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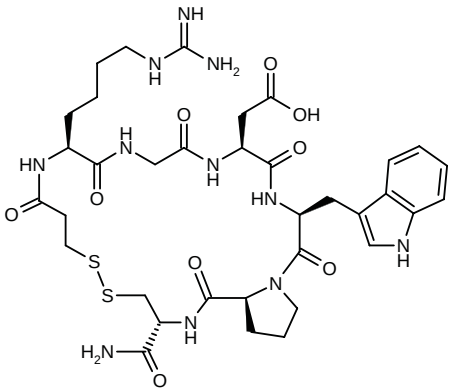
Eptifibatide

Platelet Antiaggregatory
Glycoprotein IIb/IIIa Antagonist
Fibrinogen Receptor Antagonist

Integrilin™
Integrelin
Sch-60936
C68-22
SB-1

N^6-(Aminoiminomethyl)-N^2-(3-mercapto-1-oxopropyl)-L-lysyl-glycyl-L-α-aspartyl-L-tryptophyl-L-prolyl-L-cysteinamide cyclic (1→6)-disulfide



$C_{35}H_{49}N_{11}O_9S_2$ Mol wt: 831.96

CAS: 148031-34-9

EN: 190747

Synthesis

Similar to other small disulfide-linked peptides, eptifibatide can be prepared by conventional solid-phase peptide synthesis (1) or by fragment synthesis in solution.

Description

The acetate salt of eptifibatide is a noncrystalline amorphous white powder, freely soluble in water. The product preparation is a clear, colorless, sterile solution for intravenous injection.

Introduction

Vascular occlusive artery disease remains a primary cause of death in Western cultures with the most common syndromes including myocardial infarction, angina and stroke. Platelet-mediated thrombosis is a primary underlying mechanism leading to these life-threatening clinical events (2). Platelet aggregation that occurs at the site of atherosclerotic plaque rupture initiates a cascade of thrombus formation and intravascular coagulation and is mediated by the specific platelet adhesion receptor, glycoprotein IIb/IIIa. This receptor complex, which in its active form on platelets serves to cross-link platelets through the binding of adhesive proteins such as fibrinogen and von Willebrand factor, plays a central role in thrombosis (3-7).

Thrombosis may also occur at the site of percutaneous coronary intervention (PCI), which is performed to relieve ischemia due to fixed stenosis but may also damage the vascular endothelium as a consequence. The most common procedure is percutaneous transluminal coronary angioplasty (PTCA) (8-10). Balloon catheters or other devices utilized during PCI frequently fissure the lesions containing underlying atherosclerotic plaque resulting in acute adhesion and activation of platelets accompanied by activation of coagulation pathways. Although thrombotic events can occur acutely during the PTCA procedure, leading to abrupt closure of the vessel, they can also occur in the subsequent hours or days post-PCI procedures.

Antithrombotic agents used during the PTCA procedure inhibit either platelet function (aspirin) or coagulation (heparin), but are only partially effective in reducing the acute complications during the intervention. Recently, the monoclonal antibody fragment, abciximab, was approved for use during angioplasty. This agent binds to platelet GPIIb/IIIa and blocks its adhesive function, reducing the acute complications of angioplasty (abrupt closure of the index vessel) and longer term clinical events measured as a 30-day composite endpoint which include death, MI or the need for urgent revascularization (11, 12).

Since early observations that peptides containing the arginyl-glycyl-aspartyl (RGD) sequence could effectively inhibit the adhesive function of GPIIb/IIIa (10), the search

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for more potent, short-acting and specific inhibitors of GPIIb/IIIa which are either peptides or nonpeptide mimetics of the RGD sequence have been intensively investigated (1, 13-16). The most clinically advanced of these agents have been reviewed (17, 18).

