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Lamifiban

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Contents

Abstract

▲ Lamifiban is an intravenously administered, selective, reversible, nonpeptide glycoprotein IIb/IIIa receptor antagonist which inhibits platelet aggregation and thrombus formation by preventing the binding of fibrinogen to platelets.

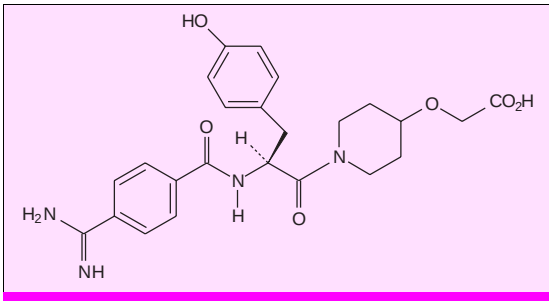
▲ In trials in patients with non-Q wave myocardial infarction (MI) or unstable angina pectoris (PARAGON A and the Canadian Lamifiban Study), the incidence of clinical events at 30 days in patients receiving lamifiban (1 to 5 μg/min) was not significantly different from that in patients receiving aspirin plus heparin or aspirin alone.

▲ In PARAGON A, the incidence of clinical events at 6 months was significantly lower after lamifiban (with or without heparin) and aspirin therapy than after standard heparin and aspirin therapy.

▲ A large phase III trial (PARAGON B) is under way comparing lamifiban plus aspirin and heparin with standard aspirin and heparin therapy in patients with non-Q wave MI or unstable angina pectoris.

▲ In clinical trials, the most common adverse events associated with lamifiban were bleeding complications which were increased by the concomitant administration of heparin.

Features and properties of lamifiban (Ro 44-9883)	
Indications	
Acute coronary syndromes (non-Q wave myocardial infarction and unstable angina pectoris)	Late phase clinical trials
Mechanism of action	
Platelet aggregation inhibitor	Glycoprotein IIb/IIIa receptor antagonist
Dosage and administration	
Usual dosage	150 to 750μg bolus then 1 to 5 μg/min for 48 to 72 hours
Route of administration	Intravenous
Frequency of administration	Infusion
Pharmacokinetic profile (0.6 or 1 μg/kg/min)	
Volume of distribution	20.3L
Protein binding	Low (approximately 6%)
Clearance	8 L/h
Elimination half-life	2.1h
Route of elimination	Renal (mainly excreted as the unchanged drug)
Adverse events	
Most frequent	Minor or intermediate haemorrhage
Serious events	Major haemorrhage



Lamifiban

Lamifiban is an intravenously administered, reversible, nonpeptide glycoprotein (GP) IIb/IIIa receptor antagonist.[1] GP IIb/IIIa is the platelet membrane receptor for fibrinogen and von Willebrand factor. Activation of the GP IIb/IIIa receptor is the final common pathway of platelet aggregation and thrombus formation.[2]

By preventing the binding of fibrinogen to platelets, GP IIb/IIIa receptor antagonists inhibit platelet aggregation and lessen the risk of arterial thrombosis. These agents are of interest as therapy in patients with acute coronary syndromes.

In this review, acute coronary syndromes are defined as unstable angina pectoris and non-Q wave myocardial infarction (MI). However, an early dose-finding study included patients with Q wave (acute) MI.

1. Pharmacodynamic Profile

Animal Models of Coronary Artery Disease

• Lamifiban (360 μg/kg bolus followed by 6 μg/kg/min infusion) reduced the size of infarcts which developed during reperfusion after myocardial ischaemia in canine models compared with control animals (infarct size 22 *vs* 41.4%, $p < 0.05$).[3]

