EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ASSESSMENT REPORT
FOR
Brilique

International non-proprietary name:
ticagrelor

Procedure No. EMEA/H/C/1241

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.□uropa.eu

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 27 October 2009 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Brilique, 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 EMA/CHMP on 18 December 2008.

The applicant applied for the following indication: prevention of thrombotic events.

The legal basis for this application refers to:

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

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on the applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/199/2009 for the following conditions:

- Thromboembolic events

on the agreement of a paediatric investigation plan (PIP) and the granting of a product-specific waiver for the condition acute coronary syndrome. The waiver applies to all subsets of the paediatric population from birth to less than 18 years of age, for film-coated tablet, age appropriate to be developed, oral use on the grounds that the disease or condition for which the specific medicinal product is intended does not occur in the specified paediatric subset(s).

The PIP is not yet completed.

Information relating to Orphan Market Exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 14 Oct 2005 and on 24 Feb 2006. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

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

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Gonzalo Calvo Rojas**

- The application was received by the EMA on 27 October 2009.
- The procedure started on 18 November 2009.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 February 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 09 February 2010.
- During the meeting on 18 March 2010, 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 18 March 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 May 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 July 2010.
- During the CHMP meeting on 22 July 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 August 2010.
- The Rapporteurs circulated the Joint Assessment Report on the response to the CHMP List of Outstanding Issues on 8 Sep 2010.
- During the meeting on 23 September 2010, 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 Brilique. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 24 Sep 2010.

2. Scientific discussion

2.1. Introduction

Acute coronary syndrome (ACS) encompasses the spectrum of threatened, evolving, and completed myocardial infarction (MI). Despite the widespread adoption of intensive monitoring and prompt treatment of cardiac electrical instability, thrombolytic therapy, acute invasive interventions, and dual antiplatelet therapy with acetylsalicylic acid (ASA) and thienopyridines, approximately 1 in 3 ACS patients dies, has a repeat MI, or requires re-hospitalisation within 6 months. Current guidelines indicate dual antiplatelet therapy with ASA and clopidogrel for all ACS patients. An electrocardiogram (ECG) shows ST-elevation myocardial infarction (STEMI) or a non-ST elevation (NSTEMI) ACS event. Those with STEMI usually receive accelerated care, including cardiac catheterisation, leading to

percutaneous coronary intervention (PCI), coronary artery bypass (CABG) surgery, or management with medication alone. For them, time from presentation to re-establishing coronary flow impacts survival. Those with NSTEMI-ACS have the same treatment options; however, interventions are less time-critical. NSTEMI-ACS patients will less urgently be diagnosed with either a documented MI (NSTEMI), or unstable angina (UA). Platelet inhibitors have been proven as effective agents for the treatment of both chronic and acute diseases of the arterial vessel wall. Low dose acetylsalicylic acid (ASA) reduces ischaemic outcomes in patients but often is insufficient to prevent ischaemic events in high-risk patients. While ASA inhibits the cyclooxygenase (COX) pathway, it has no known effect on the adenosine diphosphate (ADP) P2Y12 platelet receptor. Inhibition of ADP-mediated platelet activation and aggregation by ticlopidine and clopidogrel has been shown to provide improved efficacy for treatment of thrombotic ischaemic events, compared with ASA therapy alone, while demonstrating a favourable bleeding profile. However, both ticlopidine and clopidogrel have an irreversible inhibition of platelet aggregation (IPA).

Ticagrelor (formerly known as AZD6140) is a reversible, selective P2Y12-receptor antagonist (anti-platelet agent) being developed to reduce thromboembolic events in patients with atherosclerosis. It is orally active and does not require metabolic activation. Proposed and granted indication is: "Ticagrelor, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG)". The dosing regimen is an initial single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment is recommended for at least 12 months unless discontinuation of ticagrelor is clinically indicated.

The clinical development program of ticagrelor comprises 41 phase I and four phase II clinical pharmacology (PK and/or PD) studies, two phase II dose selection studies and a single pivotal phase III trial in over 18,000 ACS patients. A second phase III trial is planned to evaluate the benefit/risk of ticagrelor on top of aspirin in patients with a history of ACS. An overview of the clinical program is provided below. Scientific advice by EMEA was provided: EMEA/CHMP/SAWP/330223/2005 and EMEA/51999/2006. The application includes an EMA decision on the agreeing of a PIP, granting a deferral and granting a product specific waiver (P/199/2009).

2.2. Quality aspects

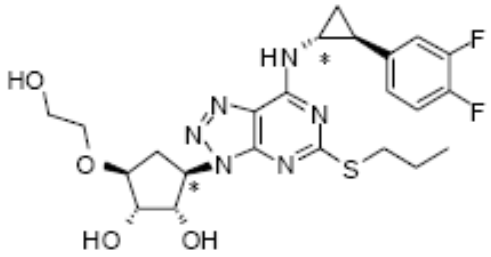
2.2.1. Introduction

Brilique is presented as round, biconvex, yellow, film-coated tablets containing 90 mg of ticagrelor as active substance. The tablets are marked with '90' above 'T' on 1 side and plain on the reverse. Other ingredients are: mannitol, dibasic calcium phosphate, sodium starch glycollate, hydroxypropyl-cellulose, magnesium stearate, hypromellose, titanium dioxide (E171), talc, polyethylene glycol and ferric oxide yellow. The tablets are packed in PVC-PVDC blisters sealed with aluminium foil and the blisters are packed in cardboard carton.

2.2.2. Active Substance

The chemical name of ticagrelor is (1S,2S,3R,5S)-3-[7-{[(1R,2S)-2-(3,4-Difluorophenyl) cyclopropyl]amino}-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)

cyclopentane-1,2-diol corresponding to the molecular formula $C_{23}H_{28}F_2N_6O_4S$ and molecular weight 522.57 g/mol.



It appears as a white or off-white to pale pink powder which does not exhibit pH dependent solubility and is defined as 'low solubility' under the Biopharmaceutics Classification System (BCS). Having also a low permeability, ticagrelor is a BCS class IV compound.

Ticagrelor is a complex carbocyclic nucleoside analogue with 6 stereocentres. Correct configurations of all stereocentres are established by stereo-selective chemistry of the starting materials. Extensive polymorph screening has confirmed the existence of several crystal modifications of ticagrelor. There are 4 non-solvated polymorphs (Polymorph I, II, III and IV) and a number of solvated crystalline modifications that are clearly distinguishable by X-Ray Powder Diffraction. Other properties such as hygroscopicity, thermal behaviour, partition coefficient and specific optical rotation have been adequately studied and discussed.

Manufacture

The commercial manufacturing process comprises 6 steps and is based on 3 starting materials for which acceptable specifications have been presented.

Ticagrelor has 6 stereocenters resulting in 64 theoretical stereoisomers including the ticagrelor molecule itself. Control of the isomers is ensured with a four-step strategy:

- stereoselective chemistry early in the synthetic pathway,
- stereochemical control of impurities in the specification of the proposed starting materials,
- thorough understanding of the potential formation of stereochemical impurities during the manufacturing process,
- thorough knowledge of the stereochemical impurities potentially present.

Data confirming stereospecificity is presented and supports that a chiral method for the detection of the enantiomer is not required.

The polymorphic form is relevant in view of the low solubility of the active substance and the solid oral dosage form in which it is presented. Consistent manufacture of the same polymorphic form is therefore essential; this has been sufficiently confirmed by batch analyses which confirm also that epimerisation does not take place during synthesis or routine storage.

The provided information and discussion on the characteristics of the active substance and potential polymorphic forms is considered sufficient.

Adequate In-Process Controls are applied during the manufacture of the active substance. The specifications and control methods for intermediate products, starting materials and reagents, have been presented and are satisfactory. Potential impurities have been well discussed in relation to their origin and potential carry-over into the final drug substance. Batch analysis data produced with the proposed synthetic routes provided show that the active substance can be manufactured reproducibly.

Quality by Design (QbD) principles were applied to the development of the ticagrelor synthetic route and manufacturing process. The critical quality attributes that have the potential to affect product performance have been identified using the principles as outlined in ICH Q8 and Q9. Failure Mode, Effects and Criticality Analysis (FMECA) has been the main tool for the risk assessment. Parameters of design spaces have been adequately translated into a control strategy. The division into key process parameters and critical process parameters is considered correct.

Specification

The active substance specifications includes tests for description, identification (IR), assay (HPLC), residual solvents (GC), catalysts, organic impurities (HPLC), potential genotoxic impurity, sulphated ash, particle size and polymorphic form.

The specifications reflect all relevant quality attributes of the active substance. Impurity limits in the specifications are justified by toxicological studies.

Stability

Stability studies were conducted in line with ICH guidelines. Stability data on the active substance have been provided for three full scaled batches stored at 25°C/60% RH (24 months), 30°/75% RH (12 months) and 40°C/75% RH (6 months) plus one additional production scaled batch manufactured at another location covering 3 months at all three conditions. All results remain within the specification over the tested period at all conditions what corroborates that the substance is very stable. The proposed re-test period and storage conditions are acceptable.

Degradations products were also investigated in one batch under stress conditions stability studies (thermal, humidity and light).

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development was to develop an immediate release tablet containing 90 mg of ticagrelor.

Because ticagrelor is a low soluble drug substance (not ionised in the physiological pH range) and exhibits a moderate intrinsic permeability, there is potentially a higher risk that changes in formulation and processing parameters can affect clinical performance, and this was taken into account during development. Moreover, this low aqueous solubility of ticagrelor leads to an increase of relevance of particle size. Nevertheless, extensive dissolution studies, including solubility studies in human intestinal fluids, were performed and suggest that ticagrelor may be less sensitive to process and formulation parameters than what would be expected from its formal BCS classification.

The pharmaceutical development of the product has been adequately performed using the principles of quality risk management described in ICH Q8 'pharmaceutical development'; Failure Mode, Effects and

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

Criticality Analysis (FMECA) has been the main tool used for risk assessment throughout the development process.

The compatibility of ticagrelor with a range of commonly used pharmaceutical excipients, suitable for tablets has been investigated throughout development and the following were retained: mannitol (as a diluent), dibasic calcium phosphate (as a diluent), sodium starch glycollate (as a disintegrant), hydroxypropyl-cellulose (as a binder), magnesium stearate (as a lubricant), purified water (as a lubrication fluid), hypromellose (as a film former), titanium dioxide (as an opacifier), talc (as an opacifier and lubricant), polyethylene glycol (as a plasticiser), ferric oxide yellow (as a colouring agent) and purified water (as solvent). The choice and function of the excipients in the final formulation have been described and justified. The composition of the tablets has evolved since the phase I studies but in vivo bioequivalence studies have confirmed the equivalence of the formulations. The excipients are conventional and meet the requirements of the Ph. Eur. Except ferric oxide which complies with the specification s of the Annex of Directive 95/45/EC.

None of the materials used in the synthesis of ticagrelor active substance and excipients used in the film-coated tablets is of animal or human origin and therefore there is no risk of TSE contamination.

A wet granulation process was chosen and the formulation was optimised using multivariate experiment design. Satisfactory discussion on the development of the formulation and the dissolution characteristics is provided in the dossier. Critical aspects that could affect the dissolution have sufficiently been discussed (e.g. polymorphic form, particle size, production parameters etc.)

When developing the manufacturing process, a quality target product profile has been made, critical quality attributes have been defined and discussed, the manufacturing process has been selected based on these aspects and a control strategy has been defined.

A quality by design approach was applied to the container closure system and three design space boundaries have been set: chemical compatibility, moisture ingress and the level of protection against UV light. Stability studies on the tablets have thus confirmed the suitability of the chosen packaging: PVC/PVDC/Alu blisters.

Manufacture of the product

Ticagrelor film-coated tablets are manufactured using conventional manufacturing techniques. The manufacturing process consists of 8 consecutive steps: 1) granulation including dry mixing; 2) wet granulation; 3) drying; 4) milling; 5) lubrication; 6) compression; 7) coating and 8) packaging.

A flow diagram of each step is presented including reference to the IPCs. A tabulated overview of typical equipment is presented including relevant references. Justifications for the manufacturing process elements of the ticagrelor tablets design space are provided. Critical steps are controlled by in-process testing applied during the manufacturing process to ensure that the critical quality attributes are met.

Data from batches of ticagrelor film-coated tablets manufactured at pilot scale, at both development and proposed commercial manufacturing sites are presented. Continuous process verification, as important aspect of QbD approach, is applied.

Product Specification

The product specification at release includes tests for description, identity tests (NIR, or HPLC/UV, or UPLC/UV), identity of colorant, assay (HPLC or NIR or UPLC), degradation products (HPLC or UPLC),

dissolution (Ph. Eur.) and uniformity of dosage units (Ph. Eur.). The same requirements apply for shelf life requirements.

The analytical methods have been adequately described and validated. Batch analytical data on 42 full scale batches from the proposed production sites demonstrates that the finished product can be manufactured reproducibly according with the release specification.

Stability of the product

Data from 3 pilot batches manufactured at the production site is presented. The stability studies have been performed in accordance with ICH guideline Q1A under long-term, intermediate, accelerated and stressed conditions (24 months at 25°C/60% RH, 24 months at 30°C/75% RH and 6 months at 40°C/75% RH). The parameters studied are the same as at shelf life; water content and hardness were added during the stability studies.

An increase in water content was observed under all conditions; nevertheless, this change is not considered significant and do not impact on any of the critical quality attributes such as assay, degradation products, dissolution and microbiology). Based on the available data, the proposed shelf life and storage conditions for the bulk product or for the drug product packed in the proposed blister as stated in the SPC are accepted.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

In general satisfactory documentation has been provided to confirm the acceptable quality of this medicinal product, and no major objections have been raised during evaluation. The drug substance has been adequately characterized and the specification is acceptable in view of the route of synthesis and the various ICH guidelines. The solid drug substance is stable with respect to degradation. Concerning the finished product the complete control strategy and an established manufacturing process guarantees consistent control of the product quality which should have a satisfactory and uniform performance in the clinic. The drug product is stable with respect to degradation.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ration of the product. The applicant provided a letter of undertaking and committed to resolve these as Follow Up Measures after the opinion within an agreed timeframe.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Primary pharmacodynamic studies

Ticagrelor and its major circulating metabolite AR-C124910XX are potent antagonists of the platelet P2Y12 receptor that produces reversible and concentration-related inhibition of ADP-induced platelet aggregation both *in vitro* and *ex vivo*. In a non-P2Y12 mediated aggregation assay, ticagrelor showed no effect on platelet aggregation. It is suggested that ticagrelor acts as an allosteric modulator of the P2Y12 receptor. *In vivo*, ticagrelor has been shown to eliminate platelet-mediated arterial thrombosis in the damaged, stenosed femoral artery of anesthetized dogs. For a given anti-thrombotic effect, ticagrelor produces significantly less impairment of homeostasis than the GPIIb/IIIa antagonist orbofiban and marginally better selectivity over the thienopyridine agent clopidogrel. The Applicant has discussed the lack of *in vivo* primary pharmacodynamic studies in the main species selected for toxicity testing (i.e. rat and marmoset monkey), considering that the species used in toxicology studies should be responsive to the primary pharmacodynamics of ticagrelor. The degree of homology of the P2Y12 receptor sequence is high, especially in the marmoset, 96.2% and maintaining the interaction sites with man. In the rat, the homology is also high, 85.7%, but three differences in the binding site were noted. These data are considered sufficient to support the relevance of the primary pharmacodynamic data in man included in the initial submission. In addition, the Applicant characterized primary pharmacodynamics of the two major metabolites: AR-C124910XX and AR-C133913XX in the relevant non-clinical species. The potency of ticagrelor, AR-C124910XX and AR-C133913XX is considered similar in human and the two relevant non-clinical species, rat and marmoset. AR-C124910XX could be even more potent in the rat and marmoset, and more potent than ticagrelor. According to previously submitted data, AR-C124910XX was a major metabolite in all non-clinical species and in man and therefore adequately qualified in the non-clinical programme.