A member of the peptide class of GPIIb/IIIa inhibitors, eptifibatide is a highly specific cyclic RGD-like heptapeptide antagonist of GPIIb/IIIa which was designed based on an active pharmacophore of the disintegrin inhibitor, barbourin, found in the venom of the southeastern pigmy rattlesnake, *Sistrurus milarus barbouri* (1, 19). Eptifibatide was developed as a short-acting parenteral antithrombotic agent to be used during PCI procedures, for the treatment of unstable angina and as an adjunct to thrombolytic agents for the treatment of acute myocardial infarction.

Pharmacological Actions

Eptifibatide selectively blocks the binding of adhesive proteins to GPIIb/IIIa and is a relatively weak inhibitor of the most closely related receptor of the integrin family, namely the vitronectin receptor, $\alpha v\beta 3$ (1). The binding of tritiated eptifibatide, [^{3}H]-C68-22, has been studied with purified GPIIb/IIIa, where it displays a K_d = 150 nM (19). Direct binding experiments of radiolabeled eptifibatide with platelets have not been reported and have proven difficult to perform, most likely because the peptide displays moderate affinity for the receptor and has very rapid dissociation rate from intact unactivated platelets. This is consistent with binding studies with a radioiodinated analog of eptifibatide, which has been shown to bind to thrombin-stimulated washed platelets with a K_d = 120 nM (21). Eptifibatide inhibits the binding of biotinylated fibrinogen to purified platelet GPIIb/IIIa with an IC_{50} value of 8.7 ± 1.2 nM (20), and inhibits human platelet aggregation induced by ADP with an IC_{50} value of 140 ± 40 nM in citrate collected platelet rich plasma (PRP) and with an IC_{50} value of 570 ± 70 nM in PPACK anticoagulated PRP (20).

Eptifibatide has been evaluated in dog and baboon models of thrombosis. In the canine Folt's model of coronary artery injury, eptifibatide completely inhibited cyclic flow variations at an average dose of 2.85 ± 1.8 μg/kg/min when administered intravenously. As the measured shear rates in the coronary artery were increased, correspondingly higher doses of eptifibatide were required to abolish the cyclic flow variations in the vessel. Total inhibition of cyclic flow variations corresponded to a 76 ± 17% reduction in *ex vivo* ADP/epinephrine-induced platelet aggregation (22). In an electrical injury-induced canine model of arterial thrombosis, eptifibatide (4 μg/kg/min) prevented primary occlusion. In this same animal model, eptifibatide (4 μg/kg/min) also reduced the time to thrombolysis of clots mediated by streptokinase by 30% and prevented reocclusion of the canine femoral arteries (23). In similar studies in dogs using tissue plasminogen activator-induced thrombolysis, eptifibatide administered at 5 μg/kg/min enhanced the lysis rate yet failed to modify the reocclusion rate. When a lower dose of eptifibatide (2.5 μg/kg/min) was administered in combination with the direct thrombin inhibitor, hirudin (10 μg/kg/min), a synergistic effect was noted with the combined regimen also reducing the reocclusion rate by 25% (24). Eptifibatide has also been studied in a cardiopulmonary bypass model in dogs. Dogs received a 90 μg/kg bolus and a 2 μg/kg/min infusion during 2.5 h of hypothermic cardiopulmonary bypass. In animals receiving eptifibatide infusion, there was a significant preservation of platelets and platelet function compared to controls. The eptifibatide-treated animals also had less postoperative bleeding (25).

