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

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Abstract

Aims

To study the pharmacodynamics and pharmacokinetics of selatogrel, a novel $P2Y_{12}$ receptor antagonist for subcutaneous administration, in patients with stable coronary artery disease (sCAD).

Methods and results

In this double-blind, randomized study of 345 patients with sCAD 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 mins post-dose and lasting ≥3 h. At 30 mins 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 ±SD) were 10 ±25 (8 mg), 4 ±10 (16 mg), and 163 ±73 (placebo) at 15 mins 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 mins post-dose. Selatogrel was safe and well tolerated with transient dyspnoea occurring overall in 7% (16/229) of patients (95% CI: 4-11%).

Conclusion

Selatogrel was rapidly absorbed following subcutaneous administration in sCAD 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.

Funding

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Key words

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 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 hours 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 an MI.[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 pharmacodynamic (PD) and pharmacokinetic (PK) properties of selatogrel in patients with atherosclerotic disease, the present study was conducted in patients with stable coronary artery disease (sCAD). Patients with sCAD 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 sCAD allows better control and stability of concomitant treatments, and therefore more accurate characterisation of the PD and PK profiles of selatogrel in the presence of background antiplatelet therapies.

The main objective of this study was to characterise the inhibition of platelet aggregation relative to placebo after a single s.c. injection of selatogrel in patients with sCAD receiving conventional background oral antiplatelet therapy.

Methods

Study population

Patients with sCAD were identified by either (a) history of CAD with coronary artery stenosis on angiography ≥ 50% or (b) previously-documented AMI occurring more than 3 months prior to randomization.

Eligible male and female patients were aged 18 to 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 ≥ 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 Online Supplement.

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 sCAD 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 1 of 8 groups based on treatment (selatogrel or matching placebo), dose (8 mg or 16 mg) and s.c. injection site (thigh or abdomen) (Figure 1). The 8 mg 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 h 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 mg 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 mins, 30 mins, and 1, 2, 4, 8 and 24 hours following the single dose of s.c. study medication.

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

Blood samples

Venous blood for PD assessment was collected into Monovette tubes containing the direct thrombin inhibitor phenylalanine-proline-arginine-chloromethyl ketone (PPACK) as anticoagulant and assessments were made within 2 hours 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 pharmacokinetic assessment was collected into Monovette tubes containing ethylene-diamine-tetraacetic acid (EDTA) and plasma derived within 30 mins of collection for storage at or below -20°C prior to analysis.

Pharmacodynamic assessments

PD 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 adenosine diphosphate (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.

PRP was prepared by centrifugation of PPACK-anticoagulated blood at 200*g* for 7 mins, then platelet-poor plasma was prepared by centrifugation at 1800*g* for 10 mins for use as calibration only. Light transmittance aggregometry (LTA) was performed pre-dose and 30 mins, 1, 2 and 8 h post-dose using the available aggregometer at each site (see Online Supplement) with aggregation recorded as maximum percentage platelet aggregation over 6 mins 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 hours 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 (95% CI), or median and interquartile range (IQR), 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 mins 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 versus placebo using a hierarchical 2-step approach. 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 comparison 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, 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 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 sCAD 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 Online Supplement (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 mins 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 (Online Supplement figure S2).

Light transmittance aggregometry 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-mins timepoint (t_{max}, mean ±SD, selatogrel 8mg: 40 ±14 mins;

selatogrel 16 mg: 44 ±18 mins) (Figure 4). The C_{max} (mean ±SD) following administration of selatogrel 8 mg and 16 mg was 316 ±117 ng/mL and 513 ±171 ng/mL, respectively. Plasma selatogrel concentrations declined steadily over the 24-hour post-dose period with estimated mean ± SD levels of 0.4 ±0.6 ng/mL and 2.1 ±0.9 ng/mL at 24 h following 8 mg and 16 mg doses, respectively. There was no difference in plasma selatogrel concentration according to the site of injection, i.e., thigh or abdomen (Online Supplement 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 mg and 16 mg, respectively, vs. 6.9% (95% CI: 3.0-13.1%) with placebo. Transient dyspnoea (mild in all but 1 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 mg 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 mg 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 ECG 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 (Online Supplement Table S1 and Figure S4). There were no notable treatment-related changes in biochemistry or haematology parameters (Online Supplement Table S2).

Discussion

The present study is the first to characterize the antiplatelet effect of selatogrel (8 and 16 mg) in sCAD 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 (figures 3B-D). This is particularly relevant in the case of patients who sustain thrombotic events in the context of poor pharmacodynamic 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 1-2h in sCAD 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 sCAD patients, the fast onset of platelet aggregation inhibition within 15 mins 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 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 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 recognised 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 platelet-rich plasma (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 ionised 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 sCAD, 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 mins that was maintained for ≥8 h and reversible within 24 h. The PD and PK profiles characterised 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.

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Author role and contribution

RFS was Principal Investigator for the study and wrote the first draft of the manuscript in conjunction with DJA and PAG. J-MF, CB and colleagues from Idorsia Pharmaceuticals Ltd. designed and oversaw the conduct of the study with support from RFS. MU was accountable for analysis of PK data. AH performed the statistical analyses and checked the data included in the manuscript. RFS, PAG, JtB, GDD, DAG, VK, SKJ, J-FT, HT, DT, PVdH, AWJVH and DJA were site investigators for the study and oversaw the study procedures. All authors critically revised the manuscript for important intellectual content and approved the final version of the manuscript.

One-sentence summary:

Selatogrel, a novel reversibly-binding $P2Y_{12}$ inhibitor, achieves potent platelet inhibition within 30 minutes after subcutaneous administration that is sustained for at least 8 hours and reversed at 24 hours in patients with stable coronary artery disease.

Figure legends

Figure 1. Patient screening and randomization schedule.

Figure 2. Effects of selatogrel on ADP-induced platelet aggregation. (A) $P2Y_{12}$ reaction units (PRU) assessed by VerifyNow PRUTest assay and (B) maximum platelet aggregation response to ADP 20 μmol/L determined by light transmittance aggregometry 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% CI. Exploratory P values comparing each dose of selatogrel with placebo at each time point are derived from Student's t test.

Figure 3. Effects of selatogrel on platelet reactivity assessed as $P2Y_{12}$ reaction units (PRU) 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% CI. Exploratory P values comparing each dose of selatogrel with placebo at each time point are derived from 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 PRU test showing response to subcutaneous administration of selatogrel 8mg, selatogrel 16mg or placebo within 60 minutes, between 2 and 8 hours, and at 24 hours. Data are mean and error bars indicate 95% CI.

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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[1]	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[1] or $P2Y_{12}$ inhibitor	2 (2)	0 (0)	0 (0)
Aspirin[1] + clopidogrel	22 (19)	19 (17)	28 (24)
Aspirin[1] + ticagrelor	7 (6)	11 (10)	10 (9)
Aspirin[1] + 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)

[1]Including carbasalate calcium; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; ACE: Angiotensin-converting enzyme.

Table 2. Treatment-emergent AEs

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 1 patient in any treatment group are shown.

