EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Pradaxa

International Nonproprietary Name: dabigatran etexilate

Procedure No. EMEA/H/C/000829/X/13/G

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

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List of abbreviations

ACC	American College of Cardiology
ACT	Activated Clotting Time
AE(s)	Adverse Event(s)
AF	Atrial Fibrillation
AHA	American Heart Association
Alk. Phos.	Alkaline Phosphatase
ALT	Alanine Aminotransferase (=SGPT)
aPTT	Activated Partial Thromboplastin Time
ARB	Angiotension Receptor Blocker
ASA	Acetylsalicylic Acid
AST	Aspartate Aminotransferase (=SGOT)
AUC	Area under the plasma-concentration time curve
AV	atrioventricular
BI	Boehringer Ingelheim
bid	*bis in die* (twice daily)
BMI	Body Mass Index
BP	Blood Pressure
C2,ss	plasma concentration at 2 hours after drug administration at steady state
Cmax	maximum concentration in plasma
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHADS2	Cardiac Failure, Hypertension, Age, Diabetes, Stroke (Doubled)
CHF	Congestive Heart Failure
CI	Confidence Interval
CK-MB	Creatinine Kinase-MB (muscle brain)
Cpre,ss	trough plasma concentration at steady-state
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTP	Clinical Trial Protocol
CV	Coefficient of Variation
DBP	Diastolic Blood Pressure
DC	Direct Current
DE	dabigatran etexilate
DE 110	dabigatran etexilate 110 mg bid
DE 150	dabigatran etexilate 150 mg bid
DQRM	Data Quality Review Meeting
DSMB	Data Safety Monitoring Board
Emax	Maximum effect
Epre,ss	Predose effect at steady state immediately before administration of the next dose
EC50	The drug dose required to attain 50% of the maximum effect

ECG(s)	Electrocardiogram(s)
ECT	Ecarin Clotting Time
ESC	European Society of Cardiology
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gCV	geometric Coefficient of Variation
GI	gastrointestinal
gMean	geometric Mean
gp	glycoprotein
HF	heart failure
HIPAA	Health Insurance Portability and Accountability Act
HPLC-MS/MS	High Performance Liquid Chromatography-Tandem Mass
	Spectrometry
HPMC	hydroxyl, propyl-methyl cellulose
i.v.	intravenous
ICD	Implantable Cardioverter Defibrillator
ICH	International Conference on Harmonisation
	Intra-cranial hemorrhage
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
ISF	Investigator Site File
IVRS	Interactive Voice Response System
LFT	Liver Function Test
LVD	Left Ventricular Dysfunction
LVEF	Left Ventricular Ejection Fraction
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NCB	Net Clinical Benefit
PCI	Percutaneous Coronary Intervention
PCR	Polymerase Chain Reaction
PE	Pulmonary Embolism
P-gp	P-glycoprotein
PK	Pharmacokinetic(s)
PPS	Per Protocol Set
PROBE	Prospective Randomized Open trial with Blinded Evaluation
	of outcomes
PT	Prothrombin Time
PTCA	Percutaneous Transluminal Coronary Angioplasty
qd *quaque die*	qid quart in die (four times daily)

SAE(s)	Serious Adverse Event(s)
SAF	Safety Analysis Set
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SEE	Systemic Embolic Event
SGOT	Serum Glutamate Oxaloacetate Transferase (=AST)
SGPT	Serum Glutamate Pyruvate Transferase (=ALT)
SOC	System Organ Class
SOP	Standard Operating Procedure
SPAF	Prevention of stroke and systemic embolic events in subjects with non-valvular atrial fibrillation
ss	Steady State
TIA	Transient Ischemic Attack
tid	ter in die (three times daily)
TSAP	Trial Statistical Analysis Plan
TT	Thrombin Time
TTC	Threshold of toxicological Concern
TTR	time in therapeutic range
ULN	Upper Limit of Normal
VKA	Vitamin K antagonist

1. Background information on the procedure

1.1. Submission of the dossier

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 05 January 2010 an application for a group of variations consisting of an Extension of the Marketing Authorisation, 6 Type II variations, 12 Type IB variations and 17 Type IA variations (including 3 Type IA_{IN}).

The extension of the Marketing Authorisation for the above mentioned medicinal product concerns a new strength: 150 mg.
The applicant has also applied for an update of the SmPC to include a new indication for the new strength (150 mg) and for 110 mg strength: *Prevention of stroke and systemic embolism in adult patients with atrial fibrillation.*

In addition, the variations to the terms of the Marketing Authorisation, concern the changes to the first generation synthesis, and the addition of an alternate routes of synthesis. It further concerns changes to the first generation synthesis related to the specifications and suppliers of starting materials and intermediates, testing of the drug substance and specification of the same. The application also concerns a new drug product manufacturing method and further changes related to manufacture, in-process controls, testing, specifications and shelf-life of the drug product for the registered and the new 150 mg strengths.

Finally, information addressing FUM 005, related to the development of a new in-process control at the isolation step, has been also presented.