In baboon studies, eptifibatide (SB-1) inhibited baboon platelets *in vitro* with an IC_{50} value of 160 nM. Infusion of SB-1 (2-10 μg/kg/min) produced a steady-state inhibition of *ex vivo* platelet aggregation within 15 min of initiating infusion, suggesting a short *in vivo* half-life. To assess antithrombotic effects, eptifibatide was infused at 5 and 10 μg/kg/min into baboons with ongoing thrombus formation quantitated by λ-scintillation camera imaging of ^{111}In-platelet accumulation onto Dacron vascular grafts placed within femoral arteriovenous shunts. The two infusion regimens reduced subsequent thrombus formation over 75 min by 24% and 55%, respectively. When shunts were placed 15 min after initiation of eptifibatide infusion, platelet deposition was reduced by the two doses of eptifibatide by 47% and 80%, respectively. Measured bleeding times in control animals averaged 4.4 ± 0.2 min and were prolonged to 7.3 ± 1.3 min in the 5 μg/kg/min infusion animals and to 11.7 ± 1.2 min in the 10 μg/kg/min infusion animals (26). When collagen coated grafts were stenosed to reduce cross-sectional areas by 50%, 75% and 90% creating wall shear rates that ranged between 1250-20,000 s^{-1}, infusion of eptifibatide at 10 μg/kg/min was found to be effective in inhibiting platelet deposition at all shear rates (27).

Pharmacokinetics and Metabolism

The pharmacokinetic parameters measured for eptifibatide have been obtained and evaluated from five phase I studies enrolling 99 healthy volunteers where the plasma clearance (CL) of eptifibatide ranged between 150-300 ml/kg/h and the plasma half-life ($t_{1/2}$) ranged between 0.6-1.80 h. In patients with mild renal impairment (creatinine clearance = 30-60 ml/min), CL was 80-85 ml/kg/h with a $t_{1/2}$ value of 2.4 h. In phase II and phase III studies, the plasma clearance of eptifibatide has ranged between 80-250 ml/kg/h and the $t_{1/2}$ values have ranged between 1.8-3.0 h (28). The estimates of plasma clearance were consistently lower and the plasma half-life consistently longer in these patients. There has been no indication of an interaction of eptifibatide with either heparin or aspirin in these studies.

Eptifibatide is cleared by both nonrenal and renal mechanisms, with renal clearance accounting for approx-

imately 40% of total body clearance in healthy subjects. Within the first 24 h, the drug is primarily excreted in the urine as unmodified eptifibatide (34%), deamidated eptifibatide (19%) and more polar metabolites (13%) (29). There is evidence of extrarenal clearance of eptifibatide, as the estimated clearance consistently exceeds the normal glomerular filtration rate and urinary recovery of the drug and metabolites is well below 100% of the administered dose. Following its elimination from plasma, eptifibatide undergoes rapid and extensive degradation in urine. A major metabolite identified in animal studies, deamidated eptifibatide, has been shown to be formed in urine *ex vivo*. This metabolite has not been detected in significant amounts in plasma.

Toxicity

Safety evaluation studies with eptifibatide do not indicate any evidence of unexpected toxic effects in rats, rabbits and monkeys. In monkeys, administration up to 7.2 mg/kg/day for 28 days by continuous intravenous infusion did not produce any signs of toxicity. In a 14-day study of a higher dose (72 mg/kg/day), contusions, excessive bleeding and petechial hemorrhages were observed. These effects are the expected pharmacological responses to this potent platelet aggregation inhibitor.

Clinical Studies

In a randomized, double-blind, placebo-controlled study in 63 normal healthy volunteers, eptifibatide (0.2-1.5 μg/kg/min) administration was well tolerated (30). Plasma levels of the drug were found to be proportional to its effects on *ex vivo* platelet aggregation inhibition. Rapid inhibition of *ex vivo* platelet aggregation was noted which readily returned to control values upon discontinuation of infusion. Complete inhibition of ADP-induced platelet aggregation *ex vivo* was observed at infusion rates above 1.0 μg/kg/min and the highest infusion rate only slightly prolonged the template bleeding time in individuals (31). No episodes of clinical bleeding were noted. The plasma half-life of eptifibatide was found to be 50-60 min. Coadministration of heparin (aPTT, 1.5-2.0 times control) during eptifibatide infusion did not potentiate platelet aggregation inhibition or enhance bleeding times.

