17 December 2015
EMA/CHMP/18297/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Brilique

International non-proprietary name: TICAGRELOR

Procedure No. EMEA/H/C/001241/0029/G

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

Quality

Al	Aluminium
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human use
CQA	Critical Quality Attribute
DOE	Design of experiments
EC	European Commission
FMEA	Failure mode effects analysis
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of
PAR	Proven Acceptable Range
Ph. Eur.	European Pharmacopoeia
PVC	Poly vinyl chloride
PVDC	Polyvinylidene chloride
QbD	Quality by design
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
UPLC	Ultra-high performance liquid chromatography
UDU	Uniformity of dosage units
UV	Ultraviolet

Clinical

ACCF	American College of Cardiology Foundation
ACS	Acute coronary syndrome(s)
ADP	Adenosine diphosphate
ADR	Adverse drug reaction
AE	Adverse event
AHA	American Heart Association
ALP	Alkaline phosphatase
ApoA	Apolipoprotein A
ApoB	Apolipoprotein B
ALT	Alanine aminotransferase
AR-C124910XX	Active metabolite of ticagrelor (formerly AZD6140)
ASA	Acetylsalicylic acid
AST	Aspartate aminotransferase
ATP	Adenosine tiphosphate
AUC	Area under the plasma concentration-time curve from zero to infinity
ATC	Anatomical, Therapeutical, and Chemical
AV	Atrioventricular
AZD6140	Former name for ticagrelor
bd	Twice daily (dosing)
BMI	Body mass index
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CEC	Clinical endpoints committee
CHD	Coronary heart disease
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPT	Clinical project team
CrCL	Creatinine clearance
CSED	Common study end date
CSP	Clinical study protocol
CV death	Cardiovascular death
CYP3A	Cytochrome P450 isoenzyme 3A
DAE	Discontinuation of study drug due to adverse events
DES	Drug-eluting stent
DME	Designated medical event

ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EoS	End of study (visit)
EoT	End of treatment (visit)
EQ-5D	Euro Quality of Life-5 Dimensions
ESC	European Society of Cardiology
FAS	Full analysis set
GCP	Good Clinical Practice
GRand	AstraZeneca Global Randomisation system
GUSTO	Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries Trial
HEOR	Health economics outcomes research
HR	Hazard ratio
ICF	Informed consent form
IDMC	Independent data monitoring committee
IEC	Independent ethics committee
IPA	Inhibition of platelet aggregation (previously known as PAI)
IRB	Institutional review board
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention to treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
JWG	Joint working group
KM	Kaplan-Meier
MDRD	Modification of Diet in Renal Disease
MedDRA™	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
n	Number of patients in category or analysis
N	Number of patients in treatment group
NSAID	Non-steroidal anti-inflammatory drug
NSTEMI	Non-ST elevation myocardial infarction
od	Once daily dosing
P2Y12	A subtype of receptor found on platelets
PAR-1	Protease-activated receptor-1
PBRER	Periodic Benefit-Risk Evaluation Report
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PEGASUS-TIMI 54	Study: PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group
P-gp	P-glycoprotein
PI	Principal investigator
PK	Pharmacokinetic(s)
PLATO	Study: A study of PLATelet inhibition and Patient Outcomes
PMDA	Pharmaceuticals and Medical Device Agency (Japan)
PT	Preferred term
RMP	Risk management plan
RRR	Relative risk reduction
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SMQ	Standardised MedDRA queries
STEMI	ST-segment elevated myocardial infarction
TIA	Transient ischaemic attack
Tica, Ti, T	Ticagrelor
TIMI	Thrombolysis In Myocardial Infarction – A cardiology clinical trials study group
TNT	Treating to New Targets
UK	United Kingdom
US	United States
WCT	Worldwide Clinical Trials

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 3 March 2015 an application for a group of variations consisting of an extension application and a Type II variation to the European Medicines Agency (EMA) for Brilique in accordance with Article 7(2)b of Commission Regulation (EC) No 1234/2008.

The applicant applied for a group including:

- an extension of the marketing authorisation for a new strength Brilique 60 mg film coated tablets with a new indication for the prevention of atherothrombotic events in adult patients with a history of myocardial infarction (MI occurred at least one year ago) and a high risk of developing an atherothrombotic event.

- a type II variation : To update the product information of the approved 90 mg film-coated tablet with important clinical information from the PEGASUS study.

The legal basis for this application refers to:

Annex I of Regulation (EC) No 1234/2008, point (c) - Extensions of marketing authorisations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/973755/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request for consideration

Additional Data/Market exclusivity

The applicant requested consideration of one year data/market exclusivity in regards of its application for a new indication in accordance with Article 14(11) of Regulation (EC) 726/2004.

The MAH withdrew the request during the procedure.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Arantxa Sancho-Lopez

- The application was received by the EMA on 3 March 2015.

- The procedure started on 26 March 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on16 June 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 June 2015 PRAC RMP Assessment Report adopted by PRAC on 9 July 2015.
- During the meeting on 23 July 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 September 2015.
- The following GCP inspection was requested by the CHMP and its outcome taken into consideration as part of the Safety/Efficacy assessment of the product:
  - A GCP inspection at two clinical investigator sites in Colombia and one clinical investigator site in Chile were conducted in August 2015. The integrated inspection report of the inspections carried out was issued on 16 October 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 October 2015.
- PRAC RMP Assessment Report adopted by PRAC on 6 November 2015.
- During the CHMP meeting on 19 November 2015, 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 24 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 December 2015.
- During the meeting on 17 December 2015, 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.

2. Scientific discussion

2.1. Introduction

European Society of Cardiology (ESC) and American College of Cardiology Foundation (ACCF)/AHA guideline recommendations for antiplatelet therapy after acute coronary syndrome (ACS) include dual therapy with complementary agents, such as ASA and a $P2Y_{12}$ inhibitor (ticagrelor, clopidogrel, or prasugrel), for up to 1 year following an ACS event. These recommendations are based on studies in ACS patients demonstrating the superiority of dual antiplatelet therapy over ASA alone for up to a year. The optimum duration of dual antiplatelet therapy in patients with stable CAD is still to be established. The ESC guidelines do not currently recommend the use of combined antiplatelet therapy beyond 1 year after an ACS event, but state that it may be beneficial in selected patients at high risk of ischaemic events. The AHA secondary prevention guideline states that dual antiplatelet therapy with clopidogrel plus ASA may be considered in patients with stable CAD. The continued risk of further CV events in the years following an initial MI represents an unmet medical need that may be addressed by establishing the optimal

duration and combination of antiplatelet therapy with a positive benefit-risk profile. The rationale for investigating ticagrelor in this setting was based on a hypothesis supported by the mechanism of action of ticagrelor, and by the results of the post-hoc analysis of the CHARISMA study with clopidogrel and the PLATO study with ticagrelor. The results of these studies suggest that extended dual antiplatelet therapy targeted to a high-risk population with prior MI may provide clinical benefit. In addition, the more recent studies, TRA2°P-TIMI 50 with the PAR-1 antagonist vorapaxar, and the Dual Antiplatelet Therapy study (the 'DAPT study') provide further support to the hypothesis that intensive antiplatelet therapy over a longer period of time may be beneficial, although the populations studied and the study designs were quite different.

Ticagrelor and its major circulating metabolite AR-C124910XX are antagonists of the platelet P2Y12 receptor that produces reversible and concentration-related inhibition of ADP-induced platelet aggregation. Ticagrelor, an oral, reversible, antiplatelet agent, has previously been registered as Brilique 90 mg, for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS). It was approved in the EU in December 2010, in the US in July 2011, and subsequently in over 100 countries for the following indication (minor variations of the indication wording occur in some regions):

Ticagrelor is indicated for the prevention of thrombotic events (Cardiovascular death, MI, and stroke) in patients with ACS (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).

Approved dosing regimen:

Brilique treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Patients taking Brilique should also take ASA daily, unless specifically contraindicated.

Treatment with Brilique 90 mg is recommended for up to 12 months in ACS patients unless discontinuation of Brilique is clinically indicated (see section 5.1).

Within this application, the MAH applied for an extension application and a type II variation application:

- Extension application for new strength Brilique 60 mg with a new indication:
  "*Ticagrelor is indicated for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago), and a high risk of developing a thrombotic event.*
- Type II variation application, to update the product information of the existing Brilique 90 mg license with important clinical information from the PEGASUS-TIMI 54 (hereafter PEGASUS) study.

Proposed dosing regimen for this new indication was:

In patients with a history of Myocardial Infarction (MI occurred at least one year ago), no loading dose of ticagrelor is required and the recommended dose is 60 mg twice daily. Long term treatment is recommended unless discontinuation of ticagrelor is clinically indicated.

Following the assessment, the CHMP granted the following indication for the new 60mg and the approved previously 90mg strength:

Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with:

- *acute coronary syndromes (ACS) or*

- *a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.*

The agreed dosing regimen for 60 and 90 mg strengths is:

Acute coronary syndromes

Ticagrelor treatment should be initiated with a single 180 mg loading dose (two tablets of 90 mg) and then continued at 90 mg twice daily. Treatment with ticagrelor 90 mg twice daily is recommended for 12 months in ACS patients unless discontinuation is clinically indicated.

History of myocardial infarction

Ticagrelor 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment may be started without interruption as continuation therapy after the initial one-year treatment with ticagrelor 90mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

If a switch is needed, the first dose of ticagrelor should be administered 24 hours following the last dose of the other antiplatelet medication.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 60 mg of ticagrelor as active substance.

Other ingredients are:

Tablet core: mannitol (E421), calcium hydrogen phosphate dihydrate, magnesium stearate (E470b), sodium starch glycollatetype A, hydroxypropyl cellulose (E463).

Tablet coating: titanium dioxide (E171), iron oxide black (E172), iron oxide red (E172), macrogol 400, hypromellose (E464).

The product is available in PVC-PVDC/Al transparent blister (with sun/moon symbols) as described in section 6.5 of the SmPC.

2.2.2. Active Substance

The active substance ticagrelor has already been approved as active substance in Brilique 90 mg film-coated tablets of the same applicant. No new information on the active substance, except batch analysis results of batches used in clinical drug product batches, has been provided within this line extension application. All batches complied with the approved specification.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The aim of the pharmaceutical development was to develop immediate release tablets containing 60 mg of ticagrelor, which meet compendial and other quality standards and are differentiated by colour, size and markings from the existing 90 mg ticagrelor tablets. The potential critical quality attributes (CQAs) identified were: description, identification, assay, degradation products, uniformity of dosage units and

microbiological quality. These are in line with the approved 90 mg tablets, which as explained below, are derived from the same common blend.

The ticagrelor tablet QTPP, in conjunction with knowledge on the physicochemical properties of ticagrelor, was used to direct the formulation development programme.

Ticagrelor is a BCS class IV compound since it has a low soluble active substance (not ionised in the physiological pH range) and exhibits a moderate intrinsic permeability. Therefore, there is potentially a higher risk that changes in formulation and processing parameters can affect clinical performance. Moreover, this low aqueous solubility of ticagrelor leads to an increase of relevance of particle size. This was taken into account during development, and extensive dissolution studies, including solubility studies in human intestinal fluids, were conducted. The formulation development of the 60 mg was based on the 90 mg tablets.

The compatibility of ticagrelor with a range of commonly used pharmaceutical excipients, suitable for tablets was investigated throughout development of Brilique 90 mg tablets 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), hydroxypropyl methylcellulose (as a film former), titanium dioxide (as an opacifier), polyethylene glycol (as a plasticiser), ferric oxide red and black (as a colouring agents) 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 60 mg core tablets is proportional to the composition of the 90 mg core tablets. Only the ingredients of the non-functional coating differ between the 60 mg and 90 mg tablets.

The formulation used during Phase 3 clinical trials is similar to the one intended for marketing. They have identical tablet core composition; the only difference is the non-functional film-coating (white for the phase 3 formulation, pink for the commercial formulation). *In vitro* dissolution studies were conducted, using the approved commercial dissolution method, to demonstrate that the 60 mg (clinical and commercial formulations) and 90 mg tablet strengths exhibit equivalent *in vitro* dissolution performance.

In addition, chemical compatibility with the Phase 3 and commercial coating excipients were studied and confirmed that no degradation products are formed in film-coated tablets on both long-term and accelerated stability.

The 60 mg tablets are presented as round, biconvex, pink, film-coated tablets with a diameter of 8 mm, containing 60 mg of ticagrelor. The tablets are marked with ‘60’ and ‘T’ on one side and plain on the reverse.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except ferric oxide red and black which comply with European requirements. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The manufacturing process development has been evaluated through the use of risk assessment and multivariate design of experiments to identify the critical product quality attributes and critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge from the 90 mg tablets as well as on experience from formulation development, process design and scale-up studies.

The same wet granulation manufacturing process as for the marketed ticagrelor tablet 90 mg was employed. The formulation and the process were optimised using multivariate design of experiments.

Additional studies were performed and nominal values were determined. The knowledge gained from these experimental studies also allowed the definition of a design space for the granulation step and proven acceptable ranges (PARs) for all other unit operations.

The primary packaging is common for this dosage form and identical to the approved packaging of the 90 mg tablets. It consist of a 'push-through' type blister, formed from clear (transparent) unplasticised polyvinyl chloride (PVC), film-coated with polyvinylidene chloride (PVDC). The PVC/PVDC is sealed to hard temper aluminium foil coated with heat seal lacquer. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

Ticagrelor film-coated tablets are manufactured using conventional manufacturing techniques. The manufacturing process consists of eight consecutive steps: dry mixing, wet granulation, drying, milling, lubrication, compression, coating and packaging. The process is considered to be a standard manufacturing process.

Steps and process parameters that are considered critical for the quality of the product were identified. Major steps of the manufacturing process have been validated by a number of studies. As described above, based on the results from the DOE studies a design space for the granulation step, and PARs for all other unit operations have been defined.

The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed design space and PARs.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process. In line with the CHMP guideline on process validation (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1), a process validation scheme to be executed at production scale has been provided in the dossier.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form description, identification (HPLC/UV, or UPLC/UV), identification of ferric oxide (colour test), assay (HPLC or UPLC), degradation products (HPLC or UPLC), dissolution (Ph. Eur.) and uniformity of dosage units (Ph. Eur.). The same requirements apply for shelf-life.

Adequate justifications have been provided for the omission of the tests for identification of polymorphic form chiral identity, water content, residual solvents and microbial limits.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

The analytical methods used have been developed to match the ones used from the 90 mg tablets. These have been adequately described and, where necessary, appropriately validated in accordance with the ICH guidelines to demonstrate their suitability for the analysis of the 60 mg tablet strength. Since the same reference standards as currently used for the 90 mg tablet strength are used, no additional information has been provided within this line extension application.

Batch analysis results are provided for eighteen commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of three commercial batches of ticagrelor 60 mg manufactured at the proposed production site and stored under long term conditions for 24 months at 25 ºC / 60% RH, 24 months at 30°C/75% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing, with the addition of intaglation for the commercial tablets, and were packed in the primary packaging proposed for marketing (PVC/PVDC blister packs) or the commercial aluminium foil bags used for bulk pack of the tablets.

The parameters studied were the same as at shelf life, with the addition of water content and hardness. All the tests are performed at each time point with the exception of the water content test and microbial limits test. The analytical procedures used are stability indicating.

No significant changes in description, assay, degradation products, dissolution, water content and microbial quality was observed in the batches stored in PVC/PVDC blister packs at any of the conditions tested.

Stability data from tablets stored in aluminium foil bags showed little or no change in description, assay, degradation products, dissolution and water content after 12 months storage at 30 °C / 75% RH.

In addition, a photostability study on ticagrelor 60 mg film-coated tablets packed in PVC/PVDC blisters and stored directly exposed to light for 5 days was conducted. Samples were tested for description, assay, degradation products and dissolution. Little or no change was observed in the parameters tested.

In conclusion, based on available stability data, the proposed holding time of 12 months in the commercial bulk pack and the proposed shelf-life of 36 months with no special storage conditions, as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

No new information on the active substance has been provided within this line extension application. The active substance has already been approved as active substance in Brilique 90 mg film-coated tablets of the same applicant.

Satisfactory documentation has been provided to confirm the acceptable quality of this new strength of ticagrelor tablets and no major objections have been raised during evaluation.

Information on development, manufacture and control of the 60 mg tablets, which was based on the already approved 90 mg tablets, has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product, which resulted in the establishment of a design space for the granulation step and PARs for the other unit operations. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical studies in support of the present Extension Application and Type II Variation Application have not been provided and it was considered acceptable.

A comprehensive nonclinical package, including pharmacology, safety pharmacology, pharmacokinetics, and toxicology studies, supported the initial marketing authorization application (MAA) of ticagrelor. These studies have already been assessed and accepted previously as part of the initial MAA.

2.3.2. Ecotoxicity / environmental risk assessment

The dossier on the environmental risk was completed before. The risk assessment for the STP, the aquatic, the groundwater and the sediment compartments could be completed. No risk was anticipated for each of these compartments. Based on the submitted information, it was concluded that ticagrelor is not PBT, nor vPvB.

Table 1-Summary of main study results

Substance (INN / Invented Name): ticagrelor			
CAS-number (if available): 274693-27-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} > 4.0 (at pH 5, 7, 9)	Potential PBT (Y)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log D_{ow}	> 4.0	
	BCF	< 6.4 L/kg	not B
Persistence	ready biodegradability	not ready	
	DegT50	$DT_{50,\ water}$ = 4.7/6.2 d $DT_{50,\ sediment}$ = 49/66 d $DT_{50,\ system}$ = 23/42 d	DT_{50} values corrected to 12°C. Conclusion: not P
Toxicity	NOEC algae NOEC crustacea NOEC fish	0.82 mg/L 0.53 mg/L ≥ 1.8 mg/L	not T
	CMR	not investigated	potentially T
PBT-statement :	ticagrelor is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, default F_{pen}	0.9	µg/L	> 0.01 threshold (Y)
Other concerns (e.g. chemical class)			(N)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OPPTS 835.1110 OECD 308	K_d = 1571 L/kg K_{oc} = 849 L/kg	%o.c. not determinedin OPPTS study; mean of 12 values from OECD308

Ready Biodegradability Test	OECD 301F	not ready			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 2.2/2.9 d $DT_{50, sediment}$ = 23/31 d $DT_{50, whole\ system}$ = 11/20 d shifting to sediment > 10%			DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Selenastrum capricornutum*	OECD 201	NOEC	0.82	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.53	mg/L	growth
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	≥ 1.8	mg/L	Mortality, length, hatchability, dry weight
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50	> 100	mg/L	respiration
Phase IIb Studies					
Bioaccumulation/ *Oncorhynchus mykiss*	OECD 305	BCF	< 6.4	L/kg	total radioactivity, not lipid normalised
Sediment dwelling organism/ *Chironomus riparius*	OECD 218	NOEC	52.6	mg/kg	normalised to 10% o.c.; mean development rate; sex ratio; total emergence

2.3.3. Conclusion on the non-clinical aspects

No new nonclinical studies were provided. The pharmacological, pharmacokinetic and toxicological properties of ticagrelor are well known and have been adequately summarised in the Non-clinical Overview. Therefore the CHMP considered the approval of current application for ticagrelor acceptable from a non-clinical point of view.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

In connection with the examination of the current application, the Committee for Medicinal Products for Human Use has asked for an GCP inspection to be carried out of the conduct of the clinical study D5132C00001 in accordance with Article 57 of Council Regulation (EC) No. 726/2004 and Article 15 of Directive 2001/20/EC. The scope of inspection was to verify the compliance with GCP and applicable regulations.

Inspections concerned a site in Chile, in which 70 patients have been randomised, a site in Colombia, in which 83 have been randomised, and another site in Colombia, in which 70 have been randomised. The entire study included 1161 sites and included 21162 patients.

Despite the fact of serious GCP departures observed during the inspections, the composite of CV death, non-fatal MI, or non-fatal stroke used in the setting of the primary efficacy variable were so evident and its collection process so robust that the deficiencies observed have no impact on the demonstration of this variable as well as the safety aspects. Other secondary objectives and variables may be impacted in a limited way if the data are used in their calculations. The number of subjects at the sites inspected (226)

compared to the total number of subjects enrolled in the whole trial (21,326) was representing 1,06% of the data collected, so even if the data were not used for the analysis, the impact in the final results would be marginal.

The Inspection Report concluded that efficacy and safety data submitted for the inspection were considered acceptable for the evaluation in support of the current application for the marketing authorisation of Brilique.

The CHMP concurred with the conclusions of the Inspection Report.

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

Table 2 Studies included in this Summary of Clinical Pharmacology

Study Number	Study Design	Subjects type, No. (M/F), age: mean (range)	Treatments (dosage form, route, duration)	Objectives
D5132C00001 (PEGASUS):	Multinational, randomised, double-blind, placebo-controlled, parallel group study	Patients with a history of MI and high risk of developing atherothrombotic events Study population: 21162 (16102/5060) Age 65 y (47-95) PK population: 4426 (3485/941) Age 64 y (50-89)	Ticagrelor 90 mg bd, ticagrelor 60 mg bd or placebo bd. All patients received low-dose ASA 75 mg to 150 mg od throughout the study.	**Population PK objectives:** 1. To develop a population model describing the plasma PK of ticagrelor and AR-C124910XX, including associated interindividual variability and residual unexplained variability following oral ticagrelor administration of 60 mg or 90 mg bd. 2. To evaluate the impact of covariates on CL/F of ticagrelor and AR-C124910XX. 3. To derive individual predictions of exposure ($C_{ss,av}$) of ticagrelor and AR-C124910XX. **Exposure-response objective:** To graphically evaluate the possible relationships between $C_{ss,av}$ of ticagrelor and AR-C124910XX and the primary efficacy endpoint (CV death, MI, stroke) as well as key safety endpoint (TIMI Major bleeding).
D5130L00012	Multicentre, randomised, open label, multiple dose, crossover study in the US	Hispanic patients with stable CAD 40 (28/12) Age 64 y (42-88)	Treatment A: Ticagrelor 180 mg loading dose, then 90 mg bd for 7, 8 or 9 days. Treatment B: Clopidogrel 600 mg loading dose, then 75 mg od for 7, 8 or 9 days. All patients received low-dose ASA.	Primary: On-treatment platelet reactivity of ticagrelor vs clopidogrel at 2 h post-loading dose, as measured by PRU. Secondary: PRU at 0.5 and 8 h post-loading dose, and 2 and 8 h on Day 7 and the end of the dosing interval on Day 8; to evaluate plasma concentration of ticagrelor and its active metabolite AR-C124910XX at times of the PRU assessment

- ASA Acetylsalicylic acid; bd twice daily; CAD Coronary artery disease; CL/F apparent clearance; $C_{ss,av}$ average plasma concentration at steady state; CV cardiovascular; F female; M male; MI myocardial infarction; od once daily; PK pharmacokinetic; PRU $P2Y_{12}$ reaction units; TIMI Thrombolysis in Myocardial Infarction Study Group; US United States

2.4.2. Pharmacokinetics

Within initial MAA for ticagrelor only the 90 mg tablets were authorised. The additional indication concerned the 60 mg strength. The MAH intended to market an intagliated, pink 60 mg commercial tablet, which differed slightly from the plain, white 60 mg clinical tablet used in the clinical study PEGASUS.

The PEGASUS study evaluated 2 doses of ticagrelor: 90 mg bd (using the already marketed 90 mg tablet formulation) and 60 mg bd (using a 60 mg clinical tablet formulation). Based on the efficacy and safety data from PEGASUS, 60 mg bd was the proposed recommended dose for use in the proposed new indication ("*patients with a history of the MI at high risk of atherothrombotic events*").

According to the applicant, sufficient bridging data are available between the currently marketed formulation (90mg), the formulation used in the PEGASUS study and the final commercial formulation. Therefore, no additional biopharmaceutical or other pharmacokinetic/pharmacological studies were considered needed and reference was made to the original dossier of ticagrelor. The CHMP agreed with this.

Additionally, the applicant submitted interaction study D5130L00012 which provided important information on the PK and PD of ticagrelor compared with clopidogrel in a Hispanic population. This study was not included in the original MAA for ticagrelor.

2.4.3. Pharmacodynamics

A Randomized, Open Label, Multiple Dose, Crossover, Multiple Center Study of the Antiplatelet Effects of Ticagrelor versus Clopidogrel in Hispanic Patients with Stable Coronary Artery Disease

Primary objective: The primary objective of the study was to compare the platelet reactivity of ticagrelor versus clopidogrel at the 2-hour time point after a loading dose of each, as measured by $P2Y_{12}$ reaction units (PRU) using VerifyNow™ (Accumetrics, San Diego, US) in Hispanic patients with stable coronary artery disease (CAD) on chronic low-dose ASA.

Key secondary objectives: Compare the platelet reactivity of ticagrelor versus clopidogrel at the 0.5- and 8-hour time points after a loading dose of each, and at the 2-and 8- hour time points on Day 7, and at the end of the dosing interval (12 hours after last evening dose of ticagrelor and 24 hours after the last morning dose of clopidogrel) on Day 8, as measured by PRU, and to evaluate plasma concentration of ticagrelor and its active metabolite AR-C124910XX in Hispanic patients at times of the PRU assessment.

Population: A total of 53 patients were screened, and 40 enrolled (met all inclusion and no exclusion criteria) from 6 centres in the US. The mean (standard deviation [SD]) age of patients randomised was 63.8 (8.8) years, ranging from 42 to 88 years. There were 18 patients who were ≥65 years old. Twenty-eight patients (70%) were male, and 43.6% of all patients were obese (body mass index >30 kg/m^2).

Design: This was a US multicentre, randomised, open-label, multiple-dose, crossover study of the onset and repeated dose administration antiplatelet effect of ticagrelor compared with clopidogrel with chronic low-dose ASA as background therapy in Hispanic patients aged ≥18 years who had documented stable CAD (stable angina pectoris with objective evidence of CAD). Patients were randomised to receive either Treatment A (clopidogrel 600 mg loading dose followed by 75 mg od for 7, 8, or 9 days) followed by Treatment B (ticagrelor 180 mg loading dose followed by 90 mg bd for 7, 8, or 9 days) or Treatment B followed Treatment A, each separated by a washout period of 10 to 14 days.

