36 (32)	26 (23)	25 (22)
Any AE related to study treatment	26 (23)	19 (17)	13 (11)
Mild	33 (29)	25 (22)	24 (21)
Moderate	3 (3)	1 (1)	1 (1)
Severe	0	0	0
Serious AE	0 (0)	0 (0)	0 (0)
Death	0 (0)	0 (0)	0 (0)
Any bleeding event	11 (10)	5 (4)	8 (7)
Injection site bruising	3 (3)	2 (2)	0 (0)
Contusion	1 (1)	1 (1)	3 (3)
Venepuncture site bruising	4 (4)	0 (0)	3 (3)
Injection site erythema	0 (0)	2 (2)	0 (0)
Injection site pruritus	0 (0)	2 (2)	0 (0)
Dyspnoea	6 (5)	10 (9)	0 (0)
Mild	6 (5)	9 (8)	0 (0)
Moderate	0 (0)	1 (1)	0 (0)
Severe	0 (0)	0 (0)	0 (0)
Dizziness	5 (4)	4 (3)	1 (1)
Presyncope	2 (2)	0 (0)	0 (0)
Headache	3 (3)	3 (3)	5 (4)
Diarrhoea	4 (4)	1 (1)	0 (0)
Hypertension	0	1 (1)	2 (2)
Vessel puncture site erythema	2 (2)	0	0

The treatment period was defined as lasting 2 days after study medication administration. All AEs occurring in more than one patient in any treatment group are shown.

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