Inhibition of Platelet Aggregation After Subcutaneous Administration of a Single Dose of Selatogrel, a Novel $P2Y_{12}$ Receptor Antagonist, in Patients with AMI

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Disclosures

- Professor Peter Sinnaeve is a Clinical Investigator for the Fund for Scientific Research – Flanders

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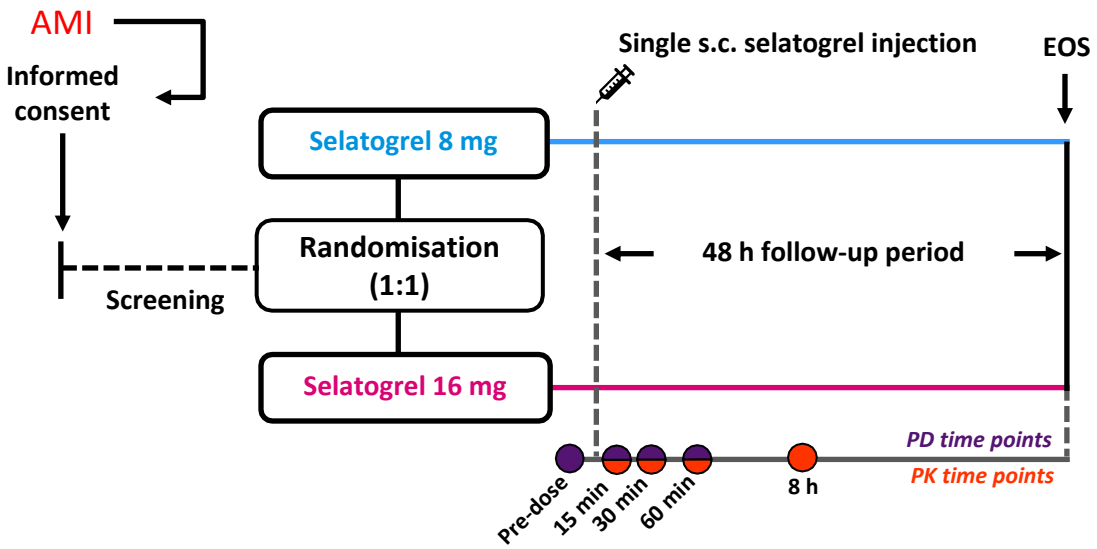
Rationale and Objective

- The onset of inhibition of platelet aggregation with oral $P2Y_{12}$ receptor antagonists is delayed in patients experiencing AMI, a condition associated with high platelet reactivity
- Thus, there is a need for an early and rapid treatment option to reduce high platelet reactivity and aggregation in patients with AMI
- Selatogrel is a potent, reversible, and highly selective $P2Y_{12}$ receptor antagonist with a rapid onset of action when administered subcutaneously
- **Primary objective:** To assess inhibition of platelet aggregation 30 min after single subcutaneous (s.c.) injection of selatogrel in subjects with AMI receiving standard of care

Study Design and Endpoints

- Prospective, open-label, Phase 2 exploratory study



- **PD:**
  - **Primary:** Proportion of responders (response defined as PRU* level <100 at 30 min post injection)
  - **Other:** PRU over time (15–60 min post dose)
- **PK:**
  - Selatogrel plasma concentrations (15, 30, 60 min, and 8 h post dose)
  - C_{max}
  - t_{max}
- **Safety:**
  - Treatment-emergent AEs and SAEs;
  - Changes from baseline in vital signs and clinical laboratory tests

*Platelet reactivity was expressed as $P2Y_{12}$ reaction units (PRU)
AE, adverse event; EOS, end of study; SAE, serious adverse event