Secondary pharmacodynamic studies

Apart from platelets, the P2Y12 receptor is also expressed in the spinal cord, brain, microglia, vascular smooth muscle cells, lymphocytes, CD34 positive stem cells and pancreatic islets. Based on the clinical experience with ticagrelor and other P2Y12 receptor antagonists already in clinical use, no clear relevance of non-platelet P2Y12 clinical effects are evident. However, in vascular smooth muscle cell preparations expressing P2Y12 receptors, ticagrelor has been shown to inhibit ADP-induced vasoconstriction, suggesting that ticagrelor might have a dual anti-ischemic effect by inhibiting both thrombus formation as well as vasospasm. Ticagrelor did not show significant agonist or antagonist activity against any other P2 receptor types. Regarding human P1 receptors, ticagrelor showed low affinity (Ki >10μM) for the adenosine A1, A2A and A2B receptors, but higher affinity (Ki = 104 nM) for the adenosine A3 receptor. The *in vitro* and *ex-vivo* data do not provide a clear conclusion to whether the interaction of ticagrelor with the adenosine A3 receptor is agonistic or antagonistic. Overall, given its affinity for the P2Y12-receptor (Ki, 2.0 nM), ticagrelor has shown 50-fold less affinity for the human P1 receptor subtypes. Ticagrelor inhibited human erythrocyte adenosine uptake. This inhibition of adenosine uptake following treatment with ticagrelor is most likely achieved by inhibiting sodium independent adenosine transporters. Under hypoxic condition, ticagrelor amplifies inhibition of adenosine uptake, suggesting that ticagrelor might show increased potency in patients suffering from hypoxic diseases like acute coronary syndromes. There might be clinical relevance for the *in vitro*

observed adenosine uptake inhibition by ticagrelor, since ticagrelor enhanced the adenosine-induced increase in coronary blood flow, following both endogenous induction of adenosine via temporary occlusion of the left anterior descending coronary artery and local administration of adenosine via a direct infusion. Ticagrelor and its metabolite did not significantly affect adenosine metabolism, since they were weak inhibitors of adenosine deaminase, the enzyme which metabolises adenosine into inosine. Next to adenosine A3 receptors and adenosine transporters, ticagrelor significantly inhibited GPR17, a G-protein coupled receptor activated by both uracil nucleotides and cysteinyl-leukotrienes. GPR17 is highly expressed in brain, heart and kidney tissue and involved in propagation of secondary ischemic damage. Hence, potent inhibition of GPR17 by ticagrelor in the nanomolar range could result in reduction of the infarct area as previously demonstrated in a rat stroke model, although it is not confirmed at the moment. There are no grounds for further safety concern regarding ticagrelor action on GPR17 receptor at this moment.

Safety pharmacology programme

Safety pharmacology studies were performed to examine the potential effects of ticagrelor on the cardiovascular, respiratory, renal, central, peripheral and autonomic nervous systems and the gastrointestinal tract. Although ticagrelor rather potently inhibited the hERG potassium channel, increase in QT prolongation is not expected since the IC50 value (1.72 µM) is approximately 80-fold higher than the maximum free plasma concentration seen in humans (0.025 µM). In addition, ticagrelor did not affect action potential duration in isolated canine Purkinje fibers. Moreover, in preclinical *in vivo* studies and in clinical trials, no prolongation of the QT interval was observed following treatment with ticagrelor. *In vivo*, no significant ticagrelor-related effects were seen on cardiovascular, central, peripheral or autonomic nervous system following administration of 1, 10 or 100 mg/kg ticagrelor. In contrast, adverse effects on the respiratory and renal system were observed following exposure to oral doses ≥ 10 mg/kg, whereas adverse effects on the gastrointestinal system were observed following exposure to oral doses of 100 mg/kg. Similar adverse effects are also observed in the clinical trials.

Pharmacodynamic drug interactions

Coadministration of ticagrelor with aspirin and the thrombin inhibitor melagatran or the other P2Y12 antagonists clopidogrel and cangrelor did not affect ticagrelor -induced thrombocyte aggregation or increase bleeding time. In addition, simultaneous treatment with desmoressin or fibrinolysis inhibitors did not significantly reverse prolongation of bleeding time or anti-thrombotic aeffects caused by ticagrelor.

2.3.2. Pharmacokinetics

The absorption, distribution, metabolism and excretion of ticagrelor were investigated in the same species, and in most cases the same strains, used to establish its non-clinical pharmacologic and toxicologic profiles (e.g. rat, dog and Marmoset monkey). In addition, the kinetics of the active metabolite AR C124910XX was investigated. However, *in vivo* absorption studies in dog showed that the exposure ratio of AR C124910XX/ticagrelor following oral ticagrelor dosing was lower in dog compared to the other species tested including man.

The analysis of ticagrelor in plasma was performed with reversed phase liquid-chromatography and single mass spectrometry (LC MS). The methods were developed to determine exposure of ticagrelor in various species and included determination of the active metabolites AR-C124910XX and AR-

C133913XX. The different methods were precise and accurate. Sample preparation prior to the LC-MS process was protein precipitation or dilution. Ticagrelor has shown indications of adhering to glass, but not to plastic containers at low organic compositions. Ticagrelor and AR-C124910XX were stable at -20°C for ≥7 months in plasma for the used species, except in Cynomolgus plasma where the stability was 87 days. The stability of AR C133913XX has not been determined as extensively as for the other analytes, but was considered to be stable for ≥48 days in mouse, rat, rabbit, and Marmoset monkey plasma at -20°C.

In rat, a moderate plasma clearance (27 ml/min×kg) and a large volume of distribution at steady state (4.8 l/kg) were calculated. The terminal half-life was determined to be about 3 h. The oral bioavailability was 88% after an oral dose of 20 mg/kg given as suspension. Female rats generally had greater ticagrelor exposure than male rats. In Marmoset monkey, the half-life of ticagrelor in the Marmoset was 5-7.5 h with a plasma clearance of 11 ml/min×kg and a volume of distribution at steady state of 3.7 l/kg. The bioavailability after oral dosing was 37%. In humans, ticagrelor undergoes rapid absorption with peak plasma concentrations attained 2 to 3 h after oral administration. AR-C124910XX is formed rapidly, attaining peak plasma concentrations 2 to 3 hours after oral ticagrelor ingestion. The steady-state volume of distribution of ticagrelor is low, indicating that it does not extensively distribute into or bind to tissues. The volume of distribution in non-clinical species and humans is very different, 4-5 l/kg in rat and Marmoset monkey and 1.25 l/kg in humans. The half-life is shorter in the non-clinical species compared to humans; 4 h versus 7 h. Tmax is comparable between humans and the non-clinical species (~3 h). The AR-C124910XX/ticagrelor AUC ratio after single oral dosing was 0.23 in human, 0.43 in rat, 0.09 in dog, 0.38 in Marmoset monkey and 1.35 in Cynomolgus monkey. Dog showed a lower exposure ratio of AR C124910XX/ticagrelor compared to human.

Cynomolgus monkeys showed a shorter half-life than rat, Marmoset monkey and human and a higher AR C124910XX/ticagrelor ratio than humans. The CHMP agreed with the applicant that dog and Cynomolgus monkey are not suitable animal species for non clinical pharmacokinetic and toxicology studies. In rat, the exposure of ticagrelor seems linear from 1 to 20 mg/kg and more than dose proportional at >20 mg/kg. In humans and Marmoset monkeys, linear kinetics was observed. The exposure of AR C124910XX increased more than dose proportional over the ticagrelor administered dose range. The data indicate linear kinetics in Marmoset monkeys and humans.

After IV and PO ticagrelor administration, radioactivity was rapidly and widely distributed. The highest concentrations of total radioactivity were observed in the organs of elimination (liver and kidney) and glandular tissues (e.g. adrenal, pituitary and thyroid glands). Also pancreas, uveal tract, heart and secretory region of the gastro-intestinal tract contained relatively high levels of radioactivity. Very low levels of radioactivity were observed in the brain. There was little evidence of melanin-specific binding of radioactivity in the pigmented tissues (uveal tract and pigmented skin). Elimination of radiolabelled components from all tissues was relatively rapid with no apparent accumulation in any tissue including the pigmented skin and eye after a single dose. However, in humans some accumulation can be expected due to the twice daily dosing and the radioactivity present in some organs (liver, lung and glandular tissues) after 16 h in rat. The radioactivity observed in the secretory region of the gastro-intestinal tract indicates active secretion of radioactivity. Entero-hepatic recirculation is possible based on the plasma concentration – time curve.

The major route of excretion of ticagrelor and its metabolites is via the faeces and is independent of route of administration or gender. Elimination via faeces in mouse, rat and Marmoset monkey was ≥92%, ~85% and ~60%, respectively. Ticagrelor was the major component excreted in faeces (40% in rat, 25% in Marmoset and 27% in humans). AR C124910XX (~5% in rat and monkey and 22% in humans) and AR C133913XX (3-5% in rat, monkey and human) were detected, but also some other metabolites were present for≥3% of the administered dose. In bile, a ketone of ticagrelor (~15%) and oxidation products of the parent and AR-C124910XX metabolite (combined total of ~20%) were the

major components. Other significant components identified in the bile were the parent compound (7%), AR-C133913XX (5%), loss of the hydroxy-ethyl side chain from AR-C133913XX (5%) and a sulphate conjugate of oxidised AR C124910XX (5%). The metabolite pattern in bile is different from faeces, indicating metabolism in the intestine back to the parent compound. Following an IV dose to bile-duct cannulated rats, ~70% of the total radioactivity was recovered in bile and ~11% was excreted in faeces, indicating active secretion via the gastro-intestinal wall. In Marmoset monkey, the excretion was relatively slow with about 40% and 50% recovered in faeces by 24 h post PO and IV administration, respectively.

After a single IV-injection at day 18 of gestation, [3H]-Ticagrelor and its radioactive metabolites transferred to the placenta, with levels about twice the level in circulating blood, but did not significantly transfer from the placenta to the foetus. However, it is not known if chronic exposure could cause transfer of ticagrelor or its metabolites into the foetus.

Radioactivity was excreted via milk and the total radioactivity was well distributed in the pup after exposure via milk. Milk samples displayed significantly higher levels of total radioactivity than maternal plasma during the whole sampling period. The total radioactivity in milk cleared at the same rate as total radioactivity in plasma. The majority of radioactivity found in the milk samples (~75%) was unchanged ticagrelor at 1h post dose. A total of seven metabolites were identified in the milk samples, AR-C144910XX was the major metabolite and accounted for about 10% of the total radioactivity. AR-C133913XX was also a significant metabolite detected.

The plasma protein binding of ticagrelor and AR-C124910XX were high (≥99%). The level of protein binding was lower for AR-C133913XX than for AR-C124910XX and ticagrelor (40-57%). The *in vitro* plasma protein binding studies showed that mice had very different protein binding levels. The association of ticagrelor with blood cells was low, ranging from about 16% in human blood to about 48% in rabbit. The data indicate that the blood-to-plasma ratio is lower in humans compared to the non-clinical species, indicating that the binding to the erythrocytes is different. Since the ratio is <1, the binding to the erythrocytes is either non-specific or when specific, with low affinity. Therefore the difference in blood-to-plasma ratio between humans and non-clinical species is considered not relevant.

Overall the metabolism was sufficiently studied. Ticagrelor and AR-C124910XX contain the difluorophenylcyclopropyl group, while AR-C133913XX does not. AR-C124910XX is active and AR C133913 not. Thus, this group seems needed for pharmacological activity. The cleavage product difluorophenyl-cyclopropyl from ticagrelor to form AR-C133913 is not expected to be of toxicological relevance.

Ticagrelor is moderately metabolised mostly by CYP3A4 and 3A5 to AR-C124910XX (oxidative loss of the hydroxyethyl side chain) and AR C133913XX (loss of the difluorophenylcyclopropyl group) and excreted as parent compound and metabolite, this is in line with the short half life of 3-4 h. The cleavage product difluorophenyl-cyclopropyl from ticagrelor to form AR-C133913 is not expected to be genotoxic. The applicant investigated several CYP isozymes for their involvement in the biotransformation of ticagrelor. However, CYP2C8 and CYP2E1 were not investigated (not as single expressed enzyme or in microsomal inhibition studies). It is unlikely that CYP2C8 is involved in the metabolism of ticagrelor. However, the involvement of CYP2E1 can not be excluded and the applicant will provide these data as a post-approval commitment. The intrinsic clearance for ticagrelor metabolism to AR C124910XX and AR-C133913XX was greater for CYP3A4 than for CYP3A5, indicating that the CYP3A5-mediated formation of this metabolite is most likely to be of less importance than CYP3A4 mediated formation. The Applicant stated that CYP3A5 is a minor form in the liver and expressed only in 30% of the population and therefore CYP3A5 is of minor importance. However, in the

population which has CYP3A5 activity, a higher clearance of ticagrelor and higher levels of its active metabolite may be observed.

Ticagrelor was metabolised in hepatocytes, liver microsomes and Aroclor induced rat liver S9 fraction to a different degree between the species. In dog hepatocytes and Cynomolgus microsomes, ticagrelor was metabolised for more than 60% while in rat and human microsomes <10% was metabolised. AR C124910XX and AR C133913XX were the major metabolites. *In vitro*, a different metabolite percentage pattern was observed between the species, including the formation of an S oxide in dog and human hepatocytes and not in rat hepatocytes; a formation of <1.7% after 4 h. No *in vivo* studies were performed in dog, but human *in vivo* metabolism data did not show the S-oxide metabolite. *In vivo*, ticagrelor was moderately metabolised. In humans, ticagrelor and 10 metabolites were observed. However, three metabolites formed via glucuronidation of ticagrelor and AR C124910XX (HM9 and HM6, respectively) and hydroxylation of ticagrelor (HM10) could not be quantified separately. In Marmoset monkeys, the same metabolites as in humans were formed except for glucuronidated AR C124910XX. In addition, Marmoset monkey produced 12 more metabolites than observed in humans. Rat produced 11 additional metabolites compared to humans. In addition, 2 metabolites (HM3 and HM4) were not formed in rats. Furthermore, metabolite HM9 was present in human urine, but present as RM13 in rat faeces. The Applicant stated that the metabolism pathways were qualitatively similar in rats, Marmoset monkeys and human although quantitative differences were observed. These data indicate differences in metabolism between the species. However, the major metabolites were the same in rats, Marmoset monkeys and humans, except for the HM9 metabolite which was formed more in Marmoset monkey compared to rat and human.

Ticagrelor showed no propensity to inhibit CYP1A2, 2B6, 2C8, 2C19 and 2E1, but showed moderate inhibition towards CYP2D6. In addition, CYP2C9 and CYP3A5 were inhibited at IC50 values of ~10 µmol/l. Ticagrelor is an inhibitor of testosterone CLint in human liver microsomes with an IC50 value of ~12 µg/ml. Activation of CYP3A4 was shown at higher concentrations of ticagrelor. In vivo drug-drug interaction could be expected for CYP2C9 and 3A4. Clinical data showed drug-drug interactions with medicinal products metabolised by CYP3A4, but not by CYP2C9. AR C124190XX showed no propensity to inhibit CYP1A2 and 2D6, but showed moderate inhibition towards CYP2B6, 2C8 and 3A4. CYP2C9, CYP2C19 and CYP3A5 were inhibited at IC50 values of ~10 µmol/l. Activation of CYP3A4 was shown at higher concentrations of AR C124910XX. *In vivo* drug drug interaction could be expected. However, clinical data showed only a drug-drug interaction with medicinal products metabolised by CYP3A4. Ticagrelor and its active metabolite AR-C124910XX are inhibitors of CYP3A5, based on the inhibition of the midazolam 4-hydroxylation metabolite. The Applicant stated that CYP3A5 isozyme is active in 25-33% of the population. Since 1'-hydroxylation is the major metabolic pathway for midazolam, the impact of ticagrelor on the clearance of midazolam *in vivo* should be small. The CHMP agreed with this conclusion. However, for compounds which are more selectively metabolised by CYP3A5, possible drug drug interactions could be expected in a significant part of the population.

Ticagrelor and AR-C124910XX are inducers of CYP2B6 and CYP2C9 at concentration >10 µg/ml and >5 µg/ml, respectively. Modest levels of induction of CYP1A2, 2B, 2C, 2E1, 2A, 3A and 4A were observed in male and female rats. However, when compared to the levels of induction produced by archetypal inducers of CYP the induction produced was not considered to be biologically significant. The CHMP agreed with this conclusion.

Ticagrelor and AR-C124910XX are P-gp substrates and inhibitors of the P-gp mediated transport of digoxin. Therefore, there is a potential for P-gp mediated drug interactions. Clinical studies showed that concomitant administration of ticagrelor with digoxin increased the digoxin Cmax (75%) and AUC (28%). In the SPC it is stated that appropriate clinical and/or laboratory monitoring is recommended when giving narrow therapeutic index P-gp dependent drugs like digoxin concomitantly with ticagrelor.

In addition, OAT1 (transporter of uric acid) was inhibited in the presence of AR-C124910XX, but was not affected in the presence of either ticagrelor or AR-C133913XX. However, all three compounds inhibited OAT3 (transporter of uric acid).