The variations submitted in the group are the following:

1

Variation(s) requested		**Type**
A.7	Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier).	IA

2

Variation(s) requested		**Type**
B.I.a.2	Changes in the manufacturing process of the active substance b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	II

3

Variation(s) requested		**Type**
B.I.a.2	Changes in the manufacturing process of the active substance	II

Variation(s) requested		Type
	b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	

4

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance b) Tightening of specification limits	IA

5

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance b) Tightening of specification limits	IA

6

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance c) Addition of a new specification parameter to the specification with its corresponding test method	IA

7

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance c) Addition of a new specification parameter to the specification with its corresponding test method	IA

8

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	IA

9

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance f) Change outside the approved specifications limits range for the active substance	II

10

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance z) Other variation	IB

11

Variation(s) requested		Type
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance z) Other variation	IB

12

Variation(s) requested		Type
B.I.b.2	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance a) Minor changes to an approved test procedure	IA

13

Variation(s) requested		Type
B.I.b.2	Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance a) Minor changes to an approved test procedure	IA

14

Variation(s) requested		Type
B.I.c.3	Change in the test procedure for the immediate packaging of active substance z) Other variation	IB

15

Variation(s) requested		Type
B.II.b.1	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product a) Secondary packaging site	IA_{IN}

16

Variation(s) requested		Type
B.II.b.1	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product a) Secondary packaging site	IA_{IN}

17

Variation(s) requested		Type
B.II.b.1	Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non sterile medicinal products.	IB

18

Variation(s) requested		Type
B.II.b.2	Change to batch release arrangements and quality control testing of the finished product a) Replacement or addition of a site where batch control/ testing takes place	IA

19

Variation(s) requested		Type
B.II.b.2	Change to batch release arrangements and quality control testing of the finished product a) Replacement or addition of a site where batch control/ testing takes place	IA

20

Variation(s) requested		Type
B.II.b.3	Change in the manufacturing process of the finished product b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	II

21

Variation(s) requested		Type
B.II.b.4	Change in the batch size (including batch size ranges) of the finished product z) Other variation	IB

22

Variation(s) requested		Type
B.II.b.4	Change in the batch size (including batch size ranges) of the finished product z) Other variation	IB

23

Variation(s) requested		Type
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product a) Tightening of in-process limits	IA

24

Variation(s) requested		Type
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product c) Deletion of a non-significant in-process test	IA

25

Variation(s) requested		Type
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product z) Other variation	IB

27

Variation(s) requested		Type
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product z) Other variation	IB

28

Variation(s) requested		Type
B.II.b.5	Change to in-process tests or limits applied during the manufacture of the finished product z) Other variation	IB

29

Variation(s) requested		Type
B.II.d.1	Change in the specification parameters and/or limits of the finished product	IA

Variation(s) requested		Type
	a) Tightening of specification limits	

30

Variation(s) requested		Type
B.II.d.1	Change in the specification parameters and/or limits of the finished product e) Change outside the approved specifications limits range	II

31

Variation(s) requested		Type
B.II.d.2	Change in test procedure for the finished product a) Minor changes to an approved test procedure	IA

32

Variation(s) requested		Type
B.II.d.2	Change in test procedure for the finished product z) Other variation	IB

33

Variation(s) requested		Type
B.II.e.3	Change in test procedure for the immediate packaging of the finished product z) Other variation	IB

34

Variation(s) requested		Type
B.II.e.3	Change in test procedure for the immediate packaging of the finished product z) Other variation	IB

35

Variation(s) requested		Type
B.II.e.5	Change in test procedure for the immediate packaging of the finished product a) *Change in the number of units (e.g. tablets, ampoules, etc.) in a pack* *2.* Change outside the range of the currently approved pack size	IB

36

Variation(s) requested		Type
B.II.f.1	Change in test procedure for the immediate packaging of the finished product a) *Reduction of the shelf life of the finished product* 1. As packaged for sale	IA_{IN}

37

Variation(s) requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/107/2010 for the following conditions:

- Prevention of the thromboembolic events
- Treatment of the thromboembolic events

on the agreement of a paediatric investigation plan (PIP) and the granting of a (product-specific) waiver.

The PIP is not yet completed.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant did not seek the scientific advice at the CHMP. The applicant received national scientific advice from Sweden and France in April 2005. The scientific advice pertained to the acceptability of a single large study and the acceptance of the open-label design.

Licensing status

Pradaxa has been given a Marketing Authorisation in the EU on 18 March 2008.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Jens Heisterberg** Co-Rapporteur: **Pierre Demolis**

- The application was received by the EMA on 5 January 2010.

