European Medicines Agency
Evaluation of Medicines for Human Use

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ASSESSMENT REPORT

FOR

Efient

International Nonproprietary Name: prasugrel

Procedure No. EMEA/H/C/000984

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 06 February 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Efient, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 25 January 2007.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Steffen Thirstrup Co-Rapporteur: Gonzalo Calvo Rojas

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 6 February 2008.
- The procedure started on 27 February 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 May 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 20 May 2008.
- During the meeting 23-26 June 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 June 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 July 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 September 2008.
- During the CHMP meeting on 22-25 September 2008, the CHMP agreed on a List of Outstanding Issues to be addressed in writing and in an oral explanation by the applicant and in addition CHMP agreed on questions to be addressed to a SAG-CVS.
- The applicant submitted the written responses to the CHMP List of Outstanding Issues on 16 October 2008.
- During a meeting of a SAG group on 30 October 2008, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 17-20 November 2008, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 15-18 December 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Efient on 18 December 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 16 December 2008.

- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 25 February 2009.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Platelets play a central role in the pathogenesis of atherothrombosis and in the formation of thrombi following coronary angioplasty, with and without stent implantation. Platelets initially adhere at sites of vascular injury, atherosclerotic plaque rupture, balloon angioplasty, and stenting. Platelet activation following these interactions results in the release of ADP, thromboxane A2, and other mediators. Released ADP promotes platelet activation via the G-protein linked P2Y1 and P2Y12 purinergic receptors leading to further platelet activation, aggregation, and other platelet functions, such as platelet shape change, secretion, and the development of pro-coagulant and pro-inflammatory activities.

Activated platelets are recruited to sites of coronary plaque rupture and intra-arterial stenting, thereby forming aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia, and myocardial necrosis in what is collectively known as Acute Coronary Syndrome (ACS). The term ACS is a pathophysiological continuum progressing from ischemic chest pain with sudden onset and worsening (UA), to ischemia severe enough to cause irreversible myocardial damage detected with cardiac biomarkers without persistent ST-segment elevation (NSTEMI), to total occlusion of the culprit coronary artery with persistent ST-segment elevation, resulting in myocardial necrosis and elevated biomarkers (STEMI).

ACS occurs in a diverse global population and has a significant socioeconomic impact as patients require hospitalization, rehabilitation, and often suffer subsequent ischemic events.

Acute coronary syndromes will likely remain one of the leading causes of hospitalisation worldwide due to the increasing prevalence of risk factors for coronary heart disease and the increasing size of the aged population.

Options for the initial management of ACS include pharmacotherapy alone or an early invasive strategy with PCI (with or without coronary stenting) or coronary artery bypass grafting (CABG) as guided by the results of coronary angiography. The current American College of Cardiology/American Heart Association (ACC/AHA) and European Society of Cardiology (ESC) guidelines recommend an early invasive strategy for ACS patients with intermediate to high-risk features. Pharmacotherapy includes both anticoagulant and anti-platelet drugs. The current standard of care for patients with ACS includes dual anti-platelet therapy with aspirin and thienopyridine in both the acute and chronic phases of treatment. This therapy improves outcome in patients with ACS and those undergoing percutaneus coronary intervention (PCI); the high risk of for early stent-associated thrombosis is substantially reduced by dual antiplatelet therapy. Ticlopidine and clopidogrel are the two currently approved thienopyridines. They are pro-drugs requiring in vivo metabolism to form the active metabolite that binds rapidly and irreversibly to platelet $P2Y_{12}$ receptors, thus inhibiting platelet aggregation mediated by the $P2Y_{12}$ receptor. Clopidogrel has largely replaced ticlopidine due to its once-daily dosing regimen, improved tolerability and lowered incidence of adverse hematolgical side effects.

Several potential limitations of clopidogrel therapy have been identified despite loading dose of clopidogrel. This includes marked inter-individual variability in platelet inhibition and relatively slow onset of action. An association between thrombotic complications following PCI and poor antiplatelet response to the approved standard clopidogrel dosing regimen (loading dose (LD) 300 mg and maintenance dose (MD) 75 mg) has been suggested. Further, it has been shown that "non-responsiveness" to a clopidogrel 600 mg LD is a strong predictor of stent thrombosis in patients receiving drug-eluting stents, and in addition, that residual platelet aggregation above the median is associated with a 6.7-fold increased risk of major adverse cardiac events (death, myocardial infarction and target vessel revascularisation) at 1 month follow-up in patients undergoing elective PCI.

These observations suggest the possibility that higher and more consistent levels of platelet inhibition may improve clinical outcome in patients with ACS undergoing PCI.

Prasugrel, a thienopyridine adenosine diphosphate (ADP) receptor antagonist, is an orally administered pro-drug requiring in vivo metabolism to form the active metabolite (R-138727) that

irreversibly inhibits platelet activation and aggregation mediated by the $P2Y_{12}$-receptor. Prasugrel has a distinct chemical structure that permits efficient conversion to its active metabolite through rapid hydrolysis by carboxylesterases and then by multiple cytochrome P450 (CYP) enzymes. Once bound, a platelet is inhibited for its remaining lifespan. After prasugrel dosing is stopped, a return to baseline levels of platelet aggregation will occur as new platelets are formed. The return to baseline typically occurs over about 7 to 10 days after treatment is stopped.
Non-clinical studies indicated that, with respect to inhibiting ex vivo platelet aggregation and in vivo thrombus formation, prasugrel was approximately 10-100-fold more potent than clopidogrel and ticlopidine, respectively. Early clinical data in healthy subjects confirmed the greater platelet inhibition and more consistent response to prasugrel compared to clopidogrel. While the active metabolites of prasugrel and clopidogrel resulted in similar levels of platelet inhibition in vitro, the amount of each active metabolite generated in vivo was quite different, with prasugrel LD (60 mg) resulting in approximately 50-fold greater exposure, on pr. Mg basis, to its active metabolite compared to clopidogrel LD of 300 mg. This observation provides a mechanistic basis for the faster, higher and more consistent inhibition of platelet aggregation (IPA) observed with prasugrel.

2.2 Quality aspects

Introduction

Efient contains prasugrel hydrochloride as active substance. Prasugrel is a member of the thienopyridine class of antiplatelet agents. Currently available thienopyridines include clopidogrel and ticlopidine. Prasugrel is an orally bioavailable prodrug metabolized to an active adenosine diphosphate (ADP) receptor antagonist, which is a potent inhibitor of platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor.
Efient is an immediate release, double-arrow shaped, film-coated, debossed tablet. Tablets contain either 5 or 10 mg of prasugrel and different strengths are differentiated by size, film-coating colour and debossing. The tablets are commercially supplied in blister packaging.

Active Substance

The INN name of the active substance is prasugrel which is present in the product in the form of the hydrochloride salt. The chemical name is 5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate hydrochloride corresponding to the molecular formula C20H20FNO3S•HCl and molecular mass of 409.90
Prasugrel hydrochloride is white to light brown crystalline solid, slightly hygroscopic and soluble to slightly soluble at pH 1-4, very slightly soluble at pH 5 and practically insoluble at pH 6-7. The pKa value of prasugrel hydrochloride was 5.1. It shows polymorphism. It is obtained as a racemic mixture; therefore, it shows no optical rotation.

Prasugrel hydrochloride is a prodrug. In aqueous media, cleavage of the ester moiety forms the hydrolysis product, which exists as a mixture of diastereomers, and which are the precursors of the active metabolite. The hydrochloride is used because of its better hydrolytic stability and because it provides a better solubility at relevant physiological pHs.

- Manufacture

The synthetic route involves 3 steps where production of an intermediate, production of prasugrel free base and production of prasugrel hydrochloride consecutively takes place.
. In-process controls performed are suitable to control the reaction progress. The starting materials are considered simple molecules and satisfactory specifications were presented.
During development of the drug substance manufacturing process, quality attributes of the drug substance were evaluated with respect to the drug product manufacturing process and with respect to their impact on the critical quality attributes of the drug product. This analysis resulted in the identification of six drug substance critical quality attributes. The drug substance specification has been established to confirm that the manufacturing process reproducibly and reliably produces a drug substance that meets the critical quality attributes. Potential critical process parameters (CPPs) were identified by statistical design methods and a mechanistic understanding of the drug substance process.

All manufacturing steps are thoroughly examined and design spaces have been developed.
Concerning the use of concentrated HCl, there is a potential risk that acetone is converted into diacetone alcohol and then to mesityl oxide. However, any level in the final substance is below the LOQ, which is below the limit of toxicological concern.
The same synthetic route has been used to prepare all of the prasugrel hydrochloride salt used in clinical and development studies and it is the synthetic route for commercial drug substance manufacture.

- Specification

The drug substance specification includes tests for appearance (visual), identification (IR for prasugrel selective precipitation for Cl), assay (HPLC), impurities (HPLC), residual solvents (GC), water (Karl Fischer), Fineness (sieving) and Specific Surface Area (BET).
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Results for 3 commercial scale batches were provided analyzed by the current analytical methods and against the current specifications. The results comply with the specification.
In addition, results of another numerous historical batches were provided as supportive data. However these batches were tested by analytical methodologies and against specifications that both have evolved during development.

- Stability

Three pilot batches (50% of full scale) were put on long-term (25°C/ 60%RH) and accelerated (40°C/ 75%RH) stability testing conditions respectively. In addition results from supporting stability studies were presented on another three earlier batches manufactured at both pilot and full scale. However the use of different equipment in the manufacture of the pilot and early batches resulted in differences in the chemical stability of the active substance and therefore the equipment yielding to more stable material was chosen. All these batches have been stored in the proposed market packaging with the exception of the supporting stability batches where desiccant was not included. 24 months of stability data were available at the long-term storage condition of 25°C/60% RH for the primary stability studies, up to 36 months for the supporting stability studies and six months data under accelerated conditions.
It was apparent from the results that generally no significant changes are seen neither at 25°C/60% RH nor at 40 °C/ 75 %RH except for an impurity which increased, but still within the limit.
The photostability of prasugrel hydrochloride in the solid state was assessed and results showed that it does not need to be protected from light in the solid state.
Finally stress testing studies have been conducted on prasugrel hydrochloride drug substance in order to gain an understanding of its degradation chemistry
The conclusion from the stress degradation, long term, and accelerated stability studies is that prasugrel hydrochloride drug substance is stable when packaged in the container closure system proposed. Prasugrel hydrochloride is susceptible to hydrolysis and therefore contact with water should be avoided. The results of these primary stability studies demonstrate that the drug substance is stable when stored at room temperature in the appropriate packaging system. The data collected to date support the proposed retest period.

Medicinal Product

- Pharmaceutical Development

Prasugrel hydrochloride is a prodrug. Initial clinical studies were conducted using prasugrel free base tablets. However, prasugrel hydrochloride was selected for commercial development based on the higher solubility of this salt form relative to the free base across the gastrointestinal pH range. Initial trials however exhibited undesirable degradation product formation and demonstrated that the hydrochloride salt was more susceptible to hydrolysis than the free base.

Nevertheless the use of the salt rather than the free base was selected as a result of clinical data indicating that the rate and/or extent of absorption of the free base is adversely affected if the patient takes concomitant medications, which increase gastric pH. Above pH 6, the bioavailability of prasugrel free base was substantially reduced. Based on these results, it was decided to develop the

prasugrel hydrochloride tablet formulations. Solubility determination results and permeability and metabolism information suggest that prasugrel HCl is a BCS class 2 compound.
Also, a food effect study and a study with a gastric pH modifier were conducted in humans to assess the in vivo performance of prasugrel hydrochloride or prasugrel free base tablets.
As prasugrel hydrochloride is susceptible to both hydrolytic and oxidative degradation, the formulation, manufacturing process, and packaging of tablets focused on approaches to maintain product stability.
An extensive formulation development has been conducted. Design spaces have been defined through statistically-designed and individual studies. Critical and non-critical process parameters have been defined. A finished product specification covering all normal parameters has been set up. The quality features are provided in prasugrel hydrochloride tablets using the concepts and elements of Quality by Design with risk assessment and risk mitigation in order to ensure that key product attributes were defined at an early stage.
The choice and function of the excipients in the formulation was based on the need for excipients that have the smallest possible impact on the degradation of the drug substance in formulation and the physical properties necessary for the manufacturing process.
During development, core tablet strengths ranging from 5 mg to 15 mg were developed that are qualitatively identical and quantitatively vary only in the percent w/w drug loading with concomitant adjustment of the diluent, the percentage of the other excipients in the core tablet are identical. A standard film coating is applied to produce tablets of uniform colour.
A number of studies were conducted to determine formulation robustness of the process and the formulation. Dissolution is affected by pH and decreases with increasing pH.
Clinical studies have demonstrated that tablet performance is not affected by formation of the free base over a range of 5%-70% conversion. AUC and C_{max} of the active metabolite were bioequivalent after 1 hour.
A reaction between prasugrel HCl and an excipient was observed late in the development studies during manufacture and storage. This reaction leads to a partial and irreversible formation of prasugrel free base in the tablets. Analysing the samples used for clinical phase 3 study indicated that salt-to-base formation of at least up to 70% had no clinical impact and a requirement has been included in the finished product specification.

Due to prasugrel hydrochloride susceptibility to hydrolytic and oxidative degradation a dry manufacturing process was selected. Extensive experiments have been conducted to ensure a robust manufacturing process through design spaces. This has been used to set up the process controls for the production batches.. The container has been chosen to minimize humidity and to provide the necessary oxygen protection through out the shelf life of the product.

- Adventitious Agents

None of the excipients are animal-sourced, thus eliminating any risk of TSE contamination in the tablet formulation. The film-coating colour mixture utilizes a single animal-sourced excipient, lactose monohydrate. The source of the lactose complies with regulations to ensure patient safety.

- Manufacture of the Product

A dry manufacturing process is utilised for the manufacture of Efient comprising the following steps: blending, dry granulation, blending, compression, coating and drying of tablets, packaging. The manufacturing process is sufficiently described and in-process controls are adequate.
Validation data on three commercial-scale 5 mg batches and three commercial-scale 10 mg batches provided satisfactory reassurance for the reproducibility and consistency of the manufacturing process.

- Product Specification

The specifications of the drug product at release and shelf-life include tests for appearance (visual), identity (IR), assay (HPLC), uniformity of dosage units (Ph.Eur.), degradation products (HPLC), dye identity test (not routinely), dissolution (Ph.Eur.), tablet form conversion (XRPD).
Batch results are provided for commercial scale batches and clinical trials batches. The results comply with the specification, confirm consistency of the product and support the acceptance criteria.

- Stability of the Product

Stability studies have been conducted according to ICH guidances.
Three production scale batches of 5 mg tablets have been stored at 25ºC/60% RH for 12 months, at 30ºC/75% RH, for 12 months and at 40ºC/75% RH for 6 months in the proposed market packaging.
Another three production scale batches of 10 mg tablets have been stored at 25ºC/60% RH for 18 months, at 30ºC/65% RH, for 18 months and at 40ºC/75% RH for 6 months in the proposed market packaging.
Bulk simulator samples of both 5 and 10 mg tablets were also stored at 25°C/60% RH and at 5°C for 12 months, at 40°C/75% RH for 1 month and at -20°C for 1 month.
Additionally a supporting study for the 10 mg tablets stored in blisters was presented.
Stability results indicate that all tested parameters remain within the specification limits. Degradation products levels tend to increase but comply with the individual specification requirements at long term conditions throughout 24 months (statistically).

Photostability: A production scale batch of each strength was tested according to ICHQ1B. It is concluded from the results that no special precautions are required since the blister provides the necessary protection and the product is to be labelled to be kept in the original package.

Stress testing: A production scale batch of each strength was used for stress testing together with a placebo.. It was found that the prasugrel in the tablets degraded with exposure to heat and moisture, particularly in an ambient oxygen environment. Prasugrel does not degrade significantly with exposure to simulated sunlight.

Tablet Form Conversion: Primary stability samples were analyzed for the level of prasugrel free base after storage in both bulk and commercial packages. The conversion of prasugrel hydrochloride to prasugrel free base is primarily due to exposure to moisture. . However the present manufacturing method is shown to provide the necessary protection against moisture.

Discussion on chemical, pharmaceutical and biological aspects
The quality of Efient film-coated tablet is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3 Non-clinical aspects

Introduction

Prasugrel belongs to the thienopyridine class of prodrugs and is inactive *in vitro*. Initial studies required dosing animals with prasugrel with subsequent blood collection to look for *in vivo* activation as reflected in *ex vivo* pharmacodynamics measurements. Once the *ex vivo* evidence for the activation of prasugrel *in vivo* was established, subsequent studies addressed the potential activity of prasugrel in disease models of target indications (thrombosis). Prasugrel administration resulted in prolongation of the bleeding time as did clopidogrel and ticlopidine as it was seen in a model of haemostasis.

Consistent with differing mechanisms of action, co-administration of aspirin showed additive/synergistic interaction in studies of both thrombosis and haemostasis. Having established the *in vivo* activity of prasugrel in disease models reflecting the clinical target indication, studies were performed to characterize the activities of the active metabolite of prasugrel by *in vitro* studies.

The rationale for the non clinical development and application for marketing approval of prasugrel is considered well established. The extent and scope of the documentation provided are appropriate to characterise the non clinical profile of the product.

The following guidelines were considered: Note for guidance on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00), Note for Guidance on Toxicokinetics: the assessment of systemic exposure in toxicity studies (CPMP/ICH/384/95), Non-clinical guideline on drug-induced hepatotoxicity (CHMP/SWP/150115/2006), Note for Guidance on carcinogenicity: testing for carcinogenicity of pharmaceuticals (CPMP/ICH/299/95), Note for Guidance on the detection of toxicity to reproduction for medicinal products and toxicity to male fertility (CPMP/ICH/386/95), Guideline on risk assessment of medicinal products on human reproduction and lactation: from data to labelling (EMEA/CHMP/203927/05), and Guidance on the Environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00).

The analytical method validation study in beagle dogs for the pharmacokinetics of prasugrel active metabolite was conducted in compliance with the GLP guidelines.

The safety pharmacology studies provide an evaluation of the safety pharmacology of prasugrel and meet the standards for general pharmacology studies in effect at the time of their conduct. This is considered acceptable by the CHMP. All pivotal toxicity studies were conducted in compliance with GLP regulations.

Pharmacology

- Primary pharmacodynamics

In *ex vivo* studies with rats, dogs, and cynomolgus monkeys, prasugrel demonstrated dose-dependent inhibition of ADP-induced platelet aggregation. Unless indicated otherwise, platelet function studies were performed using light transmission aggregometry (LTA), which monitors the increase in light transmission in stirred suspensions of platelets in citrated plasma (platelet-rich plasma, PRP) as they aggregate in response to activation with agonists such as ADP. ADP is a natural ligand for the target receptor ($P2Y_{12}$) of the thienopyridine class of oral antiplatelet agents (ticlopidine, clopidogrel, and prasugrel).

The selectivity of prasugrel for antagonism of ADP-induced platelet aggregation was demonstrated by the lesser inhibition of aggregation achieved with thrombin *vs* ADP in platelets under *ex vivo* conditions. Prasugrel's inhibitory effects were maintained after washing of the platelets, showing an irreversible platelet inhibition. Studies in rats compared prasugrel's potency with that of clopidogrel and indicated a faster onset of action, since prasugrel (1-10 mg/kg, p.o.) caused dose-dependent inhibition of platelet aggregation at 0.5 hr after dosing with an ED_{50} value of 4.2 mg/kg, suggesting an early onset of action. In contrast, clopidogrel (10-100 mg/kg, p.o) showed moderate effect at 0.5 hr (ED_{50} > 100 mg/kg). The maximum effect of both prasugrel and clopidogrel were observed at 4 hr after administration; the ED_{50} values being 1.1 mg/kg (p.o.) and 15 mg/kg (p.o.), for prasugrel and clopidogrel, respectively. The inhibitory effects of prasugrel (1- 3 mg/kg) and clopidogrel (10-30 mg/kg) were long-lasting, and these inhibitions completely disappeared at 96 hr after administration.

The *ex vivo* effects of prasugrel on platelet aggregation in male cynomolgus monkeys assessed as the ADP (10μM)-induced platelet aggregation in platelet-rich before and after oral administration of prasugrel showed that prasugrel (0.1 and 0.3 mg/kg/day) given orally once a day for 14 days inhibited platelet aggregation in a dose-dependent manner. The inhibitory effect reached a plateau on days 3 to 5, suggesting cumulative effects of prasugrel, and was maintained during the administration of prasugrel after reaching the maximal effect. The effects slowly declined after cessation of prasugrel administration. There were no significant inhibitions of platelet aggregation on the 7th day after the final dose of prasugrel (day 21). These results indicate that repeatedly administered prasugrel exhibits a potent and long-lasting antiplatelet effect.

Inhibitory effects of 14 day lasting repeated administration of prasugrel (0.03-0.3 mg/kg/day, p.o.) on platelet aggregation in the beagle dog were investigated. The ADP (8μM)-induced platelet aggregation

measurements showed inhibitory effects of prasugrel (0.1 and 0.3 mg/kg/day) reaching plateau on day 3. After cessation of administration, inhibition of platelet aggregation gradually decreased.

The *in vivo* effects of prasugrel were assessed in various non clinical pathophysiological models of thrombotic challenge:

- The arterio-venous shunt model
- The electrical injury model
- The stroke model
- The pathophysiological model of peripheral artery disease
- The bleeding time model

In the rat arterio-venous shunt model, prasugrel reduced thrombus formation in a dose-dependent manner. Similarly, prasugrel prolonged the time to occlusion and increased the patency in the electrical injury model of arterial thrombosis in a dose-dependent way. The cumulative inhibitory nature of repeat dosing with thienopyridines was demonstrated using the same model during a repeated 3 day dosing regimen. Treatment with prasugrel resulted in a dose-dependent reduction of the incidence, total area, and the number of cerebral infarcts in a model of embolic cerebral infarction in the rat, while clopidogrel had lower activity. In a model of peripheral arterial disease whereby injection of lauric acid into the rat femoral artery produces endothelial injury, platelet adhesion, and platelet aggregation, prasugrel dose-dependently inhibited progression of the lesions. Prasugrel also caused a prolongation of bleeding time in a tail transaction model in rat.

Prasugrel contains a chiral centre and thus, exists as two individual enantiomers: the R-enantiomer (R-96875) and the S-enantiomer (R-96876). The platelet inhibitory effects of the individual enantiomers were evaluated following the oral administration to both, rats and monkeys, and following single oral administration of the prasugrel's individual enantiomers to beagle dogs. Additional in vitro studies were conducted in order to evaluate the effects on platelet aggregation.

Oral administration of R-96875 and R-96876 (both at 1 and 3 mg/kg) to rats dose-dependently inhibited platelet aggregation at 2 and 4 hr after dosing, respectively. There were no statistically significant differences in the efficacy between R-96875 and R-96876 at the same dosage. The ED_{50} values at 4 hr after dosing were 1.4 mg/kg for R-96875 and 1.3 mg/kg for R-96876. Effects of a 3 day repeated administration of R-96875 and R-96876 (both at 0.3 mg/kg/day, p.o.) on ADP-induced platelet aggregation using platelet-rich plasma were also examined in cynomolgus monkeys. The wash-out periods between the two treatments was considered acceptable. Both isomers caused inhibition of platelet aggregation on day 3, and this effect was almost equal between the groups. There were no statistically significant differences in the efficacy between R-96875 and R-96876 at any point. These results indicate that oral administrations of optical isomers of prasugrel, R- 96875 and R-96876, exert a similar extent of *ex vivo* effect on platelet aggregation in rats and in cynomolgus monkeys.

The active metabolite R-138727 has two chiral centres, resulting in four enantiomers. Metabolite R-138727 has potent and selective $P2Y_{12}$ antagonistic activity. The two most potent enantiomers of R-138727, the R-125690 and R-125689, are about 100- and 10-fold more potent than enantiomers R-125687 and R-125688, respectively. The two most potent enantiomers comprised the majority of the circulating R-138727 in rats and humans.

