

Subcutaneous Administration of a P2Y₁₂ Receptor Antagonist

Field of the invention

The present invention relates to a P2Y₁₂ receptor antagonist selected from the group
 5 consisting of 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-
 amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester (hereinafter also
 referred to as "Compound 1"), (1*S*,2*S*,3*R*,5*S*)-3-[7-[(1*R*,2*S*)-2-(3,4-
 difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-
 hydroxyethoxy)cyclopentane-1,2-diol (hereinafter also referred to as "Ticagrelor"), and
 10 (1*S*,2*R*,3*S*,4*R*)-4-[7-[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-
 [1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol (hereinafter also referred to as
 "Ticagrelor-M"), or a pharmaceutically acceptable salt thereof, for use as a medicament by
 subcutaneous or intradermal administration.

Background of the invention

15 When vascular integrity is compromised, circulating platelets adhere to the damaged
 vessel wall and aggregate, forming a plug that seals off the site of injury to prevent blood
 loss. Autopsy studies demonstrated that rupture of atherosclerotic plaques can lead to
 uncontrolled platelet thrombus formation and vessel occlusion (Davies MJ et al. (1986)
 Circulation 73:418-427). Inhibition of platelet aggregation is recognized as an effective
 20 strategy for prevention of atherothrombotic events in patients with atherosclerotic disease
 in the coronary, peripheral, and cerebrovascular circulation (Davi G et al. (2007) N Engl J
 Med 357:2482-2494).

The ADP receptors P2Y₁ and P2Y₁₂ play a critical role in platelet activation and aggregation
 (Andre P et al. (2003) J Clin Invest 112:398-406). Inhibition of the P2Y₁₂ receptor is a
 25 validated concept for prevention of major adverse cardiovascular events in patients with
 acute coronary syndromes (ACS) as demonstrated by the thienopyridines ticlopidine,
 clopidogrel and prasugrel (Franchi F et al. (2015) Nat Rev Cardiol 12:30-47). These drugs
 following metabolic activation irreversibly block the P2Y₁₂ receptor and platelet function
 (Antman EM et al. (2004) Circulation 110:588-636; Anderson JL et al. (2011) Circulation
 30 123:e426-579) resulting in increased efficacy and increased bleeding (Wiviott SD et al.
 (2007) Circulation 116:2923-2932). In studies using P2Y₁₂ knockout mice it was shown that
 clopidogrel and prasugrel caused more blood loss following tail transection as compared
 with vehicle indicating that the increased blood loss may be due to off-target effects of the
 thienopyridines (Andre P et al. (2011) J Pharmacol Exp Ther 338:22-30).

Preclinical studies with the direct-acting and reversibly binding P2Y₁₂ antagonist ticagrelor demonstrated a wider therapeutic window in rat and dog thrombosis models as compared with clopidogrel (van Giezen JJ et al. (2009) *Thromb Res* 124:565-571; Becker RC et al. (2010) *Thromb Haemost* 103:535-544). It was argued that the reversibility of the binding of ticagrelor to P2Y₁₂ might account for this difference. In patients, ticagrelor achieved a higher extent of inhibition of ADP-induced platelet aggregation than clopidogrel (Husted S et al. (2006) *Eur Heart J* 27:1038-1047; Cannon CP et al. (2010) *Lancet* 375:283-293) and in the pivotal phase III trial (PLATO) in post acute coronary syndrome patients, ticagrelor showed superior efficacy and no significant difference in the risk of major bleeding events to clopidogrel. However, a significant increase in fatal intracranial bleedings and in major or minor bleedings according to the study criteria was reported for ticagrelor (Wallentin L et al. (2009) *N Engl J Med* 361:1045-1057).

Several studies confirmed the benefit of earlier administration of inhibitors of platelet function, for example glycoprotein IIb/IIIa inhibitors in patients with ST elevation myocardial infarction (STEMI), especially in those presenting very soon after symptom onset (Van't Hof AW et al. (2008) *Lancet* 372:537-546; Herrmann HC et al. (2009) *JACC Cardiovasc Interv* 2:917-924; ten Berg JM et al. (2010) *J Am Coll Cardiol* 55:2446-2455). Furthermore, various studies and meta-analyses suggested that pretreatment with clopidogrel in patients with STEMI could reduce the rate of ischemic events without excess bleeding (Sabatine MS et al. (2005) *JAMA* 294:1224-1232; Bellemain-Appaix A et al. (2012) *JAMA* 308:2507-2516; Zeymer U et al. (2012) *Clin Res Cardiol* 101:305-312). However, the effectiveness of clopidogrel is limited by its slow onset of action and the variable response (Oliphant CS et al. (2016) *J Pharm Pract* 29:26-34). The oral P2Y₁₂-receptor antagonists ticagrelor and prasugrel were reported to inhibit platelet function in less than 1 hour (Storey RF et al. (2010) *J Am Coll Cardiol* 56:1456-1462; Wiviott SD et al. (2007) *Circulation* 116:2923-2932). However, contradictory studies suggested that the full effect of prasugrel or ticagrelor on platelet function may take several hours in patients with STEMI (Alexopoulos D et al. (2012) *Circ Cardiovasc Interv* 5:797-804; Valgimigli M et al. (2012) *JACC Cardiovasc Interv* 5:268-277; Parodi G et al. (2013) *J Am Coll Cardiol* 61:1601-1606; Montalescot G et al. (2014) *N Engl J Med* 371:2339). Indeed, in the ATLANTIC clinical trial (Montalescot G et al. (2013) *N Engl J Med* 369:999-1010) it was found that the two coprimary end points did not differ significantly between a group of patients with ongoing STEMI that has received an early prehospital treatment (in the ambulance) of oral Ticagrelor and a group that has received the treatment only later in the hospital (in the catheterization laboratory). The two coprimary endpoints were (i) the proportion of patients who did not have a 70% or greater resolution of ST-segment elevation before

percutaneous coronary intervention (PCI) and (ii) the proportion of patients who did not have Thrombolysis in Myocardial Infarction flow grade 3 in the infarct-related artery at initial angiography. Montalescot et al. stated that besides an extremely short time to PCI in this study “another potential limitation is related to the delayed absorption of orally administered P2Y₁₂ receptor antagonists” and that the “onset of action may have been delayed further by morphine co-administration in half of the study population”. There is thus a strong need for a treatment option resulting in a fast and high inhibition of platelet aggregation in patients with, for instance, acute coronary syndromes, wherein the inhibition of platelet aggregation is achieved as early as possible after cardiac symptom onset. It is surprisingly found that this need can be fulfilled if a P2Y₁₂ receptor antagonist (especially Compound 1) is administered to a patient subcutaneously, especially if the P2Y₁₂ receptor antagonist is administered by the patient or a relative even before arrival of ambulance health care provider. To be useful in such a subcutaneous administration form the P2Y₁₂ receptor antagonist needs to have a specific combination of physicochemical and pharmacological properties as is the case for Compound 1 in contrast to most of the known and approved P2Y₁₂ receptor antagonists. Compound 1 is a direct-acting and reversible P2Y₁₂ antagonist (Caroff E et al. (2015) J Med Chem 58:9133-9153) and thus requires no metabolic activation that typically results in a slow onset of action and a significant dependency of pharmacodynamics from metabolism of each individual patient. No bleeding events were observed in a clinical phase I study after oral administration of Compound 1 or its prodrug (Baldoni D et al. (2014) Clin Drug Investig 34(11):807-818); and in a FeCl₃ rat thrombosis model, Compound 1 was shown to have a significantly wider therapeutic window even than Ticagrelor (Rey M et al. (2017) Pharma Res Per 5(5):e00338 (doi: 10.1002/prp2.338)). Compound 1 is very potent and highly soluble in aqueous media (75 mg/mL for the lyophilized disodium salt of Compound 1, reconstituted in water, pH = 8.4) and is therefore compatible with the limited volume that can be administered subcutaneously in a typical bolus-injection. Results from a clinical phase I study in healthy volunteers indicate that the pharmacokinetic and pharmacodynamic properties of Compound 1 are suitable for a subcutaneous administration. For instance, at doses $\geq$ 8 mg Compound 1, the peak %IPA (inhibition of platelet aggregation) exceeded 85% in less than 15 min.