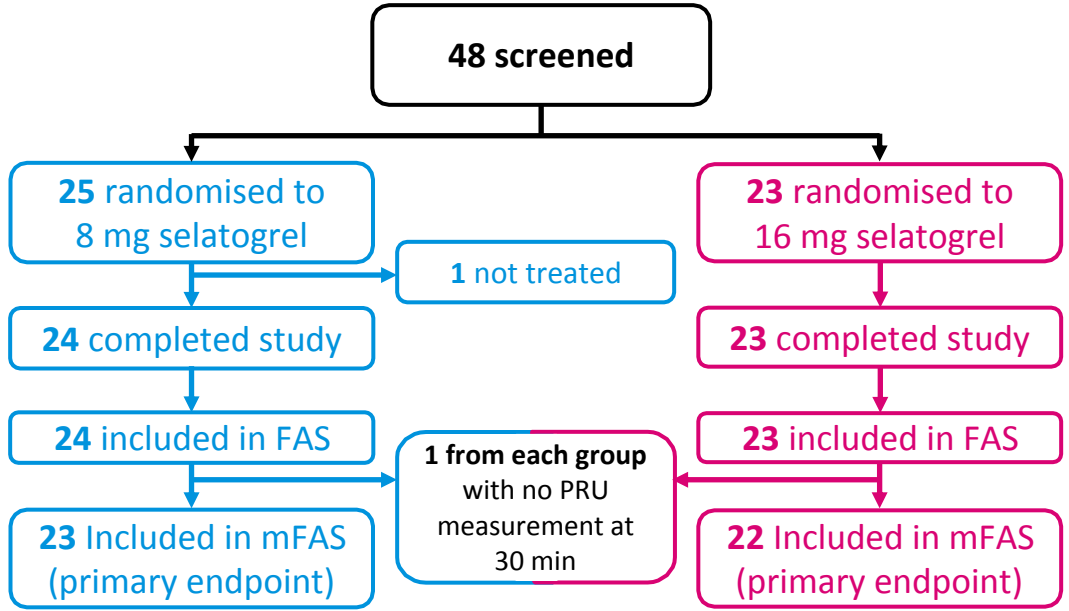
Methodology

- **Single s.c. selatogrel injection**
- **Blood sampling**
  - PD assessment: PPACK anticoagulant tubes
  - PK assessment: EDTA tubes
- **Platelet reactivity assessment**
  - VerifyNow® (PRU)
- **Analysis sets**
  - **FAS:** all randomised subjects who received treatment
  - **mFAS (main analysis):** subjects from FAS who had PRU measured at 30 min post dose
  - **PK**: All subjects who received selatogrel with ≥1 PK measurement post dose

Subject Eligibility and Disposition

Key eligibility criteria

- ✓ Adult males and post-menopausal females aged ≤85 y
- ✓ Type 1 AMI (STEMI and NSTEMI)
- ✓ AMI symptom onset >30 min and <6h
- ✗ Severe haemodynamic instability (e.g. Killip class 3/4)
- ✗ Loading dose of oral $P2Y_{12}$ receptor antagonist prior to randomisation
- ✗ Fibrinolytic therapy



Study Population

Demographics and baseline characteristics	Selatogrel 8 mg (N=24)	Selatogrel 16 mg (N=23)
Male / Female, n	16 / 8	18 / 5
Age, median (min, max), years	69 (40, 85)	71 (49, 83)
Caucasian, n	22	21
BMI, mean (SD), kg/m²	28 (5)	27 (4)
Time from AMI symptom onset to selatogrel injection, median (min, max), h	4.7 (1.2, 6.2)	3.4 (1.3, 6.3)
STEMI diagnosis, n	16	13
TIMI risk score ≥3, n	7	7
NSTEMI diagnosis, n	8	10
TIMI risk score ≥ 5, n	2	4
Killip Class I / II, n	22 / 2	22 / 1
Risk factors, n		
Diabetes Mellitus	8	5
Chronic kidney disease	0	3
Hypertension	15	12
Prior MI	1	2