In pharmacodynamic mechanistic studies, the active metabolite of prasugrel, R-99224, affected $P2Y_{12}$-specific biomarkers, including alpha granule release, fibrinogen binding, and restoration of ADP-induced reduction of PGE_1- induced elevation cAMP. In contrast, $P2Y_1$ biomarkers (platelet shape change, Ca^{2+} mobilisation) were unaffected by pre-incubation of platelets with prasugrel's active metabolite. This confirms that the inhibition of the platelet aggregation by prasugrel is mediated by $P2Y_{12}$ receptors. The pharmacological effects are most probably dependant on the production of the active metabolites of prasugrel.

Inhibitory effects of orally administered optical isomers of prasugrel on platelet aggregation investigated in beagle dogs was measured as the platelet aggregation induced by ADP (8 μM) at 2 and 4 hr post dosing. There were no significant differences in baseline values of platelet aggregation

among all groups. In the control group, there were no obvious changes in aggregation after vehicle administration. In contrast, each isomer (0.1-1 mg/kg, p.o.) inhibited platelet aggregation in a dose-dependent manner. There were no statistically significant differences in platelet aggregation at 2 and 4 hr post dose between the two isomers at corresponding doses. In addition, ED_{50} values for the two isomers were similar at 2 and 4 hr post dose. These results show that an oral administration of the optical isomers of prasugrel produces anti-platelet effects of similar potency in beagle dogs. This pharmacodynamic study supports the use of racemic prasugrel, since all four enantiomers are formed as was shown in a pharmacokinetic study in dogs.

In general, the *ex vivo* studies with rats, dogs, and cynomolgus monkeys demonstrated dose-dependent inhibition of ADP-induced platelet aggregation by prasugrel. Studies in rats also demonstrated prasugrel's potency compared to clopidogrel and suggested a faster onset of action. The selectivity of prasugrel antagonism of ADP-induced platelet aggregation was demonstrated by the lesser inhibition of aggregation achieved with thrombin *vs* ADP in platelets *ex vivo*. The inhibitory effect was maintained after washing of the platelets, showing an irreversible platelet inhibition.

- Secondary pharmacodynamics

No secondary pharmacodynamic studies were made on binding and activity to other proteins than $P2Y_{12}$ and $P2Y_1$ and the secondary pharmacology data were derived from the results of the safety pharmacology studies. The effects observed in these *in vitro* safety studies occur at a concentration at least more than 10-fold higher than the maximum therapeutic concentration observed in humans. Both, the non clinical *in vivo* studies and clinical studies, did not provide any evidence for unexpected secondary pharmacodynamic effects of prasugrel. Thus, further studies are deemed unnecessary. Nevertheless, the results of a screening of prasugrel and its metabolite M1 in a standard battery of receptor binding assays were requested by the CHMP. Thus, M1 and prasugrel were tested in a battery of receptor binding assays. Neither prasugrel nor M1 showed affinity for the tested receptor at concentrations up to 10 μM.

- Safety pharmacology programme

Assessments of *in vivo* activity of prasugrel included evaluation of cardiovascular, central nervous system (CNS), respiratory, renal, and gastrointestinal (GI) functioning in rodents or dogs.

Effects on the GI and CNS occurred at high doses of prasugrel. At an oral dose of 100 mg/kg, prasugrel produced a significant decrease in paradoxical sleep in rats, without altering the total percentage of time spent sleeping. Increased sensitivity to touch was observed in rats at the 300 mg/kg oral dose. Other CNS endpoints, including body temperature, clinical observations, precipitated seizure thresholds, spontaneous activity, and thiopental-induced sleep times, were not altered following administration of single oral doses of prasugrel up to 300 mg/kg. Examination of the effects on autonomic nervous system and smooth muscle showed that prasugrel inhibited spontaneous movement of isolated rabbit ileum at $1x10^{-4}$ g/ml and inhibited the amplitude and increased frequency of spontaneous motility of isolated pregnant rat uterus. Prasugrel at $1x10^{-5}$ g/ml significantly inhibited acetylcholine-, histamine- and serotonin induced contractions in isolated guinea pig ileum.

The potential for prasugrel to inhibit cardiac repolarisation was evaluated by examining the effect of three prasugrel metabolites on potassium currents in hERG-transfected cells. The metabolites R-138727 and R-106583 were evaluated because these are the active and the most abundant inactive human metabolites, respectively, and R-95913 was evaluated because it is the intermediary step between prasugrel and the active metabolite. No significant effects on the potassium currents in hERG-transfected CHO-K1 cells were observed at up to the highest concentrations tested (30 μM for R106583 and R138727; 15 μM for R-95913) which were greater than approximately 485 times the expected free C_{max} values of the three metabolites following a clinical loading dose of 60 mg prasugrel. Therefore, the hERG data for prasugrel metabolites do not suggest a potential impact of prasugrel on cardiac repolarisation due to inhibition of potassium currents. Prasugrel (30 and 100 mg/kg, ID) showed no major effects on heart rate, blood pressure, respiration rate, carotid blood flow, or pressure response to acetylcholine, norepinephrine or bilateral carotid occlusion in the anesthetised dogs. No effects on QT interval were observed in quantitative electrocardiograms evaluated in the 3 and 9

month repeat dose studies in dogs at doses approximately nine times the 60 mg clinical loading dose calculated as mg/m^2.

Prasugrel produced a decreased gastric acid content and gastric volume at 100 mg/kg in rats. Furthermore, prasugrel decreased gastric emptying in mice when given for 3 days at the dose of 300 mg/kg. However, the doses at which these effects occurred were ≥14 times the 60 mg clinical loading dose calculated as mg/m^2. Prasugrel (10-100 mg/kg, p.o.) had no effects on urinary volume, excretion of electrolytes or osmotic pressure in rats.

- Pharmacodynamic drug interactions

Thienopyridine antiplatelet agents are commonly used in combination with aspirin as "dual antiplatelet therapy". The use of the combination is based on the alternative receptor/signalling pathways that each of these agents inhibits and the additive, or synergistic, platelet inhibitory effects that results from co-administration. Pharmacodynamic studies were conducted with the combination of prasugrel/aspirin. An additional study involved co-administration of other drugs, in which the comparisons of the pharmacokinetics and pharmacodynamics of prasugrel base and hydrochloride salt were made in the presence of the proton pump inhibitor lansoprazole.

The additive activity of prasugrel and aspirin has been demonstrated in several studies of platelet aggregation (*ex vivo*) in rats and dogs, thrombus formation (*in vivo*) in rats, and bleeding time in rats. Consistent with these findings, *in vitro* studies with blood from human volunteers demonstrated that a combination of R-138727 and aspirin has additive effects on collagen-induced platelet aggregation.

The antiplatelet effects of two tablet formulations of prasugrel, the free base tablet and hydrochloride salt tablet, were compared in beagle dogs pretreated with lansoprazole, a proton pump inhibitor. Plasma concentrations of prasugrel metabolites at 1 hr post dosing were not significantly different from those of the free base tablet and hydrochloride salt tablet given to dogs. These results suggest that the free base tablet and hydrochloride salt tablet have similar antiplatelet potency in lansoprazole-treated dogs.

Pharmacokinetics

Absorption, distribution, metabolism, and excretion profile of prasugrel was investigated in mice, rats, and dogs, which are also the species used in the toxicological evaluation of the compound. Analytical methodology evolved adequately. In initial pharmacokinetic and absorption studies, some inactive metabolites of prasugrel were measured and their pharmacokinetic parameters used as indicators of the absorption and metabolism of prasugrel. A number of new metabolites were quantified and a method for determination of prasugrel's active metabolite concentrations in plasma was ultimately developed. Most studies were conducted following oral administration, the intended clinical route of administration.

Prasugrel is rapidly absorbed in all species including humans; T_{max} of the active metabolite R-138727 is less than 1 hour. Prasugrel itself was not detected in plasma after oral administration. The decline of prasugrel related radioactivity was biphasic in rats and dogs. The radioactivity terminal elimination half-life seemed to be similar in mice and rats, approximately 24 h, but it is considerably longer in dogs, approximately 3 days. In humans, the average terminal elimination half-life of the active metabolite R-138727 was approximately 7 hours. Approximately 21% of a [^{14}C]-prasugrel dose is excreted in human faeces within 48 hours. The pharmacokinetic studies have only been conducted in male animals. However, no apparent sex differences were observed during the repeat-dose toxicity studies. Following single oral doses of prasugrel base or prasugrel hydrochloride, the exposure to prasugrel metabolites was evaluated in the mouse, rat, and dog. Exposure parameters to prasugrel metabolites were higher for prasugrel hydrochloride compared with prasugrel base at doses of ≥500 mg/kg in the rat and at 100 mg/kg in the dog. Tissue distribution of radioactivity related to prasugrel was studied in rats following single and repeated oral administration. Radioactivity was widely and rapidly distributed throughout the body. The radioactivity concentration was highest in most tissues involved in the absorption and elimination of the compound and its metabolites, i.e., stomach, intestines, liver, kidney and urinary bladder. Prasugrel distributed to the bone marrow of rats with a

tissue-to-plasma ratio of less than 0.5. Following repeated daily dosing, accumulation consistent with the elimination half-life of prasugrel was observed in most organs. After a single oral dose of 5 mg/kg ^{14}C-prasugrel to rats on Day 13 of pregnancy, the fetal concentration of prasugrel radioactivity was 0.27 times that in maternal blood 1 hour after administration and declined thereafter, suggesting low placental transfer of prasugrel or its metabolites. Due to instability of the active metabolites R-138727 in plasma, the protein binding was only investigated in human serum albumin, where the metabolite was highly bound by 98% and the species differences in protein binding of the active metabolites R-138727 were not assessed. The protein binding of the inactive metabolites R-100932, R-106583 and R-95913 was similar in rats, dogs and humans (>80%) while the protein binding of the inactive metabolite R-119251 was significantly lower in dogs (26-36%) as compared to rats (71-77%) and humans (76-77%). Prasugrel was extensively metabolised in all species. A total of eighteen metabolites were identified in human plasma. Based on a mean radioactivity above 10%, the following major metabolites could be identified: diastereomers of M1, M2 (R-95913) and M5 (R-106583). The metabolites of prasugrel found in human plasma, urine and faeces were also detected in mouse, rat and dog; the only exception being M16, which was only identified in the mouse. M16 is M10 conjugated to glucuronic acid and M10 was found in all species. Furthermore, the extent of formation of a given metabolite varied significantly by species. Metabolite M1 was formed in large amounts in humans and was detected in animal plasma, but quantification was not conducted in animals due to co-eluting of the radioactive peaks. Metabolites M2, M5, M7 and M14 were also formed in larger amounts in humans as compared to the animal species.

In dogs, the hydrolysis of prasugrel led to a formation of essentially equal amounts of the four enantiomers of R-95913. All enantiomers of the active metabolite R-138727 were generated from R-95913. The R-125690 and R-125689 enantiomers accounted for approximately 50-64% of the R-138727 in dog plasma and >99% in rat plasma. The CHMP also inquired about levels in mice and rabbits. It was shown that all tested animal species were exposed to the most potent of enantiomers of R-138727, R-125690 and R-125689, at concentrations significantly higher than those observed in humans and thus, adequate margins of safety could be assured. Also, all animal species were exposed to the least potent of R-138727 enantiomers at concentrations higher than those in humans, with the exception of the rat as R-125687 and R-125688 concentrations could not be quantified.

Considering that isomers can have different or even antagonistic effects towards the same receptor system, these opposite effects might occur in species are capable of forming all four enantiomers of R-138727. Nevertheless, in the course of several studies of the antagonistic profile of the enantiomers using light transmission aggregometry, no evidence of agonistic activity was noted between R-125690 and R-125689 isomers of R-138727.

When administered at high doses (≥100 mg/kg) to rats, prasugrel induced CYP450 enzymes (CYP2B and CYP3A2) and phase II metabolizing enzymes UDP-glucuronosyltransferase and glutathione-S-transferase, however, based on the *in vitro* non clinical study with human hepatocytes, this induction is not observed in humans. Furthermore, the AUC for each measured metabolite decreased after multiple dosing compared with the values obtained after the first dose in mice at ≥100 mg/kg/day, in rats at 100 and 300 mg/kg/day, and in dogs at 20 mg/kg/day (after 20 weeks of dosing and beyond). However, the exposure data in dogs administered prasugrel at 20 mg/kg for one month were essentially unchanged. In the nine month study with dogs, the AUC data for two of the metabolites R-100932 and R-106583 decreased after 20 weeks of dosing, while the AUC values of the other metabolite, R-95913 were higher in dogs dosed with prasugrel at 20 mg/kg. Thus, the data show some auto-induction of prasugrel's metabolism at the 20-mg/kg dose in dogs. Since induction was not observed either *in vitro* or *in vivo* in humans and the non-clinical data suggest that induction of CYP3A4 due to administration of prasugrel is unlikely at clinically relevant plasma concentrations, this is not considered a major issue.

In mice, 90% of the dose was excreted during the first 24 hours post dosing mainly *via* the urinary elimination route. In rats and dogs, the majority of the radioactivity (>90%) was excreted within the first 72 hours of dosing in faeces presumably *via* bile. Approximately 20% of the dose was excreted via urine. Radioactivity related to prasugrel was also detected in milk of lactating rats at

concentrations up to approximately five times higher than the plasma level. However, the radioactivity from milk ($T_{½}$=9.5 h) was eliminated more rapidly than that from the plasma ($T_{½}$ approximately 24 h).

No pharmacokinetic drug interactions studies were conducted in animals and this was justified with the sufficient evaluation of pharmacokinetic drug interactions in a clinical setting.

Toxicology

The toxicological and toxicokinetic profile of prasugrel was investigated in a comprehensive programme, including studies on systemic toxicity after single and repeat dose administration, reproductive toxicity studies, genotoxicity studies as well as studies addressing specific issues, such as antigenicity, phototoxicity, toxicity of impurities, dermal and ocular irritation.

Prasugrel base was used during the major part of the toxicology program. However, a change was made to the hydrochloride salt of prasugrel later in development. Repeat dose studies comparing the base and the hydrochloride salt of prasugrel were conducted in mice with two week duration and rats and dogs with one month duration. A single dose comparison study was conducted in rats.

- Single dose toxicity

Single dose toxicity studies following the oral administration were conducted in rats and mice at doses up to 2000 mg/kg. Clinical observations in female rats given 2000 mg/kg included some non-specific signs of irregular respiration, reduced locomotor activity, ptosis, lacrimation, and staggering gait. In a comparison single dose rat study of prasugrel base *vs* prasugrel hydrochloride, no deaths occurred at doses of prasugrel base up to 2000 mg/kg, while 3 out of 5 males and 4 out of 5 females administered 2000 mg/kg prasugrel hydrochloride died. Systemic exposure to prasugrel metabolites in the prasugrel hydrochloride group was 1.2 to 3.5 times higher than that of the prasugrel base group and this difference is believed to account for the difference in mortality. In an escalating dose study in beagle dogs, platelet aggregation was inhibited, consistent with the pharmacological action of the compound. Emesis was observed after administration at doses ≥300 mg/kg, and serum ALP was increased following the 2000 mg/kg dose. Slight hepatocellular atrophy and ground glass appearance of hepatocellular cytoplasm were also observed in these dogs. Data from mice, rat and dog showed that prasugrel has low acute toxicity.

- Repeat dose toxicity (with toxicokinetics)

Repeat dose studies of up to three, six, and nine months in duration were conducted with prasugrel administered orally to mice, rats, and dogs. In most of these studies prasugrel base was used as the tested compound. Bridging studies comparing the toxicity of prasugrel base and prasugrel hydrochloride were conducted in each species.

Mortality, decreased body weight, and anaemia were observed in mice at repeated administration of a dose of 1000 mg/kg prasugrel. Anaemia was attributed to subclinical blood loss rather than to haematopoietic suppression, since an increase in the reticulocyte ratio was also observed, and there were no histologic effects on bone marrow. Liver was the primary target organ and increased liver weight and hypertrophy of centrilobular hepatocytes most likely due to induction of drug metabolising enzymes were observed. In the two week study, increased ALT and AST activity and the single cell necrosis indicated toxic effects on liver at a 2000 mg/kg dose of prasugrel, which was also lethal. The maximum tolerated dose (MTD) of prasugrel in mice was considered to be 300 mg/kg. Similar effects were observed in a fourteen day bridging study conducted in mice to compare the toxicity of prasugrel base and prasugrel hydrochloride. Some effects, e.g. the decreased erythrocytic parameters and liver histopathology findings, were more apparent in the prasugrel hydrochloride group.

No animals died during the studies in which rats were administered 0, 10, 30, 100, and 300 mg/kg of prasugrel orally for 3 months. Body weights decreased relative to control by 10% and 6% for males and females, respectively, in the 300 mg/kg group. Platelet counts increased in males given ≥100 mg/kg and in females given 300 mg/kg. Prothrombin times in males and activated partial thromboplastin times were prolonged in rats receiving ≥100 mg/kg. Evidence of enzyme induction included increased liver weight, hypertrophy, and acidophilic cytoplasm of hepatocytes, in male rats

given ≥100 mg/kg and female rats given 300 mg/kg. The enzyme induction effects and alterations in coagulation parameters were considered compensatory and pharmacologic in nature and thus not adverse.

Administration of similar doses of prasugrel orally for 6 months did not result in any deaths and similar blood effects were observed at higher doses. Clinical chemistry effects included decreased total cholesterol in males of the 300 mg/kg group, decreased triglycerides in males of the 100 mg/kg and slight decrease in potassium and chloride in females of the 300 mg/kg group. These changes were attributed to decreased food consumption. Increased total bilirubin, total protein and β-globulin and albumin were thought to be caused by the acceleration of protein synthesis in the liver accompanying induction of drug metabolizing enzymes. An increase in calcium was observed in both sexes given doses ≥100 mg/kg and was considered to be due to the increase in serum protein and the consequent increase in protein bound calcium. Liver weight increase was noted. Histopathological examination revealed hypertrophy of the hepatocytes and are consistent with the occurrence of enzyme induction. Other changes included decreased thymus weight in females of the 100 and 300 mg/kg groups, decreased prostate weight in the 100 and 300 mg/kg groups, and decreased uterine weight in the 300 mg/kg group. These were all slight changes without accompanying histopathological changes. The NOAEL of prasugrel in this study was 30 mg/kg.

Prasugrel base and prasugrel hydrochloride were administered daily for 28 days to rats to examine their differences in toxicity. Prasugrel hydrochloride was administered at dose levels of 0, 30, 100, and 300 mg/kg, and prasugrel base was administered at 300 mg/kg. Decreased body weight gain associated with decreased food consumption was recorded in females at 100 mg/kg and in males and females at 300 mg/kg with prasugrel hydrochloride. Administration of prasugrel hydrochloride was associated with a tendency toward decreased erythrocyte parameters in males and females at 300 mg/kg and an increase in reticulocyte percentage in females at 300 mg/kg. Platelet count, activated partial thromboplastin time, and fibrinogen were also increased. Anomalous levels of triglycerides, glucose, potassium, chloride, calcium, total protein, albumin, α2-globulin and ß-globulin were observed. These findings were comparable at 300 mg/kg between prasugrel hydrochloride and prasugrel base. The observed increase in liver weight, thought to be caused by an induction of drug metabolizing enzymes, was observed in males at 30 mg/kg and in males and females at 100 mg/kg and above in the prasugrel hydrochloride group and at 300 mg/kg in the prasugrel base group. Macroscopic examination revealed dark discoloration of the liver in males and females at 300 mg/kg for both compounds, and histopathological examination revealed hypertrophy of hepatocytes at each dose level for both compounds. The quantitative differences in exposure parameters and toxicological findings between prasugrel base and hydrochloride were discussed by the CHMP, especially in terms of the choice of the compound for the long term toxicological studies. It was, however, justified that the observed differences in animals treated with prasugrel hydrochloride or prasugrel base were not indicative of qualitative differences in toxicologic responses. The comparability of the pharmacokinetic and toxicity profiles between the base and the salt in bridging studies up to one month in duration in mice, rats, and dogs supported the appropriateness of using the salt for long term toxicology studies.

Beagle dogs were administered 0, 0.8, 4, or 20 mg/kg of prasugrel orally for 3 and 9 months. In animals receiving 4 mg/kg or more, hypertrophy of hepatocytes accompanied by the ground glass appearance of cytoplasm was observed. Animals receiving 20 mg/kg showed increased alkaline phosphatase activities and electron microscopic examination revealed a slight proliferation of the smooth endoplasmic reticulum in hepatocytes. These changes were considered to be due to activation of drug metabolism enzymes induced by administration of prasugrel. Decreased total cholesterol levels occurred in animals receiving 20 mg/kg.

An oral toxicity study to compare the toxicities of prasugrel base and prasugrel hydrochloride was conducted in which the compounds were administered orally once daily for 28 days. There were no compound related clinical signs or effects on body weight, food consumption, ophthalmology, electrocardiography, urinalysis, haematology, or gross pathology. Elevation of ALP activity occurred in males and females of the groups at 100 mg/kg prasugrel hydrochloride and 100 mg/kg prasugrel base. The increases in alkaline phosphatase levels occurred earlier and were more pronounced in the female dogs treated with 100 mg/kg prasugrel hydrochloride than in female dogs given 100 mg/kg

prasugrel base. The histopathological examination revealed lamellar inclusion bodies in the hepatocellular cytoplasm after administration of prasugrel hydrochloride. Hypertrophy of hepatocytes was observed with both compounds and was attributed to the induction of drug metabolizing enzymes. Slight hypertrophy of the thyroid follicular epithelia was observed in a male dog given 100 mg/kg prasugrel base. The changes observed in the thyroids were secondary to the accelerated metabolism of thyroid hormones due to elevated hepatic drug metabolizing enzymes.

The histopathological liver alterations and the serum hepatic enzymes changes were observed continuously throughout the repeat dose toxicity studies in mice, rats and dogs. The CHMP's concern regarding these findings, their relevance for prediction of human hepatotoxicity, especially considering that induction of CYPP450 is not observed in humans, and the overall potential hepatotoxicity of thienopyridines was appropriately addressed. Despite the lack of evidence for hepatotoxicity, hepatotoxicity is identified as a precautionary approach as a Potential Risk in the Risk Management Plan (RMP) and is subject to a range of surveillance activities.

- Genotoxicity

Prasugrel did not exhibit genotoxic properties when tested in a battery of standard *in vitro* (Ames and chromosome aberration) and *in vivo* (mouse micronucleus) assays. However, the CHMP requested the information concerning the purity of the tested batches and specifically, the impurity levels in the batches with regards to the genotoxicity tests. In response, the impurity level in the batches used for the pivotal toxicity studies were characterised based on an analysis of the actual amount of the impurities in the administered doses at the NOAEL. Sufficient levels have been achieved. In case of MFTP and PFTP, the level of impurities in the lots used for the *in vitro* genotoxicity studies are regarded as sufficient for qualification at the proposed specifications (0.20% and 0.15%, respectively). Although the proposed specification for OHTP (0.20%) cannot be deemed qualified by the *in vitro* genotoxicity studies, the margins of safety for the *in vivo* micronucleus study are significantly high to qualify the proposed specification for OHTP (>57 based on mg/m^2 and a prasugrel salt *vs* base exposure ratio of 3.5). Thus, OHTP, MFTP, and PFTP are considered qualified at the proposed specification.

- Carcinogenicity

Studies conducted over 24 months with mice at doses up to 300 mg/kg and rats with doses up to 100 mg/kg aimed at the assessment of the carcinogenic potential of prasugrel. When treated with prasugrel hydrochloride, mice developed adenomas of the liver, but not carcinomas. In view of the lack of genotoxicity, the increase in mice tumours was assumed to be caused by the adaptive enzyme induction response. The mice are prone to developing tumours under such circumstances and the mechanism is unlikely to be relevant for humans. Furthermore, hepatocellular hypertrophy, thought to be the result of microsomal enzyme induction, but no tumour induction was observed in the rat study. The increase in liver tumours in mice administered prasugrel is not considered to be a relevant human risk and this is adequately reflected in the proposed prescribing information.