Tcheng *et al.* (32) studied eptifibatide in 150 patients undergoing elective percutaneous coronary interventions who were randomly assigned to placebo, a 90 μg/kg bolus + 1.0 μg/kg/min infusion of eptifibatide for 4 h or a 90 μg/kg bolus + 1.0 μg/kg/min infusion for 12 h. At 1 h after administration of the eptifibatide bolus, 86% inhibition of *ex vivo* platelet aggregation was observed which was maintained during the 4 or 12 h infusion. There was a trend toward reduction in endpoint events at 30 days which was not statistically significant. Minor bleeding was increased in the eptifibatide-treated patients but major bleeding was not increased over that in the placebo group.

Harrington *et al.* (33) also studied eptifibatide in patients undergoing elective coronary angioplasty. Patients were randomized to placebo (n = 19) or 4 different eptifibatide dosing regimens (total n = 54). The doses studied were 180 μg/kg bolus + 1.0 μg/kg/min infusion, 135 μg/kg bolus + 0.75 μg/kg/min infusion or 0.5 μg/kg/min infusion, and 90 μg/kg bolus + 0.75 μg/kg/min infusion for 18-24 h with concomitant aspirin and heparin regimens. The two highest eptifibatide bolus dosing regimens provided > 80% inhibition of ADP-induced platelet aggregation in > 75% of the patients at 15 min after the bolus. A constant eptifibatide infusion of 0.75 μg/kg/min maintained a steady-state platelet aggregation inhibitory effect over the 18-24 h period which reversed rapidly with platelet aggregation approaching control values 4-6 h postinfusion termination. No significant increase in serious bleeding events was noted among the eptifibatide-treated patients. In a subgroup of patients, the effects of eptifibatide infusion (135 μg/kg bolus + 0.75 μg/kg/min infusion) on *ex vivo* flow models of platelet adhesion/aggregation were determined. Under these conditions in viscometer experiments, shear-induced platelet aggregation was reduced by 61-71% in samples collected at 45 min into the infusion and was readily reversed upon termination of drug infusion (34).

The IMPACT II investigators (35-37) have examined eptifibatide in a study enrolling 4010 patients undergoing elective, urgent or emergency coronary intervention. Patients were assigned to one of three treatments: placebo (n = 1328), a bolus of 135 μg/kg eptifibatide followed by a continuous infusion of 0.50 μg/kg/min for 20-24 h (n = 1349), or 135 μg/kg eptifibatide bolus with a 0.75 μg/kg/min continuous infusion (n = 1333). The primary endpoint measured in this study was the 30-day composite occurrence of death, myocardial infarction, urgent surgical or repeat percutaneous revascularization, or coronary stent implantation for abrupt closure (by intention to treat). The primary safety endpoints were major and minor bleeding. By a "treated as randomized" analysis, the 135/0.50 group produced a significant reduction in the composite endpoint (11.6 *vs.* 9.1%, $p = 0.035$) and the 135/0.75 group also produced reduction in the efficacy endpoint which was not however statistically significant (11.6 *vs.* 10.0%, $p = 0.18$). A reduction in death and MI was also sustained for up to at least 6 months. The rates of major bleeding, transfusion or other morbidity did not increase with either eptifibatide regimen. As might be expected for an agent whose effects are readily reversible, clinical efficacy was greatest during the infusion period. Secondary analysis at the 24 h composite endpoint demonstrated significant differences in composite event rates between treatment and placebo groups - placebo group 124 (9.3%) compared with 92 (6.8%) in the 135/0.50 group ($p = 0.017$) and 93 (7.0%) in the 135/0.75 group ($p = 0.026$). At 24 h, the 135/0.50 and the 135/0.75 regimens reduced the incidence of the composite endpoint in relation to placebo by 31% and 28%, respectively, for patients who received treatment.

Schulman *et al.* (38) studied two doses of eptifibatide in patients with unstable angina. All patients received heparin and aspirin and were randomized to receive eptifibatide (45 μg/kg bolus + 0.50 μg/kg/min) infusion or eptifibatide (90 μg/kg bolus + 1.0 μg/kg/min) infusion for 24-72 h. Holter monitoring of all patients was performed. Patients receiving high-dose eptifibatide experienced fewer ischemic episodes and the duration of episodes was reduced compared to placebo. No rebound ischemia was observed in eptifibatide-treated patients upon withdrawal of study drug. Overall, the eptifibatide regimens were well tolerated and bleeding complications were similar between eptifibatide- and placebo-treated patients.