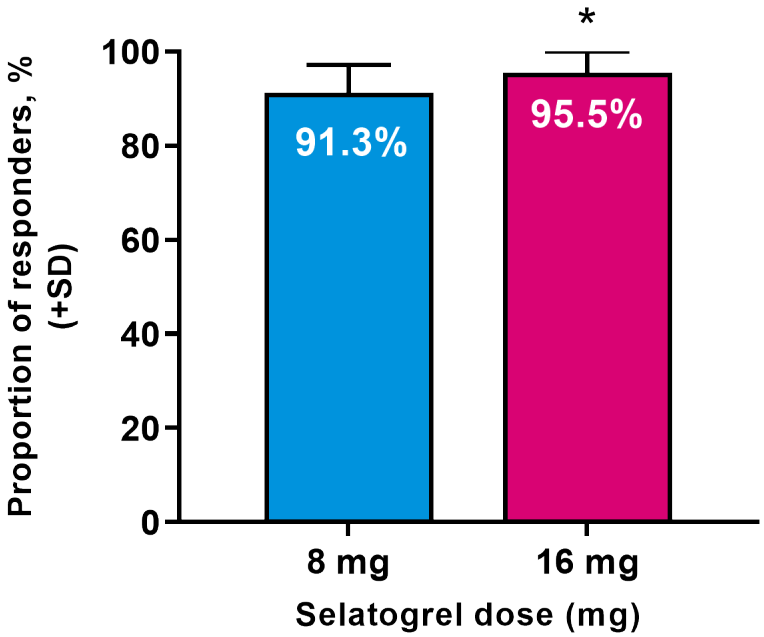
Full Analysis Set (FAS)

Concomitant Medications

n (%)	Selatogrel 8 mg (N=24)	Selatogrel 16 mg (N=23)
Platelet aggregation inhibitors		
Acetylsalicylic acid	23 (96)	23 (100)
Ticagrelor*	21 (88)	22 (96)
Time after selatogrel administration, median (min, max), h	*0.53 (2 min, 9.3h)*	*0.67 (1 min, 25.7h)*
Clopidogrel	2 (8)[†]	0
Eptifibatide	1 (4)	0
Tirofiban	0	1 (4)
Heparin group	22 (92)	22 (96)
Nitrates	16 (67)	16 (70)
ACE inhibitors	16 (67)	15 (65)
Beta blocking agents	18 (75)	12 (52)
Dihydropyridines	8 (33)	10 (44)
Morphine	12 (50)	6 (26)
Angiotensin II antagonists	5 (21)	5 (22)

*All subjects received ticagrelor after selatogrel injection
[†]One subject was receiving clopidogrel prior to study inclusion
Full analysis set

Proportion of Responders at 30 min



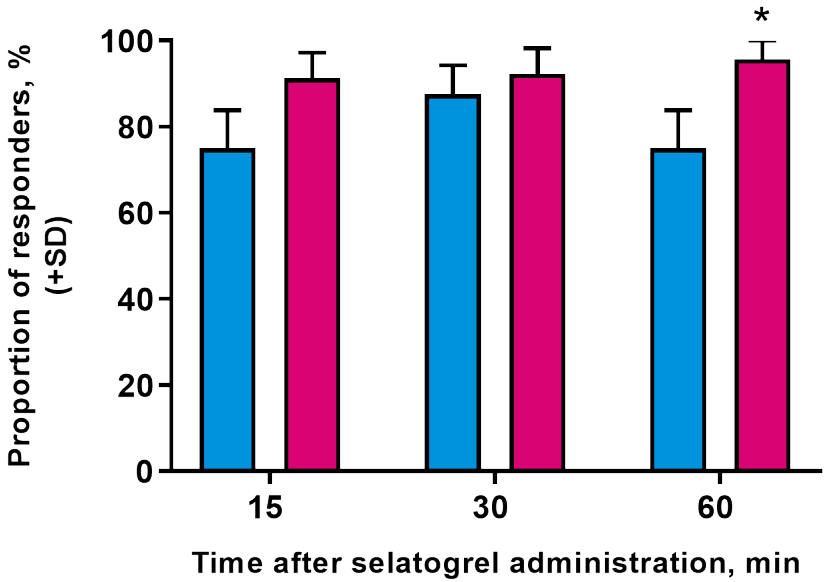
Selatogrel Dose	Responders/ Total	Proportion of responders, %	97.5% CI (one -sided)	p-value†
8 mg	**21**/23	91.3	79.8, 100.0	0.1416
16 mg	**21**/22	95.5	86.8, 100.0	***0.0093**

†Each of the two doses were tested with a one-sided Z-test at a significance level of 0.025, testing proportion of responders ≤ 85% (H_0)