- On 21 December 2010 the applicant submitted a request for a shortened review time, which was not endorsed by the CHMP.
- The procedure started on 21 January 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 09 April 2010 (Annex 1). The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 April 2010 (Annex 2).
- During the meeting on 20 May 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant (Annex 3).
- The summary report of the GCP inspection carried out at the following sites: Population Health Research Institute (PHRI), Boeringer Ingelheim Pharmaceuticals, Inc., Investigators' Site 075, Investigators' Site 901 between 16 August 2010 and 16 September 2010 was issued on 03 November 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 09 November 2010.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 November 2010 (Annex 4).
- During the CHMP meeting on 16 December 2010, the CHMP agreed on a list of outstanding issues to be addressed in writing and by the applicant (Annex 5).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 14 February 2011.
- During the CHMP meeting on 17 March 2011, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and by the applicant (Annex 6).
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 17 March 2011.
- During the meeting on 14 April 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension associated with a grouped variation. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 13 Apr 2011 (Annex 7).
- As corrections to CHMP AR adopted in April 2011 were required to reflect the updated clinical data set submitted by the applicant and assessed during the procedure, on 10 June 2011 the CHMP adopted a revised opinion via written procedure.

2. Scientific discussion

2.1. Introduction

The need for development of new orally effective anticoagulants in the treatment of patients with chronic atrial fibrillation (AF) is well established. AF is the most common sustained cardiac rhythm disturbance. The prevalence of paroxysmal or persistent AF is estimated at 0.4% of the general population, including up to 1% of all adults. The prevalence of AF increases with age. It occurs in less

than 1% of those under 60 years of age but in more than 6% of those over 80 years of age. It has a heterogeneous clinical presentation. It can occur with or without symptoms and, although it is often associated with heart disease, AF occurs in many patients with no other detectable cardiac disease. By convention, the term "non-valvular AF" is restricted to cases in which the rhythm disturbance occurs in the absence of rheumatic mitral stenosis or a prosthetic heart valve. AF increases the risk of stroke and death. Most of the strokes, fatal and nonfatal, associated with AF are ischemic in nature, usually a result of a thromboembolism with the origin in a left atrial thrombus. One of every six strokes occurs in patients with AF. Estimated annual incidence of stroke in the non-treated AF population ranges from 2-5% per year in moderate risk subjects to 5-10% per year in high risk subjects. The severity of AF in terms of stroke and systemic embolisation rates is determined by patient risk factors. Risk factors for stroke and systemic embolism in patients with non-valvular AF are a history of previous stroke or TIA, a history of hypertension, left ventricular dysfunction (LVD) or congestive heart failure (CHF), advanced age (generally, over 75), diabetes mellitus, and coronary artery disease. Patients without any of these risk factors, i.e., lone AF, have a more favourable prognosis with respect to the occurrence of stroke, thromboembolic events and mortality. Prevention of thromboembolism is thus recommended for all patients with AF, except for those with lone AF or those with contraindications ([1]).

The vitamin K antagonists (VKAs, coumarins), in particular warfarin, are the most widely prescribed oral anticoagulants. In several adequate and well-controlled trials, warfarin decreased the risk of stroke/systemic thromboembolism by 68% versus placebo. This class of drugs when used in patients with AF also has shown to have a higher risk of bleeding at therapeutic doses than ASA alone. VKAs have a slow onset and offset of action, high inter- and intra-individual variability in their effective plasma concentrations, and have a high potential for food and drug interactions. Because of these facts, and the narrow therapeutic window with this class of agent, treatment with VKAs creates a major burden for the health care systems in each country. Special anticoagulation clinics for periodic monitoring and adjustment of the anticoagulant dose have been established at many medical centres, clinics and physician's offices. Monitoring is based on normalized prothrombin times (International Normalized Ratio [INR]).

Dabigatran etexilate (DE) is the oral pro-drug of the active moiety dabigatran (INN). Dabigatran is a potent, synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin. Since thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation. DE does not inhibit thrombin or factor Xa, respectively, demonstrating that the pro-drug does not possess anticoagulant activity. The pharmacokinetic (PK) profile is characterized by peak plasma concentrations of dabigatran that occur 2 hours after oral administration of the prodrug and a terminal elimination half-life of 12-14 hours. With bid dosing the steady state is attained within 3 days, and the maximum concentration in plasma (Cmax) at steady state is about 30% higher than after the first dose. Dabigatran is eliminated primarily by the kidneys with urinary excretion accounting for up to 80 % of the dose administered intravenously.

Dabigatran etexilate has been approved in the EU on 18 March 2008 for the indication: "Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery".

This grouped application concerns an Extension application for a new pharmaceutical strength (Pradaxa, 150 mg, hard Capsules) and associated variations consisting of Type II, Type IB and Type IA

[1] ESC Guidelines for the management of atrial fibrillation. European Heart Journal (2010) 31, 2369–2429

variations, submitted in accordance with Article 7.2.(b) of Commission Regulation (EC) No 1234/2008. The main components of this application are following:

(1) An application involving the new indication, "Prevention of stroke and systemic embolism in adult patients with atrial fibrillation",

(2) As the 110 mg strength will also be needed for special population in the "Prevention of stroke and systemic embolism in patients with atrial fibrillation", a new pack size is introduced for the 110 mg,

(3) An alternate drug substance synthesis and further drug substance changes for the registered strengths of 75 mg and 110 mg. These changes also apply to the new 150 mg dose strength,

(4) A new drug product manufacturing method and further drug product changes for the registered strengths of 75 mg and 110 mg. These changes also apply to the new 150 mg dose strength.