Results: The mean (SD) PRU at 2 hours after loading dose was 34.1 (31.6) and 201.3 (87.5) following administration of ticagrelor and clopidogrel. The least squares (LS) mean PRU at 2 hours after loading dose was lower for patients who received ticagrelor compared with clopidogrel resulting in a difference in LS means between treatment groups of -167.2 (95% CI: -197.0, -137.4) that was statistically significant ($p<0.001$). At all post-dose time points following the loading and multiple doses, reactivity was lower for ticagrelor vs clopidogrel ($p<0.001$).

In addition, a larger percentage reduction from baseline in PRU activity was observed for patients who received ticagrelor compared with clopidogrel, resulting in a difference in LS means between treatment groups of 57.6 percentage points (95% CI: 48.4, 66.8) that was statistically significant ($p<0.001$). The LS mean percent inhibition of platelet $P2Y_{12}$ receptor activity from baseline platelet function independent of $P2Y_{12}$ inhibition was 87.9% for patients who received ticagrelor compared with 29.2% for those who received clopidogrel. The difference in LS means was statistically significant (difference: 58.7%; 95% CI: 49.9%, 67.5%; $p<0.001$).

Summary statistics and graphical presentations of plasma concentrations for ticagrelor (**Error! Reference source not found.**) and its AR-C124910XX metabolite (Figure 2) indicated similar exposure to those observed in previous studies of ticagrelor in Caucasians.

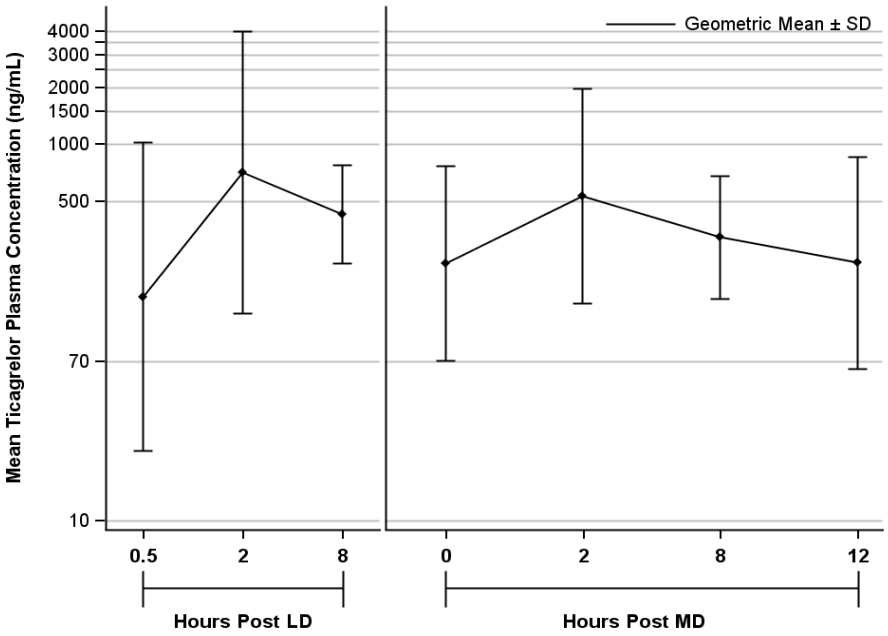


Figure 1 Geometric mean ticagrelor plasma concentrations after the loading and maintenance doses, by protocol time (PK analysis set) (D5130L00012)

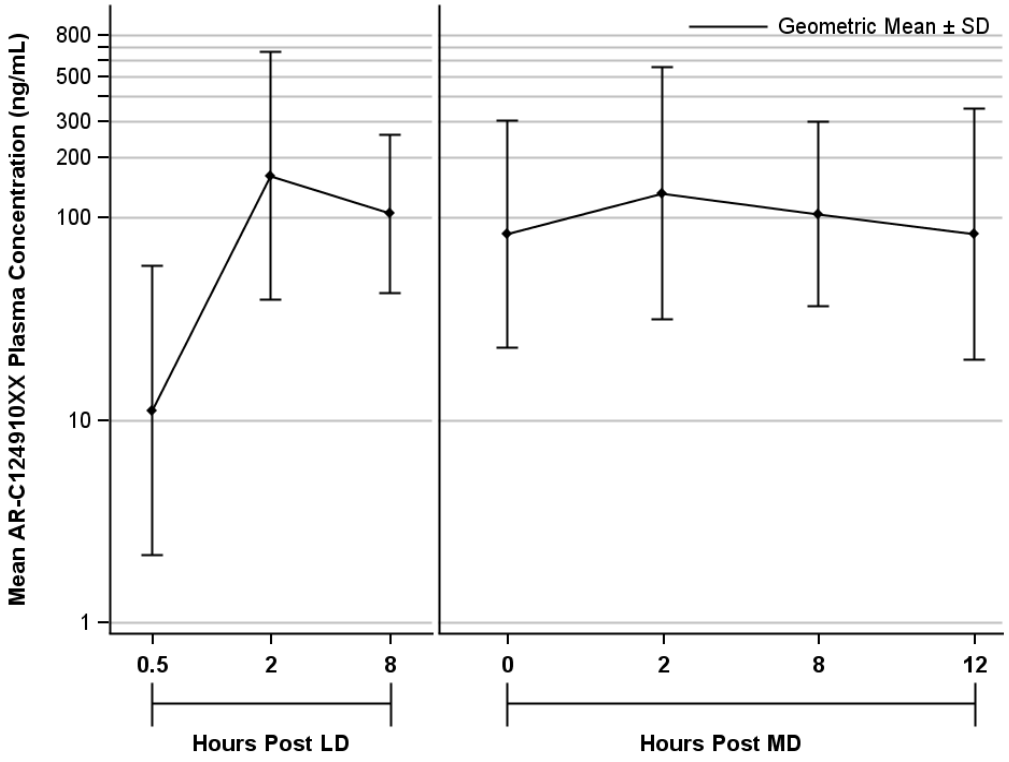


Figure 2 Geometric mean AR-C124910XX plasma concentrations after the loading and maintenance doses, by protocol time (PK analysis set) (D5130L00012)

2.4.4. Discussion on clinical pharmacology

A small PD study was submitted within the current application. The primary objective of the study was to compare the platelet reactivity of ticagrelor versus clopidogrel, as measured by P2Y12 reaction units (PRU) in Hispanic patients with stable CAD on chronic low dose ASA. Platelet reactivity as measured by PRU was decreased to a greater extent after a loading dose and maintained throughout the maintenance dose of ticagrelor compared with clopidogrel at all-time points. Plasma concentrations for ticagrelor and its metabolite AR-C124910XX indicated similar exposure to those observed in previous studies with ticagrelor. Ticagrelor was well tolerated and safety findings were consistent with the adverse event profile of this medicinal product.

2.4.5. Conclusions on clinical pharmacology

In a small PD study (D5130L00012) in a Hispanic population submitted within the current application platelet reactivity as measured by PRU was decreased to a greater extent after a loading dose and maintained throughout the maintenance dose of ticagrelor compared with clopidogrel at all-time points. Ticagrelor was well tolerated and safety findings were consistent with the adverse event profile of this medicinal product.

No additional biopharmaceutical or other pharmacokinetic/pharmacological studies were submitted or considered needed as the reference was made to the original MAA of ticagrelor.

2.5. Clinical efficacy

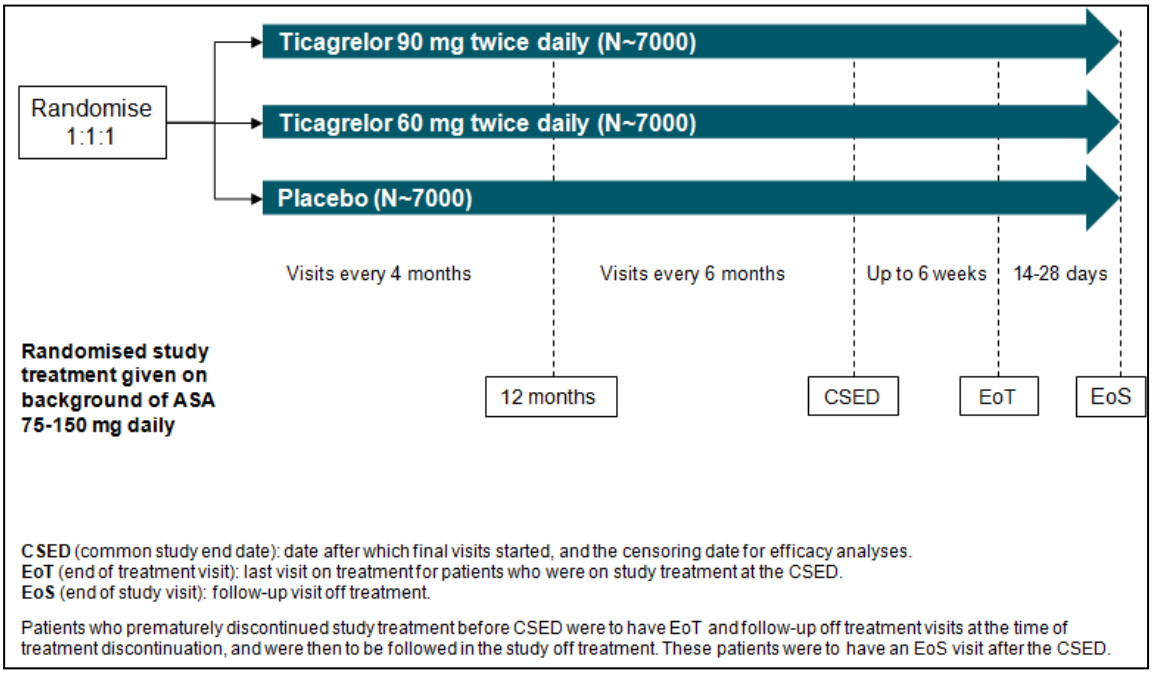
2.5.1. Dose response study

No dose-response studies have been conducted for the new indication. Alternatively, the company has investigated two different dosing regimens of ticagrelor in the pivotal PEGASUS study (60 mg and 90 mg bid). The rationale for testing of the ticagrelor 90 mg bid dose was well supported by the dose finding studies from the initial MAA (DISPERSE and DISPERSE 2 trials). Ticagrelor 60 mg bid dose has not been directly tested for efficacy prior to the PEGASUS study but, based on PK and PD modelling of IPA response and clinical findings in the DISPERSE study, it was expected to provide greater mean platelet inhibition and less variability than clopidogrel 75 mg daily. Lower ticagrelor doses were also considered but modelling predicted that, e.g. ticagrelor 45 mg bd would not generate a sustained IPA level greater than clopidogrel 75 mg and, furthermore, intra-individual variability in IPA increases with decreasing dose of ticagrelor and would be 2-3 times greater with 45 mg than with 90 mg bd. As there is a time-varying risk of recurrent thrombotic events following an MI (lower after 1 year than during the first year after a MI), it was postulated that a lower intensity of platelet inhibition than utilised in the ACS setting may be sufficient to prevent major cardiovascular events during chronic therapy.

2.5.2. Main study

A Randomised, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction [PEGASUS: PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group]

Methods



Patients in PEGASUS were randomised (in a 1:1:1 ratio) to 1 of 3 treatment groups: ticagrelor 90 mg BID ticagrelor 60 mg BID, or placebo bd. No loading dose was given. Randomised study drug was given on a background of ASA at a dose between 75 and 150 mg OD. The parallel-group design, along with an actual median treatment duration of 29 months and a maximum treatment duration of 48 months, permitted the assessment of long-term efficacy and safety outcomes.

The common study end date (CSED) was the censoring date for efficacy analyses, including events occurring on or prior to CSED. At least the target number of adjudicated primary events (ie, 1360) was to be reached on or before the CSED. On 12 May 2014, the CSED was set for 14 September 2014. Final visits were as follows:

- Patients who were on study drug when the CSED was reached were to attend an End of Treatment visit (EoT) as their last visit on treatment. A follow-up visit off-treatment took place 14 to 28 days after the EoT, and for these patients, this visit was also their end of study (EoS) visit.
- Patients who prematurely permanently discontinued study drug before the CSED were to have their EoT and follow-up off treatment visits at the time of study drug discontinuation, and were then to be followed in the study off treatment. These patients were to attend an EoS visit (preferably in person) after the CSED.
- 'Lost to follow-up' was defined as unknown vital status after CSED for patients who had not withdrawn consent. Searches were conducted in publicly available sources for the vital status of patients who withdrew consent or whom the investigator was unable contact, except in countries where this was prohibited.

Study Participants

Patients were eligible to participate if they were aged 50 years or over, with a history of MI (1 to 3 years prior to randomisation), and had at least 1 of the following risk factors for atherothrombosis: age 65 years or over, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, or chronic non-end-stage renal dysfunction.

Important exclusion criteria reflect current SmPC recommendations and were: planned use of ADP receptor blockers, planned coronary, cerebrovascular, or peripheral arterial revascularisation, CABG in last 5 years, concomitant oral or intravenous therapy with strong CYP3A inhibitors, patients with higher risk of bleeding, history of ischaemic stroke, severe liver disease, renal failure.

Treatments

At Visit 2 (Randomisation), eligible patients were randomly assigned to 1 of 3 treatment groups:

- Ticagrelor 90 mg BID
- Ticagrelor 60 mg BID, or
- Placebo BID.

The 2 ticagrelor tablets administered in the study had different sizes. All patients therefore needed to take 2 tablets bid to guarantee the blinding: (1) ticagrelor 90 mg and ticagrelor 60 mg placebo, (2) ticagrelor 90 mg placebo and ticagrelor 60 mg, or (3) ticagrelor 90 mg placebo and ticagrelor 60 mg placebo.

Randomisation and treatment pack assignment were managed via the central Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) and the first dose of study drug was to be taken as soon as possible at Visit 2. Subsequent maintenance doses were to be taken morning and evening, at approximately 12-hour intervals, for the remainder of the treatment period. Study drug was to be swallowed whole with water. Study drug could be taken with or without food. Study drug was not to be altered (e.g. crushed, put in another vehicle) and was not to be given by nasogastric tube or other routes. Missed doses of ticagrelor or placebo were not to be made up (i.e. if a dose was missed, the next regularly scheduled dose was to be taken and not doubled).

Objectives

The primary objective of the study was to compare the effect of long-term treatment with ticagrelor versus placebo on a background of low-dose ASA (75 to 150 mg daily) on the event rate of the composite of cardiovascular death (CV death), non-fatal MI, or non-fatal stroke in patients with history of MI and high risk of developing atherothrombotic events.

Outcomes/endpoints

Primary endpoint: Time to first occurrence after randomisation of any event from the composite of CV death, MI, or stroke.

Table 3 Efficacy objectives and variables.

	Objectives	Variables
Primary	To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of the composite of CV death, MI, or stroke in patients with history of MI and high risk of developing atherothrombotic events	Time to first occurrence after randomisation of any event from the **composite of CV death, MI, or stroke**
First secondary	To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of CV death in patients with history of MI and high risk of developing atherothrombotic events	Time to occurrence of **CV death** after randomisation
Second Secondary	To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA on the event rate of all-cause mortality in patients with history of MI and high risk of developing atherothrombotic events	Time to occurrence of **all-cause mortality** after randomisation
Other efficacy objectives and variables (not under Type I error control)	To compare the effect of long-term treatment with ticagrelor vs. placebo on a background of ASA in patients with history of MI and high risk of developing atherothrombotic events on the following:	Time to first occurrence after randomisation of:
	• Event rate of the composite of CV death, MI, stroke, or urgent coronary revascularisation.	• Any event from composite of CV death, MI, stroke, or **urgent coronary revascularisation**
	• Event rate of the composite of CV death or coronary or cerebrovascular arterial thrombosis hospitalisation (including MI, stroke, urgent coronary revascularisation, unstable angina, or transient ischaemic attack)	• Any event from the composite of CV death or **coronary or cerebrovascular arterial thrombosis hospitalisation**. The individual components were also to be examined in an analogous manner
	• Event rate of the composite of coronary heart disease (CHD) death, MI, or stroke	• Any event from the composite of **CHD death**, MI, or stroke. The individual component CHD death was also to be examined in an analogous manner
	• Evaluate **net clinical benefit** of long-term treatment with ticagrelor vs placebo on a background of ASA	• Any event from the **composite of CV death, MI, stroke, or TIMI Major bleeding**
	• Incidence of coronary stent thrombosis	• **Coronary stent thrombosis**

ASA Acetylsalicylic acid ; CHD Coronary heart disease; CV Cardiovascular; MI Myocardial infarction; TIMI Thrombosis in Myocardial Infarction

Secondary endpoints: CV death and all-cause mortality.

The primary composite endpoint and secondary endpoints (CV death and all-cause mortality) were part of the hierarchical confirmatory statistical testing under type I error control.

Sample size

PEGASUS was an event-driven study. The expected primary composite efficacy event rate was 3.5%/12 months. The assumed underlying relative risk reduction (RRR) for ticagrelor was 20% (equivalent to a HR of 0.7971). Using IPA data from the DISPERSE study (Husted et al 2006) and assuming that the log HR was proportional to the ratio of mean IPA for the 60 mg dose relative to the 90 mg dose, an estimated HR for ticagrelor 60 mg of 0.814 was obtained. Under the above assumptions, with 24 months accrual period and a 14-month follow-up period, randomisation of 21,000 patients was expected to yield 1360 primary events (518, 425, and 417 in the placebo, 60 mg, and 90 mg group, respectively). If there were 2 interim efficacy analyses by the IDMC, this would provide 89.2% power (935 events) for 90 mg versus placebo

and 82.5% power (943 events) for 60 mg versus placebo at 2.59% significance level. The sample size was based on 14 months minimum follow-up, but the study could be stopped after 12 months of minimum follow-up if the targeted number of events had been reached. Sample size calculation was considered acceptable. The final HR for the main efficacy endpoint versus placebo was 0.85 instead of the predicted 0.78, but allowed for obtaining statistically significant results.

Randomisation

Treatment allocation was double-blind. Randomisation and treatment pack assignment were managed via the central Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS).

Blinding (masking)

Since the ticagrelor 90 mg and 60 mg tablets are different sizes, patients had to take 2 tablets BID using matching placebo tablets to maintain the blind.

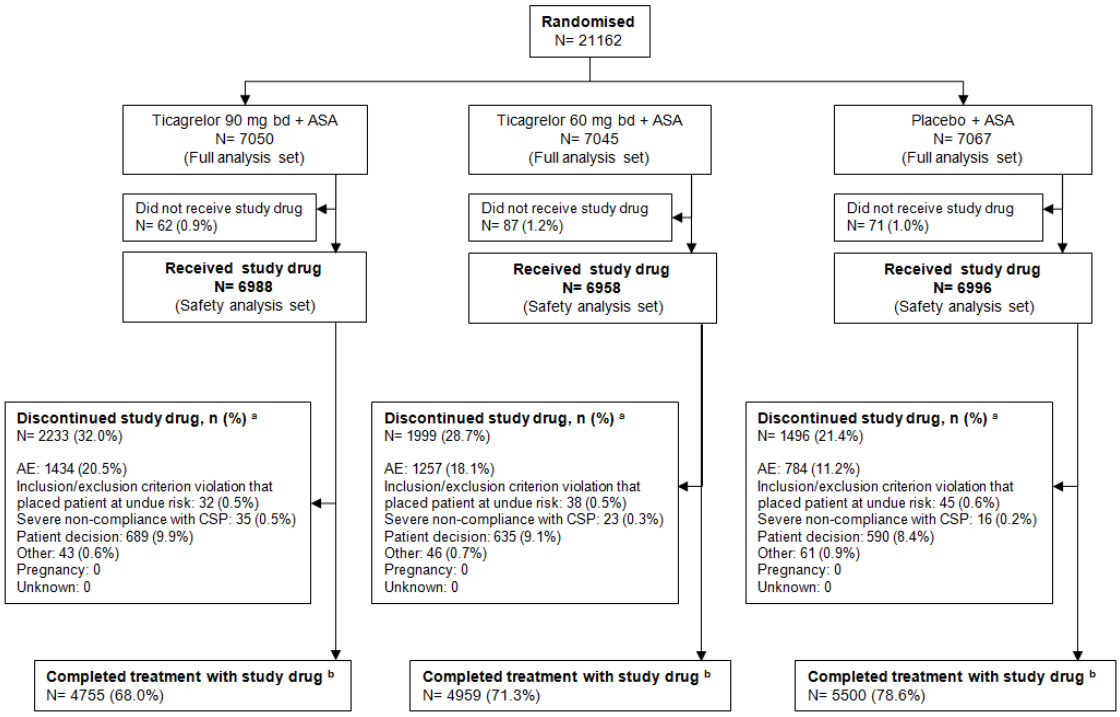
Statistical methods

Statistical methods in PEGASUS were considered acceptable. An interim analysis was conducted. The adjusted significance level for each dose-placebo comparison of the primary endpoint in the final analysis was 0.02598. A Hierarchical testing procedure was applied. The primary endpoint was significant for both doses (p=0.0080 for ticagrelor 90 mg vs. placebo and p=0.0043 for ticagrelor 60 mg vs. placebo). Then CV death was tested at significance level 0.02478. CV death was not significant for any of the two doses. Therefore, the hierachical testing was stopped and the analysis of all-cause mortality had to be considered exploratory (anyway it was not statistically significant for any of the doses).

Results

Participant flow

A number of 100000 patients were screened of whom approximately 54500 patients met the main inclusion criteria of MI 1-3 years prior, age ≥50 years and ≥ 1 or more additional risk factors. Approximately 15000 patients did not fulfill ≥ 1 exclusion criteria of which 4500 were related to bleeding.



Source: CSR Table 11.1.1.1.1

The Full Analysis Set includes all randomised patients. The Safety Analysis Set includes all patients who received at least 1 dose of ticagrelor or placebo and for whom post-dose data are available.

[a] Percentages are calculated from the number of patients who received study drug. All other percentages are calculated from the number of patients randomised.

[b] Patients who did not prematurely discontinue study drug, or who died while on study drug.

ASA Acetylsalicylic acid; bd Twice daily; CSP Clinical Study Protocol

Figure 3 Patient disposition: study drug (full analysis set and safety analysis set

In this study, patients who prematurely permanently discontinued treatment with study drug, but did not withdraw from the study, continued to be followed up for SAEs and study endpoint events.

Permanent discontinuations occurred more frequently in the ticagrelor 90 mg (32.0%; n=2233), and ticagrelor 60 mg (28.7%; n=1999) groups than in the placebo group (21.4%; n=1496). The hazard ratios for permanent discontinuations showed a 62% and 42% increase for the comparison of the 90 mg and 60 mg ticagrelor doses versus placebo, respectively (HR 90 mg vs. PBO: 1.62; 95%CI: 1.52 to 1.73) (HR 60 mg vs. PBO: 1.42; 95%CI: 1.33 to 1.52). The higher proportion of patients prematurely permanently discontinued from study drug in both the ticagrelor groups than in the placebo group resulted in lower mean total duration of exposure in the ticagrelor groups (23.9, 25.3, and 27.3 months the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively). The most common reasons for permanent discontinuation of study drug were AEs/SAEs (16.6% of study patients; n=3475) and patient decision (9.1% of study patients; n=1914). The primary cause of the higher rates of permanent discontinuation in the ticagrelor treatment groups than the placebo group were discontinuations due to bleeding events and dyspnoea.

The imbalance in discontinuations was roughly one third of patients receiving ticagrelor (29%-32% discontinuation rate at 3 years; 8-11% absolute increase versus placebo), mainly due to bleeding and dyspnea, was of concern, as these are data came from a selected population with a strict follow-up, and this is followed by a rebound in MACE and deaths. The applicant was requested to calculate the maximum difference in treatment discontinuations (between ticagrelor and placebo) that would still preserve some benefit of ticagrelor in standard practice and to discuss about the external validity and applicability of the PEGASUS results to an unselected population. According to ancillary analyses provided by the Applicant, the observed benefit in extended treatment with ticagrelor was robust for discontinuation percent up to 43% for ticagrelor 60 mg within 3 years, doubtful between 44% to 62% discontinuation rate within 3 years, and not significant if >62% patients discontinue within 3 years. The description of the safety results of PEGASUS in Section 5.1 of the SmPC was updated to include the information, that the rate of discontinuations with ticagrelor 60 mg due to bleeding and dyspnoea was higher in patients >75 years (42%) than in younger patients (range: 23-31%), with a difference versus placebo higher than 10% (42% vs. 29%) in patients > 75 years.

Recruitment

This was an international study, enrolling patients from a wide range of regions and countries. The study enrolled patients at 1164 sites in 31 countries to provide results that would be representative of the world-wide target population.

Conduct of the study

There was 1 global amendment to the CSP (9 March 2011) and 9 local amendments. The global amendment occurred after the start of the study. The primary reason for the global amendment was to stop patients with history of prior ischaemic stroke from receiving study drug as there was, at the time of the amendment, growing data from studies of other antiplatelet drugs (none of them ticagrelor) suggesting that more intensive antiplatelet therapy might pose high risk of intracranial haemorrhage

(ICH) in patients with a history of ischaemic stroke (Morrow et al 2013, Wiviott et al 2007). There were 102 (0.5%) patients with history of stroke randomised to study drug. The global amendment to the study (approximately 4 months following first patient randomised) directed that these patients be discontinued from study drug.

Baseline data

The mean age of the PEGASUS study population was 65.3 years and 12.1% (n=2571) were aged over 75 years. The majority of patients (54%) were ≥65 yrs, 12% were >75 yrs and 76% were male. Mean weight was 82.0 kg (22.6% were <70 kg, 27.1% were >90 kg) and mean BMI was 28.5 kg/m^2. The demographic characteristics of the patients were balanced across the randomised treatment groups.

The population targeted for the PEGASUS study were patients with a documented history of presumed spontaneous MI, with the most recent MI occurring 1 to 3 years prior to randomisation, plus at least 1 additional risk factor and being currently prescribed and tolerating ASA. Regarding additional pre-defined atherothrombotic risk factors: 54% of the patients were aged ≥65 years, 29% had diabetes mellitus requiring medication, 17% had a history of a second prior MI (≥1 year prior to randomisation), 59% had a history of angiographic evidence of multivessel CAD, and 6% had chronic non-end stage renal dysfunction (as reported by the investigator). Almost half of the patients (48%) had 2 or more risk factors for atherothrombosis.

Most of the patients had received previous treatment with (ASA plus) clopidogrel (83.7%), prasugrel (4.4%), ticlopidine (0.5%), and only 0.4% patients had received previous treatment with (ASA plus) ticagrelor.