Description of the Figures

Fig. 1 shows the time dependency of the AF488-Fibrinogen binding intensity after subcutaneous administration of Compound 1 hydrochlorid (0.2 mg/kg) in male Balb/c mice.

Fig. 2 shows the time dependency of the AF488-Fibrinogen binding intensity after subcutaneous administration of Ticagrelor (1.0 mg/kg) in male Balb/c mice.

Fig. 3 shows the time dependency of the AF488-Fibrinogen binding intensity after subcutaneous administration of Elinogrel (30 mg/kg) in male Balb/c mice.

- 5 Fig. 4 shows the time dependency of the AF488-Fibrinogen binding intensity after subcutaneous administration of Cangrelor (0.2 mg/kg) in male Balb/c mice.

Detailed Description of the Invention

Various embodiments of the invention are presented hereafter:

- 10 1) A first embodiment of the invention relates to a P2Y₁₂ receptor antagonist, or a pharmaceutically acceptable salt thereof, for use in the prevention or treatment (preferably treatment) of a disease, wherein the disease is selected from acute arterial thromboses and acute venous thromboses; wherein the P2Y₁₂ receptor antagonist is selected from the group consisting of 4-((R)-2-[[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-
15 4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester (Compound 1), (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-
diol (Ticagrelor), and (1S,2R,3S,4R)-4-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol (Ticagrelor-M);
20 and wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered to a patient by intradermal or subcutaneous administration.
- 2) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is selected from acute arterial thromboses.
- 25 3) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is selected from acute coronary syndromes, myocardial infarction, peripheral ischaemia, amaurosis, sudden cardiac death, ischaemic stroke and transient ischaemic attack.
- 30 4) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is selected from acute coronary syndromes, peripheral ischaemia, amaurosis, ischaemic stroke and transient ischaemic attack.
- 5) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably
35 Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is acute coronary syndromes.

- 6) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is myocardial infarction.
- 7) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably
5 Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is peripheral ischaemia.
- 8) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is amaurosis.
- 10 9) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 1), wherein the disease is sudden cardiac death.
- 10) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to
15 embodiment 1), wherein the disease is selected from ischaemic stroke and transient ischaemic attack.
- 11) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 10), wherein the P2Y₁₂ receptor antagonist is administered and/or is
20 to be administered prior to hospitalization.
- 12) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 11), wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered by patient self-administration.
- 25 13) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 11), wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered by a health care professional.
- 14) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist, or a
30 pharmaceutically acceptable salt thereof, for use in the emergency treatment of suspected acute coronary syndromes (ACS) by patient self-administration prior to hospitalization; wherein the P2Y₁₂ receptor antagonist is selected from the group consisting of 4-((R)-2-[[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester (Compound 1), (1S,2S,3R,5S)-3-[7-

[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (Ticagrelor) and (1*S*,2*R*,3*S*,4*R*)-4-[7-[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3*H*-[1,2,3]triazolo[4,5-*d*]pyrimidin-3-yl]cyclopentane-1,2,3-triol (Ticagrelor-M); and wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered to a patient by intradermal or subcutaneous administration.

15) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 14), wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered to a patient by subcutaneous administration.

16) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 15), wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered by use of an auto-injector device.

17) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 11), wherein the P2Y₁₂ receptor antagonist is administered and/or is to be administered to a patient by subcutaneous administration and by patient self-administration by use of an auto-injector device.

18) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 17), wherein the patient to be treated is a patient with an atherosclerosis disease.

19) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 17), wherein the patient to be treated is a patient with a known coronary artery disease who had a prior symptomatic episode of acute coronary syndromes.

20) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 19), wherein the P2Y₁₂ receptor antagonist is 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester (Compound 1), or a pharmaceutically acceptable salt thereof.

21) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist, or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 19), wherein the P2Y₁₂ receptor antagonist is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (Ticagrelor), or a pharmaceutically acceptable salt thereof, or (1S,2R,3S,4R)-4-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol (Ticagrelor-M), or a pharmaceutically acceptable salt thereof. Preferably the P2Y₁₂ receptor antagonist is (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol (Ticagrelor), or a pharmaceutically acceptable salt thereof.

22) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 21), wherein the amount of the P2Y₁₂ receptor antagonist (notably Compound 1) that is administered and/or is to be administered is comprised between 1 mg and 75 mg per administration.

Lower limits of the amount of the P2Y₁₂ receptor antagonist (notably Compound 1) are 1 mg, 5 mg, 10 mg, and 20 mg. Upper limits are 35 mg, 40 mg, 50 mg, and 75 mg. It is to be understood that each lower limit can be combined with each upper limit. Hence all combinations shall herewith be specifically disclosed. A preferred amount of the P2Y₁₂ receptor antagonist (notably Compound 1) is from 10 mg to 40 mg per administration.

In another preferred embodiment, the amount of the P2Y₁₂ receptor antagonist (notably Compound 1) is from 5 mg to 20 mg per administration.

23) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 22), wherein the P2Y₁₂ receptor antagonist (notably Compound 1), optionally together with one or more therapeutically inert excipient(s), is dissolved in a pharmaceutically acceptable liquid to give a solution and wherein the volume of the solution that is administered and/or is to be administered is comprised between 0.1 mL and 3.0 mL per administration.

Lower limits of the volume of the solution are 0.1 mL, 0.2 mL, 0.5 mL, and 0.8 mL. Upper limits are 1.0 mL, 1.4 mL, 2.0 mL, and 3.0 mL. It is to be understood that each lower limit can be combined with each upper limit. Hence all combinations shall herewith be specifically disclosed. A preferred volume of the solution is from 0.5 mL to 1.4 mL.

24) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 23), wherein the solution is administered and/or is to be administered within an administration time between 1 sec to 90 sec.

- 5 Lower limits for the administration time are 1 sec, 3 sec, 5 sec and 8 sec. Upper limits are 15 sec, 30 sec, 60 sec and 90 sec. It is to be understood that each lower limit can be combined with each upper limit. Hence all combinations shall herewith be specifically disclosed. A preferred administration time is from 5 sec to 30 sec.