The granted indications are the following (added indication in **bold**):

75 mg and 110 mg strength

Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

110 mg and 150 mg strength

.

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors:

Previous stroke, transient ischemic attack, or systemic embolism (SEE)

Left ventricular ejection fraction < 40 %

Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2

Age ≥ 75 years

Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension

2.2. Quality aspects

2.2.1. Introduction

Pradaxa 75mg and 110 mg hard capsules have been already approved in March 2008.

In the context of the indication extension, a new 150 mg dose strength is proposed. Pradaxa 150 mg hard capsules consist of an imprinted hydroxypropylmethylcellulose (HMPC) capsule with light blue opaque cap and cream-coloured, opaque body. For 150 mg capsules, capsule size 0 are used and the cap is imprinted (black) with Boehringer Ingelheim company symbol and the body with "R150".

Capsules will be marketed in polypropylene bottle with a polypropylene/ polyethylene screw closure and in aluminium / aluminium blister strips.

In addition to the introduction of a new strength, this application concerns a large number of changes submitted as grouping of type IA, IB and type II changes.

In particular, it concerns changes to the first generation synthesis, and the addition of an alternate routes of synthesis, identified as the first generation synthesis and the second generation synthesis, abbreviated as 1st gen and 2nd gen respectively, introduced by two type II variations. Both routes of synthesis are proposed for commercial manufacture.

It further concerns changes to the 1st gen synthesis related to the specifications and suppliers of starting materials and intermediates, testing of the drug substance and specification of the same, introduced via a number of appropriate type II, IB and IA variations. All drug substance changes also apply to both the existing and the new 150 mg strengths.

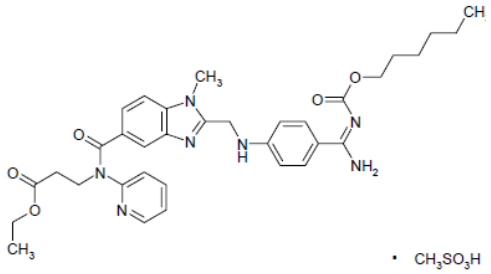
The application also concerns a new drug product manufacturing method and further changes related to manufacture, in-process controls, testing, specifications and shelf-life of the drug product for the registered and the new 150 mg strengths introduced via a number of appropriate type II, IB and IA variations. Finally, information addressing FUM 005, related to the development of a new in-process control at the isolation step, has been also presented.

A detailed table of all the changes included in this application can be found above in section 1 of this report.

2.2.2. Active Substance

Dabigatran etexilate (DE) is the oral pro-drug of the active moiety dabigatran. The dabigatran etexilate pro-drug was developed due to the limited oral availability of dabigatran, and it is converted into dabigatran (DAB) in vivo via esterases. The drug substance is the mesilate salt form of the pro-drug, called dabigatran etexilate mesilate (DEM).

The chemical name (IUPAC) of dabigatran etexilate mesilate is ethyl N-{[2-({[4-((E)-amino {[(hexyloxy) carbonyl] imino} methyl) phenyl] amino} methyl)-1-methyl-1H-benzimidazol-5-yl] carbonyl}-Npyridin-2-yl-β-alaninate methanesulfonate corresponding to the molecular formula C34H41N7O5 x CH4O3S (C35H45N7O8S) and the structure shown below:



DEM exhibits polymorphism. Two forms, modification I and II are known. The drug substance is modification I in the anhydrous form, possibly mixed with modification II. A hydrated form with a stoichiomety close to a hemihydrate also exists.

Manufacture

With regard to the 1st gen manufacturing process already approved, certain changes related to solvents and other reagent and materials used in the manufacture have been introduced by a type II variation. The proposed changes do not affect the quality of the active substance.

In addition to the above, the list suppliers of two starting materials has been updated and the impurities specification limit and method for one starting materials, the assay specification and methods of two starting materials and specification of some intermediates have been revised.

Besides the changes to the 1st gen manufacturing process, a new alternate route of synthesis abbreviated as 2nd gen has been presented.

The active substance is manufactured (2nd gen) in a number of synthetic and recrystallisation steps described in sufficient detail. The synthetic process results in isolated and purified intermediates. Control of these intermediates is critical to guarantee drug substance of consistently high quality. The specifications and controls in place for the isolated intermediates as well as the proposed IPCs, ensure the production of drug substance consistently in conformance with the proposed regulatory specification for commercial production.

Discussion on impurities with genotoxic potential in the starting material is presented.

All identified potentially genotoxic compounds are limited in the starting material specification and spiking experiments demonstrate low probability of any such substance in the drug substance considering a 300mg daily dose and corresponding TTC calculated on 5ppm. Carry over possibility was discussed and evaluated. An extensive evaluation of the known and potential genotoxic impurities has been submitted. Based on the collected data it is concluded that alkyl mesilates are not present at release of the drug substance at levels of any safety concern, and they do not form on storage. The data show that the quantitative levels of the individual potential genotoxic/genotoxic impurities in the drug substance are kept below the TTC level of 1.5µg/day and that the sum of the genotoxic impurities will most likely also be kept below the TTC due to removal or reduction in quantity during the synthesis process. The submitted data is considered acceptable.