Harrington *et al.* (39) studied eptifibatide in the PURSUIT trial designed to test the hypothesis that potent platelet inhibition would add incremental clinical benefit beyond standard treatment with heparin and aspirin in reducing adverse outcomes in patients without persistent ST-segment elevation acute coronary syndromes. In this study, conducted in 28 countries, patients were enrolled with symptoms of ischemic chest pain at rest lasting 10 min or longer within the previous 24 h provided they had either transient ST-segment elevation > 0.5 mm or transient or persistent ST-segment depression > 0.5 mm or T-wave inversion > 1 mm within 12 h of an episode of chest pain, or had a creatine kinase myocardial enzyme (MB) fraction above the upper limit of normal for that hospital. Patients were randomized in a double-blind fashion to one of three treatment groups: bolus and infusion of placebo, 180 μg/kg bolus eptifibatide followed by continuous infusion of 1.3 μg/kg/min or 180 μg/kg bolus eptifibatide followed by continuous infusion of 2.0 μg/kg/min. It was recommended that the study drug be infused for up to 72 h. If coronary intervention was performed near the end of the 72-h infusion, the infusion of the study drug could be continued for an additional 24 h. After 3218 total patients were enrolled in the trial, the data safety and monitoring committee recommended dropping the lower eptifibatide dose, as specific in the protocol, after it had been determined that the 180/2.0 regimen was safe. Randomization continued with the 180 μg/kg bolus eptifibatide followed by continuous infusion of 2.0 μg/kg/min group or placebo. The primary endpoint was the composite of death from any cause or nonfatal myocardial (re)infarction at 30 days after randomization. A total of 10,948 patients were randomized in 14 months. Data from the trial are for the primary comparison groups, 180 μg/kg bolus eptifibatide with 2.0 μg/kg/min infusion *versus* placebo. The occurrence of the composite efficacy endpoint of death and myocardial (re)infarction at 30 days was 15.7% (n = 4739) in the placebo-treated patients and 14.2% (n = 4722) in drug-treated patients ($p = 0.042$). The 1.5% absolute difference in the composite efficacy endpoint rate was reached at 3 days and was maintained to 30 days without deterioration or increase in the treatment effect. The investigator determined events at 30 days were lower and the absolute treatment effect with eptifibatide was greater (10.0% placebo *vs.* 8.0% eptifibatide, $p = 0.001$) than those adjudicated by the clinical events committee. The estimate of the treatment effect was apparent in those patients undergoing percutaneous intervention in the 72 h following randomization (14.4% event rate in placebo-treated patients (n = 631) *vs.* 9.0% in the eptifibatide-treated patients (n = 619)) compared with those patients who did not undergo early intervention (6.5% placebo-treated (n = 4108) *vs.* 5.4% eptifibatide-treated patients (n = 4103)) at 72 h. In addition, patients undergoing PCI also benefited from treatment with eptifibatide before the procedure (events in placebo-treated patients 5.5% *vs.* eptifibatide-treated patients 1.8%). However, the effects of eptifibatide treatment were evident whether or not patients went on to have percutaneous intervention, coronary artery bypass surgery (CABG) or were medically managed. All of the effects of the drug occurred within the first 72 h, essentially during drug administration (placebo event rate = 7.6%, eptifibatide treatment = 5.9%, $p = 0.001$). An absolute decrease of 1.5% in the incidence of death and/or myocardial infarction was maintained throughout the 30-day study period. Bleeding was more common among the patients receiving eptifibatide. However, the bleeding risk was as expected, the majority of the observed bleeding was mild, procedure-related and occurred at the femoral access site. There were fewer strokes among patients treated with eptifibatide compared with those receiving placebo (0.7% *vs.* 0.9%). The incidence of thrombocytopenia was similar between eptifibatide and placebo patients. The absolute occurrence of platelet counts below 100,000/μl was similar in eptifibatide-treated and placebo-treated patients.