Figure 1

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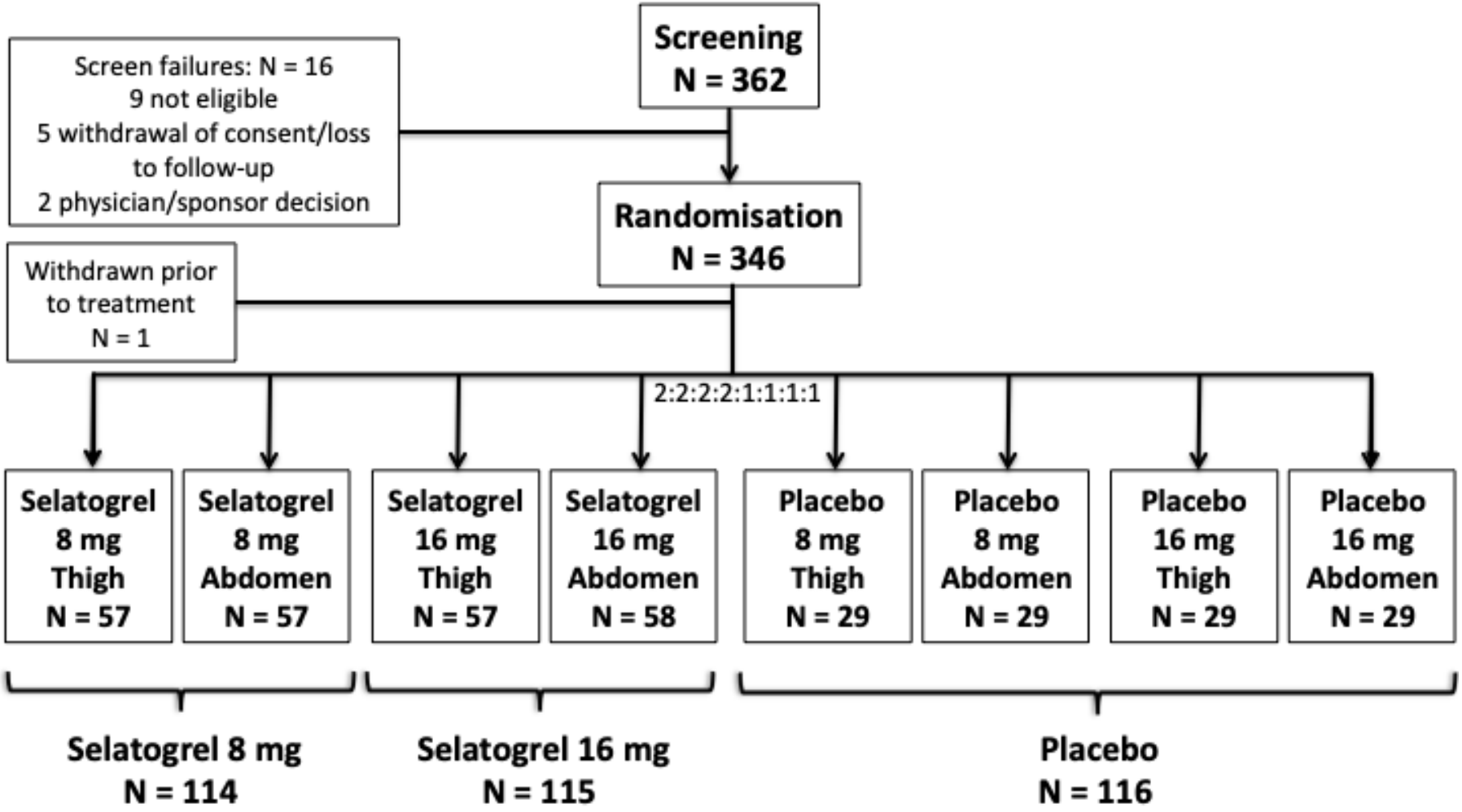

Figure 2A

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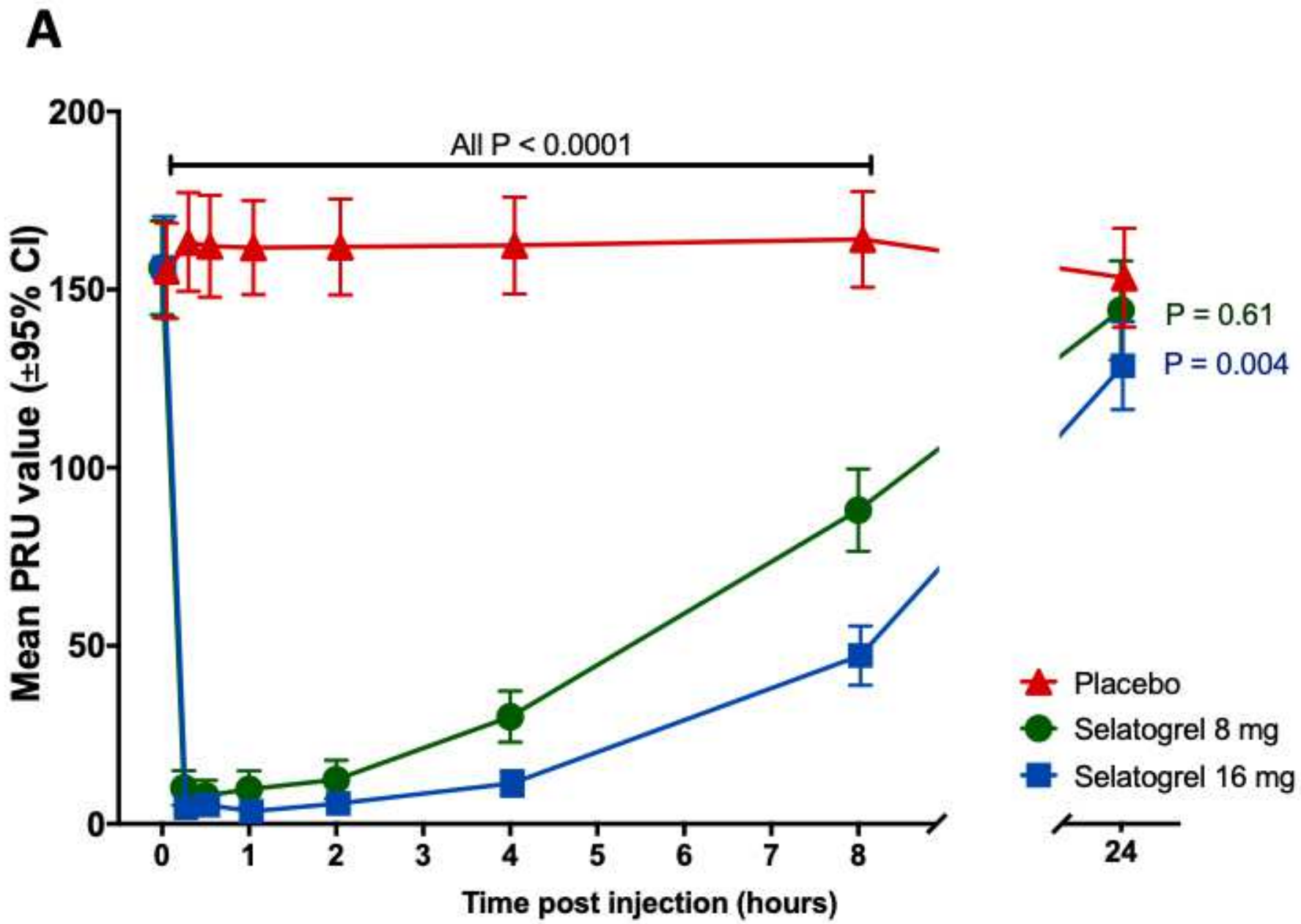

