EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 March 2017
EMA/274695/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on extension of Marketing Authorisation

Brilique

International non-proprietary name: ticagrelor

Procedure No.: EMEA/H/C/001241/X/0034

Note

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

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List of abbreviations

ACS	Acute coronary syndrome
AE	Adverse event
AR-C124910XX	Active metabolite of ticagrelor
AUC	Area under the plasma concentration-time curve from zero extrapolated to infinity
AUC(0-t)	Area under the plasma concentration-time curve from time zero to the last quantifiable concentration
BCS	Biopharmaceutics Classification System
CHMP	Committee for Medicinal Products for Human Use (European Medicines Agency)
CI	Confidence interval
Cmax	Maximum plasma (peak) drug concentration after single dose administration
CQA	Critical Quality Attribute
Css,av	Average plasma concentration at steady state
CTD	Common Technical Document
DoE	Design of experiments
EC	European Commission
FDA	Food and Drug Administration (US Department of Health and Human Sciences)
FMECA	Failure mode effects criticality analysis
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IR	Immediate release
MI	Myocardial infarction
NMT	Not more than
OD	Orodispersible ‘Orally disintegrating’ is the term used in some markets. These terms are interchangeable.
PD	Pharmacodynamic(s)
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
QC	Quality Control
QTPP	Quality target product profile
RH	Relative Humidity
SmPC	Summary of Product Characteristics
UV	Ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

AstraZeneca AB submitted on 21 April 2016 an extension of the marketing authorisation for Brilique.

The Marketing Authorisation Holder applied for an addition of a new pharmaceutical form (orodispersible tablets) associated with one strength (90 mg) and three new package sizes (10, 56 and 60 orodispersible tablets). The indication applied for is the same as for the already authorised presentations.

Furthermore, the PI is brought in line with the latest QRD template version 10.0.

The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (d) - Extensions of marketing authorisations

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0298/2015) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP (P/0298/2015) was not yet completed as some measures were deferred.

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 MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the authorised indication, which is not changing.

Scientific Advice

The MAH did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

- The application was received by the EMA on 21 April 2016.
- The procedure started on 19 May 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 August 2016.
- During the meeting on 15 September 2016, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 15 September 2016.

- The MAH submitted the responses to the CHMP consolidated List of Questions on 25 November 2016.
- The Rapporteur circulated the Assessment Report on the responses to the List of Questions to all CHMP members on 5 January 2017.
- During the meeting on 23 to 26 January 2017, the CHMP agreed on a List of Outstanding Issues to be addressed in writing by the MAH. The final List of Outstanding Issues was sent to the MAH on 26 January 2017.
- The following GCP inspections were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - GCP inspections at one clinical facility in Germany and one bioanalytical facility in the USA have been performed between September and October 2016. The outcome of the inspection carried out was issued on 1st December 2016.
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 21 February 2017.
- The Rapporteur circulated the Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on 7 March 2017.
- During the meeting on 20 to 23 March 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Brilique on 23 March 2017.

2. Scientific discussion

2.1. Problem statement

Ticagrelor, an oral, reversible, antiplatelet agent, has previously established a positive benefit-risk profile for the prevention of atherothrombotic events in patients with acute coronary syndrome (ACS). Ticagrelor is currently registered as 90 mg and 60 mg film-coated tablets. Within the current application the MAH asked for approval of Brilique 90 mg orodispersible tablets. The orodispersible (OD) 90 mg tablet has been developed to provide an alternative administration option for patients. The OD tablet disperses in saliva on the tongue and is therefore easy to administer orally. The OD tablet can also be suspended in water for administration through a nasogastric tube (size CH8 or greater), addressing a need in patients with dysphagia (approximately 5% to 10% of patients with ACS are intubated and in need of nasogastric tube for feeding and administration of drugs).

2.1.1. Management

About the product

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 film coated tablets, 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. Since 2016 also Brilique 60 mg film coated tablets has been registered, for an extended dosing regimen in patients with a history

of myocardial infarction and a high risk of an atherothrombotic events. Brilique is currently registered for the following indications:

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 (see sections 4.2 and 5.1).*

Approved dosing regimen:

Acute coronary syndromes

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

History of myocardial infarction

Brilique 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 (see section 5.1). Treatment may be started without interruption as continuation therapy after the initial one-year treatment with Brilique 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 Brilique beyond 3 years of extended treatment.

AstraZeneca now seeks additional marketing approval for Brilique 90 mg orodispersible tablets.

Type of Application and aspects on development

The application has been submitted in accordance with article 8(3) of directive 2001/83/EC, as an extension application for a new pharmaceutical form. The MAH already holds the marketing authorisation for both Brilique 90 mg and 60 mg film-coated tablets.

2.2. Quality aspects

2.2.1. Introduction

This application concerns a line extension of the currently authorised Brilique 60 mg and 90 mg film-coated tablets.

The finished product is presented as orodispersible tablets containing 90 mg of ticagrelor as active substance.

Other ingredients are:
mannitol (E421), microcrystalline cellulose (E460), crospovidone (E1202), xylitol (E967), anhydrous calcium hydrogen phosphate (E341), sodium stearyl fumarate, hydroxypropyl cellulose (E463), colloidal anhydrous silica.

The product is available in aluminium-aluminium perforated unit dose blisters 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 60 mg and 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 finished product batches, has been provided. All batches complied with the approved active substance specification.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is a white to pale pink, round, flat, bevelled edged orodispersible tablet containing 90 mg of ticagrelor. The orodispersible tablets can be distinguished from the approved film-coated tablets by colour, size, and inscription. Excipients are mannitol, microcrystalline cellulose, crospovidone, xylitol, anhydrous calcium hydrogen phosphate, sodium stearyl fumarate, hydroxypropyl cellulose, and colloidal anhydrous silica.

Brilique 90 mg orodispersible tablets were developed for patients who have difficulty swallowing the approved film-coated tablets or for situations where water is not available (e.g. for urgent treatment). The product can be administered with or without food. The tablet should be placed on the tongue, where it will rapidly disperse in saliva. It can then be swallowed with or without water. The tablet can also be dispersed in water and administered via a nasogastric tube which should be flushed through with water after administration of the mixture.

Ticagrelor has a low solubility according to the Biopharmaceutics Classification System (BCS). It exhibits moderate intrinsic permeability; absolute bioavailability is 36% (fraction absorbed 51%). It is therefore a BCS class IV compound. Despite its poor aqueous solubility, ticagrelor was found to be highly soluble in human intestinal fluid.

The product was developed using a systematic approach. Acceptable Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) were presented.

Mannitol, microcrystalline cellulose, crospovidone, xylitol, anhydrous calcium hydrogen phosphate, sodium stearyl fumarate, hydroxypropyl cellulose, and colloidal anhydrous silica are all well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The compatibility of the drug substance with the excipients used in the proposed commercial formulation has been confirmed by the results of long-term, accelerated and stressed stability studies on the proposed commercial formulation.

The applicant makes use of a co-processed fast oral disintegrating excipient in which mannitol, microcrystalline cellulose, crospovidone, xylitol, anhydrous calcium hydrogen phosphate have been co-spray dried together. As this was not considered to be a simple mixture of excipients, additional information on the manufacture and control of this co-processed excipient was requested by CHMP, and subsequently provided by the applicant. A relative bioavailability study was carried out comparing the ticagrelor 90 mg orodispersible tablets to the authorised Brilique (ticagrelor) 90 mg film-coated tablets. Dissolution of the biobatches was compared under routine QC dissolution testing conditions as well as at pH 1.2, pH 4.0, and pH 6.8. The comparative dissolution profiles of the biobatches support the conclusion of bioequivalence. For information on the clinical assessment of the bioequivalence studies, please refer section 2.4 of this report. The formulation used in the bioequivalence study is the same as that intended for marketing.

The same routine QC dissolution testing method originally developed for ticagrelor film-coated tablets is proposed for testing the orodispersible tablets. This is considered justified. The discriminatory power of the dissolution method has been demonstrated.

Manufacturing process development was carried out in a straightforward manner, incorporating initial and final risk assessments. No design space is claimed. The control strategy includes control of active substance and input materials, controls for unit operations, in-process controls, and testing of the finished product.

The primary packaging is a blister pack made from a base web of aluminium laminate and sealed to a hard temper aluminium lidding foil. The lidding foil is opened by a tear notch, one for each tablet cavity. 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

The commercial manufacturing process was adequately described including the process parameters identified as being critical during development. The process is considered to be a standard manufacturing process.