- Reproduction Toxicity

Fertility, early embryonic development and peri- and postnatal toxicity were assessed in studies with rats and embryo-fœtal development in studies in rats and rabbits. In rats prasugrel did not exhibit toxicity on fertility and early embryonic development. In rabbits and rats prasugrel did not show signs of embryo-foetal toxicity. Prenatal and postnatal development, including maternal function in rats was not affected by exposure to prasugrel. The SPC adequately reflects these findings. The CHMP noted a reduction in mean adrenal gland, seminal vesicle/prostate gland, and combined epididymis weights at prasugrel doses of 300 mg/kg/day in the fertility rat study. There were no treatment-related histopathologic changes in these tissues in the 3- and 6-month rat studies and no effects in the dogs, except one early two week pilot study, in which atrophy of seminiferous epithelium in testes with slight-to-moderate nature was observed at high doses. This observation in dogs was comparable with the historic controls and did not appear in rats. Further evaluation of the data confirmed there were no effects on fertility, sperm count and sperm motility in rats. Overall, no reproductive risk could be concluded.

- Toxicokinetic data

Toxicokinetic data were collected from repeated dose studies in mice, rats and beagle dogs. Safety margins based on plasma drug exposures were determined for the active metabolite R-138727 and for R-106583 in the relevant studies. In addition, safety margins based on administered dose/body surface area have also been determined (please see *Pharmacokinetics*).

- Local tolerance

No study on local tolerance was performed. This is considered acceptable since prasugrel is administered orally. However, exposure of the skin or the eyes to prasugrel may occur during the manufacturing process. Two irritation tests were conducted in rabbits. In the hazard evaluation studies conducted in New Zealand white rabbits, prasugrel was a mild ocular irritant and its administration to the conjunctival sac of rabbits resulted in iritis and conjunctivitis, which resolved within 24 hours and seven days after the treatment, respectively. Prasugrel did not cause dermal irritation following a single application of 1000 mg/kg to the skin of rabbits.

- Other toxicity studies

Antigenicity

Prasugrel was tested for antigenicity in mice and guinea pig. Based on the results obtained from these tests, prasugrel is not expected to be antigenic.

Immunotoxicity

No specific tests for immunotoxicity were conducted and this was justified by the results of standard toxicity tests or based on pharmacologic properties of the compounds. It was argued that the available clinical safety data did not reveal any prasugrel related hypersensitivity reactions or suggest any increase in infection in the prasugrel *vs* clopidogrel treatment groups. There is no direct link between prasugrel and allergic reactions, but due to the fact that other thienopyridines have been associated with allergic reactions, these have been identified as potential risks in the RMP and are subject to a range of surveillance activities.

Phototoxicity

Distribution studies showed that prasugrel metabolites are distributed to the skin and eye ball in levels of 1/10 of the plasma concentration after single exposure, with some potential to accumulate after repeated dosing. The phototoxic potentials of R-138727 and R-106583 were evaluated *in vitro* examining the uptake of Neutral Red in the presence or absence of light using Balb/c 3T3 cells of mouse fibroblast cell line in the range of 290-700 nm. For R-138727, the Photo Irritation Factor (PIF) was below 2 (i.e. non-phototoxic). For R-106583, the PIF was not determined because the cell survival was >50%, with or without irradiation and indicated no remarkable cytotoxicity up to the maximum concentration of 1000 µg/mL. Nevertheless, R-138727 was determined as "probably phototoxic" in a second study employing the same dose range and experimental design, with a PIF of >2 (i.e., PIF 4.31). R-106583 was negative. According to the Note for guidance on phototoxicity testing (CPMP/SWP/398/01) it was not shown that prasugrel and/or its metabolites are not phototoxic and the CHMP raised a question on this issue. In response, it was shown that other non-clinical and clinical data indicate that evidence of the phototoxic potential of prasugrel is weak and of questionable clinical relevance. Nevertheless, phototoxicity was included as a potential risk in the RMP. The lack of photoallergy and photogenotoxicity is acceptable in light of the weak evidence of the phototoxic potential.

Studies on impurities

The potential toxicities of most of the prasugrel impurities were evaluated as part of the non clinical toxicology studies. All impurities above 0.15 % were qualified either by separate genotoxocity studies and a 14-day repeat dose study or toxicological studies. Based on the studies, the overall specifications for impurities CATP and diketone were considered justified from a toxicological perspective.

Ecotoxicity/environmental risk assessment

Environmental chemistry, fate and effects data were collected for prasugrel as recommended in the Guideline for environmental risk assessment of medicinal products for human use

(CHMP/SWP/4447/00). The Phase I estimate of maximum exposure to all prasugrel residue in surface water predicted an exposure above the 0.01 µg/L and thus, a complete risk assessment (Phase II Tier A) according to the current guideline has been conducted. No likely risk has been identified with regard to aquatic organisms in either ground water or surface water, neither for sediment dwelling organisms.

2.4 Clinical aspects

Introduction

This full application concerns centralised procedure in accordance with the Regulation (EC) No 726/2004, Article 3(2)(a). It is submitted in accordance with Article 8(3) in Directive 2001/83/EC for a new active substance. Conditional approval, an approval under exceptional circumstances or an accelerated review are not requested

Prasugrel is an inhibitor of platelet activation and aggregation through the irreversible binding of its active metabolite to the $P2Y_{12}$ class of ADP receptors on platelets. Since platelets participate in the initiation and/or evolution of thrombotic complications of atherosclerotic disease, inhibition of platelet function can result in the reduction of the rate of cardiovascular events such as death, myocardial infarction, or stroke.

The approved indication is:
EFIENT, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).

Scientific advice for the product was requested from the CHMP in 2004. The given advice concerned, among others, the population included in the clinical development programme and the number of studies to be conducted, choice of a comparator and clinical endpoints in the clinical studies, use of aspirin as co-therapy or monitoring of safety of patients. It is claimed that the relevant scientific guidelines were followed.

There is no paediatric development programme. According to the European legislation valid at the time of submission, there was no need to submit a paediatric investigation plan before July 2008.

At the time of submission, the prasugrel clinical development program consisted of 46 completed placebo-controlled or active-comparator (clopidogrel) controlled studies. In the majority of studies, subjects were randomly assigned, in an open-label or blinded fashion, to treatment using either parallel or crossover designs. Across all studies, 8656 subjects received at least one dose of prasugrel.

Summary of the key studies in the prasugrel clinical development program.

Study Alias	Study Type	Subjects (N)	Overall Conclusions
H7T-EW-TAAA, H7T-EW-TAAE, H7T-EW-TAAJ	Phase 1 Dose Ranging (single dose, multiple dose regimens) +/- aspirin Doses from 5 mg - 60 mg; daily multiple doses of 5 - 15 mg for up to 21 days	Healthy TAAA (42) TAAE (45) TAAJ (68)	Higher, faster, and more consistent IPA versus 300-/75-mg LD/MD clopidogrel
H7T-EW-TAAD	Phase 1b Dose Ranging (multiple LD/MD regimens) 28-day duration	Stable atherosclerosis (101)	Higher, faster, and more consistent IPA versus300-/75-mg LD/MD clopidogrel
H7T-MC-TAAH	Phase 2 Dose Ranging Safety (multiple LD/MD regimens) 30-day duration	Elective and urgent PCI (905)	60-/10-mg LD/MD prasugrel showed comparable TIMI Major + Minor bleeding to 300-/75-mg LD/MD clopidogrel, trend towards decreased 30-day MACE
H7T-MC- TABR	Phase 1b Comparative PK/PD (60-/10-mg LD/MD prasugrel vs 600-/75-mg LD/MD clopidogrel regimens) 28-day duration	Stable CAD (110)	More rapid onset of higher and less variable IPA versus 600-/75-mg LD/MD clopidogrel
H7T-MC-TABL	Phase 2 Comparative PD (60-/10-mg LD/MD prasugrel vs 600-/150-mg LD/MD clopidogrel regimens). 30-day duration	Elective PCI (201)	More rapid onset of higher IPA versus 600-/150-mg LD/MD clopidogrel
H7T-MC-TAAL	Phase 3 Pivotal Study (60-/10-mg LD/MD prasugrel vs 300-/75-mg LD/MD clopidogrel regimens) with aspirin Maximum duration 15 months	PCI in ACS (13608)	Superior efficacy for 60-/10-mg LD/MD prasugrel vs 300-/75-mg LD/MD clopidogrel regimens with higher risk of bleeding

Abbreviations: ACS = acute coronary syndromes; CAD = coronary artery disease; IPA = inhibition of platelet aggregation; LD = loading dose; MACE = major adverse cardiovascular events; MD = maintenance dose; N = number randomly assigned to prasugrel and/or clopidogrel; PCI = percutaneous coronary intervention; PD = pharmacodynamic; PK = pharmacokinetic; PK/PD = pharmacokinetic/pharmacodynamic; TIMI = Thrombolysis In Myocardial Infarction. [[HG. Source Module 5.2.6]]

GCP

As claimed by the applicant, clinical trials were performed in accordance with GCP. A statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC was also provided. The assessment of the clinical data did not raise concerns about their compliance with GCP. No inspection was requested.

Pharmacokinetics

Prasugrel is administered as a racemic prodrug that is metabolized *in vivo* to the active moiety, R-138727, which irreversibly binds to the platelet $P2Y_{12}$ receptor and blocks activation and aggregation induced by the $P2Y_{12}$ agonist adenosine diphosphate (ADP). The R-138727 metabolite is formed very rapidly during first-pass metabolism.

The pharmacokinetics of prasugrel's active metabolite (R-138727) in healthy subjects was assessed in various clinical pharmacology studies by conventional non-compartmental methods and by population analysis. A meta-analysis of non-compartmental pharmacokinetics estimates from 16 phase 1 studies consolidated exposure estimates from 506 healthy male and female subjects and evaluated the effect of specific subject factors on exposure to the active metabolite.

Formulation development

Prasugrel development began with prasugrel base, which was used in the earlier studies in healthy subjects and subjects with stable atherosclerosis. Decision to switch to prasugrel hydrochloride was made after study TAAC showed that the C_{max} and AUC of prasugrel's inactive metabolites were greatly reduced when prasugrel base was given to healthy subjects whose gastric pH was ≥6 at the time of dosing. This was believed to be of a potential consideration for patients taking concomitant treatment with proton pump inhibitors (PPIs) or H_2-receptor antagonists, which also raise gastric pH. Because the solubility of prasugrel hydrochloride is higher than that of prasugrel base at higher pH, switching from the base to the hydrochloride salt might lessen the impact of elevated gastric pH in patients taking PPIs and H_2-receptor antagonists. Formulation strategy for the hydrochloride salt of prasugrel focused on developing an immediate-release tablet for oral administration. Initially, a 10-mg tablet was developed, which is to be used for both, the 60-mg loading dose (LD) and the daily 10-mg maintenance dose (MD). Later a 5-mg tablet was developed to provide increased dosing flexibility. The proposed commercial 10-mg tablet formulation was used in the pivotal, phase 3 study TAAL, and thus, no bioequivalence study was performed.

- Absorption

Prasugrel is rapidly absorbed after oral administration and is not detected in plasma. However, prasugrel's active metabolite (R-138727) appears in plasma rapidly after the oral dosing, reaching a peak concentration (C_{max}) in about 30 minutes and declining bi-phasically with a terminal half life of approximately 7.4 hours. The average C_{max} of active metabolite is 475 ng/ml after a 60-mg LD and 70 ng/mL during 10-mg MD. The time to reach the maximum plasma concentration (t_{max}) is at a median of 0.5 hours. It was estimated that approximately 79% of a prasugrel dose is absorbed. The between-subject and within-subject variability is 27.6% and 19.3%, respectively, for active metabolite AUC, and 30.1% and 38.1% respectively, for active metabolite C_{max}.

It was found that two 5-mg prasugrel hydrochloride tablets were bioequivalent with one 10-mg prasugrel hydrochloride tablet. During tablet manufacturing and storage, prasugrel hydrochloride tablets can convert to prasugrel base. The conversion from salt to base up to 70% has no impact on the extension and rate of the bioavailability of prasugrel at normal gastric pH, and furthermore, as study TACR confirmed, a 5 to 70% conversion of prasugrel hydrochloride tablets to prasugrel base did not affect the AUC or C_{max} of R-138727 in healthy subjects with normal gastric pH. There is a procedure in place with the aim of controlling the conversion and keeping it within this rate. The influence of food was assessed with a 25 mg and 15 mg dose of prasugrel. One of the effect of food on R-138727 AUC was the lower absorption rate, with C_{max} being 48.8% lower in the fed state, t_{max} delayed from 0.5 to 1.5 hours. Although an important pharmacokinetic parameter during maintenance dose is AUC, C_{max} is considered relevant in patients who receive a loading dose in order to achieve a more rapid onset of the pharmacological effect. Although the percutaneous coronary intervention (PCI) is usually performed in the fasted state, it is necessary to point out the importance of the administration of prasugrel loading dose in fasted state in the SPC. The CHMP thus proposed to revise the SPC wording to reflect that the onset of action of the loading dose may be most rapid in the fasted sate and this new wording was accepted.

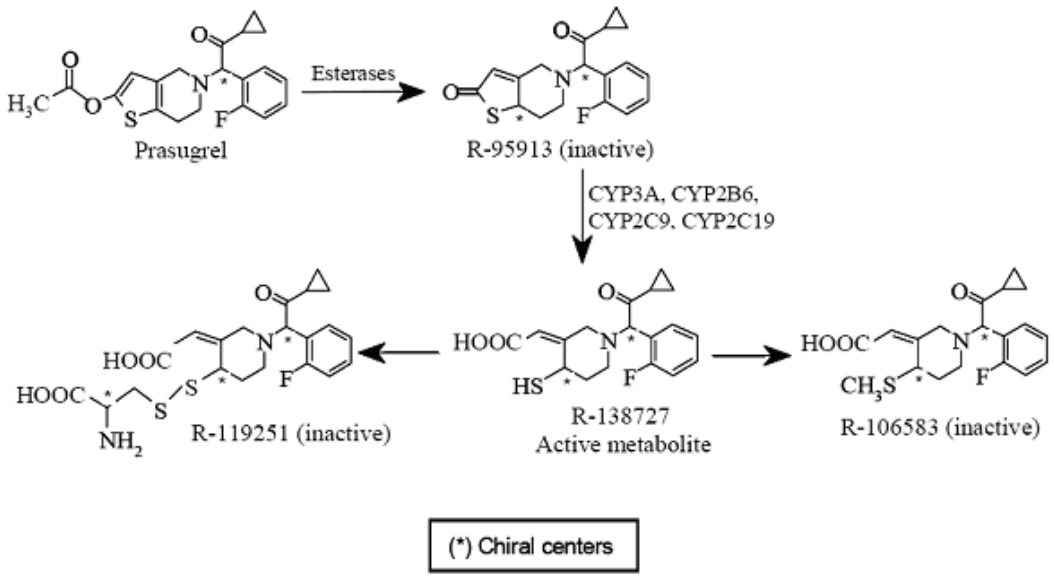
- Distribution

Estimates of apparent volume of distribution of R-138727 ranged between 40.3-66.4 l in healthy subjects and subjects with stable atherosclerosis. Prasugrel metabolites demonstrated limited penetration into red blood cells and the plasma-to-whole blood ratio was generally greater than one suggesting that radioactivity in the plasma was greater than that in an equivalent volume of blood cells. Because R-138727 is unstable in plasma, its binding to plasma proteins could not be determined. However, in a 4% human serum albumin solution in phosphate buffer at pH 7.4, R-138727 was 98% bound. For the inactive metabolites, the fraction bound to plasma proteins at various concentrations determined by ultracentrifugation, was 94.6% for R-95913, 95.1% for R-106583, and 76.4% for R-119251. Thus, the active metabolite is highly bound to protein and the measured concentration will depend on the protein content, which may be influenced by factors such as renal function, age and concomitant medication. However, only a minor fraction is unbound and this is not likely to change

significantly. Although the total concentration of the active metabolite might be lower, the effect of the drug may be similar patients with renal failure to that found in healthy persons.

- Elimination

Prasugrel is *in vivo* rapidly hydrolysed by esterases and the product of this hydrolysis, the pharmacologically inactive thiolactone R-95913, is metabolised to the active metabolite R-138727 mainly by cytochrome P450 CYP3A and CYP2B6, and, to a lesser extent, by CYP2C9 and CYP2C19. R-138727 is further metabolised to two inactive compounds by S-methylation or conjugation with cysteine (R-119251 and R-106583). Other prasugrel metabolites are formed by oxidation and/or conjugation and are not pharmacologically active. In case of the active metabolite R-138727, which is eliminated by S-methylation and conjugation with cystein, it is unclear which enzyme is involved in the elimination of the active metabolite. The CHMP was concerned about the clinical relevance of this issue and requested further clarifications. Based on the *in vitro* study, it would appear that thiopurine S-methyltransferase (TPMT) is not responsible for the S-methylation of R-138727 to R-106583 and that the S-methylation appeared mainly in human liver microsomes. Formation of R-106583 was inhibited by an inhibitor of thiol S-methyltransferase (TMT). The results thus suggest that TMT, and not TPMT, is responsible for R-106583 formation from prasugrel's active metabolite in human liver. However, possible inhibition of TMT by other drugs is unknown. It is considered beneficial that the rapid and efficient generation of the active metabolite of prasugrel results in its rapid appearance in plasma and consequently, in a rapid and extensive inhibition of platelet aggregation. Prasugrel exposure appears to be essentially unaffected by CYP inhibitors, inducers, and competitive inhibition by CYP substrates.



Simplified prasugrel metabolic pathway.

Approximately half of the active metabolite amount appearing in plasma is formed during absorption and/or during first-pass metabolism in liver, which explains the rapid appearance of active metabolite in plasma. Other prasugrel metabolites are formed by oxidation and/or conjugation and are not pharmacologically active.

Approximately 95% of a [^{14}C]prasugrel dose was recovered after oral administration. It was estimated that ca 68% of the prasugrel dose is excreted in urine and 27% in faeces in form of the inactive metabolites over a period of 10 days. Thus, urinary excretion is the major pathway for the elimination of prasugrel metabolites. The elimination half-life of R-138727 is about 7.4 hours. No R-138727 is detected in urine or faeces.

- Dose proportionality and time dependencies

Time dependency has not been specifically addressed. Several clinical studies support the evidence that exposure to prasugrel's active metabolite is dose-proportional. Furthermore, the comparison of $AUC_{(0-4)}$ and C_{max} values for the active metabolite with the dose shows a linear relationship with no discernable deviation from linearity over the entire dose range of 5 - 60 mg.

- Special populations

Impaired renal function

The effect of renal impairment on the disposition of prasugrel metabolites and platelet aggregation was investigated in three clinical studies (TAAO, TABW, and TACJ). Included were subjects with end stage renal disease, subjects with moderate renal impairment

Moderate Renal Impairment and End Stage Renal Disease (ESDR)

The $AUC_{(0-tlast)}$ and C_{max} values for the active metabolite R-138727 both averaged 38% lower in subjects with ESRD on dialysis across the dose range of 5- 60mg than in subjects with normal renal function. The lower active metabolite exposure in subjects with ESRD is generally consistent with an analysis across all three studies, TAAO, TABW and TACJ, in subjects with ESRD who received a 60-mg LD of prasugrel. Despite the differences in active metabolite exposure, platelet aggregation response to prasugrel is similar in ESRD and healthy subjects. Although subjects older than 65 typically have some degree of renal impairment, no differences in AUC or C_{max} of the active metabolite were observed in a clinical setting. Exposure to the active metabolite was comparable in subjects with moderate renal impairment (estimated creatinine clearance of 30-50 mL/min) and matched healthy controls; although median exposure to prasugrel's active metabolite was higher by approximately 22% in subjects with mild renal impairment than in subjects with normal renal function. The analyses of subjects with renal impairment in clinical pharmacology studies and in the substudy in phase 3 trial do not support the need for a dose adjustment for renal impairment. The CHMP, however, requested more information regarding the observed inconsistency in the pharmacokinetic parameters, especially as patients with end stage renal function seem to have lower levels of the active metabolite compared to healthy subjects. Plausible explanations for the comparable efficacy between ESRD patients and healthy adults were provided and these do not suggest that the dose adjustments are warranted. Nevertheless, the risk of bleeding episodes may be increased in patients with ESRD and the need for caution is reflected in the SPC.

Impaired hepatic function

Two Studies were performed in patients with mild to moderate hepatic function (Child-A and Child-B). Based on these results no dose adjustment in this population appears necessary, however, caution should be exercised in patients with moderate hepatic impairment. Clinical trials performed with prasugrel have not included patients with severe hepatic impairment (Child-C). As this population has a higher risk of bleeding, a contraindication in the SPC for patients with severe hepatic impairment (Child Pugh Class C) was included.

Gender

The pharmacokinetic meta-analysis of 16 clinical pharmacology studies detected no effect of gender on the exposure to prasugrel's active metabolite.

Race

The effect of ethnic origin was assessed in the pharmacokinetic meta-analysis of 16 clinical pharmacology studies. Most of the 437 subjects evaluated after a prasugrel LD and 284 subjects evaluated during prasugrel MD were Caucasian, although about 22% were Asian. Most Asian subjects in the meta-analysis originated from the three clinical pharmacology studies specifically designed to assess the influence of Asian ethnicity on prasugrel pharmacokinetics and pharmacodynamics. In each of these studies, Caucasian subjects served as the reference population.

Active metabolite exposure was similar in Chinese, Japanese, and Korean subjects after a 60-mg LD and during 10-mg and 5-mg MDs. However, the analysis showed that $AUC_{(0-tlast)}$ in Asians was 40% higher during MD and compared to Caucasians, the higher exposures in Asians produced higher inhibition of platelet aggregation (IPA) at most time points. Asians and Caucasians in the LD portion

of the pharmacokinetic meta-analysis had mean body weights of 65 kg and 77 kg, respectively, so the meta-analysis compared weight normalised $AUC_{(0\text{-tlast})}$ and C_{max} values between Asians and Caucasians to assess the contribution of weight to exposure. After adjusting for body weight, the $AUC_{(0\text{-tlast})}$ of the active metabolite was still approximately 19% higher in Chinese, Japanese, and Korean subjects compared to that of Caucasians, predominantly related to higher exposure in Asian subjects <60 kg. No dose adjustment is recommended based on ethnicity alone, but therapeutic experience with prasugrel is limited in Asian patients and therefore, prasugrel should be used with caution.

Weight
Analyses of several clinical studies in healthy subjects, subjects with stable atherosclerosis and subjects with acute coronary syndrome undergoing PCI consistently show that the AUC of the prasugrel active metabolite increases with a decreasing body weight. The relationship between the body weight and the active metabolite AUC was assessed using a conventional statistical approach that relied on univariate and multivariate analyses to quantify the magnitude of the body weight effect on active metabolite exposure. In healthy subjects, weight was one of the two covariates declared clinically significant in a multivariate analysis of these data, the other being Asian ethnicity. The univariate analysis supports consideration of dose adjustment at any weight threshold from ≥55 kg through 80 kg, while the multivariate analysis supports dose adjustment consideration at any weight threshold from ≥50 kg through 80 kg. In subjects with ACS undergoing PCI in Study TAAL, weight was one of the tree covariates declared significant during a multivariate analysis of these data, the other two being age and gender. The univariate analysis of the body weight effect supports consideration of dose adjustment for subjects <70 kg, but not for subjects ≥75 kg. The multivariate analysis of the body weight effect supports dose adjustment consideration for subjects <55 kg, but not for subjects ≥59 kg. The similarity in conclusions between the univariate and multivariate analyses clearly show that body weight is an important covariate. Further analyses of the risk for TIMI bleeding by different weight indicate that the odds ratio for bleeding with 10 mg prasugrel increases rapidly in the vicinity of 60 kg (and 75 years of age); supporting these values as cut-off choices for dose adjustment. A PK/PD model to assess the effect of the reduced dose (5 mg) in subjects < 60 kg or ≥75 years of age was developed and although the results are reassuring, clinical confirmation is needed (please see section Clinical Efficacy). Thus, the CHMP accepted the follow up measure to conduct a clinical study in subjects with stable CAD to compare the PK, PD, safety, and tolerability of prasugrel in subjects <60 kg to that of subjects ≥60 kg**.** Subjects will be treated with a maintenance dose of either prasugrel 5-mg, prasugrel 10-mg, or clopidogrel 75-mg. This study will exclude subjects ≥75 years. In addition, the SPC advises that the 10 mg maintenance dose is not recommended in subject weighing <60 kg.