Furthermore, ticagrelor, AR-C124910XX and AR C133913XX showed a potential weak inhibitory effect and no transport-enhancing effect on the URAT1-mediated [14C]-uric acid uptake.

Ticagrelor has a high plasma protein binding (>99%). Ticagrelor is likely to be combined with aspirin. Aspirin is known to displace a number of drugs (tolbutamide, chlorpropamide, methotrexate, phenytoin, probenecid, valproic acid and NSAIDs) from protein binding sites in the blood. Furthermore, as much as 80% of therapeutic doses of salicylic acid is metabolised in the liver. No pre-clinical studies were performed on possible drug-drug interactions of ticagrelor with aspirin. However, this was investigated in the clinical trials and no interactions on plasma protein binding or on metabolism were observed.

Ingestion of a high-fat meal resulted in a 21% increase in ticagrelor AUC and 22% decrease in the active metabolite Cmax, indicating a possible interaction with P-gp and/or CYP3A4/5. The Applicant concluded that these changes are considered of minimal clinical significance. The *in vivo* pharmacokinetic studies were performed under fed conditions.

2.3.3. Toxicology

Single and repeat dose toxicity

There was evidence of sub-clinical bleeding in all species tested in the pivotal studies. Direct effects on blood cell parameters and adaptive changes were observed. These changes were considered due of the pharmacological effect of ticagrelor. The liver was a primary target organ in mice and rats. Increases in liver weight coincided with centrilobular hypertrophy and is indicative of an adaptive change in the liver. In the 24-month rat carcinogenicity study, focal necrosis in the liver was seen in males at all dose groups, albeit at low incidence and without a dose response. No liver effects were seen in marmosets and signals of liver toxicity in clinical trials are questionable, therefore this effect is likely a rodent specific response to increased liver load. Nevertheless, from these results, it cannot be completely ruled out that ticagrelor treatment induces liver toxicity, and liver toxicity in humans will be further investigated as a follow up measure (FUM 5). Another primary target organ of ticagrelor treatment is the gastrointestinal tract, in particular manifesting itself as irritation and inflammation. The location and nature of the pathology varied across each species. Exposure margins were 4.3 and 14 respectively for rat and mouse, although this margin was almost negligible in the marmoset (i.e. 1.4). Gastrointestinal effects observed in rats (1- and 3-month studies) and marmosets (3- and 12-month studies) were reversible following an off-dose period. The cause of these gastrointestinal adverse effects could not be solely attributed either to an irritant local effect or to the primary pharmacological activity of ticagrelor. Platelet inhibition could impair healing of the lesions induced either by stress or to high local concentrations of ticagrelor in the gastric mucosa. In addition, as observed in rats, delayed intestinal transit and inhibition of gastric emptying may exacerbate this potential local toxicity or pre-existing lesions. Relevance for humans cannot be excluded. Signs of inflammation were not only seen in the gastrointestinal tract, but also in other organs (lung, adrenal gland and kidney) particularly in rats. Increases in lymphocytes and monocytes might indicate chronic inflammation. Signs of inflammation (white blood cells) were not increased among patients treated with ticagrelor, and therefore a clinical relevance is unlikely. Besides inflammatory effects, other effects were shown on the adrenal gland in mice and rats, which is another target organ of ticagrelor treatment in rodents. The relative weight was increased in all species, mice showed cortical cell

hyperplasia and rats cortical vacuolation and hypertrophy. It was shown in a mechanistic *in vitro* study, that corticosterone production in rat adrenal cells was inhibited by ticagrelor. The effects on the adrenal gland could therefore be the result of a negative feedback mechanism. These effects do not appear to be species specific, as all species showed an increased adrenal weight. Moreover, inhibition of corticosterone synthesis occurred at clinically relevant concentrations, and there was no safety margin for histopathological changes in the rat. However, there were no signs of any effects on the adrenal glands in clinical trials, and therefore a clinical relevance is unlikely. A lack of *corpora lutea* was seen in mice at 750 mg/kg/day, a dose that was not tolerated. No other effects were noted and no effects on fertility were noted in rats. There is no concern for human fertility.

Genotoxicity

The battery of genotoxicity studies performed has shown that ticagrelor and its metabolite C124910XX do not possess genotoxic potential.

Carcinogenicity

There was no clear evidence that ticagrelor was carcinogenic in mice and male rats. In the mouse carcinogenicity study, when combining data on broncho-alveolar adenomas for males and females, there is an increased incidence of such tumours in exposed animals compared to concurrent controls. However, the incidences were not statistically significant and also within the range of historical control data. Also haemangioma/haemangiosarcoma found in the mesenteric lymph node and some other organs did not display a linear dose-response and falls within the expected background range.

In female rats, ticagrelor at the high dose (exposure margin of 29), showed an increased incidence of uterine adenocarcinomas and hepatic adenomas. The applicant concluded that the slight increase in liver tumours is likely to be related to the enzyme induction observed and concerned a species specific adaptive response. The Applicant demonstrated that the tumour pattern of increased uterine tumours and reduced mammary and pituitary tumours are indicative of prolonged reduction in prolactin levels and consistent with the observed reduction of body weight in female rats at the high dose. In addition the interactions with the dopamine transporter and perturbations to circulating sex steroids are likely to contribute to the permissive hormonal environment from which this tumour pattern emerges in rats. Some mechanisms of direct relevance to humans (e.g. aromatase inhibition, oestrogen receptor interactions) have been ruled out. The literature data on prolactin clearly indicate that this major indirect feedback influence on uterine tumour development is not present in primates and would be therefore irrelevant in man. However, because this hypothesis is based on prolactin levels, and the Applicant did not measure these levels directly, uterine tumours should be monitored in humans which should be included in the RMP.

Reproduction Toxicity

No effects on male and female fertility were shown in rats up to 16-20 times the intended human exposure. In rats minor developmental anomalies were seen at a maternal toxic dose of 300 mg/kg/day. The NOAEL of 100 mg/kg/day for embryofoetal toxicity provides a safety margin of 5.1 to the human therapeutic dose based on AUC. In rabbits a slight delay in hepatic maturity and skeletal development was seen in foetuses from dams in the high dose group (63 mg/kg/day) without showing maternal toxicity. The NOAEL of 42 mg/kg/day provides a safety margin of 4.5 based on AUC. In rats 180 mg/kg/day of ticagrelor caused slight maternal and developmental toxicity characterised by reduced maternal body weight gain during gestation and reduced post-natal pup viability, reduced

birth weight and delayed growth of the pups. The NOAEL of 60 mg/kg/day provides a safety factor of 4.6 based on AUC. According to the Applicant the results from the reproductive toxicity studies do not indicate a reproductive risk to the foetus, suckling neonate or to adults at tolerated exposures. Based on this, it is considered that ticagrelor is unlikely to affect reproduction at therapeutic exposures. However, the safety margins based on AUC are 3 to 5 which are relatively low. Thus it is preferable not to use ticagrelor during pregnancy as a precautionary measure.

Local Tolerance

Three local tolerance studies showed that ticagrelor is unlikely to cause a local irritant effect during intravenous administration to a human subject. Because ticagrelor is administrated as tablets, these studies are only informative.

Other toxicity studies

Immunotoxicity

The Applicant did not perform immunotoxicity studies, because changes in immune related tissues like thymus and blood cells, which were of low severity, are secondary to other toxicity and not due to a direct effect of ticagrelor on the immune system. The absence of an immunotoxic potential is further demonstrated by the chronic toxicity studies and carcinogenicity studies. The chronic toxicity studies also did not identify the immune system as target organ of toxicity. The carcinogenic studies also showed no effects on the immune system.

Impurities

Impurities UL127, UL133 and UL134 (also an important metabolite) are above the qualification level of 0.15% but non-genotoxic. Although the Applicant did not perform the animal qualification study with the recommended amount in line with the proposed specification or higher of impurities UL127 and UL133 respectively, the Applicant showed by extensive comparison of studies with different amounts of these impurities that it is highly unlikely that especially UL127 but also UL133 at the proposed limits in the product pose a significant risk for toxicity in humans. Several of impurities have been tested for genotoxicity and found negative. The impurities AZ13232761 and C3RO were found positive and the applicant stated that these impurities are kept below the threshold of toxicological concern.

Phototoxicity

Data provided by the Applicant confirm that ticagrelor, AR-C124910XX and ARC133913XX absorb in the UV spectrum at wavelengths from 290 to approximately 340 nm. However, considering that in the non-clinical pharmacokinetic studies ticagrelor was shown to reach the skin following systemic administration (p.o.), to a limited extent and only 3 out of 18,000 treated patients presented adverse effects potentially related to photosensitivity on ticagrelor, specific non-clinical photosafety testing is not considered necessary at this point.

2.3.4. Ecotoxicity/environmental risk assessment

The dossier for the environmental risk assessment of ticagrelor was completed at day 150 of the assessment. All outstanding issues have been addressed satisfactorily. A PECsurface water of 4.5 µg/L was calculated using an Fpen of 0.01 (default value). Risk quotients were below 1 for the environmental compartments considered: STP, surface water, groundwater and sediment. It can be

concluded that the use of ticagrelor as intended, does not pose an unacceptable risk to the environment.

2.3.5. Discussion on non-clinical aspects

The Applicant provided sufficient non-clinical data to describe ticagrelor as a potent, selective, orally active, direct P2Y12 receptor antagonist, providing mechanistic support for its utility use in the prevention of secondary cardiovascular events in patients with ACS. The absorption, distribution, metabolism and excretion of ticagrelor were well investigated in mouse, rat and marmoset and found mostly in line with the human situation. However, one question remains unresolved about the influence of ticagrelor on CYP2E1 and will be handled as a follow up measure. The Applicant provided extensive data on single and repeat-dose toxicity, genotoxicity, carcinogenicity, and reproductive toxicity. Repeat-dose toxicity tests showed gastrointestinal effects in mouse, rat and marmoset, of which relevance for humans cannot be excluded. Ticagrelor is not genotoxic, however, some carcinogenicity at high dose was seen in liver and uterus of female rats, which is probably not relevant for humans. At high dose some signs of reproductive toxicity were shown. Immunotoxicity, impurities and phototoxicity do not pose problems. Ticagrelor does not pose an unacceptable risk to the environment.

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical point of view there were no objections to a marketing authorization of ticagrelor. There is however the pharmacokinetic issue that needs to be resolved as a follow up measure given that based on the data provided by the Applicant, it can not be excluded, that CYP2E1 is involved in the metabolism of ticagrelor.

2.4. Clinical aspects

2.4.1. Introduction

The clinical development program of ticagrelor comprises 41 phase I and two phase II clinical pharmacology (PK and/or PD) studies, two phase II dose selection studies and a single pivotal phase III trial in over 18,000 ACS patients. A second phase III trial is planned to evaluate the benefit/risk of ticagrelor on top of aspirin in patients with a history of ACS. An overview of the clinical program is provided below.

Scientific advice by EMA was provided: EMEA/CHMP/SAWP/330223/2005 and EMEA/51999/2006.

GCP

The clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided 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.

Tabular overview of clinical studies

Outlined in the table below, there were 2 phase II clinical pharmacology PK/PD studies and 2 dose-finding studies evaluating efficacy and safety of several doses. In addition, one pivotal efficacy/safety study has been conducted up to 12 months and one long-term study is planned for treatment longer

than 12 months. The data from this study will be provided for review by the CHMP within agreed timeframes as a post-approval commitment.

Table 2 Tabular overview of clinical studies

Table 1 Scope of the clinical development program for ticagrelor

In vitro clinical pharmacology study	**1 study**
Phase I studies:	
Bioavailability, bioequivalence and food interaction	**9 studies**
Pharmacokinetics and initial tolerability	**5 studies**
Pharmacokinetics - intrinsic factors	**8 studies**
Pharmacokinetics - extrinsic factors (drug/drug interactions)	**15 studies**
Pharmacodynamics	**4 studies**

Phase II clinical pharmacology PK/PD studies

Study name (number)	No. and type of patients randomised	Doses and Duration of treatment	Condensed objective
OFFSET (D5130C00048)	123 Patients with stable CAD	Ticagrelor: 180 mg loading dose then 90 mg bd + ASA 75 to 100 mg Clopidogrel: 600 mg loading dose then 75 mg od + ASA 75 to 100 mg 6 weeks	Assessment of onset and offset profiles by IPA of ticagrelor and of clopidogrel.
RESPOND (D5130C00030)	98 Patients with stable CAD 41 non-responders and 57 responders to clopidogrel	Ticagrelor: 180 mg loading dose then 90 mg bd + ASA 75 to 100 mg Clopidogrel: 600 mg loading dose then 75 mg od + ASA 75 to 100 mg 2 weeks	Assessment of IPA when switching from ticagrelor to clopidogrel; switching from clopidogrel to ticagrelor; and, giving ticagrelor to clopidogrel non-responders.

Phase II studies providing design information for Phase III			
DISPERSE (D5130C00008)	201 Patients with documented atherosclerotic disease	Ticagrelor: 50, 100, 200, or 400 mg bd + ASA 75 to 100 mg Clopidogrel: 75 mg od + ASA 75 to 100 mg 28 days	Pharmacodynamic assessment by IPA after 14 and 28 days of various dosing regimens of ticagrelor plus ASA compared to clopidogrel plus ASA.
DISPERSE2 (D5130C00002)	990 Patients with non-ST segment elevation ACS	Ticagrelor: 270 mg loading dose then 90 or 180 mg bd +ASA 75 to 100 mg Clopidogrel: 300 mg loading dose then 75 mg od + ASA 75 to 100 mg 4, 8, or 12 weeks	Safety and tolerability assessment by adjudicated bleeding events after 4 weeks of 2 doses of ticagrelor plus ASA compared with clopidogrel plus ASA.
Phase III study			
Study name (number)	**No. of patients randomised**	**Dose of ticagrelor Comparator Duration of treatment**	**Primary objective**
PLATO (D5130C05262)	18 624 patients with ACS Ticagrelor: 9333 Clopidogrel: 9291	Ticagrelor: 180 mg loading dose then 90 mg bd + ASA 75 to 325 mg Clopidogrel: ≤600 mg loading dose then 75 mg od + ASA 75 to 325 mg 6 to 12 months	To test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with ACS.
Planned studies			
PEGASUS (D5132C00001)	Planned: 13 500 Patients with ACS event 1 to 3 years in the past.	Ticagrelor: 90 mg bd + ASA 75 to 150 mg Placebo + ASA 75 to 150 mg At least 12 months up to 36 months	To compare long-term treatment with ticagrelor plus ASA to ASA alone in reducing the composite endpoint of CV death, non-fatal MI, and non-fatal stroke.

ACS Acute coronary syndromes; ASA acetylsalicylic acid; bd twice daily; CAD coronary artery disease; CV cardiovascular; IPA inhibition of platelet aggregation; MI Myocardial infarction; od once daily; PK/PD pharmacokinetic/pharmacodynamic.

2.4.2. Pharmacokinetics

Ticagrelor is an entirely synthetic new chemical entity which binds reversibly to the P2Y12 platelet ADP receptor. Ticagrelor has a relative low solubility. Pharmacokinetic data was derived from a total of 21 phase I studies including 575 volunteers and 2 phase II studies including 219 patients. In addition to the 21 phase 1 studies, 15 studies have been performed on drug-drug interactions with ticagrelor. Population PK analysis for ticagrelor and its major metabolite, AR-C124910XX, was conducted using data from the Phase IV studies D5130C00002 (DISPERSE2) and Study D5130C05262 (PLATO), including data of 7090 subjects.

Absorption

At least 56% (26% excretion in urine and 30% excretion of radioactivity in the form of metabolites in faeces) of ticagrelor is absorbed. Ticagrelor is absorbed throughout the whole small intestine, although absorption decreases further down the gastrointestinal tract. The absolute bioavailability for ticagrelor

was approximately 36%. This is consistent with the estimated fraction absorbed >56% based on the excretion data. Higher metabolite: parent ratios for Cmax and AUC after oral administration versus IV administration indicate that the majority of AR-C124910XX formation occurs during first pass metabolism. No clinically relevant food effect was observed for ticagrelor.

Bioequivalence

The ticagrelor tablets manufactured at a commercial-scale facility in Gartuna Sweden (tablets to be marketed) were bioequivalent to those manufactured in a pilot-scale plant in Charnwood UK, used in phase III studies. Bridging between the different formulations used during clinical development was done. The mannitol-based tablets had a a 17% higher AUC than the lactose-based tablets. Tablets with micronized ticagrelor were bioequivalent to tablets with non-micronized ticagrelor.