Prospective validation of the finished product manufacturing process will be completed prior to launch of finished product produced at the commercial manufacturing site. An acceptable process validation scheme has been provided.

Product specification

The finished product release specifications include appropriate tests for an orodispersible tablet: description (visual), identification (HPLC/UV), uniformity of dosage units (Ph. Eur.), assay (HPLC), degradation products (HPLC), disintegration (Ph. Eur.) and dissolution (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. The reference standards used for assay and impurities testing are the same as those used for testing ticagrelor active substance and Brilique film-coated tablets.

Batch analysis results are provided for three pilot scale and three commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The proposed finished product specification is acceptable.

Stability of the product

Stability data of three pilot scale batches of finished product stored under long term conditions for 24 months at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. These batches are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, disintegration, dissolution, water content, and microbial limits. The analytical procedures used were stability indicating. No significant changes or obvious trends were observed in any of the parameters tested.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The product was shown to be photostable outside the primary packaging.

Based on this available stability data, the proposed shelf-life of 3 years without any special storage conditions, as stated in the SmPC (section 6.3), is acceptable.

Adventitious agents

n/a

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of ticagrelor 90 mg orodispersible tablets has been presented in a satisfactory manner. 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. Recommendation(s) for future quality development

n/a

2.3. Non-clinical aspects

2.3.1. Introduction

No new non-clinical data were provided within current application.

2.3.2. Ecotoxicity / environmental risk assessment

The revised ERA was not submitted with the current application. The MAH justified that since the dose, indication and patient population for this extension application have not changed, no increase in the predicted environmental exposure concentration is foreseen and ticagrelor is not expected to pose a risk to the environment. Accordingly, based on EMA CHMP guideline documents (*Guideline on the environmental risk assessment of medicinal products for human use [EMEA/CHMP/SWP/4447/00 corr 2]*; and *Questions and answers on 'Guideline on the environmental risk assessment of medicinal products for human use [CHMP/SWP/44609/2010]*), a revision of the ERA for ticagrelor was not required.

2.3.3. Conclusion on the non-clinical aspects

No new non-clinical data were provided. The CHMP agreed that no increased exposure of ticagrelor to the environment is to be expected from this extension application as the maximum daily dose of ticagrelor, administered via either the film-coated or orodispersible tablets, will remain 180 mg. Therefore, a revision of the Environmental Risk Assessment previously approved assessed within procedure Brilique X/29, was considered not warranted.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The MAH 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.

To support this line extension application for the ticagrelor 90 mg orodispersible (OD) tablet, the applicant has submitted two pivotal bioequivalence studies, the pooled results of both studies and additional PK/PD modelling. A short description of these studies is given below. Further the MAH refers to the dossiers previously submitted to support the Brilique 90mg and 60mg (immediate release (IR)) tablets.

- Tabular overview of clinical studies

Study		Type of study	Test and reference	Population
D5139C00003	Pivotal	Bioequivalence	ticagrelor 90 mg OD tablet ticagrelor 90 mg IR tablets	Western healthy volunteers
D5139C00004	Pivotal	Bioequivalence	ticagrelor 90 mg OD tablet ticagrelor 90 mg IR tablets	Japanese healthy volunteers
	Supportive	PK/PD models	ticagrelor 90 mg IR tablets	D513C00048 (onset/offset) D513C05262 (plato) D513C00001 (Pegasus)

2.4.2. Pharmacokinetics

2.4.2.1. Study D5139C00003

Study D5139C00003 was a randomised, 4-period, 4-treatment crossover study in 36 subjects/volunteers.

A single dose of ticagrelor 90 mg OD tablet dispersed in saliva and swallowed with or without water, or suspended in water and administered through a nasogastric tube into the stomach, was compared to a single dose of ticagrelor 90 mg IR tablet administered orally. The pharmacokinetic parameters for ticagrelor and equipotent active metabolite ARC124910XX observed in Study D5139C00003 were presented in Table 1.

Table 1 Pharmacokinetic parameters for Ticagrelor and ARC124910XX Study D5139C00003

	OD 90 mg tablet			IR 90mg tablet
Pharmacokinetic parameter	**(A) with water**	**(B) Without water**	**(C) suspended in water through nasogastric tubes**	**(D)**
	geometric mean(CV%)			
	N=30	**N=31**	**N=33**	**N=33**
Ticagrelor				
C_{max} (ng/mL)	428 (25.0)	499 (34.0)	479 (32.1)	520 (29.0)
$_{Max}t_{max}$*(h)	2.02 (1.00, 4.02)	2.00 (1.00, 4.00)	2.00 (0.98, 4.00)	2.00 (0.98 (4.00)
AUC (ng*h/mL)	3068 (29.2)	3228 (44.2)	3226 (42.9)	3423 (41.8)
AUC(0-t)	3023 (28.6)	3172 (42.6)	3174 (40.9)	3358 (40.0)
t1/2λz (h)	8.02 (1.25)	8.21 (1.46)	7.99 (1.83)	8.18 (1.71)
ARC124910XX				
C_{max} (ng/mL)	118 (26.5)	126 (24.7)	126 (30.4)	129 (31.8)
t_{max}*(h)	3.00 (1.98, 6.00)	3.00 (1.98, 4.00)	2.00 (1.98, 4.02)	2.00 (1.98, 4.00)
AUC (ng*h/mL)	1138 (19.1)	1155 (20.7)	1154 (23.6)	1197 (22.5)
AUC(0-t)	1087 (19.7)	1104 (20.7)	1101 (24.4)	1140 (23.0)
t1/2λz (h)	9.48 (1.43)	9.35 (1.81)	9.36 (2.18)	9.47 (2.02)

C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration (* median, range)
AUC	area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
t1/2λz (h)	half life (arithmetic mean (SD)).

The results from this study demonstrated that when dispersed in saliva and swallowed without water, or suspended in water and administered through a nasogastric tube into the stomach, ticagrelor 90 mg OD tablets were bioequivalent in terms of C_{max}, AUC and $AUC_{(0-t)}$ to ticagrelor 90 mg IR tablets.

However, when dispersed in saliva and swallowed with water, ticagrelor 90 mg OD tablets were not bioequivalent for the C_{max} when compared to ticagrelor 90 mg IR tablets; the lower limit of the 90% CI of the geometric mean ratio for ticagrelor C_{max} (76.77%) fell below the bioequivalence acceptance interval of 80% to 125%, and mean ticagrelor C_{max} was 15% lower than that for ticagrelor 90 mg IR tablets. The AUC values were within the bioequivalence acceptance interval of 80 to 125%.

The PK parameters for the equipotent active metabolite ARC124910XX were within the bioequivalence acceptance interval of 80% to 125%. Both formulations were well tolerated under all tested conditions. The statistical analysis for ticagrelor and ARC124910XX in Study D5139C00003 was presented in Table 2.

Table 2 Statistical analysis for Ticagrelor and ARC124910XX Study D5139C00003

	Geometric Mean Ratio Test/Reference (90% Confidence Intervals)		
Pharmacokinetic parameter	**A/D**	**B/D**	**C/D**
Ticagrelor	**N=30**	**N=31**	**N=33**
C_{max}	84.85 (76.77, 93.78)	96.61 (88.22, 105.79)	92.16 (85.59, 99.25)
AUC	94.96 (90.27, 99.89)	95.24 (89.81, 100.99)	94.40 (90.26, 97.73)
AUC(0-t)	95.04 (90.33, 99.99)	95.41 (89.94, 101.21)	94.66 (90.53, 98.98)
ARC124910XX			
C_{max}	89.84 (82.03, 98.39)	97.45 (90.53, 104.90)	97.07 (90.83, 103.74)
AUC	94.82 (91.36, 98.42)	95.71 (91.78, 99.82)	96.50 (93.26, 99.87)
AUC(0-t)	94.67 (90.94, 98.56)	96.00 (91.87, 100.33)	96.56 (93.08, 100.17)

2.4.2.2. Study D5139C00004

Study D5139C00004 was an open-label, randomized, 3-period, 3-treatment, crossover study in 42 healthy Japanese subjects.

Pharmacokinetic parameters observed for ticagrelor and ARC124910XX in Study D5139C00004 were presented in Table 3.

Bioequivalence between the formulations was demonstrated when ticagrelor 90 mg OD tablets were dispersed in saliva and swallowed with or without water (see Table 4). Both formulations were well tolerated under the tested conditions.