Responder: subject with a PRU value <100, 30 min after selatogrel injection (mFAS)

CI, confidence interval; SD, standard deviation

Proportion of Responders Over Time



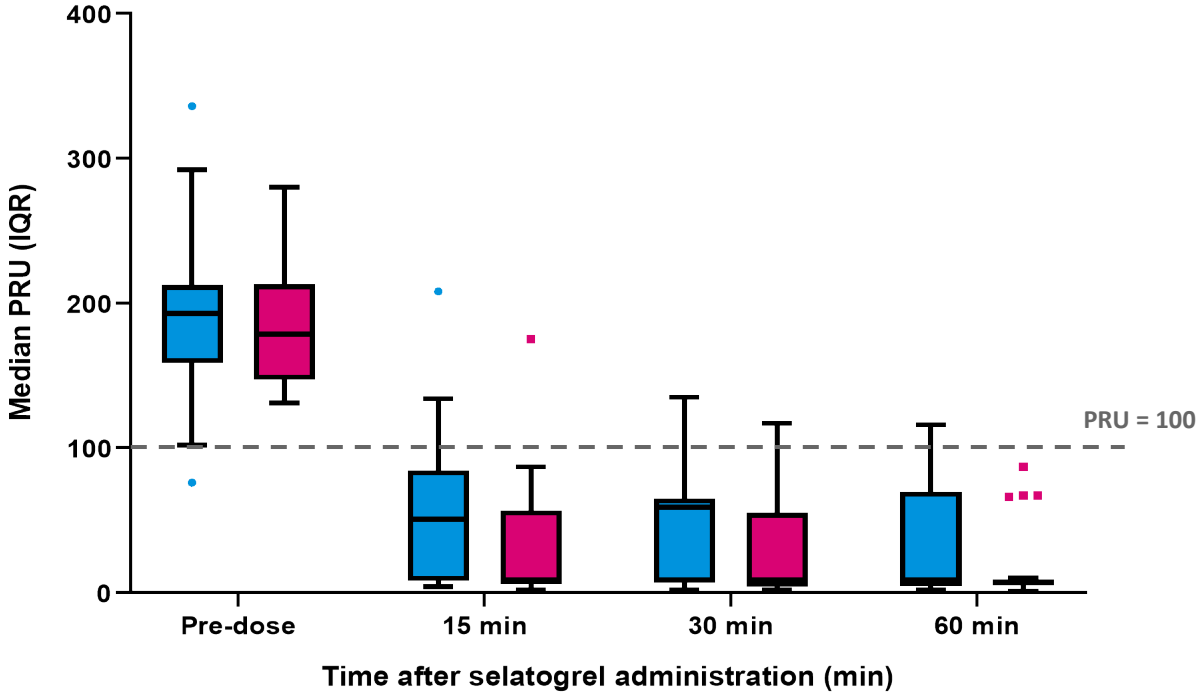
Selatogrel dose	Time point	Responders/ Total	Proportion of responders, %	97.5% CI (one-sided)	p-value†
8 mg	15 min	**18**/24	75.0	57.7, 100.0	0.8711
	30 min	**21**/24	87.5	74.3, 100.0	0.3556
	60 min	**18**/24	75.0	57.7, 100.0	0.8711
16 mg	15 min	**21**/23	91.3	79.8, 100.0	0.1416
	30 min	**21**/23	91.3	79.8, 100.0	0.1416
	60 min	**22**/23	95.7	87.3, 100.0	***0.0061**

†For each time point, each of the two doses were tested with a one-sided Z-test at a significance level of 0.025, testing proportion of responders ≤ 85% (H_0)

Responder: subject with a PRU value <100 (FAS)