Distribution

Ticagrelor has a steady-state volume of distribution of approximately 87.5 L. This indicates that it does not extensively distribute into or bind to tissues. Both ticagrelor and its primary active metabolite bind extensively (>99.7%) to plasma proteins. Age, gender, severe renal impairment, and mild hepatic impairment do not affect protein binding. The mean radioactivity plasma/blood ratio was 1.69. The distribution across the placenta and during lactation was not investigated in humans.

Elimination

For ticagrelor a total of 10 metabolites are characterized from urine, faeces, and plasma. Total recovery upon oral administration of a radioactive ticagrelor dose was 84.3% (26.5% in urine and 57.8% in faeces). Unchanged ticagrelor found in faeces was measured to be 27%. Radioactive components in faeces and plasma were identified as ticagrelor and its active metabolite AR-C124910XX. Major components in urine were metabolite ARC133913XX and its glucuronide conjugate. Recoveries of unchanged ticagrelor and AR-C124910XX in urine were both less than 1% of the dose, indicating that both compounds are extensively metabolised and that renal impairment might have little effect on systemic exposure to ticagrelor and AR-C124910XX.

Dose proportionality and time dependencies

After loading dose of 180 mg ticagrelor in the phase II studies with patients the C_{max} of ticagrelor and AR-C124910XX were approximately 1200 and 240 ng/mL. The AUC_{0-8} of ticagrelor and AR-C124910XX were approximately 5000 and 1200 ng h/mL. At steady state, at the clinical proposed dose of 90 mg bd ticagrelor, the C_{max} of ticagrelor and AR-C124910XX after last maintenance dose was approximately 750 and 210 ng/mL. The AUC0-8 of ticagrelor and AR-C124910XX were approximately 4000 and 1325 ng h/mL. Ticagrelor pharmacokinetics were dose-proportional up to a daily dose of 600 mg. Inter-individual variability of systemic exposure of ticagrelor is relatively low with coefficients of variation ranging from 16%-44%. The intra-individual variability is approximately 20% for AUC and 30% for C_{max} and similar between patients and healthy subjects.

Special populations

Severe renal impairment did not significantly influence the AUC and Cmax of ticagrelor and AR-C124910XX, as is expected in light of the small amount excreted renally. Plasma protein binding of ticagrelor and its metabolites are not altered in renally impaired volunteers. Mild hepatic impairment did not clinically significantly influence the AUC and C_{max} of ticagrelor and AR-C124910XX. Ticagrelor

has not been studied in patients with moderate or severe hepatic impairment; therefore ticagrelor is contraindicated in these patients. The pharmacokinetics of ticagrelor and AR-C124910XX are not clinically significantly influenced by smoking, weight or race. Exposure to ticagrelor in patients over 75 years is about 21% (males) and 25% (females) higher than in those less than 65 years old. This is not considered a clinically relevant difference.

Pharmacokinetic interaction studies

In vitro studies showed that ticagrelor and AR-C124910XX have no or low potential to induce CYP1A1, CYP1A2, CYP2C9, CYP2B6 and CYP3A4. *In vitro* studies showed that ticagrelor and AR-C124910XX have the potential to moderately inhibit CYP3A4, CYP2C9, CYP3A5, and CYP2D6 activities. Additionally it was shown that ticagrelor showed no propensity to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C19 CYP2D6, and CYP2E1. Ticagrelor may affect substrates transported by Pgp, URAT1 or OAT3.

Several clinical interaction studies were performed.

Ketoconazole (strong CYP3A4 inhibitor) increased ticagrelor C_{max} by 2.4-fold and AUC by 7.3 fold, and decreased AR-C124910XX C_{max} by 89% and AUC by 56%. Concomitant administration of strong CYP3A4 inhibitors with ticagrelor is contraindicated in the SPC.

Rifampicin (CYP3A inducer) decreased ticagrelor C_{max} by 73% and AUC by 86%. In section 4.5 is mentioned that rifampicin and other CYP3A4 inducers would be expected to decrease the exposure to ticagrelor and may result in reduced efficacy of ticagrelor. Although ticagrelor is still beneficial in combination with CYP3A4 inducers, the rates of primary efficacy events are higher in patients treated with potent CYP3A4 inducers at some time during randomisation versus those who did not receive concomitant CYP3A4 inducers (12.5% vs. 8.8% in the ticagrelor group). The Applicant includes a warning in section 4.4 of the SPC regarding concomitant treatment of ticagrelor with potent CYP3A4 inducers.

Simvastatin (CYP3A4 substrate) concomitant administration with ticagrelor increased both simvastatin C_{max} and AUC by 81% and 56%, respectively. Simvastatin acid C_{max} and AUC was increased by 64% and 52%, respectively. Some individual increases of 2- to 3-fold were observed. Therefore, consideration should be given especially to changes on simvastatin exposure in patients requiring more than 40 mg of simvastatin, in light of the possible higher chance of developing rhabdomyolysis as is expressed in the SPC. Interactions with other statins metabolised by CYP 3A4 cannot be excluded.

Digoxin (P-glycoprotein substrate) concomitant administration with ticagrelor increased mean trough digoxin levels about 30%, with some individual maximum increases about 200%. Ticagrelor pharmacokinetics were unaffected. Other P-gp substrate drugs might have similar exposure changes in the presence of ticagrelor. According to the Applicant appropriate clinical or laboratory monitoring is recommended when giving the narrow therapeutic index, P-gp-dependent drug digoxin concomitantly with ticagrelor as is expressed in section 4.5 of the SPC.

Diltiazem (moderate CYP3A4 inhibitor) did not significantly influence the pharmacokinetics of ticagrelor, however the slight increase in bleeding risk was observed.

Co-administration with ticagrelor did not influence the pharmacokinetics of *atorvastatin* (CYP3A4 substrate) and *midazolam* (CYP3A4/3A5 substrate) to a clinically significant degree. No interaction was observed between *tolbutamide*, a CYP2C9 substrate and ticagrelor. This result can be extrapolated to other CYP2C9 substrates but not to the coumarin derivatives as a pharmacodynamic interaction might occur. Ticagrelor did not clinically significantly influence the pharmacokinetics of *levonorgestrel and ethinylestradiol.* Contraceptive efficacy is expected to be unchanged when co-administered with ticagrelor. The pharmacokinetics of ticagrelor and its metabolite AR-C124910XX were unaltered by co-

administration *midazolam*, *atorvastatin*, *ASA*, *heparin*, *enoxoparin*, and *desmopressin*. ASA, heparin, enoxoparin, and desmopressin do not have an influence on the plasma protein binding of ticagrelor and AR-C124910XX. No interactions were observed in population PK evaluation when ticagrelor is used concomitantly with *nitrates* or *proton pump inhibitors*. The interaction with P glycoprotein substrates was evaluated using population PK data concerning the concomitant use of ticagrelor and verapamil, the exposure to ticagrelor is slightly higher (30-40%) in this population. As the data on verapamil do not allow discerning between an interaction due to inhibition of CYP3A or inhibition of P-gp transporting system, and P-glycoprotein interactions are known to be bi-directional an additional DDI with a P-glycoprotein substrate with a narrow therapeutic index is warranted. This study will be conducted as a post-approval commitment (FUM 4).

Ticagrelor is a CYP2D6 inhibitor *in vitro*, but interaction studies with substrates of CYP2D6 have not been conducted. At least one DDI study with a CYP2D6 substrate should be conducted and this study will be presented as post approval commitment (FUM 3).

Pharmacokinetics using human biomaterials

2.4.3. Pharmacodynamics

Mechanism of action

Ticagrelor is a member of the chemical class cyclopentyltriazolopyrimidines (CPTP), which is a selective adenosine diphosphate (ADP) receptor antagonist acting on the P2Y12 ADP-receptor that can prevent ADP-mediated platelet activation and aggregation. Ticagrelor is orally active, and reversibly interacts with the platelet P2Y12 ADP-receptor. Ticagrelor does not interact with the ADP binding site itself, but interacts with platelet P2Y12 ADP-receptor to prevent signal transduction.

Primary and Secondary pharmacology

The main studies encompassing the clinical pharmacodynamic evaluation were the OFFSET and RESPOND trials.

The OFFSET trial evaluated the onset and offset of ticagrelor in comparison to clopidgrel. Ticagrelor demonstrates a rapid onset of effect, with inhibition of platelet aggregation (IPA) statistically significant at all times (0.5 hours to max respons at 8 hours) with ticagrelor 180 mg compared to clopidogrel 600 mg. Onset of maximum %IPA was higher for ticagrelor than clopidogrel (appr. 85% vs 50%). The slope of the offset curve of ticagrelor is significantly different from the offset curve of clopidogrel ((–1.037 vs –0.482% per hour; $p < 0.0001$). Because mean final extent %IPA was higher for ticagrelor 90 mg compared with the clopidogrel 75 mg, IPA was higher before the 24 hour time point and started to be significantly lower thereafter, with levels approaching baseline after 5 days for ticagrelor and 7 days for clopidogrel (see Figure 1).

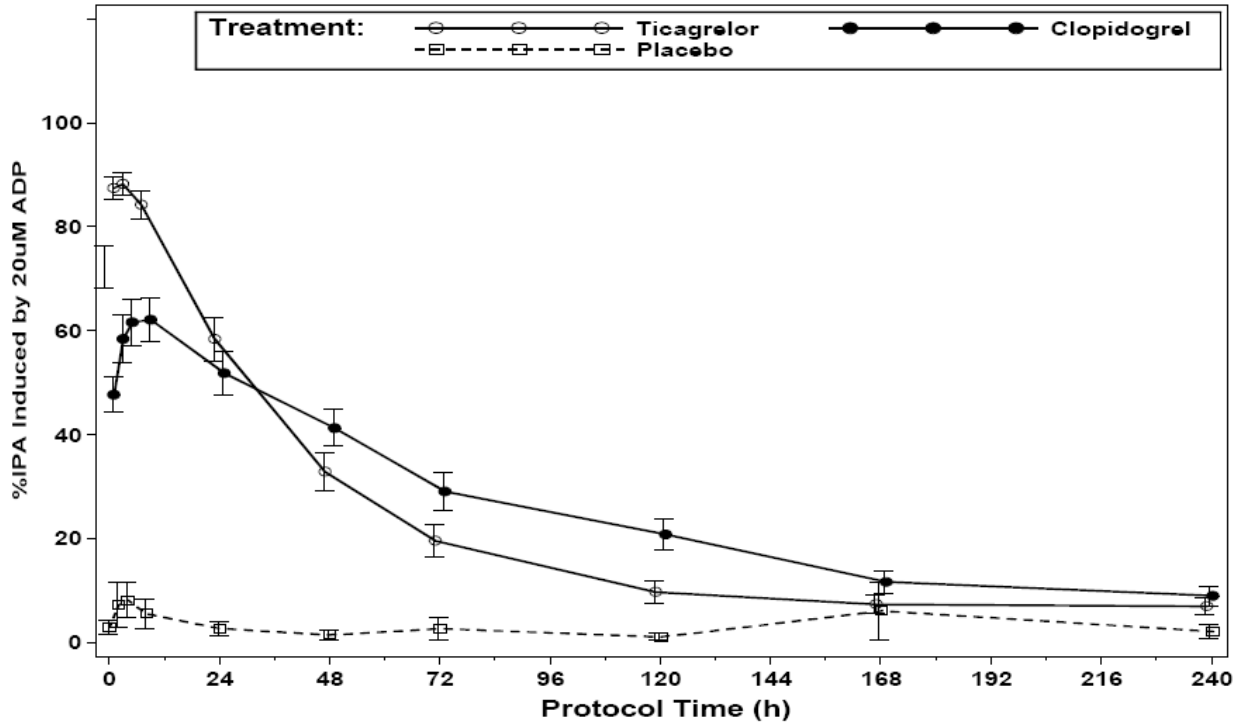


Figure 1 Mean final extent %IPA induced by 20 µM ADP after the last dose ±SE by protocol time (ITT analysis set)

The RESPOND trial evaluated whether switching from clopidogrel to ticagrelor or visa versa in responders or non-responders to clopidogrel would result in a different extent of inhibition of platelet aggregation. This design failed to show a statistical significant difference between ticagrelor and clopidogrel for the primary evaluation of the proportion of non-responders becoming responders (achieving >10% IPA; similar or less than 10%IPA was defined as non-responders) after switching from clopidogrel to ticagrelor. However, this resulted in a higher %IPA (26.6%-36.6%). Responders switching from clopidogrel to ticagrelor at steady state dose showed a mean 26.4% increase in %IPA. Conversely, switching from ticagrelor to clopidogrel, responders had a mean 24.5% decrease in %IPA.

The 50, 100, 200 and 400 mg dose were evaluated in 200 patients for relation between plasma concentration and effect for single dose and steady state. Maximum IPA was found to reach plateau from Cmax and UAC corresponding to 100 mg dose and higher.

The pharmacodynamic interaction of ticagrelor with ASA, heparin and enoxaparin was evaluated as secondary endpoints in 3 separate small studies in respectively 16, 30 and 30 patients. Inhibition of ADP-induced platelet aggregation was not affected by 300 mg of ASA co-administered for both ticagrelor doses of 50 and 200 mg. However, bleeding times were longer with the co-administration with ASA.

The results for IPA were not statistically significantly different between ticagrelor with and without heparin, except final extent IPAmax and AUEC2-12 (Area under the effect curve) were slightly decreased (4.0% and 7.3%, respectively), and maximum extent IPAmax was slightly decreased (4.0%) when heparin was co-administered with ticagrelor.

Ticagrelor (180 mg) with and without enoxaparin (1 mg/kg subcutaneous) showed similar concentration-effect profiles and parameter estimates for ticagrelor with and without enoxaparin.

Genetic differences in PD response were evaluated in 71 patients (28 clopidogrel non-responders and 43 responders) from the RESPOND trial. No statistically significant differences could be observed in both ticagrelor 90 mg and clopidogrel 75 mg for categories of extensive metabolisers, median metabolisers, and poor metabolisers of CYP2C19 for pharmacological response of platelet aggregation and inhibition of platelet aggregation.

2.4.4. Discussion on clinical pharmacology

Ticagrelor demonstrated a dose response relation with a maximum effect between 100 mg and 200 mg dose at both single and steady state dosing. The minimum dose of platelet inhibition has not been well identified, since the Applicant was targeting to identify the maximum dose. Further studies were conducted with the 90mg dose due to supra-bioavailability of the new dose form. In a study in non-responders to clopidogrel it was not directly apparent that the switch from clopidogrel to ticagrelor would result in more patients responding as the number of patients with >10% IPA was not significantly different between clopidogrel and ticagrelor. However, maximum IPA% was increased with 26.6%-36.6% when switching from clopidogrel non-responders to ticagrelor. The offset of inhibition of platelet aggregation is faster with ticagrelor than with clopidogrel according to data on markers of platelet inhibition. However, as with the proposed dose of ticagrelor the inhibition of platelet aggregation is higher and the level at drug discontinuation is thus higher. Despite this higher start level at drug discontinuation the complete offset is 5 days instead of 7 days with ticagrelor vs. clopidogrel based on ADP induced platelet inhibition. However, as IPA is not always considered a good marker for bleeding risk in the clinical situation also other markers were evaluated. With markers of Hb concentration and chest tube drainage, no difference in offset of bleeding risk could be shown between ticagrelor and clopidogrel. Any statements on less variability based on metabolic differences between ticagrelor compared to clopidogrel are not justified based on genetic differences. Although a trend towards less efficacy and more major bleeding with ticagrelor in extensive metabolisers cannot fully be excluded, no statistically significant interaction was observed.

With the administration of warfarin or NSAID's no clear impact of an increased incidence of bleedings was observed. However, with the addition of SSRI's a higher incidence of major + minor bleedings was observed. Still, this potential mechanistic interaction with oral anticoagulants, SSRI's and NSAID's is specifically addressed in the SmPC.

2.4.5. Conclusions on clinical pharmacology

The Applicant used inhibition of platelet aggregation (IPA) as the method to demonstrate anticoagulant efficacy, although the relevance to clinical effect is sometimes questioned. It was demonstrated that the optimal dose would be between 100 and 200 mg. Switching from clopidogrel to ticagrelor results in an increase in IPA, albeit not in a significant change in subjects defined as responders. The claimed faster offset based on IPA can be questioned, as other markers showed similar offset results as with clopidogrel.