So far, a large number of batches of the 2nd gen synthesis have been manufactured. The drug substance batches, manufactured at both proposed sites, are comparable with regard to batch results and stability data.

Specification

A common specification is proposed for the active substance produced by either of the two methods. The specifications for the control of the drug substance includes tests for appearance (visual), identification (IR), colour and clarity of solution (Ph.Eur.), purity and polymorphism (DSC), impurities (HPLC), residual solvents (GC), heavy metals (Ph.Eur.), water content (Ph.Eur.), sulphated ash (Ph.Eur.), assay (HPLC and titration), particle size (Laser-beam diffraction).

Based on drug substance batch experience and manufacturability aspects of the drug substance a widening of the polymorphism limit and widening of particle size distribution range were introduced. Drug product manufacturability has also been demonstrated following the changes.

Dissolution data and clinical batch experience showed that any variation in particle size within the new proposed range should have no impact on drug product dissolution. Furthermore, the widening of the polymorphism specification is supported by an in vivo bioequivalence study (1160.66).

Also, minor changes to the assay titration method, to the HPLC method for testing related substances, to the GC method for residual solvents, to the particle size method and to the methods for heavy metal, water content and sulphated ash have been made. The impurities limit has been tightened.

Finally, minor changes to the information related to the reference standard materials used for the control of active substance have been introduced and descriptions of the methods used for the testing of immediate packaging of the active substance have been provided.

The quality of drug substance produced either according to the 1st gen synthesis or to the 2nd gen synthesis is considered equivalent and that is supported by equivalent specifications for both. There is only one difference in the impurity profile as one impurity occurs in the 1st gen synthesis but cannot be

formed in the 2nd gen synthesis. Both processes guarantee a uniform particle size distribution (PSD) of the final active substance independent of the route of synthesis. Mean PSD is same for both synthesis routes.

Stability

Stability data for three production-scale primary stability batches manufactured at the proposed commercial site by the 1st generation includes 24 months long-term data obtained at 25°C/60% RH and 6 months accelerated data obtained at 40°C/75% RH. These batches are representative of the commercial drug substance. The stability samples were packaged in a container/closure system which mimics the one which will be used for the commercial drug substance.

Both at long term and accelerated conditions no changes in tested parameters were observed apart from an increase in one degradation impurity and total impurities. From the statistical evaluation on the long term stability results it was concluded that results would comply also after 24 months storage.

Stability data for six production-scale primary stability batches manufactured at the proposed commercial sites by the 2nd generation includes data up to 24 months long-term and 6 months accelerated. These batches are representative of the commercial drug substance. The stability samples were packaged in a container/closure system which mimics the one which will be used for the commercial drug substance.

Both at long term and accelerated conditions no changes in tested parameters were observed apart from an increase in one degradation impurity and total impurities. From the statistical evaluation on the long term stability results it was concluded that results would comply also after 24 months storage.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The new 150 mg strength is directly proportional to the two authorised strengths. As already mentioned above data (including bioequivalence study 1160.66) have been presented to support a higher content of modification II in drug substance and finished product.

Stability data show that no conversion of modification I into modification II occurs in bulk drug substance as well as in drug product during storage. The solubility of the two modifications in aqueous media at a variety of pHs is not significantly different, and the in vitro dissolution of the drug products of the two modifications is similar.

The particle size distribution of the drug substance can potentially impact the manufacturing process and drug product dissolution.

It has been shown that the difference in drug substance particle size has no impact on the in vitro dissolution behaviour of capsules. The drug product manufacturability has been demonstrated for both the 1st gen and the 2nd gen processes over a range of drug substance particle sizes. The current drug substance quality produced according to the current 1st gen and 2nd gen routes of synthesis is controlled to tight particle size upper limits to ensure suitable drug product manufacturing yield. Dissolution data and clinical batch experience show that any particle size variation within this range of quality should have no impact on the drug product dissolution.

The dissolution behaviour of HPMC capsules with different dosage strengths and capsule sizes was tested to guarantee identical dissolution characteristics independent of the dosage strength and of the

capsule size. The dissolution characteristics of the HPMC capsules are all comparable and show no significant differences concerning dosage strength and capsule size.

Finally a new pack size for 110 mg capsules has been introduced.

Adventitious agents

No excipients of human or animal origin are used in the manufacture of Pradaxa 150 mg capsules.

Manufacture of the product

The new 150 mg strength is manufactured by the same manufacturing process as the existing 75 and 110 mg strengths.

However, this common manufacturing process compared with the process originally approved (referred to as 1st gen DP) has been modified (referred to as 2nd gen DP). Comparative dissolution profiles over a range of pH were provided as well as comparative release and stability data for the main changes during development. Comparative batch data bridging the main changes were also presented.