CI, confidence interval; SD, standard deviation

Platelet Reactivity Over Time

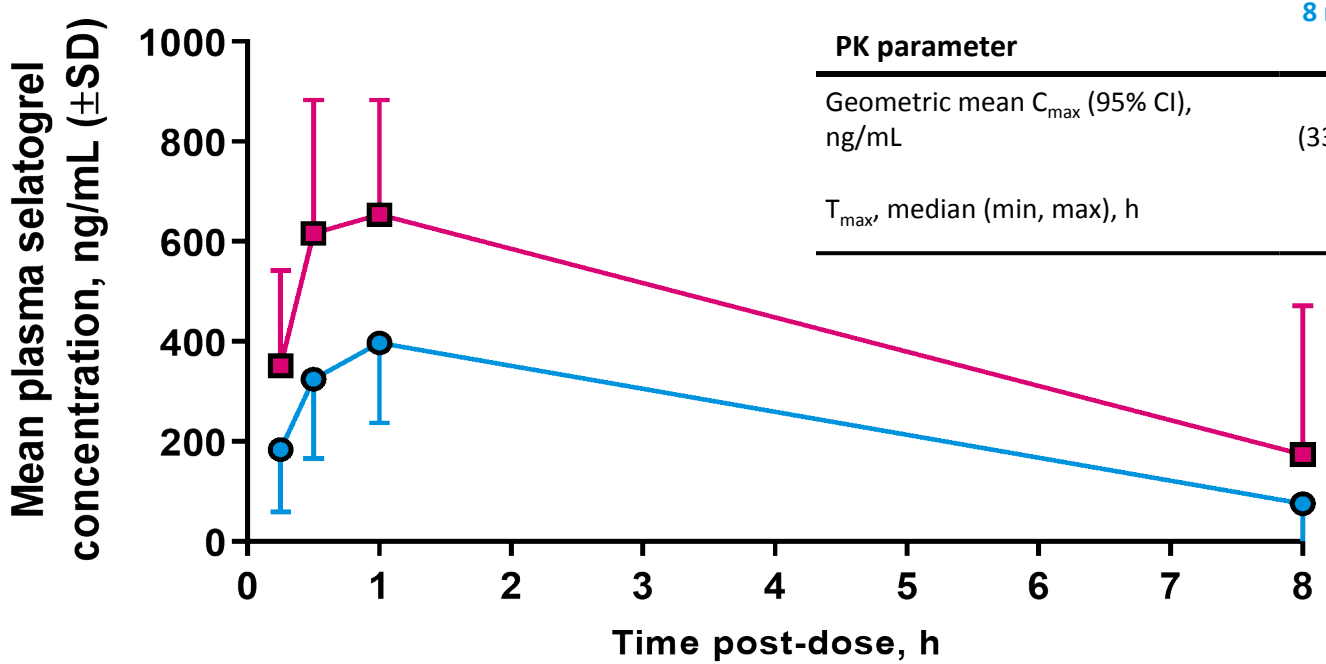


8 mg selatogrel

16 mg selatogrel

Box plots present the median, upper (75th) and lower (25th) quartiles

Pharmacokinetics



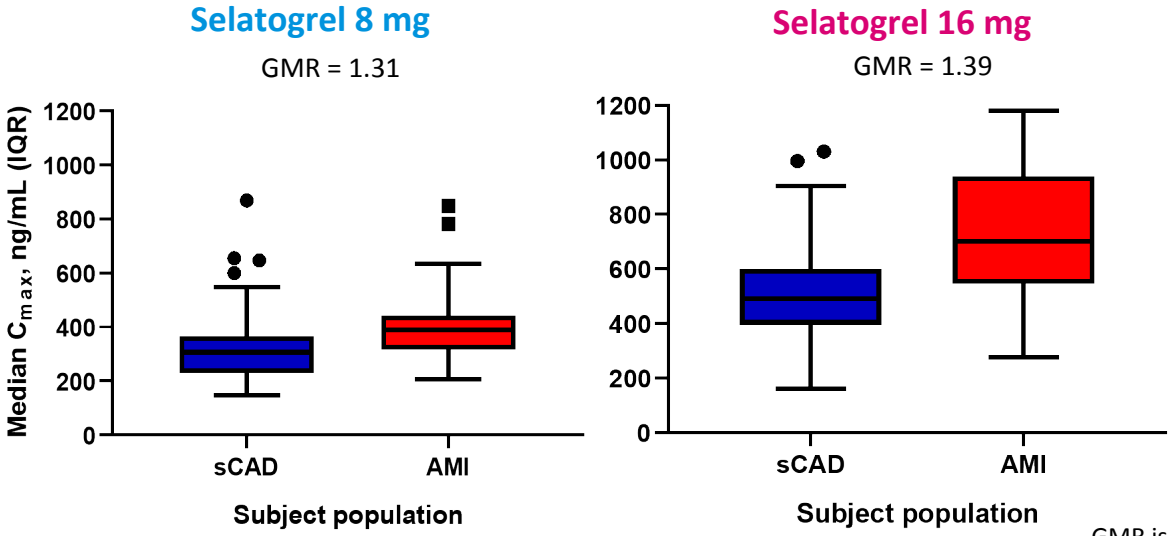
PK parameter	8 mg selatogrel (N=24)	16 mg selatogrel (N=22)
Geometric mean C_{max} (95% CI), ng/mL	390.09 (338.70, 449.28)	672.59 (573.55, 788.72)
T_{max}, median (min, max), h	1.00 (0.50, 1.27)	0.97 (0.25, 1.15)

