SCIENTIFIC DISCUSSION

This module reflects the initial scientific discussion and scientific discussion on procedures which have been finalised before 1 October 2004. For scientific information on procedures after this date please refer to module 8B.

1. Introduction

Eptifibatide is the active substance of the medicinal product Integrilin. Eptifibatide is an anti-platelet agent with high affinity and specificity for the Glycoprotein (GP) IIb/IIIa receptor that mediates platelet aggregation. Eptifibatide is an inhibitor of platelet aggregation and belongs to a new class of RGD mimetics- arginin (R), glycin (G), aspartic acid (D). Eptifibatide reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the GP IIb/IIIa receptors. Another product in this field is Reopro (abciximab) an antibody directed against the GP IIb/IIIa receptors.

Platelets and fibrin thrombi are observed in the pathophysiology of unstable angina and platelet deposition and aggregation may have a pivotal role also in the acute reocclusion of coronary arteries either after coronary artery reperfusion with thrombotic agents or after Percutaneous Transluminal Coronary Angioplasty (PTCA). Therefore the approach to inhibit platelet aggregation independent of the nature of platelet agonist, such as RGD containing peptide, may be helpful in these pathologies.

Integrilin is indicated for the prevention of early myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 24 hours and with ECG changes and/or elevated cardiac enzymes.

Patients most likely to benefit from Integrilin treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early PTCA (see also 5.1).

Integrilin is intended for use with acetylsalicylic acid and unfractionated heparin.

Integrilin is formulated as a sterile solution for intravenous (IV) injection in a single dose of 20 mg/10 ml vial, and as a sterile solution for IV continuous infusion in a single dose of 75 mg/100 ml vial. The recommended dose is an intravenous bolus of 180 µg/kg administered as soon as possible following diagnosis, followed by a continuous infusion of 2 µg/kg/min for up to 72 hours (96 hours in patients undergoing coronary angioplasty).

2. Part II: Chemical, pharmaceutical and biological aspects

Composition and product development

Composition: Integrilin is formulated as a buffered, sterile, aqueous solution for intravenous injection in a single dose of 20 mg vial of 10 ml, and for intravenous infusion in a single dose of 75 mg vial of 100 ml. The solution is hypotonic. The ingredients included are citric acid monohydrate and sodium hydroxide.

Containers: The primary package system is a Type I glass vial with grey bromobutyl closure and aluminium seals. This package was found to be compatible with the formulation in the ongoing long-term stability studies. The secondary package system is folding carton required to protect the drug from the light.

Clinical trial formula: Early clinical trials were performed with the 2 mg/ml formulation, with sodium citrate dihydrate instead of sodium hydroxide.

Development pharmaceutics: The active ingredient is a cyclic heptapeptid that has a molecular weight of 831.96. It is soluble in water, methanol and ethanol. Preformulation studies showed an optimum stability in the pH range between 5 and 6, and a citrate buffer for a pH range of 5.0 to 5.5 was chosen. The method of manufacture is dissolution of the ingredients in water, and a sterilisation by aseptic filtration. A terminal sterilisation by heat is not possible with this active ingredient. The final formulation is not oxygen-sensitive. It can be exposed to freeze-thaw conditions (3 cycles between -20°C and room temperature), or stored for up to 45°C for 3 days before use. The product does not

need to be protected from light during manufacture, packaging, distribution and administration (no change after one day exposure), but is adversely affected after 10 days of light exposure. The product should be kept in its secondary package. The pH specification of 5.0-5.5 at the recommended product storage condition is justified by a stability study of batches prepared at the lower and upper pH limits.

Manufacturing process: The vials are sterilised by dry heat and the stoppers by autoclaving. The drug substance is dissolved in 1M citric acid solution and diluted and adjusted for pH. In process control tests are performed on the bulk solution, which is then sterilised by filtration (0.22 µm membrane) into a collection vessel and then filled into vials. Membrane integrity tests are performed before and after filtration as an additional in process control measure.

Active substance

Eptifibatide is chemically synthesised and is a cyclic heptapeptide containing six aminoacids including one cysteine amide and one mercaptopropinonyl (desamino cysteinyl) residue. An EDMF on the active substance has been submitted. The proposed specification is acceptable.
The retest period is 24 months when stored in a freezer less than -15°C, and the results of stability studies support this.

Finished product

Specifications of the medicinal product: The controls on the finished product are comprehensive and include: clarity, colour, pH, identification / quantification of the active substance, particulate matter etc.
Stability of the medicinal product: Stability studies were performed under ICH conditions but with the 30°C stress condition in place of the normal 40°C condition. An increase of 1% of the total level of impurities has been observed during the storage for 36 months at 5°C. In general, the results after 36 months of storage show that the quality of the product is satisfactory.

Shelf life: 36 months when stored at 2 to 8°C. Protection from light is required.

In vitro drug compatibility studies have been performed with Integrilin and Nitroglycerin, Tissue Plasminogen Activator, Verapamil, Metoprolol, Heparin, Lidocaine, Midazolam, Morphine, Dobutamine, Atropine, Furosemide (incompatibility) and Meperidine.

3. Part III: Toxico-pharmacological aspects

Pharmacodynamics

The performed pharmacodynamic studies intended to confirm the role of platelet GP IIb/IIIa complex as a mediator of platelet aggregation in different models and to demonstrate the antithrombotic activity of eptifibatide.

Among the different species tested, only the Cynomolgus monkey had platelet GPIIb/IIIa affinity for eptifibatide identical to human. Even baboons and dogs, which were sensitive species, had a significantly lower GPIIb/IIIa affinity for eptifibatide.

The basis for selecting doses related to therapeutic efficacy and hemorrhagic risk was provided in the baboon, using the ex-vivo inhibition of platelet agregation as surrogate endpoint.

Seven pharmacodynamic studies were performed. One of them assessed the effects of eptifibatide on GPIIb/IIIa receptor binding and platelet aggregation (human platelets in vitro), whereas the antithrombotic activity of eptifibatide was assessed in two experimental models of thrombosis in vivo in six studies (species: baboon and dog): two studies were performed in baboon in order to assess the prevention of occlusion in the extracorporeal circulation and four studies were performed in dogs in order to assess coronary artery thrombosis.

Eight studies that were performed in guinea pig, rat, dog, pig, mouse and also in human smooth muscle cells in culture, suggest that eptifibatide is devoid of significant effect on Central Nervous System, cardiovascular, renal, gastrointestinal symptoms and immunological properties.

Two additional in vitro studies (in M21 human melanoma cells and in Human Umbilical Vein Endothelial cells) were performed in order to show specificity of Integrilin on platelet GP IIb/IIIa

receptors. The studies were designed to compare the inhibition of cell adhesion induced by eptifibatide to that of a reference substance specific of integrins, although the design did not allow direct comparison of eptifibatide concentration which inhibit platelet aggregation to the concentration which inhibits adhesion of these cells.

Two additional studies were performed on the ex-vivo inhibition of platelet aggregation. One study was performed in the baboon and the other in the baboon and in the dog. The ex-vivo and in vivo data from an experimental model of thrombosis demonstrate the dose-dependent and rapidly reversible effect of eptifibatide. The anti-thrombotic and anti-adhesion activity of the product was also demonstrated in the dog where eptifibatide exerted protective effects either on the reduction of flow after stenosis of the coronary artery or on the platelet number during cardiopulmonary bypass. In the dog, eptifibatide was also effective in a model of myocardial infarction, accelerating the rate of rt-PA-induced thrombolysis and reducing the reocclusion time.

Miscellaneous safety pharmacological studies performed as preliminary of eptifibatide, have been performed in rats and mice, suggesting that the compound is devoid of activity in a wide range of pharmacological tests on peripheral and central nervous system, on gastrointestinal activity and immunology. Eptifibatide did not cause significant lysis of human blood cells nor significant flocculation of plasma protein in human plasma. It is shown that eptifibatide did not affect myocardial contractility nor the cardiac metabolism in the isolated guinea pig heart and did not affect renal plasma flow and renal filtration in rats and dogs.

Pharmacokinetics

Eleven pharmacokinetic studies were performed: six of them were single dose and were performed in rat and monkeys, three were repeated administration and were performed in rat rabbit and monkey and two were in vitro studies in rat, rabbit, monkey and human plasma.