Elderly
Age was one of 3 covariates declared statistically significant during a multivariate analysis of TAAL data as described above. When exposure was normalized by body weight, the 90%CI for the effect of age was below 1.25 for all age thresholds from 50 to 80 years old. Despite the lack of relationship between age and AUC in the multivariate analyses above, safety analyses of study TAAL revealed a strong relationship between bleeding risk and age, with a higher rate of bleeding in subjects ≥75 years old compared to those <75 years old. This prompted more extensive assessments of active metabolite exposure in the elderly.

The analysis focused on exploring the differences in exposure in patients approximately at and below the median age in the TAAL study compared to exposure in patients whose age was above specific thresholds up to 85 years. Based on this, a consideration of dose adjustment should be made at 70 years and more, with specific dose recommendations and the age thresholds associated with those recommendations depending on safety. Furthermore, an assumption was made about the anticipated clinical use of prasugrel where patients <60 kg would receive a 5-mg MD rather than a 10-mg MD, and patients ≥60 kg would then be considered for dose adjustment based on their actual age. In this approach a univariate analysis of age effect in subjects ≥60 kg is clinically more relevant and when this subgroup of patients ≥60 kg is assessed, the active metabolite AUC for patients ≥74 years is significantly larger than that for patients <74 years. Consistent with this difference, more than 60% of

patients ≥60 kg and ≥75 years old had concentrations above the median exposure in the TAAL study. This supports consideration of dose adjustment at any age threshold of 75 years or older, although specific dose recommendations and the age thresholds associated with those recommendations depend on safety.

In summary, age is a significant risk factor for bleeding. A cut-off level of 75 years based on a pharmacokinetic univariate analyses in subjects ≥ 60 kg is suggested.. This issue was addressed during the Scientific Advisory Group (SAG) meeting and in the oral explanation held at the CHMP meeting (please see section on Clinical Efficacy). Based on the CHMP discussions following the SAG meeting, Company written responses and oral explanation, the CHMP requested a strict SPC wording, which advises that the use of prasugrel in patients ≥ 75 years of age is generally not recommended. If use is deemed necessary based on careful individual benefit/risk evaluation by the prescribing physician, then following a 60 mg loading dose a reduced maintenance dose of 5 mg should be prescribed. An educational programme with regard to this topic is part of the conditions for the safe and effective use of the product (see sections 2.4 and 2.5). The results of the analysis conducted *via* a PK/PD model to evaluate the dose 5 mg in patients < 60 kg or ≥ 75 years of age need clinical confirmation and the Company is conducting such studies as part of the follow-up measures..

- Pharmacokinetic interaction studies

In vitro, prasugrel metabolites R-138727 and R-106583 did not inhibit the activities of cytochrome P450 CYP2D6, CYP2C9, CYP2C19, CYP1A2 and CYP3A4 hepatic isoforms up to 200 μM. The other major metabolite, the hydrolysis product R-95913, did not inhibit CYP1A2, but did inhibit CYP2D6, CYP2C9, CYP2C19 and CYP3A4. The projected maximum inhibition ranged from 2% for CYP2C9 to 21% for CYP2C19. None of these effects were deemed as a cause of a significant effect in the clearance of drugs metabolised by these enzymes. The effect of prasugrel on CYP1A2 and CYP3A4 was also assessed in primary cultures of human hepatocytes from four donors at various concentrations. No effect was observed on CYP1A2, but R-95913 showed a slight to moderate induction of CYP3A4 at a clinically relevant concentration. In order to further assess the clinical consequences of the signals detected from *in vitro* studies, a number of *in vivo* studies, including the assessment of pharmacokinetic interactions with aspirin, rantitidine, ketoconazole (CYP3A4/5 inhibitor), rifampicin (inducer of several CYP enzymes), atorvastatin, bupropion (a CYP2B6 substrate), warfarin, and heparin was conducted. An interaction study with digoxin was also conducted; aiming at the assessment of the effect of prasugrel on P-glycoprotein. Only a slight inhibitory effect of prasugrel on CYP2B6 (decreased hydroxibupropion exposure by around 20-30%) was observed. This effect is likely to be of clinical concern only if prasugrel is co-administered with drugs for which CYP2B6 is the only metabolic pathway and have a narrow therapeutic window. This concern of the CHMP is adequately expressed into the SPC of this medicinal product. Furthermore, inhibition or induction of CYP3A4 enzyme did not indicate any significant effect on prasugrel. Co-administration of prasugrel with digoxin at steady state did not significantly affect digoxin renal clearance and overall pharmacokinetics. Furthermore, prasugrel showed a lack of influence on the pharmacokinetics of S-warfarin, but caution should be exercised when prasugrel and warfarin are given together due to the potential increased risk of bleeding. Similarly, additional consideration is necessary during the co-administration of prasugrel with heparin as stated in SPC ("an increased risk of bleeding is possible when Efient is co-administered with heparin"). Daily co-administration of products elevating the gastric pH value, e.g. ranitidine or lansoprazole, did not change the metabolite's AUC and T_{max}, but decreased the C_{max} by 14% and 29%, respectively. Although in the maintenance therapy the C_{max} changes could be considered of less clinical relevance, in the loading dose when the intention is to achieve maximum inhibition of the platelet aggregation as quickly as possible, the C_{max} is considered a clinically relevant parameter. Therefore, a recommendation in the SPC that administration of the loading dose without concomitant administration with proton pump inhibitors may provide most rapid onset of action was included. In summary, the potential for pharmacokinetic interactions with prasugrel was adequately studied both *in vitro* and *in vivo*.

Pharmacodynamics

Platelets play a central role in the pathogenesis of atherothrombosis and in the formation of thrombi following coronary angioplasty, with and without stent implantation. Platelets initially adhere at sites of vascular injury, atherosclerotic plaque rupture, balloon angioplasty, and stenting. Platelet activation following these interactions results in the release of adenosine diphosphate (ADP), thromboxane A2, and other mediators. Released ADP promotes platelet activation *via* the G-protein linked $P2Y_1$ and $P2Y_{12}$ purinergic receptors leading to further platelet activation, aggregation, and other platelet functions, such as platelet shape change, secretion, and the development of pro-coagulant and pro-inflammatory activities. Activated platelets are recruited to sites of coronary plaque rupture and intra-arterial stenting, thereby forming aggregates that may lead to platelet-rich thrombi, vascular occlusion, tissue ischemia, and myocardial necrosis in what is collectively known as acute coronary syndromes.

Prasugrel is a thienopyridine ADP receptor antagonist that irreversibly inhibits platelet activation and aggregation mediated by the P2Y12 receptor. Prasugrel has a distinct chemical structure that permits efficient conversion to its active metabolite through rapid hydrolysis by carboxylesterases and then by multiple CYP450 enzymes.

- Mechanism of action

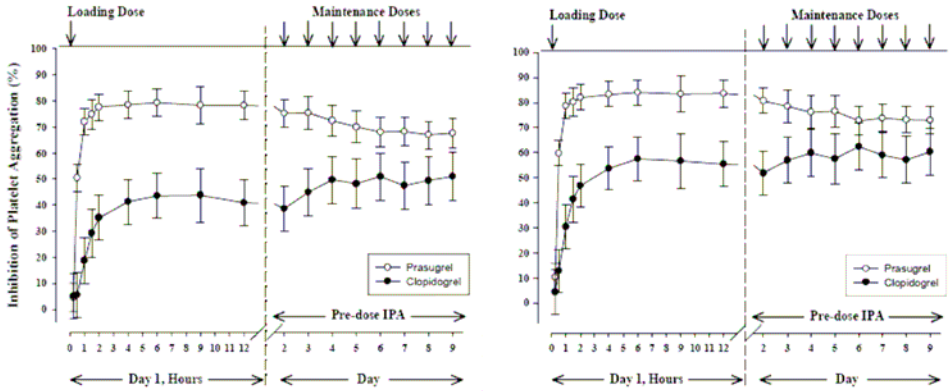
Prasugrel's pharmacological action is analogous to that described for other thienopyridines and results from covalent and irreversible binding of the active metabolite R-138727 to the $P2Y_{12}$ platelet ADP receptor. Once bound, a platelet is rendered ineffective for its remaining lifespan. After prasugrel administration is stopped, return to baseline platelet aggregation occurs only as new platelets are formed. The return to the baseline typically occurs at about 7 - 10 days after treatment is interrupted.

- Primary and Secondary pharmacology

Four initial studies assessing the safety, pharmacokinetic and pharmacodynamics of prasugrel in small numbers of healthy subjects allowed for the initial assessment of prasugrel activity, but did not analyze for prasugrel's active metabolite. Subsequently, four studies aimed at characterisation of the prasugrel hydrochloride salt and four initial clinical studies were conducted with prasugrel base to characterise pharmacokinetic, pharmacodynamics and tolerability in healthy subjects. Pharmacodynamics effects of thienopyridines on platelet function may be assessed by inducing platelet aggregation with various concentrations of ADP. Response to 20 µM ADP has been used as the primary pharmacodynamic parameter considering that it is a specific indicator of $P2Y_{12}$ function. Four clinical studies were conducted to evaluate the prasugrel-mediated inhibition of platelet aggregation and to characterise prasugrel's safety and tolerability, its pharmacokinetic and pharmacodynamic profile, effects on platelet function and bleeding time. In all tests, effective inhibition of platelet aggregation was observed with the onset of effect occurring within 1 hour of dosing. The effect continued through 48 hours post dosing. Platelet aggregation returned to normal levels at day 7. Reported adverse events included gastrointestinal disturbances, autonomic disturbances and general disorders, but none were serious.

A meta-analysis of pharmacodynamic data across the studies in healthy subjects and in subjects with stable atherosclerosis was conducted (see figure below) and the results indicate that within 30 minutes, the average inhibition of platelet aggregation (IPA) exceeds 50%. This time point is a key value, because it is the first assessed time point at which the IPA shows a statistically significant difference from baseline. Furthermore, within 1 hour, 97% of the subjects achieved an IPA above 20%, with the average IPA exceeding 70%. Over 89% of all subjects achieved at least 50% IPA by 1 hour, and over 90% of the maximum mean IPA is achieved by that time. One hour is a relevant time point because the average IPA across all subjects after a prasugrel 60-mg LD is nearly as high as the peak IPA eventually reached. By 4 hours, the average IPA is about 80%. More than 99% of the prasugrel subjects in the meta-analysis had an IPA above 20%, and about 90% of subjects achieved 90% of their individual maximum IPA by then. At each of these time points, a 300-mg clopidogrel LD showed a lower peak of IPA, fewer subjects achieved $\geq$20% IPA. The results in response to 5 µM ADP are similar. Following the administration of a single dose of prasugrel to healthy subjects not taking acetylsalicylic acid, platelet aggregation returned to normal levels by day 6 after a single administration of 30- or 75-mg dose of prasugrel base. After multiple doses of prasugrel to healthy

subjects taking acetylsalicylic acid, platelet aggregation returned to baseline levels in 5 days following discontinuation of MD at steady-state.



Abbreviations: CI = confidence interval; IPA = inhibition of platelet aggregation; LD = loading dose; MD = maintenance dose.
Note: Arrows (↓) indicate dosing.
Source: Meta-analyses of PK and PD, Figure APP2.7.2.12

Figure 2.7.2.10. Least squares mean (±95% CI) IPA to 20 μM (left panel) and 5 μM (right panel) after prasugrel 60-mg LD/10-mg MD and clopidogrel 300-mg LD/75-mg MD – PD Meta-analysis.

In summary, the results of the evaluation of the pharmacodynamic effects of prasugrel as an inhibitor of platelet aggregation were expressed as maximum platelet aggregation (MPA), which decreases with increasing pharmacodynamic response, and IPA, which is derived from the MPA determination and increases with increasing pharmacodynamic response. Clinical studies comparing the pharmacodynamic response of prasugrel with that of clopidogrel at the loading or loading/maintenance doses showed that the maximum mean IPA was achieved faster and was greater with prasugrel. Greater pharmacodynamic response for prasugrel is believed to be the result of the more rapid and more extensive formation of its active metabolite and has a less response variability compared to clopidogrel.

No relevant pharmacodynamic interactions were noticed when prasugrel is coadministered with unfractioned ranitidine, ketoconazole, atorvastatin, unfractionated heparin, digoxin and warfarin. There is an additive pharmacodynamic interaction between aspirin and prasugrel, in terms of suppression of platelet aggregation induced by collagen. The pivotal evidence of prasugrel in the claimed indication has been obtained as an add on therapy to low dose aspirin and thus, the potential safety risk of this interaction has been evaluated. In addition, the metabolic pathways for aspirin are separate from those for prasugrel and therefore no metabolic interaction would be expected. Co-administration of ketoconazole, a potent inhibitor of CYP3A4 and CYP3A5, with prasugrel did not significantly affect the exposure of the active metabolite of prasugrel, or the drug's effect on platelet inhibition. The possibility that the pharmacokinetics of prasugrel could be affected by inhibiting two or more pathways involved in prasugrel's metabolism was considered; however, only ticlopidine was listed as an acceptable CYP2B6 inhibitor. In addition, clopidogrel is the other drug that was clinically shown to be potent, mechanism-based inhibitor of CYP2B6. Because co-administering either of these drugs with prasugrel would not be considered in clinical practice, clinical evaluation of concomitant administration of prasugrel and of CYP2B6 (ticlopidine or clopidogrel) was not conducted. A clinical study aiming to assess the effect of 80 mg of prasugrel (single dose) on cardiac repolarisation was conducted including placebo and moxifloxacin as positive controls. The study design was in agreement with the ICH-E14 guideline. No effect of prasugrel on QT was observed above the threshold of regulatory concern (10 msec) at any time point. The positive control (moxifloxacine) showed a maximum QT prolongation effect within the expected range.

Clinical efficacy

The following studies have been conducted in order to support the use of prasugrel for the reduction of atherothrombotic events (CV death, nonfatal MI, or nonfatal stroke) in subjects with ACS:

Study Alias	Study Type	Subjects (N)	Primary Objective	Overall Conclusions
H7T-MC-**TAAH**	Phase 2 Dose Ranging Safety (multiple LD/MD regimens) Prasugrel (40-mg LD, 7.5-mg MD) Prasugrel (60-mg LD, 10-mg MD) Prasugrel (60-mg LD, 15-mg MD Clopidogrel (300-mg LD, 75-mg MD): All treatments were co-administered with aspirin. 30-day duration	Elective and urgent PCI (905)	1) Evaluate the safety of increasing doses of prasugrel by observing the rate of Non-CABG-associated significant bleeding (that is, Major plus Minor bleeding at 30 to 35 days after PCI). 2) Compare the safety of prasugrel to a standard regimen of clopidogrel (a 300-mg LD during PCI and 29 to 34 days of a 75-mg once daily MD) by observing the rate of Non- CABG- associated significant bleeding 30 to 35 days after PCI	60-/10-mg LD/MD prasugrel showed comparable TIMI Major + Minor bleeding to 300-/75-mg LD/MD clopidogrel, trend towards decreased 30-day MACE
H7T-MC-**TABL**	Phase 2 Comparative PD (60-/10-mg LD/MD prasugrel vs 600-/150-mg LD/MD clopidogrel regimens). 30-day duration	Elective PCI (201)	1) To compare the inhibition of platelet aggregation (IPA) with 20 μM ADP measured at 6 hours (±30 minutes) after prasugrel 60-mg LD versus clopidogrel 600-mg LD in subjects who did not receive a GP IIb/IIIa antagonist. 2) To compare the IPA with 20 μM ADP measured after 14±2 days of prasugrel 10-mg daily MD versus the IPA after 14±2 days of clopidogrel 150 mg daily MD in the "on-treatment population" who received PCI regardless of GPIIb/IIIa antagonist use (this included subjects receiving prasugrel and clopidogrel, in either order, during crossover)	60-/10-mg LD/MD prasugrel showed more rapid onset of higher IPA versus 600-/150-mg LD/MD clopidogrel
H7T-MC-**TAAL**	Phase 3 Pivotal Study (60-/10-mg LD/MD prasugrel vs 300-/75-mg LD/MD clopidogrel regimens) with aspirin Maximum duration 15 months	PCI in ACS (13608)	To demonstrate superiority of prasugrel co-administered with aspirin relative to clopidogrel co-administered with aspirin, as measured by a reduction in the composite endpoint of CV death, onfatal MI, or nonfatal stroke at a median follow up of at least 12 months.	Superior efficacy for 60-/10-mg LD/MD prasugrel vs 300-/75-mg LD/MD clopidogrel regimens with higher risk of bleeding

Abbreviations: ACS = acute coronary syndromes; CAD = coronary artery disease; IPA = inhibition of platelet aggregation; LD = loading dose; MACE = major adverse cardiovascular events; MD = maintenance dose; N = number randomly assigned to prasugrel and/or clopidogrel; PCI = percutaneous coronary intervention; PD = pharmacodynamic; PK = pharmacokinetic; PK/PD = pharmacokinetic/pharmacodynamic; TIMI = Thrombolysis In Myocardial Infarction.

- Dose response studies

Phase 3 dose selection was based primarily on 2 randomized clinical studies in subjects with stable atherosclerosis using the approved clopidogrel 300-/75-mg LD/MD regimen as the active comparator. The first study (TAAD) was a 28-day, phase 1b, dose-ranging pharmacokinetic/pharmacodynamic study in aspirin-treated subjects (N=101) comparing platelet inhibition using standard aggregometry. The second study (TAAH) was a 30-day, phase 2, dose-ranging safety study in aspirin-treated subjects (N=905) undergoing elective or urgent PCI (see below). Study TABL was conducted in parallel with the pivotal study TAAL to investigate the safety and pharmacodynamics of prasugrel against higher dose regimens of clopidogrel.

Study TAAD
This was a 28-day, phase 1b, dose-ranging pharmacokinetic/pharmacodynamic study in stable atherosclerosis patients (N=101) treated with aspirin (375 mg), in which the platelet inhibition was compared using the standard aggregometry. It is worth noting that the participants in this study are not entirely representative of those claimed in the indication of the current submission. In this study four different regimens (40 mg/5 mg, 40 mg/7,5 mg, 60 mg/10 mg and 60 mg/15 mg) were compared with the approved clopidogrel LD/MD regimen (300mg/75 mg). Overall, both the 40-mg and 60-mg prasugrel LDs resulted in more rapid onset with significantly greater IPA to 20 µM ADP from 2 to 6 hours after administration than the 300-mg LD of clopidogrel. Both the 10- and 15-mg prasugrel MDs achieved consistent and significantly greater IPA than the 75-mg clopidogrel MD; however, the 15-mg MD of prasugrel was associated with higher bleeding adverse events. In contrast, the prasugrel 5- and 7.5-mg MD groups were not consistently and statistically different in IPA from the clopidogrel 75-mg MD group.

Study TAAH
This was a double-blind, randomized, multicentre, dose-ranging trial of prasugrel compared with clopidogrel in subjects undergoing PCI. The primary endpoints evaluated the safety of increasing doses of prasugrel (a loading dose during PCI and once-daily maintenance dosing for 29 to 34 days) and compared prasugrel's safety with a standard regimen of clopidogrel (300-mg LD during PCI and 75-mg once-daily maintenance dose for 29 to 34 days) by observing the rate of non-CABG-associated significant bleeding (i.e. major and minor bleeding at 30 to 35 days after PCI).

The overall observed rate of all bleeding events was higher for subjects in the combined prasugrel group (29/650 subjects, 4.5%) compared with subjects in the clopidogrel group (9/254 subjects, 3.5%), but this difference was not statistically significant. With regard to the bleeding events, neither the differences among prasugrel dose groups (p=0.933), nor the differences between prasugrel and clopidogrel (p=0.590) were statistically significant. Thus, it was concluded that there was no statistically significant difference in the safety of increasing doses of prasugrel and no statistically significant difference between the safety of prasugrel and the standard clopidogrel regimen. The overall rate of non-CABG-associated significant bleeding was lower than anticipated and this resulted in reduced statistical power to assess the safety of prasugrel. A reduction of dose in the very elderly was recommended based on the pivotal study and is described later.

- Main studies

The pivotal phase 3 Study (H7T-MC-TAAL, further referred to as TAAL) was a global, multicentre, parallel-group, randomized, double–blind, double-dummy, active-controlled study. The primary objective of Study TAAL was to test the hypothesis that prasugrel is superior to clopidogrel in the treatment of subjects with ACS undergoing PCI, as measured by a reduction in the primary composite efficacy endpoint of CV death, nonfatal MI, or nonfatal stroke. This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices (GCP) and the applicable laws and regulations of where the study was conducted. Study TAAL was evaluated based on several relevant guidelines:

- The CONSORT statement (The Lancet 2001;357:1191-94),
- Points to consider on the clinical investigation of new medicinal products for the treatment of unstable angina pectoris or non-Q-wave myocardial infarction, CPMP/EWP/570/98,
- Points to consider on application on one pivotal study (CPMP/EWP/2330/99),
- Points to consider on the clinical development of fibrinolytic medicinal products in the treatment of patients with ST segment elevation acute myocardial infarction (STEMI), CPMP/EWP/967/01.

In addition, scientific advice given by the CHMP in 2004 was considered when planning this pivotal study.

METHODS

Study Participants

Participants were to be of a legal age (and at least 18 years of age) and competent mental condition to provide written informed consent. For women of child-bearing potential, only those tested negative for pregnancy between ACS presentation and enrolment and agreed to use a reliable method of birth control during the study were included. Subjects with ACS (subjects with unstable angina and non-ST-segment elevation myocardial infarction [UA/NSTEMI] with TIMI risk score ≥3 or ST-segment elevation myocardial infarction [STEMI]) who are to undergo PCI were eligible to enter the study. The main inclusion criteria were:

- Moderate- to high-risk UA was defined as a history of chest discomfort or ischemic symptoms of ≥10 minutes duration at rest ≤72 hours prior to randomization, with persistent or transient ST-segment deviation ≥1 mm in one or more ECG leads without elevation of CK-MB or troponin T or I but with a TIMI risk score ≥3.
- Moderate- to high-risk NSTEMI was defined as a history of chest discomfort or ischemic symptoms of ≥10 min duration at rest ≤72 hours prior to randomization with no evidence of persistent ST-segment elevation. Subjects must also have CK-MB or troponin T or I greater than the upper limit of normal (ULN) and a TIMI risk score ≥3.
- ST-segment elevation myocardial infarction (STEMI) is defined as a history of chest discomfort or ischemic symptoms of >20 minutes duration at rest ≤14 days prior to randomization with one of the following present on at least one ECG prior to randomization: a) ST-segment elevation ≥1 mm in two or more contiguous ECG leads. b) New or presumably new left bundle branch block (LBBB). c) ST-segment depression ≥1 mm in two anterior precordial leads (V1 through V4) with clinical history and evidence suggestive of true posterior infarction.

Subjects with STEMI could be enrolled within 12 hours of symptom onset if primary PCI was planned or within 14 days if delayed PCI was planned following initial pharmacotherapy for STEMI.

Exclusion criteria were extensive. In general, these excluded subjects at increased risk of bleeding (for example, anaemia, thrombocytopenia, intracranial pathology, severe hepatic dysfunction, oral anticoagulants, chronic non-steroidal anti-inflammatory drug (NSAID) use, or use of any thienopyridine within 5 days of the main treatment), patients with refractory ventricular arrhythmia, class IV congestive heart. The inclusion/exclusion criteria are considered acceptable. Diagnosis and short-term risk stratification is based on the combination of ischaemic symptoms, ECG changes, biomarkers in some cases and risk score results. The recommendations of the European Society of Cardiology guidelines (2007) were followed.