2.5. Clinical efficacy

2.5.1 Dose response studies

Dose response is evaluated in the DISPERSE and DISPERSE2 trials.

The DISPERSE trial was a 28-day randomised, double-blind, double-dummy, parallel group, multicentre study mainly comparing the PD and PK of several doses of ticagrelor (50 mg bd, 100 mg bd, 200 mg bd and 400 mg od) plus ASA with clopidogrel (75 mg od) plus ASA, in subjects with documented atherosclerotic disease. A starting dose of ticagrelor demonstrated more platelet aggregation inhibition than clopidogrel for all ticagrelor doses, expressed as %IPA.

At steady state (day 14 or 28) ticagrelor 50 mg bd resulted in platelet aggregation inhibition comparable to clopidogrel 75 mg od; higher doses produced greater inhibition of platelet aggregation than clopidogrel, with little difference in the level of inhibition of platelet aggregation between these higher doses of ticagrelor. A dose dependency for the total number of AEs was observed for ticagrelor (58, 63, 73 and 88 AEs for AZD6140 doses of 50, 100, 200 bd and 400 mg od, respectively). Although mean bleeding times were longer for all ticagrelor dose levels compared to clopidogrel, there was no simple dose relationship and considerable variability in individual data was observed.

The second DISPERSE2 trial was a double-blind, double-dummy, parallel group, randomised, multicentre study comparing the safety and tolerability of 2 doses of ticagrelor (90 and 180 mg) with clopidogrel 75 mg (all in combination with ASA) in 990 patients with non-ST segment elevation ACS (in the previous 48h). The cumulative total bleeding event rate appeared higher for the ticagrelor 90 mg bd group over the first 6 weeks than the other 2 groups, but this difference was not maintained over the remainder of the study. At week 4, adjudicated bleeding event rates for major fatal/life threatening and major other bleeding events were similar for all groups. An apparent dose-related trend towards an increase in minor bleeds was observed: ticagrelor 90 mg bd 9 (2.7%), ticagrelor 180 mg bd 12 (3.7%) and clopidogrel 75 mg 4 (1.2%) patients. The number of patients experiencing *dyspnoea* in the ticagrelor 90 mg bd and 180 mg bd groups, was 26 (8%) and 38 (12%), respectively and greater than clopidogrel 75 mg od with 15 (5%) patients.

There appeared to be a small increase in the numbers of patients with arrhythmias reported in the ticagrelor groups. Although in the Holter substudy, in total, 24% patients experienced episodes of ischaemia ≥1.0 mm ST depression or elevation on Holter monitoring, there were no apparent differences between the treatment groups.

2.5.2 Main study

Title of Study

PLATO (PLATelet inhibition and patient Outcomes)

Methods

This was a 18 624 patients randomised, double-blind, parallel group, phase III, efficacy and safety trial, that compared ticagrelor to clopidogrel for prevention of vascular events in patients with non-ST or ST- elevation ACS. The trial enrolled a population of patients with ACS (UA, NSTEMI, STEMI), including patients planned for invasive management, i.e. coronary angiography with PCI or CABG, as well as patients intended for medical management. The duration of treatment ranged from 6 to 12 months with planned study completion at 6, 9 and 12 months depending on the date the patients entered the study according to the following study design:

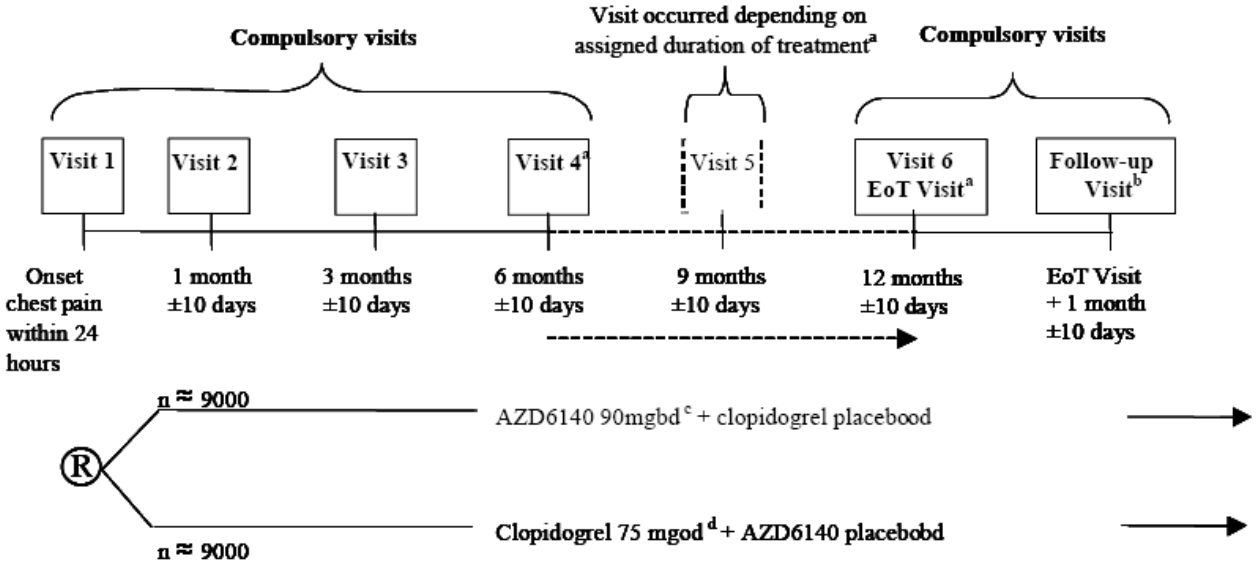


Figure 2 PLATO study design.

Study Participants

Patients were included within 24 hour presentation of ST segment elevation ACS, or non-ST elevation ACS and additional markers of possible ACS such as troponin or CK-MB elevations, and/or additional CAD risk factors in a way that this would mostly reflect clinical diagnostic decision making.

Patients were excluded mainly based on bleeding risk (if they had a known bleeding incidence within last 6 months or elevated bleeding risk, oral anticoagulation therapy that could not be stopped, current or planned fibrinolytic therapy), based on close to randomisation ACS risk, increased risk of bradycardic events, and metabolic associated problems (moderate to severe hepatic impairment, strong CYP3A inhibitors, CYP3A substrates with narrow therapeutic indices, or strong CYP3A inducers).

Treatments

All patients were treated with concomitant ASA 75 to 100 mg daily in addition to randomised study medication during the treatment period, according to local practice, unless they were allergic or intolerant to ASA.

Table 3 Treatment posology

Study drug	Loading dose at randomisation	Maintenance dose	Loading dose for PCI <24 hours post randomisation	Loading dose for PCI >24 hours post randomisation
Ticagrelor blinded study medication	180 mg	90 mg bd	None	An additional 90 mg
Clopidogrel blinded study medication	300 mg for clopidogrel-naïve patients; 75 mg for patients who received open-label clopidogrel treatment prior to randomisation.	75 mg od	An additional 300 mg at the discretion of the investigator	An additional 300 mg at the discretion of the investigator

bd Twice daily dosing; od Once daily dosing; PCI Percutaneous coronary intervention.

Objectives

The primary objective of this study was to test the hypothesis that ticagrelor is superior to clopidogrel for the prevention of vascular events in patients with non-ST or ST elevation ACS.

The secondary objectives were:

1. To assess the safety and tolerability of ticagrelor compared with clopidogrel.

2. To assess the efficacy and safety of ticagrelor compared with clopidogrel in those patients who underwent CABG surgery or PCI during the study and in relation to the timing of these interventions.

3. To assess the occurrence of arrhythmic episodes detected by Holter monitoring with ticagrelor compared with clopidogrel both during the initial period after randomisation and at 1 month and the relation of these episodes to clinical outcomes.

Outcomes/endpoints

The primary efficacy endpoint was time to first occurrence of any event from the composite of death from vascular causes, MI and stroke.

The following secondary efficacy endpoints were analysed in the order presented using a hierarchical procedure: the primary endpoint for patients with intent for invasive management; endpoint of all-cause mortality, MI, and stroke; composite of death from vascular causes, MI (including silent MI by ECG), stroke, severe recurrent cardiac ischaemia (SRI), recurrent cardiac ischaemia (RI), transient ischaemic attack (TIA) and other arterial thrombotic events (ATEs); each component of the primary composite efficacy endpoint in the order of MI, death from vascular causes and then stroke; all-cause mortality. As part of the secondary efficacy endpoints, a supportive analysis was conducted examining the primary endpoint following PCI in patients with planned invasive management who received PCI within 24 hours of randomisation. This is most critical in patients with STEMI with a totally occluded coronary vessel who undergo immediate primary PCI.

The primary safety endpoint was time to first occurrence of any total major bleeding event.

Sample size

Based on an expected event rate in the clopidogrel treatment arm of 11% over 12 months (Mehta et al 2000; Yusuf et al 2001), approximately 1780 events in the primary composite endpoint would yield 90% power to detect a target RRR of 13.5%, accounting for study medication discontinuations.

Randomisation

At Visit 1 (randomisation) eligible patients were randomly assigned to 1 of 2 treatment groups, ticagrelor 90 mg bd or clopidogrel 75 mg od, taken orally.

Randomisation and treatment pack assignment was managed via the central Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) and patients took the first dose of study medication directly after randomisation at Visit 1. Patients took subsequent maintenance doses in the morning and evening, at approximately 12-hour intervals, for the remainder of the treatment period.

Blinding (masking)

Blinding was secured by treating each treatment group with the same combination of matching active and placebo tablets and matching active and placebo capsules (the same number, size and packaging of the tablets and capsules).

Statistical methods

One formal interim analysis of the primary composite efficacy endpoint was planned when approximately 1200 adjudicated events (2/3rds of the total target number of 1780 events) were observed. The interim analysis was guided by the Peto-Haybittle group sequential boundary corresponding to a critical p-value of 0.001. To maintain the overall significance level at 5%, the critical p-value at the final analysis was 0.0497. The intention-to-treat approach for efficacy analyses utilised the Full Analysis Set, consisting of all patients randomised to study treatment, for their duration of participation in PLATO. The primary analysis employed Cox proportional hazards of time to event with treatment group as factor. The formal hierarchical analysis pre-specified the order of consideration for secondary endpoints, thus controlling the experiment-wise type I error.

Results

Participant flow

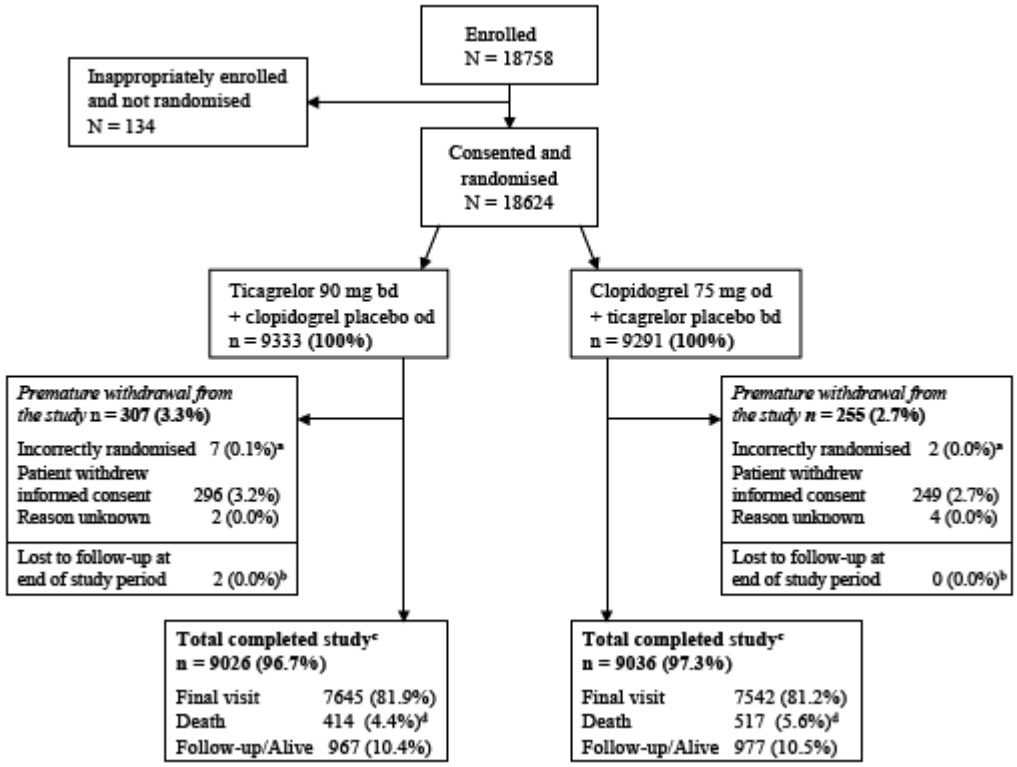


Figure 3 Participant flow in PLATO

Conduct of the study

PLATO, a randomised, double-blind, double-dummy, parallel group, international, multicentre study, compared the efficacy and safety of ticagrelor 90 mg bd with clopidogrel 75 mg od in the prevention of CV death, MI, and stroke in patients with non-ST or ST elevation ACS. The duration of treatment ranged from 6 to 12 months with planned study completion at 6, 9 and 12 months depending on the date the patients entered the study (e.g., patients that entered towards the end of the enrolment period would have the shortest duration of treatment). An interim analysis was performed when approximately 1200 adjudicated events were available. The double-dummy design enabled the blinding to be maintained because the study used an active comparator with a different dosing regimen than that used for ticagrelor as well as independent modification of dosing in advance of surgical procedures.

Baseline data

Patients were properly randomised and presented the following baseline characteristics: male (72%), a gender distribution typical for ACS; 57.1% of patients were <65 years and 42.8% were ≥65 years, predominantly Caucasian, wide range of global regions and countries: Europe, Middle East and Africa (74.2%; of which 94% were within Europe alone), North America (9.9%), Asia and Australia (9.2%),

and Central and South America (6.7%); 66% hypertension, 45% AP, 20% MI, 47% dyslipidemia, and 25% DM2.

Numbers analysed

The full analysis set is 9333 patients for ticagrelor and 9291 patients for clopidogrel. The safety analysis set (received >1 dose study drug) was 9235 (98.9%) and 9186 (98.9%), respectively.

Outcomes and estimation

For the primary endpoint (CV death, MI, and stroke), ticagrelor demonstrated a relative lower risk of 16% and an absolute risk reduction of 1.9% over 12 months in patients with ACS events (UA, NSTEMI and STEMI) compared to clopidogrel (HR 0.84; p=0.0003) (see figure 3). This can be reflected in the NNT of treating 54 patients with ticagrelor instead of with clopidogrel for 12 months preventing 1 event in the primary composite outcome. A beneficial effect was already significant from day 30 onwards (HR 0.88; p=0.0446).

Ticagrelor, compared to clopidogrel, was shown to decrease separately the rates of cardiovascular death (4.0% vs 5.1%; HR 0.79 (95% CI 0.69, 0.91); p=0.0013, ARR 1.1%,) and of MI (5.8% vs 6.9%; HR 0.84 (95% CI 0.75, 0.95); p=0.0045, ARR 1.1%), but not that of stroke (1.5% vs 1.3%; HR 1.17 (95% CI 0.91-1.52) p=0.2249). All cause mortality was also significantly reduced (HR 0.78 (95% CI 0.69, 0.89); p=0.0003).