Table 3 Pharmacokinetic parameters for Ticagrelor and ARC124910XX Study D5139C00004

	OD 90mg tablet		IR 90mg tablet
Pharmacokinetic parameter	**(A) with water**	**(B) Without water**	**(C)**
	N=41	**N=41**	**N=41**
Ticagrelor			
C_{max} (ng/mL)	529 (38.4)	534 (29.8)	569 (37.0)
t_{max}*(h)	3.00 (1.00, 4.02)	3.00 (1.02, 5.97)	2.00 (1.00, 6.00)
AUC (ng*h/mL)	3520 (45.1)	3485 (42.8)	3606 (46.3)
AUC(0-t)	3462 (43.8)	3423 (41.4)	3546 (45.0)
t1/2λz (h)	7.74 (1.19)	794 (1.19)	7.86 (1.09)
ARC124910XX			
C_{max} (ng/mL)	165 (31.4)	158 (36.5)	170 (35.5)
t_{max}*(h)	3.07 (2.00, 6.00)	3.00 (2.00, 6.02)	3.00 (1.00, 8.00)
AUC (ng*h/mL)	1547 (23.3)	1503 (24.0)	1573 (22.3)
AUC(0-t)	1488 (23.5)	1441 (24.5)	1513 (22.7)
t1/2λz (h)	9.13 (1.91)	9.12 (1.81)	9.05 (1.68)

C_{max}	maximum plasma concentration
t_{max}	time for maximum concentration (* median, range)
AUC	area under the plasma concentration-time curve
AUC_{0-t}	area under the plasma concentration-time curve from time zero to t hours
t1/2λz (h)	half life (arithmetic mean (SD))

Table 4 Statistical analysis for Ticagrelor and ARC124910XX Study D5139C00004

	Geometric Mean Ratio Test/Reference (90% Confidence Intervals)	
Pharmacokinetic parameter	**A/C**	**B/C**
Ticagrelor		
C_{max}	93.16 (85.80, 101.15)	93.67 (87.88, 99.84)
AUC	97.75 (94.40, 101.21)	96.50 (93.31, 99.80)
AUC(0-t)	97.76 (94.46, 101.18)	96.38 (93.24, 99.63)
ARC124910XX		
C_{max}	96.79 (88.27, 106.14)	92.32 (85.04, 100.23)
AUC	98.46 (94.85, 102.20)	95.47 (91.99, 99.08)
AUC(0-t)	98.43 (94.75, 102.25)	95.15 (91.59, 98.85)

2.4.2.3. Pooling of study D5139C00003 and study D5139C00004

Data from Study D5139C00003 and D5139C00004 were pooled and the statistical comparison of key PK parameters was performed with the same design as in the clinical study reports.

The company used ANOVA tests in the evaluation of the pooled studies. ANOVA test included the factors treatment, study unique sequence, period and subject-within-sequence. All PK parameters were log-transformed prior to analysis. The estimated treatment differences and the 90% CIs on the log scale were back transformed to obtain the geometric mean (Gmean) ratios for each pair of treatments. The least squares means (and 95% CIs), Gmean ratios and 90% CIs were tabulated for each comparison and analyte (ticagrelor and AR-C124910XX).

Table 5 presents an inferential analysis comparing exposure (C_{max}, AUC(0-t), and AUC) for ticagrelor and AR-C124910XX in the pooled dataset.

Table 5 Statistical comparison of key PK parameters (PK analysis set) – pooled analysis

						Pairwise comparisons	
	Trt	**N**	**n**	**Geometric LS mean**	**Geometric LS mean 95% CI**	**Pair**	**Pair Ratio (%)**	**90% CI**
Ticagrelor								
AUC	A	71		3347	(3259, 3439)			
(h*ng/mL)	D	74	71	3465	(3375, 3558)	A/D	96.60	(93.89, 99.40)
	B	72		3384	(3285, 3486)			
	D	74	72	3526	(3426, 3630)	B/D	95.96	(93.06, 98.95)
	C	33		3220	(3100, 3345)			
	D	74	33	3411	(3283, 3544)	C/D	94.40	(90.26, 98.73)
AUC(0-t)	A	71		3292	(3205, 3382)			
(h*ng/mL)	D	74	71	3407	(3318, 3498)	A/D	96.65	(93.94, 99.43)
	B	72		3323	(3226, 3423)			
	D	74	72	3462	(3364, 3564)	B/D	95.97	(93.07, 98.96)
	C	33		3168	(3050, 3290)			
	D	74	33	3347	(3222, 3476)	C/D	94.66	(90.53, 98.98)
C_{max}	A	71		486.9	(459.1, 516.4)			
(ng/mL)	D	74	71	543.8	(513.3, 576.1)	A/D	89.55	(84.15, 95.30)
	B	72		517.1	(491.9, 543.5)			

	D	74	72	544.7	(518.7, 572.0)	B/D	94.92	(90.13, 99.96)
	C	33		477.9	(448.7, 509.0)			
	D	74	33	518.6	(486.9, 552.3)	C/D	92.16	(85.59, 99.25)
ARC124910XX								
AUC	A	71		1360	(1327, 1395)			
(h*ng/mL)	D	74	71	1403	(1369, 1438)	A/D	96.97	(94.43, 99.58)
	B	72		1348	(1313, 1384)			
	D	74	72	1410	(1374, 1447)	B/D	95.59	(93.02, 98.23)
	C	33		1154	(1120, 1188)			
	D	74	33	1195	(1161, 1231)	C/D	96.50	(93.26, 99.87)
AUC(0-t)	A	71		1304	(1270,*1338)			
(h*ng/mL)	D	74	71	1346	(1312, 1381)	A/D	96.89	(94.25, 99.60)
	B	72		1291	(1257,*1327)			
	D	74	72	1352	(1316, 1388)	B/D	95.53	(92.88, 98.26)
	C	33		1100	(1066,*1135)			
	D	74	33	1139	(1104, 1175)	C/D	96.56	(93.08, 100.2)
C_{max}	A	71		142.0	(133.6,*150.9)			
(ng/mL)	D	74	71	151.2	(142.5, 160.5)	A/D	93.88	(88.04, 100.1)
	B	72		142.6	(135.2,*150.4)			
	D	74	72	150.9	(143.2, 159.0)	B/D	94.50	(89.41, 99.87)
	C	33		125.4	(118.5,*132.7)			
	D	74	33	129.2	(122.1, 136.7)	C/D	97.07	(90.83, 103.7)

A: Ticagrelor 90 mg OD tablet dispersed in saliva and swallowed with water.
B: Ticagrelor 90 mg OD tablet dispersed in saliva and swallowed without water.
C: Ticagrelor 90mg OD tablet suspended in water, administered through nasogastric tube into stomach with a total of 200 mL water (this arm performed in Study D5139C00003 only).
D: Ticagrelor 90 mg IR tablet, administered with water.

Only the data for the comparison under investigation was included in the statistical analysis. Result based on ANOVA of log transformed PK parameter with treatment, study unique sequence, period and subject within sequence as fixed effects. Geometric mean ratio and CI are back-transformed and presented as percentages. Geometric LS mean and 95% CI were also back-transformed. ANOVA analysis of variance; AUC area under the plasma concentration-time curve from zero to infinity; AUC(0-t) area under the plasma concentration-time curve from time zero to time t; CI confidence interval; Cmax maximum plasma concentration; IR immediate release; LS least-squares; N all subjects in the pharmacokinetic analysis set; n all subjects included in the statistical comparison analysis; OD orodispersible; PK pharmacokinetic; Trt treatment.

A pooled analysis of t_{max} is shown in Table 6. In the pooled data, there was no difference in median ticagrelor t_{max} across the treatment groups, and a 1 hour delay of the t_{max} of the active metabolite AR-C124910XX.