- 25) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably
10 Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 24), wherein the P2Y₁₂ receptor antagonist (notably Compound 1) is administered and/or is to be administered in a bolus injection.

- 26) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one
15 of embodiments 1) to 24), wherein the P2Y₁₂ receptor antagonist (notably Compound 1) is administered and/or is to be administered in a first subcutaneous injection that is a bolus injection and in at least one further subcutaneous injection.

- 27) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to
20 embodiment 26), wherein the further subcutaneous injection is a continuous injection lasting for up to 5 hours.

- It is understood that the continuous injection may last for up to 5 hours, up to 4 hours, up to 3 hours, up to 2 hours, up to 1 hour, up to 30 min or up to 15 min. It is further understood that the continuous injection is administered and/or is to be administered with a lower flow
25 rate than the bolus injection. The flow rate of the continuous injection may be in the range of 0.01% to 10% of the flow rate of the bolus injection. Lower limits of the flow rate of the continuous injection are 0.01%, 0.05%, 0.1% and 0.5% of the flow rate of the bolus injection. Upper limits are 0.5%, 1%, 2%, 5% and 10%. It is to be understood that each lower limit can be combined with each upper limit. Hence all combinations shall herewith be
30 specifically disclosed. The continuous injection may start immediately after the end of the bolus injection or may start with a delay of up to 2 hours, up to 1 hour, up to 30 min or up to 15 min after the end of the bolus injection.

28) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to

embodiment 26), wherein the further subcutaneous injections are 1 to 10 further bolus injections.

Lower limits of the number of further bolus injections are 1 and 2. Upper limits are 3, 5, 7 and 10. It is to be understood that each lower limit can be combined with each upper limit.

- 5 Hence all combinations shall herewith be specifically disclosed. The time between any two consecutive bolus injections may be in the range of 5 min to 120 min. Lower limits of the time between any two consecutive bolus injections are 5 min, 10 min, 15 min and 30 min. Upper limits are 30 min, 60 min, 90 min and 120 min. It is to be understood that each lower limit can be combined with each upper limit. Hence all combinations shall herewith be
- 10 specifically disclosed. The volume that is administered and/or is to be administered in a further bolus injection is in the range of 5% to 100% of the volume of the first bolus injection. Lower limits of the volume of a further bolus injection are 5%, 10%, 20% and 30% of the volume of the first bolus injection. Upper limits are 30%, 50%, 70% and 100%. It is to be understood that each lower limit can be combined with each upper limit. Hence all
- 15 combinations shall herewith be specifically disclosed.

- 29) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 28), wherein an inhibition of platelet aggregation of at least 75% is reached within 30 min after onset of administration of the P2Y₁₂ receptor antagonist in at
- 20 least 80% of the patients.

30) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 29), wherein an inhibition of platelet aggregation of at least 80% is reached.

- 31) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably
- 25 Compound 1), or a pharmaceutically acceptable salt thereof, for use according to embodiment 29), wherein an inhibition of platelet aggregation of at least 85% is reached.

- 32) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 31), wherein the inhibition of platelet aggregation is reached within
- 30 25 min after onset of administration of the P2Y₁₂ receptor antagonist in at least 80% of the patients.

33) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 31), wherein the inhibition of platelet aggregation is reached within

20 min after onset of administration of the P2Y₁₂ receptor antagonist in at least 80% of the patients.

34) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 33), wherein the inhibition of platelet aggregation is reached in at least 85% of the patients.

35) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 29) to 33), wherein the inhibition of platelet aggregation is reached in at least 90% of the patients.

36) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 35), wherein an inhibition of platelet aggregation of at least 75% (notably at least 80% and especially at least 85%) is reached in at least 80% of the patients and lasts for at least 3 hours after onset of administration of the P2Y₁₂ receptor antagonist.

37) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 35), wherein an inhibition of platelet aggregation of at least 75% (notably at least 80% and especially at least 85%) is reached in at least 80% of the patients and lasts for an inhibition time between 3 hours and 12 hours after onset of administration of the P2Y₁₂ receptor antagonist.

Lower limits of the inhibition time are 3 hours, and 4 hours. Upper limits are 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 10 hours and 12 hours. It is to be understood that each lower limit can be combined with each upper limit. Hence all combinations shall herewith be specifically disclosed. A preferred inhibition time is from 4 hours to 8 hours.

38) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 37), wherein the P2Y₁₂ receptor antagonist is administered to a patient by subcutaneous administration.

39) A further embodiment of the invention relates to a P2Y₁₂ receptor antagonist (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 37), wherein the P2Y₁₂ receptor antagonist is to be administered to a patient by subcutaneous administration.

40) A further embodiment of the invention relates to a pharmaceutical composition comprising, as active principle, a P2Y₁₂ receptor antagonist selected from Compound 1, Ticagrelor and Ticagrelor-M (notably Compound 1), or a pharmaceutically acceptable salt thereof, for use according to any one of embodiments 1) to 37), wherein the
5 pharmaceutical composition is administered and/or is to be administered to a patient by subcutaneous administration and wherein the pharmaceutical composition further comprises at least one therapeutically inert excipient.

The production of subcutaneous pharmaceutical compositions of Compound 1 (or Ticagrelor or Ticagrelor-M) can be effected in a manner which will be familiar to any person
10 skilled in the art (see for example Remington, *The Science and Practice of Pharmacy*, 21st Edition (2005), Part 5, "Pharmaceutical Manufacturing" [published by Lippincott Williams & Wilkins]) by bringing Compound 1 (or Ticagrelor or Ticagrelor-M) or a pharmaceutically acceptable salt thereof into a galenical administration form together with suitable, non-toxic, inert, pharmaceutically acceptable solid or liquid carrier materials and, if desired, usual
15 pharmaceutical adjuvants/excipients.

Whenever a P2Y₁₂ receptor antagonist (Compound 1 and/or Ticagrelor and/or Ticagrelor-M), or a pharmaceutically acceptable salt thereof, is described to be useful for the prevention or treatment (notably treatment) of a disease, it is understood that the P2Y₁₂ receptor antagonist (Compound 1 and/or Ticagrelor and/or Ticagrelor-M), or a
20 pharmaceutically acceptable salt thereof, is also useful for the preparation of a medicament for the prevention or treatment (notably treatment) of said disease. The present invention thus encompasses especially the following additional embodiments:

41) A further embodiment of the invention relates to the use of a P2Y₁₂ receptor antagonist selected from Compound 1, Ticagrelor and Ticagrelor-M, or a pharmaceutically acceptable
25 salt thereof, for the preparation of a medicament for use according to any one of embodiments 1) to 39).

42) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use according to any one of embodiments 1) to 20) or 22) to 39).