In *in vivo* studies, eptifibatide was poorly bound to rat, monkey and human plasma proteins (12-24%). In male rats, the plasma half life is about 11-12 min. Eptifibatide was cleared by biliary excretion and ultimately, was eliminated mainly by urine, with a lesser amount in the faeces as carbon dioxide. A significant amount was found only in liver and kidney. In pregnant rats, the highest concentrations following intravenous (iv) administration were observed in kidney, bladder, liver and intestinal tract.

Plasma and urine profile after iv administration in both rats and monkeys, showed that eptifibatide was extensively metabolised to the deaminated product and at least 3 more polar metabolites. The latter have not been tested for possible pharmacological activity.

Most drug-derived radioactivity was rapidly eliminated into bile and then excreted via the urine in rats and monkeys and about 8-14% was eliminated in faeces. In rats, about 12% of an iv dose resulted expired as carbon dioxide.

Toxicology

In vitro studies testing eptifibatide as an antagonist to the GP IIb/IIIa receptors demonstrated that platelets isolated from humans, non-human primates (Cynomolgus monkeys, baboon) and dogs, share a similar sensitivity to the receptor antagonists. Hence these preclinical data bear relevance to human especially the Cynomolgus monkey which was the animal species that was more useful in calculating a safety factor for human use (due to affinity for platelet GPIIb/IIIa receptor similar to human).

Single dose toxicity: the single dose toxicity has been evaluated in Sprague Dawley rats, in albino New Zealand rabbits and in Cynomolgus monkeys. Animals of both sexes were administered by intravenous infusion over 90 min and at several doses and were observed for 14 days. At the end of the observation period, terminal necropsy revealed no drug related gross pathological effects.

Repeated dose toxicity: a 14-day continuous intravenous toxicity study and a 28-day continuous toxicity study with a 14-day recovery period were performed in the rat and the Cynomolgus monkey. The single and repeated dose toxicity studies performed in rats and monkeys did not reveal target organs or toxicological signs different from those related to the exaggerated pharmacodynamic properties of eptifibatide, i.e. the anti-aggregatory action (haemorrhages).

Reproduction studies: fertility studies have been performed in female and male rats. Maternal and paternal reproductive parameters were unaffected. The foetal weights were not affected by the

treatment. Teratology studies have been performed in female pregnant rat and rabbit. The uterine, foetal resulted unaffected by the treatment.

Genotoxicity: the clinical use of eptifibatide is limited to short-term dosing, and it has been shown to be non-genotoxic in a standard battery of clastogenic and mutagenicity assays.

Carcinogenicity potential: carcinogenicity studies were not conducted: the short elimination half-life, the lack of accumulation in tissues and the short human therapeutic schedule preclude the conduction of such studies.

Local tolerance: eptifibatide did not cause vascular irritation after 15 min infusion in rabbits.

Special toxicity studies: it was found not to be antigenic in guinea pig nor induced delayed hypersensitivity in mice. No supplementary tests have been performed for neurotoxicity and behavioural toxicity.

4. Part IV: Clinical aspects

Introduction

The clinical database for this centralised application includes 20 clinical studies. Included among them are two phase III large-scale studies IMPACT II and PURSUIT. The proposed indication is supported mainly on the results of the PURSUIT study. In all studies, weight-adjusted intravenous administration of eptifibatide was chosen as an initial bolus injection followed immediately by continuous infusion to obtain a significant acute effect on platelet aggregation followed by maintenance or enhancement of effect over time. In most studies, eptifibatide was administered in combination with aspirin and heparin.

Clinical Pharmacology

The clinical pharmacology of eptifibatide has been evaluated in a total of 18 studies into which 565 subjects (135 women and 430 men) were enrolled. These included 168 enrolled volunteers, 9 subjects with impaired renal function and 388 patients hospitalised for the treatment of coronary artery disease. Additional results have been submitted from one large-scale study (PURSUIT), which includes 10,948 patients with UA or NQMI. Most Integrilin administration regimens in these studies included an intravenous bolus followed by a continuous intravenous infusion up to 96 hours. Bolus doses have ranged from 20-250 µg/kg while infusion rates have ranged from 0.2-3.0 µg/kg/min.

Pharmacodynamics

Mechanism of action: Eptifibatide, a synthetic cyclic heptapeptide containing six amino acids, including one cysteine amide, and one mercaptoproprionyl (desamino cysteinyl) residue, is an inhibitor of platelet aggregation and belongs to the class of RGD (arginine-glycin-aspartic acid)-mimetics. Eptifibatide reversibly inhibits platelet aggregation by preventing the binding of fibrinogen, von Willebrand factor and other adhesive ligands to the glycoprotein (GP) IIb/IIIa receptors.

Pharmacodynamic effects: The pharmacodynamic effects of eptifibatide were evaluated in four studies which correlate eptifibatide dose and plasma concentrations to the following: a) ex-vivo platelet aggregation induced by ADP or TRAP b) GP IIb/IIIa receptor occupancy using a Ligand-Induced Binding Site assay and c) simplate bleeding time. The data indicate that there is a dose dependent inhibition of ex vivo platelet aggregation and a dose dependent increase in platelet occupancy with eptifibatide and that there is a strong relationship between concentrations and inhibition of platelet aggregation or platelet-receptor occupancy. There is variability according to the type of measure (aggregation or membrane glycoprotein sites), the anticoagulant (citrate sodium or PPACK) or the agonist (ADP or TRAP).

The efficacy and safety of eptifibatide at a bolus dose of 180 µg/kg immediately followed by a continuous infusion of 2.0 µg/kg/min has been demonstrated in the PURSUIT trial. At this dosing regimen, platelet GP IIb-IIIa receptor occupancy (using PPACK-collected blood) was on average >78% immediately after the bolus and generally 80% during the continuous infusion (based on PERIGEE data, a substudy of PURSUIT). This degree of receptor blockade was associated with 90% inhibition of platelet aggregation immediately after the bolus and during 24-72 hours of continuous infusion. The degree of GP IIb-IIIa receptor occupancy and the degree of inhibition of platelet

aggregation was greater for blood collected in sodium citrate. However, the very low Ca^{++} concentrations associated with citrate anticoagulation have been shown to enhance the apparent inhibitory activity of eptifibatide and therefore data obtained using PPACK-collected blood are considered more appropriate. Although platelet aggregation studies in the PERIGEE study (as well as PRIDE) used both ADP and TRAP (Thrombin Receptor Agonist Peptide) as agonists, the results using ADP are considered more appropriate since they show a better concordance with the degree of platelet GP IIb-IIIa receptor blockade.

Regarding the simplate bleeding time, there is a dose and duration -dependent increase in healthy volunteers, which reaches approximately a 5-fold increase from baseline with a 2 µg/kg/min infusion. This observation is also generally supported by data from earlier studies, which also showed that eptifibatide administered alone or in combination with heparin had little or no effect on simplate bleeding time when given at low infusion rates (0.5 µg/kg/min) for short duration (90 minutes). The increase in bleeding time after eptifibatide administration is rapidly reversible on terminating the infusion.

Pharmacokinetics

Pharmacokinetics in healthy volunteers and in patients

The pharmacokinetic parameters of eptifibatide were evaluated in healthy volunteers in three studies. These studies show that eptifibatide plasma concentrations exhibited a bi-exponential decline with a distribution half-life of 10-22 min and with a terminal half-life of 1.1-2.4 hours. Eptifibatide is not extensively distributed. The apparent steady-state volume of distribution was 17-19 l whereas the central volume of distribution was 9 l. Eptifibatide is poorly bound to plasma protein (<39%). The total clearance of eptifibatide is 136-165 ml/min. The mean renal clearance ranges from 32-44 ml/min and accounts for 25-30% of the total clearance. The pharmacokinetics of eptifibatide is linear since the area under the curves and steady concentrations increase in a dose proportional manner across a range of IV bolus (90-180 µg/kg) and infusion (0.5-2.0 µg/kg/min) doses. The coefficient of variation of clearance was 15-20%.

(a) Special patient groups

The pharmacokinetic data in special populations were obtained from some specific studies and a phase III trial. In the latter study, a population pharmacokinetic approach (NONMEM program) was implemented to determine population clearance by using a single steady-state concentration determined in 1725 evaluable patients.

Age: The population pharmacokinetic study showed an inverse relationship of age and weight to the plasma clearance of eptifibatide. From 60 years of age, the model predicted a decrease in clearance by -5.3% for every decade. The slight trend of eptifibatide concentrations to increase with age does not necessitate adjusting the dose.