Figure 2B

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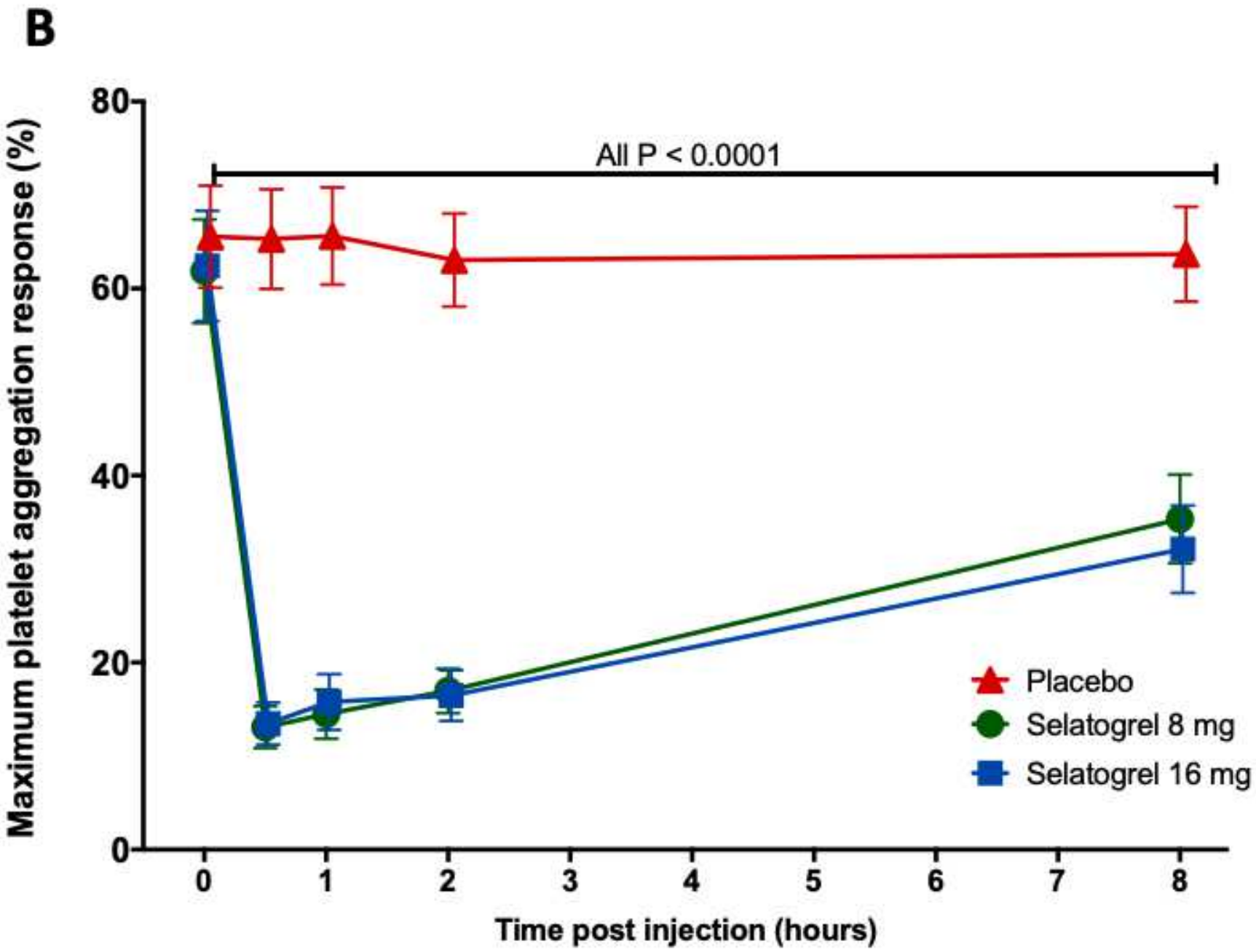

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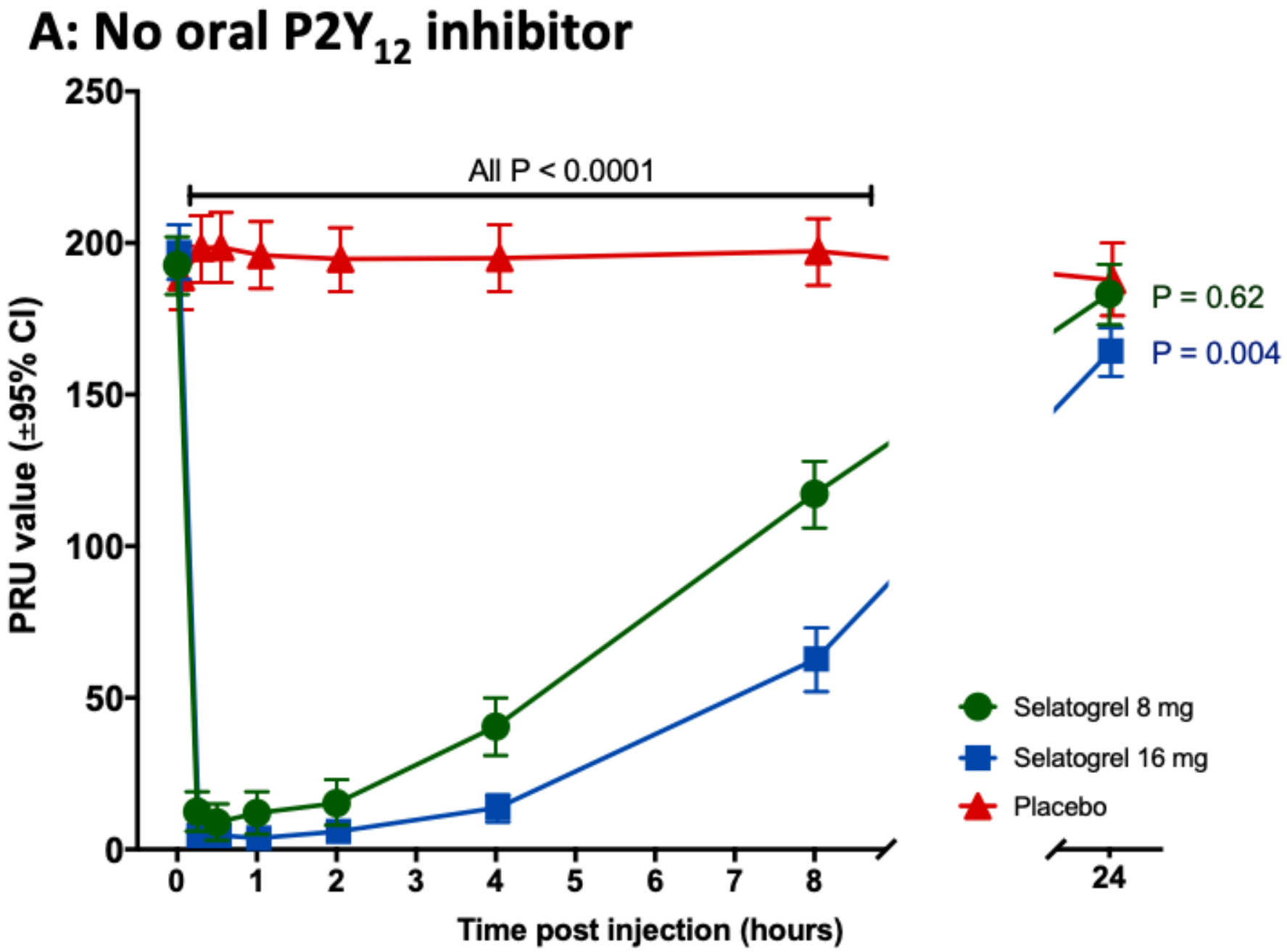