8 mg selatogrel 16 mg selatogrel

C_{max}, maximum concentration; t_{max}, time to maximum concentration

Pharmacokinetics: AMI and Stable CAD

- PK data from subjects with AMI (n=46, current study) and sCAD (n=226, parallel study)



T_{max} median (min, max) , h	sCAD	AMI
8 mg	0.52 (0.38, 1.05)	1.00 (0.50, 1.27)
16 mg	0.53 (0.23, 2.02)	0.97 (0.25, 1.15)

GMR is the ratio of C_{max} for AMI verus sCAD

GMR, geometric mean ratio, sCAD, stable coronary artery disease

Safety

- 20 (43%) patients had ≥1 treatment-emergent AE, mainly of mild/moderate intensity
  - The most frequent treatment-emergent AE was ventricular tachycardia (8 mg, n=4;16 mg, n=3), 2 of which (1 in each group) were reported as SAEs
  - One case of mild dyspnea (16 mg)

- One patient in the 8 mg group had a mild post-procedural haemorrhage
  - Bleeding at radial access after PCI ~1 h post dose

Summary and Conclusions

- The target response (PRU<100 at 30 min) was achieved in 91% and 96% of patients with 8 and 16 mg selatogrel, respectively
- PRU <100 was achieved as early as 15 min post dose, and maintained through 60 min post dose
  - The antiplatelet effect was faster, more pronounced, and more consistent in the 16 mg group than in the 8 mg group
- Selatogrel was well tolerated with no major bleeding events
- These data support further clinical investigation of selatogrel in a larger population of patients with AMI

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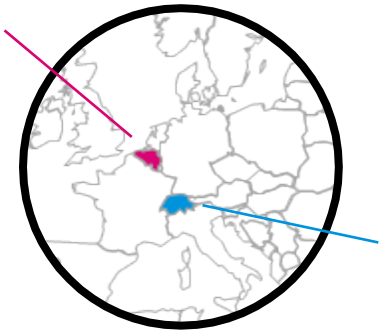

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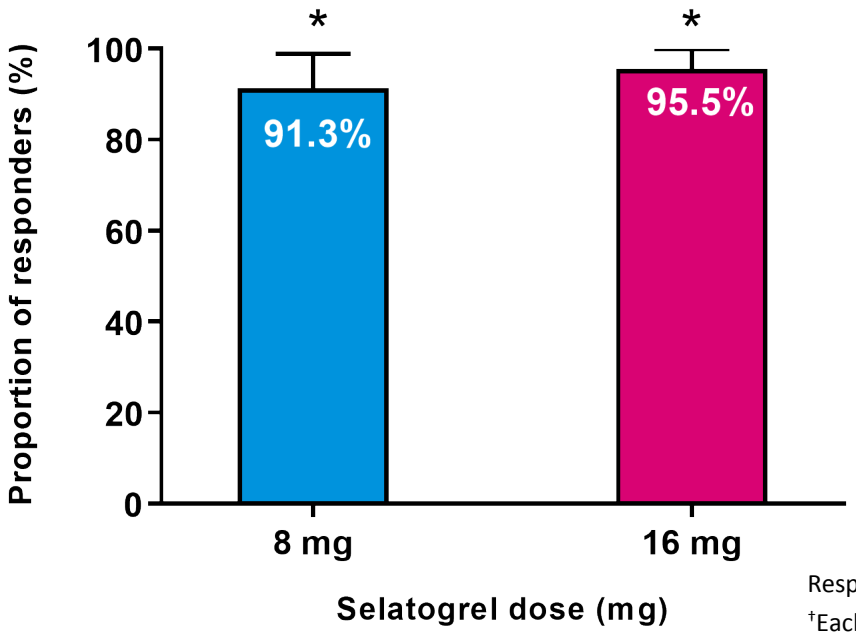
Backup slides