Renal impairment: Results of comparative study in patients with moderate renal impairment (n = 6 patients; 47.6 ml/min < Clcr < 59.4 ml/min) and age matched normal volunteers (n = 7 subjects, 72.3 ml/min < Clcr < 94.5 ml/min) did not demonstrate any significant difference between the two groups. In the population pharmacokinetic study, the model predicted a decrease of 4.6% in eptifibatide clearance for every 10 ml/min fall in creatinine clearance from 72 ml/min. Given the limited data available in patients with low creatinine clearance, eptifibatide is contra-indicated in patients with creatinine clearance < 30 ml/min.

Impaired liver function: No pharmacokinetic data are submitted in patients suffering from well-defined hepatic diseases. Eptifibatide is contra-indicated in patients with clinically significant hepatic impairment.

(b) Paediatric use:

Safety and efficacy in children and adolescents < 18 years of age have not been established. Therefore, use in patients younger than 18 years of age is not recommended.

(c) Interaction studies:

In phase I or phase II studies, the pharmacokinetic profile of eptifibatide indicated no evidence of a pharmacokinetic interaction with aspirin and/or heparin. In addition alcohol, amlodipine, atenolol,

atropine, captopril, cefazolin, diazepam, digoxin, diltiazem, diphenhydramine, enalapril, fentanyl, furosemide, heparin, lidocaine, lisinopril, metoprolol, midazolam, morphine, nifedipine, nitrates, warfarin and tobacco did not seem to affect eptifibatide clearance in the population pharmacokinetic study. Given the poor protein binding and the low therapeutic concentrations of eptifibatide there is no potential for drug interaction at the plasma protein binding sites.

d) Pregnancy and lactation:

No clinical studies with Integrilin have been conducted in pregnant women. Therefore, the use of Integrilin during pregnancy is recommended only if the benefit to the mother outweighs the potential risk to the foetus. It is not known whether Integrilin is excreted in human milk. Interruption of breast-feeding during the treatment period is recommended.

Clinical Experience

The clinical experience with eptifibatide comprises 20 separate protocols, including one pivotal phase III study PURSUIT, to support the claim that eptifibatide (Integrilin) is an effective adjunct to standard therapies in the prevention of the consequences of acute coronary ischemic events associated with unstable angina and non-Q-wave myocardial infarction. The IMPACT II study supporting the first submission in the prevention of ischemic cardiac complications in patients undergoing PCIs was performed at a lower dosing regimen (bolus of 135 µg/Kg following by a continuos infusion of 0.5 µg /kg/min for 20-24 hours) and was considered as non-acceptable by the CPMP in September 1996.

Efficacy

Description of the main study (PURSUIT) with regard to UA/NQMI

Design: This study was a 726-center, 27 country, double-blind, randomised, placebo-controlled study: 10,948 patients presenting with UA or NQMI were enrolled and among them 4680 were treated with the recommended dosing regimen of eptifibatide (180 µg/kg/2.0/µg/kg/min).

Population: Patients could be enrolled only if they had experienced cardiac ischemia at rest (lasting ≥ 10 min) within the previous 24 hours and had either ST segment changes or increased CK-MB above the upper limit of normal.

Conventional antithrombotic therapy: 90% of patients received heparin that was administered iv or sc at the physician's discretion. 93% of patients received ASA (75-325 mg once daily). The vast majority of patients received acetylsalicylic acid (75-325 mg once daily) and/or un-fractionated heparin (iv bolus of 5,000 U followed by a continuous infusion of 1,000 U/h), which was administered iv or sc at the physician's discretion.

Primary pre-specified endpoint: The primary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (evaluated by a blinded Clinical Events Committee, CEC) within 30 days of randomisation.

MI definition

MI after enrollment was defined by one or more of the following:

a) increase in CK-MB enzymes to a value greater than the upper normal limit and ≧ 3 % of total CK at the time of a known or suspected episode of myocardial ischemia and again 8 and/or 16 hours afterward, or

b) finding of new significant Q waves with duration ≥ 0.04 sec in at least two contiguous leads of an ECG obtained within 24 hours of a known or suspected episode of myocardial ischemia.

The CEC reviewed for occurrence of MI all cases identified by a «trigger program», which continually searched the database for any evidence of potential MI according to the above definition (eg, elevated cardiac enzymes even moderately, notation of MI by independent core ECG laboratory), including all cases identified by the investigators. These cases were thoroughly investigated by the CEC, which could have included requesting additional information from the site that might not have been available at the time the investigator completed the assessment of whether an MI had occurred.

In particular, the CEC adjudication included a formalised interpretation of MI as defined by changes in CK-MB or total CK, even in the absence of other signs or symptoms.

Treatments: Patients were randomised to one of three arms:

- placebo (n=4739),
- Integrilin 180 µg/kg bolus + 1.3 µg/Kg/Min continuous infusion (n=1487), or
- Integrilin 180 µg/kg bolus + 2.0 µg/Kg/ Min continuous infusion, (n=4722).

The infusion was continued: until hospital discharge, until the time of coronary artery bypass grafting, or for up to 72 hours, whichever occurred first. If PCI was performed, the Integrilin infusion was continued for 24 hours after the procedure, allowing for duration of infusion up to 96 hours.

Secondary endpoints

Other relevant endpoints (secondary endpoints) included occurrence of death/MI as assessed by the investigators at 30 days, death/MI in subsets of the patients (for example stratified by age), at earlier time points (for example 96 hours, 7 days), and in patients undergoing PTCA, among others.

A follow-up contact was to be arranged for 6 months after enrollment to allow assessment by the investigators of the long-term effects of treatment.

Events beyond 30 days were not adjudicated by the CEC, and MI was assessed by the investigators only in the interval after 30 days to 6 months.

Safety endpoints: Safety was assessed by the evaluation of:

a) bleeding complications (including haemorrhagic stroke), serious non-bleeding adverse events (including non-haemorrhagic stroke) and laboratory data collected during the initial hospitalisation

b) serious bleeding and non-bleeding adverse events reported at the hospital discharge and the 30 day visit and

c) occurrence of stroke between the 30-day visit and 6-month follow-up contact. The intensity of bleeding was mainly assessed according to the guidelines provided by the TIMI trials (Thrombolysis in Myocardial Infarction Trials):

- major bleeding was defined as any intracranial bleeding, or any other bleeding associated with decrease in haemoglobin ≥ 5 g/dl (or in hematocrit ≥ 15 percentage points)
- minor bleeding was defined as:
- Spontaneous gross haematuria or haematemesis
- Spontaneous or non-spontaneous blood loss associated with decrease in haemoglobin
- 3 g/dl and ≤ 5 g/dl (or in hematocrit ≥ 10 and ≤ 15 percentage points)
- decrease in haemoglobin ≥ 4 g/dl and ≤ 5 g/dl (or hematocrit ≥ 12 but ≤ 15 percentage points) with no bleeding site identified despite a search ;
- Insignificant bleeding was defined as any blood loss insufficient to meet the definitions above and by the number and nature of transfusions required.

Efficacy results

The results were. analysed in the «all randomised» (ITT), «treated as randomised» (including all patients who received any portion of a treatment regimen)and «as treated» populations.

The primary analysis was planned to be the «treated as randomised analysis».

Of the 10,849 patients treated, 4,697 were «treated as randomised» in the placebo group and 4,680 were «treated as randomised» in the eptifibatide 180/2.0 group.

The 2 groups placebo and eptifibatide 180/2.0 were well balanced regarding all baseline variables.

Compared to placebo, Integrilin administered as 180/2.0 significantly reduced the incidence of the primary endpoint events (table 1). This represents around 15 events avoided for 1000 patients treated:

Table 1
Incidence of Death/CEC-Assessed MI («Treated as Randomised» Population)

Time	Placebo	Integrilin	p-Value
30 days	743/4,697 (15.8 %)	667/4,680 (14.3 %)	0.034[a]
a: Pearson's chi-square test of difference between placebo and Integrilin.			

Mortality at 30 days was 3.8% (placebo) versus 3.5% (Integrilin). Thus results on the primary endpoint were principally attributed to the occurrence of MI.

The usual ITT analysis also showed statistical benefit.

Secondary endpoints:

Among them should be highlighted the following:

- The reduction in the incidence of endpoint events in patients receiving Integrilin appeared early during treatment (within the first 72-96 hours).
- This reduction was maintained through 6 months on the combined endpoint.

At 6 months, death or MI had occurred in 19.1 % of placebo-treated patients vs 17.8 % of eptifibatide-treated patients (p = 0.079), using the CEC definition of MI during the first 30 days, and 13.6 % vs 12.2 %, respectively (p = 0.028), using the investigator-assessed definition of MI throughout follow-up.