30 43) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease, wherein the disease is selected from acute arterial thromboses and acute venous thromboses, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

44) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease, wherein the disease is selected from acute arterial thromboses, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

45) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease, wherein the disease is selected from acute coronary syndromes, myocardial infarction, peripheral ischaemia, amaurosis, sudden cardiac death, ischaemic stroke and transient ischaemic attack, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

46) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease, wherein the disease is selected from acute coronary syndromes, peripheral ischaemia, amaurosis, ischaemic stroke and transient ischaemic attack, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

47) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of acute coronary syndromes, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

48) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of myocardial infarction, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

49) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of peripheral ischaemia, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

50) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of amaurosis, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

51) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the

treatment of sudden cardiac death, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

52) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a disease, wherein the disease is selected from ischaemic stroke and transient ischaemic attack, and wherein the medicament is administered and/or is to be administered to a patient by subcutaneous administration.

53) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 41) to 52); wherein Compound 1, or the pharmaceutically acceptable salt thereof, is administered to a patient by subcutaneous administration.

54) A further embodiment of the invention relates to the use of Compound 1, or a pharmaceutically acceptable salt thereof, according to any one of embodiments 41) to 52); wherein Compound 1, or the pharmaceutically acceptable salt thereof, is to be administered to a patient by subcutaneous administration.

55) A further embodiment of the invention relates to the use of a P2Y₁₂ receptor antagonist selected from Compound 1, Ticagrelor and Ticagrelor-M (preferably Compound 1), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in the emergency treatment of suspected acute coronary syndromes (ACS) by patient self-administration prior to hospitalization; wherein the P2Y₁₂ receptor antagonist is administered to a patient by subcutaneous administration.

56) A further embodiment of the invention relates to the use of a P2Y₁₂ receptor antagonist selected from Compound 1, Ticagrelor and Ticagrelor-M (preferably Compound 1), or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for use in the emergency treatment of suspected acute coronary syndromes (ACS) by patient self-administration prior to hospitalization; wherein the P2Y₁₂ receptor antagonist is to be administered to a patient by subcutaneous administration.

Based on the dependencies of the different embodiments as disclosed hereinabove, especially the following embodiments are thus possible and intended and herewith specifically disclosed in individualized form:

1, 2+1, 3+1, 4+1, 5+1, 6+1, 7+1, 8+1, 9+1, 10+1, 11+1, 11+3+1, 11+5+1, 12+11+1, 12+11+3+1, 12+11+5+1, 13+11+1, 13+11+3+1, 13+11+5+1, 14, 15+1, 15+3+1, 15+5+1, 15+11+1, 15+11+3+1, 15+11+5+1, 15+12+11+1, 15+12+11+3+1, 15+12+11+5+1, 15+14, 16+1, 16+3+1, 16+5+1, 16+11+1, 16+11+3+1, 16+11+5+1, 16+12+11+1, 16+12+11+3+1, 16+12+11+5+1, 16+14, 16+15+1, 16+15+3+1, 16+15+5+1, 16+15+11+1, 16+15+11+3+1, 16+15+11+5+1, 16+15+12+11+1, 16+15+12+11+3+1, 16+15+12+11+5+1, 16+15+14, 17+1, 17+3+1, 17+5+1, 17+11+1, 17+11+3+1, 17+11+5+1, 18+1, 18+3+1, 18+5+1, 18+11+1, 18+11+3+1, 18+11+5+1, 18+12+11+1, 18+12+11+3+1, 18+12+11+5+1, 18+14, 18+15+1, 18+15+3+1, 18+15+5+1, 18+15+11+1, 18+15+11+3+1, 18+15+11+5+1, 18+15+12+11+1, 18+15+12+11+3+1, 18+15+12+11+5+1, 18+15+14, 19+1, 19+3+1, 19+5+1, 19+11+1, 19+11+3+1, 19+11+5+1, 19+12+11+1, 19+12+11+3+1, 19+12+11+5+1, 19+14, 19+15+1, 19+15+3+1, 19+15+5+1, 19+15+11+1, 19+15+11+3+1,

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In the list above, the numbers refer to the embodiments according to their numbering provided hereinabove whereas “+” indicates the dependency from another embodiment. The different individualized embodiments are separated by commas. In other words, “11+3+1” for example refers to embodiment 11) depending on embodiment 3) depending on embodiment 1), i.e. embodiment “11+3+1” corresponds to embodiment 1) further limited by the features of the embodiments 3) and 11).

It is understood that a P2Y₁₂ receptor antagonist (notably Compound 1) that is described to be useful in the treatment or prevention of a disease according to any one of embodiments 1) to 38) is also useful in a method of treatment and/or prophylaxis of the disease wherein the method comprises the subcutaneous administration of a pharmaceutically active amount of the P2Y₁₂ receptor antagonist, or a pharmaceutically acceptable salt thereof, to a human subject in need thereof.

The present invention especially relates to a method for the emergency treatment of acute coronary syndromes (ACS) by patient self-administration prior to hospitalization of a pharmaceutically active amount of Compound 1, Ticagrelor or Ticagrelor-M (especially Compound 1), or a pharmaceutically acceptable salt thereof, wherein the method comprises the subcutaneous administration to the patient in need thereof.

The present invention also relates to a method for the treatment of a disease that is responsive to the inhibition of platelet activation and/or platelet aggregation comprising subcutaneous administration of a pharmaceutically active amount of Compound 1, Ticagrelor or Ticagrelor-M (especially Compound 1), or a pharmaceutically acceptable salt thereof, to a human subject in need thereof.

The present invention also relates to a method for the treatment of a disease that is responsive to a P2Y₁₂ receptor antagonist comprising subcutaneous administration of a pharmaceutically active amount of Compound 1, Ticagrelor or Ticagrelor-M (especially Compound 1), or a pharmaceutically acceptable salt thereof, to a human subject in need thereof.

The pharmaceutical composition comprising the P2Y₁₂ receptor antagonist (Compound 1, Ticagrelor, or Ticagrelor-M), or a pharmaceutically acceptable salt thereof, may be in the form of an aqueous or oily solution, suspension or emulsion (preferably an aqueous solution) and may optionally contain one or more additional excipients. An additional excipient may be for instance a pharmaceutically acceptable acid or base (to adjust the pH value of the pharmaceutical composition) or a pharmaceutically acceptable salt such as sodium chloride (to adapt the tonicity of the pharmaceutical composition).

The pharmaceutical composition may be in the form of a ready-to-use solution, suspension or emulsion or in the form of a powder for injection comprising the P2Y₁₂ receptor antagonist, wherein the powder for injection requires reconstitution in a pharmaceutically acceptable liquid to give the aqueous or oily solution, suspension or emulsion prior to subcutaneous administration. The said solid may be in crystalline or amorphous form or in any mixture thereof.

The general terms and expressions used hereinbefore and/or hereinafter preferably have, within this disclosure, the following meanings:

5 The term “acute coronary syndromes” (ACS) refers to syndromes due to sudden decreased or interruption of blood flow in some coronary arteries. Acute coronary syndromes encompass ST elevation myocardial infarction (STEMI), non ST elevation myocardial infarction (NSTEMI) or unstable angina. It is understood that a P2Y₁₂ receptor antagonist that is disclosed to be useful in the prevention or treatment of ACS is likewise useful in the prevention or treatment of STEMI, NSTEMI and/or unstable angina.