Treatments

This study involved a comparison of prasugrel (60-mg LD, 10-mg MD) and clopidogrel (300-mg LD, 75-mg MD). Both treatments were administered orally as a one-time LD followed by a once daily MD. The loading and maintenance doses of prasugrel for this Phase 3 PCI study were selected on the basis of non-clinical thrombosis models, non-clinical toxicology studies, dose-escalation studies in healthy subjects, a dose-ranging study versus clopidogrel in subjects with stable coronary artery disease (Study TAAD), and a dose-ranging study versus clopidogrel in subjects undergoing elective or urgent PCI (Study TAAH). Owing to the link observed between thrombosis complications following PCI and poor antiplatelet response to clopidogrel, recommendations for the use of doses higher than the standard in PCI have been reported. There is evidence of some increase in the speed of onset and the level of platelet inhibition with both 600 mg and 900 mg of clopidogrel LDs. Still, these assumptions are based on limited data and require further sound confirmation. Thus, the use of the standard 300 mg LD (administration as soon as possible) and 75 mg/day MD of clopidogrel is acceptable.

Objectives

Primary objective: To test the hypothesis that prasugrel (co-administered with aspirin) was superior to clopidogrel (co-administered with aspirin) in the treatment of subjects with acute coronary syndromes who were to undergo percutaneous coronary intervention, as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median follow-up of at least 12 months.

The secondary efficacy objectives were to compare both treatments with respect to the:

- risk of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke through 90 days.
- risk of CV death, nonfatal MI, or nonfatal stroke through 30 days.
- risk of CV death, nonfatal MI, or urgent target vessel revascularization through 90 days.
- risk of CV death, nonfatal MI, or urgent target vessel revascularization through 30 days.
- risk of all-cause death, nonfatal MI, or nonfatal stroke at study end.
- risk of CV death, nonfatal MI, nonfatal stroke, or rehospitalisation for cardiac ischemic events at study end.
- risk of definite or probable stent thrombosis per Academic Research Consortium (ARC) definition at study end.

The safety objectives of this study were to compare prasugrel with clopidogrel with respect to the:

- risk of non-coronary artery bypass graft (Non-CABG) Thrombolysis in Myocardial Infarction Study Group (TIMI) Major bleeding in subjects receiving prasugrel or clopidogrel.
- risk of Life-Threatening bleeding (a subset of Non-CABG-related TIMI Major bleeding) in subjects receiving prasugrel or clopidogrel.
- risk of Non-CABG-related TIMI Minor bleeding in subjects receiving prasugrel or clopidogrel.
- The overall safety and tolerability of prasugrel administration based on clinical findings, laboratory values, and the occurrence of treatment-emergent adverse events.

Outcomes/endpoints

The primary efficacy measure was time to first event of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke at study end. Cardiovascular Death (CV Death) was defined as death due to documented cardiovascular cause. Additionally, death not clearly attributable to non-cardiovascular causes was considered CV death. The definition of myocardial infarction (MI) was adapted from the standard American College of Cardiology (ACC) definition and was dependent on the clinical timing of the event in relation to presenting syndrome and cardiovascular procedures. A peri-procedural event must be distinct from the index event. If an ischemic biomarker was elevated at the onset of the suspected event, there must be demonstration of a falling biomarker level prior to the onset of the suspected event, and the subsequent peak must be greater than 1.5 times the value prior to the onset of the event. The biomarker levels required for the diagnosis of MI were dependent on relationship to cardiac procedures:

- If the suspected event was within 48 hours of a PCI, the CK-MB value (on at least two samples) must be >3x ULN or >5xULN on the last available sample provided it was obtained ≥12 hours after the PCI; no symptoms were required.
- If the suspected event was within 48 hours of a CABG, the CK-MB value (on a single measure) must be >10xULN; no symptoms were required.
- If the suspected event was not within 48 hours of a PCI or CABG, the diagnostic criteria were met if the subject had CK-MB or cardiac troponin >ULN and the presence of either chest pain ≥20 minutes in duration or ST-segment deviation ≥1 mm on the ECG.

In any clinical circumstance, the appearance of new Q-waves on the ECG distinct from a prior event or pathologic evidence (such as autopsy) showing a new MI felt to be distinct from a prior event were considered appropriate evidence for MI, as would ST-segment elevation lasting for at least 20 minutes and accompanied by ischemic chest pain or haemodynamic decompensation. Nonfatal stroke was defined as the rapid onset of new, persistent neurologic deficit lasting more than 24 hours. In the case of clinical diagnosis of nonfatal stroke, computed tomography (CT) or magnetic resonance imaging (MRI) scan imaging was strongly recommended. CT or MRI scans were considered by the Clinical Events Committee (CEC) to support the clinical impression. Supplemental information from head CT or MRI scans determined if there was a demonstrable lesion compatible with an acute nonfatal stroke. Furthermore, nonfatal stroke was classified as either ischemic or hemorrhagic based on imaging data, if available, or uncertain cause if imaging data were not available.

Secondary efficacy endpoints included:

- CV death, nonfatal MI, or nonfatal stroke through 30 days and 90 days post randomization.
- CV death, nonfatal MI, or UTVR through 30 days and 90 days post randomization. UTVR required both of the following: PCI or CABG, for recurrent ischemia that, in the investigator's opinion, could not be delayed for more than 24 hours and was defined by the investigator as a

non-elective procedure (urgent), and revascularization, either with CABG or PCI, had to include one or more vessel(s) dilated at the initial (qualifying) procedure.
- All cause death, nonfatal MI, or nonfatal stroke.
- CV death, nonfatal MI, nonfatal stroke, or re-hospitalization for cardiac ischaemic events.
- Definite or probable (Academic Research Consortium (ARC) definition) stent thrombosis.

Safety endpoints were set as follows: Non-CABG-related TIMI Major bleeding, Non-CABG-related TIMI Life-Threatening bleeding, and Non-CABG-related TIMI Minor bleeding.
Non-CABG-related TIMI Major bleeding was any intracranial haemorrhage (ICH) OR any clinically overt bleeding including bleeding evident on imaging studies) associated with a fall in haemoglobin (Hgb) of ≥5 gm/dL from baseline. Non-CABG-related TIMI Life-Threatening bleeding was any Non-CABG-related TIMI Major bleeding that was fatal, led to hypotension that required treatment with intravenous inotropic agents, or required surgical intervention for ongoing bleeding, or necessitated the transfusion of 4 or more units of blood over a 48-hour period, or any symptomatic ICH. Non-CABG-related TIMI Minor bleeding was any clinically overt bleeding associated with a fall in Hgb of >3 gm/dL but <5 gm/dL from baseline.

Sample size
Study TAAL was intended to continue until an estimated 875 subjects with UA/NSTEMI reached one of the events described in the triple composite endpoint (CV death, nonfatal MI, or nonfatal stroke) and a median duration of therapy of at least 12 months and a minimum follow-up of 6 months was achieved. A power calculation to assess superiority was performed, assuming a hazard ratio of 0.80 and based on a two-sided log-rank test using a two-sided significance level of 0.05. In view of an anticipated lack of proportionality of hazard, the Gehan-Wilcoxon test was used in the primary analysis. The statistical power of the Gehan-Wilcoxon test depends on the direction and size of the deviation from proportional hazards. It is expected, however, that the power of the Gehan-Wilcoxon test is approximately 90% if the non-proportionality is not severe. A total of around 13,000 subjects with ACS were to be enrolled, so that 9500 subjects with UA/NSTEMI would be enrolled. The number of subjects with STEMI was to be capped at 3500 subjects, which was deemed to be adequate to assess the consistency of treatment effect and safety within the STEMI population.

Randomisation
Subjects were randomized via an interactive voice response system (IVRS) to either prasugrel or clopidogrel in a 1:1 ratio. Randomization was carried out at the site level and stratified by clinical presentation. Subjects were randomized only after diagnostic angiography confirmed anatomy suitable for PCI, except for patients presenting with STEMI with onset of symptoms < 12 hours. Overall, the randomization procedure was assessed as successfully implemented. For a few patients (1.7%) the randomization was based on incorrect strata and the site monitoring identified a small number of patients (≤ 1.3%), who were given the wrong kit/drug. The impact of these protocol violations on the study results is believed to be negligible.

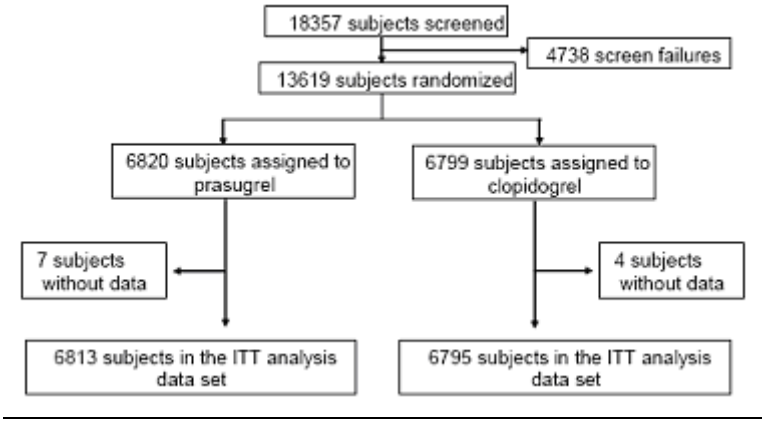
Blinding (masking)
Participants, the sponsors, and all study site personnel were blinded to study drug. Selected clinical study personnel not associated with the study or its operations were granted access to randomization table and treatment assignments. These personnel were limited to those who prepared unblinded summaries and analyses for the periodic safety reviews by the Data Safety Monitoring Board (DSMB) and/or regulatory agencies.

Statistical methods
All efficacy analyses were performed using an intent-to-treat dataset, consisting of all randomized subjects. The safety analyses were carried out using the treated data set that includes all subjects who received at least one dose of study drug, either a loading dose or maintenance dose. Primary efficacy analyses were conducted on endpoints adjudicated by an independent CEC, including CV death, myocardial infarction, stroke, urgent target vessel revascularization, and stent thrombosis. The comparison of the primary endpoint was evaluated using the Gehan-Wilcoxon test from a time-to-first event analysis at a two-sided alpha level of 0.05. Subjects experiencing multiple occurrences of an endpoint were censored at the time of first occurrence. All other key efficacy and safety analyses were

conducted using the log-rank test from a time-to-first event analysis. All efficacy and safety analyses were carried out first for subjects with UA/NSTEMI, followed by analysis of the same endpoint in the All ACS population (UA/NSTEMI plus STEMI subjects) if superiority of prasugrel was demonstrated in the UA/NSTEMI population. The primary outcome was also analyzed in the STEMI population. Analyses including all subjects with ACS included clinical presentation UA/NSTEMI *vs* STEMI as a stratification factor in the time-to-first event analyses. For the secondary analyses no formal adjustment of the grade of statistical significance is considered necessary, due to the presence of a predefined hierarchical strategy. The statistical analysis plan was well prepared and follows the recommendations in the CHMP Guideline CPMP/EWP/2330/99 (Points to Consider on multiplicity issues and on application with one pivotal study).

Results

Participant flow in study TAAL



There were 7 subjects randomly assigned to prasugrel, and 4 subjects randomly assigned to clopidogrel without data available for inclusion in the final analysis dataset due to an incomplete informed consent document. The most frequent reason for screen failure was that subjects did not meet the inclusion criteria. The majority (98.9%) of subjects completed the study and the number of patients withdrawing consent or considered lost to follow-up was similar between treatment groups.

Recruitment

The enrolment period for Study TAAL was 5 November 2004 to 14 January 2007. The last subject visit occurred on 22 July 2007. The geographic variation, which is likely to depict the future use of the drug, is shown below.

Region of Enrollment n (%)a	**Prasugrel, n=6813**	**Clopdogrel, n=6795**
North America	2164 (31.8)	2146 (31.6)
United States	2039 (29.9)	2020 (29.7)
Europe	3436 (50.4)	3439 (50.6)
Eastern Europe	1657 (24.3)	1665 (24.5)
Western Europe	1779 (26.1)	1774 (26.1)
South America	270 (3.96)	264 (3.89)
Rest of World	943 (13.8)	946 (13.92)

Conduct of the study

Study TAAL was conducted in 725 centres in 30 countries around the world. The following changes were made in the conduct of the study after the start of the study: The definition of nonfatal peri-procedural myocardial infarction (PPMI) within 48 hours after percutaneous coronary intervention was modified (protocol amendment A). The modified definition maintains the original definition and extends the definition of PPMI to include a CK-MB >5xULN on one sample if it is the last available sample and was drawn ≥12 hours after PCI. This change affected only the CEC adjudication of PPMI

within 48 hours of PCI. The criteria for investigator-identified nonfatal clinical MI that were also adjudicated by the CEC remained unchanged..
Overall, changes made during study conduct were not considered major.

Baseline data
Summary of baseline characteristics for subjects in study TAAL is presented below.

Characteristic	**Prasugrel**	**Clopidogrel**
Clinical Presentation n (%)	**N=6813**	**N=6795**
UA/NSTEMI	5044 (74.0)	5030 (74.0)
STEMI	1769 (25.9)	1765 (26.0)
STEMI ≤12 hours [a]	1203 (17.7)	1235 (18.2)
STEMI >12 hours [a]	564 (8.3)	530 (7.80)
Age (Years)	**N=6813**	**N=6795**
Overall Mean (SD)	60.9/11.2	60.9/11.4
≥75 Years n (%)[a]	901/13.2	908/13.4
Sex n (%a)	**N=6813**	**N=6795**
Female	1705 (25.0)	1818 (26.8)
Region of Enrollment n (%)a	**N=6813**	**N=6795**
North America	2164 (31.8)	2146 (31.6)
United States	2039 (29.9)	2020 (29.7)
Europe	3436 (50.4)	3439 (50.6)
Eastern Europe	1657 (24.3)	1665 (24.5)
Western Europe	1779 (26.1)	1774 (26.1)
South America	270 (3.96)	264 (3.89)
Rest of World	943 (13.8)	946 (13.92)
Body Weight (kg)	**N=6722**	**N=6715**
Mean (SD)	83.6 (16.8)	83.2 (16.9)
Creatinine Clearance	**N=6699**	**N=6681**
<60 ml/min	717 (10.7)	774 (11.6)
Index Procedure(s)	**N=6813**	**N=6795**
PCI	6715 (98.6)	6698 (98.6)
Multivessel PCI	967 (14.7)	946 (14.4)
CABG	25 (0.37)	23 (0.34)
Any Stent	6018 (95.7)	6004 (96.1)
Bare Metal Stent	3190 (51.0)	3185 (51.0)
Drug Eluting Stent	2860 (45.5)	2872 (46.0)
GPIIb/IIIa inhibitor use	3670 (53.9)	3733 (55.0)
Medical History n (%)[a]	**N=6813**	**N=6795**
Diabetes Mellitus	1576 (23.1)	1570 (23.1)
Hypertension	4370 (64.1)	4371 (64.3)
Hypercholesterolemia	3790 (55.6)	3790 (55.8)
Prior MI	1226 (18.0)	1208 (17.8)
Prior PCI	904 (13.3)	926 (13.6)
Prior CABG	541 (7.94)	497 (7.3)
Prior TIA	94 (1.38)	117 (1.7)
Prior Stroke	181 (2.66)	160 (2.35)

Abbreviations: CABG = coronary artery bypass graft; MI = myocardial infarction; N = number of subjects randomly assigned; n = number of subjects in sub-category; NSTEMI = non-ST segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SD = standard deviation; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; UA = unstable angina.

[a] % is percent (rounded to nearest whole number) of number of subjects with non-missing values for category.

The majority of subjects were male and Caucasian. The mean age was 61 years and the mean weight was 83 kg. The subject characteristics were well balanced across the treatment groups; in UA/STEMI, STEMI, and all ACS populations. Exceptions of statistically significant differences were age and

diabetic treatment in the STEMI population, gender in the All ACS population, and the use of angiotensin-converting enzyme inhibitors (ACEI) in the UA/NSTEMI and the All ACS populations. The magnitude of the imbalances was small and these imbalances are not believed to affect the outcome of the study. It is of note that TIMI Risk Index score at baseline was identical in the all ACS population in the two treatment arms. There is a small difference - albeit statistically insignificant - in number of patients with a history of prior stroke between the two treatment arms.

Numbers analysed
The ITT population is defined as all randomized subjects except where otherwise specified. The Safety population is formed by all randomised patients who received at least one dose of the medication and had at least one contact with the investigator afterwards. Overall compliance with taking study drug was high (approximately 96%).

Outcomes and estimation
Study TAAL demonstrated that treatment with prasugrel, as compared with clopidogrel at the standard, approved dose, resulted in a statistically significant reduction in the rate of the primary efficacy endpoint (the composite of CV death, nonfatal MI, or nonfatal stroke at a median of 14.5 months follow-up). In addition, there was a statistically significant reduction in all pre-specified secondary efficacy endpoints. This was shown across the full spectrum of ACS with planned PCI. The primary and secondary efficacy endpoints were analyzed first in subjects with unstable angina and non-ST-segment elevation myocardial infarction (UA/NSTEMI), followed by an analysis of the same endpoints in all subjects in the All ACS population (UA/NSTEMI and ST-segment elevation myocardial infarction (STEMI)). The data were then also analysed in patients presenting with STEMI. For subjects presenting with UA/NSTEMI, the number and percentage of subjects reaching the primary composite endpoint were 469/5044 (9.30%) and 565/5030 (11.23%) for those randomized to prasugrel or clopidogrel, respectively, (HR=0.820 (95% CI 0.726-0.927)). For subjects presenting with STEMI, the number and percentage of subjects reaching the primary composite endpoint were 174/1769 (9.84%) and 216/1765 (12.24%) for those randomized to prasugrel or clopidogrel, respectively, (HR=0.793 (95% CI 0.649-0.968)). In the all ACS population, the number and percentage of subjects reaching the primary composite endpoint were 643/6813 (9.44%) and 781/6795 (11.49%) for those randomized to prasugrel or clopidogrel, respectively, (HR=0.812 (95% CI 0.732-0.902)). Thus, on average a relative risk reduction of approximately 20% was achieved. An absolute risk reduction of approximately 2% was observed.

Considering the individual components of the main endpoints significant reductions in the prasugrel group in the rates of ischemic events were observed. This differences were largely related to reduction in nonfatal MI (6.97% P *vs* 9.12% C, HR 0.757, p<.001) and all MI (7.12% P vs. 9.32% C, HR 0.757, p<.001). Positive results were evident within the first 24 hours following PCI, thus data seem to demonstrate a reduction in the early ischemic events such as peri-procedural MI. The risks of nonprocedural clinical MI were significantly reduced in the prasugrel group, as was the risk of new ST-elevation MI. However, this effect was not associated with a difference in the incidence of all cause death or CV death between treatment groups. It is of note that the higher level of platelet inhibition achieved relatively fast with the LD of prasugrel, leads to a reduction of the risk of thrombotic complications in the acute phase. Statistically significant differences in favour of prasugrel were also detected for all the planned secondary efficacy endpoints (see Methods, Objectives on page 35).

Study TAAL Primary Efficacy Endpoint and Components at Study End				
Event	**Prasugrel**	**Clopidogrel**	**Hazard Ratio**	**p-Value[c]**
	n (%)[a]	**n (%)[a]**	**(95% CI)[b]**	
UA/NSTEMI	**N=5044**	**N=5030**		
Primary End Point CV Death, Nonfatal MI, or Nonfatal Stroke	469 (9.30)	565 (11.23)	0.820 (0.726,0.927)	0.002
CV Death	90 (1.78)	92 (1.83)	0.979 (0.732,1.309)	0.885
Nonfatal MI	357 (7.08)	464 (9.22)	0.761 (0.663,0.873)	<0.001
Nonfatal Stroke	40 (0.79)	41 (0.82)	0.979 (0.633,1.513)	0.922
All Cause Death	130 (2.58)	121 (2.41)	1.076 (0.840,1.378)	0.563
All MI	366 (7.26)	476 (9.46)	0.760 (0.663,0.871)	<0.001
All Stroke	49 (0.97)	46 (0.91)	1.068 (0.714,1.597)	0.748
STEMI	**N=1769**	**N=1765**		
Primary End Point CV Death, Nonfatal MI, or Nonfatal Stroke	174 (9.84)	216 (12.24)	0.793 (0.649,0.968)	0.019
CV Death	43 (2.43)	58 (3.29)	0.738 (0.497,1.094)	0.129
Nonfatal MI	118 (6.67)	156 (8.84)	0.746 (0.588,0.948)	0.016
Nonfatal Stroke	21 (1.19)	19 (1.08)	1.097 (0.590,2.040)	0.770
All Cause Death	58 (3.28)	76 (4.31)	0.759 (0.539,1.068)	0.113
All MI	119 (6.73)	157 (8.90)	0.748 (0.589,0.949)	0.016
All Stroke	26 (1.47)	25 (1.42)	1.032 (0.596,1.787)	0.911
All ACS	**N=6813**	**N=6795**		
Primary End Point CV Death, Nonfatal MI, or Nonfatal Stroke	643 (9.44)	781 (11.49)	0.812 (0.732,0.902)	<.001
CV Death	133 (1.95)	150 (2.21)	0.886 (0.701,1.118)	0.307
Nonfatal MI	475 (6.97)	620 (9.12)	0.757 (0.672,0.853)	<0.001
Nonfatal Stroke	61 (0.90)	60 (0.88)	1.016 (0.712,1.451)	0.930
All Cause Death	188 (2.76)	197 (2.90)	0.953 (0.781,1.164)	0.639
All MI	485 (7.12)	633 (9.32)	0.757 (0.673,0.852)	<0.001
All Stroke	75 (1.10)	71 (1.04)	1.055 (0.763,1.460)	0.745

Abbreviations: ACS = acute coronary syndromes; CI = confidence interval; CV = cardiovascular; MI = myocardial infarction; N = number of randomly assigned subjects; n = number of subjects in sub-category; NSTEMI = non-ST-elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina.

[a]Percentage of randomly assigned subjects reaching the primary endpoint.
bHazard ratio and a 95% CI used as an estimate of overall relative risk, prasugrel versus clopidogrel, over the course of the study.
cTwo-sided p-values are based on Gehan–Wilcoxon test comparing event free survival distributions of prasugrel and clopidogrel for the composite primary endpoint. The individual components of the endpoints were tested using log-rank test. Clinical presentation, UA/NSTEMI versus STEMI, was used as a stratification factor in analysis involving All ACS subjects.

Efficacy was preserved across major pre-specified subgroups: sex, age (older or younger than 65 years), history of diabetes, type of stent employed, use of glycoprotein inhibitors, mono- or poly antithrombin use, dose of aspirin, renal function, geographical region. The treatment benefit was durable. The incidence of primary and secondary composite endpoints was statistically significantly lower in subjects treated with prasugrel compared to clopidogrel in the acute phase (within 3 days), the subacute phase (within 30 days), and in the long-term phase.

Secondary Outcome Events in Study TAAL – All ACS population				
Outcome Events	**prasugrel + ASA (N=6813) %**	**Clopidogrel +ASA (N=6795) %**	**Hazard Ratio (95% CI)**	**p-value**
CV death, nonfatal MI or nonfatal stroke through 90 days	6.8	8.4	0.797 (0.705,0.901)	<0.001
CV death, nonfatal MI or nonfatal stroke through 30 days	5.7	7.4	0.767 (0.672,0.876)	<0.001
CV Death, Nonfatal MI or urgent target vessel revascularisation (UTVR) through 90 days	6.9	8.7	0.794 (0.703,0.896)	<0.001
CV death, nonfatal MI, or UTVR through 30 days	5.9	7.4	0.784 (0.688,0.894)	<0.001
All cause death, nonfatal MI, or nonfatal stroke through study end	10.2	12.1	0.831 (0.751,0.919)	<0.001
CV death, nonfatal MI, nonfatal stroke or rehospitalisation for cardiac ischemic event through study end	11.7	13.8	0.838 (0.762,0.921)	<0.001
Definite or probable stent thrombosis through study end[a]	0.9	1.9	0.494 (0.361, 0.677)	<0.001

a N=6422 for EFIENT and N=6422 for clopidogrel.