Minor changes in relation to the manufacture of pellets have been introduced. The pellets are drug product intermediates manufactured by routine production. The holding times for the above types of pellets have also been re-established.

Due to introduction of 2nd gen DP manufacturing process the batch size is increased.

The applied in-process controls (IPCs) for the drug product intermediates and packaging of the finished product have been revised in accordance with new manufacturing process, by deleting non significant tests, tightening limits, changing the methods used or adding alternate ones.

New information on development of a new in-process control at the isolation step in order to fulfil the EMEA/H/C/829 FUM 005, which is considered fulfilled by the data presented.

With regard to the manufacturing sites involved, a manufacturing site has been deleted and a new one has been introduced, two new sites for secondary packaging have also been introduced and site for drug product testing has been added.

For the 2nd gen DP process, process evaluation was successfully carried out on three pilot batches of each strength of Pradaxa capsules.

Product specification

The Pradaxa 150 mg capsules specification for batch release and shelf-life is in line with the already authorised strengths and includes the following tests: appearance (visual), loss on drying for pellets (gravimetry), loss on drying for capsule shell (gravimetry), identification (HPLC, UV- at release only), active ingredient content (HPLC), degradation products (HPLC), uniformity of dosage units (Ph. Eur.-at release only), dissolution (Ph. Eur.), microbiological purity (Ph. Eur.).

Compared with the specification initially approved, the related substances shelf-life limits have been tightened for two impurities for capsules in blister. The limit for loss on drying (LOD) of pellets and capsule shell at release and shelf-life has also been tightened. Minor changes to the approved LOD test

procedure for pellets and capsules, to the HPLC method for ID, active ingredient content and active ingredient degradation and to the dissolution test procedure for 75 mg and 110 mg capsules have been made. New batch analysis data from new batches of reference standards have been also included.

Sufficient justification for applying no testing requirement of polymorphism and for alkyl methanesulfonate in the release specification has been provided (see discussion above on pharmaceutical development and manufacture of active substance).

Count method, weighing and visual test method descriptions) always used for the lidding foil were submitted, together with method descriptions for the LOD and weighing tests used for the screw cap.

Results from the 2nd gen DP process are presented on seven batches for the 75 mg strength, on six batches for the 110 mg strength and on seven batches for the 150 mg strength. The results of all batches comply with the specification and confirm consistency of the product.

Stability of the product

Three batches of each strength have been stored at 25ºC/60% RH for 12 months and at 40ºC/75% RH for 6 months in the proposed market blister and bottle packaging.

No significant changes are observed at long term or accelerated condition for any strength in blister or in bottle. At long term condition no clear trend over 12 months was observed, apart from very minor changes for LOD (capsule shells) one degradation product and total degradation products at long term conditions and slightly higher at accelerated condition.

Statistical evaluation on stability data was presented and showed that results are likely to be within specification after the proposed 24 months storage in blister and bottle.

Photostability

Pradaxa was found photostable. There were no differences between the directly exposed sample and the dark control.

In-use stability

The in-use stability was tested over 30 days and the studies were performed at 25°C/60% RH on one primary stability batch of Pradaxa of each strength that had been previously stored for 12 months at 25°C/60% RH storage condition. The results of in-use stability study indicated that the desiccant in the cap of the polypropylene bottle was still active after the 30 days in-use period.

Stress stability studies

After open storage at 60°C/- for up to 85 days there was a decrease in the loss on drying values for pellets and capsule shells, and simultaneously only a slight increase in the degradation product levels.

Following the changes in the manufacture of the active substance and the finished product and because of the limited stability data available the shelf-life on Pradaxa batches manufactured by the 2nd gen DP manufacturing process using active substance from the new method (2nd gen) of synthesis the shelf-life of Pradaxa capsules has been reduced without changes in the storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality information of Pradaxa covering the active substance and the whole range of capsule strength has been substantially updated by a number of appropriate variations submitted as grouping together with the extension application for the addition of a new strength on 150 mg. All the applied changes have been accepted apart from one referring to the widening of limits for active degradation limits in the specification of 75 mg and 110 mg finished product in PP bottles submitted as type II variation. The reason for rejecting this variation was that based on batch results and stability results in

both packaging materials the proposed changes in shelf-life limits of some related substances are not justified from the presented data on 3 strengths manufactured according to the 2nd gen DP process.
The quality of Pradaxa is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented.
Satisfactory information with regard to FUM 005 was also presented.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The updated quality information of Pradaxa including the results of tests carried out and the specification set for the dabigatran active substance and Pradaxa capsules indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life. FUM 005 is considered fulfilled.