10 The term “emergency treatment of suspected acute coronary syndromes” refers to a treatment of a patient wherein the patient shows symptoms of ACS such as suddenly occurring chest pain, chest discomfort (intermittent or not), persistent retrosternal pressure or heaviness radiating to the left arm, neck, back or jaw lasting for at least 10 min, nausea/vomiting, shortness of breath, fatigue, palpitations, lightheadedness or syncope (and notably clear symptoms of ACS such as suddenly occurring chest pain, chest
15 discomfort (intermittent or not), or persistent retrosternal pressure or heaviness radiating to the left arm, neck, back or jaw lasting for at least 10 min); and wherein the patient is to be treated and/or requires treatment before an electrocardiogram, a chest X-ray and/or blood tests could be performed. In one embodiment, the patient is a patient who was already known to have a high risk to suffer from ACS before the symptoms (notably clear
20 symptoms) of ACS occurred, such as for instance a patient with a known coronary artery disease who had a prior symptomatic episode of acute coronary syndromes. In a further embodiment, the treatment is effected by patient self-administration before hospitalization; it is preferred that the patient has received a training by a health care professional to better assess the symptoms of ACS before any such self-administration.

25 The term “coronary artery disease” (CAD) refers to a group of diseases that includes myocardial infarction, unstable angina, stable angina and sudden cardiac death.

The term “a patient who had a prior symptomatic episode of acute coronary syndromes” refers to a patient who had a myocardial infarction (STEMI or NSTEMI) or an unstable angina.

30 The term “subcutaneous administration” refers to an administration of a pharmaceutical composition into the subcutis by injection. Typical administration sites are the outer area of the upper arm, the abdomen (avoiding the area close to the umbilicus), the front of the thigh, the thorax, the neck, the upper back and the upper area of the buttock; preferred are the abdomen and the front of the thigh. A subcutaneous administration can be performed

using any kind of a suitable injection device such as for instance a syringe or an autoinjector device.

The term “intradermal administration” refers to an administration of a pharmaceutical composition into the dermis by injection. Typical administration sites are the inner surface
5 of the forearm and the upper back, under the scapula.

The term “bolus injection” if used in the context of a subcutaneous administration/injection refers to an injection of a discrete amount of a P2Y₁₂ receptor antagonist (notably in a pharmaceutical composition suitable for subcutaneous administration) within a relatively short period of time (typically between 1 sec to 90 sec).

10 The term “patient” refers to a mammal, especially a human, having a disease or disorder that can be prevented or treated with a P2Y₁₂ receptor antagonist. In a preferred embodiment, a patient is a human having a disease or disorder that can be prevented or treated (especially treated) with a P2Y₁₂ receptor antagonist wherein said human was already known before to have a statistically increased risk to develop the disease or
15 disorder.

The term “patient self-administration” refers the administration of a pharmaceutical composition to a patient by the patient himself/herself or by an acquaintance having minimal medical training, such as a relative, a friend or a neighbour (and especially by the patient himself/herself).

20 The term “administration by a health care professional” refers to the administration of a pharmaceutical composition to a patient by a person who is professionally trained to perform such administrations such as for instance a nurse or a physician. It is preferred that any such administration is performed prior to hospitalization of the patient (e.g. in the ambulance or at any other place before the patient reaches the hospital).

25 The term “autoinjector device” refers to a medical device for automated injection of a pharmaceutical composition after pressing a trigger or an activator or the like. Autoinjector devices may be for instance in the form of a pen device, a patch device or a patch pump.

Any reference to a P2Y₁₂ receptor antagonist in this specification is to be understood as referring also to the pharmaceutically acceptable salts of such a P2Y₁₂ receptor antagonist.

30 The term “pharmaceutically acceptable salt” refers to salts that retain the desired biological activity of the subject compound and exhibit minimal undesired toxicological effects. Such salts include inorganic or organic acid and/or base addition salts depending on the presence of basic and/or acidic groups in the subject compound. For reference see for example ‘Handbook of Pharmaceutical Salts. Properties, Selection and Use.’, P. Heinrich

Stahl, Camille G. Wermuth (Eds.), Wiley-VCH, 2008 and 'Pharmaceutical Salts and Co-crystals', Johan Wouters and Luc Quéré (Eds.), RSC Publishing, 2012.

A preferred pharmaceutically acceptable salt of Compound 1 is a hydrochloride salt of Compound 1. Another preferred pharmaceutically acceptable salt of Compound 1 is a 2-amino-2-(hydroxymethyl)-1,3-propanediol or a sodium salt of Compound 1.

The term "pharmaceutically acceptable liquid" refers to a liquid that gives an injectable solution, suspension or emulsion (especially a solution) if admixed with the P2Y₁₂ receptor antagonist (especially Compound 1), or a pharmaceutically acceptable salt thereof, optionally together with one or more therapeutically inert excipient(s), and that exhibits minimal undesired toxicological effects. A preferred example for a pharmaceutically acceptable liquid is water, especially water for injection and notably sterile water for injection.

Unless used regarding temperatures, the term "about" placed before a numerical value "X" refers in the current application to an interval extending from X minus 10% of X to X plus 10% of X, and preferably to an interval extending from X minus 5% of X to X plus 5% of X. In the particular case of temperatures, the term "about" placed before a temperature "Y" refers in the current application to an interval extending from the temperature Y minus 10 °C to Y plus 10 °C, and preferably to an interval extending from Y minus 5 °C to Y plus 5 °C.

Whenever the word "between" is used to describe a numerical range, it is to be understood that the end points of the indicated range are explicitly included in the range. For example: if a volume range is described to be between 0.1 mL and 3.0 mL, this means that the end points 0.1 mL and 3.0 mL are included in the range; or if a variable is defined as being an integer between 1 and 4, this means that the variable is the integer 1, 2, 3, or 4.

Experimental Part

Abbreviations:

The following abbreviations are used throughout the specification and the examples:

ACS	Acute coronary syndromes
aq.	Aqueous
ET	External temperature
FACS	Fluorescence-activated cell sorting
h	hour(s)
IPC	In-process control
IT	Internal temperature
min	Minute(s)

	PBS	Phosphate-buffered saline
	PCI	Percutaneous coronary intervention
	PEG 400	Poly(ethylene glycol)
	RT	Room temperature
5	sat.	saturated
	sec	second(s)
	vol.	L solvent per kg starting material

Preparation of Compound 1 and its HCl salt:

10 Compound 1 may be prepared according to the procedures as disclosed in WO 2009/069100 (example 2) or Caroff E et al., *J. Med. Chem.* (2015), **58**, 9133-9153. Alternatively, Compound 1 and its HCl salt may be prepared according to the following procedure:

A 15 L reactor was charged with sodium (S)-6-(3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxylate (584 g, 1.82 mol) and 1-hydroxy-benzotriazole mono hydrate (HOBt) (274 g, 1.1 eq.). Water (1305 mL, 2.0 vol.) was added. The pH of the suspension was 5-6. Butyl (R)-4-(2-amino-3-(diethoxyphosphoryl)propanoyl)piperazine-1-carboxylate (665.7 g, 1.0 eq) was dissolved in tetrahydrofurane (THF) (1960 ml, 3.0 vol.). The solution was added to the reaction at 20-30 °C during 5-10 min. A solution of 1-ethyl-3-20 (3-dimethylaminopropyl)carbodiimide (EDCI) (389 g, 1.2 eq.) in water (1305 ml, 2.0 vol.) was added to the reaction at 20-30 °C during 15-30 min. The pH of the reaction stayed between 6-7. The reaction was stirred during 4 h at 20-30 °C. An IPC showed 93% conversion. The reaction was diluted with dichloromethane (DCM) (3265 ml, 5.0 vol.) and ½ sat. aq. sodium hydrogencarbonat solution (3265 ml, 5.0 vol.). The layers were 25 separated. The organic layer was washed again with ½ sat. aq. sodium hydrogencarbonat solution (3265 ml, 5.0 vol.). The layers were separated. An IPC showed the complete removal of HOBt. The organic layer was washed with aq. 10% citric acid (3265 ml, 5.0 vol.). In total 3.75 L of solvents were distilled off at minimal 800 mbar and ET = 75-80 °C during 40 min. The residual solution was cooled to 20-30 °C. Aq. 32% HCl (3 L, 19 eq.) 30 was added during 5-10 min at 20-30 °C. An IPC after 4 h of stirring showed complete hydrolysis. Water (5.2 L, 8 vol.) was added at 20-30 °C. The reaction was diluted with DCM (5.2 L, 8 vol.). The layers were separated. The aqueous layer was extracted again 2 x with DCM (5.2 L, 8 vol.). All DCM layers were combined and filtered through a polycap 75 HD filter. In total 14 L of solvents were distilled off during 2 h at atmospheric pressure and ET = 35 75-80 °C. Acetone (21.6 L, 33 vol.) was added to the refluxing reaction mixture at ET = 70-

75 °C. To the refluxing fine suspension water (325 mL, 0.5 vol.) was added. The fine, pale suspension was stirred at reflux during 1.5 h and a thick white slurry was obtained. The slurry was cooled to IT = 25 °C during 1 h (ramp). The solid product was isolated by filtration. The filter cake was rinsed with acetone (4.5 L, 7 vol.) and was dried by blowing
5 nitrogen through it to give 750 g (69%) of ((R)-3-(4-(butoxycarbonyl)piperazin-1-yl)-2-(6-((S)-3-methoxypyrrolidin-1-yl)-2-phenylpyrimidine-4-carboxamido)-3-oxopropyl)phosphonic acid hydrochloride as a white solid. The LC MS purity was > 99% a/a, the ¹H-NMR assay purity was 98% w/w.

Formulation of Compound 1 (lower dose of 1 mg/mL):

10 An aqueous solution of 2-amino-2-(hydroxymethyl)-1,3-propanediol (Tris base, 21.6 mL, 1.0 M) was added to 4.80 L Water for Injection (WFI) in a glass vessel. 4-((R)-2-[[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (6.00 g) and mannitol (210 g) were added successively and the mixture was stirred until complete dissolution. Additional Tris
15 base was added to pH = 7.4 ± 0.1. The solution was diluted to a final volume of 6.00 L with WFI, refilled into glass vials (1.1 mL per vial), dried by lyophilisation and reconstituted prior to administration with 1.0 mL WFI to give a solution of Compound 1 for subcutaneous administration.

Formulation of Compound 1 (higher dose of 20 mg/mL):

20 An aqueous solution of 2-amino-2-(hydroxymethyl)-1,3-propanediol (Tris base, 21.6 mL, 1.0 M) was added to 4.80 L Water for Injection (WFI) in a glass vessel. 4-((R)-2-[[6-((S)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester hydrochloride (120 g) and mannitol (120 g) were added successively and the mixture was stirred until complete dissolution. Additional Tris
25 base was added to pH = 7.4 ± 0.1. The solution was diluted to a final volume of 6.00 L with WFI, refilled into glass vials (1.1 mL per vial), dried by lyophilisation and reconstituted prior to administration with 1.0 mL WFI to give a solution of Compound 1 for subcutaneous administration.

**In-vivo measurements of time dependent platelet inhibition after subcutaneous
30 administration of P2Y₁₂ receptor antagonists:**

Animals:

Male Balb/c mice were purchased from Charles River laboratories (Sulzfeld, Germany). All animals were maintained under identical conditions in accordance with the guidelines of the Basel-Landschaft cantonal veterinary office. Husbandry was accomplished in professional
35 animal housing facilities, which provided group-cages, standard diet/water ad libitum, and

standard illumination and climate conditions. The technical assistants performed at least one inspection per day. Sufficient time was provided for the animals to be accustomed to the experimental environment. Stress reduction was provided also by enrichment of cages, and providing the possibility to retire to dark housings (taking advantage of the color blindness of albino mice in the red range of the light spectrum). Inside the red housing the animals have the impression of being in the dark, while this housing remains visible to normal human vision.

Reagents: The hydrochloride salt of Compound 1 was synthesized according to the above mentioned procedure. Ticagrelor was extracted from commercially available tablets (Brilique).

Fibrinogen from Human Plasma Alexa Fluor TM 488 conjugate, catalogue number F-13191 was purchased from Molecular Probes and handled as described on provider's data sheet.

Preparation of test compounds: Compound 1 hydrochloride (0.04 mg/mL), Ticagrelor (0.2 mg/mL), Elinogrel (6 mg/mL) or Cangrelor (0.04 mg/mL) were dissolved in 25% PEG 400 / water.

Experimental groups: Compounds were administrated by subcutaneous injection on the lower abdomen:

Compound 1 hydrochloride, 0.2 mg/kg (respectively 5mL/kg)

Ticagrelor, 1 mg/kg (respectively 5mL/kg)

Elinogrel, 30 mg/kg (respectively 5mL/kg)

Cangrelor, 0.2 mg/kg (respectively 5mL/kg)

Animal preparation: After an acclimatization period of at least 7 days, mice were anesthetized with Isoflurane (2-5%). The animals were then placed on a thermostatically-controlled heating table to maintain body temperature at 36–38°C. A polyurethane catheter (BTPU-027) was inserted into the right jugular vein and advanced into the vena cava for infusion of Heparin and to collect blood. In order to perform accurate platelet assays it is necessary to ensure that the blood collection does not lead to platelet activation. Therefore Heparin (4000U/kg/2.5mL) was intravenously injected to prevent blood from coagulation.

Experimental procedure: Two minutes after the injection of Heparin, 60µL of whole blood was collected via the vena cava catheter (baseline). After the baseline blood sampling the test compounds were subcutaneously injected on the lower abdomen of the animals. 10, 20, 30, 40 and 60 minutes after the subcutaneous injection of the test compounds, 60 µL of whole blood were collected via the vena cava catheter for the fibrinogen binding assay.