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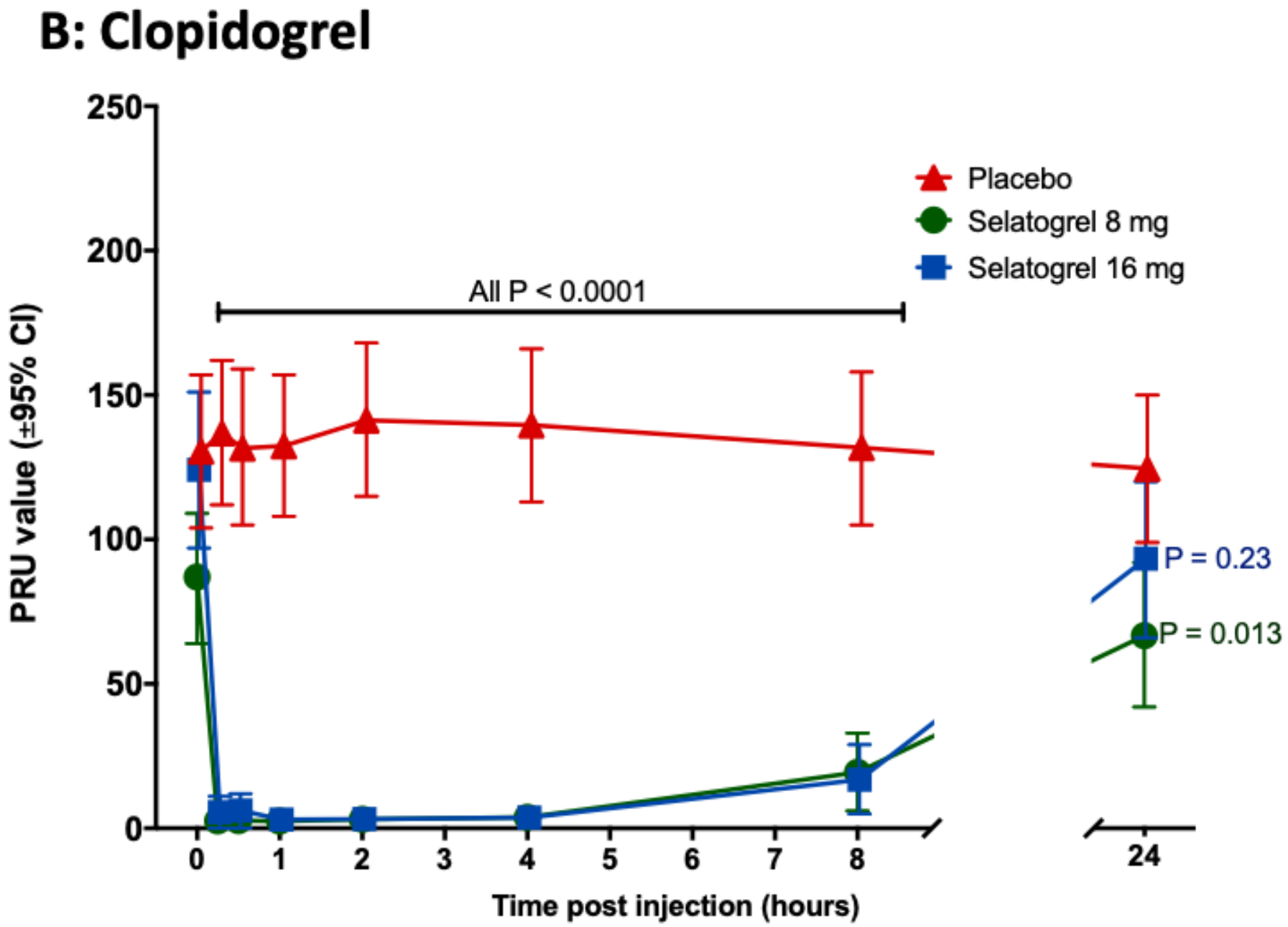

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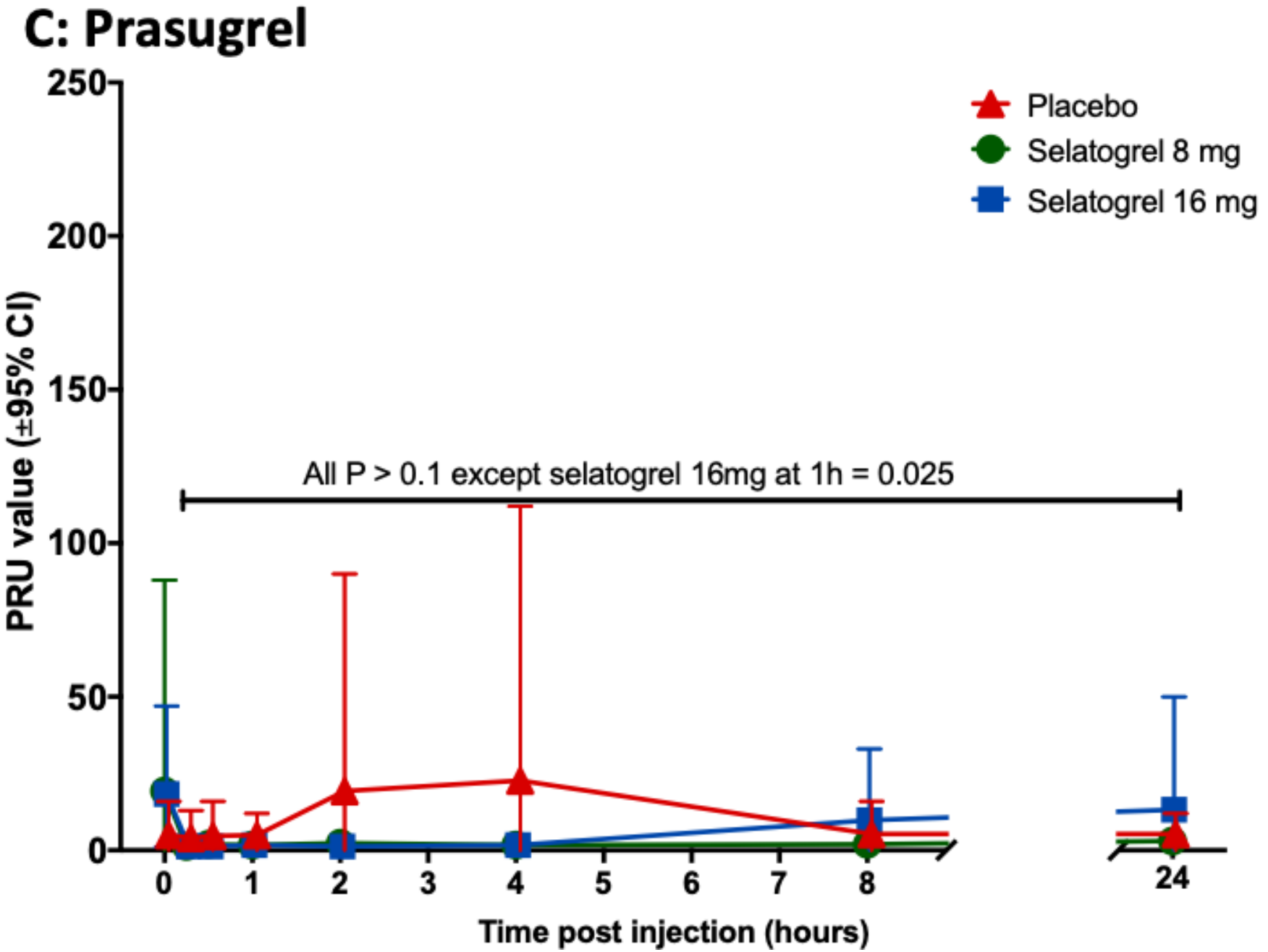