• Pretreatment with intravenous lamifiban (10 and 20 μg/kg/min) in guinea-pig models significantly prolonged the time to photochemical-induced artery occlusion [from 5 to about 15 and 18 minutes after the respective dosages ($p < 0.01$ *vs* control group). The highest dose of lamifiban [with concomitant recombinant tissue-type plasminogen activator (rt-PA)], administered after occlusion had occurred, significantly reduced the time to reperfusion by about 50% ($p < 0.05$ *vs* control animals) and both doses increased the time during which the artery was patent by about 3- to 4-fold ($p < 0.01$ *vs* control group).[4]

Effects on Platelet Aggregation and Bleeding Times in Human Studies

• In 2 double-blind, randomised, placebo-controlled trials, lamifiban 1 to 5 μg/min for 24 to 84 hours dose-dependently inhibited *ex vivo* platelet aggregation induced by adenosine diphosphate (ADP; 10 μmol) or thrombin receptor agonist peptide (TRAP; 25 or 100 μmol)[5,6] and increased Ivy bleeding times in patients with unstable angina pectoris[5] or Q wave MI[6] (fig. 1) [see section 3 for study details]. As expected by the mechanism of action of this drug, the increase in bleeding times was statistically significant (no p values reported) when ADP-induced platelet aggregation was inhibited by >80%.[5]

• The effect of lamifiban on platelet aggregation in patients with MI was not influenced by the presence of cardiovascular risk factors such as increasing age, smoking, site of infarction or the presence of diabetes or bundle branch block.[7]

• Compared with that in volunteers with normal renal function [creatinine clearance (CL_{CR}) >75 ml/min; n = 4] and patients with mild to moderate renal impairment (CL_{CR} 30 to 74 ml/min; n = 8), the infusion rate needed to achieve a 60% reduction in *ex vivo* TRAP-induced platelet aggregation was significantly lower ($p < 0.0001$) in patients with severe renal impairment (CL_{CR} 10 to 29 ml/min; n = 8) and the EC_{50} of lamifiban (mean plasma concentration of lamifiban needed to inhibit ADP- or TRAP-induced platelet aggregation by 50%) was about 1- to 3-fold lower (no p values provided).[8]

• Similarly, a 2- to 3-fold lower plasma concentration of lamifiban was needed in these patients to increase bleeding times to >20 minutes (no p values provided). Furthermore, the time taken for the