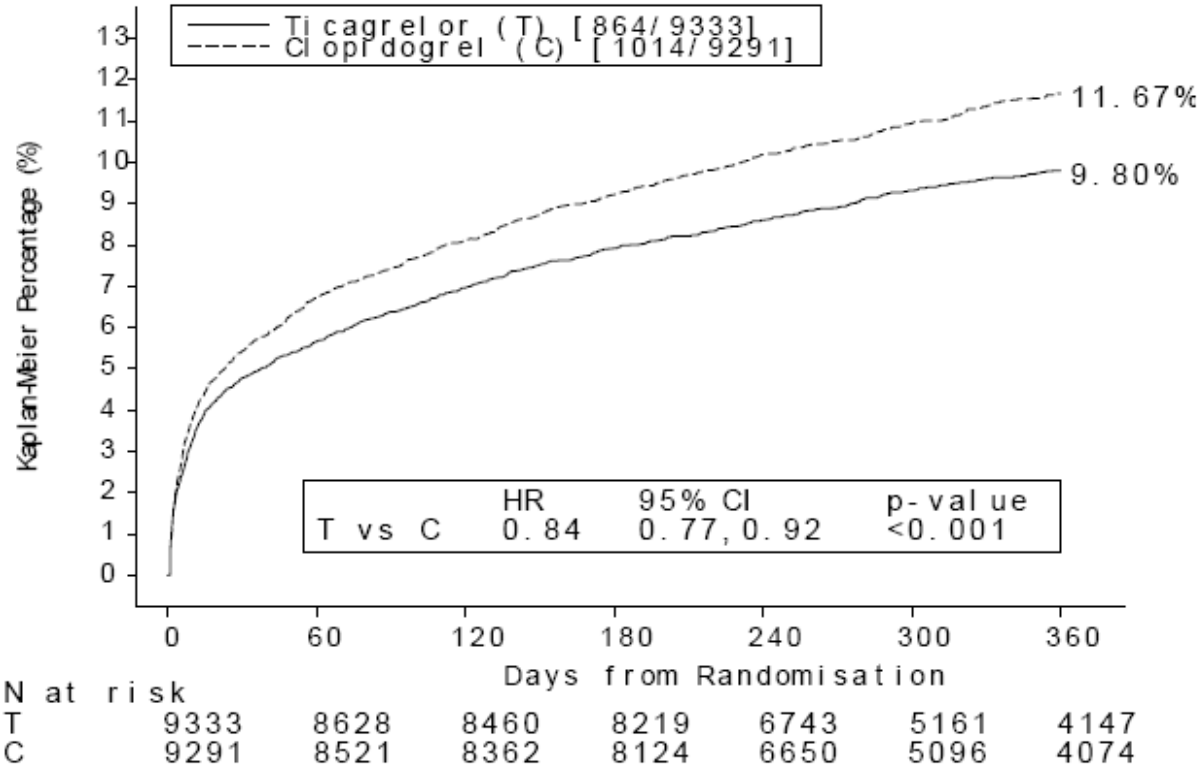


Figure 4 Kaplan-Meier plot of primary clinical endpoint events - estimate of the risk to the first occurrence of any event in the composite efficacy endpoint

In patients who actually received a PCI within 24 hours of randomisation, ticagrelor demonstrated a beneficial statistically significant primary efficacy effect (HR 0.85 (95% CI 0.74, 0.99); p=0.0305).

Patients who were treated with PCI as first procedure showed a HR of 0.88 (p=0.04).

Medically treated patients (non-invasive as first procedure) had the highest benefit with an HR of 0.78 (p=0.0006), and demonstrated a lower bleeding risk.

Ancillary analyses

The treatment effect of ticagrelor over clopidogrel appears consistent across multiple patient subgroups by demographic characteristics and by final index event diagnosis (UA, NSTEMI and STEMI) (see Figure 4). A significant p value for interaction was found for region (p=0.045), weight by gender-specific median (p=0.038), and baseline lipid lowering drug use (p=0.039). For patients not treated with a lipid lowering drug a point estimate of 1.02 (non-significant) was found.

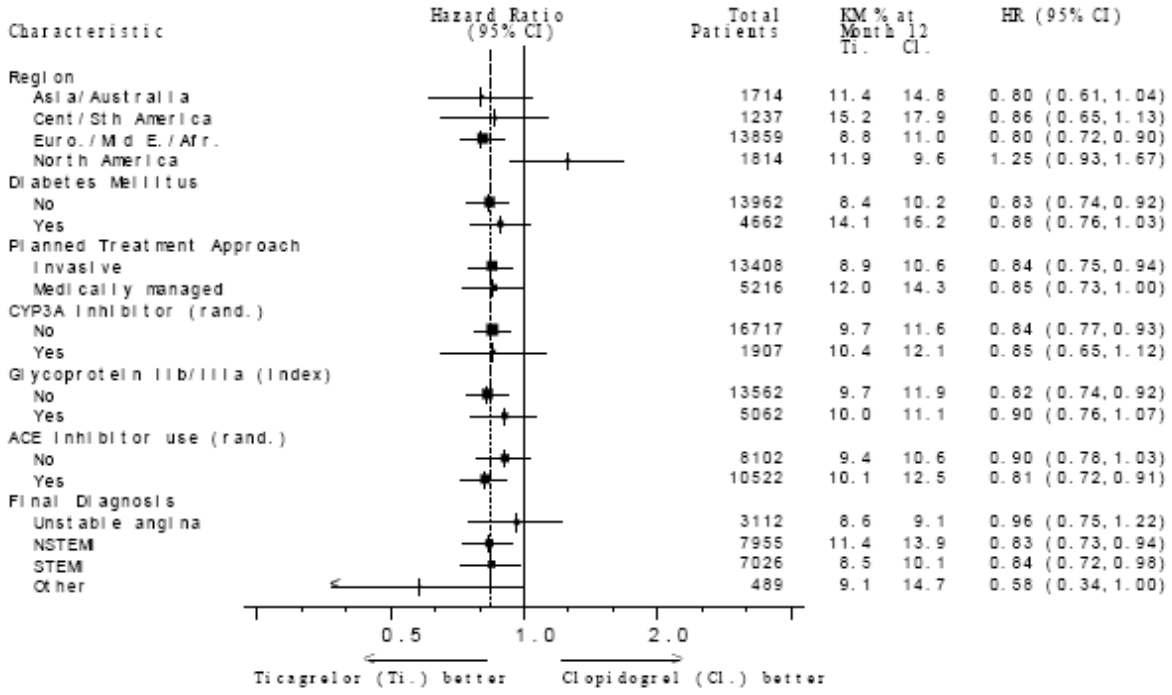


Figure 5 Treatment effect according to subgroups

Further evaluation of the region by treatment interaction showed that the North America observation was driven primarily by results in the United States (HR 1.27 (95% CI 0.92, 1.75)). These analyses suggest a possible association between ASA dose and the primary efficacy results, such that reduced efficacy was observed with ticagrelor at increasing doses of ASA. AHA/ACC Guideline recommendations for ASA in patients receiving a stent, state that a dose of 325 mg od should be administered (King et al 2007) for 6 months. In PLATO, this dose was predominantly administered to patients in North America. Only 16% of North American patients taking 325 mg ASA had the dose lowered after 6 months (patients who were on the study for more than 6 months). Other regions predominantly adhered to the chronic dose of 75 mg to 100 mg od ASA. Additional preclinical mechanistic work is underway to explore the possible relationship between ASA dose and ticagrelor efficacy versus clopidogrel.

Clinical studies in special populations

Renal impairment

Following oral administration, 20% to 27% of the dose is excreted in the urine. One study specifically addressed the impact of severe renal impairment on ticagrelor exposure, and the estimated Cmax and AUC values were similar for subjects with and without severe renal impairment. For the PLATO study, an additional exploratory efficacy analysis of the primary clinical endpoint was performed in patients with defined subgroups of baseline renal function. There was no statistically significant treatment interaction with baseline renal function, although patients with moderate and severe renal impairment demonstrated large point estimates for ARR, 5.7% and 9.5% respectively. The treatment benefit with ticagrelor for the primary clinical endpoint occurs at all levels of baseline renal function. The clinical program did not study dialysis-dependent patients.

Hepatic impairment

Ticagrelor is extensively metabolised, and cytochrome P450 (CYP) 3A4 is thought to be the major enzyme responsible for cytochrome P450 mediated metabolism of ticagrelor, and also the formation and metabolism of the major metabolite, AR-C124910XX. In the PLATO study, subjects with moderate or severe hepatic impairment were not to be included, and Phase III study data is therefore not available for this population. However, one study specifically addressed the impact of mild hepatic impairment on ticagrelor exposure. Peak and overall exposure to ticagrelor were 12% and 23% higher in patients with mild hepatic impairment (Child-Pugh class A) compared to matched healthy volunteers. Ticagrelor has not been studied in the patients with moderate or severe hepatic impairment (Child-Pugh class B or C).

2.5.3 Discussion on clinical efficacy

Ticagrelor demonstrated a clear beneficial treatment effect for the primary endpoint. This is already apparent within the first 30 days of follow-up and remains consistent until the end of follow-up of 12 months. CV death and MI are the main contributors of the composite primary endpoint, while ticagrelor does not demonstrate any beneficial treatment effect on the stroke endpoint, which only accounted for approximately 10% of the individual endpoints of the primary endpoint. The most important secondary endpoints are supportive for the primary endpoint, including all cause mortality. Post hoc analyses demonstrate ticagrelor to be effective in both subgroups of invasive and non-invasively treated patients. Ticagrelor seems to be most effective in patients who are managed medically (non-invasive as first procedure) compared to invasively treated (mainly PCI) although statistical interaction was not significant. Benefit risk evaluation in both STEMI and NSTEMI seems approximately equally effective with ticagrelor although subgroup differences appear. Further subgroup analyses demonstrated most subgroups to be consistent with the overall analysis, except for the impact of region. In the North American subpopulation ticagrelor performed worse than clopidogrel. According to the Applicant this is most likely related to the higher dose of ASA administered. Another remarkable finding was the observed benefit in mortality for patients undergoing CABG, but with no advantage over clopidogrel on the primary endpoint. A particular point of interest is whether the relative beneficial effect of ticagrelor might be observed due to a possible lack of efficacy in patients who are poor clopidogrel metabolisers, either due to genetic polymorphism or due to concomitant use of CYP2C19 inhibitors. Nevertheless, PPI treatment did not impact overall efficacy of ticagrelor as compared to clopidogrel. However, upon closer inspection it can be noticed that for CV death and overall death, event rates were larger in patients in the clopidogrel treatment arm that concomitantly received PPI treatment versus those that did not take PPI. In the ticagrelor arm there might also be a difference between PPI users and non users as KM curves show a trend toward more endpoints in PPI users comparable to clopidogrel users.

However, interpretation is complicated as it probably shows 'confounding by indication'. Patients using PPIs were slightly older (0.4 years), were more often intended for invasive management (80% vs 68%), had more often an index diagnosis of STEMI or NSTEMI vs UA/other, and were more often on concomitant statin treatment. In addition, the pharmacodynamic properties of ticagrelor (pH independent absorption, no CYP2C19 activation) suggest that PPI interaction is unlikely.

2.5.4 Conclusions on the clinical efficacy

Ticagrelor demonstrated a clear beneficial treatment effect for the primary endpoint with CV death and MI as the main contributors. This effect was also consistent for planned invasive management, and for NSTEMI and STEMI patients. However, patients managed medically seemed to have a better benefit risk balance than patients treated invasively.

2.6 Clinical safety

Patient exposure

Nearly 10-fold more patients (9235 exposed for up to 12 months) received ticagrelor in PLATO than in all Phase II studies (960 exposed for 4 to 12 weeks) combined. Therefore, safety data in PLATO was kept separate from those in earlier Phase I and II studies.

Adverse events

A higher overall percentage of AEs (72.7% vs. 69.6%) was observed with treatment of ticagrelor compared to clopidogrel. Although severe AEs were similar, AEs and SAEs led to more study drug discontinuations (7.4% vs. 5.4% and 2.8% vs. 2.4%). However, a sensivity analysis showed that this did not affect net clinical benefit.

When bleeding events were excluded, a higher number of AEs (68.6% vs. 66.6%) still remained in the ticagrelor group as compared to the clopidogrel group. However, numerically fewer SAEs (1633 (17.7%) vs. 1694 (18.4%)) and deaths (198 (2.1%) vs. 266 (2.9%)) were observed in the ticagrelor group as compared to the clopidogrel group. Numerically, more patients discontinued therapy as a result of adverse events (486 (5.3%) vs. 411 (4.5%)) in the ticagrelor group relative to the clopidogrel group (table 2).

Most common AEs with a higher incidence for ticagrelor were dyspnoea (1104 (12.0%) vs. 598 (6.5%)), headache (600 (6.5%) vs. 535 (5.8%)) and epistaxis (558 (6.0%) vs. 308 (3.4%)).

Table 4 AEs on treatment including bleedings events for PLATO

Number of Patients	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Any AE	6714 (72.7%)	6398 (69.6%)
Mild	5655 (61.2%)	5292 (57.6%)
Moderate	3322 (36.0%)	3073 (33.5%)
Severe	1019 (11.0%)	1061 (11.6%)
Any SAE	1864 (20.2%)	1866 (20.3%)
SAE excluding death	1712 (18.5%)	1685 (18.3%)
Death[a]	218 (2.4%)	285 (3.1%)
Leading to study drug discontinuation	687 (7.4%)	500 (5.4%)
SAE	259 (2.8%)	218 (2.4%)

The primary safety endpoint was defined as time to first occurrence of any total major bleeding event, which was found to be higher but non-statistically significant for ticagrelor (11.6% vs. 11.2%; HR 1.04 (95%CI 0.90-1.16); p=0.4336). This was irrespective of PLATO or TIMI-defined bleedings.

Differentiation across major fatal and life-threatening bleedings did also not demonstrate any differences. However, a statistically significant higher incidence of bleedings for ticagrelor was found when major and minor bleedings were combined (16.1% vs 14.6%; HR 1.11 (95%CI 1.03-1.20); p=0.0084).

More non-procedure-related bleedings appeared in the ticagrelor group (2.5% vs 2.0%; HR 1.31 95%CI 1.08-1.60) while procedural bleedings seemed generally lower with ticagrelor (8.2% vs 8.4%) except for PCI-related procedures (1.0% vs. 0.7%) (see table 2).

Table 5 Major bleeding events by clinical context

	Total bleeding events		Patients with ≥1 bleeding event	
Characteristic	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd N = 9235	Clopidogrel 75 mg od N = 9186
Total Major[b, c]	1031	997	961 (10.4%)	929 (10.1%)
Not related to CABG surgery	401	335	362 (3.9%)	306 (3.3%)
Not procedure-related	251	190	235 (2.5%)	180 (2.0%)
Non-CABG procedural	151	145	143 (1.5%)	133 (1.4%)
Procedure-related	773	804	756 (8.2%)	775 (8.4%)
Non-coronary	30	46	27 (0.3%)	37 (0.4%)
Coronary	743	758	732 (7.9%)	745 (8.1%)
CABG-related	623	659	619 (6.7%)	654 (7.1%)
PCI-related	97	70	93 (1.0%)	68 (0.7%)
Coronary Angiography related	23	29	23 (0.2%)	28 (0.3%)

For non-procedural major bleedings, gastro-intestinal bleedings and intracranial bleedings were most frequent. Despite an increase in intracranial total major fatal/life-threatening bleedings, there was no increase in non-intracranial total major fatal/life-threatening bleedings with ticagrelor (5.0% with ticagrelor and 5.1% with clopidogrel).

Incidence of procedural and CABG-related bleedings was lower with ticagrelor. In contrast to what would be expected based on pharmacological platelet inhibition, there was a higher incidence in total major and fatal/life threatening bleeding events for ticagrelor when study drug was discontinued within 96 hours prior to CABG. A longer period between discontinuation and invasive treatment resulted in fewer bleedings with ticagrelor (see table 6). Bleeding risk was not lower for ticagrelor compared to clopidogrel until 7 days before treatment discontinuation before CABG.

Table 6 PLATO-defined 'Major Fatal/Life-threatening' CABG-related bleeding by time from last dose of study drug to procedure

			Total Major		Fatal/Life-threatening		Fatal	
	Patients with CABG							
Hours from last dose of study drug to CABG	Ticag-relor 90 mg bd	Clopid-ogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od	Ticagrelor 90 mg bd	Clopidogrel 75 mg od
0-24	84	88	70 (83.3%)	78 (88.6%)	55 (65.5%)	52 (59.1%)	2 (2.4%)	1 (1.1%)
>24-48	106	86	95 (89.6%)	70 (81.4%)	50 (47.2%)	42 (48.8%)	1 (0.9%)	1 (1.2%)
>48-72	114	73	94 (82.5%)	56 (76.7%)	56 (49.1%)	33 (45.2%)	0	0
>72-96	84	69	72 (85.7%)	54 (78.3%)	39 (46.4%)	29 (42.0%)	1 (1.2%)	3 (4.3%)
>96-120	79	96	59 (74.7%)	76 (79.2%)	22 (27.8%)	27 (28.1%)	1 (1.3%)	0
>120-144	91	110	67 (73.6%)	83 (75.5%)	29 (31.9%)	45 (40.9%)	0	1 (0.9%)
>144-168	74	107	56 (75.7%)	87 (81.3%)	25 (33.8%)	40 (37.4%)	0	0
8-14 days	109	147	86 (78.9%)	123 (83.7%)	43 (39.4%)	65 (44.2%)	1 (0.9%)	0
Total	**741**	**776**	**599 (80.8%)**	**627 (80.8%)**	**319 (43.0%)**	**333 (42.9%)**	**6 (0.8%)**	**6 (0.8%)**

Subgroup analyses of the total major (CABG included) bleedings, only demonstrated a significantly higher incidence for the BMI >= 30 kg/m2 group (HR 1.21 (1.02, 1.45)) as compared to HR 0.99 (0.89, 1.09) for the BMI <30 k g/ m2 subgroup.