The results at 6 months were not qualitatively different from those observed at 30 days. The significant effect of eptifibatide was on the MI component of the composite endpoint. There was no effect on all causes mortality (299/4680, 6.4% in the Integrilin group vs 289/4697, 6.2% in the placebo group).

Although PTCA was a post randomisation event, it appears that for patients undergoing PTCA within 72 hours after randomisation, there was a 31% relative reduction in the incidence of the primary composite endpoint among those treated with eptifibatide as compared with placebo: 11.6% versus 16.7%, p=0.01. However, most of the Integrilin benefit occured prior to PTCA. Of note, there was only a 7% relative reduction among patients who did not undergo early revascularisation (14.5% versus 15.6%, p=0.23).

Post-hoc subgroup analysis:

The PURSUIT study was designed as a world wide clinical trial. The two largest regions North America and Western Europe contributed approximately 80% of the trial population. Special emphasis was made on analysis according to geographic region. Both subgroups were similar both in size (3,788 patients in Northern America vs 3,665 in Western Europe) and in the incidence of events in their respective placebo arms (15.1% vs 14.9%).

Although great caution should be brought to subgroup analysis, the greatest benefit appeared among North American patients.

One of the possible explanations could be difference in medical practice (i.e. higher rate of early revascularisation procedures in N America as compared to W. Europe).

Safety results:

a) Bleeding.

The incidence of major bleedings at 30 days in the Integrilin group was 10.8% versus 9.3% in the placebo group. The incidence for minor bleedings was 13.1% in the Integrilin group versus 7.6 %

in the placebo group. The incidence for serious bleeding was 16.6% in the Integrilin group versus 13.8% in the placebo group and for life threatening bleedings was 1.9% in the Integrilin group versus 1.1% in the placebo group. Drug infusion was discontinued because of bleeding in 8% in the Integrilin group versus 1% in the placebo group. Intracranial bleeding was extremely rare (0.1% with eptifibatide and 0.06% with placebo).

In the subgroup of patients undergoing PTCA major bleedings were observed in 9.7% of Integrilin patients versus 4.6% of placebo patients.

b) Non-Bleeding adverse events.

In PURSUIT, there was no difference between the two groups for serious adverse events. For non-serious adverse events, only the incidence of fever was higher in the PURSUIT group (1.0% placebo versus 1.6% eptifibatide). In IMPACT II, the only difference between the two groups for serious adverse events was nausea/vomiting that was slightly higher for Integrilin. For non-serious adverse events, back pain, injection site reaction and hypotension occurred more frequently in the Integrilin group than in the placebo group. Of potential concern among these events is the possible excess of thrombocytopenia observed in PURSUIT and in IMPACT II, 0.24% versus 0.06% and 0.6% versus 0.1% respectively.

The main issues addressed during the CPMP meeting of February 1999, were the following:

1. the clinical relevance of the benefit observed with eptifibatide in the overall population of the PURSUIT study was questionable in view of :

- the small difference in outcome between the two groups (15 non-fatal MI and/or all causes death avoided for 1000 patients treated)
- the definition of Myocardial Infarction (MI) (possible asymptomatic cardiac enzyme elevation);
- the lack of benefit (at least a positive trend) for all cause mortality with eptifibatide at 1 and 6 months

2. sub-groups analysis that highlights inconsistency in the efficacy results :

- small benefit in the medically-managed population for UA/NQMI;
- small benefit in the Western Europe population;
- concerning the first issue the following data have been provided and have been considered as acceptable:
- Consistency between diagnosis of MI by Investigators and by the CEC

Table 2: Incidence of Death/MI at 30 Days

Definition of MI	Placebo	Eptifibatide	P value
CEC	743 (15.8%)	667 (14.3%)	0.034
Investigator & CEC adjudicated	422 (9.0%)	338 (7.2%)	0.002
Investigator Assessed MI	476 (10.0%)	380 (8.1%)	0.001

All investigator-identified Myocardial Infarctions (MIs) were reviewed by the CEC. For each of the definition the subsequent 1 month and 6 month mortality data are provided. MI identified by the CEC alone was associated with at least 2-fold lower mortality compared with patients for whom MI was confirmed only by the Investigator or by the investigator and the CEC (Table 3).

Table 3: Incidence of Death at 1 & 6 Months

(1) Investigator / CEC Diagnosis of MI			Mortality	
Investigator	**CEC**		**1 month**	**6 month**
NO	NO	9,366	1.7%	3.8%
NO	YES	816	7.2%	12.6%
YES	NO	167	24%	26.3%
YES	YES	599	22%	27.7%

Regarding CK-MB elevation, and in order to validate further the importance of all grades/sizes of MI, 1-month and 6-month mortality data was based on peak CK-MB after randomisation. (Table 4)

Both 1-month and 6-month mortality are proportional to peak CK-MB. For instance, 7.4% mortality rate at 1-month and 10.6% rate at 6-months when CK-MB>5N.

Table 4: Incidence of Death at 1 & 6 Months

Peak CK-MB	**1 Month**	**6 Months**
≤ 1 x ULN	2.1%	4.3%
> 1 – 2 x ULN	3.2%	6.0%
> 2 – 3 x ULN	4.2%	8.3%
> 3 – 4 x ULN	4.7%	6.8%
> 4 – 5 x ULN	5.3%	8.0%
> 5 x ULN	7.4%	10.6%

ULN = Upper Limit of Normal

To further examine the validity of the CEC process a series of outcome analyses have been carried out using different definitions of MI (Table 5) based on CK-MB or CK levels at the time of the episode. This includes the definition of a MI (> 2x ULN & 3% of total CK). CK-MB or CK levels reported are those reported at the time of a known or suspected episode of ischemia that was adjudicated as an event (enrolment MIs are excluded).

This analysis reveals a consistent treatment effect for eptifibatide, whatever definition of MI was used. There was an absolute 1.5% event reduction (vs placebo) in patients with an elevated CK or CK-MB, but no treatment effect in patients without an elevated CK or CK-MB by these criteria.

Table 5: Incidence of Death/MI at 30 Days

Diagnostic Criterion of MI	Placebo		Eptifibatide	
CK-MB				
> 2 x ULN & > 3% of total CK	487	(10.3%)	414	(8.8%)
All Others	258	(5.4%)	258	(5.5%)
> 2 x ULN	503	(10.6%)	429	(9.1%)
All Others	242	(5.1%)	243	(5.1%)
Total CK				
> 2 x ULN	471	(9.9%)	397	(8.4%)
All Others	274	(5.8%)	275	(5.8%)

ULN = Upper Limit of Normal

Kaplan-Meier curves for each separate end-point "death" and "MI" have been (based on treated as randomised population). Each of these analyses revealed a favourable treatment effect for eptifibatide.

Subgroup analysis

Since the power of the study was based on the overall population there is no surprise that the advantage observed in the trial population was no more apparent in some subgroups. However the applicability of the PURSUIT trial results to the Western Europe population was a concern expressed by several Member States also in view of the consistent apparent lack of effect in patients not undergoing PTCA who were over represented in the European population.

5. Overall conclusions and benefit/risk assessment

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Preclinical pharmacology and toxicology

Pharmacological experimentation has been adequately performed to demonstrate the antithrombotic effect of Integrilin and its mechanism of action. *In vitro* binding and anti-aggregatory tests demonstrated the antiplatelet activity of Integrilin. *In vivo* pharmacology studies were carried out in several animal species and models.

Single and repeated dose toxicity studies, performed in rats and monkeys, did not reveal target organs or toxicological signs different from those related to the exaggerated pharmacodynamic properties of eptifibatide, i.e. the antithrombotic action (haemorrhages).

Overall the toxicological programme is considered satisfactory.

Efficacy

- The target population of PURSUIT well represented patients suffering from UA/NQMI.
- The pre-specified primary endpoint (combined endpoint non-fatal MI and/or causes death) is considered as a hard endpoint. The timespan (30 days) is valid.
- The results show a reduction of death/CEC-adjudicated MI from 15.8% (placebo) to 14.3% (Integrilin). It represents around 15 events avoided for 1000 patients treated.