AF488-Fibrinogen binding assay:

This assay is particularly well adapted for reliable studies of the effect of P2Y₁₂ antagonists on mouse platelets under in vitro and in vivo conditions. The assay allows to measure

5 ADP-induced AF488-Fibrinogen binding on mouse platelets in only 6 μ L whole blood and without washing steps.

The blood was first incubated with 4 μ L vehicle or 4 μ L Compound 1 hydrochloride (to give 2 μ M final concentration in diluted blood) for 15 minutes at RT. This concentration of Compound 1 hydrochloride was determined in prior experiments to inhibit 100 % of ADP-

10 induced AF488-Fibrinogen binding on platelets and represents the nonspecific signal. Next, 10 μ L of AF488-Fibrinogen (to give 0.5 mg/mL final concentration) were added followed by incubation of 5 minutes. To induce AF488-Fibrinogen binding, the platelets were then incubated with 10 μ L ADP (to give 20 μ M final concentration) for 5 minutes. In addition, an incubation with a platelet specific Allophycocyanin (APC) anti-Mouse CD61 (integrin beta 3)

15 antibody (clone 2C9.G2) was performed for 10 minutes. The platelets were then fixed by addition of 34 μ L cold paraformaldehyde solution (to give 0.1% final concentration) and stored at 4°C for about 20 minutes. The samples were finally diluted with 1.8 mL cold PBS and put on hold at 4°C for at least 2 hours, time necessary for gently red blood cell lysis, before measuring by flow cytometry.

20 Data Acquisition:

Flow cytometry was performed using a FACSCanto II instrument (BD Bioscience). The setting of fluorescence compensation was not required due to the use of two different lasers.

Platelets were first detected using the platelet specific fluorescence signal of APC-CD61

25 (APC-settings for fluorescence emission peak at 660 nm). The platelet population was then gated using forward-scatter (FSC) and side-scatter (SSC) and their FITC-labeled Fibrinogen signal (FITC-settings for fluorescence emission peak at 525 nm) was quantitated as Mean Fluorescence Intensity (MFI) of 5000 platelets. For each sample, the MFI from corresponding nonspecific sample was subtracted.

Table 1: Mean Fluorescence Intensities of AF488-Fibrinogen binding to platelets

Time [Minutes]	0	10	20	40	60
Compound 1 0.2 mg/kg s.c.	[MFI]	[MFI]	[MFI]	[MFI]	[MFI]
Experiment 1	6037		1721	1229	1315
Experiment 2	9042		2909	2542	2544
Experiment 3	8234		1655	1126	997
Experiment 4	7711	2509	1697	1495	1235
Experiment 5	10574	4175	2882	2638	1914
Experiment 6	13675	5806	3763	2582	2375
Ticagrelor 1 mg/kg s.c.	[MFI]	[MFI]	[MFI]	[MFI]	[MFI]
Experiment 1	8449		3351	1576	1067
Experiment 2	5864		911	510	554
Experiment 3	8707		3061	970	549
Experiment 4	8218	2001	1224	683	917
Experiment 5	6904	6537	4292	2181	1761
Experiment 6	11749	5771	3473	2340	2261
Experiment 7	6073	5625	3840	1937	1148
Elinogrel 30 mg/kg s.c.	[MFI]	[MFI]	[MFI]	[MFI]	[MFI]
Experiment 1	8124	4403	2374	1644	2034
Experiment 2	5370	4712	3847	1768	1503
Experiment 3	7045	3842	2177	1652	1515
Experiment 4	7097	3840	4078	2619	2191
Cangrelor 0.2 mg/kg s.c.	[MFI]	[MFI]	[MFI]	[MFI]	[MFI]
Experiment 1	6200	1596	713	765	1048
Experiment 2	7453	1628	1364	732	682
Experiment 3	5476	2550	1012	921	961

In-vivo measurements of time dependent inhibition of platelet aggregation (IPA) after subcutaneous administration of Compound 1 to healthy volunteers:

The time- and dose-dependency of plasma concentration and inhibition of platelet aggregation (IPA) after subcutaneous administration of Compound 1 was investigated in a clinical phase I study in healthy male subjects.

Study Design:

In a randomized, double-blind, placebo-controlled study, 48 subjects in fasted condition were exposed to single, subcutaneous doses ranging from 1 to 32 mg (1mg, 2mg, 4mg, 8mg, 16mg and 32mg) of Compound 1 (n = 6 on Compound 1 and n = 2 on placebo per dose level).

Subcutaneous Formulation of Compound 1:

Compound 1 for s.c. administration was available as sealed glass vials at the strength of 20 mg. The vials contained lyophilized Compound 1 to be reconstituted with 1 mL of water for injection to prepare stock solutions of 20 mg/mL (see above: Formulation of Compound 1 (higher dose of 20 mg/mL)). These stock solutions were further diluted with 0.9% sodium chloride to prepare 2, 4, 8, 16, and 20 mg/mL solutions. The volume injected was 0.5 mL for dose levels 1, 2, 4, and 8 mg. For dose levels 16 and 32 mg, 1 or 2 injection(s) of 0.8 mL from the 20 mg/mL solution was (were) performed.

The solution for injection was prepared for administration in a syringe suitable for s.c. injection. The solution was administered as injection(s) in the thigh.

Assessment of Pharmacokinetic (PK) Parameters:

The plasma PK parameters of Compound 1 were derived by non-compartmental analysis of the plasma concentration-time profiles. The following parameters were obtained:

maximum plasma concentration (C_{max}); time to reach C_{max} (t_{max}); area under the plasma concentration-time curve (AUC) from zero to time t of the last measured concentration above the limit of quantification (AUC_{0-t}); and terminal elimination half-life ($t_{1/2}$).

1) Blood sampling

Blood was collected by direct venipuncture or via an i.v. catheter placed in an antecubital vein in the arm in a 4 mL Monovette® or equivalent tube containing ethylene diamine tetra-acetic acid. Immediately following collection of the required blood volume, the Monovettes® were slowly tilted backwards and forwards (no shaking) to bring the anticoagulant into solution, and immediately cooled on ice. Within 30 min of collection, the Monovettes® were centrifuged at approximately 1500 g for 10 min at 4 °C. The plasma was transferred into

one labeled polypropylene tube to avoid carry-over of erythrocytes. All samples were stored in an upright position below -70°C .

2) Bioanalysis

The analysis of Compound 1 in plasma was performed using a validated liquid chromatography coupled to tandem mass spectrometry assay. The lower limit of quantification (LLOQ) was 1 ng/mL. Concentrations were calculated by interpolation from a calibration curve. Quality control (QC) samples were analyzed throughout the study. Their measured concentrations were used to determine between-run and overall precision and accuracy of the analysis.