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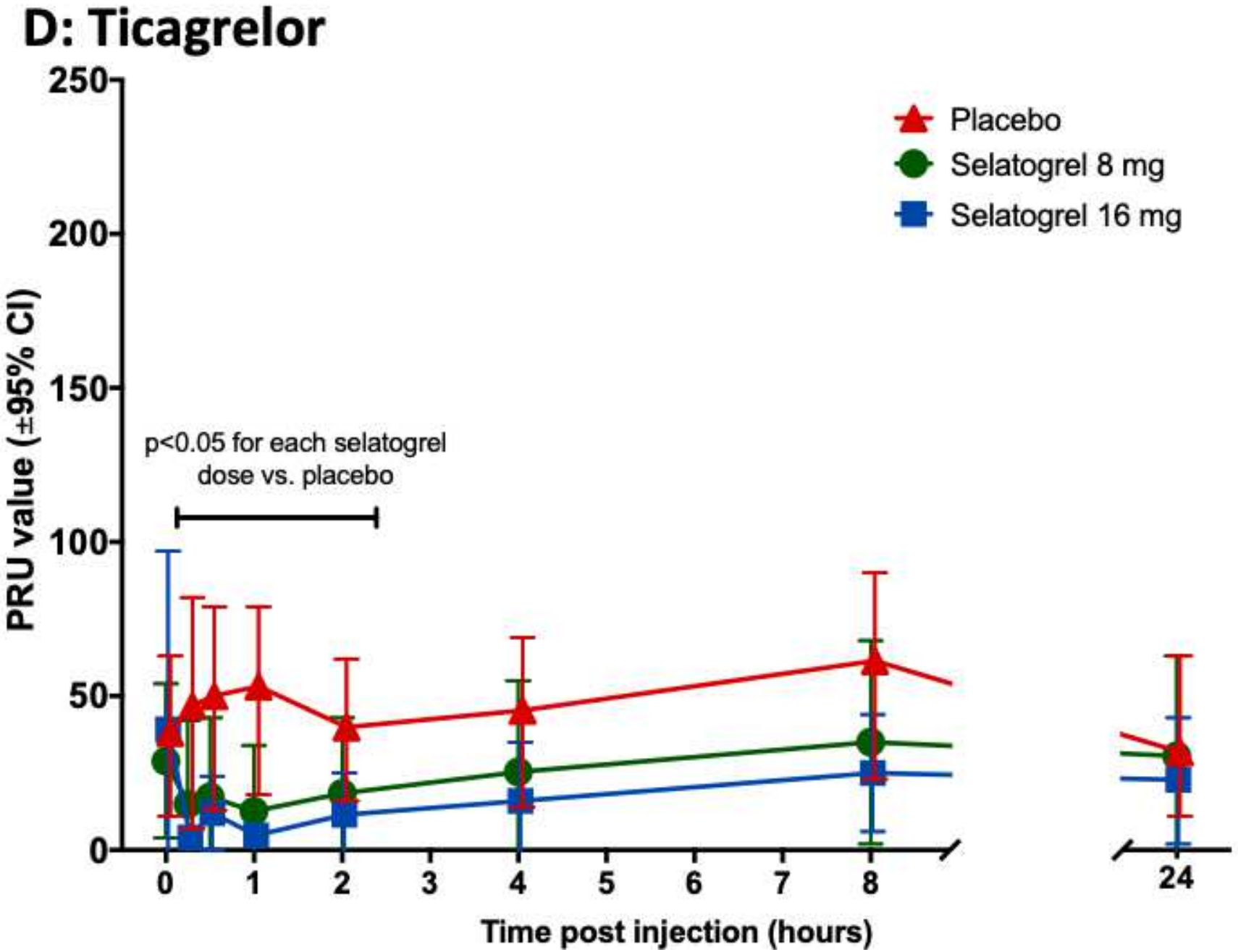

Figure 4A

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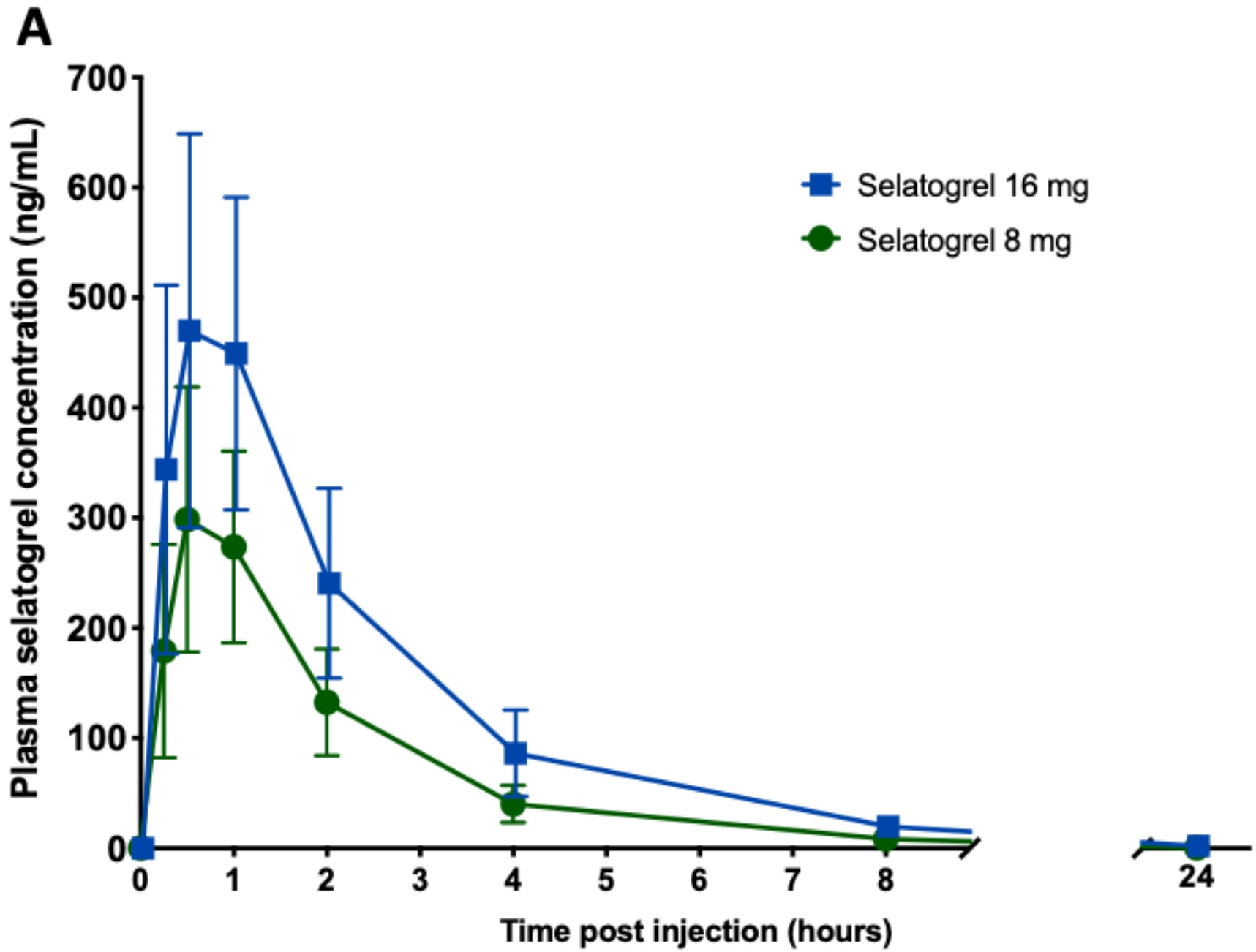