Proportion of Responders

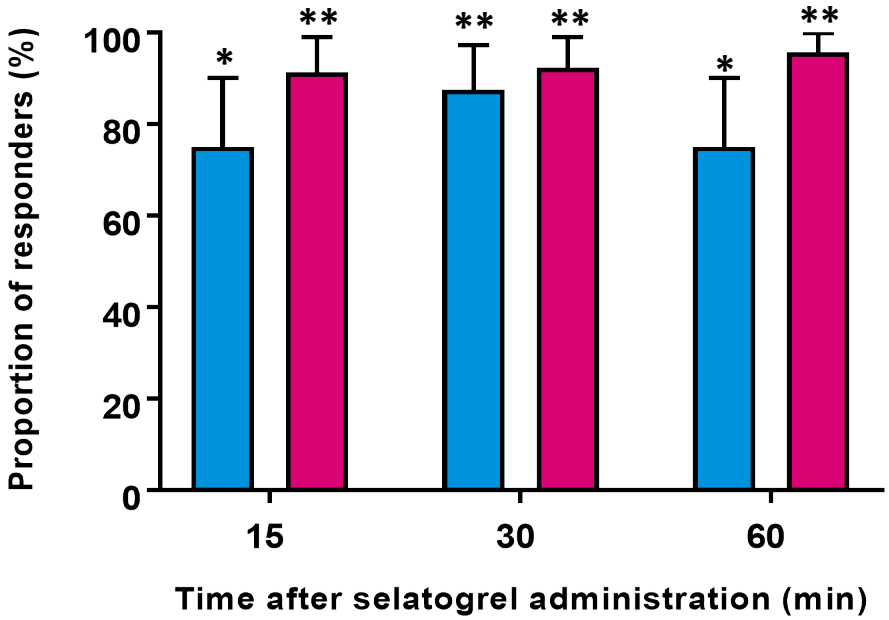


Selatogrel Dose	Responders/Total	Proportion of responders, %	95% CI	p-value†
8 mg	21/23	91.3	72.0, 98.9	***<0.0001**
16 mg	21/22	95.5	77.2, 99.9	***<0.0001**

Responder: subject with a PRU value <100, 30 min after selatogrel injection (mFAS)

†Each of the two doses were tested with a one-sided Z-test at a significance level of 0.025, testing H0: proportion of responders ≤ 50% vs. H1: proportion of responders > 50%

Proportion of Responders over time



- Response rates were independent of:
  - Time between AMI symptom onset and selatogrel administration
  - Sex
  - Age
  - STEMI/NSTEMI diagnosis

8 mg selatogrel 16 mg selatogrel

A responder is defined as a subject with a PRU value < 100 (FAS)
*p=0.0023; **p≤0.001

AMI-Related Medications

n (%)	Initiated prior to selatogrel	
	Selatogrel 8 mg (N=24)	Selatogrel 16 mg (N=23)
Platelet aggregation inhibitors		
Acetylsalicylic acid	14 (58)	14 (61)
Ticagrelor	-	-
Clopidogrel	-	-
Eptifibatide	-	-
Tirofiban	-	-
Heparin group	15 (63)	11 (48)
Nitrates	9 (38)	9 (39)
ACE inhibitors	0	1 (4)
Beta blocking agents	0	1 (4)
Dihydropyridines	1 (4)	4 (18)
Morphine	9 (38)	3 (13)

FAS