- All degrees of enzyme elevation were associated with an increased mortality rate at 1 and 6 months. The maximal effect of Integrilin was obtained within the first 72-96 hours and was sustained within the following 6 months.
- There was no significant effect of eptifibatide on mortality at 1 month and 6 months.
- Since the power of the study was based on the overall population there is no surprise that the advantage observed in the trial population was not apparent in some subgroups.
- However the applicability of the PURSUIT trial to the Western Europe population was a concern expressed by several Member States also in view of the consistent apparent lack of effect in patients not undergoing PTCA who are over represented in the European population.

Considering the above and the magnitude of the overall benefit (e.g. small difference between the two groups on the primary endpoint driven by the reduction of early MI incidence), the CPMP considered that high-risk patients could benefit more from the Integrilin treatment.

Safety

The major complication of Integrilin treatment is bleeding.

Whatever the definition of bleedings is, there were more bleeding complications in the eptifibatide group, with 10.8% versus 9.3% major bleedings and 13.1% versus 7.6% minor bleedings. Similarly, transfusions were more common in the eptifibatide group 11.8% versus 9.3% in the placebo group. However, intracranial bleeding was extremely rare (0.1% with eptifibatide and 0.06% with placebo).

The PTCA population was exposed to increased risk of major bleeding: 9.7% of Integrilin patients versus 4.6% of placebo patients

Benefit/risk assessment

The results of the PURSUIT study indicate a significant, though small, benefit of Integrilin in patients with UA or NQMI as enrolled in PURSUIT regarding the prevention of death and/or MI (when considered as cumulative endpoints). However there was a lack of Integrilin benefit mortality at 6 months.

This result is consistent with a recent meta-analysis published on the GP IIb/IIIa receptor antagonists (reference David F. Kong et al., Circulation 1998: 2829-35).

Although the haemorrhagic complications are the major safety concern, treatment with Integrilin reportedly did not increase fatal or non-fatal intracranial haemorrhage or haemorrhagic stroke.

Based on the available data on quality, safety and efficacy, the CPMP is of the opinion that the benefit/risk profile of Integrilin for the prevention of early MI in patients presenting with unstable angina or non-Q-wave myocardial infarction is considered to be positive.

Referral of the application to the EMEA for further consideration of a question of scientific and technical nature in accordance with Article 10 (3) of Council Regulation (EEC) No 2309/93

On 11 May 1999 the European Commission informed the EMEA that in accordance with Article 10 (3) of Council Regulation (EEC) No 2309/93, the decision making procedure had been suspended following the written observations on the draft decision submitted on 09 April 1999 to the Standing Committee, which in the opinion of the European Commission raised a question of scientific and technical nature. The European Commission referred the application back to the EMEA for further consideration at the May 1999 CPMP meeting.

The question related to the wording of the first sentence of section 4.1 of the SPC (Therapeutic indication): “Integrilin is indicated for the prevention of early new myocardial infarction”. Written observations indicated that the word “new” could be considered as confusing by the potential prescribers since they could think that the product should not be used in the absence of a “previous” myocardial infarction. However, in the PURSUIT trial that is the basis of the Integrilin submission the majority of the patients did not present in the distant past (e.g.history of the patient) or in the immediate past (e.g. at randomization) a myocardial infarction (68% and 55% respectively). Therefore the CPMP considered that the wording “Integrilin is indicated for the prevention of early new

myocardial infarction" needed to be replaced with "Integrilin is indicated for the prevention of early myocardial infarction".

Following transmission of the CPMP's reply to the European Commission on 20 May 1999, the Standing Committee on Medicinal Products for human use recommended the revision of section 4.1 (Therapeutic indication) of the SPC for Integrilin as following:

"Integrilin is indicated for the prevention of early myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 24 hours and with ECG changes and/or elevated cardiac enzymes.

Patients most likely to benefit from Integrilin treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early PTCA (see also section 5.1).

Integrilin is intended for use with acetylsalicylic acid and unfractionated heparin."

rather than the original description:

"Integrilin is indicated for the prevention of early new myocardial infarction in patients presenting with unstable angina or non-Q-wave myocardial infarction with the last episode of chest pain occurring within 24 hours and with ECG changes and/or elevated cardiac enzymes.

Patients most likely to benefit from Integrilin treatment are those at high risk of developing myocardial infarction within the first 3-4 days after onset of acute angina symptoms including for instance those that are likely to undergo an early PTCA (see also section 5.1).

Integrilin is intended for use with acetylsalicylic acid and unfractionated heparin."

6. ESPRIT trial

Introduction

The MAH applied for a new indication in patients undergoing non-urgent PCI with intracoronary stenting for the prevention of death, MI, urgent revascularisation and the need for acute antithrombotic rescue therapy. A new dosage has been developed for this patient population, namely a double IV bolus of 180 µg/kg with a continuous IV infusion of 2.0 µg/kg (180/2.0/180), instead of the currently recommended dosage (180/2.0). This application is supported by the published ESPRIT study (Enhanced Suppression of Platelet GPIIb-IIIa Receptor with Integrilin Therapy).

Percutaneous coronary intervention (PCI) has become a dominant approach for the correction of symptomatic coronary artery disease, and the widespread use of intracoronary stents has improved different outcomes in this setting. PCI with stenting reduces the need for repeat revascularisation at a later date. As a result of these technological advances and clinical findings, intracoronary stenting is used in approximately 70-80% of PCI cases worldwide.

Platelets play a critical role in the development of ischaemic complications following PCI. The disruption of the atherosclerotic plaque and deep vessel injury resulting from the mechanical dilation of the stenosed coronary artery by the angioplasty balloon and metallic stent stimulate the platelet cascade (adhesion, activation, and aggregation), leading to intracoronary thrombosis. The generation and release of the potent platelet agonists - thrombin, adenosine diphosphate (ADP), and thromboxane A2 - induces activation and conformational changes of the platelet GPIIb-IIIa receptors. This results in fibrinogen cross-linking and platelet aggregate formation. The end result of this process is a growing thrombotic mass composed of platelets, fibrin, and blood cell components that obstruct coronary blood flow.

Six randomised, placebo-controlled clinical trials of GPIIb-IIIa inhibitors as adjunct to PCI define our current knowledge regarding the role of such compounds in this setting. These trials comprise the positive EPIC, EPILOG, CAPTURE and EPISTENT trials carried out with abciximab (Reopro), and the questionable IMPACT II trial with carried out with eptifibatide. The most recent of these studies, EPISTENT, mainly conducted in a high-risk population (73%), directly and successfully addressed the

issue of whether the addition of a GPIIb-IIIa receptor inhibitor improves outcomes in patients undergoing intracoronary stenting during PCI. As a result, a major extension of the indication in PCI with stenting was granted through a Mutual Recognition Procedure for the reference drug Reopro**.** Of note, the Reopro studies were essentially performed in acute (high-risk) medical conditions (e.g. PCI or PTCA for unstable angina, MI…).

Despite the promise of improved clinical outcomes using GPIIb-IIIa inhibitors during PCI and stenting, the use of a GPIIb-IIIa treatment strategy has not yet been uniformly adopted as the standard of care in the catheterisation suite. Several challenges appear to have limited universal adoption, most notably safety considerations (primarily bleeding), the optimal dose selection of a GPIIb-IIIa inhibitor during PCI and the perceived lack of a need for GPIIb-IIIa inhibition in combination with a thienopyridine. This situation prompted an additional and conclusive evaluation of PCI with intracoronary stents using a GPIIb-IIIa inhibitor in addition to the current standard pharmacological administration of heparin + aspirin (ASA) + a thienopyridine. This was the basis for the ESPRIT trial, focusing on non-urgent (elective) PCI performed on chronic stable or subacute conditions.

Clinical aspects

In addition to the data on the ESPRIT trial, the Applicant has submitted a comparative analysis of the methods used in ESPRIT versus EPISTENT (a trial carried out with abciximab), and an analysis of published literature on cardiac enzyme elevation prognosis after PCI.

The ESPRIT Study:

Trial design

The ESPRIT study was a multicentre (92 centres USA/Canada), randomised, double-blind, parallel group, placebo-controlled trial evaluating the efficacy and safety of eptifibatide therapy in non-urgent PCI with stent implantation in native coronary vessels. The patient population represented a mix of patients recovering from an ACS and those with stable coronary disease. ESPRIT applied to "routine" PCI performed under chronic stable or sub-acute medical conditions, in accordance with the present state of the art (e.g. with stenting and ASA plus clopidogrel or ticlopidine combination, simplified regimen of unfractionated heparin with short duration of administration, small sheath size 6 – 7 French). All patients received an initial bolus of 60 UI/kg of unfractionated heparin adapted to a target ACT 200-300 sec and ASA (162-325 mg/day). Heparin infusion after PCI was strongly discouraged. An adjunctive thienopyridine therapy with either ticlopidin 250 mg bid or clopidogrel 75 mg qd was encouraged following stent implantation, according to common practice.