Table 6 Summary statistics of tmax (h) (PK analysis set) - pooled analysis Statistics

Analyte	Treatment	n	Mean	SD	Median	Min	Max
Ticagrelor	Ticagrelor OD 90 mg with water	71	2.6	0.94	2.02	1.00	4.02
	Ticagrelor OD 90 mg without water	72	2.6	0.85	2.03	1.00	5.97
	Ticagrelor OD 90 mg via nasogastric tube[a]	33	1.9	0.93	2.00	0.98	4.00
	Ticagrelor IR 90 mg with water	74	2.2	1.24	2.00	0.98	6.00
AR-C124910XX	Ticagrelor OD 90 mg with water	71	3.1	0.95	3.00	1.98	6.00
	Ticagrelor OD 90 mg without water	72	3.1	0.96	3.00	1.98	6.02
	Ticagrelor OD 90 mg via nasogastric tube[a]	33	2.6	0.75	2.00	1.98	4.02
	Ticagrelor IR 90 mg with water	74	2.9	1.14	2.07	1.00	8.00

[a] This arm performed in Study D5139C00003 only
IR immediate release; OD orodispersible; Max maximum; Min minimum; PK pharmacokinetic; SD standard deviation; t_{max} time to maximum plasma concentration

2.4.2.4. In vitro in vivo correlation

It has been previously shown that the dissolution rate of ticagrelor formulation does not influence ticagrelor C_{max} and area under the plasma concentration-time curve from zero to infinity (AUC). This has been shown in an *in vitro/in vivo relationship* (IVIVR) study (Study D5130C00055) for ticagrelor 90 mg IR tablets. Even if the dissolution rate is slowed down to some extent it does not influence C_{max} and area under the plasma concentration-time curve from zero to infinity (AUC). It has also been shown that this IVIVR is relevant for the ticagrelor 90 mg OD tablets since the rate limiting mechanism is the same for OD and IR tablets.

2.4.3. Pharmacodynamics

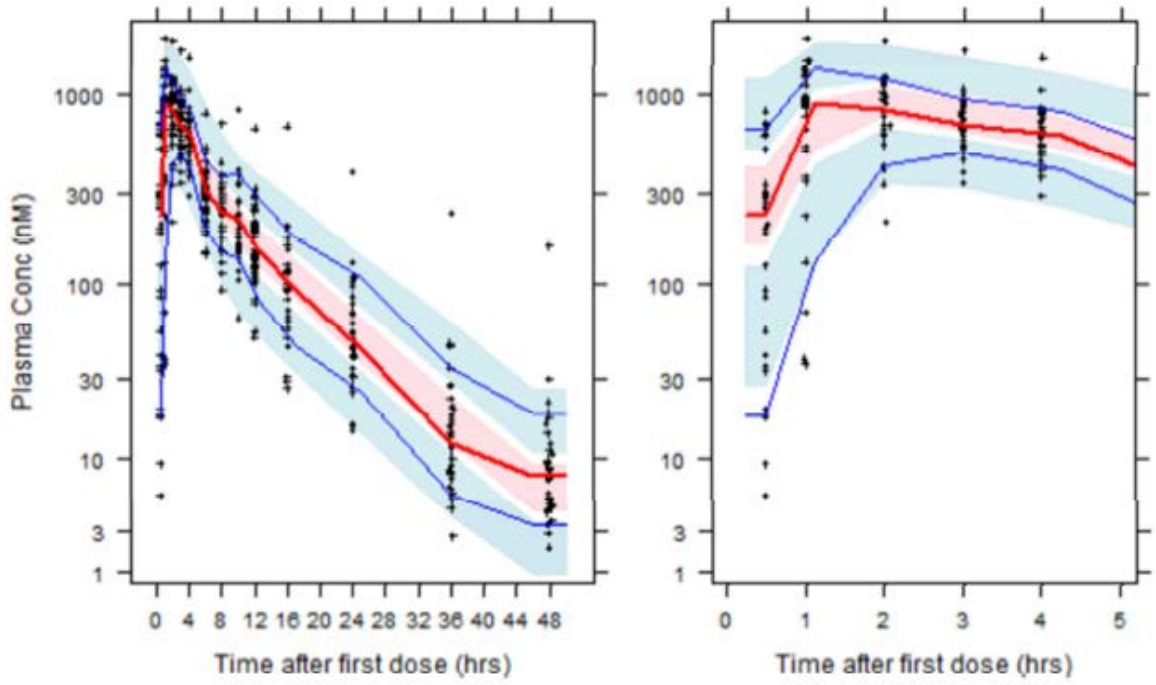
The applicant justified that the 15% lower Cmax observed with the ticagrelor 90 mg OD tablets in Study D5139C00003 when taken with water is not clinically relevant in the acute phase of the treatment of patients with acute coronary syndromes (ACS) and in the chronic treatment of patients with a history of myocardial infarction. This is based on a justification of the MAH discussing the results of several **population PK** and **PK/PD modelling analyses** that have been performed exploring the influence of a 15% reduction of Cmax and a 1 hour delay in t_{max} on steady state concentrations, platelet inhibition and clinical outcome. Further, the company has explored whether there is a relationship between lower than median plasma exposure and early events (cardiovascular [CV] death, myocardial infarction [MI], stroke, or stent thrombosis) using data from the previously submitted PLATO study (Study D5130C05262).

2.4.3.1. PK and PK-PD modelling

The PK, PK/PD and exposure-response data from 3 previously submitted clinical studies (D5130C00048 [ONSET/OFFSET], D5130C05262 [PLATO] and D5132C00001 [PEGASUS]) have been used in these models. The PK/PD models assume that there is a link between ticagrelor exposure and platelet inhibition and/or clinical outcome.

The predictive value of the population ONSET/OFFSET PK model has been verified with visual predictive check (VPC) plots using the data of studies D5139C00003. The VPC plots show that the population PK model adequately predicts the plasma concentration profile of ticagrelor 90 mg IR tablet observed in D5139C00003 (see Figure 1).

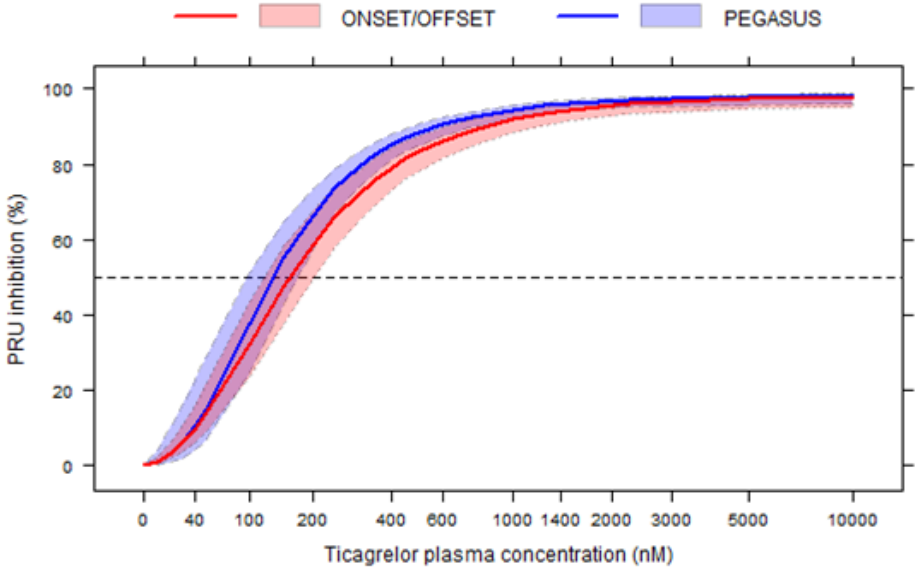
Figure 1 VPC plot of observed and predicted ticagrelor concentrations after ticagrelor 90 mg IR dosing in Study D5139C00003 versus time after dose



The graph to the right shows the early time points after dosing. The red and blue lines represent median and the 10th and 90th percentiles of the observations. The shaded areas represent 95% confidence intervals of the median (red) and the 10th and 90th percentiles (blue) predicted by the model. The black points represent the actual individual observations.
IR immediate release; VPC visual predictive plot