Table 4 Previous treatment with ADP receptor blocker any time prior to randomisation (full analysis set)

	Number (%) of patients			
Previous treatment	**Ticagrelor 90 mg bd N=7050**	**Ticagrelor 60 mg bd N=7045**	**Placebo N=7067**	**Total N=21162**
Patients previously treated with ADP receptor blocker	6271 (89.0%)	6289 (89.3%)	6285 (88.9%)	18845 (89.1%)
Clopidogrel	5922 (84.0%)	5915 (84.0%)	5878 (83.2%)	17715 (83.7%)
Prasugrel	287 (4.1%)	317 (4.5%)	325 (4.6%)	929 (4.4%)
Ticlodipine	34 (0.5%)	35 (0.5%)	38 (0.5%)	107 (0.5%)
Ticagrelor	31 (0.4%)	26 (0.4%)	38 (0.5%)	95 (0.4%)
Time from last dose to randomisation				
After first dose of study drug[b]	14 (0.2%)	23 (0.3%)	12 (0.2%)	49 (0.2%)
0-7 days	1826 (25.9%)	1816 (25.8%)	1828 (25.9%)	5470 (25.8%)
8-90 days	1243 (17.6%)	1257 (17.8%)	1243 (17.6%)	3743 (17.7%)
3-12 months	1498 (21.2%)	1520 (21.6%)	1540 (21.8%)	4558 (21.5%)
>12 months	1676 (23.8%)	1661 (23.6%)	1645 (23.3%)	4982 (23.5%)

Table 4 Previous treatment with ADP receptor blocker any time prior to randomisation (full analysis set)

	Number (%) of patients			
Previous treatment	**Ticagrelor 90 mg bd N=7050**	**Ticagrelor 60 mg bd N=7045**	**Placebo N=7067**	**Total N=21162**
Unknown	10 (0.1%)	6 (0.1%)	7 (0.1%)	23 (0.1%)

[b]Treatment with open label ADP receptor blocker continued after the first dose of study drug (protocol violation)

If clopidogrel was considered potential treatment for the patient, the study design offered an option for the patient to receive modified blinded study treatment that would ensure the patient would be taking either ticagrelor 90 mg plus ASA or clopidogrel 75 mg plus ASA. This allowed patients to receive optimal medical care while maintaining the integrity of the study drug blind.

Patient included had the following baseline characteristics.

Table 5 Demographic characteristics (full analysis set)

Demographic characteristic		Ticagrelor 90 mg bd N=7050	Ticagrelor 60 mg bd N=7045	Placebo N=7067	Total N=21162
Age (years)	n	7050	7045	7067	21162
	Mean	65.4	65.2	65.4	65.3
	SD	8.4	8.4	8.3	8.3
Sex, n (%)	Male	5368 (76.1%)	5384 (76.4%)	5350 (75.7%)	16102 (76.1%)
	Female	1682 (23.9%)	1661 (23.6%)	1717 (24.3%)	5060 (23.9%)
Race, n (%)	Caucasian	6126 (86.9%)	6077 (86.3%)	6124 (86.7%)	18327 (86.6%)
	Black	109 (1.5%)	128 (1.8%)	116 (1.6%)	353 (1.7%)
	Asian	748 (10.6%)	768 (10.9%)	765 (10.8%)	2281 (10.8%)
	Other	67 (1.0%)	72 (1.0%)	62 (0.9%)	201 (0.9%)

Table 6 Qualifying event and risk factors (full analysis set)

	Number (%) of patients			
Characteristic	**Ticagrelor 90mg bd (N=7050)**	**Ticagrelor 60mg bd (N=7045)**	**Placebo (N=7067)**	**Total (N=21162)**
Time from qualifying MI to randomisation				
<1 year	40 (0.6%)	54 (0.8%)	47 (0.7%)	141 (0.7%)
≥1 to <2 years	4276 (60.7%)	4277 (60.7%)	4286 (60.6%)	12839 (60.7%)
≥2 to ≤3 years	2682 (38.0%)	2667 (37.9%)	2683 (38.0%)	8032 (38.0%)
>3 years	41 (0.6%)	35 (0.5%)	41 (0.6%)	117 (0.6%)
Unknown	4 (0.1%)	2 (0.0%)	0 (0.0%)	6 (0.0%)
Atherothrombotic risk factors for enrolment				
Age ≥65 years	3855 (54.7%)	3755 (53.3%)	3907 (55.3%)	11517 (54.4%)
Diabetes mellitus requiring medication[a]	2006 (28.5%)	2022 (28.7%)	1999 (28.3%)	6027 (28.5%)
History of >1 MI (≥1 year prior to randomisation)	1143 (16.2%)	1168 (16.6%)	1188 (16.8%)	3499 (16.5%)
Multivessel coronary artery disease	4155 (58.9%)	4190 (59.5%)	4213 (59.6%)	12558 (59.3%)
Chronic non-end stage renal dysfunction	428 (6.1%)	403 (5.7%)	423 (6.0%)	1254 (5.9%)
Diabetes Mellitus	2241 (31.8%)	2308 (32.8%)	2257 (31.9%)	6806 (32.2%)
Number of qualifying risk factors for enrollment (≤5)				
0	46 (0.7%)	47 (0.7%)	41 (0.6%)	134 (0.6%)
1	3652 (51.8%)	3676 (52.2%)	3586 (50.7%)	10914 (51.6%)
2	2313 (32.8%)	2315 (32.9%)	2406 (34.0%)	7034 (33.2%)
≥3	1039 (14.7%)	1007 (14.3%)	1034 (14.6%)	3080 (14.6%)

Numbers analysed

The Full Analysis Set (randomised patients) was the only efficacy analysis set defined for PEGASUS included a total of 21162 patients, and was balanced across treatment groups. Only 1% of patients were excluded from the safety analysis set (for failure to receive study drug).

Table 7. Analysis sets

	Number of patients			
	Ticagrelor 90mg bd	Ticagrelor 60mg bd	Placebo	Total
Patients randomized	7050 (100%)	7045 (100%)	7067 (100%)	21162 (100%)
Patients included in full analysis set	7050 (100%)	7045 (100%)	7067 (100%)	21162 (100%)
Patients excluded from full analysis set	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Patients included in safety analysis set[a]	6988 (99.1%)	6958 (98.8%)	6996 (99.0%)	20942 (99.0%)
Patients excluded from safety analysis set (for failure to receive study drug)	62 (0.9%)	87 (1.2%)	71 (1.0%)	220 (1.0%)
Safety analysis set, by study drug received	6988 (99.1%)	6958 (98.8%)	6996 (99.0%)	20942 (99.0%)

Source: Table 11.1.2
a Safety analysis set: all patients who received at least 1 dose of randomised ticagrelor or placebo and for whom post-dose data are available
bd Twice daily.

Outcomes and estimation

Primary outcome: Long-term treatment with ticagrelor was superior to placebo in reducing the event rate of the primary composite endpoint (CV death, MI, and stroke) (Table E14). Primary composite endpoint events on or prior to CSED were reported for 493, 487 and 578 patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 7.8%, 7.8%, and 9.0%: 15% RRR, HR 0.85 (95% CI 0.75, 0.96), p=0.0080 for ticagrelor 90 mg, and 16% RRR, HR 0.84 (95% CI 0.74, 0.95), p=0.0043 for ticagrelor 60 mg.

Table 8. Key efficacy results from PEGASUS – primary and secondary endpoints (full analysis set)

Hierarchy	Endpoint	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
		Patients with events	KM %	HR (95% CI)	p-value	Patients with events	KM %	HR (95% CI)	p-value	Patients with events	KM %
Primary composite endpoint[a]	Composite of CV Death/ MI /Stroke	493 (7.0%)	7.8%	0.85 (0.75, 0.96)	0.0080 (s)	487 (6.9%)	7.8%	0.84 (0.74, 0.95)	0.0043 (s)	578 (8.2%)	9.0%
First secondary endpoint[a] and component of primary endpoint	CV death	182 (2.6%)	2.9%	0.87 (0.71, 1.06)	0.1547	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	0.0676	210 (3.0%)	3.4%
Component of primary endpoint	MI	275 (3.9%)	4.4%	0.81 (0.69, 0.95)	0.0100	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	0.0314	338 (4.8%)	5.2%
Component of primary endpoint	Stroke	100 (1.4%)	1.6%	0.82 (0.63, 1.07)	0.1403	91 (1.3%)	1.5%	0.75 (0.57, 0.98)	0.0337	122 (1.7%)	1.9%
Second secondary endpoint[a]	All-cause mortality	326 (4.6%)	5.1%	1.00 (0.86, 1.16)	0.9851	289 (4.1%)	4.7%	0.89 (0.76, 1.04)	0.1350	326 (4.6%)	5.2%

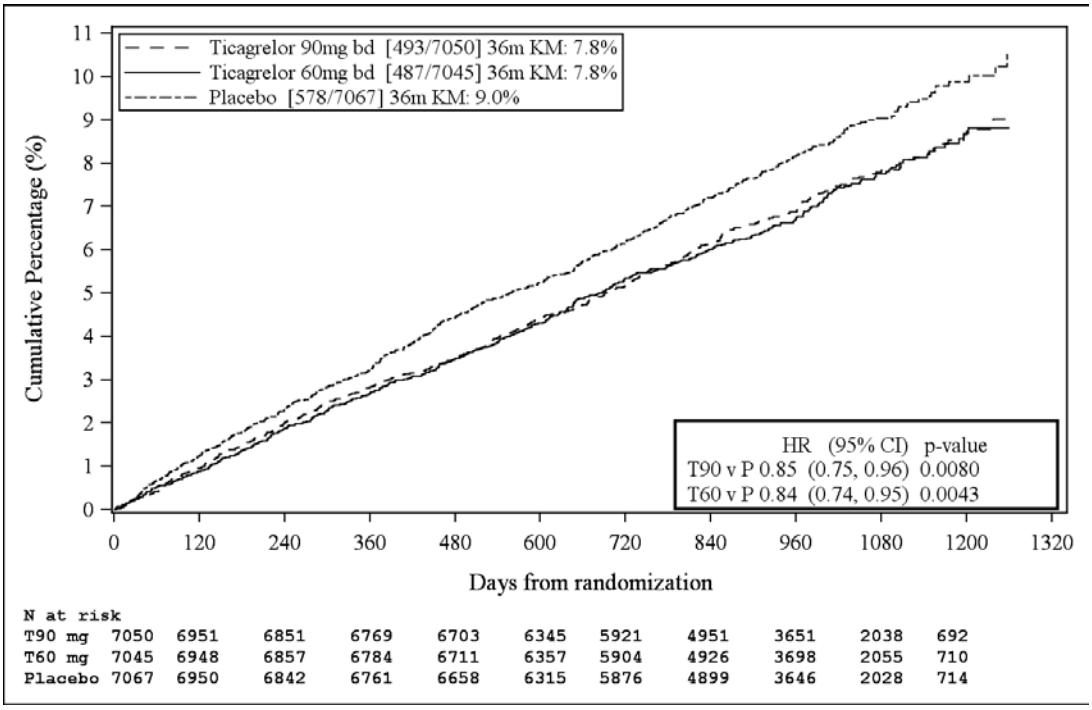
Source: CSR Tables 11.2.1 and 11.2.2
Hazard ratio and p-values calculated separately for each ticagrelor dose vs placebo from Cox proportional hazards model with treatment group as the only explanatory variable.
Kaplan-Meier percentage calculated at 36 months.
The number of first events for the components CV death, MI, and stroke are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.
(s) Indicates statistical significance
[a] Endpoints under Type I error control.
bd Twice daily; CI Confidence interval; CV Cardiovascular; HR Hazard ratio; KM Kaplan-Meier; MI Myocardial infarction; N Number of patients randomised.

Level of significance (adjusted due to interim analysis): Primary endpoint: 0.02598; CV death: 0.02478

The superior treatment effect of ticagrelor compared with placebo was similarly favourable for each of the components of the primary composite endpoint (CV death, MI, and stroke), and driven by MI (275 vs 285 vs 338 MI events with ticagrelor 90 mg, ticagrelor 60 mg and placebo, respectively).

Most (76%) adjudicated MI's were classified as Type 1 (spontaneous); 13% were classified as Type 2 (demand ischaemia, non-thrombotic), and 11% were Types 3 to 5. Type 4a MIs were adjudicated in 2 patients in each treatment group.

The superior treatment effect of ticagrelor compared with placebo was consistent throughout the study with duration of up to 47 months to CSED (median 33 months), as evident from the Kaplan-Meier plot. The curves started to separate at randomisation and continued to separate throughout the study.



Source: see CSR Figure 11.2.1
CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; N Number of patients; P Placebo; T Ticagrelor

Figure 4. Kaplan-Meier plot of primary clinical endpoint (full analysis set)

First secondary variable: Time from randomisation to occurrence of CV death

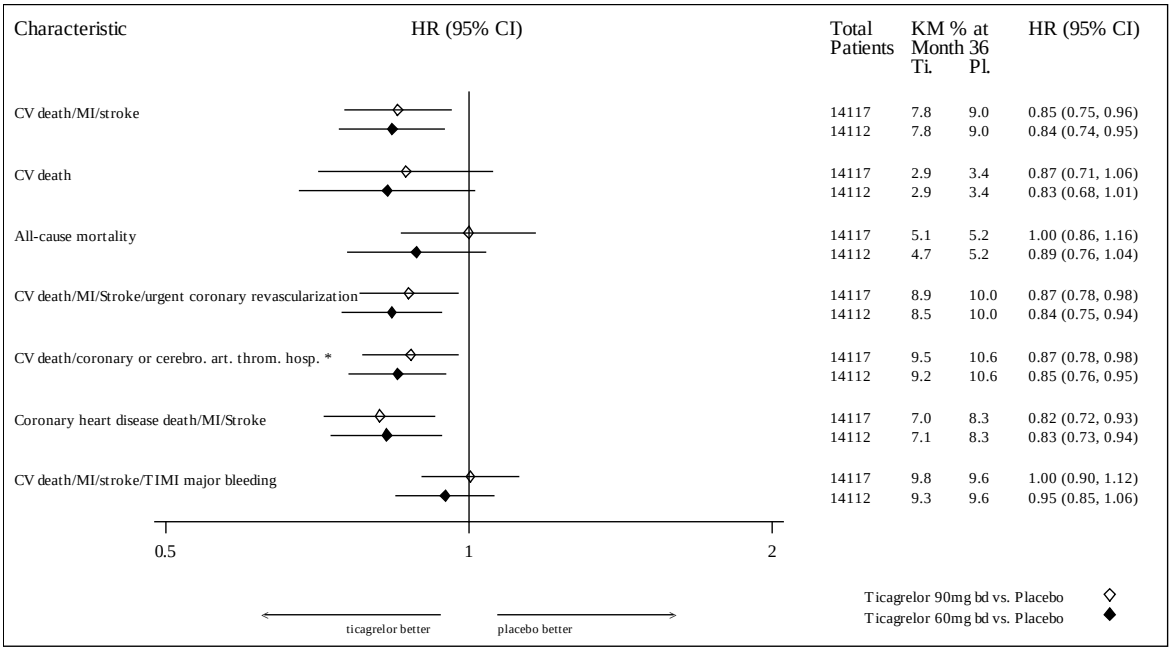
There was a numerical decrease in CV death for both ticagrelor 90 mg (13% RRR, HR 0.87 [95% CI 0.71, 1.06], p=0.1547) and ticagrelor 60 mg (17% RRR, HR 0.83 [95% CI 0.68, 1.01], p=0.0676) compared with placebo, but this endpoint did not reach statistical significance for either dose. Since no difference versus placebo for CV death could be claimed for either of the doses in the hierarchical testing procedure, the testing procedure stopped. The remaining efficacy and safety p-values presented in this report are nominal.

Second secondary variable: Time from randomisation to occurrence of all-cause mortality

The rate of all-cause mortality was similar for ticagrelor 90 mg and placebo: 0% RRR, HR 1.00 (95% CI 0.86, 1.16), p=0.9851, whereas ticagrelor 60 mg showed a numerical reduction in the rate of all-cause mortality: 11% RRR, HR 0.89 (95% CI 0.76, 1.04), p=0.1350.

Other efficacy variables

The other efficacy variables were analysed similarly to the primary and secondary variables, though they were not under type I error control. All individual components of composite efficacy variables were also analysed. **Figure 5** is a forest plot indicating the overall results for the first 4 other efficacy variables. **Figure 5** also includes the primary variable for comparison.



Source: CSR Figure 11.2.15

* CV death/coronary or cerebrovascular arterial thrombosis hospitalisation.
CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; MI Myocardial infarction; Pl Placebo; Ti Ticagrelor; TIMI Thrombolysis In Myocardial Infarction.

Figure 5 Hazard ratios and rates for primary, secondary and other efficacy endpoints (full analysis set)

Stent thrombosis: There was a numerical reduction in the rate of coronary stent thrombosis for both ticagrelor doses compared with placebo: 36% RRR, HR 0.64 (95% CI 0.41, 1.00), p=0.0499 for 90 mg, and 18% RRR, HR 0.82 (95% CI 0.54, 1.23), p=0.3328 for 60 mg.

Table 9. Analysis of time to first stent thrombosis (full analysis set)

Characteristic	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %
Patients with a history of coronary stent implantation or receiving a stent during the study	5651				5695				5661	
Stent thrombosis	32 (0.6%)	0.6%	0.64 (0.41, 1.00)	0.0499	41 (0.7%)	0.8%	0.82 (0.54, 1.23)	0.3328	50 (0.9%)	0.9%

Source: CSR Table 11.2.6.6
Hazard ratios and p-values are calculated separately for each ticagrelor dose vs placebo from Cox proportional hazards model with treatment group as the only explanatory variable.
Kaplan-Meier percentage calculated at 36 months.
For patients with stent thrombosis attributed to a stent implanted before randomisation, time is calculated from the date of randomisation.
For patients with stent thrombosis attributed to a stent implanted after randomisation, time is calculated from the date of stent implantation.
If a patient had more than 1 stent and the stent thrombosis could not be attributed to a specific stent, then it is assumed to have occurred in the most recent stent.
bd Twice daily; CI Confidence interval; HR Hazard ratio; KM Kaplan-Meier; N Number of patients in treatment group

Quality of life (QoL): There was a small increase in patient's health status (EQ-5D VAS) at end of treatment visit versus baseline in all 3 treatment groups, without apparent differences between groups (no statistical analysis provided).

Table 10. Descriptive analysis of EA-5D visual analog scale by visit (FAS)

Characteristic	Time point	Category	Number (%) of patients: Ticagrelor 90mg bd (N=7050)	Ticagrelor 60mg bd (N=7045)	Placebo (N=7067)
Patient's health status at visit	Baseline	n	6844	6831	6866
		Mean	75.6	75.3	75.6
		SD	17.0	17.5	17.3
		Median	80.0	80.0	80.0
		Min	0	0	4
		Max	100	100	100
Patient's health status at visit	36 months	n	1431	1511	1497
		Mean	77.3	77.3	77.1
		SD	14.9	15.5	15.3
		Median	80.0	80.0	80.0
		Min	5	3	0
		Max	100	100	100
	42 months	n	247	244	193
		Mean	74.6	77.0	74.1
		SD	16.1	14.6	16.1
		Median	80.0	80.0	80.0
		Min	9	8	7
		Max	100	100	100
	End of treatment visit	n	5954	5937	6021
		Mean	76.9	77.2	77.3
		SD	16.0	15.8	15.9
		Median	80.0	80.0	80.0
		Min	4	0	0
		Max	100	100	100

Source: Table 11.2.8.2 of the PEGASUS CSR.

PEGASUS study showed superiority of ticagrelor compared with placebo in reducing the event rate of the primary composite endpoint (CV death, MI, and stroke) at 3 years. Primary composite endpoint events on or prior to CSED were reported for 7.8% patients on ticagrelor 90 mg BID, 7.8% patients on ticagrelor 60 mg BID, and 9.0% patients on placebo (K-M estimates at 36 months): 15% RRR, HR 0.85 (95% CI 0.75, 0.96), p=0.0080 for ticagrelor 90 mg, and 16% RRR, HR 0.84 (95% CI 0.74, 0.95), p=0.0043 for ticagrelor 60 mg. In absolute terms, however, the reduction in risk of MACE at 3 years was of only 1.2% (approximately 0.4% reduction per year).

The treatment effect of ticagrelor compared with placebo was similarly favourable for each of the components of the primary composite endpoint (CV death, MI, and stroke), but driven by MI (0.7% of the total 1.2% difference versus placebo). Most (76%) adjudicated MI's were classified as Type 1

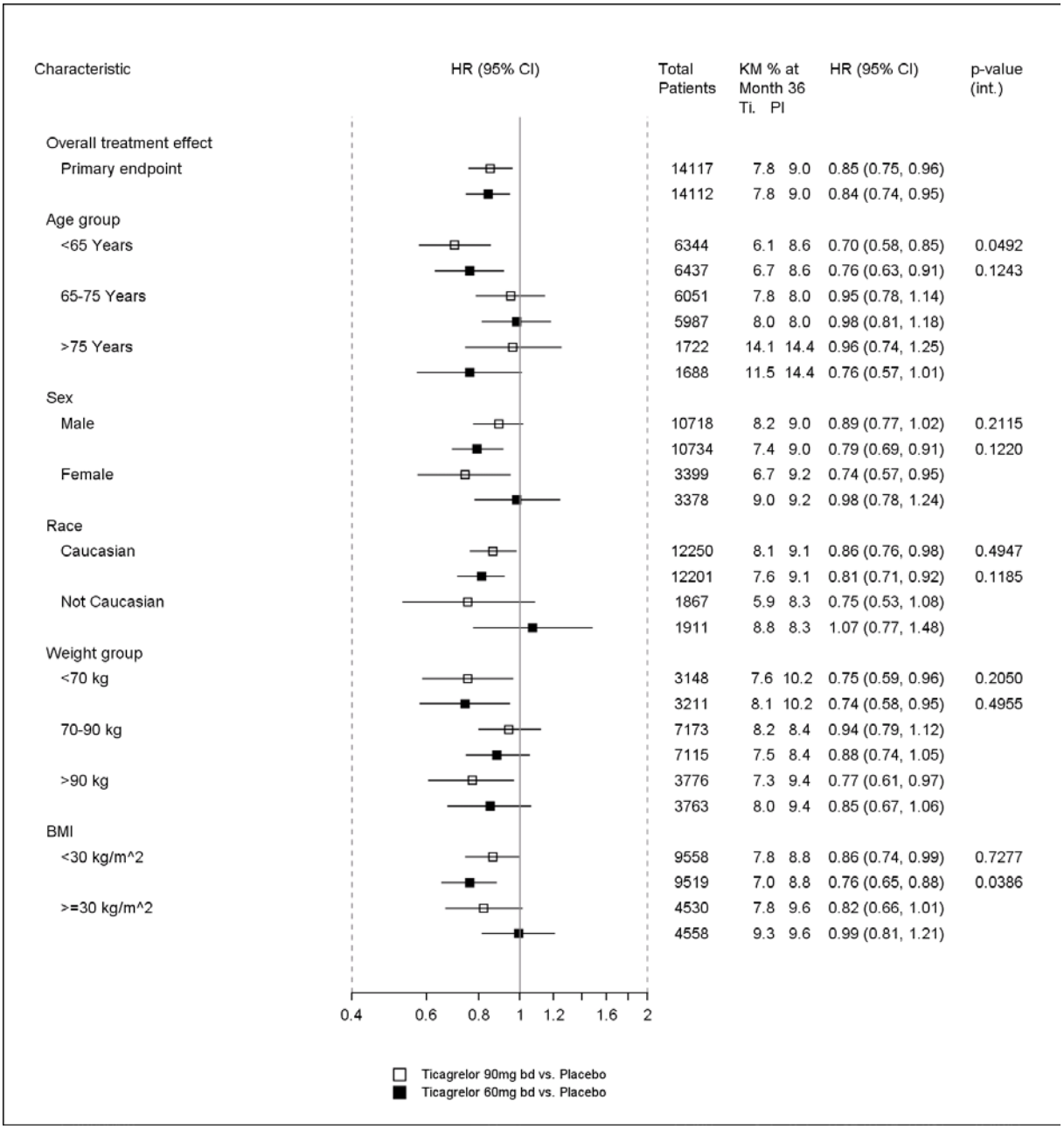
(spontaneous), and the effect was mainly obtained in this type of MI (0.6% of the total 0.7% difference in MI).

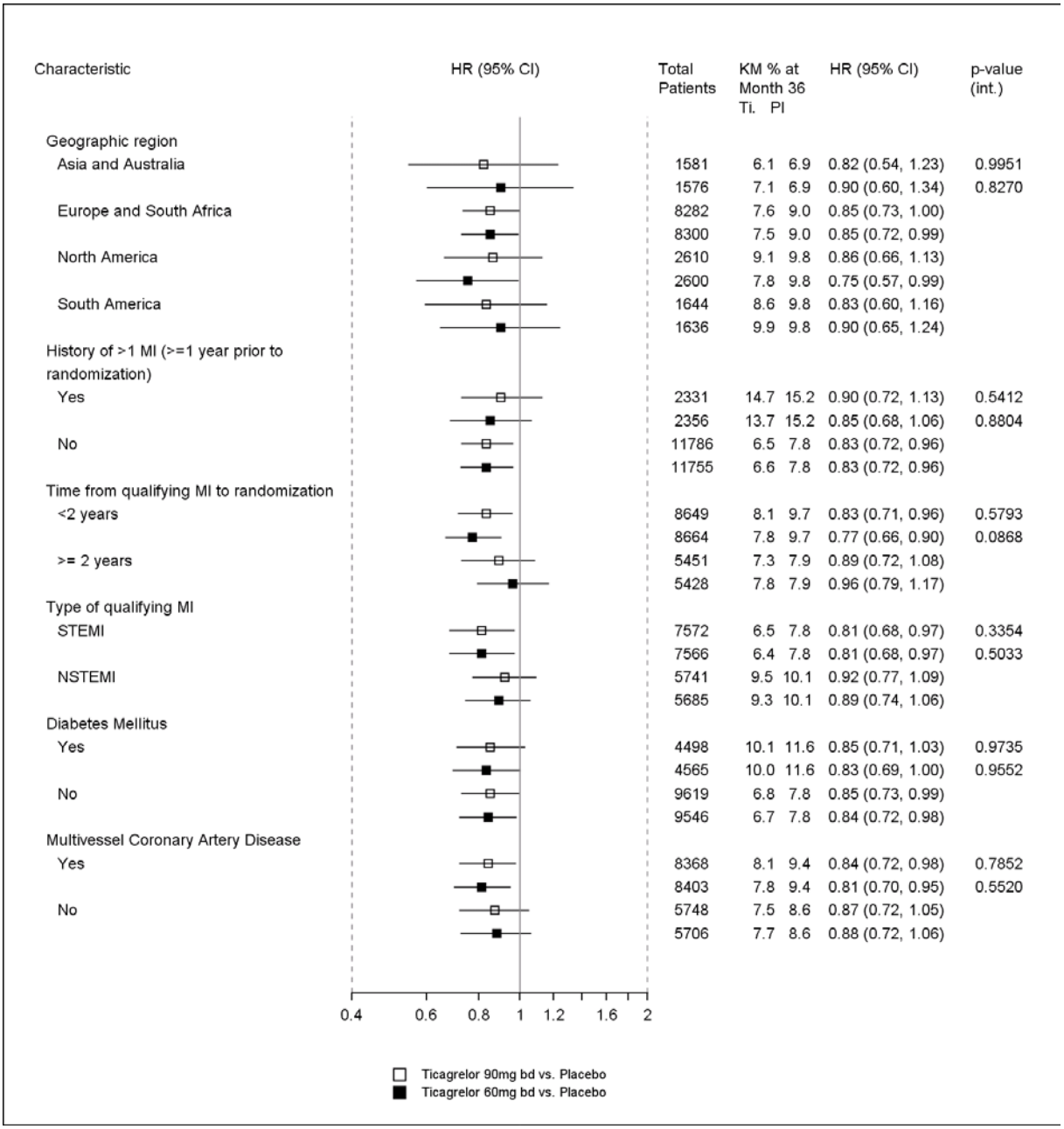
There was a numerical decrease in CV death for both ticagrelor doses compared with placebo, but this endpoint did not reach statistical significance for either dose. The rate of all-cause mortality was similar for ticagrelor 90 mg and placebo, whereas ticagrelor 60 mg showed a numerical reduction in the rate of all-cause mortality that did not reach statistical significance (p=0.1350).