Ohman *et al.* (40) studied glycoprotein IIb/IIIa blockade with eptifibatide in combination with accelerated tissue plasminogen activator (alteplase) in acute ST-segment elevation myocardial infarction. After an initial open-label, dose-escalation phase in 132 patients assigned in a 2:1 ratio receiving a bolus and continuous infusion of six different doses of eptifibatide, an additional 48 patients were randomized in a 3:1 double-blind fashion to receive the highest dose (180 μg/kg bolus + 0.75 μg/kg/min infusion) from the first phase or placebo. Patients received the eptifibatide bolus dosing within 10 min of alteplase administration followed by infusion for 24 h. The highest eptifibatide dose group from the nonrandomized phase and the randomized patients were pooled for analysis and compared to placebo. The primary endpoint was TIMI grade 3 flow at 90-min angiography. Secondary endpoints were time to ST-segment recovery and an in-hospital composite of death, reinfarction, stroke, revascularization procedures, new heart failure or pulmonary edema. Patients in the highest eptifibatide dose group had more complete reperfusion at 90 min (TIMI grade 3 flow 66% *vs.* 38% for placebo-treated patients; $p = 0.006$) and a shorter time to ST-segment recovery (65 min *vs.* 116 min for placebo; $p = 0.05$). Patients treated with eptifibatide also had greater overall patency (TIMI grade 2 + 3 flow) rates measured at 90 min (87% *vs.* 69%, $p = 0.01$). The treatment groups had similar rates of the composite endpoint (43% *vs.* 42% for

placebo) and severe bleeding (4% *vs.* 5%). From this study it is apparent that the incidence and speed of reperfusion can be enhanced with eptifibatide in combination with accelerated alteplase, aspirin and intravenous heparin. Larger studies will be required to confirm these results in acute myocardial infarction and to demonstrate effects on clinical events.

Eptifibatide (Integrilin™) has been launched in the U.S. for the treatment of patients with acute coronary syndrome, including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI), as well those patients undergoing PCI who do not present with acute coronary syndrome. It is supplied as 10-ml vials containing 2 mg/ml eptifibatide as solution for i.v. injection, and 100-ml vials containing 0.75 mg/ml eptifibatide (41).

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Manufacturers

COR Therapeutics, Inc. (US), codeveloped with Schering-Plough (US).

References

1. Scarborough, R.M., Naughton, M.A., Teng, W., Rose, J.W., Phillips, D.R., Nannizzi, L., Arfsten, A., Campbell, A.M., Charo, I.F. *Design of potent and specific integrin antagonists. Peptide antagonists with high specificity for glycoprotein IIb-IIIa.* J Biol Chem 1993, 268: 1066-73.

2. White, H.D. *Unmet therapeutic needs in the management of acute ischemia.* Amer J Cardiol 1997, 80: 2B-10B.

3. Phillips, D.R., Charo, I.F., Scarborough, R.M. *GPIIb-IIIa: The responsive integrin.* Cell 1991, 65: 359-62.

4. Davies, M.J. *Pathology of arterial thrombosis.* Brit Med Bull 1994, 50: 789-802.

5. Falk, E. *Role of thrombosis in atherosclerosis and its complications.* Amer J Cardiol 1995, 75: 3B-11B.

6. Lefkovits, J., Plow, E.F., Topol, E.J. *Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine.* New Engl J Med 1995, 332: 1553-9.

7. Coller, B.S. *Platelets and thrombolytic therapy*. New Engl J Med 1990, 322: 33-42.

8. Chesebro, J.H., Fuster, V. *Platelet-inhibitor drugs before and after coronary artery bypass surgery and coronary angioplasty: The basis of their use, data from animal studies, clinical trial data, and current recommendations.* Cardiology 1986, 73: 292-305.