For the total major CABG excluded bleedings (overall significant increase of bleedings), the following subgroups demonstrated a significantly higher incidence: age group >=65 and <75 years, male, Caucasian, BMI >= 30 kg/m2, weight >= 60 kg, no diabetes mellitus, CYP3A4 use, no glycoprotein IIb/IIIa use, ASA use, Heparin use, no history of TIA/Non-Haem stroke.

Serious adverse event/deaths/other significant events

Both treatment groups demonstrated similar profiles of severe AEs (20.2% vs. 20.3%) according to organ class with the exception of gastro-intestinal disorders (2.4% vs. 1.9%). The overall numbers of deaths were smaller among the ticagrelor treated patients (443 vs, 540). This also applied for numbers of deaths on treatment (283 (3.1%) vs. 339 (3.7%)). Bleeding deaths were similar (0.2%) in the two groups.

Laboratory findings

Approximately 5% of ticagrelor treated patients experienced a decrease in haemoglobin from normal at baseline to low that crossed the lower limit of the reference range (115 g/L for males or 105 g/L for females) versus approximately 4% of clopidogrel patients. Increases in mean serum creatinine values of less than 10% relative to baseline were observed in both treatment groups, with a numerically greater increase in patients receiving ticagrelor compared with clopidogrel. Elevated serum creatinine has been identified as a potential risk further to be evaluated in the PEGASUS trial, as a mechanistic

study seems not feasible. Renal events in patients with elevated serum creatinine were higher, however, more CV events occurred in both groups in patients with >50% creatinine elevation. Monitoring of renal function is needed and this is stated in section 4.4 of the SmPC. Mean serum uric acid increased approximately 15% from baseline for ticagrelor vs approximately 7% for clopidogrel. Absolute values and change from baseline in serum ALT, AST, ALP, and total bilirubin were generally similar over time for the ticagrelor and clopidogrel treatment groups, and there was a similar frequency of liver function test abnormalities in the 2 treatment groups. However, an imbalance in the number of patients with bilirubin increase >2xULN (ticagrelor 25 vs clopidogrel 10) was noticed. These cases often represented a moderate hyperbilirubinaemia with a mild contribution of conjugated bilirubin (<20%) without signs of cholestasis or hepatocellular liver injury. Of the patients with available samples for genotyping, most were homozygous for UGT1A1 polymorphisms known to be associated to Gilbert's Syndrome. Also the PEGASUS trial should elucidate more on liver safety.

Safety in special populations

Specific AEs

Dyspnoea SAEs were reported in 69 patients (0.7%) taking ticagrelor and 39 patients (0.4%) taking clopidogrel. Most of the dyspnoea AEs were mild to moderate in nature; severe dyspnoea AEs were identified in 35 patients (0.4%) in the ticagrelor group and 18 patients (0.2%) in the clopidogrel group. There were 2 dyspnoea AEs with an outcome of death (1 in each treatment group).

The number of patients with AEs in the cardiac arrhythmias was generally similar between treatment groups. These AEs included bradycardia (2.9% in both treatment groups), atrial fibrillation (4.2% with ticagrelor vs. 4.6% with clopidogrel), ventricular tachycardia (2.0% vs. 2.1%), or ventricular fibrillation (0.8% vs. 1.0%). The number of patients with investigator-reported on-treatment bradycardic events was numerically higher in patients taking ticagrelor compared to those taking clopidogrel (122 (1.3%) vs. 97 (1.1%)). There was a numerically higher frequency of AEs possibly related to brady-arrhytmias (13.4% vs. 13.1%) for ticagrelor. However, there was not a higher frequency of SAEs related to brady-arrhytmias with ticagrelor.

The Continuous ECG (Holter) monitoring in a subset of DISPERSE2 patients in Phase II that disclosed an imbalance among treatment groups in the incidence of largely asymptomatic ventricular pauses led to an extensive Holter monitoring substudy in PLATO for in depth safety assessment of this observation. During both monitoring periods (visit 1 and 2), numerically more patients had Holter-detected bradycardia (41.5% vs 39.1% (visit 1)) and dropped beats (33.3% vs. 30.3% (visit 1) in the ticagrelor group compared to clopidogrel; heart rates were similar between groups.

Renal related events were higher in ticagrelor vs clopidogrel (AEs (4.9% vs 3.8% and SAEs (0.8% vs. 0.7%)). The analysis of the time to first event was significantly different between treatment groups (HR 1.31 [95% CI 1.14, 1.50]). The imbalance appears to be accounted for by event terms relating to creatinine increases and renal function as well as haematuria. According to the Applicant, confounding factors mainly could have accounted for this.

Although hepatic events were similar, 110 patients (ticagrelor 62 vs. clopidogrel 48) were evaluated for potential liver injury as they had elevated liver enzymes. However, these cases often represented a moderate hyperbilirubinaemia with a mild contribution of conjugated bilirubin (<20%) without signs of cholestasis or hepatocellular liver injury.

Regardless of the degree of renal impairment at baseline, the percentage of patients reporting AEs was numerically higher for ticagrelor-treated patients compared to clopidogrel-treated patients (80.6% vs. 78.1% in moderate/severe and 75.1% vs. 73.0% in mild to normal). There was no imbalance for SAEs

(34.3% vs. 37.4% in moderate/severe and 20.0% vs. 19.6% in mild to normal). In patients with hepatic impairment AEs were similar.

Safety related to drug-drug interactions and other interactions

Discontinuation due to adverse events

On treatment, the ticagrelor group had a higher discontinuation rate due to AEs than clopidogrel (7.4% vs. 5.4%). The difference was driven mainly by respiratory disorders (0.9% vs. 0.2%), where dyspnoea was the main reason (0.8% vs. 0.1%), as well as upper respiratory tract disorders (0.4% vs. 0.1%), where epistaxis accounted for this difference.

2.6.1 Discussion on clinical safety

The safety assessment is primarily based on data from the PLATO trial. More adverse events occurred with ticagrelor, mostly due to adverse events of moderate severity. This also resulted in more patients discontinuing due to an AEs with ticagrelor. Specific adverse events already identified during phase II trials were also apparent during the PLATO trial. Regarding the higher incidence of dyspnoea observed, the Applicant could not identify a mechanism. However, it is considered that this constitutes an adenosine-mediated mechanism as a similar higher incidence has been reported for cangrelor (Tomoda, N Engl J Med. 2009 Dec 10;361(24):2385; author reply 2387-8). This is an issue that the Applicant has committed to further evaluate in the Risk Management Plan. Specific attention was also given to arrhythmic effects, also likely to be adenosine-mediated, by means of a Holter substudy. Although this substudy identified some changes related to heart rhythm (bradycardia and dropped beats), this did not translate into significantly more arrhythmic AEs in the total population. Also no clear higher incidence of bradycardia was observed for ticagrelor. However, patients with an increased risk for bradyarrhythmias without a pacemaker in place were excluded in the PLATO trial and this issue is reflected in the SmPC section 4.4. A higher incidence in uric acid was identified (probably due to adenosine degrade), which needs further follow-up during the post-marketing phase as part of pharmacovigilance activities; although no direct relation with gout was apparent. In addition, renal events were higher, which may also be related to a possible renal effect of adenosine due to deterioration in renal function by arteriolar constriction. However, the exact mechanism still remains uclear.

As with other anticoagulants specific attention was given to bleeding risk; the primary safety issue. Compared to clopidgrel there seems not to be a higher risk of major bleedings, and fatal/life threatening bleedings with ticagrelor (mostly gastro-intestinal), although it is numerically slightly increased. When combined with minor bleedings, the risk with ticagrelor treatment is increased. However, the clinical implications of minor bleedings are unclear and a focus on major bleedings is therefore of more clinical importance. Major bleeding risk is also increased for invasive treatment (PCI or CABG) leaving the net clinical benefit to be lower than for non-invasive treatment with ticagrelor (although the p-value for the interaction is not significant (0.07)). Although treatment management is different for STEMI and NSTEMI diagnosed patients there is not a clear difference in major bleedings between these patients. The course of bleedings in patients undergoing CABG while already having been treated with ticagrelor or clopidogrel is of particular importance, as it is postulated that the offset of inhibition of platelet aggregation is shorter with ticagrelor and therefore the risk of bleeding should be reduced. However, clinical data are not in line with these pharmacological data: ticagrelor confers a higher bleeding risk when discontinued within 96 hours (not until 24 hours) prior to CABG while having a lower bleeding risk when discontinued for a longer period prior to CABG. Nevertheless bleeding risk,

identified through effects on Hb concentration and chest tube drainage, showed to be similar for ticagrelor and clopidogrel treated patients. This implies that ticagrelor should also be discontinued 7 days prior to CABG as should clopidogrel. This is appropriately reflected in the SPC. In addition, it was found that ticagrelor has a higher intracranial bleeding risk, although non-intracranial bleeding risk is lower in total. As history of previous intracranial bleed was already part of the exclusion criteria, a contra-indication for history of intracranial haemorrhage is warranted in the SmPC. In addition, a higher incidence of AEs in renal impaired patients was also reflected in the SmPC. TIMI or PLATO defined bleedings seems not to differ with reference to adjudication of number of bleedings and this fact demonstrated robustness of the PLATO defined bleeding terms.

2.6.2 Conclusions on the clinical safety

The most important safety indicator for anticoagulants, risk of bleeding, is of similar level for ticagrelor as with clopidogrel for major and death/life-threatening bleedings, although specific bleedings or cases are associated with a higher bleeding risk which have been reflected in the SmPC. Bleeding risk was similar for STEMI and NSTEMI, but higher for invasive vs non-invasive treatment (the p-value for the interaction was not significant). In addition, several particular adverse events of interest have been identified already in phase II-III trials and need further intensive follow-up as part of the pharmacovigilance activities in the future (dyspnoea, arrhythmic effect, increased uric acid, higher serum creatinine) as the mechanism of action (likely adenosine-related) and clinical implication still remain unclear.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system (version 11, 21 June 2010) as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan (version 4 from 21 Sep 2010), which included a risk minimisation plan.

Table 7 Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Identified Risk: **Increased risk of bleeding**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** Detailed bleeding assessments using TIMI and PLATO scoring system in PEGASUS and Modified Rankin Score for ICH, DSMB review, and safety data from longer exposure and follow-up. **Extended DUS** – Capturing	**Routine** – Appropriate wording in the SPC: Contraindications including patients with a history of ICH in the SPC, Section 4.3. Advise caution (described in Section 4.4) in patients at increased risk of bleeding, ie, patients with a propensity

	hospitalised cases of GI bleeding, ICH and other bleeding events – will provide crude incidence rates and data on concomitant medication and baseline medical history. **Objectives**: To better characterise the nature of the bleeding risk including ICH.	to bleed, patients with concomitant administration of medicinal products that may increase the risk of bleeding. Bleeding data described in the SPC, Section 4.8.
Identified Risk: **Dyspnoea**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** - Collection of detailed baseline data regarding the severity of any baseline asthma or COPD as well as safety data from longer exposure and follow-up. **Extended DUS** – to provide crude incidence rates of hospital admissions for identified respiratory events, hospitalisation for CHF and outpatient events of dyspnoea in general practice. **Objective**: To better characterise the nature of the risk of dyspnoea. To assess the implications of longer exposure. To better characterise whether severe baseline respiratory disease patients are at higher risk.	**Routine** – Appropriate wording in the SPC. The wording in the patient information leaflet will provide additional support to the effectiveness of the SPC. Advice provided on management of dyspnoea in SPC, Section 4.4, Warnings and precautions. Dyspnoea data described in SPC, Section 4.8.
Identified risk – **Brady-arrhythmias (including Holter-detected ventricular pauses)**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** Will provide safety data from longer exposure and follow-up. **Extended DUS** – to provide crude incidence rates of hospitalised events of pacemaker insertion, bradyarrhythmia and cardiac arrest (CHD deaths occurring outside hospital and death with recording cardiac arrest), and outpatient events of syncope **Objective**: To better understand the nature of any risk.	**Routine** – Appropriate wording in the SPC. Caution advised in Section 4.4. Section 4.5 contains information for prescribers regarding the use of concomitant medications which are known to cause bradycardia. Description of Holter data provided in Section 5.1.
Identified risk – **Serum creatinine increases (Renal Impairment)**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** – Further renal data will be collected including urine data in a population with a longer exposure and follow-up. **Extended DUS** – provide crude incidence rates of hospital admissions for cases of acute renal failure. **Objective**: To better understand the nature of any risk.	**Routine** – Appropriate wording in the SPC, Advice on the monitoring of renal function outlined in Section 4.4. Section 4.8, Undesirable effects includes description about increases in serum creatinine.

Identified risk - **Hyperuricaemia**	**Routine pharmacovigilance**	**Routine -** Section 4.4 caution advised in subjects with history of hyperuricaemia, gouty arthritis or urate nephropathy. Appropriate wording in the SPC, Section 4.8, Undesirable effects, includes description of increased serum uric acid concentration.
Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; statins metabolised through CYP3A4 (i.e. simvastatin and lovastatin) and digoxin.	**Routine pharmacovigilance** **Additional pharmacovigilance** See section above for bleeding – for these events concomitant medication will be described. **Objectives**: To further understand the nature of the risk of these drug-drug interactions when ticagrelor is used in routine practice. To assess the appropriateness of the wording in the SPC and determine whether the risks have implications in "real-world" prescribing.	**Routine -** Appropriate wording in SPC, Section 4.3 Contraindication Strong CYP3A4 inhibitors, Section 4.4, Special warnings and precautions. Advice provided regarding the contraindication of strong inhibitors of CYP 3A4 and to limit dose of simvastatin and lovastatin to 40 mg. Caution with strong inducers of CYP3A4. Recommendation for close monitoring when administering digoxin concomitantly. These drug-drug interactions are described in detail in the SPC, Section 4.5, Interactions with other medicinal products and other forms of interaction.