Ancillary analyses

Elderly patients and patients with weight <60 kg

Analyses of the risk for TIMI bleeding by different weight and age cut-offs in study TAAL indicate that the odds ratio for bleeding with 10 mg prasugrel increases around the weight limit of less than 60 kg and age limit of greater than or equal to 75 years. The additional analyses presented suggest an increased bleeding risk associated with weight < 60 kg and age ≥ 75 years and the CHMP raised this as a major objection regarding the proposed reduced 5 mg MD in these two populations.. However, patients over 75 years of age weighing more than 60 kg did not seem to have an increased prasugrel exposure to the same extent as in patients weighing <60kg. This issue was also addressed in the oral explanation held at the CHMP. The results of the analysis conducted *via* a PK/PD model to evaluate the dose 5 mg in patients < 60 kg or ≥ 75 years of age need clinical confirmation and the Company is conducting such studies as part of the follow-up measures..

Comparison of 10-mg Prasugrel Exposure by Weight and Age Categories - Study TAAL

Group	N	Mean Age (years)	Mean Weight (kg)	G-Mean AUC (ng*hr/mL)	Ratio of Geometric Mean (90% CI)[a]
≥60kg and <75years	996	58	85	81.3	
<60kg and <75years	36	60	54	101.9	1.254 (1.105, 1.422)
<60kg and ≥75years	11	80	53	127.5	1.569 (1.252, 1.965)
≥60kg and ≥75years	110	79	78	94.5	1.163 (1.079, 1.253)

Abbreviations: CI = confidence interval; G-Mean = geometric least square mean; N = number of subjects in the specified subgroup.
[a]versus ≥60 kg and <75 years

The question of the proposed reduction in the maintenance dose of prasugrel by one half in elderly patients (> 75 years) to reduce the risk of bleedings while not compromising the efficacy of the drug was discussed by the Scientific Advisory Group requested by the CHMP. This was also addressed at the oral explanation. Based on the increased risk of bleeding in patients ≥ 75 years of age treated with a 10 mg maintenance dose, a very strong wording in the SPC is implemented, stating that use in patients ≥75 years of age is generally not recommended and advising caution for the use of prasugrel in the elderly ≥75 years (i.e. individual benefit/risk evaluation and reduced maintenance dose of 5 mg). Although,the evidence for a 5 mg dose is based only on PK/PD analyses and no clinical data currently exist on the safety of this dose in the very elderly, it is believed that the treatment option in specifically selected and evaluated elderly patients at increased risk for ischemic events should be open after a careful, individual risk benefit evaluation.
In addition, reliable risk minimisation measures must be put in place and safety and efficacy data from clinical trials with this sub-population must be provided to the CHMP, as stated in the list of follow up measures. Adequate educational strategies prepared along with the scientific societies are to be put in place as requested by the CHMP as a condition for the safe and effective use of this medicinal product.

- Clinical efficacy results in special populations

In-stent thrombosis

Applying the ARC definitions (which included angiographic and clinical principles), there was a significant reduction in stent thrombosis in the prasugrel group including both reductions in early (<30 days) and late (≥ 30 days) stent thrombosis that was consistent in the 3 populations (UA/NSTEMI, STEMI, and All ACS). The RRR observed in both UA/NSTEMI and STEMI groups it is stated to be of nearly a 50%. A significant reduction in the rate of the incidence of the primary endpoint was found among patients receiving prasugrel in combination with bare-metal stents (9.37% P vs. 11.59% C) alone and in those receiving prasugrel in combination with at least one drug-eluting stent (8.67% P vs. 10.86% C). A lower incidence in the need of urgent target-vessel revascularization in the prasugrel group was also found.

Previous stroke/TIA

From the multivariate analysis the only risk factors differentially influencing the primary efficacy endpoint for prasugrel compared with clopidogrel were prior TIA or stroke and diabetes (see below). In particular, primary endpoint results in the All ACS population in those that had a prior history of TIA or stroke seem to favour clopidogrel. (prasugrel N 262 n 47 (17.94%) vs clopidogrel N 256 n 35 (13.67%) HR 1.375 CI 95% (0.886, 2.132) p= 0.153). Also, a higher incidence of nonfatal stroke and all stroke either hemorrhagic or non-hemorrhagic, when compared with clopidogrel (nonfatal stroke: 5.73% versus 0.78%, p-value =.002; all stroke: 6.49% versus 1.17%, p-value =.002) was observed. These patients with prior TIA or stroke have now been contraindicated to prasugrel.

Diabetes

For the diabetic population the incidence of the primary efficacy endpoint (All ACS, prasugrel N 1576 n 180 (11.42%) vs clopidogrel N 1570 n 248 (15.80%) HR 0.709 CI 95% (0.582, 0.854) p= 0.001) and each secondary efficacy composite endpoint was lower in subjects randomized to prasugrel compared to subjects randomized to clopidogrel in all 3 populations (UA/NSTEMI, STEMI, and All ACS). Recently published clinical results have suggested that subjects with diabetes may have greater

platelet reactivity and a lower antiplatelet response during clopidogrel treatment. In contrast, the current observations suggest that in subjects with stable CAD (study TABR and TABL), prasugrel treatment provided consistent levels of platelet inhibition in those with and without diabetes. It is proposed that more potent platelet inhibition with prasugrel may result in improved clinical outcomes in ACS subjects with diabetes.

- Discussion on clinical efficacy

Regarding clinical relevance and general interpretation of the results in the context of current evidence, study TAAL could be large enough to address separately the thienopyridine-mediated platelet inhibition in the two major presentation forms of acute coronary syndrome (that is, UA/NSTEMI and STEMI). The median time from onset of qualifying symptoms to randomization in study TAAL in subjects presenting with UA/NSTEMI was 28.9 and 29.0 hours for patients randomized to prasugrel or clopidogrel treatment, respectively. Upper quartiles were 48.6 and 49.0 hours, respectively. In study TAAL, all patients with UA/STEMI were randomized after coronary pathoanatomy was known, i.e. after coronary angiography. The strategy of administering the thienopyridine LD once coronary anatomy is known appears to be preferred because of concerns about surgical bleeding in patients treated with clopidogrel that subsequently undergo CABG surgery. It is acknowledged that the optimum timing of platelet inhibition with a thienopyridine has been debated in recent years. The benefits of the early administration of clopidogrel before PCI does not come from randomised clinical trials primarily aimed to this end, but from post-hoc subgroup analyses and observational studies.

The primary objective of study TAAL was to test the hypothesis that prasugrel co-administered with aspirin was superior to clopidogrel co-administered with aspirin in the treatment of subjects with acute coronary syndromes (ACS) who were to undergo percutaneous coronary intervention (PCI), as measured by a reduction in the composite endpoint of cardiovascular (CV) death, nonfatal myocardial infarction (MI), or nonfatal stroke at a median follow-up of at least 12 months. It was pre-specified that the primary endpoint was analyzed first in subjects with unstable angina and non-ST-segment elevation myocardial infarction. Efficacy superiority of prasugrel has been fully demonstrated for the primary and all secondary endpoints. As mentioned earlier, the timing of prasugrel LD treatment in study TAAL deviated from the present treatment guidelines and this initially raised objection was addressed by presenting several lines of evidence from study TAAL, all of which suggested that the timing of clopidogrel LD did not substantially influence the overall efficacy (or safety) of prasugrel observed in this trial. It was noted that for subjects treated with GPIIb/IIIa inhibitors, there was no evidence that the relative benefit for prasugrel versus clopidogrel was reduced or that there was an excess need for bail out GPIIb/IIIa inhibitor use during PCI in those patients randomised to clopidogrel in the TAAL study. This observation could indirectly indicate that the timing of study drug LD did not substantially influence overall efficacy. Furthermore, when study drug LD is administered before or during PCI, both clopidogrel and prasugrel would be at their near-maximal levels of platelet inhibition achievable by the LD in the early hours following the PCI. This claim is well supported by pharmacokinetic data and *ex vivo* platelet inhibitory activity for prasugrel and clopidogrel, and supports that the timing of study drug LD did not substantially influence the overall efficacy. Stronger evidence for this position originates in the subgroup analysis of patients pre-treated with thienopyridine. In study TAAL, if coronary anatomy was determined or primary PCI for STEMI (≤12 hours) was planned, pre-treatment with study drug was allowed for up to 24 hours before PCI. The percentage of subjects in this pre-treated subgroup reaching the composite endpoint of CV death, nonfatal MI, or nonfatal stroke from randomisation through study end was 9.94 and 11.29, respectively, for subjects pre-treated with prasugrel or clopidogrel. Although not statistically significant for this subgroup, the difference rather strongly favours the notion that that the timing of study drug LD to a large extent did not influence overall efficacy. Additional examination of the subgroup data shows that the predominant benefit of being randomised to prasugrel treatment is not evident in the reduction in peri-procedural MI, a time when prasugrel would presumably have the greatest early advantage, but rather in the reduction in subsequent clinical MI. It is acknowledged that this observation also supports the position that timing of study drug LD is not crucial to the overall efficacy. Finally, the analysis of long-term clinical benefits in Study TAAL confirms the lack of influence of timing of study drug on efficacy. Considering all of these lines of evidence, it is unlikely

that timing of study drug LD had major importance to the overall efficacy demonstrated in Study TAAL.

Regarding the subjects presenting with STEMI, the number and percentage of subjects reaching the primary composite endpoint were 174/1769 (9.84%) and 216/1765 (12.24%) for those randomized to prasugrel or clopidogrel, respectively, (HR=0.793 (95% CI 0.649-0.968)). The treatment benefit was durable; at 3 days, at 30 days, and at study end. Regarding possible effects of prior fibrinolytic treatment, the percentage of subjects reaching the composite endpoint was 6.4% and 8.7% (randomized to prasugrel or clopidogrel, respectively) if fibrinolytic therapy was used before PCI. The corresponding percentages if fibrinolytic therapy was not used were 10.2% and 12.7%. There was no significant statistical interaction between the treatment benefit observed with prasugrel and prior treatment with a fibrinolytic agent in those presenting with STEMI. It is therefore unlikely that the efficacy benefit with prasugrel in subjects presenting with STEMI was influenced by the administration of a fibrinolytic agent prior to PCI. There was a lower incidence of the primary composite endpoint in subjects randomized to prasugrel compared to clopidogrel in the STEMI population undergoing primary (≤12 hours) PCI (10.06 % versus 11.50%; HR=0.872; p=.266). In the STEMI population undergoing delayed (>12 hrs) PCI the corresponding values were 9.40 % versus 13.96%; HR=0.649; p=.015. Initially, these data suggest that patients presenting with STEMI late after symptom onset benefit from prasugrel treatment in particular. However, these patients were in principle handled like patients with UA/NSTEMI, i.e. they were randomised and received study treatment after diagnostic coronary angiography. In addition, the description of the primary endpoint was simplified in the wording of the indication to increase the clarity, but data on each of the individual components of the primary endpoint is retained in the SPC in a relevant section.

For some patients at special risk (very elderly ≥75 years, patients weighing < 60 kg) dose reduction is suggested. After an LD of 60 mg, an MD of 5 mg once daily is recommended, but these patients were not adequately studied with a 5 mg maintenance dose. These considerations formed the basis of a major objection raised by the CHMP. New safety/efficacy analyses based on the active metabolite exposure and PK/PD simulations were presented in the CHMP oral explanation and were conducted in order to support the proposed reduction to a 5 mg prasugrel MD in subjects <60 kg or ≥ 75 years of age. The reduction of the dose is proposed for the following reasons:

- higher exposure to the prasugrel active metabolite in this sub-population associated with an increased risk of bleeding
- bleeding in subjects <60 kg or ≥75 years was predominantly confined to subjects with the highest exposure
- subjects <60 kg or ≥75 years of age with lower exposure to the active metabolite had similar risk of bleeding as subjects ≥60 kg or <75 years of age
- based on the results of a predictive model, reducing the prasugrel MD to 5 mg in subjects <60 kg or ≥75 years of age produces similar exposure as was observed in the lowest quartile exposure in the overall population in study TAAL on the prasugrel 10 mg MD, a quartile of exposure where efficacy was maintained and the risk of bleeding was lowered.

In addition, two dedicated studies aimed to compare the PK, PD, safety, and tolerability of prasugrel in subjects <60 kg or ≥75 years treated with a MD of either prasugrel 5-mg, prasugrel 10-mg, or clopidogrel 75-mg will be conducted as part of the follow up measures. Further a post-authorisation study will be performed to assess the benefit/risk of prasugrel used in real life setting. Results from the study H7T-MC-TABY (TABY) with 10,000 randomised subject assessing the efficacy and safety of prasugrel compared to clopidogrel in medically managed subjects with ACS who have experienced a recent UA/NSTEMI event will be made available to the CHMP and this commitment is part of the follow up measures. The CHMP accepted the proposed dose reduction in patients weighing < 60kg. Although, the dose-reduction in the very elderly ≥75 years and the benefit/risk with the 5 mg MD is not fully clinically supported at present, it is believed that the treatment option in specifically selected and evaluated elderly patients at increased risk for ischemic events should be open after a careful, individual risk benefit evaluation.

Clinical safety

Introduction

The clinical safety evaluation of prasugrel is primarily based on the pre-specified primary database from the pivotal TAAL study. It includes data from 13457 treated subjects with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI) who were treated with prasugrel (6741 subjects) or clopidogrel (6716 subjects), co-administered with aspirin for up to 15 months. These patients have been exposed to the proposed prasugrel dosing regimen (60-mg loading dose [LD]/10-mg maintenance dose [MD]). The secondary safety database includes data from the 4 smaller studies; TAAD, TAAH, TABL, TABR grouped into "All but TAAL (ABT)", and Study TAAL limited to the first 30 days after first dose of study drug, "TAAL-30". The tertiary safety database comprises the safety data from clinical pharmacology studies. Two major populations contributed to the All ACS population:

- UA/NSTEMI (clinical presentations being UA or NSTEMI within 72 hours)
- STEMI (clinical presentations being STEMI ≤12 hours since symptoms onset or STEMI >12 hours since symptoms onset)

The number of subjects with STEMI was capped at 3534 subjects. The majority of subjects in the All ACS population were male (74%) and Caucasian (92%). The mean age was 61 years and the mean weight was 83 kg. The geographic region of origin was Europe in approximately 50% and North America in 32%.

- Patient exposure

A total of 8656 subjects (6741 from the primary safety database, 940 from the secondary safety database and 975 from the tertiary safety database) have been exposed to at least 1 dose of prasugrel across all completed clinical and clinical pharmacology studies. The overall exposure to prasugrel in the primary safety database was 6483 subject-years. More than half of the subjects treated with prasugrel were exposed for more than 1 year. For the primary safety database "while at risk" was defined as the period from first study drug administration through 7 days after permanent study drug discontinuation (the termination visit) or through 464 days after randomisation, whichever came first.

- Adverse events

In the primary safety database, treatment-emergent adverse events (TEAEs) were reported in 80.34% of prasugrel treated patients and 80.02% of clopidogrel treated patients. Clinically significant AEs were also pre-specified apart from CEC adjudicated bleeding endpoints, and included AEs of particular interest (thrombocytopenia, thrombotic thrombocytopenic purpura [TTP], neutropenia, leucopenia, pancytopenia, torsades de pointes/QT prolongation, allergic reactions, and abnormal hepatic function). No statistically significant difference between treatments was observed for these clinically significant TEAEs (not either for TEAEs and SAEs) when the analysis was limited to the first 3 days (prasugrel 3.16%, clopidogrel 2.75%) or the first 30 days (prasugrel 5.34%, clopidogrel 5.0%). The majority of drug related adverse events were related to bleeding and the risk was higher with prasugrel than with clopidogrel.

Hemorrhagic AEs occurred with a statistically significant higher incidence in the prasugrel treated patients compared to clopidogrel, 29.70% *vs* 22.04% ($p<0.001$). Both CEC- adjudicated non-CABG-related TIMI Major Bleeding, TIMI Major or Minor Bleeding and TIMI Major, Minor, or Minimal Bleeding were statistically significantly increased in prasugrel vs. clopidogrel patients (2.17% vs. 1.65%, 4.49% vs. 3.44%, and 10.86% vs. 7.86%, respectively). Though numbers of patients undergoing CABG were small (213 in the prasugrel group, 224 in the clopidogrel group), it appeared that the risk of CABG related TIMI Major or Minor Bleeding was approximately tripled in the prasugrel arm (30 patients [14.08%] vs. 10 patients [4.46%], $p<0.001$). The overall distribution of hemorrhagic TEAEs and the higher incidence of hemorrhagic TEAEs in prasugrel and clopidogrel treated patients, respectively, was comparable between the UA/NSTEMI subgroup (prasugrel 29.95%, clopidogrel 22.21%), and the STEMI subgroup (prasugrel 28.97%, clopidogrel 21.54%). Nevertheless, although the number of STEMI patients receiving fibrinolytic treatment was small, the bleeding events were comparable between STEMI patients who received fibrinolytic treatment and the patients who did not receive fibrinolytic treatment. In addition, the efficacy benefit seen with prasugrel treatment in

the STEMI population, was not outweighed by bleeding complications in STEMI sub-population of patients managed with delayed PCI. In order of descending frequency, contusion, haematoma, epistaxis, ecchymosis, vessel puncture site haematoma, puncture site haemorrhage, haematuria, and GI haemorrhage were the common (≥1%) hemorrhagic ADRs associated with prasugrel therapy. In the secondary safety database, the overall incidence of hemorrhagic events was higher in ABT versus TAAL-30 for both treatment groups (ABT: prasugrel 35.74%, clopidogrel 20.66%; TAAL-30: prasugrel 18.29%, clopidogrel 14.34%). This was primarily due to the incidence of catheter site haematoma, catheter site haemorrhage, contusion, and epistaxis.

Non-haemorrhagic AEs occurred with a similar frequency in the two treatment groups (77.33% with prasugrel and 77.86% with clopidogrel); statistically significant differences were seen for coronary revascularisation, fatigue, MI, constipation, musculoskeletal pain, cardiac failure (more frequent with clopidogrel) and for pyrexia and tendency to bruise (more frequent with prasugrel). The incidence of infections was similar between the two treatment groups. It is believed that the observed differences in the incidence of pyrexia are in part due to the higher incidence of bleeding in subjects treated with prasugrel, who more frequently received transfusions. Additionally, the causality relationship between rash and prasugrel could not be excluded. The issues have been adequately addressed in the RMP as a potential risk and pharmacovigilance measures will be implemented.

Colon cancer was an uncommon TEAE (0.17% with prasugrel, 0.03% with clopidogrel) that occurred with a statistically significant higher incidence (p=.013) in subjects treated with prasugrel. Of the 19 reports from the prasugrel group, 10 were diagnosed as a result of a diagnostic procedure following a gastrointestinal bleeding. On the basis of these findings, it was concluded that colon cancer was diagnosed more often in subjects treated with prasugrel due to a higher rate of bleeding associated with this therapy.

- Serious adverse event/deaths/other significant events

Deaths

The overall incidence of all-cause deaths was similar between the treatment groups in the primary database (clopidogrel 2.90%, prasugrel 2.76%). The majority of deaths were cardiovascular deaths (prasugrel 1.95% *vs* clopidogrel 2.21%). In the UA/NSTEMI subpopulation, a numerically higher overall mortality was observed in the prasugrel treatment group compared to clopidogrel. However, the explanation is acceptable that the observed numerical increase in overall mortality in prasugrel-treated patients with UA/NSTEMI (9 more deaths) cannot be disentangled from the recognised increased risk of bleeding associated with prasugrel. Elderly patients constitute an especially sensitive population regarding bleeding risk, and explain most, if not all, of the numerically differences in mortality observed in the UA/NSTEMI population.

There was a higher incidence of deaths due to haemorrhage in prasugrel treated patients (both ICH (prasugrel 9 (0.13%) *vs* clopidogrel 5 (0.07%) and non-ICH (prasugrel 9 (0.13%) *vs* clopidogrel 1 (0.01%)) in the All ACS population (see below). The SPC was revised to state the increased risk of major, life-threatening and fatal bleeding associated with the use of prasugrel as compared to clopidogrel in the UA/NSTEMI and All ACS populations.

Summary of Deaths in Study TAAL; All Randomized All ACS Subjects

Deaths All ACS Population	Prasugrel N=6813 n (%)[a]	Clopidogrel N=6795 n (%)[a]	Total N=13608 n (%)[a]
Deaths during study period[b]	188	197	385
Deaths in treated subjects	181	186	367
Deaths in subjects not treated with study drug	7	11	18
Deaths outside of the study period[b]	3	0	3
All Total Deaths[c]	191	197	388
Clinical Endpoints Committee Adjudicated Deaths			
All Cause Death[c]	188 (2.76)	197 (2.90)	385 (2.83)
Cardiovascular Death	133 (1.95)	150 (2.21)	283 (2.08)
Atherosclerotic Vascular Disease[d]	0	3 (0.04)	3 (.0002)
CHF/Cardiogenic Shock	31 (0.46)	30 (0.44)	61 (0.45)
Directly related to revascularization[e]	15 (0.22)	16 (0.24)	31 (0.23)
Dysrhythmia	4 (0.06)	7 (0.10)	11 (0.08)
Pulmonary Embolism	3 (0.04)	0	3 (0.02)
Myocardial Infarction	24 (0.35)	36 (0.53)	60 (0.44)
Sudden or Unwitnessed	36 (0.53)	42 (0.62)	78 (0.57)
Intracranial Hemorrhage	9 (0.13)	5 (0.07)	14 (0.10)
Non-Hemorrhagic Stroke	5 (0.07)	6 (0.09)	11 (0.08)
Other Cardiovascular	6 (0.09)	5 (0.07)	11 (0.08)
Non-Cardiovascular Death	55 (0.81)	47 (0.69)	102 (0.75)
Accidental/Trauma	4 (0.06)	4 (0.06)	8 (0.06)
Nonintracranial Hemorrhage	9 (0.13)	1 (0.01)	10 (0.07)
Infection	11 (0.16)	10 (0.15)	21 (0.16)
Malignancy	21 (0.31)	17 (0.25)	38 (0.28)
Suicide	3 (0.04)	2 (0.03)	5 (0.04)
Other Non-Cardiovascular	7 (0.10)	13 (0.19)	20 (0.15)

Abbreviations: ACS = acute coronary syndromes; CHF = coronary heart failure; PCI = percutaneous coronary intervention; UA = unstable angina.

[a] % is percentage of randomized subjects.

[b] Study period = from randomization through a subject's study termination or 464 days from randomization, whichever was earlier.

[c] There are a total of 388 deaths during the study, with 3 deaths occurring outside the study period, which were listed in the row of "Deaths outside of study period." Therefore, "All total deaths" and "All Cause deaths" differ by 3 subjects.

[d] Atherosclerotic vascular disease excludes deaths from coronary vascular disease.

[e] Death is directly related to hemorrhagic or non-hemorrhagic complications of revascularization (CABG or PCI).

Fatal haemorrhages

Overall, in the All ACS population fatal hemorrhagic events (including CABG-related and Non-CABG-related bleeding events) occurred in 24 subjects (0.36%) in the prasugrel treatment group and 6 subjects (0.09%) in the clopidogrel treatment group. The majority (21/24 deaths in prasugrel patients, 5/6 deaths in clopidogrel patients) were non CABG related TIMI major bleedings during the at risk period. Non CABG-related spontaneous intracranial and gastrointestinal (GI) bleedings were predominant (prasugrel: spontaneous fatal bleedings in 16 patients, hereof 8 intracranial and 6 GI bleedings; clopidogrel: spontaneous fatal bleedings in 4 patients, 4 intracranial and 1 GI bleeding). Non-CABG related instrumented fatal bleedings were only seen in the prasugrel group (4 patients). The incidence of fatal bleedings was also statistically significant in the UA/NSTEMI prasugrel group. The same pattern was observed in the STEMI population but due to insufficient data the statistics could not be evaluated (prasugrel: 7 patients, 0.40%, clopidogrel 2 patients 0.12%). There were no fatal hemorrhagic events in the secondary and tertiary databases.