9. Harker, L.A. *Role of platelets and thrombosis in mechanisms of acute occlusion and restenosis after angioplasty.* Amer J Cardiol 1987, 60: 20B-8B.

10. Bittl, J.A. *Advances in coronary angioplasty.* New Engl J Med 1996, 335: 1290-302.

11. Robinson, C. *Abciximab*. Drugs Fut 1995, 20: 457-63.

12. Genatta, T.B., Mauro, V.F. *Abciximab: A new antiaggregant used in angioplasty.* Ann Pharmacol 1996, 30: 251-7.

13. Pytela, R., Pierschbacher, M.D., Ginsberg, M.H., Plow, E.F., Ruoslahti, E. *Platelet membrane glycoprotein IIb/IIIa: Member of a family of Arg-Gly-Asp-specific adhesion receptors.* Science 1986, 231: 1559-62.

14. Kouns, W.C., Roux, S., Steiner, B. *Human platelet GPIIb-IIIa receptor blockade as a therapeutic strategy.* Curr Opin Invest Drugs 1993, 2: 475-94.

15. Cook, N.S., Kottirsch, G., Zerwes, H.-G. *Platelet glycoprotein IIb/IIIa antagonists.* Drugs Fut 1994, 19: 135-59.

16. Zablocki, J.A., Nicholson, N.S., Feigen, L.P. *Fibrinogen receptor antagonists.* Exp Opin Invest Drugs 1994, 3: 437-48.

17. Topol, E.J. *Toward a new frontier in myocardial reperfusion therapy. Emerging platelet preeminence.* Circulation 1998, 97: 211-8.

18. Raddatz, P., Gante, J. *Recent developments in glycoprotein IIb/IIIa antagonists.* Exp Opin Ther Patents 1995, 5: 1163-83.

19. Scarborough, R.M., Hsu, M.A., Teng, W., Rose, J.W., Philips, D.R., Campbell, A.M., Nannizzi, L., Charo, I.F. *C68-22, a novel glycoprotein (GP) IIb-IIIa specific platelet aggregation inhibitor designed from the structure of barbourin.* Arterioscler Thromb 1991, 11: 1591a.

20. Phillips, D.R., Teng, W., Arfsten, A. et al. *Effect of Ca^{2+} on GPIIb-IIIa interactions with Integrilin: Enhanced GPIIb-IIIa binding and inhibition of platelet aggregation by reduction in the concentration of ionized calcium in plasma anticoagulated with citrate.* Circulation 1997, 96: 1488-94.

21. Suehiro, K., Smith, J.W., Plow, E.F. *The ligand recognition specificity of β_3 integrins*. J Biol Chem 1996, 271: 10365-71.

22. Strony, J., Adelman, B., Phillips, D.R., Scarborough, R.M., Charo, I.F. *Inhibition of platelet thrombus formation in an in vivo model of high shear stress by a glycoprotein IIb-IIIa specific peptide antagonist.* Circulation 1991, 84(4, Suppl. 2): Abst 0985.

23. Song, A., Scarborough, R.M., Phillips, D.R., Adelman, B., Strony, J. *Integrelin enhances fibrinolysis and prevents acute arterial reocclusion following thrombolysis in a canine anodal current model with high grade stenosis.* Circulation 1992, 86(4, Suppl. 1): Abst 1634.

24. Nicolini, F.A., Philmo, L., Rios, G., Kottke-Marchant, K., Topol, E.J. *Combination of platelet fibrinogen receptor antagonist and direct thrombin inhibitor at low doses markedly improves thrombolysis.* Circulation 1994, 89: 1802-9.

25. Uthoff, K., Zehr, K.J., Geerling, R., Herskowitz, A., Cameron, D.E., Reitz, B.A. *Inhibition of platelet adhesion during cardiopulmonary bypass reduces postoperative bleeding.* Circulation 1994, 90: II-269-74.