An independent committee called the Data Safety and Monitoring Committee (DSMC) was responsible for reviewing the progress of the trial at regular intervals to ensure patient safety and trial integrity.

Choice of dose regimen

The eptifibatide dose regimen proposed for the new indication is the one used in the ESPRIT study and is based on a modelling approach. Early preclinical data had shown that 80% occupancy of the platelet GPIIb/IIIa receptor population (ROC 80) was required to establish patency and prevent reocclusion. The human pharmacodynamic studies PRIDE and PERIGEE provided information on the relationship between the ROC 80 and the plasma concentration in patients. Using these results, a pharmacokinetic/pharmacodynamic relationship was modelled, confirming that ROC 80 was achieved when the concentrations exceeded the threshold of 1650 ng/ml. However, the single-bolus regimen resulted in a transient decrease in drug concentration below the threshold level during the early administration window, suggesting the need for higher eptifibatide concentrations during the critical periprocedural period when device deployment occurs and the stimulus for thrombogenesis is greatest. A sub-study of PRIDE was then conducted with a 180/90 double bolus 10 or 30 minutes apart plus 2.0 µg/kg infusion. The results showed that a larger second bolus would be needed. It was then predicted that the 180/2.0/180 regimen would give satisfactory results.

Trial endpoints

The pre-specified primary objective was to determine whether eptifibatide was able to reduce the incidence of the quadruple clinical composite endpoint of death, myocardial infarction (MI), urgent target vessel revascularisation (UTVR) and thrombotic "bail-out" (TBO) GPIIb/IIIa inhibitor therapy assessed at 48 hours, compared to placebo. The key secondary efficacy endpoint was a triple composite endpoint (death, MI and UTVR) evaluated at 30 days. Other secondary endpoints included the quadruple composite at 30 days, the double composite death/MI at 48 hours and 30 days and the quadruple and triple composite endpoint as assessed by investigators (before adjudication) at 48h and 30 days. The follow-up was limited to 30 days in the ESPRIT study. The independent Clinical Events Classification Committee (CEC) was responsible for adjudicating suspected endpoint events according to pre-defined criteria. Events identified for adjudication were as follows: ambiguous CK-MB core laboratory data; post-procedural abrupt closure identified on the CRF; MI identified on the CRF; repeat PCI identified on the CRF; coronary artery bypass grafting identified on the CRF and episodes of 'bail-out' identified as thrombotic on the CRF.

Details of the individual components of the efficacy endpoints were as follows:

1. death (all-cause mortality and the cause of death was not adjudicated)

2. myocardial infarction: identified as either "enzymatic" or "adjudicated"

- enzymatic MI: identified by the CK/CK-MB Core laboratory criteria corresponding to at least two CK-MB Core laboratory values ≥ 3 fold the upper limit of "normal" (with at least a 25% increase in CK-MB if the last pre-randomisation value was above the upper limits of normal), within 24 hours after the index PCI procedure. Specimens for creatine kinase (CK) and creatine kinase-MB Fraction (CK-MB) were obtained within 4 hours before drug administration and at 6, 12, 18, and 24 hours after the initiation of eptifibatide administration and were processed by a blinded core laboratory. Investigators were not given access to these results. The enzymatic MI was not adjudicated by the CEC.
- adjudicated MI**:** investigators were encouraged to collect the following information when they suspected an MI: ischaemic symptoms (i.e. chest pain), ECG changes and cardiac enzymes. The validation process by the CEC was only undertaken in one of 3 situations: i) the investigator reported an MI on the case-report form, ii) the patient was being reviewed for another event and the CEC noted that the patient had, in addition, an enzymatic MI, or iii) the patient did not meet the definition (i.e. two post-PCI enzymes ≥ 3 ULN). This review resulted in a conclusion that either an event had (adjudicated MI) or had not occurred. The follow-up was limited to 30 days.

3. UTVR: events identified by the Investigator on the CRF that were confirmed by the CEC as urgent and in the target vessel.

4. Adjudicated TBO GP IIb/IIIa inhibitor therapy: episodes of 'bail-out' identified by the Investigator as thrombotic on the CRF (e.g., abrupt closure, no reflow, visible thrombus) and confirmed as thrombotic by the CEC. All other 'bail-out' usage was adjudicated as being non-thrombotic. This 4th individual outcome is specific to the ESPRIT trial when compared to the previously mentioned trials with abciximab.

Additionally, the study evaluated the safety profile of the double bolus regimen of eptifibatide in this setting, in particular the following key safety endpoints: incidence of bleeding (GUSTO and TIMI classifications), serious unexpected adverse events, the occurrence of thrombocytopenia and the need for blood product transfusion.

Statistical considerations

The sample size for the trial was based on the key secondary efficacy endpoint, and required approximately 1200 patients per treatment group. No interim efficacy analysis of the data was planned, only two protocol-specified safety reviews (after 500 and 1400 enrolled patients). There was, however, the provision to allow the DSMC to review the efficacy data, if necessary, to examine the risk/benefit ratio to safeguard patients' welfare. For this purpose, the protocol defined an α level of 0.0001 associated with each look at efficacy data. The final analysis would then be conducted at the

significance level of $\alpha = 0.05 - k \times (0.0001)$, where k is the number of times that the DSMC sees efficacy results by treatment group.

All summaries and analyses were performed on the intent-to-treat population i.e. the population of patients who received any study medication, regardless of whether PCI or coronary stenting was performed. All tests were two-sided and performed at α=0.05 significance level. Each of the endpoints was analysed via the use of a χ^2 test without continuity correction.

Results

The ESPRIT study enrolled a total of 2064 patients, of which 72.8% were men with a mean age of 62 years and a mean weight of 85.8 kg. Risk factors for cardiovascular disease (hypertension, diabetes, hypercholesterolemia, and smoking) were common and well balanced between the treatment groups. The patient population represented a mix of patients with both well established (previous history of MI 31.6%, PCI 23.4% and CABG 10.2%) and those with no previous history of coronary vascular disease.

Early stopping decision

Due to the slow enrollment rate (approx. 50% of predicted), the DSMC decided to review the efficacy data with the intention of stopping the trial early in case of an overwhelming treatment benefit. Two tables were reviewed, one with 48-hour data and one with 30-day data, including the primary and key secondary composite endpoints, as well as the individual outcome components of these endpoints by treatment. Statistical significance of the primary endpoint was not achieved ($p = 0.0048$ at $\alpha = 0.0001$). However, it was pointed out that the study was > 99% likely to have a positive outcome if taken to completion. A second interim efficacy analysis was thus planned based on clinical considerations, in the belief that continuing a study with an overwhelming treatment benefit was not consistent with the DSMC's charter. Instead of the protocol-defined primary endpoint (D/MI/UTVR/TBO), the DSMC opted for a composite endpoint of death and MI at 48 hours as the primary endpoint for their efficacy analysis, since death and MI constitute irreversible clinical injury. It was also decided that the second look at the efficacy data would be planned with α=0.005 (as opposed to α=0.0001), to be more in line with stopping rules used for similar studies, especially since the new proposed composite endpoint (D/MI) was composed of 'harder' outcomes.

Efficacy

The trial was prematurely discontinued at 2,064 patients for alleged overwhelming efficacy based on an unplanned interim efficacy analysis.
Overall, the trial showed a significant reduction in the quadruple endpoint at 48 hours.

	Placebo N = 1024	**Eptifibatide N = 1040**	**% Reduction Relative/Absolute**	**p-value**
Primary Endpoint (Death/MI/UTVR/TBO At 48 hours)	108 (10.5%)	69 (6.6%)	37% / 3.9%	0.0015
Death	2 (0.2%)	1 (0.1%)	51% / 0.1%	0.5544
MI enzymatic (n) adjudicated (n)	92 (9.0%) 80 12	56 (5.4%) 47 9	40% / 3.6%	0.0015
UTVR	10 (1.0%)	6 (0.6%)	41% / 0.4%	0.3006
TBO	22 (2.1%)	10 (1.0%)	55% / 1.2%	0.0291

There was a 37% relative reduction in the primary composite endpoint in patients treated with eptifibatide. The results on individual outcomes were consistent but most of the benefit was due to reduction in the incidence of MI (5.4% vs 9.0%), especially the enzymatic component (80/92 eptifibatide vs. 47/56 placebo), with a low contribution of clinical MI (i.e. CEC-adjudicated). Indeed, of the 127 enzymatic MIs detected at 48h, 87 were pure enzymatic elevations without any clinical or ECG data available in the CRF.