Potential risk: **DILI**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** – In PEGASUS LFTs will be measured at 2 timepoints in all subjects (at enrolment, and at end of treatment visit) in a population with longer exposure and follow-up. Patients with baseline abnormalities in LFTs will be reviewed carefully for AEs possibly related to liver function disorder and exposure related AEs. The study team physician will use an inspection list using MedDRA SMQs to identify AEs and SAEs for review and follow up of supplemental information to complement data already captured in the CRFs to allow as full an assessment as possible. **Extended DUS** - The DUS will ascertain incident cases of acute liver injury and estimate crude incidence rate. **Objective**: To better understand the nature of any risk.	Not required
Potential Risk: **Gout/Gouty Arthritis and urate nephropathy**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** - Adverse event and laboratory data from longer exposure and follow-up will be used to evaluate the potential for ticagrelor to cause increased reports of gout/gouty arthritis. **Extended DUS** - The DUS will capture events of gout in general practice and will provide crude incidence rates of gout. **Objectives**: To determine if hyperuricaemia leads to an increased incidence of gout/gouty arthritis or urate nephropathy in the "real-world" and with longer-term prescribing.	**Routine-** Section 4.4 caution advised in subjects with history of hyperuricaemia, gouty arthritis or urate nephropathy. Appropriate wording in the SPC, Section 4.8, Undesirable effects, includes description of increased serum uric acid concentration.
Potential risk: **Uterine malignancy**	**Routine pharmacovigilance** **Additional Pharmacovigilance** **PEGASUS** will provide data in longer exposure and follow-up. **Preclinical prolactin study** in the rat **Objectives**: Better understand the nature of any risk and to confirm the mechanistic hypothesis.	**Routine –** The SPC section 5.3 describes pre-clinical findings of uterine malignancy.
Missing information:	**Routine pharmacovigilance**	**Routine –**

Potential interaction P-gp Inhibitors	**Additional phamacovigilance** A drug-drug interaction study evaluating the potential effect of cyclosporin, a probe P-glycoprotein (P-gp) inhibitor at a high dose, on the pharmacokinetics of ticagrelor in healthy volunteers and the effects of ticagrelor on the pharmacokinetics of cyclosporin. **Objective**: To determine if there is a potential for a clinically relevant drug-drug interaction between ticagrelor and P-gp inhibitors.	SPC sections 4.4 and 4.5 describes current understanding
Missing information: **Potential interaction CYP 2D6 substrates**	**Routine pharmacovigilance** **Additional pharmacovigilance** **Drug-drug interaction study** in healthy volunteers to evaluate the effect of ticagrelor on venlafaxine. **Objective**: To determine if there is a potential for a clinically relevant drug-drug interaction between ticagrelor and CYP 2D6 substrates.	Not Required
Missing Information: **Use in patients with moderate to severe liver disease**	**Routine pharmacovigilance** **Additional pharmacovigilance** **PEGASUS** - will capture baseline liver function (not confounded by the acute event of ACS as in PLATO), although there will be exclusion criteria related to baseline hepatic function. **Extended DUS** - will assess the prevalence of baseline hepatic disease (liver cirrhosis and chronic hepatitis) but disease severity cannot be captured due to database limitations. **Objectives**: To understand if inappropriate use is occurring in patients with moderate to severe hepatic disease. To utilise any data emerging to better understand the clinical consequences of ticagrelor use in these patients.	**Routine –** Detailed wording the SPC Contraindication for patients with moderate and severe hepatic impairment in Section 4.3 of SPC. SPC mentions that ticagrelor has not been studied in patients with moderate or severe hepatic impairment, SPC, Sections 4.2 and 5.2, Special Populations.
Missing Information: **Patients at potentially increased risk of bleeding :** Patients with active bleeding, past history of ICH, GI bleed within 6 months, major surgery within 30 days and clinically	**Routine pharmacovigilance** **Additional pharmacovigilance** **Extended DUS** will capture concomitant medication use and past medical history. **Objectives**: To assess whether there is usage of oral anticoagulants and fibrinolytics concomitantly with ticagrelor. If so, to better understand the safety implications ie, any increase in bleeding risk.	**Routine** – SPC provides clear guidance on appropriate use of ticagrelor. Patients with past history of ICH, or active bleeding – use of ticagrelor contraindicated, SPC, Section 4.3. Patients at increased risk of bleeding – described in SPC and advised that ticagrelor only be used with caution, SPC, Section 4.4.

relevant thrombocytopaenia or anaemia Concomitant use of Oral anticoagulants and/or fibrinolytics within 24 hours of ticagrelor dosing Concomitant use of NSAIDs		

Missing Information: **Use in patients beyond the recommended 1-year treatment duration**	**Routine pharmacovigilance** **Additional Pharmacovigilance** **PEGASUS** will treat for up to 3 years although in a slightly different population and so will provide safety data on longer term exposure. **Extended DUS** – will provide data on indication for which ticagrelor is initially prescribed. This information will be used to determine appropriate further epidemiological evaluations which may include use beyond 1 year. **Objective**: To better understand safety of longer-term dosing with ticagrelor.	**Routine –** SPC provides clear guidance on appropriate use of ticagrelor. SPC mentions that ticagrelor has not been studied in patients beyond 1-year treatment duration.
Missing Information: **Use in children**	**Routine pharmacovigilance** **Additional pharmacovigilance** A paediatric study to assess safety and efficacy of ticagrelor in the prevention of thrombosis thromboembolic events in paediatric patients with a central venous catheter (EMEA-000480-PIP01-08) (P/199/2009). **Objectives**: To identify off-label use in paediatrics. To provide safety and efficacy data and PK data in children to enable appropriate use in appropriate indications and populations.	**Routine –** SPC provides clear guidance on appropriate use of ticagrelor. SPC states that no data are available to establish efficacy and safety in children, SPC section 4.2, 5.1 and 5.2
Missing Information: **Use in pregnant or lactating women**	**Routine pharmacovigilance**	**Routine** – SPC provides clear guidance on appropriate use of ticagrelor. SPC, Section 4.6, states that no data are available in pregnant or lactating women. Ticagrelor present in animal milk. Ticagrelor not recommended for pregnant or lactating women.
Important Other information **Off-label use**	**Routine pharmacovigilance** **Additional pharmacovigilance** **Extended DUS** – will provide data on indication for which ticagrelor is initially prescribed, duration of therapy and discontinuation rate during the first year of use in clinical practice as well as data on concomitant medication use and past medical history**.** **Objective:** Assess any safety information from off-label use.	**Routine** – Clear wording in SPC describing indication and patients in which ticagrelor use is appropriate.
Other:	**Routine pharmacovigilance**	**Routine –**

Patient non-compliance	**Additional pharmacovigilance** Measure compliance in PEGASUS study and assess real-world compliance in proposed DUS study via prescription filling dates. **Objective**: To increase understanding as to whether patients comply with dosing regimen.	Prescribing information and patient information states importance of adhering to bd treatment and completing prescribed treatment.

DUS Drug utilisation study; SPC Summary of product characteristics
The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

User consultation

The results of the user consultation with target patient groups on the package leaflet show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

The pivotal trial, PLATO, compared ticagrelor to clopidogrel administration both on top of treatment with low dose ASA in prevention of thrombotic events in patients with ACS including patients managed medically, and those who are managed with PCI or CABG. This is considered justified as the common treatment approach in ACS is treatment with ASA and with the addition of clopidogrel. In the treatment of ACS conditions, there is a significant risk for recurrent MI or occurrence of death within 30 days after a patient is presented with ACS, particularly for STEMI ACS. An endpoint including CV death, MI and another objective endpoints is considered essential. In PLATO the combined endpoint of CV death, MI and stroke is considered appropriate, but overall death is also considered of substantial importance. The beneficial effect of ticagrelor is convincing as both a beneficial effect on the primary endpoint is demonstrated at 30 days of follow-up (HR 0.88; p=0.0446) and maintained in the longer term of up to 12 months for the primary endpoint (HR 0.84; (0.77-0.92), p=0.0003) as well as for overall death. An extensive group of patients has undergone invasive management, in particular PCI (approximately 60%). For both the overall intervention subgroup as well as for patients undergoing PCI the beneficial effect of ticagrelor is consistent with the overall beneficial effect. Of particular importance is that this was irrespective of timing of PCI (less than 24 hr versus at-any-time). Post hoc analyses showed that consistent benefit is observed, with a slight advantage for medically managed patients. The observed lower benefit for the North American subgroup is further discussed under risks above. Although more adverse events and discontinuations due to adverse events occurred with ticagrelor, there were fewer numbers of severe adverse events and deaths and sensitivity analyses did not demonstrate any differences in treatment effect based on differences in discontinuation.

- Uncertainty in the knowledge about the beneficial effects.

Although there is a beneficial effect demonstrated for MI and CV death, there seems to be a negative effect on stroke (HR 1.17 (0.91-1.52, P=0.2249). It is not known whether a beneficial effect could be demonstrated in patients with a history of previous intracranial bleed. However, as it was an exclusion

criterion in the PLATO trial, history of intracranial haemorrhage has been contra-indicated in the SmPC. Further, beneficial effect of ticagrelor for more than 12 months is uncertain even though 25% of patients have been treated for more than 12 months. However, a large trial is already planned to evaluate long term treatment effects of ticagrelor in patients treated longer than 12 months and the Applicant will provide these data for CHMP review as a post-marketing commitment. In addition, uncertainties for certain subgroups remain, particularly due to exclusion criteria in the PLATO trial. Hepatic impaired patients are not evaluated. Another issue is that a beneficial effect of ticagrelor could have been observed due to a lack of efficacy in poor metabolisers of clopidogrel due to genetic polymorphism or concomitant PPI use. PPI treatment did not have an impact on the overall efficacy of ticagrelor as compared to clopidogrel. Upon closer inspection, event rates were larger in patients in the clopidogrel treatment arm that concomitantly received PPI treatment versus those who did not take PPI. Also in ticagrelor patients, more endpoints was noted in survival curves for patients using PPI versus not using PPIs. However, this is probably due to confounding by indication, as these patients were slightly older (0.4 years), were more often intended for invasive management (80% vs 68%), had more often an index diagnosis of STEMI or NSTEMI vs UA/other, and were more often on concomitant statin treatment. In addition, the pharmacodynamic properties of ticagrelor (pH independent absorption, no CYP2C19 activation) suggest that PPI interaction is unlikely.

Risks

- Unfavourable effects

Bleeding is the major risk associated with anticoagulants. Although the overall bleeding risk is only numerically higher and not statistically significantly increased as compared to clopidogrel, the non-procedural bleeding risk is significantly higher with ticagrelor (2.5% vs. 2.0%). In addition, PCI related bleeding risk is also increased (1.0% vs. 0.7%). This could indicate that the intrinsic bleeding risk with ticagrelor is higher than with clopidogrel, which can be expected with a higher level of platelet aggregation inhibition. And that ticagrelor treatment can be time critical in invasive management in terms of bleeding risks. For instance, this would be in congruence with the observed higher bleeding risk in patients discontinuing ticagrelor treatment within 96 hours before CABG treatment. However, these clinical findings are inconsistent with the pharmacological evaluated lower %IPA (Inhibition of Platelet Aggregation) already observed after 24 hours with ticagrelor compared to clopidogrel. Identification of bleeding risk based on Hb concentration and chest tube drainage showed that bleeding risk was similar for patients treated with ticagrelor and clopidogrel. This means that ticagrelor should also be discontinued 7 days prior to CABG. When major bleedings and minor bleedings are combined the bleeding risk is also increased. The clinical efficacy in the North American region (10% of the patients) is found to be lower with ticagrelor (HR 1.27 [95% CI 0.92, 1.75]), according to the Applicant due to use of higher doses of ASA in many cases. This was also observed for higher doses of ASA in other regions. Also for the total patient group, the stroke endpoint demonstrated an unfavourable effect (HR 1.17 (0.91-1.52, P=0.2249). However, this endpoint is underpowered as not many of these endpoints have occurred. In addition, specific adverse events have been identified, such as dyspnoea, cardiac arrhytmias, increased uric acid and renal events, which are likely to be associated with the ADP-mediated mechanism. Also a higher incidence of adverse events in renal impaired patient was found.

- Uncertainty in the knowledge about the unfavourable effects

The pivotal trial was not a placebo controlled trial, so adverse events could only be compared to clopidogrel. This is however justified as a placebo controlled trial would be unethical. The Applicant

could not identify the mechanism of dyspnoea with ticagrelor. This will be further evaluated post-marketing and it is reflected in the RMP. Likely this is ADP mediated as has been postulated for cangrelor. Concerning the risk for cardiac arrhythmias (also likely to be ADP mediated), no clear effect was noticed in the pivotal trial. However, AEs possibly related to brady-arrhythmias (13.4% vs. 13.1%) were slightly increased with ticagrelor. Based on the Holter study bradycardia and dropped beats were also slightly increased. A clear conclusion on this can therefore not be made and the issue will be further investigated in additional pharmacovigilance activities as specified in the RMP. However, exact mechanisms for believed ADP mediated adverse events still remain unclear.

Although hepatic events were similar, 110 patients (ticagrelor 62 vs. clopidogrel 48) were evaluated for potential liver injury as they had elevated liver enzymes. However, these cases often represented a moderate hyperbilirubinaemia with a mild contribution of conjugated bilirubin (<20%) without signs of cholestasis or hepatocellular liver injury. Absolute values and change from baseline in liver serum ALT, AST, ALP, and total bilirubin were generally similar over time for the ticagrelor and clopidogrel treatment groups, and there was a similar frequency of liver function test abnormalities in the 2 treatment groups. However, an imbalance in the number of patients with bilirubin increase >2xULN (ticagrelor 25 vs clopidogrel 10) was still noticed. Of the patients with available samples for genotyping, most were homozygous for UGT1A1 polymorphisms known to be associated to Gilbert's Syndrome.

Benefit-Risk Balance

- Importance of favourable and unfavourable effects

Brilique, co-administered with acetylsalicylic acid is indicated in preventing of thrombotic events in patients with ACS (UA, STEMI and NSTEMI). Patients with STEMI and in particular NSTEMI have a poor short term prognosis if not treated optimally and are therefore treated aggressively. A reduction in recurrent MI, and CV death or overall death is of particular importance when evaluating drugs in the treatment of ACS. A reduction in these endpoints could outweigh some of the severe adverse events typically associated with the investigated drug. Bleeding is the most important risk to be evaluated with these kind of products. Particularly the major bleedings risk is of importance, as this can lead to a considerable risk of morbidity, or even death.

- Benefit-risk balance

In the case of ticagrelor a clear reduction in MI and CV death as well as overall death has been demonstrated when compared to clopidogrel. This clear beneficial effect outweighs the slightly higher risk for major bleedings, considered to be an acceptable risk in this high risk patient group. However, particular precaution should be given in certain situations where bleeding risk can be considerably increased, as there are signs that treatment with ticagrelor is more time critical in relation to invasive management (for instance CABG) than clopidogrel. This could be different for STEMI and NSTEMI patients due to different severity and different management of these patients. However, further comparison between these two groups of patients demonstrated a similar bleeding risk.

2.8.1 Discussion on the benefit-risk balance

The large PLATO trial has demonstrated that ticagrelor is more beneficial in reducing the number of primary endpoints of CV death, MI and stroke, although this is totally contributed by the CV death and MI endpoints. The effect on stroke is not found to be beneficial, although not statistically significant,

but warrants some concerns. Treatment of patients with a previous history of intracranial haemorrhage has been contra-indicated in the SmPC as these were contra-indicated in the PLATO trial and has been contra-indicated in the SmPC of prasugrel. A beneficial effect has been noticed for patients undergoing PCI irrespective of the timing of the PCI. Post hoc analyses showed that consistent benefit was also observed according to invasive or non-invasive treatment, with a slight advantage for medically managed (non-invasive) patients. Treatment with ticagrelor and timing of invasive management could be of particular importance in relation to bleeding risk, because major bleedings were noticed more frequently in patients undergoing PCI (probably due to early invasive management (within 24 hours)) and for CABG procedures too close to discontinuation of ticagrelor. Despite a difference of invasive management between STEMI and NSTEMI patients no great differences in bleeding risk was identified. The claimed faster offset of platelet aggregation of ticagrelor in comparison to clopidogrel by %IPA offset (higher within 24 hours) after discontinuation of the drug seems only to be theoretical. Other markers of bleeding risk such as Hb concentration and chest tube drainage showed that bleeding risks were similar between ticagrelor and clopidogrel. This means that ticagrelor should also be discontinued 7 days prior to CABG. Apart from the bleeding risk some typical adverse events were noticed with ticagrelor already during the phase II trial. Although the higher incidence of dyspnoea is not considered as severe that this would lead to a negative benefit/risk (although slightly more discontinuations were noticed), it is of importance to identify the mechanism of this issue. With a similar product cangrelor this adverse event was also noticed and it was postulated this was likely to be related to an ADP effect. A possible higher incidence of cardiac arrhythmias (also likely ADP mediated), in particular the bradycardia, were identified during phase II trials and could lead to severe consequences. Although bradycardia was also noticed with a slightly higher incidence in the Holter substudy, no higher incidence of severe adverse events could be noticed in the PLATO trial. Nevertheless, cardiac adverse event warrant further attention in the future, and it is reflected in the RMP, as no clear conclusions on this could be made. Also other probably ADP-mediated AEs were identified, such as rise in uric acid and renal events related to rise in serum creatinine, and other potential risks, like DILI (Drug Induced Liver Injury) or uric acid nephropathy, and should be followed within the RMP. A remarkable finding is the lower efficacy of ticagrelor in the North American population, although this is of less importance for the marketing authorisation in the EU as enough patients remain for evaluation of the target EU population (only 1300 patients in US). A higher ASA dose was the main identifiable reason of the negative effect also for non-US patients. In addition, there seems to be a lack of efficacy in the unstable angina subgroup. However, these patients are not identifiable before treatment. The combined UA/STEMI patient group showed similar benefit/risk to the STEMI patients group. A limitation of the pivotal trial is that the long-term evaluation is largely limited to 12 months, but a trial is planned for evaluation longer than 12 months. The SmPC reflects that patients undergoing CABG should stop their ticagrelor treatment with at least an interval of 7 days between discontinuation of ticagrelor and start of CABG, similar to the discontinuation warning in the SmPC of clopidogrel and prasugrel. Further, patients with moderate to severe hepatic impairment, and history of intracranial haemorrhage are not included in the study and are contra-indicated in the ticagrelor SmPC. The higher incidence of adverse events in renal impaired patients and additional information on bleeding risk in certain patients or situations have been included in section 4.4 of the SmPC.

Risk management plan

A risk management plan (version 4, 21 Sep 2010) 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

and

no additional risk minimisation activities were required beyond those included in the product information.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Brilique co-administered with acetylsalicylic acid (ASA) in the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with Acute Coronary Syndromes (unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG) was favourable and therefore recommended the granting of the marketing authorisation.