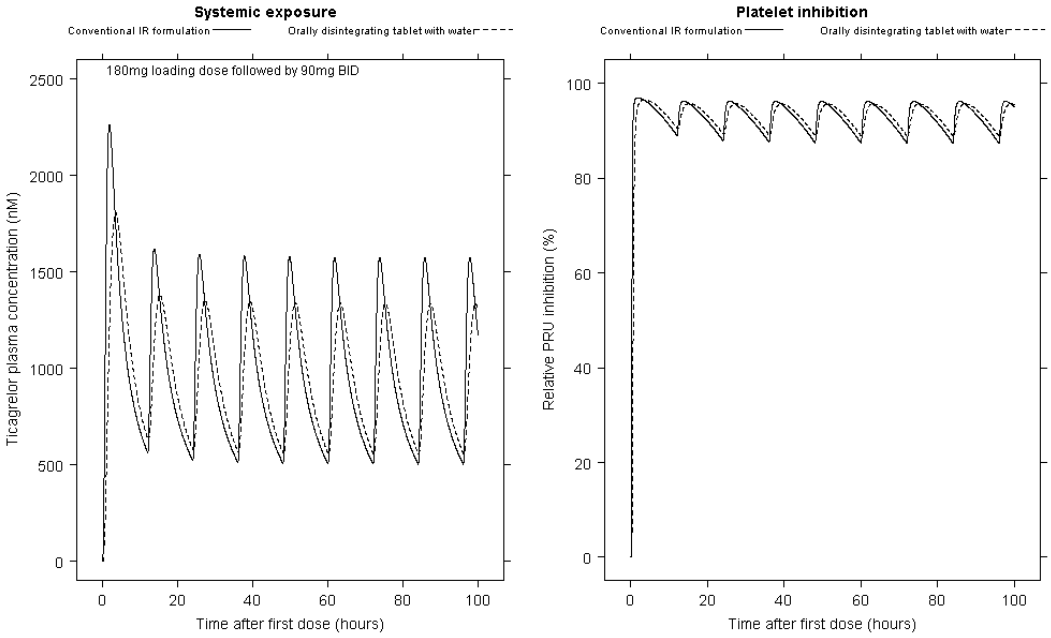
The presented ONSET/OFFSET and Pegasus PK/PD models have been compared. The presented PK/PD results suggest a similar relationship between platelet inhibition and ticagrelor plasma concentration across studies (see Figure 2).

Figure 2 Relationship between Ticagrelor concentration and PRU inhibition observed in ONSET / OFFSET and PEGASUS study



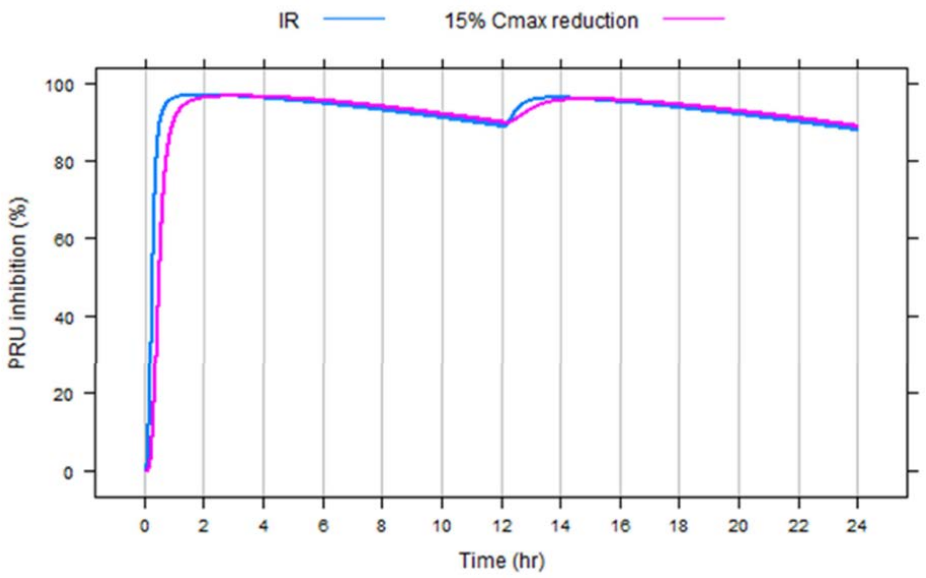
The maximal platelet inhibition at steady-state was predicted at 96.2% with the conventional ticagrelor 90 mg dosage form and at 95.7% when C_{max} was reduced by 15% (see Figure 3).

Figure 3 Simulations of ticagrelor plasma concentrations and platelet inhibition over time



This simulation has also been done with a focus on the acute phase of a coronary event. The simulation was performed with and without a C_{max} reduction of 15% at the first loading and with an accompanying delay of 69 minutes in reaching ticagrelor peak concentrations. The simulation (see Figure 4), predicts similar average maximal percent platelet inhibition after the first loading dose for the ticagrelor 90 mg OD tablet with water and the ticagrelor 90 mg IR tablet (97.0% for the ticagrelor 90 mg IR tablet, and 96.7% when C_{max} after the first dose was reduced by 15%). The predicted delay in achieving 70% platelet inhibition is less than 17 minutes. Based on the simulations, it is expected that the percentage of patients with at least 70% platelet inhibition within 2 hours after a loading dose is more than 92.8% for the IR tablet, and more than 87.3% for the OD tablet with water.

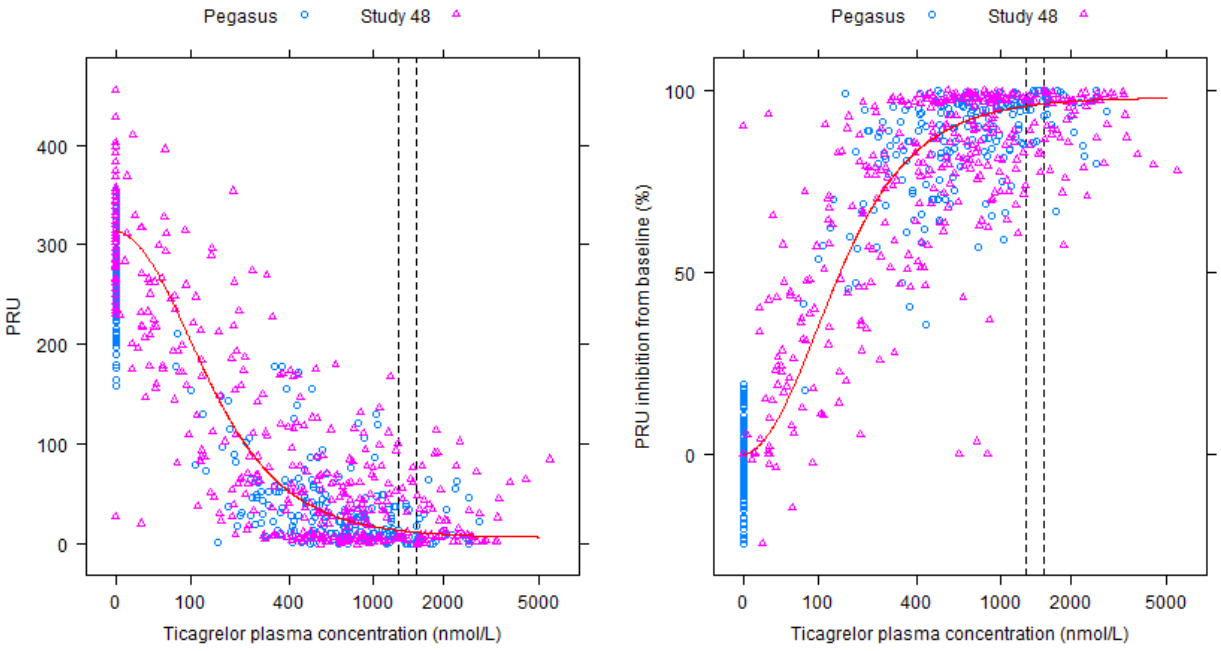
Figure 4 PK/PD simulations of platelet inhibition during the first 24 hours, after 180 mg loading dose and subsequent 90 mg twice daily dosing



To simulate a 15% C_{max} reduction after the first dose, the absorption rate constant in the model was adjusted until the C_{max} reduction was achieved. C_{max} maximum plasma concentration; IR immediate release; PK/PD pharmacokinetic/pharmacodynamic; PRU P2Y12 reaction units

The observed exposure-response data for platelet inhibition appeared to be overlapping for ONSET/OFFSET and the PEGASUS platelet function sub study, indicating a similar sensitivity to ticagrelor (ie, similar EC50) between the study populations (see also Figure 5).