No statistically significant decreases in stent thromboses were found for both ticagrelor doses compared with placebo, although the 90 mg BID seemed more effective in preventing this event than the 60 mg dose: HR 0.64 (95% CI 0.41, 1.00) for 90 mg, and HR 0.82 (95% CI 0.54, 1.23) for 60 mg.

Ancillary analyses

In general, subgroup analyses were consistent with the overall treatment effect for both doses. Differences appear between the 60 mg and 90 mg doses. Focusing on the to be registered 60 mg dose, trend differences appear in the age, sex, race, and time since previous treatment with ADP receptor blocker (see figure below).


Characteristic
HR (95% CI)
Total Patients
KM % at Month 36 Ti. Pl
HR (95% CI)
p-value (int.)
Overall treatment effect
Primary endpoint 14117 7.8 9.0 0.85 (0.75, 0.96)
14112 7.8 9.0 0.84 (0.74, 0.95)
Age group
<65 Years 6344 6.1 8.6 0.70 (0.58, 0.85) 0.0492
6437 6.7 8.6 0.76 (0.63, 0.91) 0.1243
65-75 Years 6051 7.8 8.0 0.95 (0.78, 1.14)
5987 8.0 8.0 0.98 (0.81, 1.18)
>75 Years 1722 14.1 14.4 0.96 (0.74, 1.25)
1688 11.5 14.4 0.76 (0.57, 1.01)
Sex
Male 10718 8.2 9.0 0.89 (0.77, 1.02) 0.2115
10734 7.4 9.0 0.79 (0.69, 0.91) 0.1220
Female 3399 6.7 9.2 0.74 (0.57, 0.95)
3378 9.0 9.2 0.98 (0.78, 1.24)
Race
Caucasian 12250 8.1 9.1 0.86 (0.76, 0.98) 0.4947
12201 7.6 9.1 0.81 (0.71, 0.92) 0.1185
Not Caucasian 1867 5.9 8.3 0.75 (0.53, 1.08)
1911 8.8 8.3 1.07 (0.77, 1.48)
Weight group
<70 kg 3148 7.6 10.2 0.75 (0.59, 0.96) 0.2050
3211 8.1 10.2 0.74 (0.58, 0.95) 0.4955
70-90 kg 7173 8.2 8.4 0.94 (0.79, 1.12)
7115 7.5 8.4 0.88 (0.74, 1.05)
>90 kg 3776 7.3 9.4 0.77 (0.61, 0.97)
3763 8.0 9.4 0.85 (0.67, 1.06)
BMI
<30 kg/m^2 9558 7.8 8.8 0.86 (0.74, 0.99) 0.7277
9519 7.0 8.8 0.76 (0.65, 0.88) 0.0386
>=30 kg/m^2 4530 7.8 9.6 0.82 (0.66, 1.01)
4558 9.3 9.6 0.99 (0.81, 1.21)
0.4
0.6
0.8
1
1.2
1.6
2
Ticagrelor 90mg bd vs. Placebo
Ticagrelor 60mg bd vs. Placebo


Characteristic
HR (95% CI)
Total Patients
KM % at Month 36 Ti. PI
HR (95% CI)
p-value (int.)
Geographic region
Asia and Australia 1581 6.1 6.9 0.82 (0.54, 1.23) 0.9951
1576 7.1 6.9 0.90 (0.60, 1.34) 0.8270
Europe and South Africa 8282 7.6 9.0 0.85 (0.73, 1.00)
8300 7.5 9.0 0.85 (0.72, 0.99)
North America 2610 9.1 9.8 0.86 (0.66, 1.13)
2600 7.8 9.8 0.75 (0.57, 0.99)
South America 1644 8.6 9.8 0.83 (0.60, 1.16)
1636 9.9 9.8 0.90 (0.65, 1.24)
History of >1 MI (>=1 year prior to randomization)
Yes 2331 14.7 15.2 0.90 (0.72, 1.13) 0.5412
2356 13.7 15.2 0.85 (0.68, 1.06) 0.8804
No 11786 6.5 7.8 0.83 (0.72, 0.96)
11755 6.6 7.8 0.83 (0.72, 0.96)
Time from qualifying MI to randomization
<2 years 8649 8.1 9.7 0.83 (0.71, 0.96) 0.5793
8664 7.8 9.7 0.77 (0.66, 0.90) 0.0868
>= 2 years 5451 7.3 7.9 0.89 (0.72, 1.08)
5428 7.8 7.9 0.96 (0.79, 1.17)
Type of qualifying MI
STEMI 7572 6.5 7.8 0.81 (0.68, 0.97) 0.3354
7566 6.4 7.8 0.81 (0.68, 0.97) 0.5033
NSTEMI 5741 9.5 10.1 0.92 (0.77, 1.09)
5685 9.3 10.1 0.89 (0.74, 1.06)
Diabetes Mellitus
Yes 4498 10.1 11.6 0.85 (0.71, 1.03) 0.9735
4565 10.0 11.6 0.83 (0.69, 1.00) 0.9552
No 9619 6.8 7.8 0.85 (0.73, 0.99)
9546 6.7 7.8 0.84 (0.72, 0.98)
Multivessel Coronary Artery Disease
Yes 8368 8.1 9.4 0.84 (0.72, 0.98) 0.7852
8403 7.8 9.4 0.81 (0.70, 0.95) 0.5520
No 5748 7.5 8.6 0.87 (0.72, 1.05)
5706 7.7 8.6 0.88 (0.72, 1.06)
0.4
0.6
0.8
1
1.2
1.6
2
Ticagrelor 90mg bd vs. Placebo
Ticagrelor 60mg bd vs. Placebo

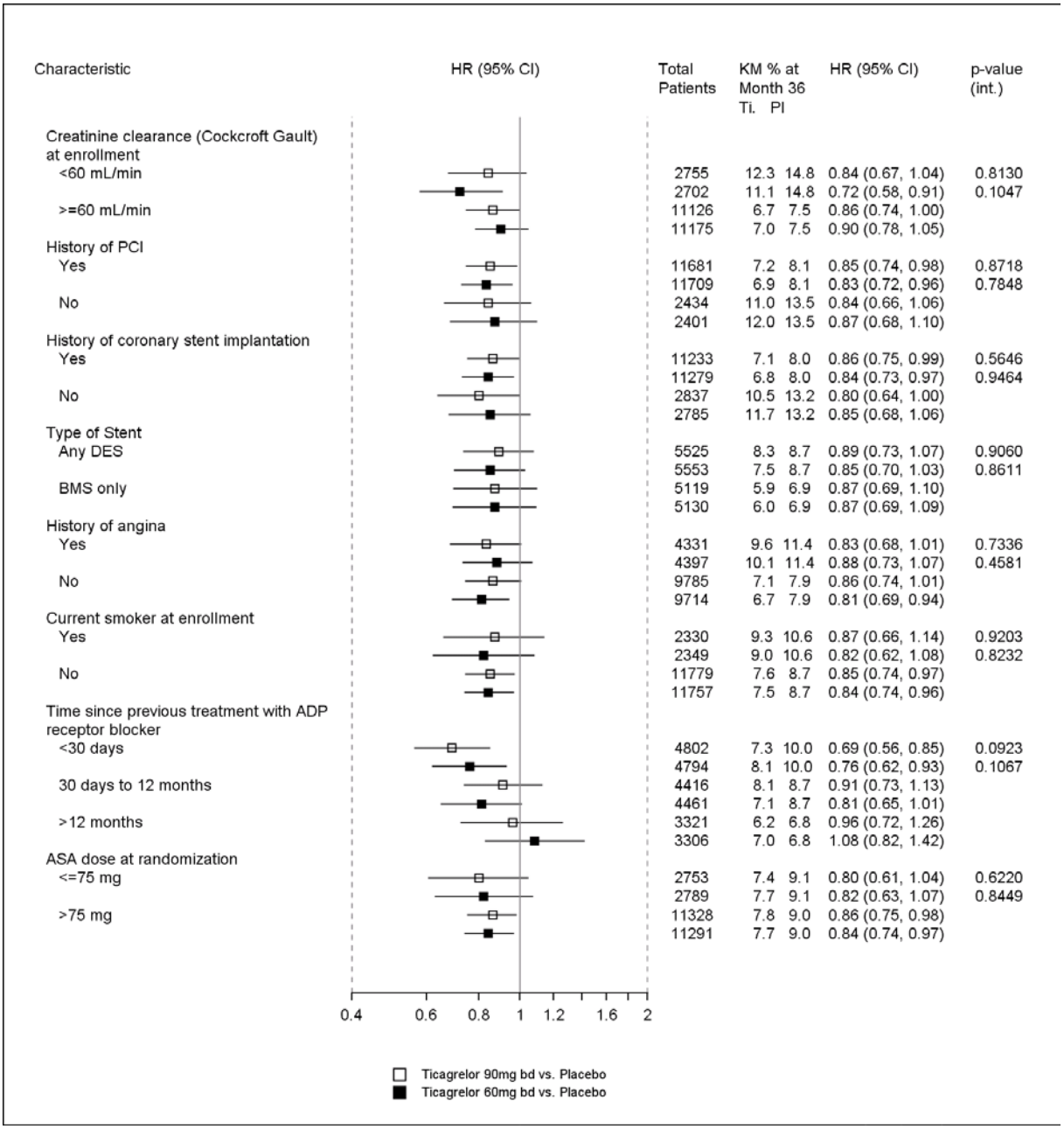


Figure 6 Hazard ratios and rates of the primary clinical endpoint by patient subgroup (full analysis set)

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 11 Summary of efficacy for trial PEGASUS

Title: A Randomised, Double-Blind, Placebo Controlled, Parallel Group, Multinational Trial, to Assess the Prevention of Thrombotic Events with Ticagrelor Compared to Placebo on a Background of Acetyl Salicylic Acid (ASA) Therapy in Patients with History of Myocardial Infarction [PEGASUS: PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk Patients with Prior AcUte Coronary Syndrome - Thrombolysis In Myocardial Infarction Study Group]				
Study identifier	D5132C00001			
Design	Randomised, double-blind, placebo-controlled, 3-arm parallel group, multinational trial			
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		minimum of 12 months < 14 days not applicable	
Hypothesis	Superiority			
Treatments groups	Ticagrelor 90 mg		N=7050 randomised, N=6988 received study drug	
	Ticagrelor 60 mg		N=7045 randomised, N=6958 received study drug	
	Placebo (ASA) + blinded clopidogrel 75 mg if needed		N=7067 randomised, N=6996 received study drug	
Endpoints and definitions	Primary endpoint		Composite of CV death, MI, stroke	
	Secondary endpoints		CV death (first), all-cause mortality (second) multiple testing under type I error	
	Secondary other endpoints		CV death, MI, stroke, or urgent coronary revascularisation CV death or coronary or cerebrovascular arterial thrombosis hospitalisation (including MI, stroke, urgent coronary revascularisation, unstable angina, or transient ischaemic attack) coronary heart disease (CHD) death, MI, or stroke net clinical benefit of long-term treatment with ticagrelor vs placebo on a background of ASA Incidence of coronary stent thrombosis	
Database lock	12 January 2015			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	Ticagrelor 90 mg	Ticagrelor 60 mg	Placebo (ASA)
	Number of subject	6988	6958	6996
	Composite of CV death, MI, stroke	493 (7.0%)	487 (6.9%)	578 (8.2%)
	HR (95% CI)	0.85 (0.75-0.96)	0.84 (0.74-0.95)	
	CV death (first)*,	182 (2.6%)	174 (2.5%)	210 (3.0%)

	HR (95% CI)	0.87 (0.71-1.06)	0.83 (0.68-1.01)	
	all-cause mortality (second)*	326 (4.6%)	289 (4.1%)	326 (4.6%)
	HR (95% CI)	1.00 (0.86-1.16)	0.89 (0.76-1.04)	
	Net clinical benefit (composite CV death, MI, stroke, TIMI Major bleeding)	618 (8.8%)	585 (8.3%)	618 (8.7%)
	HR (95% CI)	1.00 (0.90-1.12)	0.95 (0.85-1.06)	

*secondary endpoints that were tested in a hierarchical manner under type 1 error. After the composite primary endpoint, CV death was tested and all-cause mortality.

Analysis performed across trials (pooled analyses and meta-analysis)

The applicant also provided overall analyses on the benefit versus the bleeding risks according to the tables and figures below.

Table 12 Analysis of net clinical benefit, the composite of CV death, MI, stroke, and TIMI Major bleeding (full analysis set).

	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
Characteristic	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %
Composite of CV death / MI/ stroke/ TIMI Major bleeding	618 (8.8%)	9.8%	1.00 (0.90, 1.12)	0.9563	585 (8.3%)	9.3%	0.95 (0.85, 1.06)	0.3412	618 (8.7%)	9.6%
CV death	182 (2.6%)	2.9%	0.87 (0.71, 1.06)	0.1547	174 (2.5%)	2.9%	0.83 (0.68, 1.01)	0.0676	210 (3.0%)	3.4%
MI	275 (3.9%)	4.4%	0.81 (0.69, 0.95)	0.0100	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	0.0314	338 (4.8%)	5.2%
Stroke	100 (1.4%)	1.6%	0.82 (0.63, 1.07)	0.1403	91 (1.3%)	1.5%	0.75 (0.57, 0.98)	0.0337	122 (1.7%)	1.9%
TIMI Major bleeding	159 (2.3%)	2.5%	2.05 (1.57, 2.69)	<.0001	138 (2.0%)	2.2%	1.78 (1.35, 2.35)	<.0001	78 (1.1%)	1.3%

Table 13 Analysis of net clinical benefit by irreversible harm, the composite of all-cause mortality, MI, stroke, intracranial haemorrhage and fatal bleeding (full analysis set).

	Ticagrelor 90 mg bd N = 7050				Ticagrelor 60 mg bd N = 7045				Placebo N= 7067	
Characteristic	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %	HR (95% CI)	p-value	Patients (%) with events	KM %
Composite of all-cause mortality/MI/stroke, intracranial haemorrhage and fatal bleeding	643 (9.1%)	10.1%	0.93 (0.84, 1.04)	0.2194	600 (8.5%)	9.6%	0.87 (0.78, 0.97)	0.0139	686 (9.7%)	10.6%
All-cause mortality	326 (4.6%)	5.1%	1.00 (0.86, 1.16)	0.9851	289 (4.1%)	4.7%	0.89 (0.76, 1.04)	0.1350	326 (4.6%)	5.2%
MI	275 (3.9%)	4.4%	0.81 (0.69, 0.95)	0.0100	285 (4.0%)	4.5%	0.84 (0.72, 0.98)	0.0314	338 (4.8%)	5.2%
Stroke (excluding intracranial haemorrhages)	86 (1.2%)	1.4%	0.84 (0.63, 1.12)	0.2435	79 (1.1%)	1.3%	0.77 (0.58, 1.04)	0.0872	102 (1.4%)	1.6%
Intracranial haemorrhage	41 (0.6%)	0.6%	1.25 (0.79, 1.97)	0.3483	35 (0.5%)	0.5%	1.06 (0.66, 1.71)	0.8051	33 (0.5%)	0.6%
Fatal bleeding	13 (0.2%)	0.2%	0.86 (0.41, 1.82)	0.7011	13 (0.2%)	0.2%	0.87 (0.41, 1.82)	0.7049	15 (0.2%)	0.3%

Table 14 Analysis of primary efficacy endpoints by number of risk factors (FAS).

Characteristic	Group		Ticagrelor 90mg bd (N=7050)	Ticagrelor 60mg bd (N=7045)	Placebo (N=7067)
Number of qualifying risk factors	>=2	Number of patients (%)	3828 (54.3)	3854 (54.7)	3961 (56.0)
		Patients with events	355 (9.3%)	333 (8.6%)	397 (10.0%)
		KM %	10.4%	9.8%	11.1%
		Hazard Ratio (95% CI)	0.92 (0.80, 1.07)	0.86 (0.74, 0.99)	
		p-value	0.2798	0.0388	
		Risk difference	-0.71 (-2.24, 0.82)	-1.31 (-2.82, 0.20)	
	<2	Number of patients (%)	3222 (45.7)	3191 (45.3)	3106 (44.0)
		Patients with events	138 (4.3%)	154 (4.8%)	181 (5.8%)
		KM %	4.9%	5.4%	6.4%
		Hazard Ratio (95% CI)	0.73 (0.58, 0.91)	0.82 (0.66, 1.02)	
		p-value	0.0053	0.0702	
		Risk difference	-1.55 (-2.82, -0.28)	-1.07 (-2.37, 0.23)	
		p-value for interaction	0.0765	0.7320	
Number of qualifying risk factors	>=3	Number of patients (%)	1536 (21.8)	1482 (21.0)	1523 (21.6)
		Patients with events	195 (12.7%)	172 (11.6%)	216 (14.2%)
		KM %	14.3%	13.1%	15.7%
		Hazard Ratio (95% CI)	0.89 (0.73, 1.08)	0.82 (0.67, 1.00)	
		p-value	0.2283	0.0463	
Number of qualifying risk factors	<3	Number of patients (%)	5514 (78.2)	5563 (79.0)	5544 (78.4)
		Patients with events	298 (5.4%)	315 (5.7%)	362 (6.5%)
		KM %	6.1%	6.4%	7.2%
		Hazard Ratio (95% CI)	0.82 (0.71, 0.96)	0.86 (0.74, 1.00)	
		p-value	0.0126	0.0498	
		Risk difference	-1.15 (-2.18, -0.12)	-0.84 (-1.88, 0.20)	
		p-value for interaction	0.5429	0.6849	
Number of qualifying risk factors	>=4	Number of patients (%)	377 (5.3)	373 (5.3)	405 (5.7)
		Patients with events	67 (17.8%)	57 (15.3%)	79 (19.5%)
		KM %	21.7%	17.8%	20.1%
		Hazard Ratio (95% CI)	0.92 (0.67, 1.28)	0.78 (0.56, 1.10)	
		p-value	0.6286	0.1624	
		Risk difference	1.57 (-5.01, 8.16)	-2.30 (-8.52, 3.92)	
	<4	Number of patients (%)	6673 (94.7)	6672 (94.7)	6662 (94.3)
		Patients with events	426 (6.4%)	430 (6.4%)	499 (7.5%)
		KM %	7.1%	7.2%	8.4%
		Hazard Ratio (95% CI)	0.85 (0.74, 0.96)	0.85 (0.75, 0.97)	
		p-value	0.0117	0.0164	
		Risk difference	-1.27 (-2.27, -0.26)	-1.14 (-2.16, -0.13)	
		p-value for interaction	0.6499	0.6328	

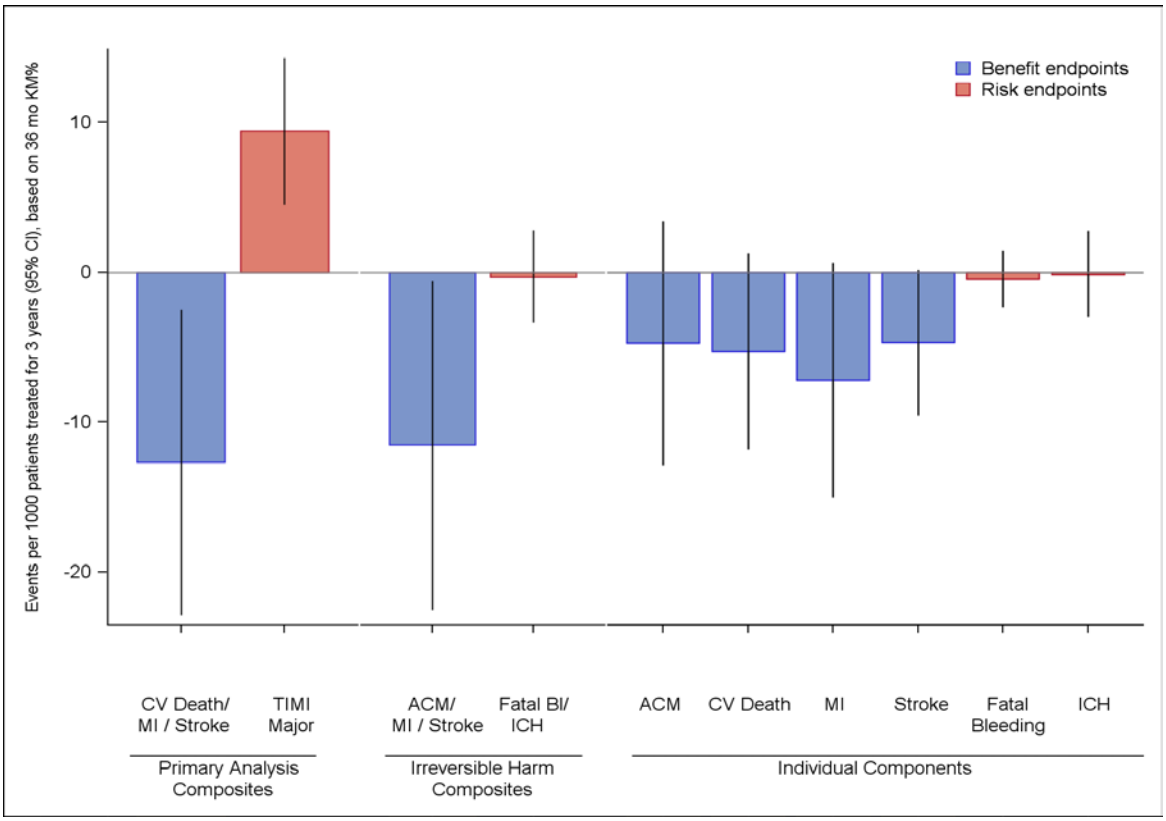


Figure 7 Estimated number of events prevented or caused for every 1000 patients treated for 3 years with ticagrelor 60 mg (Full analysis set)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study was a randomised, double-blind, placebo-controlled, 3-arm parallel group study and was considered appropriate to evaluate its primary objective. This primary objective was to compare the effect of long-term treatment with ticagrelor 90 mg bd and 60mg bd vs. placebo on a background of ASA (75 to 150 mg daily) on the event rate of the composite of CV death, non-fatal MI, or non-fatal stroke in patients with history of MI and high risk of developing atherothrombotic events. The **primary composite endpoint** of CV death, MI and stroke is robust and clinically relevant. Although overall mortality is preferred in the composite of the primary endpoint, inclusion of CV death in the composite is also considered acceptable as per *EMA Guideline on the evaluation of medicinal products for cardiovascular disease prevention (EMEA/CHMP/EWP/311890/2007)*. Key secondary endpoints, to compare the event rate of (1) CV death and (2) all-cause mortality, were considered of relevance as well. These endpoints were hierarchically tested under type 1 error, respectively.

The general design including two different doses of ticagrelor was considered acceptable, allowing comparison of the optimal dose in terms of efficacy and bleeding risk in comparison to a background therapy of low dose aspirin (ASA). A background therapy of only ASA was considered common practice although some recent trials (TRA2P-TIMI50 and the DAPT studies) have investigated dual antiplatelet therapy indicating a reduction in CV events upon longer than 1-year dual antiplatelet treatment, albeit at the cost of more bleedings. Of note, these studies have been presented later than the PEGASUS trial has been initiated. A possibility has been introduced to **additionally use clopidogrel in the placebo arm** in a blinded fashion for those patients in need for dual therapy. Although this may be a conservative

approach with regard to the efficacy evaluation, this was not considered conservative with regard to safety, in particular concerning bleeding events. The number of patients who received this modified study treatment in PEGASUS was small, and the majority of them had developed conditions for which an ADP receptor blocker was recommended (mainly ACS or arterial stenting). Clopidogrel was only administered to the placebo group, to prevent triple antiplatelet therapy in the ticagrelor arms (ASA + ticagrelor + clopidogrel). Patients were to return to their original study drug once use of an ADP receptor blocker was no longer indicated. This approach allowed patients to receive optimal medical care while maintaining the integrity of the blind. This subgroup did not influence the overall study result.