2.3. Non-clinical aspects

2.3.1. Introduction

New nonclinical studies were submitted for: primary pharmacodynamics, safety pharmacology, pharmacokinetics and toxicology. No new studies were submitted in the following chapters of Module 4, as reports have already been submitted with the initial submission in 2007:

Module 4.2.1.2	Secondary Pharmacodynamics
Module 4.2.2.3	Distribution
Module 4.2.2.5	Excretion
Module 4.2.2.6	Pharmacokinetic Drug Interactions
Module 4.2.3.1	Single-Dose Toxicity
Module 4.2.3.5.1	Fertility and Early Embryonic Development
Module 4.2.3.5.2	Embryofetal Development
Module 4.2.3.5.3	Prenatal and Postnatal Development Including Maternal Function
Module 4.2.3.6	Local Tolerance

2.3.2. Pharmacology

Dabigatran etexilate mesilate (DEM) is the oral pro-drug of the active moiety dabigatran. Dabigatran is a potent, synthetic, non-peptide competitive, rapidly acting and reversible inhibitor of thrombin. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. Dabigatran also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. As a follow up on previous concerns the applicant provided experimental documentation for competitive inhibition of thrombin. Furthermore Dabigatran is demonstrated to be equipotent for inhibiting free or clot bound thrombin.

Comprehensive experimental documentation for the off-target binding abilities of both DEM and Dabigatran showed that only DEM exhibits minor unspecific binding in this binding screen at concentrations 50-60-fold in excess of relevant concentrations in humans. A bleeding time study in

rats treated with supratherapeutic doses showed that the activated factor VII or activated prothrombinase complex would be relevant unspecific antidotes in case of bleeding episodes in man.

2.3.3. Pharmacokinetics

Absorption and Distribution

No further data was submitted and this was considered acceptable by the CHMP.

Metabolism

The glucuronidation of dabigatran was investigated in vitro by using human liver or intestinal microsomes or expressed UDP-glucuronosyltransferases (UDP = Uridine-Diphosphate). This indicated a much lower capacity of the intestine compared to the liver for the glucuronidation of dabigatran. Incubation with a broad range of UGT enzymes indicated that UTG 2B15 exhibited the highest activity for the glucuronidation of dabigatran. Additional data on the specific glucuronidation of dabigatran was obtained through co-incubation with several non-specific inhibitors indicating the contribution to the glucuronidation of dabigatran by UGT1A9, UGT2B7 and UGT2B15. It was concluded that dabigatran was a non-specific, low-affinity substrate of UGT1A9, UGT2B7 and UGT2B15; the latter UGT was probably the major catalyst for the formation of the 1-O-acylglucuronide.

Pharmacokinetic drug interaction

In vitro studies in P-gp-expressing Lewis-lung cancer porcine kidney 1 cells indicated that dabigatran etexilate mesilate was a substrate of P-gp, and dabigatran was not a substrate of P-gp. DEM was considered to be a low-to-medium-affinity substrate of P-gp with an estimated Km value of above 10 µM. Different interaction/inhibition studies in P-gp-expressing cells, using digoxin, amiodarone, clarithromycin, itraconazole, quinidine and ritonavir as probe substrates showed that the potential of DEM and dabigatran to inhibit P-gp activity was minimal indicating that neither DEM nor dabigatran would influence the biliary excretion, urinary secretion or tissue distribution of co-administered drugs that are substrates of P-gp. Some inhibitory effects on DEM transport were observed and consequently, drug-drug interactions based on the inhibition of P-gp-mediated DEM could not be ruled out if the concentrations of these P-gp modulators at the interaction sites reach or exceed the IC50 values estimated in this study (0.5 to 75 µM). However, due to high intrinsic passive permeability DEM is expected to be well absorbed in humans even during co administration of potent P-gp substrate inhibitors.

Other pharmacokinetic studies

A comparative PK study was conducted in male and female mice of two different strains (Crl:NMRI and CrllCR:CD1) following a single oral administration of DEM. The objectives of the study were to investigate possible differences between these two mouse strains concerning the PK behaviour of dabigatran and to examine the extent of circulating conjugates of dabigatran. Although a slight gender effect was observed in mice similar glucuronidation of dabigatran was recorded in NMRI and CD1 mice, in accordance with previous data on metabolite pattern in NMRI mice showing non-quantifiable traces of acyl-glucuronides of dabigatran. No significant gender related differences in pharmacokinetics were seen in rats and monkeys.

2.3.4. Toxicology

Single dose toxicology, repeat dose toxicology, local tolerance and reproductive toxicology

No further data submitted. This was considered acceptable due to comprehensive existing data and the extensive clinical use

Genotoxicity

The additional mouse lymphoma assay confirmed previous data that dabigatran did not induce any increase of mutants cells.

Carcinogenicity

Oral administration of DEM at dosages of 30, 100 or 200 mg/kg to CD-1 mice for up to 104 weeks revealed no evidence of a carcinogenic potential. The findings in this study were generally associated with an impeded clotting mechanism. Oral administration of DEM at dosages of 30, 100 or 200 mg/kg to Han Wistar rats for 104 weeks revealed no evidence of a carcinogenic potential. Increased mortality and a variety of other changes associated with an impeded clotting mechanism were observed at all dose levels, and non-neoplastic findings considered to be related to exaggerated pharmacology were seen in the prostate, ovaries, lungs, mandibular and mesenteric lymph nodes, paws and skin.