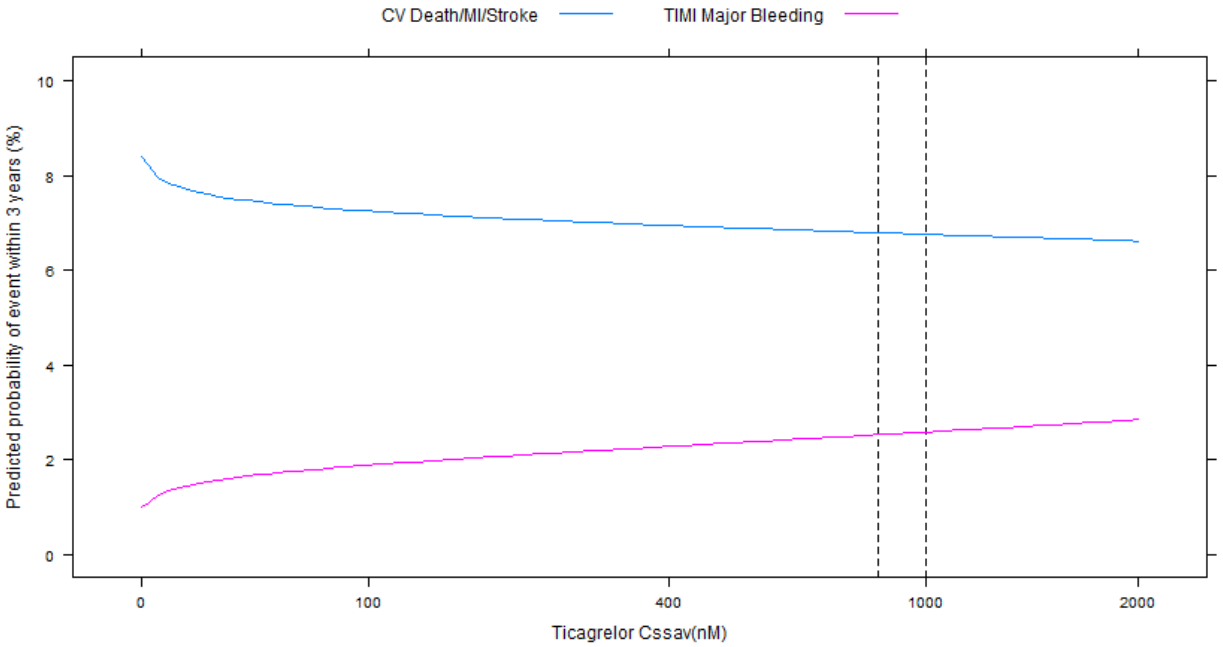
Figure 5 Observed platelet inhibition versus exposure in ONSET/OFFSET (study 48) and the PEGASUS platelet function substudy



The PEGASUS study has evaluated the relationship between ticagrelor exposure and clinical outcomes and showed a relatively flat, log-linear, relationship between exposure ($C_{ss,av}$) and the composite risk of CV death,

MI, or stroke (see Figure 3). The MAH has also plotted the 15% reduction in exposure in this graph. According to the applicant a 15% reduction in mean $C_{ss,av}$ from 998 nM to 848 nM, as a conservative surrogate metrics for the observed reduction in C_{max}, would translate into only a minor shift in the predicted CV death, MI, or stroke with a relative risk reduction from 18.5% to 18.1% for a patient with a history of a MI receiving the 90 mg dose compared with placebo (see Figure 6).

Figure 6 Model based exposure-response relationships of the primary efficacy and safety outcome in the PEGASUS study



Early outcome in PLATO and predicted ticagrelor exposure.

In addition, exposure data was integrated with the primary efficacy outcome data for ticagrelor 90 mg of the PLATO in a model based parametric time-to-event analysis including 6,366 patients. Details are described in the model based exposure-response report which was submitted with the original application. The median C_{max} for ticagrelor 90 mg was 1230 nM. Ticagrelor $C_{ss,av}$ ranged between 239 to 10300 nM; this was not a statistically significant predictor of CV death, MI, stroke or the composite of these endpoints at the studied ticagrelor 90 mg dose.

In order to investigate the potential impact of a difference in exposure on early events, PLATO (Study D5130C05262) data have been used to explore whether there is a relationship between lower than median plasma exposure and early events (as captured on Days 1, 2, 4, 7 and 14 in PLATO). Events included in the analysis were composite primary endpoint (cardiovascular [CV] death, myocardial infarction [MI], or stroke), individual components of the composite endpoint, and stent thrombosis.

Individual Css,av of ticagrelor at Visit 1 (Day 4 after initiation of therapy) was predicted based on the PLATO population PK model. This was performed for the 6366 patients (69% of the full population) in PLATO with exposure sampling (the PK subgroup). Events included in the analysis were composite primary endpoint (cardiovascular [CV] death, myocardial infarction [MI], or stroke), individual components of the composite endpoint, and stent thrombosis. The number of events are summarised in Table 7 and Table 8. For stent thrombosis, possible, probable or definite events if stent thrombosis were included. Since only patients with a stent can experience stent thrombosis, the population was made up of patients in the PK subgroup that had a

stent procedure on Day 1. This approach captured the majority of early stent thrombosis, as shown in Table 8. Stent thrombosis reported after the end of the study was not included in the analysis.

Table 7 Cumulative number of events in the PLATO PK subgroup, up to and including the day specified

Day	Number of composite primary endpoint events	Number of CV deaths	Number of MI	Number of strokes
1	43 (86)	0 (25)	37 (52)	6 (10)
2	68 (140)	0 (46)	62 (87)	6 (12)
4	83 (189)	1 (71)	73 (109)	10 (18)
7	109 (247)	10 (96)	89 (136)	13 (28)
14	170 (343)	31 (140)	125 (189)	24 (42)
Overall	485 (750)	127 (271)	338 (456)	73 (107)

The number of events in the entire PLATO data set are shown in parenthesis CV cardiovascular; MI myocardial infarction

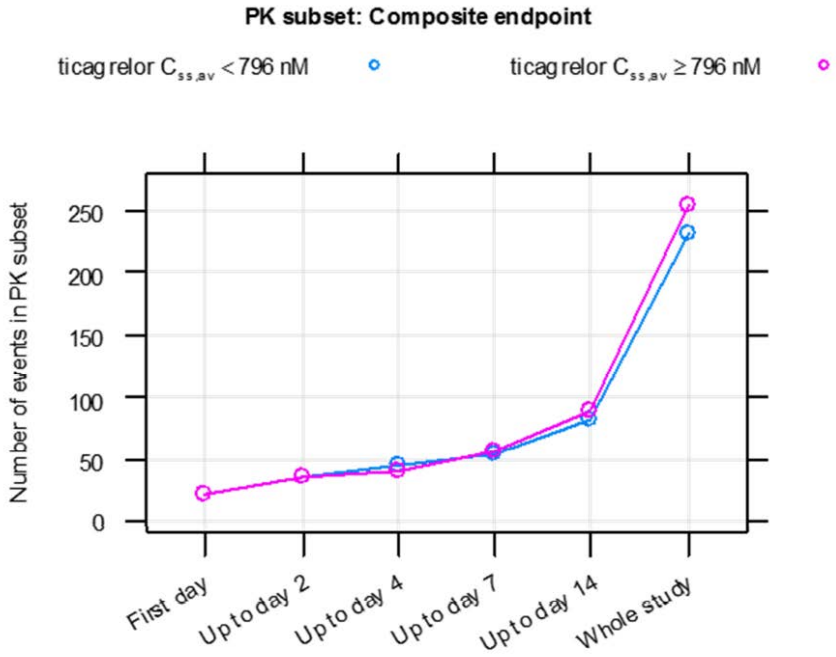
Table 8 Cumulative number of stent thrombosis events in PLATO, up to and including the day specified

Day	All patients	PK subgroup	PK subgroup with stent day 1
1	16	11	11
2	24	13	13
4	33	17	17
7	44	21	20
14	78	40	32
Overall	132	81	56

PK pharmacokinetics

The patients were stratified based on whether the predicted Css,av, based on the population PK model, was higher or lower than the median of the model-predicted Css,av at Visit 1 (796 nM). The median exposure in the population stratified in the low group was 619 nM and in the high group was 1079 nM. Figure 3 presents the results for composite endpoint at, or up to, Day 1, 2, 4, 7, 14 or the full study duration. The results support that the risk for events is not higher in patients with lower than median ticagrelor exposure. Results for CV death, MI, stroke and stent thrombosis in the PK subgroup in show a similar trend; however, these results should be interpreted with caution due to the relatively low number of events.

Figure 7 Number of patients in the PK subgroup with and without a composite event in PLATO, stratified by whether the predicted Css,av at Visit 1 was higher or lower than median of the population predicted Css,av (796 nM)



2.4.4. Discussion on clinical pharmacology

2.4.4.1. Relevance of studies D5139C00003 and D5139C00004

The applicant submitted two bioequivalence studies D5139C00003 and D5139C00004. In both studies ticagrelor 90mg orodispersible (OD) tablet was compared to the approved ticagrelor 90mg immediate release tablet. Study D5139C00003 demonstrated bioequivalence between the tablets when administered without water and via a nasogastric tube, but it failed to demonstrate bioequivalence if administered with water. The mean ticagrelor C_{max} was 15% lower for the orodispersible than that for the immediate release tablets when taken with water. Study D5139C00004 showed bioequivalence between the tablets when taken with and without water.