Figure 4B

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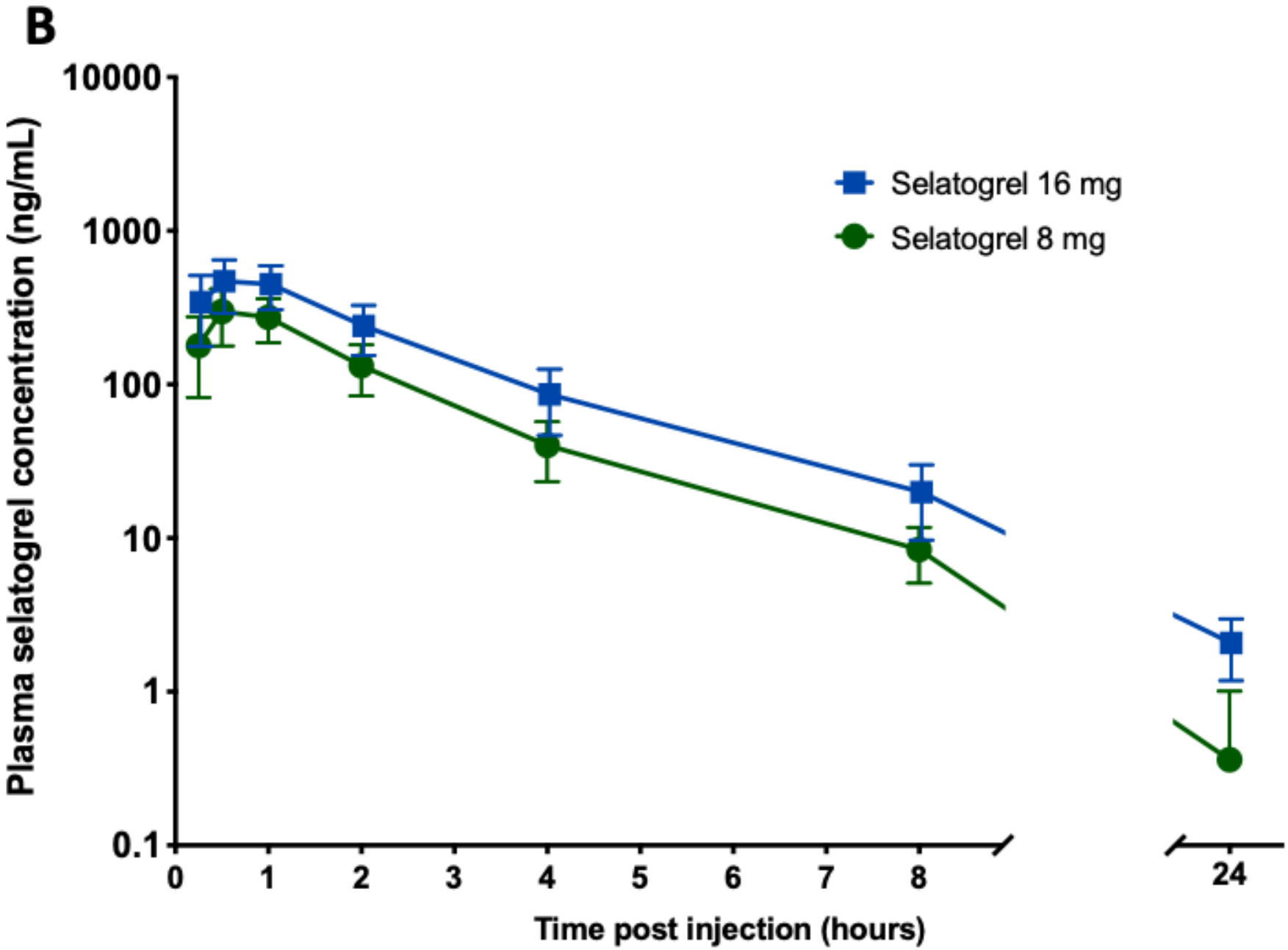

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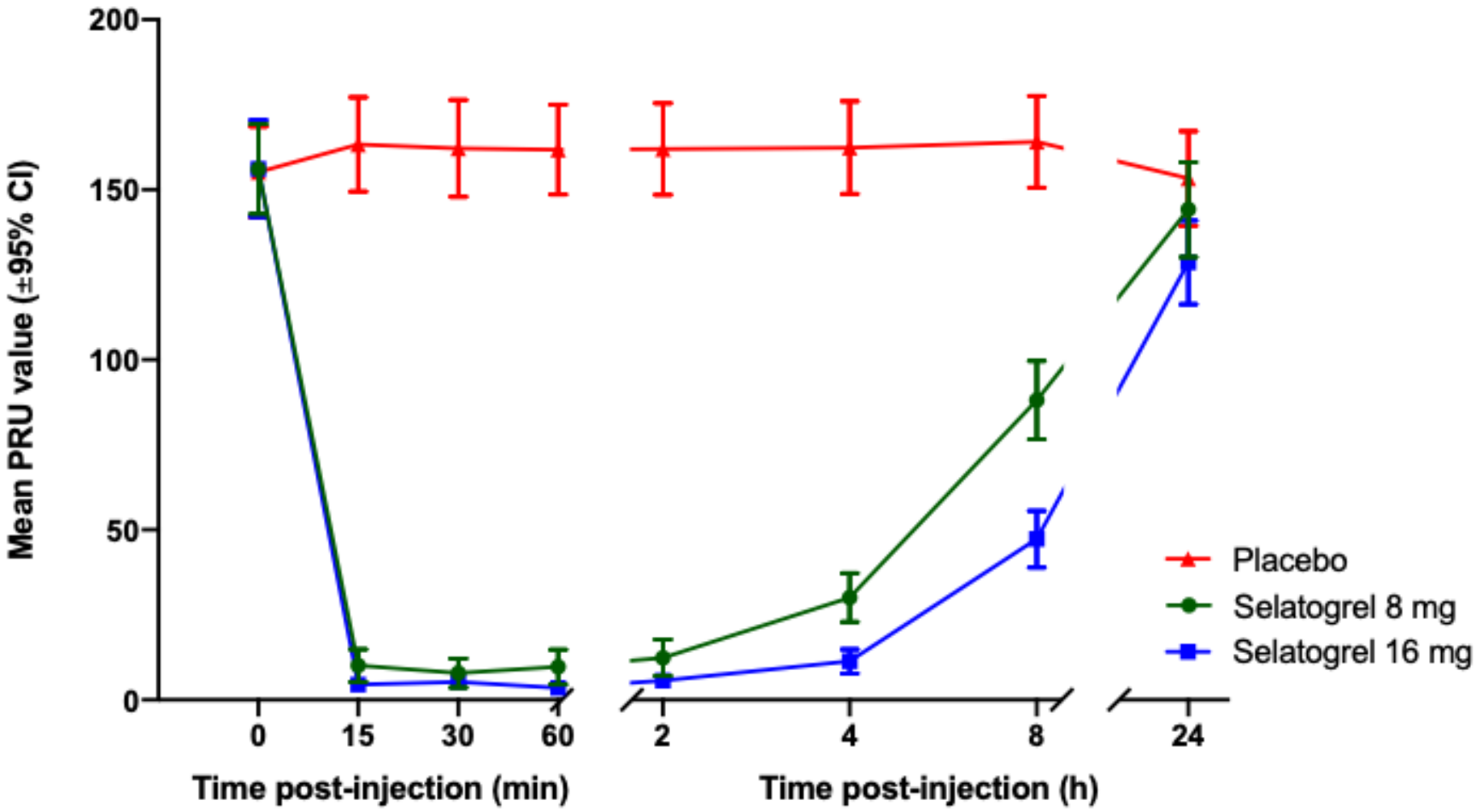

Online supplement for "Pharmacodynamics, pharmacokinetics and safety of single-dose subcutaneous administration of selatogrel, a novel $P2Y_{12}$ receptor antagonist, in patients with stable coronary artery disease"

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Inclusion and exclusion criteria

Inclusion criteria

All of the following must be met for inclusion:

1. Signed informed consent prior to any study-mandated procedure.

2. Male and female subjects aged from 18–85 years, inclusive.

3. For women of childbearing potential: Negative urine pregnancy test at screening visit and again before randomization.

4. Stable CAD defined by the presence of any of the following conditions:

    a. History of CAD with coronary artery stenosis on coronary angiogram ≥ 50%.

    b. Previously documented MI occurring more than 3 months prior to randomization.

5. Antiplatelet background therapy stable for at least 1 month prior to randomization.

6. Body weight ≥ 40.0 kg (88.2 lbs).

Exclusion criteria

1. ACS, PCI or any intervention for peripheral artery disease within 3 months prior to randomization.

2. Acute ischaemic stroke or transient ischaemic attack (TIA) within 3 months prior to randomization.

3. Active internal bleeding, or medical history of recent (< 1 month) bleeding disorders or conditions associated with high risk of bleeding (e.g., clotting disturbances, gastrointestinal bleed, haemoptysis).