26. Hanson, S.R., Kotze, H.F., Harker, L.A., Scarborough, R.M., Charo, I.F., Phillips, D.R. *Potent antithrombotic effects of novel*

peptide antagonists of platelet glycoprotein (GP) IIb-IIIa. Thromb Haemost 1991, 65: 813.

27. Hanson, S.R., Markou, C., Lindahl, A.K. et al. *Inhibition of in vivo thrombus formation in an arterial stenosis model.* Thromb Haemost 1993, 69: 540.

28. Van Wart, S., Kosoglou, T., Tcheng, J.E., Lorenz, T., Alton, K., Belanger, B., Radwanski, E. *Eptifibatide pharmacokientics in patients undergoing coronary angioplasty.* Clin Pharmacol Ther 1998, 63: Abst PIII-103.

29. Alton, K.B., Kosoglou, T., Baker, S., Affrime, M.B., Cayen, M.N., Patrick, J.E. *Disposition of ^{14}C-eptifibatide after intravenous administration to healthy men.* Clin Ther 1998, 20: 307-23.

30. Charo, I.F., Scarborough, R.M., du Mee, C.P., Wolf, D., Phillips, D.R., Swift, R.L. *Pharmacodynamics of the GPIIb-IIIa antagonist Integrelin: Phase I clinical studies in normal healthy volunteers*. Circulation 1992, 86(4, Suppl. 1): Abst 1034.

31. Phillips, D.R., Scarborough, R.M. *Clinical pharmacology of eptifibatide*. Amer J Cardiol 1997, 80: 11B-20B.

32. Tcheng, J.E., Harrington, R.A., Kottke-Marchant, K. et al. *Multicenter, randomized, double-blind, placebo-controlled trial of the platelet intregrin glycoprotein IIb/IIIa blocker Integrilin in elective coronary angioplasty*. Circulation 1995, 91: 2151-7.

33. Harrington, R.A., Kleiman, N.S., Kottke-Marchant, K. et al. *Immediate and reversible platelet inhibition after intravenous administration of a peptide glycoprotein IIb/IIIa inhibitor during percutaneous coronary intervention.* Amer J Cardiol 1995, 76: 1222-7.

34. Kamat, S.G., Turner, N.A., Konstantopoulos, K., Hellums, J.D., McIntire, L.V., Kleiman, N.S., Moake, J.L. *Effects of Integrelin on platelet function in flow models of arterial thrombosis.* J Cardiovasc Pharmacol 1997, 29: 156-63.

35. The IMPACT-II Investigators. *Randomised placebo-controlled trial of effect of eptifibatide on complications of percutaneous coronary intervention: IMPACT-II.* Lancet 1997, 349: 1422-8.

36. Tcheng, J.E. *Impact of eptifibatide on early ischemic events in acute ischemic coronary syndromes: A review of the IMPACT II trial.* Amer J Cardiol 1997, 80: 21B-8B.

37. Kleiman, N.S. *Primary and secondary safety endpoints from IMPACT II.* Amer J Cardiol 1997, 80: 29B-33B.

38. Schulman, S.P., Goldschmidt-Clermont, P.J., Topol, E.J. et al. *Effects of Integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina.* Circulation 1996, 94: 2083-9.

39. Harrington et al. *A randomized comparison of the platelet glycoprotein IIb/IIIa peptide inhibitor eptifibatide with placebo in patients without persistent ST-segment elevation acute coronary syndromes.* New Engl J Med 1998, in press.

40. Ohman, E.M., Kleiman, N.S., Gacioch, G. et al. *Combined accelerated tissue-plasminogen activator and platelet glycoprotein IIb/IIIa integrin receptor blockade with Integrilin in acute myocardial infarction. Results of a randomized, placebo-controlled dose-ranging trial.* Circulation 1997, 95: 846-54.

41. *Integrilin™ available week of June 1st.* Cor Therapeutics, Inc. Company Communication May 27, 1998.