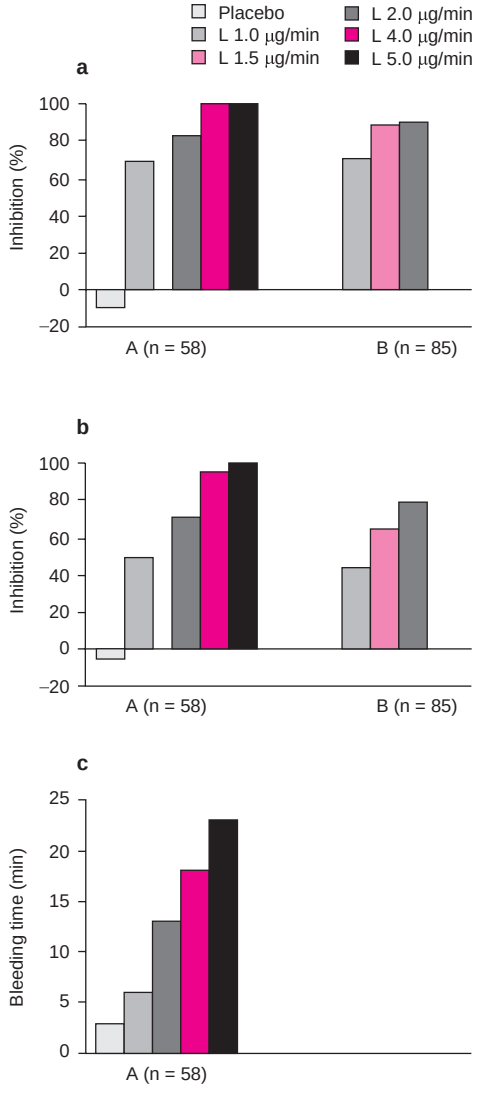


Fig. 1. Effects of lamifiban on *ex vivo* platelet aggregation and bleeding times. Effect of lamifiban (L; 1, 2, 4 or 5 μg/min[5] and 1, 1.5 and 2 μg/min[6]) on (**a**) adenosine diphosphate (ADP)- and (**b**) thrombin receptor agonist peptide (TRAP)-induced platelet aggregation and (**c**) bleeding times in patients with unstable angina pectoris or myocardial infarction.[5,6] A = Canadian Lamifiban Study (values estimated from graph and corrected for placebo)[5] B = PARADIGM trial.[6] Note for trial B: data for placebo were not provided and values for lamifiban may be corrected for placebo.[6]

effect of lamifiban on ADP-induced platelet aggregation to be reversed was relative to the severity of renal impairment; platelet recovery time was most rapid in patients with normal renal function.[8]

2. Pharmacokinetic Profile

- Plasma concentrations achieved after intravenous lamifiban 1 or 5 μg/min for a median duration of 72 hours were about 15 and 70 μg/L, respectively, in 1524 patients with unstable angina pectoris or non-Q wave MI.[9]

- In a separate analysis of the above study, blood samples from 810 patients revealed that a steady-state lamifiban concentration of 18 to 42 μg/L was associated with about a 40% reduction in the combined incidence of death and nonfatal MI at 30 days.[10]

- The volume of distribution of an intravenous infusion of lamifiban 0.6 or 1 μg/kg/min was 20.3L, the total body clearance was about 8 L/h and the elimination half-life was about 2 hours in healthy volunteers.[1,11]

- Lamifiban weakly binds to human plasma protein (6%) as assessed by *in vitro* binding studies using radiolabelled lamifiban.[1] The primary route of elimination of lamifiban is renal, and animal studies show that it is mainly excreted as the unchanged drug.[1]

- Lamifiban is unlikely to interact with drugs metabolised by the cytochrome P450 isoenzymes.[1]

- Total clearance of intravenous lamifiban (40 to 750μg loading dose then 0.09 to 5 μg/min for 4 hours) was linearly related to renal function (glomerular filtration rate and CL_{CR}) and was about 7, 4 and 1 L/h, respectively, in volunteers with normal function (CL_{CR} >75 ml/min) and patients with mild to moderately impaired (CL_{CR} 30 to 74 ml/min) and severely impaired (CL_{CR} 10 to 29 ml/min) renal function.[8]

3. Therapeutic Trials

The Canadian Lamifiban Study

• In this phase II, double-blind, randomised, dose-finding trial, the number of patients experiencing a combined event of death, MI or urgent interventions was significantly lower during, but not at 1 month after, an intravenous infusion of lamifiban 1 to 5 μg/min for a mean of 84 hours (initial bolus of 150 to 750μg) than after placebo in 365 patients with unstable angina pectoris or non-Q wave MI. 44 patients (12%) had a non-Q wave MI at baseline. All patients received concomitant aspirin (325 mg/day) and 28% of patients also received intravenous or subcutaneous heparin.[5]