SAEs

Serious adverse events occurred in 24.70% of prasugrel and 24.26% of clopidogrel treated patients in the primary database. The incidence of non-hemorrhagic SAEs was similar in the prasugrel (22.48%) and the clopidogrel (22.80%) group. Most frequent were non-cardiac chest pain, coronary artery re-

stenosis, chest pain and angina pectoris. Three non-haemorrhagic SAEs that occurred differentially among treatment groups were the higher incidence in the prasugrel group of colon cancer, hypotension, and respiratory failure (which was finally related to the simultaneous occurrence of blood loss). The incidence of hemorrhagic SAEs in the All ACS population while at risk was statistically significantly higher in subjects treated with prasugrel when compared to subjects treated with clopidogrel. Likewise, in the UA/STEMI group the incidence of hemorrhagic SAEs with prasugrel was statistically significantly higher (prasugrel 6.08% *vs* clopidogrel 4.06%). In the STEMI population the incidence was numerically higher though, not statistically different (5.34% vs. 4.26%). Non-CABG related TIMI Major Bleedings (including life threatening and fatal bleedings), TIMI Major or Minor, and TIMI Major, Minor, or Minimal Bleedings were all significantly higher in the prasugrel treated subjects compared to the clopidogrel treated subjects in the All ACS population.

Incidence of Bleeding Events—Clinical Events Committee Adjudicated – Primary Safety Database (Study TAAL) All ACS

Bleeding Events[a]	Prasugrel (N=6813) n (%)	Clopidogrel (N=6795) n (%)	Total (N=13608) n (%)	Hazard Ratio (95% CI)[b]	p-Value[c]
All ACS	6741	6716	13457	NE	NE
Non-CABG-related					
TIMI Major	146 (2.17)	111 (1.65)	257 (1.91)	1.315 (1.028, 1.683)	.029
Life-Threatening	85 (1.26)	56 (0.83)	141 (1.05)	1.517 (1.083, 2.126)	.015
Fatal	21 (0.31)	5 (0.07)	26 (0.19)	4.191 (1.580, 11.113)	.002
Symptomatic ICH	19 (0.28)	17 (0.25)	36 (0.27)	1.119 (0.582, 2.152)	.736
IV Inotrope Required	21 (0.31)	8 (0.12)	29 (0.22)	2.617 (1.159, 5.908)	.016
Surgery Required	19 (0.28)	19 (0.28)	38 (0.28)	0.998 (0.528, 1.885)	.995
Transfusion of ≥4 Units	45 (0.67)	30 (0.45)	75 (0.56)	1.499 (0.945, 2.379)	.084
Instrumented	45 (0.67)	38 (0.57)	83 (0.62)	1.182 (0.767, 1.820)	.447
Spontaneous	92 (1.36)	61 (0.91)	153 (1.14)	1.508 (1.091, 2.085)	.012
TIMI Minor	164 (2.43)	125 (1.86)	289 (2.15)	NE	NE
TIMI Major or TIMI Minor	303 (4.49)	231 (3.44)	534 (3.97)	1.314 (1.107, 1.559)	.002
TIMI Minimal	460 (6.82)	314 (4.68)	774 (5.75)	NE	NE
TIMI Major, Minor, or Min	732 (10.86)	528 (7.86)	1260 (9.36)	1.400 (1.252, 1.566)	<.001
Any Transfusion Required[d]	244 (3.62)	182 (2.71)	426 (3.17)	1.34 (1.11, 1.63)	.003
CABG-related	(N=213)	(N=224)	(N=437)		
TIMI Major or Minor	30 (14.08)	10 (4.46)	40 (9.15)	3.587 (1.702,7.557)[e]	<0.001
Fatal	2 (0.94)	0	2 (0.46)	NE	NE

Abbreviations: ACS = acute coronary syndromes; CABG = coronary artery bypass graft surgery; CI = confidence interval; HR = hazard ratio; ICH = intracranial hemorrhage; IV = intravenous; Min = minimal; N = number of subjects in the specified subgroup; n = number of subjects within the specified subgroup reaching the endpoint; NE = not evaluated due to insufficient sample size; NSTEMI = non-ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; UA = unstable angina.
a Subjects experiencing multiple bleeding events may be included in more than one category.
b HR and two-sided 95% CI derived using Cox proportional hazards model.
c Two-sided log-rank p-value based on time to first event analysis compares the event free survival distributions for prasugrel and clopidogrel. Clinical presentation, UA/NSTEMI versus STEMI, was used as a stratification factor in analyses of All ACS subjects.
d Bleeding requiring any transfusion (whole- or packed-blood).
e Odds ratio is based on the frequency procedure. Two-sided p-values are based on Cochran-Mantel-Haenszel general association test with clinical presentation as a blocking factor in All ACS.

In the All ACS population, the significantly higher incidence of TIMI Major bleedings in subjects treated with prasugrel was related to higher rates of GI bleeding (prasugrel 0.93% vs. clopidogrel 0.64%), surgical site bleeding (0.15% vs. 0.01%), and bleeding at other sites not pre-specified or unknown (0.13% vs. 0.01%). A higher incidence of retroperitoneal bleeding was also observed in subjects treated with prasugrel (0.21% vs. 0.12%). Intracranial hemorrhages and puncture site bleeding events were similar between treatment groups (0.28% vs. 0.25% and 0.42% vs. 0.45%, respectively).

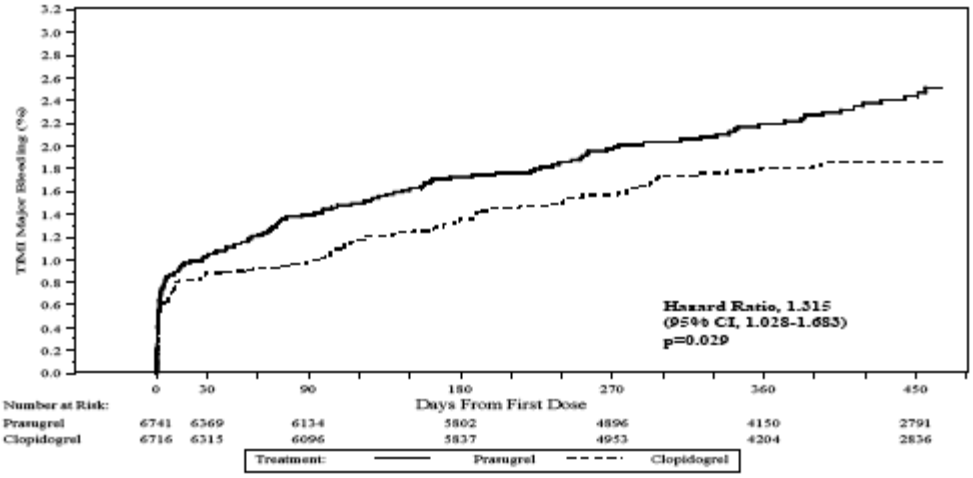
Non-CABG-related TIMI Major and TIMI Life-Threatening bleeding events through 3 days after the first dose of study: The incidence in the All ACS population was numerically higher in subjects treated with prasugrel compared to clopidogrel (prasugrel 0.74% vs. clopidogrel 0.61% for TIMI major and 0.43% vs. 0.31% for Life threatening bleeding), primarily related to a numerically higher incidence of GI bleeding which was reflected by a higher incidence of spontaneous bleeding events. Likewise, in the UA/NSTEMI population, there were numerically more spontaneous and instrumented, bleeding

events in subjects treated with prasugrel compared to clopidogrel through 3 days. In the STEMI population there were no relevant differences between the 2 treatment groups.

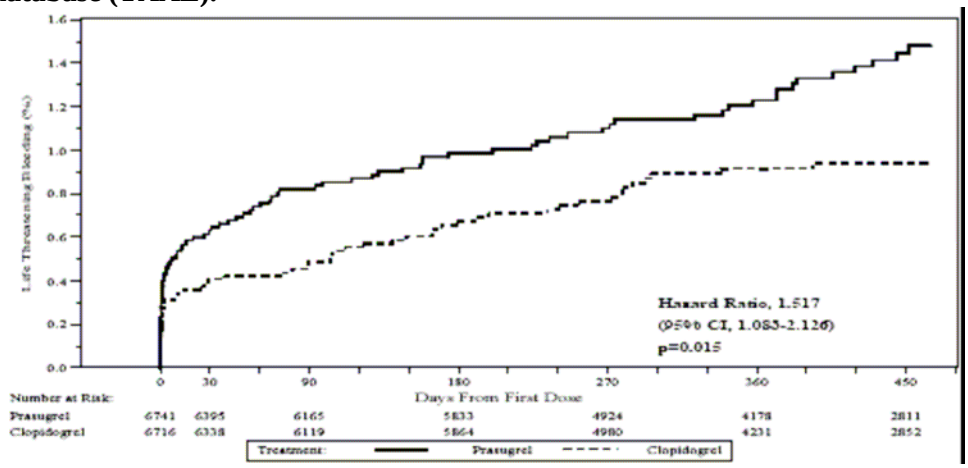
Non-CABG-related TIMI Major and TIMI Life-Threatening bleeding events beyond 3 days after the first dose of study: The incidence was statistically significantly higher in subjects in the All ACS population treated with prasugrel compared to clopidogrel (1.45% vs. 1.05% for TIMI major, 0.84% vs. 053% for TIMI life threatening bleeding), primarily driven by a numerically higher incidence of GI bleeding (0.78% *vs* 0.59%), surgical site bleeding (0.10% *vs* 0.02%), and bleeding at sites not pre-specified or unknown (0.10% *vs* 0%). A higher numerical incidence of retroperitoneal bleeding (0.09% *vs* 0.03%) and surgical site bleeding events (0.10% vs. 0.02%) was observed with prasugrel compared to clopidogrel, which resulted in a statistically significant higher incidence of spontaneous bleeding events (1.14% *vs* 0.78%) and a numerically higher incidence of instrumented bleeding events (0.19% *vs* 0.12%) with prasugrel compared to clopidogrel. For the subcategory of TIMI Life-Threatening bleeding, subjects treated with prasugrel had a statistically significant higher incidence of fatal bleeding (0.24% *vs* 0.06%) and a numerically significant higher incidence of bleeding requiring intravenous inotropic medication in addition to multiple transfusion units. A higher incidence in Non-CABG-related TIMI Life-Threatening bleeding events was observed in the UA/NSTEMI population, but not in the STEMI population.

The time course of TIMI major bleeding events and its subgroup Life threatening bleedings is shown in the following figures.

Kaplan-Meier estimates of the incidence of Non-CABG related TIMI major bleeding events while at risk—CEC adjudicated for all treated All ACS subjects in primary safety database (TAAL).



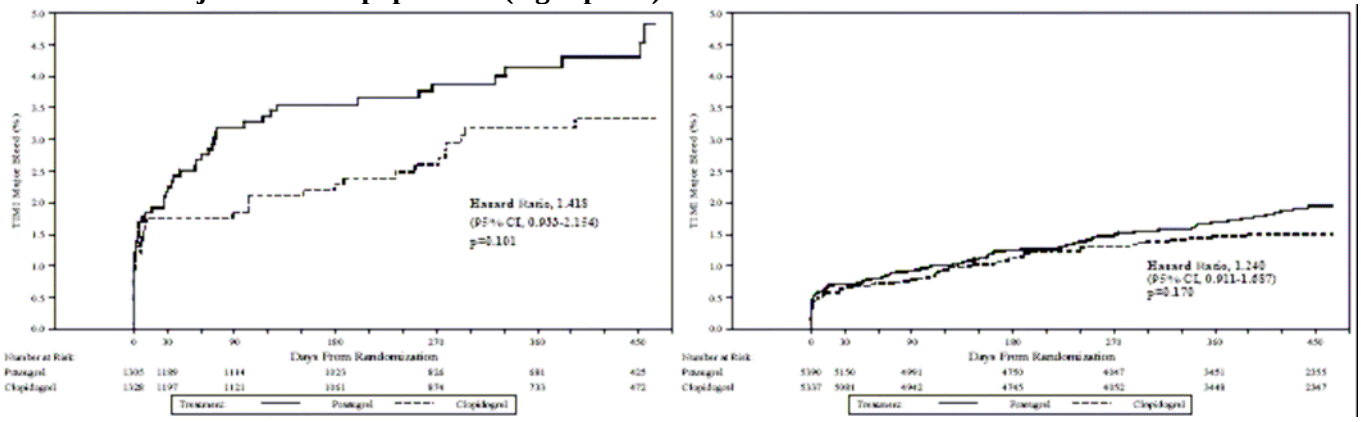
Kaplan-Meier estimates of the incidence of Non-CABGrelated TIMI life-threatening bleeding events while at risk— CEC adjudicated for all treated All ACS subjects in primary safety database (TAAL).



The Kaplan Meier curves separated early for Non-CABG-related TIMI Major and TIMI Life-Threatening bleeding events while at risk, favouring clopidogrel. Another separation is seen beyond 1 year and potentially also at around 30 days. Multivariate analyses identified independent risk factors for increased occurrence of Non-CABG-related TIMI Major bleeding. These were prasugrel treatment, weight < 60 kg, age ≥ 75 years, history of hypertension, history of prior TIA or stroke, and use of GPIIb/IIIa inhibitor (from symptom onset through 3 days after randomization).

Further analyses which demonstrated that mainly patients at risk (patients with a prior history of TIA/stroke, patients with body weight < 60 kg and patients ≥ 75 years of age) are responsible for the unfavourable safety profile of prasugrel, were provided during the evaluation. The figures below display the Kaplan Meier curves for Non-CABG related TIMI Major bleeding events in the "ideal population" (excluding subjects with a history of TIA or stroke, subjects ≥75 years of age taking a MD of 10 mg/day, or subjects <60 kg taking a MD of 10 mg/day) and in the non-ideal population (subjects with history of TIA or stroke, ≥75 years of age or weighing <60 kg). The difference between prasugrel and clopidogrel between 30 and 90 days, is explained by the higher bleeding risk in subjects in the non-ideal population. However, major bleedings also appear to accrue beyond 1 year. The CHMP therefore requested to limit the treatment duration with prasugrel to 12 months, consistent with the existing treatment duration recommendation for clopidogrel in this clinical setting.

Kaplan-Meier estimates of the incidence of non-CABG-related TIMI Major bleeding events while at risk – CEC adjudicated treated ACS subjects in non-ideal population (left panel) and treated ACS subjects in ideal population (right panel).



Considering the ideal population only, the rate of Non-CABG-related TIMI Major and Life-Threatening bleeding in prasugrel treated subjects was numerically, but not statistically higher compared to clopidogrel-treated subjects. The number of fatal bleeding events beyond 3 days of treatment was 7 in prasugrel-treated subjects versus 2 in clopidogrel-treated subjects, as compared to 21 versus 5 in the All ACS population for the entire treatment duration ("at risk period"). Three of the 7 fatal bleeding events in prasugrel-treated subjects resulted from procedural complications, while 4 were fatal ICH (1 traumatic). Both clopidogrel fatal events were spontaneous ICH. Consequently, the number of spontaneous fatal bleeding events beyond 3 days during MD was similar between treatment groups. During the first 3 days, CABG and non-CABG related fatal bleedings were as follows: one fatal bleeding occurred in the clopidogrel group and 6 fatal bleedings (3 each from UA/NSTEMI and STEMI) occurred in the prasugrel group. Four of these patients belonged to the ideal population, and 3 of these had an instrumented or traumatic bleeding. Major bleeding may increase the short-term risk of ischemic events and the risk of death. This was evident in study TAAL. In addition, it was shown that for the All ACS population and both treatment groups together, there was no statistically significant difference between treatment groups for the risk of ischemic events (CV death, CV death/MI, CV death/MI/stroke) beyond and within 30 days in patients having experienced no major bleed versus patients having experienced a major bleed, although the risk was numerically higher for those with major bleed. A comparison of all-cause deaths within and beyond 30 days by treatment group and clinical presentation (UA/NSTEMI, STEMI) shows that mortality within 30 days is roughly comparable for prasugrel and clopidogrel (for the STEMI population even numerically slightly more favourable for prasugrel) if patients did not have a TIMI major bleeding. However, all cause death in patients with a TIMI major bleeding and treated with prasugrel was higher when compared to patients treated with clopidogrel (all ACS population 15.6% vs. 10.9% (p=0.06), similarly in the UA/NSTEMI and STEMI subgroups). Analysis of the "ideal population" shows that all cause death is still numerically higher for prasugrel compared to clopidogrel but the difference is not statistically significant (all ACS population 9.4% vs 7.3%, p=0.52). These deaths are predominantly attributable to fatal bleedings and the increased bleeding risk with prasugrel is clearly stated in the SPC. Beyond 30 days, mortality is comparable for prasugrel and for clopidogrel treated patients not having had a major bleed. For patients with major bleed, events are too few to draw firm conclusions. .

- Laboratory findings

The safety data suggests that prasugrel therapy is not associated with clinically significant thrombocytopenia, neutropenia, or leucopenia. The number of subjects with normal Hct, Hgb, or RBC at baseline, and abnormally low values at any time post-baseline, was statistically significantly higher in subjects treated with prasugrel compared to clopidogrel and probably reflects the higher incidence of bleeding events. Hepatotoxicity of prasugrel is not suggested by the laboratory data.

- Safety in special populations

Renal impairment: In total, 707 patients in the prasugrel group and 769 in the clopidogrel group had a creatinine clearance ≤ 60 ml/min (measured by Cockroft-Gault formula). For both treatments (prasugrel *vs* clopidogrel) a higher incidence of TIMI major or minor bleeding events was observed in patients with creatinine clearance ≤ 60 ml/min compared to patients with normal renal function (9.48% and 6.76%, p=0.052 *vs* 3.89% and 2.98%). The same tendency was observed for life threatening bleeding events (2.26% and 1.04%, p= 0.059 vs. 1.09% and 0.78%). Multivariate analysis did not identify renal impairment as expressed by creatinine clearance as a predictor of higher bleeding risk. More than half of patients with creatinine clearance <30ml/min were also very elderly patients. When analysing bleedings excluding these patients >75 years, the bleeding risk was still elevated but not significantly different between prasugrel and clopidogrel.

Hepatic impairment: Active metabolite exposures in subjects with moderate hepatic impairment and in healthy subjects are comparable. Patients with severe hepatic impairment were excluded from TAAL and a contraindication for these patients is included in the SPC. There were only a limited number of patients with less severe forms of hepatic impairment included in TAAL. Although safety did not seem to be compromised in these patients, safety conclusions must be drawn cautiously.

Age: In total, 901subjects in the prasugrel group and 908 subjects in the clopidogrel group were ≥ 75 years. In both treatment groups, twice as many subjects ≥75 years experienced Non-CABG-related

TIMI major or minor- (prasugrel 8.98%, clopidogrel 6.94%) as well as life-threatening bleeding events (prasugrel 2.58%, clopidogrel 1.57%) compared to patients below the age of 75 years. This was observed for both treatment groups. Furthermore, for prasugrel-treated patients ≥75 years (UA/NSTEMI as well as All ACS), twice as many experienced any stroke compared to clopidogrel treatment (2.89% *vs* 1.43%). A statistically significant difference was seen on the incidence of fatal bleeding in favour of clopidogrel. Use of prasugrel in this patient population is generally not recommended. If prescribed after a careful individual risk/benefit evaluation, a lower MD of prasugrel 5 mg should be used (please refer to section on Clinical efficacy). Further information on the 5-mg dose in this population will be obtained from future or ongoing clinical studies.

Prior Transient Ischemic Attack or Stroke: In total, 262 subjects of 6484 in the prasugrel group and 256 subjects of 6464 in the clopidogrel group had a prior history of TIA or stroke. Subjects with a history of prior TIA or stroke and treated with prasugrel had a statistically significant higher incidence of nonfatal stroke (15/262 (5.73%) vs. 2/256 (0.78%), p<0.001) and all stroke (both, fatal and nonfatal, hemorrhagic or non-hemorrhagic) (17/262 (6.49%) vs. 3/256 (1.17%), p<0.001), when compared to clopidogrel. A similar, statistically significant pattern was observed in the UA/NSTEMI population, whereas the number of stroke events in the STEMI population with prior history of TIA/stroke was too low to allow any reliable conclusions. In addition, a history of prior TIA/stroke in the all ACS population was associated with a higher risk of Non-CABG-related TIMI Major or Minor bleeding events (Prasugrel: 20/257 (7.78%) vs. clopidogrel: 10/252 (3.97%), p=0.054) and of Non-CABG-related TIMI Major Life-Threatening bleeding events (11/257 (4.28%) vs. 3/252 (1.19%), p=0.026, including fatal bleeding and symptomatic ICH) with prasugrel therapy. Regarding the fatal ICH, 2 out of 9 patients in the prasugrel group had a prior history of TIA/stroke *vs* 0 out of 5 patients in the clopidogrel group. The higher bleeding risk in patients with prior TIA or stroke was not associated with higher exposure during MD. Thus, patients with a prior history of TIA or stroke are contraindicated for prasugrel.

Low body weight: The risk of Non-CABG-related TIMI Major or Minor bleeding events for patients weighing below 60 kg was greater for prasugrel treated patients compared to clopidogrel treated, though not significantly different. However, the number of patients weighing less than 60 kg was very low (664 subjects in total in both treatment groups). PK data has shown that the active metabolite exposure increases as body weight decreases (see section on clinical pharmacology). A lower prasugrel 5 mg MD for this subgroup could be used. A PK/PD study to investigate the 5 mg dose in this patient population will be conducted as part of the FUMs.

Ethnicity: Prasugrel active metabolite exposure in Asian subjects was 43% higher after a 60-mg prasugrel LD and 40% higher during 10-mg prasugrel MD compared to Caucasian subjects. Based on point estimates for comparisons between Asians and Caucasians, body weight accounted for about one-third of the exposure difference between the two ethnic groups. There were so few Non-CABG-related Major or Minor bleeding events in the non-Caucasian populations that a meaningful comparison could not be done. A new PK/PG study in approximately 715 Asian ACS subjects in order to clarify which could be the optimal dose for this population will be conducted. Until this data become available a cautious approach is appropriate by including a warning in the SPC.

- Safety related to drug-drug interactions and other interactions

Specific *in vivo* drug-interaction studies were conducted with prasugrel and aspirin, ketoconazole (a potent CYP3A inhibitor), rifampicin (a potent inducer of CYP3A and CYP2B6 and an inducer of CYPs 2C9, 2C19, and 2C8), atorvastatin (a statin metabolized by CYP3A), warfarin (an anti-coagulant metabolized by CYPs 2C9 and 2C19), heparin, bupropion (a CYP2B6 substrate), and digoxin (a P-glycoprotein [P-gp] substrate). The effect of smoking and alcohol consumption were also evaluated across clinical pharmacology studies. Overall, these analyses detected no clinically relevant drug interactions.

Proton pump inhibitors may slow the rate, but not the extent, of appearance of prasugrel's active metabolite in plasma. Prasugrel can be co-administered with a proton pump inhibitor (PPI) or a H2-receptor antagonist. However, the SPC was revised to state that administration of the loading dose without co-administration with PPI may provide most rapid onset of action.

- Discontinuation due to adverse events

In the All ACS populations, overall incidence of study drug discontinuation due to treatment-emergent adverse events (TEAEs) was higher in subjects treated with prasugrel (462/6741 (7.15%)) compared to clopidogrel (390/6716 (6.02%)). The rate of discontinuation of study drug due to an AE was similar between treatment groups through 90 days, at which time the Kaplan-Meier curves diverge in favour of clopidogrel. The higher incidence of study drug discontinuation with prasugrel due to AE was primarily due to the higher incidence of hemorrhagic events (with GI hemorrhage (33/3741 (0.49%) vs. 21/6716 (0.32%)) and epistaxis (0.31% vs. 0.12%) being the most common). Atrial fibrillation (20/6741 (0.31%) vs. 33/6716 (0.51)) and rash (0.28% vs. 0.42%) were the non-hemorrhagic events leading to the highest incidence of permanent study drug discontinuation, but the rate between the 2 treatment groups was similar. In the secondary database there were no observed treatment differences between prasugrel and clopidogrel in the incidence of SAEs and non-serious TEAEs leading to premature discontinuation of study drug.