4. Haemoglobin ≤ 10 g/dL at screening.

5. Loss of at least 250 mL of blood within 3 months of screening.

6. Use of anticoagulants (oral, parenteral) or fibrinolytic therapy within 24 h prior to screening (Visit 1).

7. Known platelet disorders (e.g., thrombasthenia, thrombocytopenia, von Willebrand disease).

Conditions that may prevent subject from complying with study requirements or may be a confounder for the study interpretation:

8. Pregnant or breastfeeding women.

9. Uncontrolled hypertension according to investigator's judgment.

10. Known and documented moderate or severe hepatic impairment.

11. End-stage renal failure requiring dialysis.

12. Any clinically significant findings on a physical exam, or laboratory tests prior to screening that in the investigator's judgment would preclude safe or reliable participation of a subject in the study.

13. Concomitant diseases (e.g., advanced liver cirrhosis, mental illness, neurodegenerative disease, terminal malignancy, etc.) or conditions (e.g., inability to communicate well with the investigator in the local language) that, in the opinion of the investigator, may prevent subject from complying with study requirements or may be a confounder for the study interpretation.

14. Veins unsuitable for i.v. puncture on either arm (e.g., difficult to locate, access, or puncture) according to the investigator's judgment.

15. Clinically relevant skin disease that prevents s.c. injection in the thigh or abdomen, according to the investigator's judgment.

16. Use of inhibitors of organic anion-transporting polypeptide (OATP)1B1 or OATP1B3 at screening (Visit 1).

17. Known hypersensitivity to ACT-246475, any of its excipients, or drugs of the $P2Y_{12}$ class.

18. Previous exposure to any investigational drug within 3 months prior to screening.

Light transmittance aggregometry

The following aggregometers were employed in this study:

ChronoLog (Havertown, Pennsylvania, USA)

PAP-4 (Biodata Corporation, Horsham, Pennsylvania, USA)

PAP-8E (Biodata Corporation, Horsham, Pennsylvania, USA)

APACT 4004 (Haemochrom Diagnostica, Essen, Germany)

***Post hoc* comparison of the differences in platelet reactivity between 24 hours and baseline in each group**

Further exploratory analysis was performed *post hoc* to assess the return to baseline of PRU values at 24 h by considering the absolute difference from baseline to 24 h and tested using a one-sample t-test. PRU levels at 24 h were not significantly different to baseline in the placebo arm (153 ± 74 vs. 155 ± 73; mean absolute difference -0.2; P = 0.94) but were lower for both selatogrel 8 mg (144 ± 74 vs. 156 ± 71; mean absolute difference -11.8; P <0.0001) and selatogrel 16 mg (129 ± 65 vs. 156 ± 77; mean absolute difference -28.8; P <0.0001).

Supplementary Table S1. Mean change in electrocardiographic parameters from baseline to post-dose

Mean absolute change ± SD	Selatogrel 8 mg n = 114	Selatogrel 16 mg n = 115	Placebo n = 116
Heart rate, beats per min			
Baseline to 1 h post-dose	-4.2 ± 8.5	-4.4 ± 5.7	-4.4 ± 5.8
Baseline to 24 h post-dose	0.9 ± 8.6	1.5 ± 5.6	1.4 ± 7.1
PR interval, msec			
Baseline to 1 h post-dose	1.0 ± 13.2	0.2 ± 11.1	2.0 ± 9.9
Baseline to 24 h post-dose	-3.3 ± 10.8	-3.4 ± 11.9	-3.4 ± 11.0
QT interval, msec			
Baseline to 1 h post-dose	11.2 ± 20.4	11.9 ± 16.1	10.5 ± 16.3
Baseline to 24 h post-dose	-3.7 ± 24.2	-3.5 ± 15.8	-6.5 ± 16.7
QTcB interval, msec			
Baseline to 1 h post-dose	-3.1 ± 21.6	-3.2 ± 15.0	-4.7 ± 15.6
Baseline to 24 h post-dose	-0.5 ± 20.8	1.7 ± 12.5	-2.7 ± 15.0

Supplementary Table S2. Change in laboratory from baseline to 24 hours post-dose

Mean absolute change ± SD	Selatogrel 8 mg n = 114	Selatogrel 16 mg n = 115	Placebo n = 116
Laboratory parameters			
Haemoglobin, g/L	-1.1 ± 7.2	-0.5 ± 6.0	-0.8 ± 5.7
Haematocrit, L/L	-0.001 ± 0.028	0.000 ± 0.021	-0.002 ± 0.022
Leukocytes, x 10^9/L	-0.003 ± 1.083	-0.034 ± 1.135	0.113 ± 1.187
Platelets, x 10^9/L	1.6 ± 28.3	-0.2 ± 27.0	1.1 ± 22.6
Prothrombin time, INR	0.01 ± 0.06	-0.01 ± 0.08	0.01 ± 0.05
Alanine aminotransferase, U/L	-0.8 ± 4.1	-0.3 ± 4.8	-0.2 ± 3.5
Aspartate aminotransferase, U/L	-1.3 ± 3.9	-0.9 ± 4.6	-0.6 ± 3.3
Alkaline phosphatase, U/L	-0.5 ± 7.7	-0.5 ± 5.4	-1.0 ± 6.2
Creatinine, μmol/L	0.8 ± 9.4	-0.1 ± 8.0	0.9 ± 9.1
Urea, mmol/L	-0.24 ± 1.19	-0.27 ± 1.07	-0.23 ± 1.11
Urate, μmol/L	-5.8 ± 26.0	-8.1 ± 28.3	-7.1 ± 34.7
Sodium, mmol/L	0.2 ± 1.9	0.1 ± 2.0	-0.1 ± 1.9
Potassium, mmol/L	0.12 ± 0.31	0.00 ± 0.35	0.09 ± 0.35
Chloride, mmol/L	0.2 ± 2.2	0.3 ± 2.2	0.1 ± 1.8