From the perspective of the ticagrelor 90 mg OD tablet dispersed in saliva and swallowed with water, both Studies D5139C00003 and D5139C00004 can be considered equally relevant.

There were some differences between these studies:

	administration	Race	Volume of water
Study D5139C00003	• dispersed in saliva and swallowed with water • dispersed in saliva and swallowed without water	Caucasian subjects	200ml

	• through a nasogastric tube		
Study D5139C00004	• dispersed in saliva and swallowed with water • dispersed in saliva and swallowed without water	Japanese subjects	150ml

Besides the lack of a treatment arm of ticagrelor 90 mg OD tablet suspended in water and administered through a nasogastric tube in Study D5139C00004, there were 2 key differences between the studies:

- Race of the subjects (D5139C00003, majority (94%) White; D5139C00004, Asian [Japanese])
- Volume of water used by the subjects to swallow the tablets (IR and dispersed OD) (D5139C00003, 200 mL; D5139C00004, 150 mL).

The applicant has discussed the potential influence of race and the volume of water on the outcome of the study.

There are known differences in the PK profile of ticagrelor according to race. This is reflected in the SmPC: 'Patients of Asian descent have a 39% higher mean bioavailability compared to Caucasian patients. In clinical pharmacology studies, the exposure (C_{max} and AUC) to ticagrelor in Japanese subjects was approximately 40% (20% after adjusting for body weight) higher compared to that in Caucasians.' However, there are no known differences in GI physiology between Japanese and Caucasian subjects that would trigger a difference in the oral absorption process. Bioequivalence studies can be conducted in any healthy volunteer population if a crossover design is selected, as every subject is its own control. Therefore, it is considered unlikely that differences due to race would have affected the conclusions on bioequivalence.

The use of the different volumes of water in terms of dissolution and gastric emptying cannot explain the differences between the studies:

Dissolution: Any true difference in formulation performance in vivo would primarily be related to a difference in drug dissolution, pH, or effect of excipients on GI transit or permeability. However, the current clinical data did not consistently imply such an effect. A dissolution or excipient effect would be observed when administering both with and without water, which was not the case. Indeed, when administering without water, the dissolution rate would be expected to be further reduced for a low solubility compound, and the effect of an excipient would also be expected to be stronger given the higher concentration of excipient obtained due to the smaller water volume.

Bioequivalence was demonstrated for the OD tablet administered both with 150 mL water or without water versus the IR tablet in Study D5139C00004, which used the same test and reference batches as Study D5139C00003. Given this, it was considered unlikely that a difference of 50 mL between the 2 studies in volume of water used (200 vs 150 mL) had any impact on the dissolution of the OD or IR tablets.

Gastric emptying: The water volume influences the gastric emptying where a bigger volume triggers a more rapid gastric emptying rate (Oberle et al 1990). However, the difference in volume between Studies D5139C00003 and D5139C00004 was relatively small, and this effect would therefore be marginal and unlikely to be significant in relation to other sources of variation such as timing of administrations in relation to the different stages of the motility cycle (Oberle et al 1990). This water volume difference also compensated for the average difference in body size between White and Japanese subjects making conditions more similar with respect to ratio between water and gastric volumes. In addition, if this factor had been critical, a faster gastric emptying and more rapid absorption would be expected for the higher water volume, which was not the case.

Therefore, it was concluded that differences in race and the administered volume of water were both not expected to have affected the conclusions on bioequivalence.

2.4.4.2. Pooling of the studies D5139C00003 and D5139C00004

According to the *EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)* the body of evidence must be considered as a whole, if two relevant studies have been performed of which one demonstrates bioequivalence and one does not. As both studies could be considered equally relevant for the use of ticagrelor 90 mg OD tablet dispersed in saliva and swallowed with water, the total body of evidence was assessed.

Bioequivalence between the ticagrelor 90 mg IR and OD tablet has been appropriately shown when the provisionally pooled results of the bioequivalence studies D5139C00003 and D5139C0000 were taken into account.

The company did not provide a detailed description of the statistical methodology. The company used ANOVA tests with the factors treatment, study unique sequence, period and subject-within-sequence. It was not clear how study effects were taken into account and how period effects were dealt with. Although, the method of pooling was not sufficiently described and therefore not completely understood, the provisionally pooled results confirmed bioequivalence between IR 90 mg and OD 90 mg tablets with water. The lack of a detailed description of the statistical methodology of the pooling exercise was not further pursued by the CHMP as the totality of evidence indicated that any difference between the IR and OD formulation was very unlikely to be clinically relevant.

2.4.4.3. Worst case scenario: 15% decreased C_{max} a potential delay of t_{max}

Study D5139C00004 showed bioequivalence between the tablets when taken with and without water and study D5139C00003 demonstrated bioequivalence between the tablets when administered without water and via a nasogastric tube but failed to demonstrate bioequivalence if administered with water. The mean ticagrelor C_{max} was 15% lower for the orodispersible than that for the immediate release tablets when taken with water. The applicant has adequately discussed possible explanations for the lower C_{max} observed in study D5139C00003 and potential delay of t_{max}. However, the lack of BE only in this specific situation was discussed in depth by the CHMP. There was no clear explanation found for the observed difference in C_{max} for the ticagrelor 90 mg OD tablets dispersed in saliva and swallowed with water compared with ticagrelor 90 mg IR tablets in Study D5139C00003. Differences in dissolution, excipients and the use of different amounts of mannitol were not considered plausible explanations for the observed difference. The presented IVIVR data showed that relatively large differences in in-vitro dissolution do not result in clinically relevant changes of the exposure and C_{max}.

Studies D5139C00003 and D5139C00004 were both not designed to assess differences in time to reach peak concentration (t_{max}) accurately. Due to infrequent sampling in the absorption phase it was not possible to determine any delay with precision. Although, a potential delay of t_{max} could not be excluded, any difference is likely to be less than 1 hour, probably about 0.5 hour based on arrhythmic means. As a consequence also C_{max} was not optimally accurate.

The applicant submitted a justification to support that if the 15% lower C_{max} found in the pivotal BE study D5139C00003 and the potentially delayed t_{max} were true (worst case scenario), this was not expected to be clinically relevant. This justification adequately addressed the impact on acute phase of the treatment of patients with acute coronary syndromes and the steady state levels of ticagrelor and the long-term treatment with ticagrelor. To further elucidate on this, the applicant tried to estimate the implications for the lower C_{max} found in the BE study for the OD formulation when taken with water using different PK modelling, PK/PD

modelling and exposure outcome modelling techniques. In a simulation based on a PK/PD model the company predicted that the delay in achieving 70% platelet inhibition would be less than 17 minutes, and that 87.3% of the patients with the oral dispersible tablet administered with water had final extent of inhibition of platelet inhibition >70% by 2 hours post-dose. Further, the company has investigated the potential impact of a difference in exposure on early events (cardiovascular [CV] death, myocardial infarction [MI], stroke, or stent thrombosis), based on previously submitted PLATO (Study D5130C05262) data. Based on these data a lower plasma exposure does not appear to increase the risk for early events in the acute phase. Furthermore, any possible lower exposure will unlikely be of clinical relevance for longer treatment as well as a relatively flat, log-linear, relationship between exposure ($C_{ss,av}$) and the composite risk of CV death, MI, or stroke was modelled based on data from the PEGASUS study. The company did not provide an exposure-response model for the PLATO trial to predict the impact of a lower $C_{av,ss}$ (although this was considered unlikely, as a conservative consequence of lower C_{max}) however the CHMP agreed that it is likely that such PLATO modelling would provide similar results as for the PEGASUS modelling.

2.4.5. Conclusions on clinical pharmacology

Based on the totality of data from bioequivalence studies (D5139C00003 and D5139C00004) and the submitted supportive data it was concluded that the pharmacokinetics and pharmacodynamics of the ticagrelor 90mg orodispersible (OD) tablet and the immediate release (IR) tablet are comparable.

Based on the totality of data it was considered unlikely that there is a true difference between the OD and IR formulation with respect to C_{max} only in the specific situation when the ticagrelor 90 mg OD tablets were dispersed in saliva and swallowed with water compared with ticagrelor 90 mg IR tablets in Study D5139C00003. A potential delay of t_{max} could not be excluded, as the sampling schemes of the studies were not designed to assess differences in t_{max}.