The presented **inclusion criteria** were considered acceptable and represent a population with a high risk of CV events. This population is different in comparison with the PLATO study, as patients in PEGASUS had a *history* of MI (1 to 3 years prior to randomisation), while in PLATO patients were included with an ACS. The exclusion criteria were appropriate to reflect the SmPC exclusion criteria and warning statements. In PEGASUS a large proportion of patients had previously been treated with clopidogrel (approximately 84%) with smaller proportions treated with other ADP inhibitors (89% in total). Termination of this treatment was largely within the year immediately before randomisation. However, starting dual therapy in a late stage, more than 1 year after single therapy, seems questionable. The Applicant was asked to discuss the benefit/risk (primary endpoint of CV death, MI or stroke / major bleedings) and the net clinical benefit of ticagrelor 60 mg in **patients with old MI** (greater than 2 years after the onset of the qualifying MI) comparatively to those with more recent MI (< 2 years), and provide the baseline characteristics of this population. At the end a statement was included in section 5.1 of the SmPC that there was no evidence of benefit (no reduction in the primary clinical composite endpoint of CV death, MI and stroke MACE, but and increase in major bleeding) when ticagrelor 60 mg BID was re/introduced in clinically stable **patients >2 years from the MI**, or **more than one year after stopping previous ADP receptor inhibitor** treatment.

Sample size calculation was considered appropriate. The method of randomisation was considered acceptable. The blinding method for investigator and patients was considered appropriate. Central adjudication also ensures proper blinding of the adjudication of the endpoints and bleeding events.

Efficacy data and additional analyses

A large proportion of patients could be followed-up, with only 0.7% of patients who withdrew consent and minimal unblinding events (0.2%), which was reassuring. However, of concern was the **large proportion of patients discontinuing study drug** in both the ticagrelor 90 mg (32.0%) and 60 mg (28.7%) groups, which was substantially larger than in the placebo group (21.4%) and could impact study outcome depending on the analyses methods chosen. These were largely due to drug related AEs and patients' decision to withdraw consent. A very large number of patients had to be screened to fulfil the number of patients eligible for inclusion, which somehow mitigates external validity of the trial.

Randomisation was successful, with only slight differences between treatment groups. The largest proportion of patients had 1 risk factor qualifying for inclusion (51%). Most prominent risk factors were age (54%) and multivessel CAD (59%). One third has 2 risk factors qualifying for inclusion (33%). Taken together, the population included seems to be in line with the **high-risk inclusion definition**, although a broad risk spectrum exists. Almost all patients were Caucasian, consequently, other races were underrepresented. The number of patients >75 years of age (approximately 10%) was also limited.

Assessment based on the Full Analysis Set was considered acceptable. However, taken the large proportion of patients prematurely discontinuing treatment, other analyses may also offer valuable information on the benefit risk balance of ticagrelor and were assessed.

The efficacy of ticagrelor based on the **primary endpoint has been demonstrated for both doses of ticagrelor**. Both doses presented an approximately similar treatment effect with 493, 487, and 578 patients having a first event on ticagrelor 90 mg, 60 mg, and placebo, respectively, corresponding to Kaplan-Meier percentages at 36 months of 7.8%, 7.8%, and 9.0%: 15% relative risk reduction (RRR), HR 0.85 (95% CI 0.75, 0.96), p=0.0080 for ticagrelor 90 mg, and **16% RRR, HR 0.84 (95% CI 0.74, 0.95), p=0.0043 for ticagrelor 60 mg**. The effect seemed to be consistent throughout the study period; the relative risk reduction (RRR) was 13% for 90 mg, 17% for 60 mg, during the first 360 days and was from 361 days and onwards 16% for 90 mg and 16% for 60 mg.

The effects on **the individual components of the primary endpoint were consistent with the composite**, although efficacy was more robust for the 60 mg BID dose than the 90 mg dose with significant effects both for the occurrence of MI and stroke, but not for CV death, while the 90 mg BID dose was only significant for stroke. The hierarchical testing was terminated due to insignificant effect on CV death. **MI events seem to contribute the most to the overall effect** (898 events), followed by CV deaths (566 events) and stroke (313 events). **Consistent numerical findings were also observed on the all-cause mortality for the 60 mg** dose, however, no difference in treatment effect was observed for the higher 90 mg dose.

In general, **subgroup analyses** showed consistent results with the overall treatment effect for both doses, although differences appear between the 60 mg and 90 mg doses. Focusing **on the 60 mg dose, trend differences appear in the age, sex, race, obesity, time since qualifying MI and time since previous treatment with ADP receptor blocker**. As for most of these subgroups differences are likely **due to chance finding** and may not be easily explained based on any possible mechanism. However, an attenuated effect with increasing time since previous use of an ADP receptor-blocker and with increasing time since last MI were of concern and this was reflected in the SmPC.

A claimed **broad target population during unrestricted long term use** was questioned by the CHMP and in-depth discussed. In subgroup analyses **elderly patients (>65 years)** seemed to benefit less, while bleeding risks seemed to be somewhat higher. The MAH's proposed a broad indication and it was questioned whether a high risk population could be identified that would stand to benefit most in view of the small net clinical benefit in the overall study, as the reduction in thrombotic events was partly offset by an increased number of bleedings.

The MAH performed a number of – post hoc - subgroup analyses to investigate further the relation of age and multiple qualifying risk factors (for future thrombotic events) on outcome, primary endpoint, bleedings and net clinical benefit.

First, the MAH presented outcome data for six age strata. These data suggested absence of an age effect. The observation of a possibly diminished effect in populations above 65 in the pre-specified subgroup analysis was not reproduced in these additional analyses. In the 65-69 year age stratum the treatment effect was attenuated in both ticagrelor dose groups, while in all other strata the effects were close to the overall – beneficial - effect observed. These findings would indeed suggest that **the observed effect of age is likely due to random variation**.

Next, the MAH provided post hoc subgroup analyses to evaluate **the impact of the number of qualifying risk factors on the primary endpoint and bleeding endpoints**. First, across all subgroups of patients with single or multiple (2 or more) qualifying risk factors the relative treatment effect was approximately similar, without any obvious outliers. Second, as expected with increasing number of qualifying risk factors, the event rate tended to increase. The groups with increasing number of multiple risk factors seemed to have slightly greater reduction in risks (>= 2 QRF: HR 0.86 (0.74, 0.99); >=3 QRF: HR 0.82 (0.67, 1.00); >=4 QRF: HR 0.78 (0.56-1.10)). Thus, both the absolute and

relative risk reductions were greatest in patients with more qualifying risk factors. Nevertheless, these results for subgroups with >3 and 4 qualifying risk factors should be interpreted with care due to the limited patient numbers in those subgroups and the effect is already present when 2 risk factors are present. Yet, this potential increase in benefit appears to go along with an increased risk of TIMI major bleedings (>= 2 QRF: HR 2.50 (1.69, 3.71); >=3 QRF: HR 3.11 (1.68, 5.76); >=4 QRF: HR 20.8 (2.75-156), data on treatment) in the 60 mg group. Accordingly, the analysis on the subgroup of >=2 or <2 qualifying risk factors demonstrate a higher risk of bleeding in the higher risk category (>= 2 QRF: HR 2.50 (1.69, 3.71) vs < 2 QRF: HR 2.06 (1.17, 3.63). However, the low number of bleedings events prohibits drawing strong conclusions.

Next, the MAH presented analyses of **treatment benefits and bleeding effects of specific combinations of qualifying risk factors**. These subgroup analyses combining various risk factors of interest indicated that the numerically largest benefit was seen in the subgroups of patients with the combination of age ≥65 years and creatinine clearance <60 mL/min, or the combination of multivessel disease and creatinine clearance <60 mL/min. Consistent with above described subgroup analyses, a higher bleeding risk could be observed, but as said, the number of bleeding events was very limited (29 vs 13 and 18 vs 6, respectively). Therefore, it is difficult to draw any firm conclusions in these specific subgroups.

The MAH also presented **an analysis of net clinical benefit** showing that the net clinical benefit of treating 1000 patients who have ≥2 qualifying risk factors for 3 years with ticagrelor 60 mg instead of placebo is estimated to be the prevention of 9 events of all-cause mortality, MI, or stroke, with no extra events of fatal bleeding or intracranial haemorrhage. This is a slightly smaller benefit than what was seen for the overall study estimation of 12 events of all-cause mortality, MI, or stroke, prevented with no extra events of fatal bleeding or intracranial haemorrhage.

The MAH combined the older PLATO study results with those of PEGASUS as the former study included patients immediately after a qualifying ACS. Combining results of PLATO and PEGASUS would result in prevention of 81 events of all-cause mortality, MI, or stroke per 10000 patient-years, while causing 5 GUSTO severe bleedings (PLATO: 210 events and 20 fewer GUSTO severe bleedings; PEGASUS: 39 fewer events and 9 GUSTO severe bleedings). However, these data also clearly indicate that the long-term treatment (PEGASUS) has a much smaller benefit than treatment in the first year after the MI as seen in PLATO.

In conclusion, age and number of risk factors did not clearly identify patients' groups in which the benefit – risk balance might be better or worse, therefore restrictions of the intended patient group were not considered necessary. The benefit with ticagrelor was larger early after the MI index event than after long-term treatment, but in some patients at a high risk of developing atherothrombotic event cardiovascular risk continuation of treatment was justified without further specification of the risk.

Given that ticagrelor therapy could start at an ACS event with 90 mg strength bid, and could continue beyond one year with 60 mg strength bid in patients with high risk of atherothrombotic events it was agreed that the indication for ticagrelor in patients after an myocardial infarction should not be a separate indication, but should be added to the already authorised indication as a subset of patients at the highest risk of recurrence. Hence the combined indication including the indication already authorised and the new agreed indication is following:

Brilique, co-administered with acetylsalicylic acid (ASA), is indicated for the prevention of atherothrombotic events in adult patients with

acute coronary syndromes (ACS) or

a history of myocardial infarction (MI) and a high risk of developing an atherothrombotic event.

2.5.4. Conclusions on the clinical efficacy

PEGASUS study provided insight in dual antiplatelet therapy beyond 1 year after MI. The applicant demonstrated a consistent effect for both doses of 60 mg BID and 90 mg BID on the primary endpoint of CV death, MI and stroke. The Kaplan–Meier rates at 3 years were 7.8% in the 90 mg BID ticagrelor group, 7.7% in the 60 mg BID group, and 9.0% in the placebo group. This translated in hazard rates (HR) of 0.85 (95% CI 0.75, 0.96), p=0.0080 for ticagrelor 90 mg, and HR of 0.84 (95% CI 0.74, 0.95), p=0.0043 for ticagrelor 60 mg. The observed impact on secondary endpoints was consistent with these findings, although more robust for the 60 mg strength. The large proportion of patients discontinuing ticagrelor treatment and an attenuated effect observed with increasing time since previous use of an ADP receptor-blocker and with increasing time since last MI were of concern and therefore all these findings were addressed in the SmPC. Given that ticagrelor therapy could start at an ACS event with 90 mg strength bid, and could continue beyond one year with 60 mg strength bid in patients with high risk of atherothrombotic events it was agreed that the indication for ticagrelor in patients after an myocardial infarction should not be a separate indication, but a subset of patients at the highest risk of recurrence added to the already approved indication in patients with ACS.

2.6. Clinical safety

Patient exposure

A total of 20942 patients (99% of randomised patients) received at least 1 dose of randomised study drug (ticagrelor or placebo), of which 6988 received ticagrelor 90 mg, 6958 received ticagrelor 60 mg, and 6996 received placebo. For the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, median total duration of exposure was 28.3, 29.4, and 30.4 months, respectively. A higher proportion of patients prematurely discontinued study drug in both the ticagrelor 90 mg (32.0%) and 60 mg (28.7%) groups than in the placebo group (21.4%). The most common reasons for permanent discontinuation of study drug were AEs/SAEs (16.6% of study patients; n=3475) and patient decision (9.1% of study patients; n=1914).

Adverse events

Overall, AEs were reported more frequently in the ticagrelor groups than on placebo, with frequencies of 76.2%, 75.7% and 69.1%, for ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively.

Table 15 AEs (including bleeding) in any category - on treatment (safety analysis set)

	Number (%) of patients[a]		
AE category	**Ticagrelor 90mg bd (N=6988)**	**Ticagrelor 60mg bd (N=6958)**	**Placebo (N=6996)**
Any AE	5327 (76.2%)	5268 (75.7%)	4837 (69.1%)
Any AE with outcome = death	161 (2.3%)	149 (2.1%)	203 (2.9%)
Any SAE (including events with outcome = death)	1514 (21.7%)	1499 (21.5%)	1511 (21.6%)
Any AE leading to discontinuation of study drug	1306 (18.7%)	1117 (16.1%)	596 (8.5%)
Any SAE leading to discontinuation of study drug	256 (3.7%)	255 (3.7%)	211 (3.0%)

The **most commonly reported AEs** on ticagrelor by preferred term were dyspnoea, epistaxis, and increased tendency to bruise; all occurred at a higher rate in the ticagrelor groups than on placebo.

Table 16 Most common AEs (including bleeding) by preferred term (with frequency >1%) - on treatment (safety analysis set)

	Ticagrelor 90 mg bd (N=6988)		Ticagrelor 60 mg bd (N=6958)		Placebo (N=6996)	
Preferred term	**Number(%) of patients[a]**	**Event rate (per 100 pt years)[b]**	**Number(%) of patients[a]**	**Event rate (per 100 pt years)[b]**	**Number(%) of patients[a]**	**Event rate (per 100 pt years)[b]**
Patients with any AE	5327 (76.2%)	38.23	5268 (75.7%)	35.93	4837 (69.1%)	30.35
Dyspnoea	1087 (15.6%)	7.80	865 (12.4%)	5.90	309 (4.4%)	1.94
Epistaxis	511 (7.3%)	3.67	422 (6.1%)	2.88	156 (2.2%)	0.98
Increased tendency to bruise	460 (6.6%)	3.30	419 (6.0%)	2.86	62 (0.9%)	0.39
Contusion	376 (5.4%)	2.70	349 (5.0%)	2.38	108 (1.5%)	0.68
Nasopharyngitis	340 (4.9%)	2.44	347 (5.0%)	2.37	349 (5.0%)	2.19
Non-cardiac chest pain	316 (4.5%)	2.27	341 (4.9%)	2.33	374 (5.3%)	2.35
Dizziness	304 (4.4%)	2.18	290 (4.2%)	1.98	261 (3.7%)	1.64
Spontaneous haematoma	269 (3.8%)	1.93	218 (3.1%)	1.49	41 (0.6%)	0.26
Hypertension	240 (3.4%)	1.72	282 (4.1%)	1.92	290 (4.1%)	1.82
Bronchitis	217 (3.1%)	1.56	187 (2.7%)	1.28	180 (2.6%)	1.13
Diarrhoea	210 (3.0%)	1.51	228 (3.3%)	1.55	173 (2.5%)	1.09
Back pain	195 (2.8%)	1.40	226 (3.2%)	1.54	226 (3.2%)	1.42
Traumatic haematoma	193 (2.8%)	1.38	160 (2.3%)	1.09	45 (0.6%)	0.28
Headache	192 (2.7%)	1.38	175 (2.5%)	1.19	182 (2.6%)	1.14

AEs due to bleeding events were reported in 32.3%, 29.1%, and 11.5% of patients in the ticagrelor 90 mg, 60 mg, placebo groups, respectively.

Table 17 Analyses of bleeding events using TIMI and PLATO definitions – on treatment (safety analysis set)

	Ticagrelor 90 mg bd (N=6988)				Ticagrelor 60 mg bd (N=6958)				Placebo (N=6996)	
Characteristic	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**	**HR (95% CI)**	**p-value**	**Patients (%) with events**	**KM%**
TIMI Major bleeding	127 (1.8%)	2.6%	2.69 (1.96, 3.70)	<.0001	115 (1.7%)	2.3%	2.32 (1.68, 3.21)	<.0001	54 (0.8%)	1.1%
Fatal	6 (0.1%)	0.1%	0.58 (0.22, 1.54)	0.2719	11 (0.2%)	0.3%	1.00 (0.44, 2.27)	1.0000	12 (0.2%)	0.3%

Table 17 Analyses of bleeding events using TIMI and PLATO definitions – on treatment (safety analysis set)

	Ticagrelor 90 mg bd (N=6988)				Ticagrelor 60 mg bd (N=6958)				Placebo (N=6996)	
Characteristic	Patients (%) with events	KM%	HR (95% CI)	p-value	Patients (%) with events	KM%	HR (95% CI)	p-value	Patients (%) with events	KM%
ICH	29 (0.4%)	0.6%	1.44 (0.83, 2.49)	0.1898	28 (0.4%)	0.6%	1.33 (0.77, 2.31)	0.3130	23 (0.3%)	0.5%
Other Major	95 (1.4%)	2.0%	4.34 (2.79, 6.74)	<.0001	83 (1.2%)	1.6%	3.61 (2.31, 5.65)	<.0001	25 (0.4%)	0.5%
TIMI Major or Minor bleeding	192 (2.7%)	3.9%	3.05 (2.32, 4.00)	<.0001	168 (2.4%)	3.4%	2.54 (1.93, 3.35)	<.0001	72 (1.0%)	1.4%
PLATO Major bleeding	199 (2.8%)	4.0%	3.12 (2.38, 4.07)	<.0001	172 (2.5%)	3.5%	2.57 (1.95, 3.37)	<.0001	73 (1.0%)	1.4%
Fatal/life-threatening	133 (1.9%)	2.7%	2.72 (1.99, 3.71)	<.0001	122 (1.8%)	2.4%	2.38 (1.73, 3.26)	<.0001	56 (0.8%)	1.1%
Fatal	6 (0.1%)	0.1%	0.58 (0.22, 1.54)	0.2719	11 (0.2%)	0.3%	1.00 (0.44, 2.27)	1.0000	12 (0.2%)	0.3%
Other major	67 (1.0%)	1.3%	4.46 (2.62, 7.59)	<.0001	53 (0.8%)	1.1%	3.37 (1.95, 5.83)	<.0001	17 (0.2%)	0.3%

The **incidence of major bleedings over time** seems constant (see figure below).

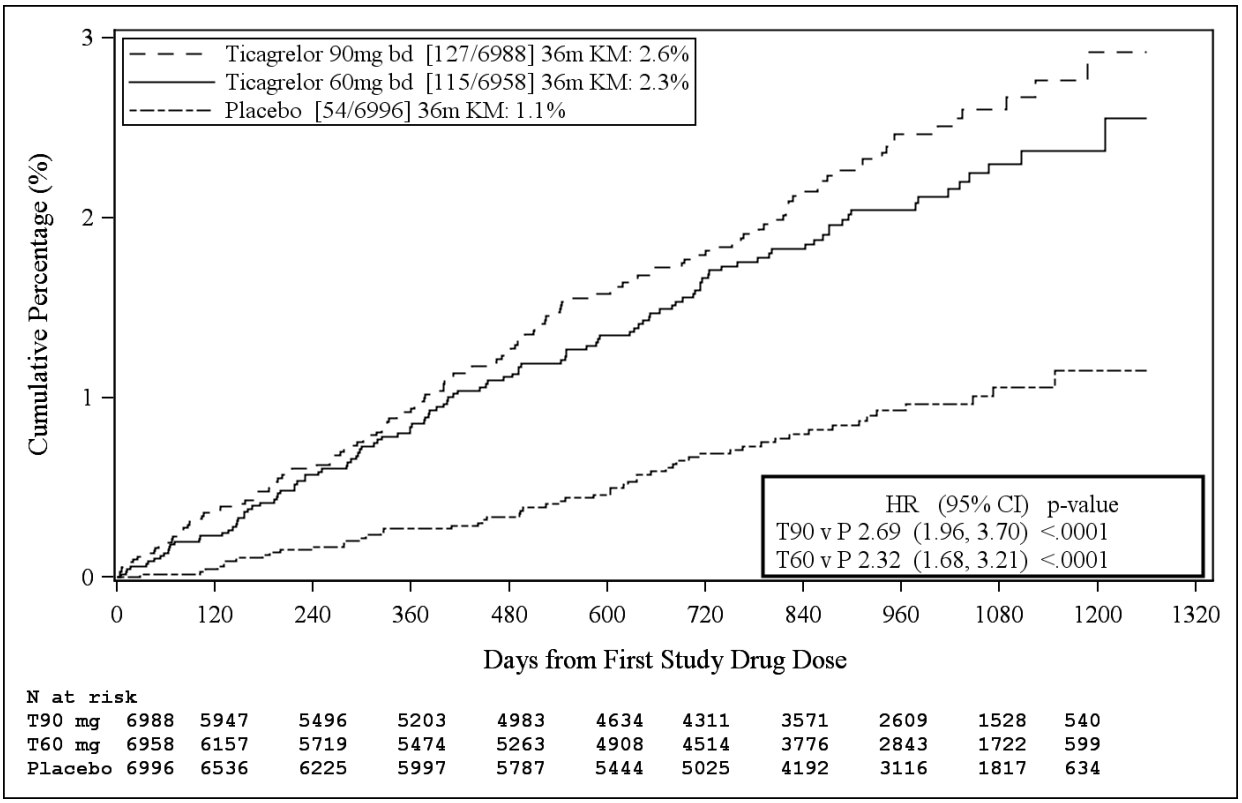


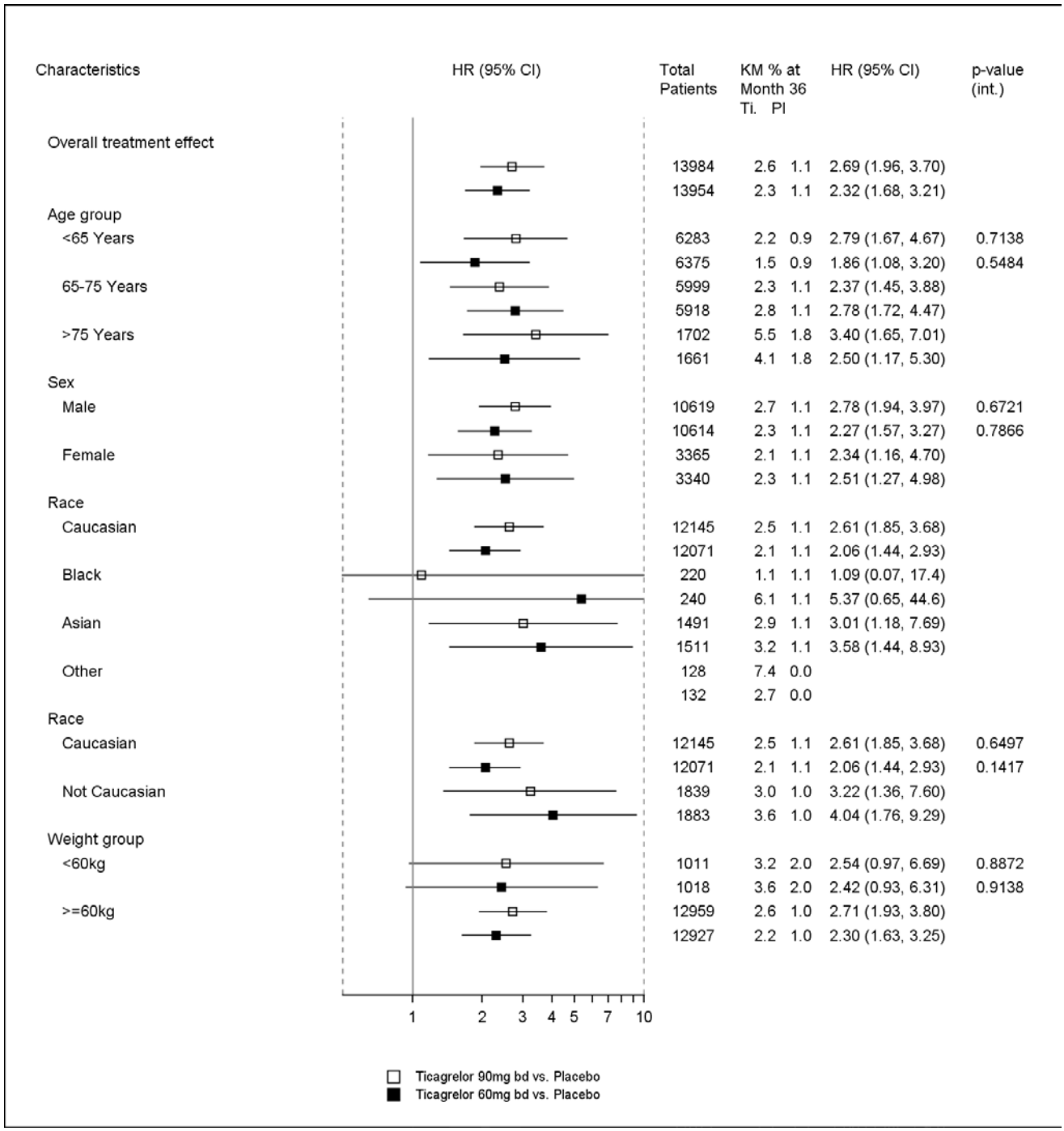
Figure 8 KM plot of the cumulative percentage of patients with TIMI major bleeding events – on treatment (safety analysis set).