INR: International Normalised Ratio

Supplementary figures legends

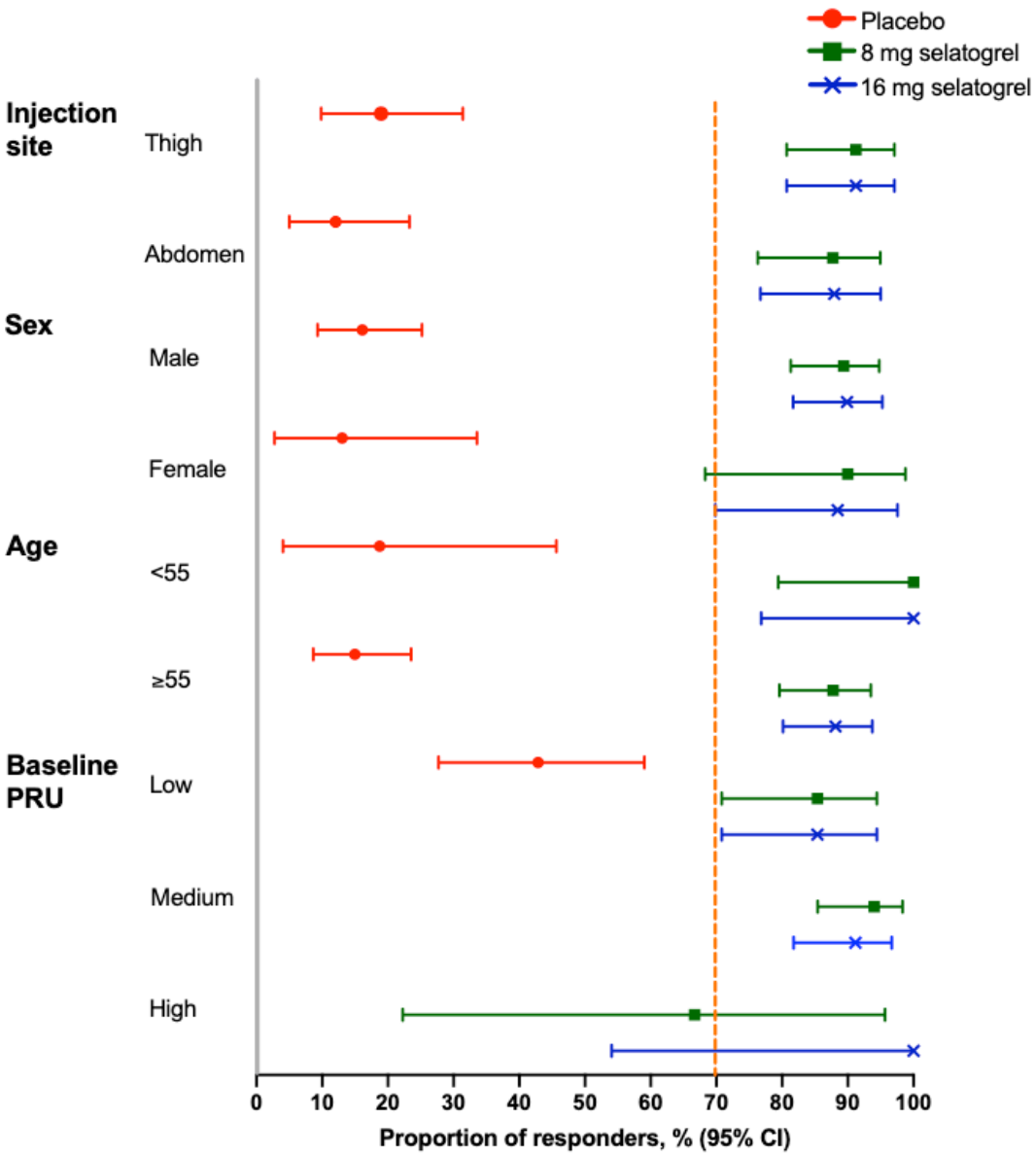
Supplementary figure S1. Proportion of responders (PRU <100 30 mins after injection lasting ≥3 h) analysed by injection site, sex, and baseline PRU. The 70% threshold used in statistical analyses is highlighted. Data are point estimates and bars indicate the 95% CI (based on Clopper-Pearson method).

Supplementary figure S2. $P2Y_{12}$ reaction units (PRU) assessed by VerifyNow $P2Y_{12}$ assay according to injection site (abdomen or thigh) following selatogrel at a single subcutaneous dose of either 8 mg or 16 mg. Data are mean and error bars indicate 95% CI.

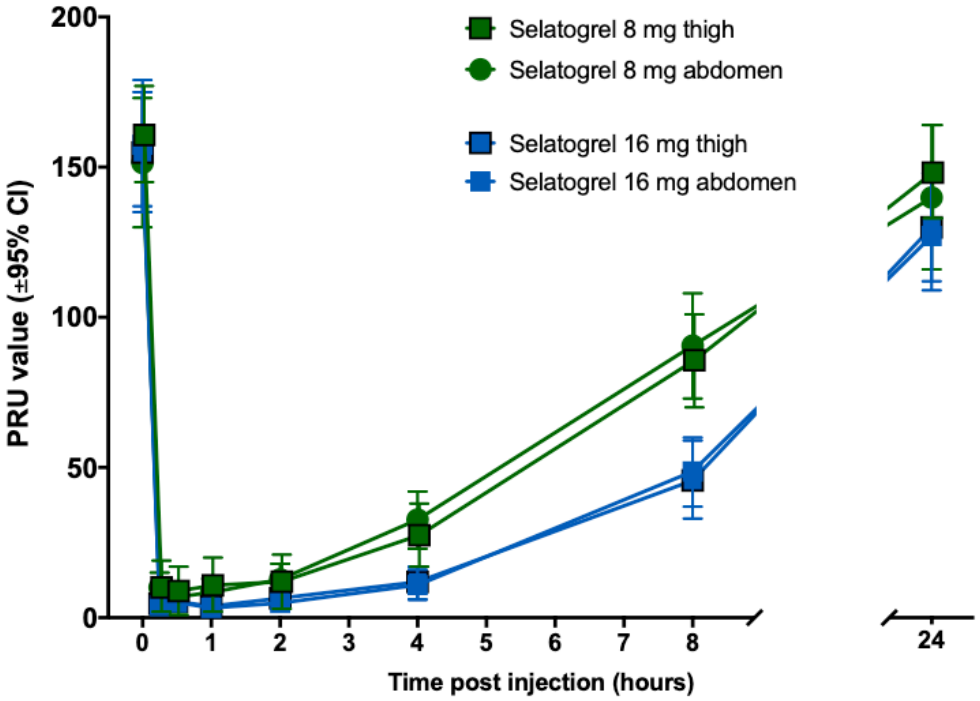
Supplementary figure S3. Selatogrel concentrations over time and by dose according to injection site (abdomen or thigh). Plasma concentrations (ng/mL) of selatogrel following single doses of either 8 mg or 16 mg measured using a validated liquid chromatography tandem mass spectrometry assay. Data are mean and error bars indicate standard deviation.

Supplementary figure S4. Vital signs at baseline and following subcutaneous injection of selatogrel 8 mg, selatogrel 16 mg or placebo, showing (A) pulse rate and (B) blood pressure. Data are mean and error bars indicate indicate 95% CI.

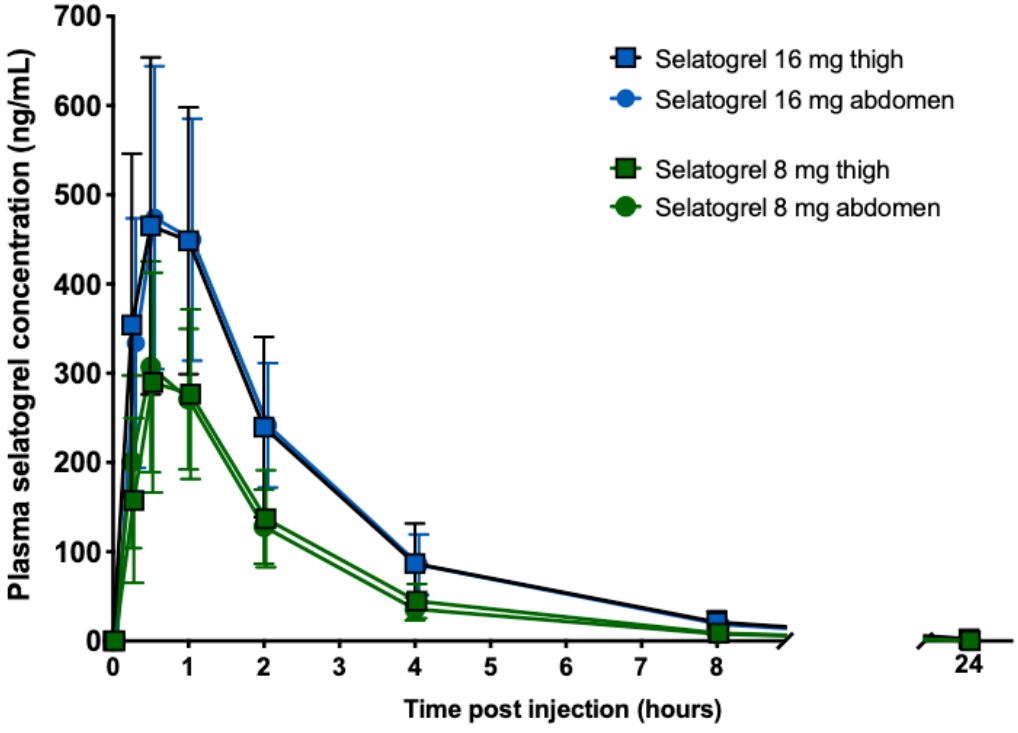
Supplementary figure S1



Supplementary figure S2



Supplementary figure S3



Supplementary figure S4