The company had adequately discussed the clinical relevance of a decrease of 15% in C_{max} and the potentially delayed t_{max} in the acute phase of the treatment of patients with ACS (worst case scenario) and the long-term treatment with ticagrelor. A decrease of 15% in C_{max} was predicted to result in a delay of about a quarter of an hour in achieving adequate platelet inhibition based on PK/PD modelling. And the lower plasma exposure did not appear to increase the risk for early events based on data from PLATO (Study D5130C05262). Steady state ticagrelor levels and platelet inhibition were not affected. If any small reduction in exposure would occur this will not translate into a clinical relevant effect. Therefore, it was agreed that, if the observed reduced C_{max} and delayed t_{max} of the ticagrelor 90 mg OD tablet were true, it was highly unlikely that this would translate into a clinically relevant impact in the acute phase of an ACS or the more chronic treatment with the ticagrelor 90mg OD tablet.

2.5. Clinical efficacy and safety

There were no new clinical efficacy and safety data submitted within the current application. The clinical evidence for the efficacy and safety of ticagrelor was derived from two phase 3 trials: the PLATO study [PLATelet Inhibition and Patient Outcomes] study, a comparison of ticagrelor to clopidogrel, both given in combination with ASA and other standard therapy AND the PEGASUS TIMI-54 study [PrEvention with TicaGrelor of SecondAry Thrombotic Events in High-RiSk AcUte Coronary Syndrome Patients], a comparison of ticagrelor combined with ASA to ASA therapy alone. These studies were submitted and assessed previously.

2.5.1. Conclusions on the clinical efficacy and safety

There were no new clinical efficacy and safety data submitted within current application. No new data were requested by the CHMP. In this line extension application, there were no new issues related to the clinical efficacy and safety. All the clinical efficacy and safety aspects were considered to be adequately reflected in the Product Information.

2.5.2. PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR refers to the EURD list which remains unchanged.

2.6. Risk Management Plan

The MAH has not submitted an updated RMP as part of this line extension procedure. The CHMP agreed that the RMP did not need to be updated and that the last approved version of the RMP remains valid.

2.7. Pharmacovigilance

Pharmacovigilance system

The pharmacovigilance system has not been updated within this extension application. The last approved version of the pharmacovigilance system remains valid.

2.8. Product information

2.8.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH 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

The current application concerns the PK assessment of a new pharmaceutical form of an orodispersible tablet (OD) compared to an immediate release (IR) tablet. Therefore the benefit-risk balance section was adapted to reflect this assessment.

3.1. Therapeutic Context

3.1.1. Disease or condition

Ticagrelor, 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.

In ACS 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. In patients with a history of MI 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 with 60 mg twice daily dose 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 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.

3.1.2. Available therapies and unmet medical need

Ticagrelor was so far registered as 90 mg and 60 mg film-coated tablets. The orodispersible (OD) 90 mg tablet has been developed to provide alternative administration option for patients. The OD tablet rapidly disperses in saliva on the tongue and is therefore easy to administer orally with or without water. Some patients may prefer the option of drinking water after the tablet has dispersed on the tongue. The OD tablet can also be suspended in water for administration through a nasogastric tube (CH8 or greater), which could fulfil a need in patients with dysphagia due to the severity of their condition or age. It was estimated that approximately 5% to 10% of patients with ACS are intubated and in need of nasogastric tube for feeding and administration of drugs.

3.1.3. Main clinical studies

3.2. Favourable effects

In two studies, bioequivalence (with regards to C_{max} and AUC) has been evaluated for the 90 mg OD tablet versus the existing immediate release (OR) tablet of 90 mg. Bioequivalence (BE) has been demonstrated for the 90 mg OD tablet when taken without water or when dissolved in water and administered via a nasogastric tube with that of the existing immediate release (OR) tablet of 90 mg.

3.3. Uncertainties and limitations about favourable effects

The C_{max} in the BE study in a Western population was lower and did not follow BE criteria for the OD tablet compared to the registered IR tablet when taken with water, while in the Japanese study bio-equivalence, also in terms of C_{max}, was demonstrated. Further there appears to be a delay of the t_{max}. Although, a potential delay of t_{max} cannot be excluded, any difference is likely to be less than 1 hour, probably about 0.5 hour based on arithmic means. A worst case scenario of a 15% reduction in C_{max} could potentially be clinically relevant in patients with acute coronary syndromes. However, the applicant has justified and the CHMP agreed that this appears unlikely.

3.4. Unfavourable effects

Bioequivalence has been demonstrated for the 90 mg OD tablet when taken without water or when dissolved in water and administered via a nasogastric tube with that of the existing immediate release (IR) tablet of 90 mg. Therefore, safety is to be expected to be similar between both doses for these routes of administration.

3.5. Benefit-risk assessment and discussion

The MAH has developed an orodispersible (OD) 90 mg tablet for the treatment of the ACS population to provide a convenient administration option for these patients. However, the orodispersible (OD) tablet has not been developed for patients with a history of MI, who are likely to be treated with the 60 mg dose following treatment of 1 year with the 90 mg dose. The reason was that the indication for extended treatment with 60 mg dose was not yet authorised when the development of the OD tablet was started.

Although, one bioequivalence study in a Western population demonstrated similar PK characteristics between the approved immediate release (IR) tablet and the to-be-registered 90 mg OD formulation when taken without water or administered via a nasogastric tube, bioequivalence was not shown for C_{max} when taken with water. In contrast, bio-equivalence, also in terms of C_{max}, was demonstrated in the Japanese BE study.

Based on the totality of data from these bioequivalence studies, it was considered unlikely that there is a true difference between the OD and IR formulation with respect to C_{max}. It was considered that only in the specific situation when the ticagrelor 90 mg OD tablets were dispersed in saliva and swallowed with water BE could not be shown for C_{max} compared with ticagrelor 90 mg IR tablets (Study D5139C00003). The current clinical data do not consistently imply that this difference could be related to a true difference of formulation performance *in vivo* based on a difference in drug dissolution or effect of excipients (the use of different amounts of mannitol) on the gastrointestinal (GI) transit or permeability. In addition, the observed difference in BE when taken with water did not affect steady state levels.

A potential delay of t_{max} could not be excluded, as the sampling schemes of both studies were not designed to assess differences in t_{max}. Based on the presented data any difference in t_{max} is likely to be less than 1 hour, (probably about 0.5 hour) based on arithmetic means and as a consequence also C_{max} is not optimally accurate.

In accordance with the *EMA Guideline on the investigation of bioequivalence* the total body of evidence should be taken into account if two equally relevant studies were conducted. Therefore the results of the studies were pooled. The provisionally pooled results of the bioequivalence studies D5139C00003 and D5139C00004 indicated bioequivalence between IR 90 mg and OD 90 mg tablets when administered with water.

3.5.1. Importance of favourable and unfavourable effects

The MAH has discussed the clinical relevance of a decrease of 15% in C_{max} and the delayed t_{max} in the acute phase of the treatment of patients with ACS (worst case scenario) and the long-term treatment with ticagrelor. A decrease of 15% in C_{max} was predicted to result in a delay of about a quarter of an hour in achieving adequate platelet inhibition based on PK/PD modelling. This lower plasma exposure did not appear to increase the risk for early events based on data from (assessed previously) PLATO study (Study D5130C05262), while any worst-case lower exposure did not affect the risk for events either. Therefore it was agreed that, if the observed reduced C_{max} and delayed t_{max} of the ticagrelor 90 mg OD tablet were true, it was highly unlikely that this would translate into a clinically relevant alteration of the treatment effect, and thus this observation did not alter the benefit-risk profile of ticagrelor.

3.5.2. Balance of benefits and risks

Based on the totality of data from two bioequivalence studies: D5139C00003 and D5139C00004, and the submitted supportive data it was concluded that the pharmacokinetics and pharmacodynamics of ticagrelor 90mg orodispersible (OD) tablet and the immediate release (IR) tablet are comparable. Consequently, the

positive benefit-risk profile of the immediate release formulation was considered applicable to the new orodispersible ticagrelor 90mg formulation.

3.6. Conclusions

The overall B/R of Brilique 90mg orodispersible tablet is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Brilique 90 mg orodispersible tablets is favourable in the following indication:

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 CHMP therefore recommends the extension of the marketing authorisation for Brilique subject to the following conditions:

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.