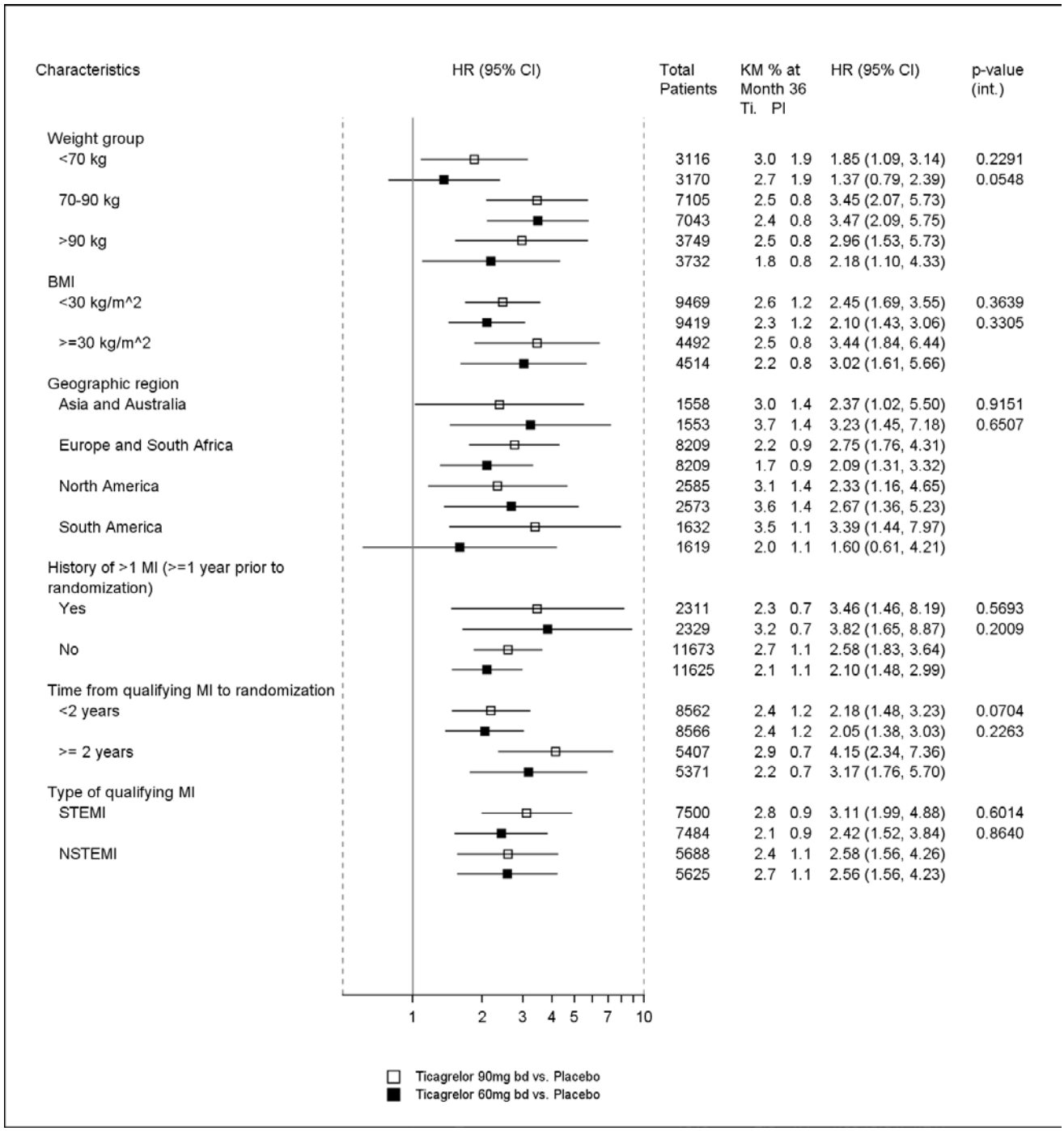
The **increased frequency of bleeding** events translated to a higher frequency of transfusions and hospitalisations due to bleeding events in the ticagrelor groups compared with placebo. As a consequence of a bleeding AEs, transfusions were required in 3.2%, 3.1%, and 1.7% of the patients in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively. Hospitalisations due to bleeding events were reported in 3.7%, 3.1%, and 1.6% of the patients in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively.

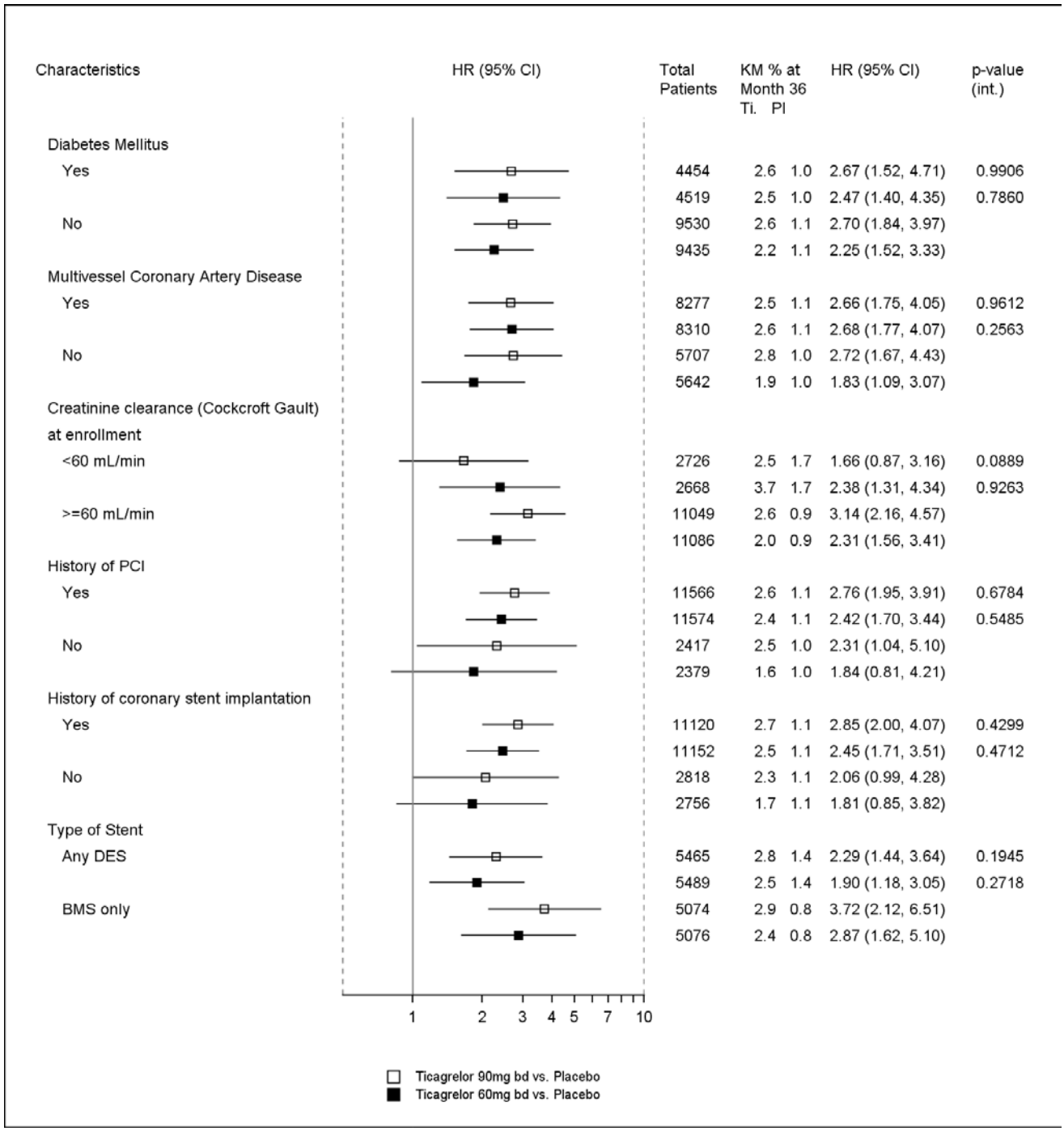
Fatal bleeding was adjudicated as an event where bleeding led directly to death within 7 days. Fatal bleeding events were few and the frequencies similar across the treatment groups. They were reported in 6, 11, and 12 patients on ticagrelor 90 mg, 60 mg, and placebo, respectively. Most fatal bleeding events were spontaneous and the most frequently reported anatomical location was intracranial. Bleeding events adjudicated as contributing to death were defined as bleeding events that were part of a causal chain of medical events that ultimately led to death within 30 days of the bleed, but the bleeding was not directly and/or immediately related to the patient's death. Few bleeding events adjudicated as contributing to death were reported: 9, 5, and 4 patients in the ticagrelor 90 mg, 60 mg, and placebo groups, respectively.

There were few **intracranial haemorrhage events**, with slight differences between the ticagrelor and placebo groups. Intracranial haemorrhage events were reported in 29, 28, and 23 patients on ticagrelor 90 mg, 60 mg, and placebo, respectively. Spontaneous intracranial haemorrhage events were reported in 11, 13, and 13 patients in the ticagrelor 90 mg, 60 mg, and placebo groups, respectively.

In general, the **major bleeding risk across subgroups** seems consistent, with some small differences in subgroups of time from qualifying MI > or < 2 years, and type of stent.


Characteristics
HR (95% CI)
Total Patients
KM % at Month 36 Ti. Pl
HR (95% CI)
p-value (int.)
Overall treatment effect
13984 2.6 1.1 2.69 (1.96, 3.70)
13954 2.3 1.1 2.32 (1.68, 3.21)
Age group
<65 Years
6283 2.2 0.9 2.79 (1.67, 4.67) 0.7138
6375 1.5 0.9 1.86 (1.08, 3.20) 0.5484
65-75 Years
5999 2.3 1.1 2.37 (1.45, 3.88)
5918 2.8 1.1 2.78 (1.72, 4.47)
>75 Years
1702 5.5 1.8 3.40 (1.65, 7.01)
1661 4.1 1.8 2.50 (1.17, 5.30)
Sex
Male
10619 2.7 1.1 2.78 (1.94, 3.97) 0.6721
10614 2.3 1.1 2.27 (1.57, 3.27) 0.7866
Female
3365 2.1 1.1 2.34 (1.16, 4.70)
3340 2.3 1.1 2.51 (1.27, 4.98)
Race
Caucasian
12145 2.5 1.1 2.61 (1.85, 3.68)
12071 2.1 1.1 2.06 (1.44, 2.93)
Black
220 1.1 1.1 1.09 (0.07, 17.4)
240 6.1 1.1 5.37 (0.65, 44.6)
Asian
1491 2.9 1.1 3.01 (1.18, 7.69)
1511 3.2 1.1 3.58 (1.44, 8.93)
Other
128 7.4 0.0
132 2.7 0.0
Race
Caucasian
12145 2.5 1.1 2.61 (1.85, 3.68) 0.6497
12071 2.1 1.1 2.06 (1.44, 2.93) 0.1417
Not Caucasian
1839 3.0 1.0 3.22 (1.36, 7.60)
1883 3.6 1.0 4.04 (1.76, 9.29)
Weight group
<60kg
1011 3.2 2.0 2.54 (0.97, 6.69) 0.8872
1018 3.6 2.0 2.42 (0.93, 6.31) 0.9138
>=60kg
12959 2.6 1.0 2.71 (1.93, 3.80)
12927 2.2 1.0 2.30 (1.63, 3.25)
1
2
3
4
5
7
10
Ticagrelor 90mg bd vs. Placebo
Ticagrelor 60mg bd vs. Placebo


Characteristics
HR (95% CI)
Total Patients
KM % at Month 36 Ti. Pl
HR (95% CI)
p-value (int.)
Weight group
<70 kg
3116 3.0 1.9 1.85 (1.09, 3.14) 0.2291
3170 2.7 1.9 1.37 (0.79, 2.39) 0.0548
70-90 kg
7105 2.5 0.8 3.45 (2.07, 5.73)
7043 2.4 0.8 3.47 (2.09, 5.75)
>90 kg
3749 2.5 0.8 2.96 (1.53, 5.73)
3732 1.8 0.8 2.18 (1.10, 4.33)
BMI
<30 kg/m^2
9469 2.6 1.2 2.45 (1.69, 3.55) 0.3639
9419 2.3 1.2 2.10 (1.43, 3.06) 0.3305
>=30 kg/m^2
4492 2.5 0.8 3.44 (1.84, 6.44)
4514 2.2 0.8 3.02 (1.61, 5.66)
Geographic region
Asia and Australia
1558 3.0 1.4 2.37 (1.02, 5.50) 0.9151
1553 3.7 1.4 3.23 (1.45, 7.18) 0.6507
Europe and South Africa
8209 2.2 0.9 2.75 (1.76, 4.31)
8209 1.7 0.9 2.09 (1.31, 3.32)
North America
2585 3.1 1.4 2.33 (1.16, 4.65)
2573 3.6 1.4 2.67 (1.36, 5.23)
South America
1632 3.5 1.1 3.39 (1.44, 7.97)
1619 2.0 1.1 1.60 (0.61, 4.21)
History of >1 MI (>=1 year prior to randomization)
Yes
2311 2.3 0.7 3.46 (1.46, 8.19) 0.5693
2329 3.2 0.7 3.82 (1.65, 8.87) 0.2009
No
11673 2.7 1.1 2.58 (1.83, 3.64)
11625 2.1 1.1 2.10 (1.48, 2.99)
Time from qualifying MI to randomization
<2 years
8562 2.4 1.2 2.18 (1.48, 3.23) 0.0704
8566 2.4 1.2 2.05 (1.38, 3.03) 0.2263
>= 2 years
5407 2.9 0.7 4.15 (2.34, 7.36)
5371 2.2 0.7 3.17 (1.76, 5.70)
Type of qualifying MI
STEMI
7500 2.8 0.9 3.11 (1.99, 4.88) 0.6014
7484 2.1 0.9 2.42 (1.52, 3.84) 0.8640
NSTEMI
5688 2.4 1.1 2.58 (1.56, 4.26)
5625 2.7 1.1 2.56 (1.56, 4.23)
1
2
3
4
5
7
10
Ticagrelor 90mg bd vs. Placebo
Ticagrelor 60mg bd vs. Placebo


Characteristics
HR (95% CI)
Total Patients
KM % at Month 36 Ti. Pl
HR (95% CI)
p-value (int.)
Diabetes Mellitus
Yes 4454 2.6 1.0 2.67 (1.52, 4.71) 0.9906
4519 2.5 1.0 2.47 (1.40, 4.35) 0.7860
No 9530 2.6 1.1 2.70 (1.84, 3.97)
9435 2.2 1.1 2.25 (1.52, 3.33)
Multivessel Coronary Artery Disease
Yes 8277 2.5 1.1 2.66 (1.75, 4.05) 0.9612
8310 2.6 1.1 2.68 (1.77, 4.07) 0.2563
No 5707 2.8 1.0 2.72 (1.67, 4.43)
5642 1.9 1.0 1.83 (1.09, 3.07)
Creatinine clearance (Cockcroft Gault) at enrollment
<60 mL/min 2726 2.5 1.7 1.66 (0.87, 3.16) 0.0889
2668 3.7 1.7 2.38 (1.31, 4.34) 0.9263
>=60 mL/min 11049 2.6 0.9 3.14 (2.16, 4.57)
11086 2.0 0.9 2.31 (1.56, 3.41)
History of PCI
Yes 11566 2.6 1.1 2.76 (1.95, 3.91) 0.6784
11574 2.4 1.1 2.42 (1.70, 3.44) 0.5485
No 2417 2.5 1.0 2.31 (1.04, 5.10)
2379 1.6 1.0 1.84 (0.81, 4.21)
History of coronary stent implantation
Yes 11120 2.7 1.1 2.85 (2.00, 4.07) 0.4299
11152 2.5 1.1 2.45 (1.71, 3.51) 0.4712
No 2818 2.3 1.1 2.06 (0.99, 4.28)
2756 1.7 1.1 1.81 (0.85, 3.82)
Type of Stent
Any DES 5465 2.8 1.4 2.29 (1.44, 3.64) 0.1945
5489 2.5 1.4 1.90 (1.18, 3.05) 0.2718
BMS only 5074 2.9 0.8 3.72 (2.12, 6.51)
5076 2.4 0.8 2.87 (1.62, 5.10)
1
2
3
4
5
7
10
Ticagrelor 90mg bd vs. Placebo
Ticagrelor 60mg bd vs. Placebo

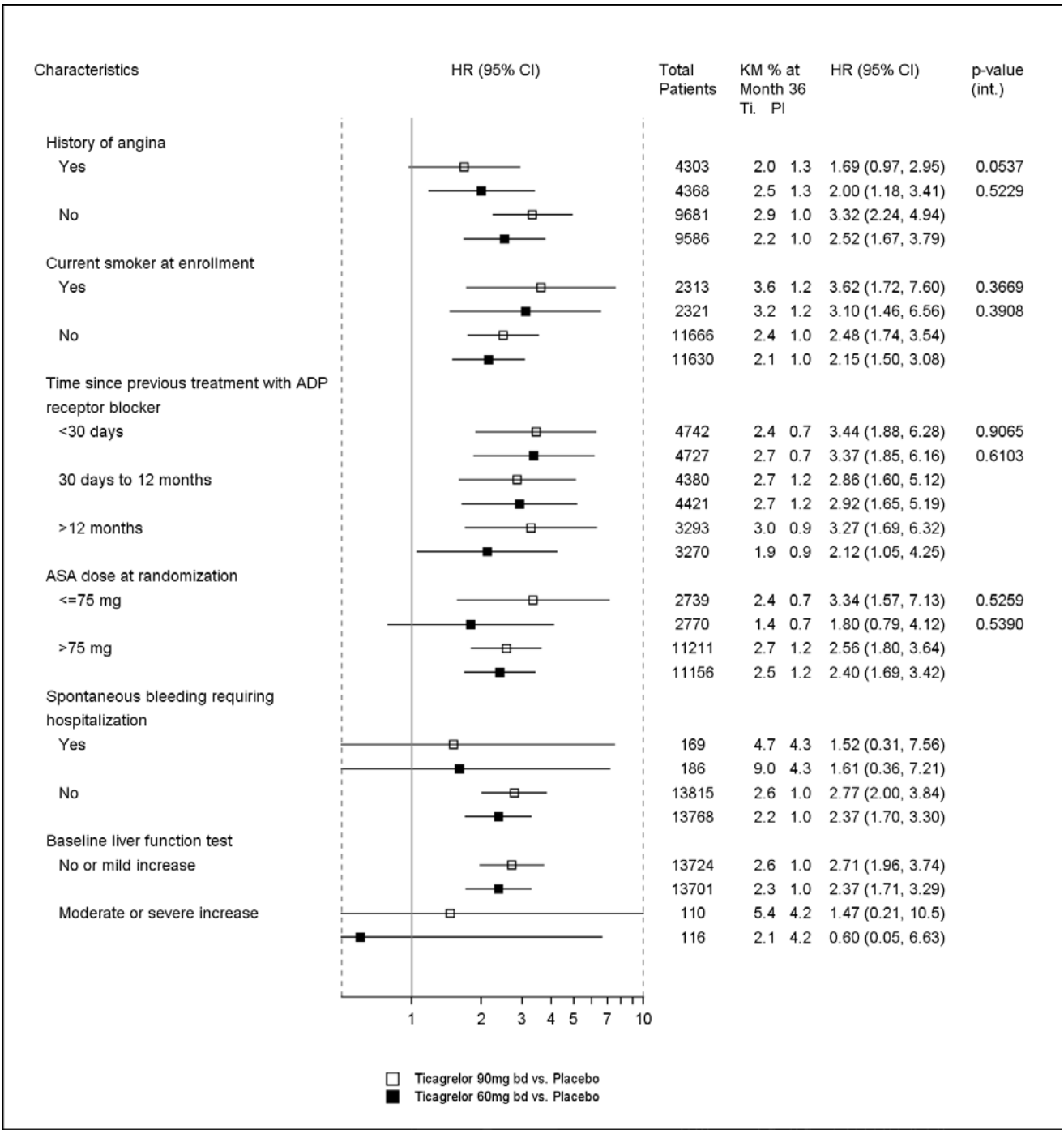


Figure 9 Hazard ratios and rates of TIMI major bleeding events by subgroup - on treatment (safety analysis set)

Table 18 TIMI major bleeding by numbers of qualifying risk factors –on treatment (safety analysis set)

Characteristic	Group		Ticagrelor 90mg bd (N=6988)	Ticagrelor 60mg bd (N=6958)	Placebo (N=6996)
Number of qualifying risk factors	>=2	Number of patients (%)	3789 (54.2)	3801 (54.6)	3920 (56.0)
		Patients with events	73 (1.9%)	79 (2.1%)	36 (0.9%)
		KM %	2.8%	3.0%	1.2%
		Hazard Ratio (95% CI)	2.46 (1.65, 3.66)	2.50 (1.69, 3.71)	
		p-value	<.0001	<.0001	
		Risk difference	1.59 (0.79, 2.39)	1.80 (0.99, 2.61)	
	<2	Number of patients (%)	3199 (45.8)	3157 (45.4)	3076 (44.0)
		Patients with events	54 (1.7%)	36 (1.1%)	18 (0.6%)
		KM %	2.4%	1.5%	0.8%
		Hazard Ratio (95% CI)	3.21 (1.88, 5.48)	2.06 (1.17, 3.63)	
		p-value	<.0001	0.0121	
		Risk difference	1.52 (0.74, 2.30)	0.65 (-0.02, 1.31)	
		p-value for interaction	0.4312	0.5845	
Number of qualifying risk factors	>=3	Number of patients (%)	1520 (21.8)	1461 (21.0)	1504 (21.5)
		Patients with events	25 (1.6%)	37 (2.5%)	14 (0.9%)
		KM %	2.3%	4.0%	1.3%
		Hazard Ratio (95% CI)	2.09 (1.09, 4.02)	3.11 (1.68, 5.76)	
		p-value	0.0274	0.0003	
		Risk difference	0.99 (-0.21, 2.20)	2.71 (1.15, 4.27)	
Number of qualifying risk factors	<3	Number of patients (%)	5468 (78.2)	5497 (79.0)	5492 (78.5)
		Patients with events	102 (1.9%)	78 (1.4%)	40 (0.7%)
		KM %	2.7%	1.9%	1.0%
		Hazard Ratio (95% CI)	2.90 (2.01, 4.18)	2.09 (1.42, 3.05)	
		p-value	<.0001	0.0002	
		Risk difference	1.68 (1.06, 2.31)	0.91 (0.37, 1.46)	
		p-value for interaction	0.3836	0.2748	
Number of qualifying risk factors	>=4	Number of patients (%)	371 (5.3)	368 (5.3)	403 (5.8)
		Patients with events	5 (1.3%)	16 (4.3%)	1 (0.2%)
		KM %	1.9%	7.6%	0.4%
		Hazard Ratio (95% CI)	7.01 (0.82, 60.06)	20.75 (2.75, 156.46)	
		p-value	0.0755	0.0033	
		Risk difference	1.50 (-0.56, 3.57)	7.16 (3.17, 11.14)	
	<4	Number of patients (%)	6617 (94.7)	6590 (94.7)	6593 (94.2)
		Patients with events	122 (1.8%)	99 (1.5%)	53 (0.8%)
		KM %	2.6%	2.1%	1.1%
		Hazard Ratio (95% CI)	2.61 (1.89, 3.60)	2.02 (1.45, 2.82)	
		p-value	<.0001	<.0001	
		Risk difference	1.54 (0.97, 2.12)	0.96 (0.44, 1.49)	
		p-value for interaction	0.3923	0.0256	

In PEGASUS, the known effect of **dyspnoea AEs** were also reported at a higher frequency on ticagrelor compared with placebo, and a higher frequency on 90 mg compared with 60 mg: 19%, 15.9%, and 6.4%: HR 3.55 (95% CI 3.17, 3.99) for 90 mg, and HR 2.82 (95% CI 2.50, 3.17) for 60 mg. The majority of dyspnoea events, in either ticagrelor dose group, was classed by the investigator as mild or moderate in

severity. Severe AEs of dyspnoea were infrequent. The **time to onset of first dyspnoea AE** was shorter in the ticagrelor treatment groups: 35.0%, 28.0%, and 8.1% of patients with dyspoea AEs reported a dyspnoea AE within 3 days from start of treatment in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively. The pattern of dyspnoea AEs, SAEs, and disocntinuations due to AEs in the ticagrelor groups compared with placebo was similar, regardless of whether patients had a medical history of COPD or asthma.

Bradyarrhythmic AEs were reported in 2.0% for ticagrelor 90 mg, 2.3% for 60 mg, and 2.0% for placebo: HR 1.14 (95% CI 0.87, 1.49) for 90 mg, and HR 1.25 (95% CI 0.96, 1.63) for 60 mg. **Hypotension AEs** were reported in 2.2% for 90 mg, 2.1% for 60 mg, and 1.5% for placebo: HR 1.43 (95% CI 1.08, 1.88) for 90 mg, and HR 1.40 (95% CI 1.06, 1.84) for 60 mg. AEs of **syncope** were reported for a slightly higher number of patients on ticagrelor compared with placebo. Syncope AEs were reported in 1.6% for 90 mg, 1.6% for 60 mg, and 1.1% for placebo: HR 1.47 (95% CI 1.05, 2.06) for 90 mg, and HR 1.48 (95% CI 1.06, 2.06) for 60 mg.

In PEGASUS the frequency of **renal-related AEs** was similar across the treatment groups. Renal-related AEs were reported in 3.3%, 3.4%, and 2.9%: HR 1.17 (95% CI 0.94, 1.46) for 90 mg, and HR 1.17 (95% CI 0.94, 1.45) for 60 mg. Mean values for absolute change from baseline in creatinine increased slightly over time in the ticagrelor treatment groups, but values at the follow-up visit were similar in all treatment groups. The frequencies of patients with changes in serum creatinine and eGFR were similar across all treatment groups, with few patients having large changes from baseline.

A **reversible increase in serum uric acid levels** of 6.3% and 5.6% from baseline to last observation on treatment was found for ticagrelor 90 mg and ticagrelor 60 mg, respectively, compared with a 1.5% decrease in the placebo group. AEs of gout or gouty arthritis were infrequent, but more common in the ticagrelor groups: 2.3%, 2.0%, and 1.5%: HR 1.77 (95% CI 1.32, 2.37) for 90 mg, and HR 1.48 (95% CI 1.10, 2.00) for 60 mg.

In PEGASUS, **hepatic-related AEs** were infrequent.

Table 19 Hepatic-related AEs by preferred term – on treatment (safety analysis set)

	Number(%) of patients[a]		
Preferred term[b]	**Ticagrelor 90 mg bd (N=6988)**	**Ticagrelor 60 mg bd (N=6958)**	**Placebo (N=6996)**
Patients with at least 1 hepatic AE[c]	**29 (0.4%)**	**41 (0.6%)**	**29 (0.4%)**
Hepatic steatosis	16 (0.2%)	22 (0.3%)	15 (0.2%)
Liver disorder	7 (0.1%)	5 (0.1%)	1 (0.0%)

There were few hepatic-related SAEs (n=6) or DAEs (n=3); the frequencies were similar across treatment groups. There were no hepatic-related AEs with outcome death reported on ticagrelor.

In PEGASUS, the number of men with **AEs of gynaecomastia** was low and evenly distributed across the groups: 10 on ticagrelor 90 mg, 8 on 60 mg, and 11 on placebo.

Serious adverse event/deaths/other significant events

The 3 **most commonly reported SAEs** by preferred term were non-cardiac chest pain, atrial fibrillation, and pneumonia.