The incidence of enzymatic MI did not increase at 30 days (n= 127 as well), suggesting that the risk of elevated enzyme release was increased in the context of the procedure (angioplasty). As expected, early death incidence was extremely low (overall 3 patients). Complementary analyses at 12h, 24h, 7 days and 30 days demonstrate that the treatment benefit with eptifibatide was apparent within 12 hours. The early treatment benefit seems to be maintained through the 30-day observation period of the study.

Statistical significance was also achieved when considering the double combined endpoint (death/MI) favoured by the DSMC, as shown below:

Death/MI	**Placebo N = 1024**	**Eptifibatide N = 1040**	**% Reduction Relative/Absolute**	**p-value**
48 hours	94 (9.2 %)	57 (5.5 %)	40% / 3.7%	0.0013
30 days	104 (10.2 %)	66 (6.3 %)	38% / 3.8%	0.0016

Regarding the key secondary endpoint, a significant relative reduction of 35% was observed, as shown in the table below:

	Placebo N = 1024	**Eptifibatide N = 1040**	**% Reduction Relative/Absolute**	**p-value**
Death/MI/UTVR at 30 days	107 (10.4 %)	71 (6.8 %)	35% / 3.6%	0.0034
Death	6 (0.6 %)	4 (0.4 %)	34% / 0.2%	0.5102
MI enzymatic (n) adjudicated (n)	99 (9.7%) 80 19	64 (6.2 %) 47 17	36 % / 3.5%	0.0031
UTVR	17 (1.7 %)	11 (1.1%)	36% / 0.6%	0.2368

It should be noted however, that the reduction observed with the quadruple composite endpoint and the triple composite endpoint of events as assessed by the investigators (before adjudication) were not statistically significant at 48h or 30 days. Overall the data confirm the initial results that no major divergence is observed beyond the first 24 hours, where 90 % of the events corresponding to the main end point occurred.

Long term follow-up data and data on the composite death/large MI

Following CPMP concerns regarding the clinical relevance of the reduction in the incidence of post-PCI enzymatic MI and death based on a 1-month follow-up, the MAH provided additional **retrospective** information on long-term (6-month and 1-year) follow-up, and on the incidence of the composite death/large MI (defined by increase in CK-MB > 5 ULN). These data were accrued mostly after the time the initial report was filed. Complete clinical data through 6 months and 12 months were available for 1980 (95.9%) and 1964 patients (95.1%) out of 2064, respectively. In addition, vital status (i.e. whether dead or alive) on 2042 and 2024 patients was also available. Additional data on diabetic patients were also obtained, including whether they were treated with diet alone, oral hypoglycaemic agents or insulin.

The following table compares the results for the different endpoints at various time points post administration.

Comparative incidences of identified major endpoints at 48h, D30, 6 months and 1 year in ESPRIT				
Total patients 48h / D30 : n=2064 6 mths : n= 2042 1 yr : n= 2024	**Placebo (n/%)** 48h / D30 : n=1024 6 mths : n= 984 1 yr : n= 976	**Eptifibatide (n/%)** 48h / D30 : n=1040 6 mths : n= 1027 1 yr : n= 1017	**% Reduction Relative/Absolute**	**P value**
Death/MI				
48h	94 (9.2)	57 (5.5)	**40** (3.7)[a]	**0.0013**
Day 30	104 (10.2)	66 (6.3)	38 (3.8)	**0.0016**
6 months	117 (11.5)	77 (7.4)	40 (4.1)	**0.0015**
1 year	126 (12.4)	83 (8.0)	43 (4.4)	**0.001**
Death				
48h	2	1	1	NS
Day 30	6	4	2	NS
6 months	14 (1.4)	8 (0.8)	6	NS (0.187)
1 year	20 (2.0)	14 (1.4)	6	NS (0.280)
MI				
48h	92 (9.0)	56 (5.4)	**40** (3.6)[b]	**0.0015**
Day 30	99 (9.7)	64 (6.2)	**36 (**3.5)[c]	**0.0031**
6 months	106 (10.4)	72 (7.0)	34 (3.4)	**0.0047**
1 year	109 (10.7)	74 (7.2)	35 (3.5)	**0.0040**
Death/ large MI as defined by an increase in CK-MB : 5 ULN				
48h	~~5.1%~~**. Not available**	~~3.4%~~ **Not available**	~~1.7%~~ **-**	~~0.0528~~ **-**
Day 30	5.5%	3.7%	1.8%	**0.048**
6 months	Not available	Not available		
1 year	Not available	Not available		
Death/MI/(U)TVR				
Day 30 (TVR)	10.4%	6.8%	35(3.6)	0.0034
6 months (TVR until D30 /UTVR thereafter)	187 (18.5%)	146 (14.3%)		0.0072
1 year (id)	222 (22.1%)	178 (17.5%)		0.0068
(U)TVR				
6 months (id)	96 (9.7)	88 (8.7)	8 (1.0)	0.4676
1 year (id)	129 (13.1)	117 (11.7)	12 (1.4)	0.3505

There is no significant effect on 1-year mortality (p=0.28), but a trend in favour of eptifibatide. The corresponding figures are very low (20 placebo and 14 eptifibatide). Thus, as observed with the 30-day data, the significance of the different composites is driven by the eptifibatide-induced reduction in MI. Very few supplementary MIs occurred between 48h and one year, and new incidences were almost identical in each group [+15 between 48h and day 30 (7 placebo group and 8 eptifibatide, and + 20 between day 30 and one year (10 in each treatment group). MIs identified beyond 30 days are not solely enzymatic any longer, but were linked to a clinical event. However, in view of the few supplementary MIs identified between day 30 and 1 year, this does not influence the overall results. It should be noted that the eptifibatide-induced absolute reductions in MI were similar at 48h, 30 day, 6 month and one year, and so the corresponding relative reductions slightly decrease over time as the number of occurrences slightly increases.

Post-hoc subgroup analyses

The statistical methodology specified in the protocol did not include any analysis of subgroups. However a number of subgroup analyses were performed for the planned and post-hoc endpoints. The most salient observations are:

- Correlation between the observed peri-procedural CK-MB increase and the incidence of one-year clinical events:

*17(56.7%) of documented deaths occurred in patients without peri-procedural elevation of CK-*MB, and 13 (43.3%) of documented deaths occurred in patients with CK-MB elevation (4 out of 34 with missing CK-MB values**).**

- Incidences of 6-month and one-year clinical events as identified by investigators on CRFs in ESPRIT:
  When clinical events beyond Day-30 (where MI were computerised assessments of increases in CK-MB > 3 ULN) are identified by investigators as clinical MI, no endpoint is statistically significant any longer. The benefit of Eptifibatide is thus restricted to the prevention of peri-procedural increases in CK-MB, as assessed at 48h. Hence, the few further MI that occurred between one month and one year (10 in each treatment group) provided significant between-group differences at 6 months and 1 year, when CEC adjudicated the event (adjudication on the basis of enzymatic elevations only was possible), but no longer significant between-group differences at 6 months and one year, when considering the clinical events as identified during the 6- and 12-month follow-up by principal investigators in the CRFs.
- The patient population experiencing the greatest treatment benefit comprises the sickest patients, i.e. UA/NQMI, recent MI.

Safety

All patients enrolled in the study were included in the safety analyses. No unexpected side effects were reported. Between-treatment group comparisons were performed on bleeding rates and transfusion rates using a χ^2 test without continuity correction. No formal statistical analyses were planned for the other safety parameters.

Bleeding

As with other GP IIb/IIIa inhibitors, the most common complication of eptifibatide administration was bleeding. Regardless of the definition (TIMI or GUSTO), there were about 3 times more major bleedings in the eptifibatide group (1.3 % vs 0.4 % in the control group). The most common site of major bleeding was at the arterial access site. The incidence of intracranial bleedings appeared low, with a total number of 3 (2 eptifibatide vs 1 placebo). Minor bleedings (TIMI criteria), including femoral artery access and haematuria, were 2.4 % in the eptifibatide group vs 1.8 % in the placebo group. The number of patients requiring transfusion of red blood cells was very small (1.0 % placebo vs 1.4 % eptifibatide).