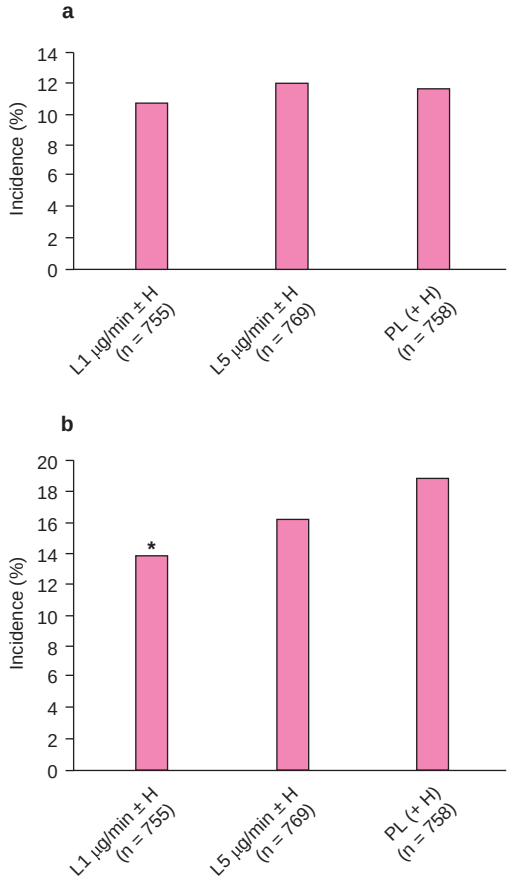


Fig. 2. Kaplan-Meier estimated effects of lamifiban on cardiac events in patients with unstable angina or non-Q wave myocardial infarction. Effect of lamifiban (L) 1 or 5 μg/min with or without concomitant heparin (H) for 72 hours on the combined incidence of death/myocardial infarction at (**a**) 30 days or (**b**) 6 months in 2282 patients with unstable angina pectoris or non-Q wave myocardial infarction.[9] * $p < 0.03$ *vs* heparin plus aspirin. All patients received concomitant aspirin. **PL** = placebo.

• No significant differences were observed in the individual rates of death, nonfatal infarction, refractory ischaemia requiring urgent medical intervention (angioplasty or bypass surgery), recurrent ischaemia or recurrent angina pectoris between lamifiban (results from all doses combined) and placebo during the infusion or at 1 month. The concomitant administration of heparin did not influence the incidence of death or reinfarction.[5]

• However, the incidence of recurrent ischaemia and the total number of events per patient during the infusion were lower after lamifiban 5 μg/min than after placebo (recurrent ischaemia 4.9 *vs* 12.2%, $p < 0.02$ *vs* placebo; events per patient 1.5 *vs* 4.1, $p < 0.01$ *vs* placebo). The number of events per patient was also significantly lower than with placebo when all doses of lamifiban were combined (2.8 *vs* 4.1, $p < 0.01$). Clinical benefit was not dose dependent.[5]

• MI at study entry resulted in a worse outcome at 1 month than unstable angina pectoris in the whole study population: death or reinfarction occurred in 11.4% of 44 patients with MI versus 4.4% of 321 patients with unstable angina pectoris ($p = 0.05$).[5]

The PARAGON A Study

• The phase II/III, double-blind, randomised PARAGON A study (Platelet IIb/IIIa Antagonists for the Reduction of Acute coronary syndrome events in a Global Organization Network) compared lamifiban 1 or 5 μg/min for a median duration of 72 hours (initial bolus of 300 or 750μg) with standard heparin/aspirin (plus placebo) therapy in 2282 patients with unstable angina pectoris or non-Q wave MI. Lamifiban was administered with or without concomitant standard heparin, and all lam-

ifiban patients also received concomitant aspirin (80 to 325 mg/day).[9]

• No significant differences were observed in the individual or combined incidence of all-cause death or nonfatal MI at 30 days between lamifiban (with or without heparin) and the combination of heparin and aspirin (fig. 2a).[9]

• However, at 6 months the combined incidence of clinical events was significantly lower after low-dose lamifiban (with or without heparin) [odds ratio 0.73, $p < 0.03$] than heparin and aspirin (fig. 2b). Low dose lamifiban with concomitant heparin produced the greatest significant reduction in clinical events at 6 months (12.6%, $p = 0.03$) but no significant differences were observed between the other lamifiban groups and heparin/aspirin recipients.[9]

• At 1 year, the incidence of death from any cause was not significantly different between patients receiving lamifiban and those receiving heparin plus aspirin and ranged from 7.3 to 8.9%.[9]

• In a retrospective analysis of 810 patients from this trial, a correlation was found between the lamifiban plasma concentration and the incidence of clinical events. A therapeutic plasma concentration of 18 to 42 μg/L resulted in about a 40% reduction in the 30-day and 6-month rates of clinical events. Thus, doses used in future clinical trials will be titrated to achieve this optimal plasma concentration range (fig. 3).[10]