- Post marketing experience

There is currently no post-marketing experience with the use of this product.

- Discussion on clinical safety

The key safety findings associated with prasugrel treatment were a statistically higher incidence of hemorrhagic AEs. Adjudicated non-CABG-related TIMI Major Bleeding, TIMI Major or Minor Bleeding and TIMI Major, Minor, or Minimal Bleeding were statistically significantly increased in the prasugrel group compared to the clopidogrel group as well as fatal hemorrhagic AEs which were also higher in the prasugrel group. The Kaplan-Meier curves separated early for Non-CABG-related TIMI Major and TIMI Life-Threatening bleeding events while at risk, favouring clopidogrel. It seems that the curves remained parallel between 90 and 360 days. However, between 30 and 90 days as well as beyond 360 days, events continued to increase in subjects treated with prasugrel while a diminished accrual rate was seen in subjects treated with clopidogrel. Patients for whom a 10 mg maintenance dose is not recommended (those with a history of TIA or stroke – contraindication- , subjects ≥75 years of age taking a MD of 10 mg/day, or subjects <60 kg taking a MD of 10 mg/day) are responsible for the accrual between 30 and 90 days. The apparent accrual beyond 350 days cannot be explained. At the same time, the clinical benefit of prasugrel beyond 12 months seems not sufficiently supported by clinical data, this is why the CHMP has recommended that dual antiplatelet therapy with prasugrel should be restricted to 12 months treatment duration, in line with current clinical recommendations for dual antiplatelet therapy. This was also accepted by the Scientific Advisory Group of the CHMP.

The observation that fatal bleedings were higher in the prasugrel group compared to the clopidogrel group was of concern. However, the number of the spontaneous fatal bleeding events was similar between treatment groups, especially considering the ideal population for whom the prasugrel 10-mg MD would be recommended (subjects without a history of TIA or stroke, subjects ≥75 years of age, or subjects <60 kg). The rate of Non-CABG-related TIMI Major or Minor bleeding events in the ideal population was not statistically different between treatment groups but numerically higher for prasugrel. Though numbers of patients undergoing CABG were small, the risk of CABG related TIMI Major or Minor Bleeding was approximately tripled in the prasugrel arm, in particular in patients undergoing CABG within 7 days of the last dose of study drug. Bleeding events were also the primary reason for treatment discontinuations.

Subgroups associated with a statistically significant increase in Non-CABG-related TIMI Major bleeding were: ≥75 years old, body weight <60 kg, and history of prior TIA or stroke. The lastly mentioned patients have been contraindicated. For patients < 60 kg the events were associated with higher exposure of the active metabolite, supporting the proposed prasugrel 5-mg MD in this subgroup. For patients ≥ 75 years the events were partly associated with increased exposure to the active metabolite along with a greater susceptibility to bleeding. A dose adjustment strategy was justified by further analyses and planned future clinical studies for both the low weight patients and the very elderly. The use of prasugrel in patients ≥ 75 years of age is generally not recommended. If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age subgroup then following a 60 mg loading dose, a reduced prasugrel 5 mg MD should be prescribed.

The evidence for the 5 mg MD is based only on PK/PD analyses and no clinical data currently exist on the safety of this dose in the ≥ 75 years age group.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
1. Haemorahage: (Intracranial haemorrhage, Gastrointestinal haemorrhage, Intraocular haemorrhage Percutaneous Coronary Intervention-Related Haemorrhage, Coronary Artery Bypass Graft-Related Haemorrhage Other Procedure-Related Haemorrhage, Epistaxis)	• Routine pharmacovigilance: monitor AEs and SAEs through routine clinical trial and spontaneous post-marketing surveillance. • Targeted surveillance for specific AEs preidentified for targeted follow-up. • In-hospital registry to monitor prasugrel use and bleeding risk during the index hospitalisation compared to clopidogrel in a real life EU clinical setting.	• Contraindication for patients with history of stroke or transient ischaemic attack (TIA) and for patients with active pathological bleeding in Section 4.3 of SPC. • Section 4.2: dose adjustment for patients with risk factors for increased risk of bleeding: patients ≥ 75 years of age and patients <60 kg. • Wording in sections 4.2 and 4.4 of the SPC regarding the restricted use of EFIENT in patients ≥ 75 years of age, and maintenance dose reduction in these patients. • Caution for patients with a propensity to bleed, and with risk factors for an increased risk of bleeding (section 4.4) • Caution with concomitant administration of medicinal products that may increase the risk of bleeding (section 4.4) • Further recommendations to minimise the risk of haemorrhage, including CABG-related haemorrhage, are given in Section 4.4 (Surgery) and Section 4.8 of the SPC. Section 4.4 of the SPC recommends discontinuation of EFIENT at least 7 days prior to surgery. • Epistaxis is listed as ADR in Table 2, Section 4.8 of SPC. • Additional risk minimisation for patients ≥ 75 years of age will be provided by health care professional education to ensure that the information and recommendations in the SPC are adequately communicated. The MAH commits to work with scientific societies to develop educational vehicles for this purpose.
2. Anaemia	• Routine pharmacovigilance: monitor AEs and SAEs through routine clinical trial and spontaneous post-marketing surveillance. • Targeted surveillance for specific AEs preidentified for targeted follow-up.	• Listed as ADR in Table 2, Section 4.8 of SPC.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Potential Risks		
Risks associated with off-label use	• Routine pharmacovigilance: monitor AEs and SAEs through routine clinical trial and spontaneous post-marketing surveillance. • Targeted surveillance for specific AEs preidentified for targeted follow-up. • In –hospital registry to monitor prasugrel use and bleeding risk during the index hospitalisation compared to clopidogrel in a real life EU clinical setting. • Off-Label Use in Patients Post-Discharge: To monitor the off-label use post-discharge in patients treated with prasugrel. The databases will capture data pertaining to drug utilisation to monitor in what patients prasugrel is used, and at what doses.	• Not in proposed SPC as not confirmed signal.
Phototoxicity (Skin or Ocular)	As bullet 1 above.	• Not in proposed SPC as not confirmed signal.
Drug-Induced Hepatic Injury	As bullets 1 and 2 above.	• Not in proposed SPC as not confirmed signal.
Allergic Reactions	As bullets 1 and 2 above.	• Not in proposed SPC as not confirmed signal.
Thrombocytopenia	As bullets 1 and 2 above.	• Not in proposed SPC as not confirmed signal.
Neutropenia	As bullets 1 and 2 above.	• Not in proposed SPC as not confirmed signal.
Thrombotic Thrombocytopenic Purpura	As bullets 1 and 2 above.	• Warning in Section 4.4 of the SPC includes a description of this serious event.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Missing Information		
Concomitant use with fibrinolytics, clopidogrel, and chronic use of NSAIDs (non ASA).	• Continue to analyse AE reports in clinical trials • Periodically review and analyse safety database • Any spontaneously reported case associated with an exposure condition (EC) is managed according to internal procedures for clarification. • Safety surveillance intends to identify signals associated with the ACS subpopulations and use of drugs associated with an increased risk of bleeding. Concomitant drug use will also be monitored in the in-hospital registry.	• Sections 4.4 and 4.5 of the SPC contain language cautioning against concomitant use with these drugs.
Paediatric population	• Continue to analyse paediatric data from clinical trials • Periodically review and analyse safety database for any potential post-marketing use in the paediatric or adolescent population.	• Section 4.2 of SPC states that EFIENT is not recommended for use in children and adolescents due to a lack of data on safety and efficacy.
Pregnant/Lactating women	• Continue to analyse AE reports in clinical trials • Periodically review and analyse safety database for any potential post-marketing use in pregnant or lactating women • Routine pharmacovigilance, targeted surveillance with specific follow-up form for pregnancy and lactation, safety surveillance for safety signal detection associated with these events. Pharmacovigilance, targeted surveillance with specific follow-up form for exposure condition, safety surveillance for safety signal detection associated with the exposure condition.	• Section 4.6 of SPC recommends a risk/benefit evaluation approach with regard to pregnancy, and does not recommend use of EFIENT during breastfeeding.

Summary of the Risk Management Plan for EFIENT (prasugrel) – concluded

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Missing Information (cont.)		
Subjects without clinical manifestation of ACS or with ACS not managed by PCI (requiring immediate CABG or suitable for medical management only)	• Continue to analyse AE reports in clinical trials • Periodically review and analyse safety database for any spontaneously reported case associated with these situations • CAD subjects with no symptom of ACS may be detected by routine pharmacovigilance activities. • Medically-managed ACS subjects not planned to be managed by PCI will be studied in Study TABY.	• Indication statement in Section 4.1 of the SPC includes definition of the targeted population for EFIENT, i.e. ACS *undergoing* PCI.
Subjects with severely compromised cardiac status (cardiogenic shock, Class IV CHF, refractory ventricular arrhythmia)	• Routine pharmacovigilance, safety surveillance for safety signal detection associated to prasugrel use in this specific subpopulation.	• Indication statement in Section 4.1 of the SPC describes the target patient population as follows: o patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI).
Subjects with severe hepatic impairment.	• Continue to analyse AE reports in clinical trials • Periodically review and analyse safety database for any spontaneously reported case associated with severe hepatic impairment • In –hospital registry will allow for identification of subjects with possible liver damage.	• Contraindication for patients with "severe hepatic impairment (Child Pugh Class C)" in Section 4.3 of the SPC.

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:
The MAH should provide educational material to all physicians who may be involved in treating patients with prasugrel. The format and means of dissemination, of this material should be discussed with the appropriate learned societies. The results of the discussion, and where appropriate the material, should be agreed with the national competent authority and be available prior to launch in each member state.

The educational material should include:
- A copy of the SPC
- Emphasis that:

- Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg
- Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.
- If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5mg should be prescribed.
- Patients weighing < 60 kg should have a reduced maintenance dose of 5mg
  The evidence for a 5mg dose is based only on PK/PD analyses and no clinical data currently exist on the safety of this dose in the at risk sub groups.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the 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. There are a number of quality issues that will be resolved as Follow-up Measures within an agreed timeframe. None of these issues is expected to have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The non clinical pharmacological programme provided an adequate characterisation of the pharmacological properties of prasugrel. In *ex vivo* studies with rats, dogs, and cynomolgus monkeys, prasugrel demonstrated dose-dependent inhibition of ADP-induced platelet aggregation. The *in vivo* effects of prasugrel were assessed in nonclinical pathophysiological models of thrombotic challenge. Administration of prasugrel at clinical doses is not expected to produce secondary pharmacology effects related to CNS, cardiovascular, respiratory, renal, or GI function or to have an affect on QT interval. Additive or synergistic platelet inhibitory effects of the co-administration of prasugrel with aspirin have also been demonstrated. The active metabolite of prasugrel R-138727 is chiral; with two most potent enantiomers of R-138727 comprise approximately 84% of the metabolite in human plasma. The overall metabolism of prasugrel was thoroughly investigated.
The primary effects of prasugrel observed during repeat-dose toxicology studies included decreased body weight relative to control in rodents that was occasionally accompanied by decreased food consumption, and increased liver weight and histologic changes in the liver considered to be related to microsomal enzyme induction. Prasugrel did not exhibit genotoxic properties when tested *in vitro* nor *in vivo*. The increase in liver tumours observed in mice dosed with prasugrel is not considered a relevant human risk, and this is adequately reflected in the proposed prescribing information. Prasugrel did not exhibit toxicity towards fertility and early embryonic development and did not show embryo-foetal toxicity. The SPC obtains adequate statements.

Non-clinical and clinical data indicate that evidence of the phototoxic potential of prasugrel is weak and of questionable clinical relevance. Nevertheless, phototoxicity was included as a potential risk in the RMP.

A complete environmental risk assessment has been conducted for prasugrel. No likely risk has been identified for aquatic organisms in either ground water or surface water, or for sediment dwelling organisms.

Efficacy

A single pivotal superiority trial supports the use of prasugrel (60 mg LD and 10 mg MD) in patients with ACS with scheduled PCI. This study demonstrated that treatment with prasugrel, as compared with clopidogrel at the standard approved dose resulted in a statistically significant reduction in the rate of the primary composite efficacy endpoint of cardiovascular death, nonfatal MI, or nonfatal stroke. The reduction of the incidence of primary composite endpoint was primarily driven by a

reduction in the number of cardiac ischemic events, in particular nonfatal MI. These events are not considered to be harmless periprocedural increases in biochemical markers after index PCI alone. Prasugrel treatment might initially protect against smaller myocardial infarctions related to index PCI, however, the absolute reduction of nonfatal myocardial infarction in the all ACS population continued to increase throughout the study period. The absolute percentage reductions were 0.94, 1.57, 1.65, and 2.15 at 3 days, 30 days, 90 days, and at study end, respectively. When similar analyses are done separately in UA/NSTEMI and STEMI populations, continued increases in the absolute reduction of nonfatal myocardial infarction were also observed. This data suggests that prasugrel treatment protects against short-term as well as long-term cardiac ischemic events. A relative risk reduction of about 20% was observed in UA/NSTEMI, STEMI, and all ACS populations. The approximate 2% absolute risk reduction observed in these populations is considered clinically meaningful.

Data from subgroup analyses suggest that patients with a history of diabetes mellitus could benefit from prasugrel treatment. In response to a question on this topic from the CHMP, a general discussion of platelet reactivity and ischemic risk in diabetic patients in the setting of ACS preceded a presentation of clinical outcomes in subjects with diabetes mellitus in study TAAL. Diabetic subjects, not on insulin, had higher relative and absolute risk reduction if randomized to prasugrel, compared to non-diabetic patients randomized to prasugrel. Even higher risk reductions were observed in diabetic patients on insulin, with the absolute risk reduction (primary efficacy endpoint) with prasugrel *vs* clopidogrel being 6.4%. The relative risk reduction was 37% in this sub-population. Qualitatively similar effects of diabetic status were observed for a number of other efficacy endpoints. Diabetic status seems to affect efficacy and safety differentially, favouring prasugrel treatment in diabetic subjects in particular. It is also acknowledged that consistency of the efficacy benefit across pre-specified primary and secondary endpoints supports the notion that the treatment benefit in diabetic subjects is not a chance finding. However, in contrast the clinical data indicate that patients with a history of prior TIA or stroke are harmed by treatment with prasugrel when compared to treatment with clopidogrel. This effect on the primary efficacy endpoint seems to be driven primarily by an increase in new strokes. For this reason, a history of prior stroke or TIA is now listed under contraindications in the SPC.

In the < 60 kg group, a reduced maintenance dose of 5 mg following a 60 mg loading dose should be prescribed. If treatment is deemed necessary in the ≥ 75 years age group, a reduced maintenance dose of 5 mg following a 60 mg loading dose should be prescribed after a careful individual benefit/risk evaluation by the prescribing physician. There are no adequate clinical data to support this recommendation; thus, the positive clinical outcome of this reduced maintenance dose remains to be seen. Further clinical studies to address this issue will be conducted.

Safety

The safety of prasugrel was comparable to clopidogrel with respect to the incidence of AEs, SAEs and deaths, as well as pre-specified, non-hemorrhagic, clinically relevant TEAEs and laboratory values (thrombocytopenia, neutropenia, leucopenia, allergic reactions, including angioedema, abnormal hepatic function, and torsades de pointes/QT prolongation). The overall incidence of study drug discontinuation was higher in the prasugrel group compared to clopidogrel (approximately 1% greater) primarily due to a higher incidence of hemorrhagic AEs.
Adverse events related to haemorrhage occurred with a statistically significantly higher incidence in the prasugrel treated patients compared to clopidogrel and this was consistent in the majority of subgroups of bleeding events.

Recent clinical studies of anti-thrombotic agents have suggested that major bleeding events may predict an increased risk of CV or non-CV death in the early weeks following the bleeding event and the administration of blood units are called to play a special role on this. This increased risk is also evident in study TAAL. Additionally in this regard, there is ongoing controversy about the efficacy and safety of blood transfusions in the ACS context. To the extent that current recommendations indicate that in mild to moderate anaemia (Hct >25% and Hb >8 g/dl) blood transfusions may be related with an increase risk of death at 30 days and should be avoided if haemodynamically well tolerated. As mentioned earlier, in a post hoc analysis in Study TAAL assessment of long-term

outcomes for subjects experiencing a Non-CABG-related TIMI Major bleeding event indicated that, after 30 days from the event, the risk for major adverse CV events was not higher than that observed in subjects not experiencing the bleeding event. Beyond 30 days, mortality was comparable in those patients who did not have a major bleeding and those who had a major bleeding. Likewise, within 30 days, mortality was comparable for prasugrel and clopidogrel treated patients who did not experience a major bleeding. However, after a TIMI major bleeding, mortality (within 30 days) was significantly higher for prasugrel treated patients compared to clopidogrel treated patients for the All ACS population and its clinical presentations UA/NSTEMI and STEMI. When considering only the so-called ideal population (patients without a history of TIA or stroke, subjects ≥75 years of age, or subjects <60 kg), all cause mortality is still numerically higher after TIMI major bleeding in prasugrel compared to clopidogrel but the difference was not statistically significant. The deaths were predominantly attributable to fatal bleedings.

Apart from the direct haemodynamic consequences of the bleeding episode, which is also associated with the risk of ischemic events occurring in relation to bleeding induced hypotension or transfusions, an important component of the risk is the potential need to interrupt the antiplatelet and antithrombotic drugs which can lead to an increase of ischemic events. In clinical practice the risk of interrupting antithrombotic and antiplatelet treatments must be weighed against the risk of a thrombotic event, particularly if the patient has been submitted to revascularization and stent implantation. The SPC states that premature discontinuation of any antiplatelet agent could result in increased risk of ischaemic events. Further, the SPC includes a warning that in patients with active bleeding in whom reversal of pharmacological effects of prasugrel is required, platelet transfusion may be appropriate.

Colon cancer occurred with a higher incidence in patients treated with prasugrel, but this was assumed to be the consequence of a higher rate of detection rate due to bleeding associated with this therapy.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 2.5 adequately addressed these concerns

- User consultation

User testing of the package leaflet was performed using methodology, which methodology follows the readability guideline. No revisions of the PL were made between test rounds. In conclusion, the user testing of this PL version is judged acceptable.

Risk-benefit assessment

Superiority of prasugrel over clopidogrel was shown in the clinical setting when the primary composite efficacy endpoint - CV death, nonfatal MI, or nonfatal stroke at a median follow-up of 14.5 months - is considered, and was primarily driven by a reduction in MIs. Peri-procedural as well as spontaneous MIs were decreased with prasugrel.

The treatment benefit associated with prasugrel was generally preserved across the major pre-specified subgroups. The reduction in ischemic events with prasugrel was evident regardless of the adjunctive therapy or stent type selected during PCI. Clinical data suggest that patients with a history of diabetes could benefit in particular from treatment with prasugrel. Vice versa, although not reaching statistical significance, the data also suggest that subjects with a history of prior TIA or stroke are harmed by treatment with prasugrel compared to treatment with clopidogrel. This patient subgroup is contraindicated.

Key safety issues were primarily related to the risk of bleeding. A statistically higher incidence of hemorrhagic AEs was observed for prasugrel *vs* clopidogrel. These were related to higher rates of GI bleeding, surgical site bleeding, bleeding at other sites not pre-specified or unknown and retroperitoneal bleeding. Fatal hemorrhagic AEs were higher in the prasugrel group. The finding of significantly increased hemorrhagic events in the prasugrel studies was in general seen for the All-

ACS population and the UA/NSTEMI population. In the STEMI subgroup incidences of the different hemorrhagic events were in general numerically higher in the prasugrel group compared to the clopidogrel group, however, the differences were in most cases not statistically significant. Subgroups vulnerable to bleeding were patients ≥75 years old, patients with body weight <60 kg, and patients with a history of prior TIA or stroke. Further analyses indicated that increased mortality after TIMI major bleedings with prasugrel within the first month of treatment appeared to be related mainly to fatal bleedings. The higher bleeding risk associated with the use of prasugrel is appropriately described in the SPC and guidance has been given to minimise the use of prasugrel in populations at higher risk of bleeding.

It should also be remembered that safety in a real clinical setting tends to be worse than observed under controlled conditions. Attention should therefore be paid to the possible risk of ischemic events which may occur in relation to major bleeding events, e.g. by discontinuation of antiplatelet therapy, bleeding induced hypotension, or transfusions.

For patients ≥ 75 years, treatment is generally not recommended. For selected subgroup of patients ≥75 years for whom prasugrel treatment is deemed necessary, a reduced maintenance dose of 5 mg should be prescribed. Patients < 60 kg should receive a reduced maintenance dose of 5 mg. The main limitation of this recommendation for a prasugrel dose adjustment is the current lack of clinical data supporting the safety and efficacy for the treatment of these subgroups with a reduced maintenance dose of 5 mg. Additional clinical studies to assess the 5 mg dose in the relevant at risk populations are necessary and are planned, as discussed earlier.

In summary, the following table describes Number Needed to Treat (NNT) and Number Needed to Harm (NNH) for different subgroups.

NNT (Primary Efficacy Outcome) and NNH (TIMI Major bleedings) - Study TAAL; All randomized Subjects

Subgroup	Efficacy Sample size	NNT (Primary efficacy [1])	NNT (All death, MI, Stroke)	NNH (TIMI Major)	NNH (TIMI Life-Threatening)
All ACS	13608	49	52	195	234
UA/NSTEMI	10074	52	58	163	186
STEMI	3534	42	40	444	888
Gender					
Female	3523	72	59	109	226
Male	10085	44	50	254	229
Age					
≥75 years	1809	102	192	110	98
<75 years	11799	45	47	220	295
Weight					
<60 kg	668	81	58	36	81
≥60 kg	12769	48	52	267	284
Region					
North America	4310	35	36	328	1243
Western EU	3553	73	70	198	222
Eastern EU	3322	61	75	102	163
Medical History					
Diabetics	3146	23	22	795	313
Non-diabetics	10462	74	87	159	218
Prior TIA/Stroke	518	-23	-20	33	32
No prior TIA/Stroke	13090	43	45	243	311
Ideal population[2]	10,804	39	40	312	368

[1] CV death, non-fatal MI, or non-fatal stroke
[2] that is, population for whom a 10 mg MD is recommended

Sufficient evidence has been provided that the timing of clopidogrel LD, which is recommended to be given immediately, and not, as in study TAAL after diagnostic angiography, did not substantially influence the efficacy of prasugrel *vs* clopidogrel.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- the following additional risk minimisation activities were required:

The MAH should provide educational material to all physicians who may be involved in treating patients with prasugrel. The format and means of dissemination, of this material should be discussed with the appropriate learned societies. The results of the discussion, and where appropriate the material, should be agreed with the national competent authority and be available prior to launch in each member state.

The educational material should include:

- A copy of the SPC
- Emphasis that:
  - Severe haemorrhagic events are more frequent in patients ≥ 75 years of age (including fatal events) or those weighing < 60 kg
  - Treatment with prasugrel is generally not recommended for patients of ≥ 75 years of age.

- If, after a careful individual benefit/risk evaluation by the prescribing physician, treatment is deemed necessary in the ≥ 75 years age group then following a loading dose of 60 mg, a reduced maintenance dose of 5mg should be prescribed.
- Patients weighing < 60 kg should have a reduced maintenance dose of 5mg
  The evidence for a 5mg dose is based only on PK/PD analyses and no clinical data currently exist on the safety of this dose in the at risk sub groups.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Efient "co-administered with acetylsalicylic acid (ASA), for the prevention of atherothrombotic events in patients with acute coronary syndrome (i.e. unstable angina, non-ST segment elevation myocardial infarction [UA/NSTEMI] or ST segment elevation myocardial infarction [STEMI]) undergoing primary or delayed percutaneous coronary intervention (PCI)" was favourable and therefore recommended the granting of the marketing authorisation.