98% of patients received a thienopyridine concomitantly, mainly clopidogrel (75 mg/d), and 53% of them were pre-treated with clopidogrel before entering the cath lab, of which 88% received at least 300 mg loading dose. A post-hoc analysis requested by CPMP, showed that 48-hour TIMI major bleedings were higher in eptifibatide-treated patients who received a loading dose of clopidogrel prior to entry into the catheter laboratory [6 (1.3 %) eptifibatide vs. 1 (0.2%) placebo], compared with those who did not receive a dose at that time [3(0.7 %) eptifibatide vs. 2(0.5%) placebo]. The investigators' assessment of GUSTO for both frequency and severity of bleedings paralleled the TIMI results: 2 (0.4%) eptifibatide vs. 2 (0.4%) control for pre-treated patients, compared to 2 (0.4%) eptifibatide vs. 2 (0.4%) control for non pre-treated patients. However, the results were comparable for the frequency of TIMI minor bleeds, and the need for transfusions.

Deaths

The overall number of deaths within the 30-day follow-up period was 10 (0.4% eptifibatide and 0.6% placebo).

Other (non-bleeding) serious adverse events were distributed similarly between the eptifibatide and control patient groups. Thrombocytopenia of < 100,000/mm^3 occurred in 13 patients, of which 11 (7 eptifibatide vs. 4 in the control group) had moderate thrombocytopenia (50,000 to 100,000/mm^3). Two patients in the eptifibatide group had profound thrombocytopenia (nadir platel count < 20,000/mm^3). In neither case was a platelet transfusion required nor were there any clinical sequaelae of the thrombocytopenia. Thrombocytopenia was rapidly reversed with simple discontinuation of drug.

Discussion

Efficacy

No formal dose finding phase II studies were performed prior to the initiation of ESPRIT.

The primary endpoint is different from the primary triple composite endpoint (death/MI/urgent revascularization) evaluated at 30 days used in other clinical trials of GP IIb/IIIa inhibitors in the setting of PCI (EPIC, EPILOG, CAPTURE and EPISTENT with abciximab and IMPACT II with eptifibatide). Moreover the primary follow-up was shortened from 30 days to 48 hours, although the study had been powered on a 30-day evaluation. Regarding the individual components of the endpoint, the TBO component is rather "soft" and may depend on both subjective judgements of the investigators and available facilities. The UTVR component is also a "soft" endpoint, since "urgent revascularization" is difficult to define and depends on local use patterns and available facilities, although the double blind nature of the trial should balance their occurrence in both groups. The death component cannot contribute largely to the efficacy results due to the low incidence in these patients and the limited sample size for this endpoint. Moreover, mortality is more a safety issue than an efficacy issue in non-urgent PCI, since most deaths occurring after non-urgent PCI are related either to the invasive procedure or to bleeding complications of adjuvant antithrombotic treatment. Nonetheless, some patients may die from the consequences of iatrogenic thrombosis in the coronary artery, and the reduction of mortality at 48 hours can be disputed in such patients.

The MI component information was collected through 2 different ways. The adjudicated MI, constitutes the hardest endpoint with clinical relevance, but its incidence was very low (12/92 placebo vs. 9/56 eptifibatide). The trial data showed that the significance of the several composite endpoints was driven by the eptifibatide-induced reduction in purely enzymatic MI. The enzymatic MI was robustly defined, but the relevance of a purely enzymatic MI as a surrogate for clinical MI is questionable. Although some retrospective studies indicate that an enzyme rise after PCI is associated with an increased risk of death during long-term follow-up (up to several years), this correlation remains to be established for Integrilin in the context of PCI with stenting, which is a procedure known to increase the risk of elevated enzyme release. Indeed, the incidence of enzymatic MI did not increase at 30 days, suggesting that the risk of elevated enzyme release was increased in the context of the procedure (angioplasty).

Thus, the applicant has clearly demonstrated the ability of Integrilin to significantly reduce the amount of necrosis at the time of the procedure by around 50 %, regardless of the size of the necrosis. Almost all the benefit of eptifibatide therapy, consisting in a prevention of PCI-induced procedural enzymatic increases, was observed at 48h without effect on mid-term events. One-year data showed no additional benefit of eptifibatide when compared to 30-day data, but confirm that there was no mid-term deleterious or rebound effect. There is no significant effect on one-year mortality but the results point in the right direction for eptifibatide. However, the mid-term clinical relevance of the new pathophysiological surrogate (enzymatic MI) is still controversial.

The main findings of the ESPRIT trial are described in section 5.1 of the SPC.

Safety

The lack of appropriate dose-finding studies with the consequential unnecessary increased haemorrhagic risk in individual patients is addressed in the efficacy discussion. As expected, bleeding was the most frequent adverse event. Whatever the definition (TIMI or GUSTO), there were more major bleedings in the eptifibatide group (1.3%) than in the control group (0.4%), as reflected in the SPC. This is consistent with findings in other clinical studies with GPIIb/IIIa inhibitors.

A post-hoc analysis has shown that the frequency of TIMI major bleeds were higher in Integrilin-treated patients who received a dose of a thienopyridine (mainly clopidrogel) before entering the cath lab as compared with those who did not receive a dose at this time (1.9% vs 0.4%).

The incidence of non-bleeding events was low and occurred with similar frequency in both groups.

The main findings of the ESPRIT trial are described in section 4.8 of the SPC.

Analysis of published literature

A detailed evaluation of the published literature submitted by the MAH has been carried out by the Rapporteur. Since 1995, several studies have linked the peri-procedural CK-MB elevation (5-30% of cases) with a subsequent risk of cardiac death. The corresponding required threshold for CK-MB elevation varies from "only minor" to > 5 ULN. Other, often more recent studies, do not find any relationship between peri-procedural cardiac enzyme elevation and further mid-term clinical events, or define an at least 5 or 10 ULN threshold to observe these events.

Of special relevance is the consensus document of the joint European Society of Cardiology and the American College of Cardiology committee, which clarifies the clinical relevance of enzymatic elevations. The consensus defines an MI as a "typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis in at least 2 successive blood samples with at least one of the following:

- ischaemic symptoms,
- development of pathologic Q waves on the ECG,
- ECG changes indicative of ischaemia (ST elevation or depression), or
- coronary artery intervention (e.g. coronary angioplasty). "

The consensus highlights the fact that the term MI should not be used without further qualifications i.e. location of MI, infarct size as assessed by the amount of cell loss (quantification of enzyme elevation) and timing of the necrosis relative to the timing of observation (evolving, healing or healed). This implies repeating serial measurements in order to observe a fall following the rise in cardiac enzyme. This subsequent fall was not documented in the submitted ESPRIT data, probably due to practical reasons (early hospital discharge in this setting).

The consensus specifically states that this new definition should be applied in the frame of a trial design in PCI, and that the reduction of infarct size should be documented. Indeed, it states that "analysis of the actual distribution of infarct sizes observed (area under the curve of biomarker or peak value) is more appropriate than analysis of the presence or absence of events only". Finally, the Consensus document does not recommend any threshold of CK-MB increase when used as MI endpoint in clinical trials, but describes the usual ones used in the US (CK-MB > 3 ULN in the specific frame of coronary artery interventions) and specifies that such choices still need to be validated.

Overall Benefit/Risk assessment

The ESPRIT trial has demonstrated that Integrilin, in combination with standard therapies (unfractionated heparin, aspirin and clopidogrel) has an acute effect (first 48h) in the prevention of ischaemic complications of percutaneous angioplasty with intracoronary stenting in subacute or stable angina patients versus placebo. This effect was accompanied with a low rate of major bleedings but more than 3-fold the rate observed in the placebo group. In view of the fact that the most significant individual outcome in the study, i.e. enzymatic MI, has not been validated and its relevance remains under debate, the CPMP is of the opinion that the trial findings are best presented in section 5.1 and 4.8.

7. Post-marketing safety updates

Very rare cases of fatal bleeding have been reported; the majority involved central and peripheral nervous system disorders (cerebral or intracranial haemorrhages). Anaphylaxis, rash, application site disorders such as urticaria, haematoma and anaemia have been rarely reported

Thrombocytopenia, including acute profound thrombocytopenia, has been observed during Integrilin administration. Appropriate recommendations for treating such patients, icluding the monitoring of platelet counts, have been included in the SPC.

Immunogenic response or anti-bodies against Integrilin have been observed *in isolated cases* in *naïve patients or in rare cases of patients re-exposed to* Integrilin.