• In a separate analysis of the PARAGON A study, the incidence of death and/or MI at 6 months was significantly lower by about 36 to 43% ($p < 0.01$ *vs* no lamifiban) in patients with diabetes mellitus who were receiving lamifiban (with or without heparin). This difference was not observed in nondiabetic patients. Patients with diabetes were older and had more risk factors for coronary artery disease at baseline than nondiabetic patients.[12]

The PARAGON B Study

• This large phase III study is under way to compare the efficacy of lamifiban in combination with heparin and aspirin with that of standard therapy

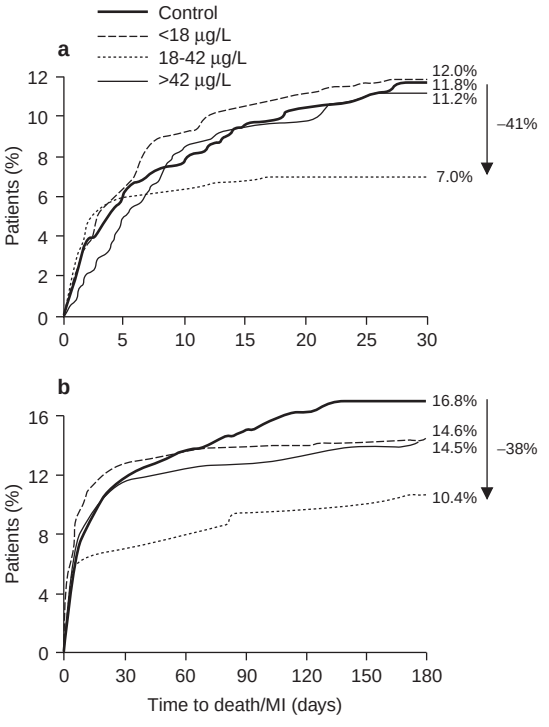


Fig. 3. Effects of lamifiban steady-state plasma concentrations on cardiac event rates. The effects of high (> 42 μg/L), medium (18 to 42 μg/L) and low (< 18 μg/L) steady-state plasma concentrations of lamifiban on the combined incidence of death and myocardial infarction at (**a**) 30 days and (**b**) 6 months in 810 patients with non-Q wave myocardial infarction or unstable angina.[10]

with aspirin and heparin in patients with unstable angina pectoris or non-Q wave MI. The dose of lamifiban used in this trial will be individualised according to patients' renal function to achieve the optimal plasma concentration identified in PARAGON A.

• The trial will include 4000 patients who will be randomised to receive lamifiban (500μg bolus then 1 to 2 μg/min infusion depending on renal function) or placebo in conjunction with standard heparin and aspirin (150 to 325 mg/day) regimens.[13]

• Primary and secondary clinical end-points include individual and combined incidence of death, (re-)infarction or severe recurrent ischaemia need-

ing intervention at 7 and 30 days, the 6-month incidence of MI or death and the 1-year incidence of death. Health economic and safety and tolerability issues will also be addressed.[13]

The PARADIGM Trial

- In the phase II, double-blind, randomised, dose-finding PARADIGM study (Platelet Aggregation Receptor Antagonist Dose Investigation and reperfusion Gain in Myocardial infarction),[6] 323 patients with Q wave MI received intravenous lamifiban 1.5 or 2 μg/min for 24 or 48 hours (initial bolus of 400μg) or placebo in conjunction with thrombolytic therapy (rt-PA 100mg over 90 minutes or streptokinase 1.5 million units over 1 hour) and standard intravenous heparin. All patients received concomitant aspirin (160 to 325 mg/day).[6]

- 30 additional patients, who received lamifiban (1 or 2 μg/min) for 24 hours in a nonblind section of the study which aimed to evaluate the effect of lamifiban on agonist-induced platelet aggregation (see section 2), were also included in the efficacy analysis.[6]