Table 20 SAEs (including bleeding) by preferred term (with frequency > 0.2%) – on treatment (safety analysis set)

	Number (%) of patients[a]		
Preferred term	**Ticagrelor 90 mg bd (N=6988)**	**Ticagrelor 60 mg bd (N=6958)**	**Placebo (N=6996)**
Patients with any SAE	1514 (21.7%)	1499 (21.5%)	1511 (21.6%)
Non-cardiac chest pain	88 (1.3%)	91 (1.3%)	91 (1.3%)
Atrial fibrillation	57 (0.8%)	74 (1.1%)	52 (0.7%)
Pneumonia	46 (0.7%)	41 (0.6%)	55 (0.8%)
Chronic obstructive pulmonary disease	40 (0.6%)	28 (0.4%)	34 (0.5%)
Cardiac failure congestive	36 (0.5%)	37 (0.5%)	31 (0.4%)
Angina pectoris	35 (0.5%)	36 (0.5%)	46 (0.7%)
Cardiac failure	30 (0.4%)	39 (0.6%)	38 (0.5%)

Deaths

The frequency of **death (including bleeding)** was 4.8% (n=333), 4.2% (n=290), and 4.7% (n=329) for the ticagrelor 90 mg, ticagrelor 60 mg and placebo groups, respectively. **When bleeding events were excluded**, the frequency of death was 4.4% (n=304), 3.9% (n=274), and 4.4% (n=309) for ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively. The frequency of AEs with outcome of death 'on treatment' was lower for the ticagrelor groups compared with placebo: 161 patients (2.3%), 149 (2.1%), and 203 (2.9%) for ticagrelor 90 mg, 60 mg, and placebo, respectively. The most common AEs with outcome of death, by SOC were General disorders and administration site conditions, Cardiac disorders, and Neoplasms benign, malignant and unspecified (incl cysts and polyps). These were reported at a similar frequency across the treatment groups. By preferred term, the most common AEs with outcome of death were sudden cardiac death, death, and acute myocardial infarction, all reported at lower frequencies in the ticagrelor groups compared with placebo.

Kaplan-Meier percentages for adjudicated **non-CV deaths** for the safety analysis set 'on treatment' were: 0.6%, 0.5%, and 0.7% for ticagrelor 90 mg, 60 mg, and placebo, respectively; and for 'on and off treatment' were: 2.3%, 1.8%, and 1.8%, respectively, attributable to the most common causes, ie, malignancies and infections. For **adjudicated non-CV deaths classified as infections**, the Kaplan-Meier percentages for the safety analysis set 'on treatment' were 0.2%, 0.1%, and 0.1% for the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively; and for 'on and off treatment' were: 0.5%, 0.4%, and 0.4%, respectively.

For **malignancy AEs**, no imbalance was seen for ticagrelor 60 mg versus placebo in either 'on treatment' or 'on and off treatment' analyses. There was no consistency with regard to ticagrelor dose or location of neoplasms for either the reported malignancy AEs or adjudicated malignancy deaths. Since neoplasms may be detected following a bleeding, patients who had a bleeding event prior to reported malignancy or classification of death due to malignancy were analysed. The results may indicate a potential bias in the detection of malignancy events and in classification of deaths towards malignancy.

Table 21 Reported AEs of neoplasms in the SMQ Malignant or unspecified tumours presented by HLGT – on and off treatment (safety analysis set)

	Number (%) of patients		
High level group term	**Ticagrelor 90 mg N=6988**	**Ticagrelor 60 mg N=6958**	**Placebo N=6996**
Patients with at least 1 malignancy event	**376 (5.4%)**	**335 (4.8%)**	**328 (4.7%)**
Gastrointestinal neoplasms malignant and unspecified	84 (1.2%)	76 (1.1%)	69 (1.0%)
Skin neoplasms malignant and unspecified	75 (1.1%)	64 (0.9%)	77 (1.1%)
Reproductive neoplasms male malignant and unspecified	52 (0.7%)	50 (0.7%)	49 (0.7%)
Respiratory and mediastinal neoplasms malignant and unspecified	63 (0.9%)	36 (0.5%)	40 (0.6%)
Renal and urinary tract neoplasms malignant and unspecified	40 (0.6%)	44 (0.6%)	30 (0.4%)

There were 77, 63, and 53 **deaths classified as malignancy** in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups 'on and off treatment', respectively, corresponding to Kaplan-Meier percentages at 36 months of 1.2%, 1.0%, and 0.9%: HR 1.45 (95% CI 1.02, 2.06) for 90 mg, and HR 1.19 (95% CI 0.82, 1.71) for 60 mg. Of the adjudicated non-CV death classified as malignancy, **48 were preceded by any TIMI bleeding** requiring medical attention or higher category of bleeding: 20, 19, and 9 in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo groups, respectively. Of the 145 reports not preceded by a reported bleeding event, there were numerically more such events in the ticagrelor 90 mg group and equal numbers in the ticagrelor 60 mg and placebo groups: 57, 44, and 44, respectively: HR 1.42 (95% CI 0.96, 2.10) for 90 mg, and HR 1.07 (95% CI 0.71, 1.63) for 60 mg. These results, showing a smaller imbalance between ticagrelor and placebo than was observed in the overall analysis of adjudicated deaths classified as malignancy, indicate bias may play a contributing role.

Laboratory findings

There were no apparent treatment differences in either mean values or mean changes from baseline in erythrocytes, platelets, leucocytes, lymphocytes, basophils, eosinophils, neutrophils, and monocytes. A minor trend for decreased mean haemoglobin values from baseline was observed during treatment with ticagrelor compared with placebo.

There were no apparent treatment differences in either mean value or mean change from baseline in ALP, AST, ALT, total bilirubin, or glucose. Five patients had combined ALT or AST (>3xULN) and bilirubin (>2xULN) elevations at the end of treatment (2, 1, and 2 patients in the ticagrelor 90 mg, ticagrelor 60 mg, and placebo treatment groups, respectively). Each of these patients had significant medical history which alone could have resulted in these observations. In PEGASUS, data on urinalysis was collected at baseline, after 12 months on treatment, and at the end of treatment visit. There were no apparent differences across the treatment groups.

Safety in special populations

Table 53 summarizes AE frequencies by the requested categories and age groups. The data suggest that the AE profile was generally consistent across age groups, though events rates increased with age across all treatment groups. Small numerical differences between treatment groups were occasionally observed; however, given the multiple analyses, and varying sizes of the subgroups compared, the impact of any

interactions should be interpreted with caution. The data presented do not indicate any safety concerns for treatment with ticagrelor in elderly patients.

Table 53 Adverse event categories by age - on treatment (safety analysis set)

Category	Number (%) of patients		
Treatment group	**< 65 yrs**	**65-75 yrs**	**>75 yrs**
Total number of patients			
Ticagrelor 90 mg	3160	2955	873
Ticagrelor 60 mg	3252	2874	832
Placebo	3123	3044	829
Total - patients with any AE			
Ticagrelor 90 mg	2290 (72.47)	2334 (78.98)	703 (80.53)
Ticagrelor 60 mg	2320 (71.34)	2269 (78.95)	679 (81.61)
Placebo	2030 (65.00)	2191 (71.98)	616 (74.31)
Fatal [a]			
Ticagrelor 90 mg	57 (1.80)	67 (2.27)	37 (4.24)
Ticagrelor 60 mg	50 (1.54)	67 (2.33)	32 (3.85)
Placebo	78 (2.50)	78 (2.56)	47 (5.67)
Serious			
Ticagrelor 90 mg	621 (19.65)	649 (21.96)	244 (27.95)
Ticagrelor 60 mg	590 (18.14)	674 (23.45)	235 (28.25)
Placebo	599 (19.18)	682 (22.40)	230 (27.74)
Withdrawal [b]			
Ticagrelor 90 mg	445 (14.08)	618 (20.91)	243 (27.84)
Ticagrelor 60 mg	375 (11.53)	532 (18.51)	210 (25.24)
Placebo	204 (6.53)	283 (9.30)	109 (13.15)
CNS (confusion / extrapyramidal) [c]			
Ticagrelor 90 mg	9 (0.28)	17 (0.58)	5 (0.57)
Ticagrelor 60 mg	14 (0.43)	12 (0.42)	5 (0.60)
Placebo	11 (0.35)	20 (0.66)	9 (1.09)
AE related to falling [d]			
Ticagrelor 90 mg	572 (18.10)	635 (21.49)	193 (22.11)
Ticagrelor 60 mg	570 (17.53)	628 (21.85)	197 (23.68)
Placebo	377 (12.07)	488 (16.03)	159 (19.18)
CV events [e]			

Table 53 Adverse event categories by age - on treatment (safety analysis set)

Category	Number (%) of patients		
Treatment group	< 65 yrs	65-75 yrs	>75 yrs
Ticagrelor 90 mg	535 (16.93)	495 (16.75)	174 (19.93)
Ticagrelor 60 mg	574 (17.65)	548 (19.07)	191 (22.96)
Placebo	538 (17.23)	612 (20.11)	205 (24.73)
Cerebrovascular events [f]			
Ticagrelor 90 mg	31 (0.98)	24 (0.81)	11 (1.26)
Ticagrelor 60 mg	18 (0.55)	27 (0.94)	10 (1.20)
Placebo	34 (1.09)	28 (0.92)	10 (1.21)
Infections [g]			
Ticagrelor 90 mg	694 (21.96)	668 (22.61)	207 (23.71)
Ticagrelor 60 mg	704 (21.65)	659 (22.93)	195 (23.44)
Placebo	664 (21.26)	716 (23.52)	227 (27.38)

Source: Table Q46.1.
a Any AE with outcome = death.
b Any AE leading to discontinuation of study drug.
c High Level Term=Confusion and disorientation OR High Level Group Term = Movement disorders (incl Parkinsonism).
d Accidents and injuries SMQ (see preferred terms listed in Appendix J), OR High Level Term=Coordination and balance disturbances, OR any of the preferred terms related to falling (see Appendix J).
e System organ class = Cardiac disorders OR Vascular disorders.
f Cerebrovascular disorders SMQ (see preferred terms listed in Appendix J).
g System organ class = Infections and infestations.
Patients with multiple events are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Includes adverse events with an onset date on or after the date of first dose and up to and including 7 days following the date of last dose of study drug.
MedDRA version 17.0.

Safety related to drug-drug interactions and other interactions

For the 1157 patients treated with concomitant moderate CYP3A4 inhibitors, overall frequencies for TIMI Major, TIMI Minor, and PLATO Major bleeding events were similar to the frequencies for these events in the overall study population.

Discontinuation due to adverse events

A higher proportion of patients prematurely discontinued from study drug in both the ticagrelor 90 mg (32.0%) and 60 mg (28.7%) groups than in the placebo group (21.4%). The frequency of patients with discontinuations due to AEs was higher in the ticagrelor groups than in the placebo group: 18.7%, 16.1%, and 8.5% of patients on ticagrelor 90 mg, 60 mg, and placebo, respectively. The proportion of patients who discontinued study drug due to SAEs was higher in the ticagrelor groups than on placebo: 3.7%, 3.7%, and 3.0% on ticagrelor 90 mg, 60 mg, and placebo, respectively.

Table 22 AEs (including bleeding) leading to discontinuation of study drug, by preferred term (with frequency >0.1%) – on treatment (safety analysis set)

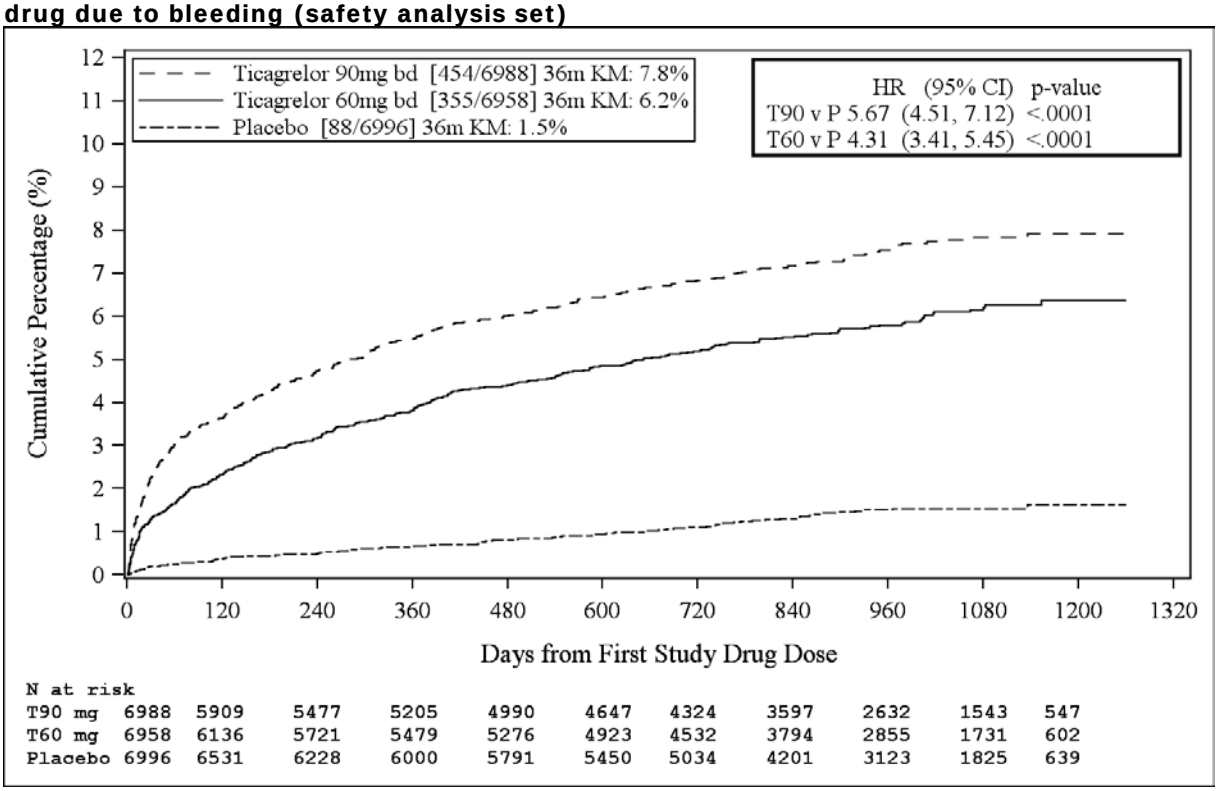
	Number (%) of patients[a]		
Preferred term	**Ticagrelor 90 mg bd (N=6988)**	**Ticagrelor 60 mg bd (N=6958)**	**Placebo (N=6996)**
Patients with an AE leading to discontinuation[b]	**1306 (18.7%)**	**1117 (16.1%)**	**596 (8.5%)**
Dyspnoea	420 (6.0%)	281 (4.0%)	49 (0.7%)

Table 22 AEs (including bleeding) leading to discontinuation of study drug, by preferred term (with frequency >0.1%) – on treatment (safety analysis set)

	Number (%) of patients[a]		
Preferred term	**Ticagrelor 90 mg bd (N=6988)**	**Ticagrelor 60 mg bd (N=6958)**	**Placebo (N=6996)**
Increased tendency to bruise	90 (1.3%)	61 (0.9%)	5 (0.1%)
Epistaxis	69 (1.0%)	49 (0.7%)	13 (0.2%)
Atrial fibrillation	59 (0.8%)	84 (1.2%)	78 (1.1%)
Spontaneous haematoma	58 (0.8%)	42 (0.6%)	3 (0.0%)
Dizziness	32 (0.5%)	29 (0.4%)	19 (0.3%)
Diarrhoea	24 (0.3%)	27 (0.4%)	14 (0.2%)
Nausea	23 (0.3%)	19 (0.3%)	15 (0.2%)
Headache	20 (0.3%)	19 (0.3%)	12 (0.2%)
Contusion	19 (0.3%)	18 (0.3%)	4 (0.1%)
Ecchymosis	17 (0.2%)	17 (0.2%)	0 (0.0%)
Fatigue	17 (0.2%)	20 (0.3%)	8 (0.1%)
Haematuria	16 (0.2%)	18 (0.3%)	6 (0.1%)
Traumatic haematoma	15 (0.2%)	9 (0.1%)	0 (0.0%)
Abdominal pain upper	13 (0.2%)	24 (0.3%)	17 (0.2%)
Asthenia	13 (0.2%)	12 (0.2%)	6 (0.1%)
Traumatic intracranial haemorrhage	12 (0.2%)	13 (0.2%)	7 (0.1%)
Dyspepsia	11 (0.2%)	15 (0.2%)	7 (0.1%)
Iron deficiency anaemia	10 (0.1%)	3 (0.0%)	3 (0.0%)
Rash	10 (0.1%)	4 (0.1%)	6 (0.1%)
Gastric ulcer haemorrhage	9 (0.1%)	7 (0.1%)	3 (0.0%)
Atrial flutter	8 (0.1%)	8 (0.1%)	11 (0.2%)
Gingival bleeding	8 (0.1%)	5 (0.1%)	4 (0.1%)
Pruritus	8 (0.1%)	7 (0.1%)	6 (0.1%)
Rectal haemorrhage	8 (0.1%)	8 (0.1%)	3 (0.0%)
Vertigo	8 (0.1%)	8 (0.1%)	5 (0.1%)
Dyspnoea exertional	7 (0.1%)	12 (0.2%)	2 (0.0%)
Gastrointestinal haemorrhage	7 (0.1%)	16 (0.2%)	6 (0.1%)
Haemorrhoidal haemorrhage	7 (0.1%)	4 (0.1%)	1 (0.0%)
Insomnia	7 (0.1%)	7 (0.1%)	3 (0.0%)
Malaise	7 (0.1%)	2 (0.0%)	4 (0.1%)
Pain in extremity	7 (0.1%)	4 (0.1%)	2 (0.0%)
Palpitations	7 (0.1%)	9 (0.1%)	2 (0.0%)
Traumatic haemorrhage	7 (0.1%)	5 (0.1%)	1 (0.0%)

Discontinuations due to any bleeding event were reported for a greater proportion of patients in the ticagrelor 90 mg (6.5%) and ticagrelor 60 mg (5.1%) groups than in the placebo (1.3%) group. The most common bleeding DAEs were increased tendency to bruise, epistaxis, and spontaneous haematoma; these were more frequent on ticagrelor compared with placebo.

Table 23 Kaplan-Meier estimate of time to premature permanent discontinuation of study drug due to bleeding (safety analysis set)



The frequency of **dyspnoea discontinuations due to AEs** was higher on ticagrelor than on placebo, and higher in the 90 mg group than the 60 mg group. Dyspnoea DAEs were reported in 6.5%, 4.5%, and 0.8%: HR 8.89 (95% CI 6.65, 11.88) for ticagrelor 90 mg and HR 6.04 (95% CI 4.48, 8.12) for ticagrelor 60 mg.

Of the patients who permanently discontinued study drug due to dyspnoea, 49.5%, 43.9% and 23.5% of patients on ticagrelor 90 mg, ticagrelor 60 mg, and placebo, respectively, discontinued within the first 7 days of treatment.

2.6.1. Discussion on clinical safety

Almost 7000 patients have been included in each treatment group to be able to demonstrate a difference in treatment effect. A total of 20942 patients (99% of randomised patients) received at least 1 dose of randomised study drug (ticagrelor or placebo). The large number of patients provided substantial placebo-controlled information on safety of ticagrelor. This included 6988 patients who received the known dose of ticagrelor 90 mg, 6958 receiving the new investigated dose ticagrelor 60 mg, and 6996 receiving placebo. The safety information was complemented by existing information on ticagrelor, from clinical trials and post-marketing use.

AEs were reported at a higher frequency for ticagrelor than for placebo (76.2%, 75.7% and 69.1%, for 90 mg, 60 mg and placebo, respectively). The most commonly reported AEs on ticagrelor and reported

at a higher frequency were dyspnoea (15.6%, 12.4%, 4.4%), epistaxis (7.3%, 6.1%, 2.2%), and increased tendency to bruise (6.6%, 6.0%, 0.9%).

The definition used to identify and define bleeding events was in accordance with general and accepted definition categories (TIMI, PLATO. GUSTO and ISTH) and therefore appropriate, in particular the TIMI scale as the main analysis method for bleeding events. As can be expected a higher AE risk for bleeding was reported, 32.3%, 29.1%, and 11.5% of patients in the ticagrelor 90 mg, 60 mg, and placebo, and seemed dose related. Bleeding risk was also significantly increased after 36 months of treatment and consistently across all bleeding scales used. Fatal bleedings were rare and approximately similar numbers were reported across the treatment groups. There was no sign of dose relation as more fatal events (11 cases) were reported in the 60 mg dose group compared to the 90 mg dose (6 cases), and 12 cases in the placebo group, mostly due to intracranial bleedings. The number of intracranial bleedings was limited, but higher for ticagrelor, with similar frequency for both doses (29 [on 90 mg], 28 [on 60mg], and 23 [on placebo] patients). The higher bleeding risk with ticagrelor was clearly observed for the major bleedings with a significant higher frequency in the ticagrelor groups, 95, 83, and 25 patients on ticagrelor 90 mg, 60 mg, and placebo, HR 2.69 (95% CI 1.96, 3.70), p<0.0001 for 90 mg, and HR 2.32 (95% CI 1.68, 3.21), p<0.0001 for 60 mg, and were mainly attributed to GI tract bleedings. This had a major impact as it also translated into a higher frequency of hospitalisations (3.7%, 3.1%, and 1.6%) and transfusions (3.2%, 3.1%, and 1.7%).

In general, the observed higher bleeding risk of ticagrelor-treated patients was consistent across subgroups, with only small differences in the subgroups 'time from qualifying MI > or < 2 years', and 'type of stent' used. Further analyses within the 60 mg dose group also indicated a higher bleeding risk with more qualifying risk factors.

Dyspnoea is a known adverse event of ticagrelor, which has been specifically followed within the clinical program. Also in PEGASUS a significant dose related effect on the frequency of dyspnoea was observed (19%, 15.9%, and 6.4%: HR 3.55 (95% CI 3.17, 3.99) for 90 mg, and HR 2.82 (95% CI 2.50, 3.17) for 60 mg), as well as for the onset of AE of dyspnoea (35.0%, 28.0%, and 8.1% within 3 days fom start of treatment). As known from previous evaluation, dyspnoea did not impact pulmonary or cardiac function (DISPERSE II and PLATO).

Specific attention has been given to bradyarrhythmic AEs, with no apparent differences in frequency of these adverse events observed between treatment groups, which was considered reassuring (2.0% for ticagrelor 90 mg, 2.3% for 60 mg, and 2.0% for placebo). Dizziness and hypotension could be associated with bradyarrhythmic AEs. Dizziness was not observed at a higher frequency for ticagrelor while hypotension was (2.2% for 90 mg, 2.1% for 60 mg, and 1.5% for placebo). This could have been related to baseline differences. Syncope, also known to be possibly related with bradyarrhythmic AEs, was reported at a higher frequency (1.6% for 90 mg, 1.6% for 60 mg, and 1.1% for placebo), few cases may have been related to bradyarrhythmic AEs. No dose response was observed with these types of adverse events. Given this observation and the absence of differences in bradyarrhythmic AEs, this was considered reassuring.

Specific attention was given to renal related AEs. However, there seemed no clear evidence of any impact of ticagrelor on AEs-related to renal function or the kidney; (3.3%, 3.4%, and 2.9% for 90 mg, 60 mg of ticagrelor and placebo respectively). Although slight differences appeared in the mean serum creatinine and eGFR values over time, this was not supported by the number of individuals with changes in eGFR nor by the renal related AEs.

A known effect of reversible increase in uric acid was observed for ticagrelor (6.3% and 5.6% from baseline to last observation on treatment for ticagrelor 90 mg and 60 mg, respectively, compared with a

1.5% decrease in the placebo), which seemed dose related, with corresponding infrequent observation of a significantly higher frequency in AEs of gout or gouty arthritis (115, 101, and 74 patients; HR 1.77 (95% CI 1.32, 2.37) for 90 mg, and HR 1.48 (95% CI 1.10, 2.00) for 60 mg). For gout and urate nephropathy, differences appeared to be substantial according to gender for the 60 mg dose (male (n=10.614): HR 1.68 (1.21-2.33 vs female (n=3365): HR 0.61 (0.26-1.44)). However, these data were not consistent with the observation for renal AEs, where no clear difference could be observed according to gender.

Hepatic related events did not to raise concern, although any conclusions were difficult to draw based on the limited number of events.

No differences in AEs of gynaecomastia were observed with very limited AEs identified.

SAEs were reported at similar frequency, with 21.7%, 21.5%, and 21.6 SAE's for the ticagrelor 90 mg, 60 mg, and placebo groups, respectively. Non-cardiac chest pain, atrial fibrillation, and pneumonia were the most frequently reported SAE's. Atrial fibrillation, chronic obstructive pulmonary disease, and cardiac failure congestive were the most frequently reported SAEs for which the frequency was higher for ticagrelor.

Deaths were reported as SAEs as well as efficacy endpoints in PEGASUS. Ticagrelor treatment did not lead to a higher frequency of death, as well as for the 'on treatment' frequency. Based on the efficacy endpoint the HR for overall mortality was estimated at HR 1.00 (95% CI: 0.86-1.16) and 0.89 (95% CI: 0.76-1.04) for the 90 and 60 mg, respectively.

Only few cases of infections leading to death were reported, with highest numbers observed in the 90 mg dose. A numerical higher number of AEs classified as malignancies was found in the 'on and off treatment' analysis; HR 1.15 (0.99-1.33), p= 0.066 for 90 mg BID and HR 1.03 (0.88-1.19) for 60 mg ticagrelor). This was likely due to detection bias. Since neoplasms may be detected following a bleeding, patients who had a bleeding event prior to reported malignancy or classification of death due to malignancy were analysed. The results may indicate a potential bias in the detection of malignancy events and in classification of deaths towards malignancy. The number of nonfatal malignancy AEs that were not preceded by a bleeding event were approximately similar (290, 254, and 289 patients; HR 1.09 (95% CI 0.92, 1.28) for 90 mg, and HR 0.94 (95% CI 0.79, 1.11) for 60 mg). A small numerical higher number of malignancy-related deaths not preceded by a bleeding event were also found for ticagrelor (57, 44, and 44: HR 1.42; 95% CI 0.96, 2.10) for 90 mg, and HR 1.07 (95% CI 0.71, 1.63) for 60 mg). Although, for the 60 mg BID no clear signal emerges and for the higher dose this may still be a chance finding. Reassuring is the outcome of the PLATO study, which did not find any imbalances for malignancies between the treatment groups. Any clear evidence of a pharmacological effect could also not be identified. Therefore, a treatment related increase in malignancies was considered unlikely.

No clinical impact could be observed for haematology parameters for ticagrelor. The impact on serum creatinine and serum uric acid has already been discussed. The impact on liver enzymes seems not relevant and could have been impacted by patient history.

In general, a similar safety in specific populations (age, sex, race) could be observed for dyspnoea, bradyarrhythmias, renal impairment, gout and urate nephropathy, hepatic-related AEs, gynaecomastia, and drug-drug interactions with moderate and strong CYP3A4 inhibitors.