3) Results

Table 2: Summary table of pharmacokinetic parameters of Compound 1 following subcutaneous doses of 1 to 32 mg

Parameter [unit]	1 mg (N = 6)	2 mg (N = 6)	4 mg (N = 6)	8 mg (N = 6)	16 mg (N = 6)	32 mg (N = 6)
$C_{\max}$ [ng/mL]						
G.M.	33.654	58.437	128.394	272.731	435.035	929.632
95% CI	25.4, 44.7	48.5, 70.4	76.5, 215	211, 353	335, 565	786, 1100
$t_{\max}$ [h]						
Median	0.500	0.500	0.500	0.500	0.750	0.750
Min, Max	0.25, 1.00	0.42, 1.00	0.37, 1.00	0.33, 1.00	0.25, 1.00	0.50, 1.00
AUC_{0-t} [ng*h/mL]						
G.M.	56.053	115.599	260.652	585.336	1119.438	2343.485
95% CI	45.3, 69.4	89.8, 149	181, 375	449, 763	951, 1317	1956, 2807
$t_{1/2}$ [h]						
G.M.	1.337	1.916	2.663	3.975	7.204	9.203
95% CI	1.09, 1.64	1.18, 3.11	2.02, 3.51	2.38, 6.63	4.89, 10.6	6.15, 13.8

G.M.: geometric mean; 95% CI: 95% confidence interval of geometric mean

Assessment of Pharmacodynamic (PD) Parameters (inhibition of platelet aggregation):

1) Blood sampling

PD blood samples were collected by direct venipuncture or via an i.v. catheter placed in an antecubital vein in the arm, using 18–21 gauge needles. The first 2 mL of blood were discarded, and, thereafter, blood was drawn gently into two open 3.5 mL collection tubes.

Collection tubes for LTA (light transmission aggregometry) assays contained phenylalanine-proline-arginine-cholormethylketone (PPACK) as an anticoagulant.

2) Bioanalysis

Adenosine diphosphate (ADP)-induced platelet aggregation was evaluated by a LTA assay measuring platelet-induced aggregation as an increase in light transmittance (Michelson AD, Methods for the measurement of platelet function (2009) Am J Cardiol 103(3):20A-26A).

LTA assay: The two 3.5 mL blood samples were centrifuged to prepare platelet-rich plasma (PRP) and platelet-poor plasma (PPP). If needed, PRP was adjusted to a final platelet count of 260×10^9 platelets per liter by dilution with PPP from the same donor. The assay was performed with an 8-channel platelet aggregometer, recording the aggregation after addition of $20 \mu\text{M}$ ADP as agonist for 6 min. The results are expressed as percent change in light transmittance at maximum (peak) platelet aggregation (MPA), calculated relative to the baseline signal of 0%. The measurements were performed in duplicate.

3) Results

Table 3: Summary table of pharmacodynamic parameters (%IPA (inhibition of platelet aggregation) calculated using maximum platelet aggregation values) following subcutaneous doses of 1 to 32 mg

Time [h]	1 mg (N = 6)	2 mg (N = 6)	4 mg (N = 6)	8 mg (N = 6)	16 mg (N = 6)	32 mg (N = 6)
	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD	mean $\pm$ SD
0.25	61.4 $\pm$ 15.1	60.3 $\pm$ 48.3	79.7 $\pm$ 6.0	88.9 $\pm$ 8.4	92.8 $\pm$ 5.5	95.5 $\pm$ 2.7
0.5	64.4 $\pm$ 12.8	79.5 $\pm$ 10.8	84.7 $\pm$ 5.4	90.0 $\pm$ 8.5	93.1 $\pm$ 3.6	94.5 $\pm$ 2.0
3	15.8 $\pm$ 20.0	36.8 $\pm$ 30.0	58.5 $\pm$ 7.2	77.9 $\pm$ 19.5	95.0 $\pm$ 1.2	94.5 $\pm$ 2.0
4	-10.0 $\pm$ 24.2	35.5 $\pm$ 18.9	50.6 $\pm$ 22.1	70.9 $\pm$ 12.5	88.2 $\pm$ 4.7	91.2 $\pm$ 1.9
5	-6.1 $\pm$ 26.0	14.1 $\pm$ 28.4	47.9 $\pm$ 17.9	75.2 $\pm$ 11.5	87.6 $\pm$ 5.5	92.1 $\pm$ 2.6
12	-4.5 $\pm$ 24.7	31.3 $\pm$ 28.9	37.4 $\pm$ 16.7	64.0 $\pm$ 10.4	76.0 $\pm$ 13.8	83.5 $\pm$ 12.9
48	-47.7 $\pm$ 29.9	11.3 $\pm$ 38.5	2.1 $\pm$ 16.3	-1.3 $\pm$ 33.7	-1.6 $\pm$ 43.8	29.8 $\pm$ 20.9

SD: standard deviation

As can be seen from Table 3, at each dose level, peak %IPA was achieved within approximately 15–30 min post dosing. Peak %IPA exceeded 85% at doses ≥ 4 mg (at doses ≥ 8 mg even in less than 15 min). The duration of PD effects was dose-dependent. Mean %IPA $\geq 85\%$ was sustained for approximately 5 h and 12 h post administration of 16
5 mg and 32 mg Compound 1, respectively.

Claims:

1. Use of a P2Y₁₂ receptor antagonist, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the prevention or treatment of a disease, wherein the disease is selected from acute arterial thromboses and acute venous thromboses;

5 wherein the P2Y₁₂ receptor antagonist is 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester; and wherein the P2Y₁₂ receptor antagonist is to be administered to a patient by subcutaneous administration.
2. The use according to claim 1, wherein the disease is selected from acute coronary syndromes, myocardial infarction, peripheral ischaemia, amaurosis, sudden cardiac death, ischaemic stroke and transient ischaemic attack.
3. The use according to claim 1, wherein the disease is acute coronary syndromes.
4. The use according to claim 1, wherein the disease is myocardial infarction.
5. The use according to any one of claims 1 to 4, wherein the P2Y₁₂ receptor antagonist

15 is to be administered prior to hospitalization.
6. The use according to claim 5, wherein the P2Y₁₂ receptor antagonist is to be administered by patient self-administration.
7. Use of a P2Y₁₂ receptor antagonist, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the emergency treatment of suspected acute coronary syndromes by patient self-administration prior to hospitalization; wherein

20 the P2Y₁₂ receptor antagonist is 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester; and wherein the P2Y₁₂ receptor antagonist is to be administered to a patient by subcutaneous administration.
8. The use according to any one of claims 1 to 7, wherein the amount of 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester that is to be

25 administered is comprised between 1 mg and 75 mg per administration.
9. The use according to any one of claims 1 to 8, wherein the P2Y₁₂ receptor antagonist

30 is to be administered in a bolus injection.
10. The use according to any one of claims 1 to 9, wherein an inhibition of platelet aggregation of at least 75% is reached within 30 min after onset of administration of the P2Y₁₂ receptor antagonist in at least 80% of the patients.
11. Use of 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino]-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester, or a

35 pharmaceutically acceptable salt thereof, in the preparation of a medicament for the

treatment of a disease, wherein the disease is selected from acute coronary syndromes, myocardial infarction, peripheral ischaemia, amaurosis, sudden cardiac death, ischaemic stroke and transient ischaemic attack, and wherein the medicament is to be administered to a patient by subcutaneous administration.

- 5 12. Use of the P2Y₁₂ receptor antagonist 4-((*R*)-2-[[6-((*S*)-3-methoxy-pyrrolidin-1-yl)-2-phenyl-pyrimidine-4-carbonyl]-amino}-3-phosphono-propionyl)-piperazine-1-carboxylic acid butyl ester, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the emergency treatment of suspected acute coronary syndromes by patient self-administration prior to hospitalization; wherein
- 10 the P2Y₁₂ receptor antagonist is to be administered to a patient by subcutaneous administration.