- This dose-finding study did not have adequate statistical power to detect small to moderate differences in clinical outcome.[6]

- Reperfusion was more rapid and complete in the first 24 hours of hospitalisation after lamifiban than after placebo as assessed by continuous electrocardiogram (ECG) parameters. However, no significant differences were observed between lamifiban and placebo recipients in the combined or individual incidence of clinical events (death, reinfarction, need for revascularisation, or refractory or recurrent ischaemia) at the final assessment point (30 days[14]).[6]

4. Tolerability

The information presented in this section has been obtained from 2 large trials in patients with unstable angina pectoris or non-Q wave MI[5,9] and from a dose-finding study in patients with Q wave MI[6] (see section 3 for study details).

The Canadian Lamifiban Study and the PARAGON A Study

- Intravenous lamifiban (1 to 5 μg/min) resulted in major or minor bleeds in about 3 and 11%, respectively, of patients in 1 trial (n = 365).[5] The incidence of minor, but not major, bleeding events was significantly greater after lamifiban than placebo (about 11 *vs* 1.6%, p = 0.002).[5] In the PARAGON A trial (n = 2282), lamifiban 5 μg/min (with or without heparin) resulted in a significantly higher rate of major or intermediate bleeds than lamifiban 1 μg/min or placebo (plus heparin) [10.7 *vs* 6 *vs* 5.5%, p = 0.002].[9]

- The incidence of bleeding was increased by the concomitant administration of heparin: rates were 6% after lamifiban and heparin, 3.4% after heparin and placebo, 1.7% after lamifiban and 0% after placebo.[5] The concomitant administration of heparin with lamifiban was also associated with a higher incidence of intermediate bleeding in PARAGON A (no further data provided).[9]

- Transfusion was needed by significantly more patients receiving lamifiban plus heparin (7.5%, p = 0.03) than lamifiban without heparin (5.7%) or monotherapy with heparin (4.4%) in the larger study.[9]

- Stroke occurred in 1.1, 0.7 and 0.4% of patients, respectively, after lamifiban 1 and 5 μg/min (with or without heparin) and after placebo plus heparin, and the combined incidence of major bleeding, thrombocytopenia and stroke was 2.8, 3.5 and 1.8%, respectively. Intracranial haemorrhage occurred in 1 patient receiving lamifiban 5 μg/min (with no heparin).[9]

- Thrombocytopenia occurred in 0% of patients after lamifiban and 3.9% of patients after placebo (plus heparin and aspirin) in 1 trial,[5] and 1.9, 0.8 and 1.1% of patients after lamifiban without heparin, lamifiban with heparin or placebo with heparin, respectively, in the second study.[9]

The PARADIGM Trial

- In the dose-finding PARADIGM study, major or intermediate bleeding was twice as frequent (3 and 4%, respectively) with lamifiban (1.5 or 2 μg/min) as with placebo but significance values for these findings were not provided. The incidence of bleeding was increased by the concomitant administration of rt-PA or streptokinase (further data not provided).[6]

- Major or intermediate bleeding was mainly related to gastrointestinal bleeding, bypass surgery or femoral artery access site sources. Intracranial haemorrhage occurred in 2 patients receiving lamifiban (with thrombolytic therapy). Transfusion was needed by 16.1 and 10.3% of patients receiving lamifiban or placebo plus thrombolytic agents, respectively (p values not provided).[6]

- Thrombocytopenia occurred in 1.7 *vs* 0.9% of patients after lamifiban or placebo (plus thrombolytic agents), respectively.[6]

5. Lamifiban: Current Status

Lamifiban is an intravenously administered GP IIb/IIIa receptor antagonist. It is currently in phase III clinical trials worldwide for acute coronary syndromes (non-Q wave MI and unstable angina pectoris). It has shown clinical efficacy in these 2 conditions in recent trials.

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