A large proportion of patients discontinued treatment with ticagrelor, which subside the usability for long term treatment in clinical practice (32.0%, 28.7%, and 21.4%). This was mainly driven by experiencing of adverse events, mainly bleeding events and dyspnoea. As known, dyspnoea occurs mainly at start of treatment, consequently discontinuations were mainly observed within the first 7 days of treatment. For

bleedings, discontinuation was also mainly observed with the first months of treatment, with additional wearing off of the discontinuation rate.

The applicant proposed has decided to remove 9 current ADR terms from the core prescribing information, as the data showed no increased risk with ticagrelor compared to placebo, according to the applicant. The removed ADR terms were: headache, paraesthesia, abdominal pain, constipation, dyspepsia, gastritis, vomiting, rash, and hypersensitivity reactions. For paraesthesia and vomiting, frequencies and rates clearly indicate no substantial differences, and therefore deletion of these ADRs can be considered appropriate. For hypersensitivity reactions, also no differences were found, but due to a higher frequency in clinical practice, this ADR remained in the SmPC. For headache, dyspepsia, rash, constipation, a higher frequency and rate were identified. The decision of removal from the list of ADRs based on a difference in event rate of less than 0.20 per 100 patient-years between ticagrelor and placebo appeared to be rather arbitrary. For headache, rash and constipation, KM rates over time remained above placebo level. For dyspepsia this was less clear. Therefore, it was not considered appropriate to delete headache, rash and constipation from section 4.8 of the SmPC.

2.6.2. Conclusions on the clinical safety

AEs were reported at a higher frequency for ticagrelor than for placebo (with SAEs were reported at similar frequency) . A clear higher bleeding risk was observed for ticagrelor treatment than placebo. This was judged to be dose dependent with lower frequencies observed with the 60 mg dose compared to the 90 mg dose. Despite the higher bleeding risk, fatal and intracranial bleedings were approximately similar across the treatment groups and comparable to placebo. A treatment related increase in malignancies was considered unlikely to occur. A large proportion of patients discontinued, what was largely driven by dyspnoea and bleedings. This could impact on long term treatment with ticagrelor. Other AEs were in line with the known safety profile of ticagrelor.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 10, dated 7 December 2015 is acceptable.

The CHMP endorsed the Risk Management Plan version 9 with the following content:

Safety concerns

Important identified risks	• Increased risk of bleeding • Dyspnoea • Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; drugs metabolised through CYP3A4 (eg, simvastatin), digoxin (inhibition of P-gp transporter by ticagrelor) and cyclosporine (P-gP and CYP3A inhibitor)
Important potential risks	• Bradyarrhythmias
Missing information	• Use in patients with moderate or severe hepatic impairment • Use in patients with risk factors for bleeding • Use in children • Use in pregnant or lactating women • Long-term use in patients with prior ischaemic stroke • Use in patients with renal failure requiring dialysis

As per post-authorisation measure MEA006 within current application the MAH presented a summary of drug induced liver injury (DILI) findings in PLATO, PEGASUS, and PSUR reports. The hepatic laboratory data from PLATO did not give any evidence that ticagrelor affects hepatic function. This conclusion was confirmed in PEGASUS study. Similarly, evaluations of the PSUR data in the last years have not raised any safety concerns. Nevertheless it has been recommended that DILI should be discussed in future submission if new relevant safety information is identified. The argument of the MAH was agreed to remove DILI from the list of important potential risks.

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned started)	Date for submission of interim or final reports (planned or actual)
DUS in Sweden (D5130N00010) A pharmaco-epidemiological study to examine patient characteristics, drug utilisation pattern, and crude incidence rates of selected outcomes in new users of ticagrelor, clopidogrel, and prasugrel in national registries in Sweden Non-interventional cohort, category 3	To provide a detailed description of patients who are prescribed ticagrelor for the first time and to compare them with patients who are prescribed clopidogrel and prasugrel for the first time, and estimate potential off-label use of ticagrelor. To ascertain incident cases of selected outcomes and estimate crude incidence rate of selected outcomes among new users in the 3 cohorts of ticagrelor, clopidogrel, and prasugrel.	Increased risk of bleeding; Dyspnoea; Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; drugs metabolised through CYP3A4 (eg simvastatin), digoxin (inhibition of P-gp transporter by ticagrelor) and cyclosporine (P-gP and CYP3A inhibitor); Bradyarrhythmias; Use in patients with moderate or severe hepatic impairment; Use in patients with risk factors for bleeding	Started	Final report planned for Q4 2015.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important Identified Risk: **Dyspnoea**	**Routine** Appropriate wording in the SmPC, Section 4.4, 4.8 and in the Package Leaflet.	None
Important Identified risk: **Drug-drug interactions: Strong inhibitors/inducers of CYP3A4; moderate inhibitors of CYP3A4; drugs metabolised through CYP3A4 (eg simvastatin), digoxin (inhibition of P-gp transporter by ticagrelor) and cyclosporine (P-gP and CYP3A inhibitor)**	**Routine** Appropriate wording in the SmPC, Section 4.3, 4.4, 4.5 and in the Package Leaflet.	None
Important Potential risk: **Bradyarrhythmias**	**Routine** Appropriate wording in the SmPC, Section 4.4, 4.5 and in the Package Leaflet.	None
Missing information: **Use in patients with moderate or severe hepatic impairment**	**Routine** Appropriate wording in the SmPC, Section 4.2, 4.3, 4.4 and in the Package Leaflet.	None
Missing information: **Use in patients with risk factors for bleeding**	**Routine** Appropriate wording in the SmPC, Section 4.3, 4.4 and in the Package Leaflet.4.	None
Missing information: **Use in children**	**Routine** Appropriate wording in the SmPC, Section 4.2 and in the Package Leaflet.	None
Missing Information: **Use in pregnant or lactating women**	**Routine** Appropriate wording in the SmPC, Section 4.6 and in the Package Leaflet.	None
Missing Information **Long-term use in patients with prior ischaemic stroke**	**Routine** Appropriate wording in the SmPC, Section 4.4 and in the Package Leaflet.	None
Missing information **Use in patients with renal failure requiring dialysis**	**Routine** Appropriate wording in the SmPC, Section 4.2 and in the Package Leaflet.	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Ticagrelor, an oral, reversible, antiplatelet agent, has previously been approved for the 90 mg BID dose for the prevention of atherothrombotic events in patients with acute coronary syndrome (unstable angina, NSTEMI or STEMI) including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG). Under this indication treatment is recommended for up to 12 months unless earlier discontinuation of ticagrelor is clinically indicated. With current application a new 60 mg tablet strength and a new indication were proposed for the prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke) in patients with a history of myocardial infarction (MI occurred at least one year ago), and a high risk of developing a thrombotic event for the 60 mg BID dose. This is based on the results of the PEGASUS trial; a randomised, double-blind, placebo-controlled, 3-arm parallel group (90 mg and 60 mg ticagrelor on top of ASA), multinational, event-driven study for a median of 21.8 months in 20942 patients.

A consistent beneficial effect on the **composite primary endpoint** of CV death, MI and stroke was demonstrated for both the 90 mg and 60 mg BID dose. The Kaplan–Meier rates at 3 years were 7.8% in the 90 mg BID ticagrelor group, 7.7% in the 60 mg BID group, and 9.0% in the placebo group. This translated in hazard rates (HR) of 0.85 (95% CI 0.75, 0.96), p=0.0080 for ticagrelor 90 mg, and HR of 0.84 (95% CI 0.74, 0.95), p=0.0043 for ticagrelor 60 mg. The effect was consistent throughout the treatment period; hazard rates were constant for the first year and subsequent years of treatment. MI contributed the most to the overall effect (898 events), followed by CV deaths (566 events) and stroke (313 events). A consistent effect was demonstrated for the **individual components of the primary endpoint**, although efficacy was more robust for the 60 mg BID dose than the 90 mg dose with significant effects both for the occurrence of MI and stroke, but not for CV death, while the 90 mg BID dose was only significant for stroke.

The net clinical benefit of ticagrelor in comparison to a background treatment of ASA displays a neutral effect for the 90 mg BID dose based on the **composite for CV death, MI, stroke and TIMImajor bleedings in the full analysis set** and a numerical small beneficial effect for the 60 mg dose [HR 0.95 (95%CI 0.85-1.06) with 33 fewer patients (585 on ticagrelor vs. 618 on placebo) with an event of net clinical benefit during the study period. Another composite of net clinical benefit, comprised **all-cause mortality, MI, stroke, intracranial haemorrhage, and fatal bleeding** showed stronger beneficial effects with a HR 0.93 (0.84-1.04) for the 90mg BID dose and statistically significant findings HR 0.87 (0.78-0.97) for the 60 mg BID dose. Although these effects were modest, the effect was maintained during the entire study period. The net clinical benefit on the composite for **CV death, MI, stroke and major bleedings based on the 'on treatment' analysis** was consistent with these findings, with numerically greater effects on thrombotic events prevented, but also numerically more bleedings.

The effect was maintained also when excluding patients treated with additional blinded clopidogrel in the placebo arm (n=303, 4.3%). The majority of them had developed conditions for which an ADP receptor blocker is recommended (mainly ACS or arterial stenting).

Uncertainty in the knowledge about the beneficial effects.

Some **differences in subgroup analyses** were noticed between the 60 mg and 90 mg BID doses. Focusing on the approved with current application 60 mg BID dose, trend differences appeared in the age, sex, race, obesity, time since qualifying MI and time since previous treatment with ADP receptor blocker. Differences were likely due to chance finding and not easily explained based on any possible mechanism. However, **attenuated effects observed with increasing time since receiving an ADP receptor blocker and with increasing time since last MI** were of concern and therefore it was reflected in the SmPC that clinically stable patients over 2 years from the MI, or more than one year after stopping previous ADP receptor inhibitor treatment should not be treated with ticagrelor. Also, **almost all patients were Caucasian**, consequently, other races are underrepresented. The absolute risk reduction was greatest in patients with more qualifying risk factors. Yet, this potential increase in benefit appears to go hand in hand with an increased risk of TIMI major bleedings.

Risks

Unfavourable effects

From a total of 20942 patients, who received at least one dose of study drug, a higher frequency of AEs was reported for ticagrelor than for placebo (76.2%, 75.7% and 69.1%, for 90 mg, 60 mg and placebo, respectively). The most commonly reported AEs on ticagrelor and reported at a higher frequency than placebo were **dyspnoea** (15.6%, 12.4%, 4.4%), **epistaxis** (7.3%, 6.1%, 2.2%), and **increased tendency to bruise** (6.6%, 6.0%, 0.9%), respectively. SAEs were reported at a similar frequency. Atrial fibrillation, chronic obstructive pulmonary disease, and congestive heart failure were the most frequently reported SAEs for which the frequency was higher for ticagrelor.

As can be expected **a higher frequency of bleedings** was reported, 32.3%, 29.1%, and 11.5% of patients in the ticagrelor 90 mg, 60 mg, and placebo, according to the TIMI scale, and was dose related and consistently increased for all bleeding scales used (TIMI, PLATO, GUSTO, ISTH). The higher bleeding risk with ticagrelor was clearly observed for the major bleedings with a significantly higher frequency for ticagrelor, 95, 83, and 25 patients on ticagrelor 90 mg, 60 mg, and placebo, HR 2.69 (95% CI 1.96, 3.70), p<0.0001 for 90 mg, and HR 2.32 (95% CI 1.68, 3.21), p<0.0001 for 60 mg, and were mainly attributed to GI tract bleedings. This had a major impact as it also translated into a higher frequency of hospitalisations (3.7%, 3.1%, and 1.6%) and transfusions (3.2%, 3.1%, and 1.7%).

A large proportion of patients (32.0%, 28.7%, and 21.4%) **discontinued treatment** with ticagrelor, which was of concern for a drug intended for long-term treatment. The principal reason for discontinuation was because patients experienced adverse events, mainly bleedings and dyspnoea. As known, dyspnoea occurs mainly at start of treatment, consequently discontinuations were mostly observed within the first 7 days of treatment. For bleedings, discontinuations were mostly observed within the first months of treatment. A wearing off of the discontinuation rate mirrored this observation.

Dyspnoea was dose related with HR 3.55 (95% CI 3.17, 3.99) for 90 mg, and HR 2.82 (95% CI 2.50, 3.17) for 60 mg) compared to placebo.

Deaths were reported as SAEs and as efficacy endpoints in PEGASUS study. Ticagrelor treatment did not lead to a higher frequency of death. Based on the efficacy endpoint the HR for overall mortality was estimated at HR 1.00 (95% CI: 0.86-1.16) and 0.89 (95% CI: 0.76-1.04) for the 90 and 60 mg, respectively.

The known dose related, but reversible, **increase in uric acid** was also observed in PEGASUS study with corresponding slightly but significantly higher frequency of gout or gouty arthritis AEs (HR 1.77 (95% CI 1.32, 2.37) for 90 mg, and HR 1.48 (95% CI 1.10, 2.00) for 60 mg).

Abdominal pain and gastritis AEs occurred at similar rates (0.50, 0.60 and 0.51; 0.66, 0.59 and 0.66) in both ticagrelor groups and placebo. Deletion of these events from the label was thus considered acceptable.

Uncertainty in the knowledge about the unfavourable effects

Fatal bleedings were rare and were observed at approximately similar rates across the treatment groups. There was no sign of dose relation as more fatal events (11 cases) were reported in the 60 mg dose group compared to the 90 mg dose (6 cases), and 12 cases in the placebo group, mostly due to intracranial bleedings. The number of intracranial bleedings was limited, but higher for ticagrelor, with similar frequency for both doses (29, 28, and 23 patients, for ticagrelor 90mg, 60mg and placebo, respectively).

Only few cases were reported of **infections leading to death**, with highest numbers observed in the 90 mg dose.

A numerically higher number of AEs classified as **malignancies** was found in the 'on and off treatment' analysis; HR 1.15 (0.99-1.33), p= 0.066 for 90 mg BID and HR 1.03 (0.88-1.19) for 60 mg ticagrelor). In the opinion of the CHMP this was likely due to detection bias. Since neoplasms may be detected following a bleeding, patients who had a bleeding event prior to reported malignancy or classification of death due to malignancy were analysed. The results may indicate a potential bias in the detection of malignancy events and in classification of deaths towards malignancy. The number of nonfatal malignancy AEs that were not preceded by a bleeding event were approximately similar (290, 254, and 289 patients; HR 1.09 (95% CI 0.92, 1.28) for 90 mg, and HR 0.94 (95% CI 0.79, 1.11) for 60 mg). A small numerical higher number of malignancy-related deaths not preceded by a bleeding event was also found for ticagrelor with a HR 1.42; 95% CI 0.96, 2.10) for the 90 mg dose, and HR 1.07 (95% CI 0.71, 1.63) for the 60 mg dose. Thus, for ticagrelor 60 mg BID dose no clear signal emerges regarding malignancies and for the higher dose this may still be a chance finding. Reassuring was the lack of imbalance in the PLATO study, which did not find any imbalances for malignancies between ticagrelor 90 mg and clopidogrel. Any clear evidence of a pharmacological effect could also not be identified. Therefore, a treatment related increase in malignancies was unlikely.

In general, the risk of **major bleedings** seemed consistent across subgroups, with some small differences in subgroups of 'time from qualifying MI > or < 2 years', and 'type of stent'. Also, bleeding risk was higher for patients with more qualifying risk factors (≥ 2).

No difference was found for **bradyarrhythmic AEs** (2.0% for ticagrelor 90 mg, 2.3% for 60 mg, and 2.0% for placebo), although AEs likely to be associated with bradyarrhythmic AEs such as **hypotension** and **syncope** were reported at a higher frequency in ticagrelor arms. On the other hand, **dizziness** that may also be associated with bradyarrhythmia occurred at a similar frequency. These adverse events did not occur in higher frequency with increasing dose of ticagrelor. This observation was reassuring also given that no differences in bradyarrhythmic AEs were observed.

No clear evidence of any impact of ticagrelor on **AEs related to the renal function** was observed, with only slightly increased frequency of AEs for ticagrelor treatment (166, 173, and 161 patients; at 36 months 3.3%, 3.4%, and 2.9%, respectively for ticagrelor 90 mg, 60 mg, and placebo). Although some slight differences appear in the mean serum creatinine and eGFR values over time, this was not supported by the number of individuals with changes in eGFR nor by the AEs related to the renal function. For gout

and urate nephropathy, differences appear to be substantial according to gender for the 60 mg dose (male (n=10.614): HR 1.68 (1.21-2.33 vs female (n=3365): HR 0.61 (0.26-1.44)). However, these data were not consistent with the observation for renal function AEs, where no clear difference could be observed according to gender.

Hepatic-related events do not to raise concern, due to limited number of patients experiencing such events, although this makes any conclusions difficult. Bleedings related to hepatic adverse events were very rare.

In general, a similar **safety in specific populations** (age, sex, race) could be observed for dyspnoea, bradyarrhythmias, renal impairment, gout and urate nephropathy, hepatic-related AEs, gynaecomastia, and drug-drug interactions with moderate and strong CYP3A4 inhibitors.

For paraesthesia and vomiting, frequencies and rates clearly indicate no substantial differences, and therefore deletion of these ADRs can be considered appropriate. For hypersensitivity reactions, also no differences were found, however, due to a higher frequency in clinical practice, this ADRs were still mentioned in the SmPC.

Effects Table

Table 24 Effects Table for ticagrelor 60 mg (data cut-off: 19-05-2015.

Effect	Short Description	Unit	Treatment 60 mg ticagrelor	Control ASA± clopidogrel	Uncertainties/ Strength of evidence	References
Favourable Effects						
CV outcome	Composite CV death, MI, stroke	3 year KM % (FAS)	7.8	9.0	HR 0.84 (95% CI 0.74, 0.95), p=0.0043 Consistent for individual components (MI, stroke significantly better; CV death numerically better) Trend towards less effect with longer duration of previous ADP receptor antagonist treatment (p for interaction unknown)	Efficacy section of the AR
	CV death (under type 1 error)	3 year KM %	2.9	3.4	HR 0.83 (95%CI 0.68-1.01)	
Overall mortality		3 year KM %	4.7	5.2	HR 0.89 (95% CI 0.76, 1.04)	
Unfavourable Effects						

Effect	Short Description	Unit	Treatment 60 mg ticagrelor	Control ASA± clopidogrel	Uncertainties/ Strength of evidence	References
Bleeding	Major bleedings (TIMI)	3 year KM % (FAS)	2.2	1.3	HR 1.78 (95% CI 1.35-2.35)	Safety section of the AR
	ICH	3 year KM %	0.5	0.6	HR 1.06 (95% CI 0.66-1.71)	
	Fatal	3 year KM %	0.2	0.3	HR 0.87 (95% CI 0.41-1.82)	
	Discontinuations due to AEs	% on treatment	5.1	1.3	Mostly within first month	
Dyspnoea	Patient with at least 1 AEs	% on treatment	14.2	5.5	Time to onset of first dyspnoea AE was shorter in the ticagrelor treatment (28.0% and 8.1% of patients with dyspnoea within 3 days after start)	
	Discontinuations due to AEs	3 year KM % on treatment	4.5	0.8	Mostly within first 7 days: 43.9% and 23.5%	
Non-CV Deaths	non-CV deaths classified as infections	3 year KM % on treatment	0.1	0.1		
	deaths classified as malignancy	3 year KM % on and off treatment	1.0	0.9	Not preceding a bleeding: n=44 vs n=44	
Bradyarrhythmias		3 year KM %	2.3	2.0		
Renal-related AEs		3 year KM %	3.4	2.9	Slightly increase in creatinine vs baseline, but similar at the follow-up visit. Frequencies of patients with changes in eGFR were similar.	
Hepatic AEs	Patient with at least 1 AE	% on treatment	0.6	0.4		
Gout related AEs	Increase in uric acid	% change from baseline	5.6	1.3	reversible	
	Gout	% on treatment	1.4	1.0		
	Gouty arthritis	% on treatment	0.1	0.1		

Abbreviations: FAS=Full Analysis Set; TIMI= TIMI bleeding definition; ICH= intracranial bleeding

Balance

Importance of favourable and unfavourable effects

In addition to the 90 mg BID dose that has been authorised previously for the prevention of atherothrombotic events in adult patients with ACS up to one year after the event, the 60 mg BID dose of ticagrelor, co-administered with low dose acetylsalicylic acid, is now proposed to be indicated for the prevention of atherothrombotic events in patients with a history of MI of at least one year ago and a high risk of developing a new atherothrombotic event.

Ticagrelor demonstrated **a consistent reduction in the composite endpoint of CV death, MI, and stroke**, a clinical relevant endpoint in evaluation of CV prevention trials. Efficacy was more robust for the 60 mg BID dose than for the 90 mg dose with significant effects both for the occurrence of MI and stroke, but not for CV death, while the 90 mg BID dose was only significant for stroke. This lack of dose response in efficacy remained unexplained.

The **risk spectrum** in patients included in the PEGASUS study **was considered broad**, with 51% of patients having 1 risk factor and 33% with two qualifying risk factors for a recurrent atherothrombotic event. Age of >65 years (54%) and multi-vessel CAD (59%) were the dominant risk factors (patients were eligible to participate if they were aged 50 years or over, with a history of MI [1 to 3 years prior to randomisation], and had at least one of the following risk factors for atherothrombosis: age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, or chronic non-end-stage renal dysfunction).

Analyses **across subgroups could not clearly identify a subgroup that would benefit most**, as for example an absolute increased risk reduction according to increased number of risk factors, was associated with increased risk for bleeding, resulting in a similar net clinical effect. The only exceptions that was found, with reasonable amount of patients to draw acceptable conclusion upon, was that for starting treatment in patients with >2 years since last MI, and for patients who have not been treated > 1year with clopidogrel as DAPT therapy, a lack of effect was observed. This finding was included in the SmPC.

The beneficial effects came at the cost of a substantially increased risk of bleeding, similar to other combinations of dual antiplatelet therapy. Particularly the increase in major bleedings risk was considered of importance, as this could lead to risk of morbidity, or even death. The bleeding risk seemed dose dependent, with the 60 mg demonstrating fewer bleedings than the 90 mg ticagrelor, which has led to the decision of the applicant not to register the 90 mg for this indication. The CHMP agreed to this and ticagrelor 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event

Bleedings also were one of the main components to cause patients to discontinue treatment, in particular in the first months after start of the treatment. The known effect of dyspnoea also importantly contributed to discontinuation already within the first week of treatment.

Other adverse events observed in the PEGASUS study were expected as based on the known safety profile of ticagrelor and did not raise additional concerns.

Benefit-risk balance

The substantially higher bleeding risk compromises the benefits and results in a small absolute positive clinical benefit of dual antiplatelet therapy of ticagrelor on top of ASA during long-term use. This small beneficial effect was maintained during the entire study period and for the agreed target population.

Based on the agreed indication and the additional subgroup analyses regarding the influence of timing when initiating the treatment, an indication for 60 mg strength separate from that of the 90 mg strength was not seen as logical. Thus, the two indications have now been combined, covering both the period of up to one year and the extended treatment period with the switch from 90 to 60 mg BID dose thereafter. A drawback of the PEGASUS study was a large number of discontinuations (mainly due to bleeding and dyspnoea), an observation that was already known from the previous PLATO trial. Heterogeneity in some other subgroups was also observed (trend differences appeared in the age, sex, race, obesity, time since qualifying MI and time since previous treatment with ADP receptor blocker), and was considered to be likely due to chance. Overall, the benefit/ risk balance for continued ticagrelor treatment with the 60 mg BID dose in patients with a history of MI of at least one year and a high risk of an atherothrombotic event was considered positive.

Discussion on the benefit-risk assessment

PEGASUS study provided insight in dual antiplatelet therapy beyond 1 year after MI, for which data have been generated in other studies using dual (or triple) antiplatelet therapy. Two studies have been performed with clopidogrel investigating the effect of continued dual antiplatelet therapy beyond 12 months after ACS event (CHARISMA, DAPT). Also, one study has been performed with vorapaxar where patients were included earlier after ACS event (between 2 weeks and 1 year [TRA2°P-TIMI 50]). For clopidogrel, these studies have not led to changes in the SmPC, therefore its use remain limited for one year after event of ACS. For vorapaxar longer term treatment was approved using the time criteria of the TRA2°P-TIMI 50, starting treatment any time between 2 weeks and 12 months following the acute event.

In the currently adopted simplified indication only patients with a history of MI and a high risk of developing an atherothrombotic event could be considered for extended treatment with ticagrelor, as this reflects the included population of PEGASUS with the acute and chronic phase separated. Ticagreor 60 mg twice daily is the recommended dose when an extended treatment is required for patients with a history of MI of at least one year and a high risk of an atherothrombotic event. Treatment with may be started without interruption as continuation therapy after the initial one year treatment with ticagrelor 90 mg or other adenosine diphosphate (ADP) receptor inhibitor therapy in ACS patients with a high risk of an atherothrombotic event. Treatment can also be initiated up to 2 years from the MI, or within one year after stopping previous ADP receptor inhibitor treatment. There are limited data on the efficacy and safety of ticagrelor beyond 3 years of extended treatment.

In addition, it was added to the SmPC which patients are at high risk of developing an atherothrombotic event, including age ≥65 years, diabetes mellitus requiring medication, a second prior MI, evidence of multivessel CAD, or chronic non-end-stage renal dysfunction.

Some patients may not benefit in the long-term from this therapy as reflected in a large proportion of patients who discontinued treatment due to bleeding. It was stated in the SmPC that long-term treatment is recommended unless earlier discontinuation of ticagrelor is clinically indicated. The small net beneficial effect remains positive in absolute terms during the entire period studied, but the need for longer treatment should be balanced for each individual.

The MAH also applied for a new 60 mg tablet strength in this group of variations, for which the quality was considered acceptable. The CHMP recommends the approval of this new 60 mg tablet.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Brilique 60 mg *co-administered with acetylsalicylic acid (ASA), indicated for the prevention of atherothrombotic events in adult patients with: acute coronary syndromes (ACS) or a history of myocardial infarction and a high risk of developing an atherothrombotic event (see sections 4.2 and 5.1).*

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions below.

In addition, based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I, II, IIIA, IIIB

Update of sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC of the 90 mg film-coated tablet with clinical information from the PEGASUS study. The Package Leaflet is updated in accordance.

In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and Annex A.

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.