Phototoxicity

The phototoxic potential of DEM has been evaluated in the 3T3 NRU assay using BALB/c 3T3 cells, and it was concluded that dabigatran may have a weak phototoxic potential under in vitro conditions at concentrations of ≥15.63 µg/mL. The mean maximum plasma level (likely comparable to skin level) of dabigatran in humans after administration of 400 mg dabigatran etexilate was 291 ng/mL, approximately 50-fold lower than the concentration of 15.63 µg/mL. A review of the clinical safety database for possible evidence of a clinical signal, however, did not show evidence for a phototoxic effect in clinical trial data from over 8500 patients exposed to dabigatran (over 950 patient years of exposure) in completed clinical trials. Therefore, it was concluded that dabigatran does not have a phototoxic potential under in vivo conditions in man.

Impurities toxicity

The MAH submitted an extensive evaluation of the impurity profile. The MAH stated that a safety assessment had been performed for all known genotoxins and for impurities with structural alerts for genotoxicity identified using appropriate software (i.e., DEREK and MCASE).

2.3.5. Ecotoxicity/environmental risk assessment

The environmental risk assessment based upon the extended indications and the maximum dose of 300 mg showed that it is unlikely that dabigatran will cause environmental risk.

2.3.6. Discussion on non-clinical aspects

The additional mouse lymphoma assay confirmed previous data that dabigatran did not induce any increase of mutants cells. Oral administration of DEM at dosages of 30, 100 or 200 mg/kg to CD-1 mice or Han Wistar rats for up to 104 weeks revealed no evidence of a carcinogenic potential. The findings were generally associated with an impeded clotting mechanism. The phototoxic potential of DEM was evaluated in the 3T3 NRU assay using BALB/c 3T3 cells, and it may be concluded that dabigatran may have a weak phototoxic potential under in vitro conditions at concentrations of ≥15.63 µg/mL. A review of the clinical safety database for possible evidence of a clinical signal, however, did not show evidence for a phototoxic effect in clinical trial data from over 8500 patients exposed to dabigatran (over 950 patient years of exposure) in completed clinical trials. Therefore, it was concluded that dabigatran does not have a phototoxic potential under in vivo conditions in man. The

impurities and degradation products BIBR 951, BIBR 1087, BIBR 1150, BIBR 1154, BIBR 1155 and CDBA 513 are considered qualified up to the specified limits. It is unlikely that dabigatran use will result in an environmental risk.

2.3.7. Conclusion on the non-clinical aspects

New non-clinical studies were submitted for: primary pharmacodynamics, safety pharmacology, pharmacokinetics and toxicology. Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Effects observed and assessed within initial marketing authorisation application in the repeat-dose toxicity studies were due to the exaggerated pharmacodynamic effect of dabigatran. An effect on female fertility was observed in the form of a decrease in implantations and an increase in pre-implantation loss at 70 mg/kg (5-fold the plasma exposure level in patients). At doses that were toxic to the mothers (5 to 10-fold the plasma exposure level in patients), a decrease in foetal body weight and viability along with an increase in foetal variations were observed in rats and rabbits. In the pre- and post-natal study, an increase in foetal mortality was observed at doses that were toxic to the dams (a dose corresponding to a plasma exposure level 4-fold higher than observed in patients). In conclusion, following the assessment of the nonclinical data submitted with this application Section 5.3 of the SmPC was updated with the information that in lifetime toxicology studies in rats and mice, there was no evidence for a tumorigenic potential of dabigatran up to maximum doses of 200 mg/kg.

2.4. Clinical aspects

2.4.1. Introduction

The MAH applied for the following indication for 110 and 150 mg strengths:

Prevention of stroke and systemic embolism in adult patients with atrial fibrillation.

The following indication was granted for 110 and 150 mg strengths:

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: Previous stroke, transient ischemic attack, or systemic embolism (SEE); left ventricular ejection fraction < 40 %; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.

The new indication is mainly supported by one pivotal trial enrolling 18113 patients: the RE-LY study, a Randomized Evaluation of Long term anticoagulant therapy (RE-LY) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a prospective, parallel-group, non-inferiority trial.

In addition for this grouped application the MAH has submitted 3 bioequivalence and 8 new drug interaction studies and 2 dose response studies (PETRO and PETRO-EX).

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.

An inspection of the RELY study was requested by the EMA. The GCP inspection was triggered at D120 of the procedure motivated by inconsistencies observed by the FDA in the transfer of INR data from case record forms to company data sets in the RELY study in addition to the fact that the application is primarily based on one, single pivotal study, the RE-LY study. Four inspections were performed from 16th August to 16th September: the Sponsor, the CRO (Population Health Research Institute (PHRI)) and 2 investigator sites (in the US and Greece). Two critical findings were identified during the inspection of the sponsor relating to 1) lack of proper oversight and documentation when implementing edit checks to the trial database at the CRO PHRI and 2) critical trial management due to poor oversight of delegated task, study kick-off and use of unapproved documents. Two critical finding were identified during the inspection of the Greek investigator site 901 relating to 1) gaps of more than the pre-specified 4 weeks between two consecutive INR measurements and 2) inclusion of one subject with a violation of an exclusion criterion (CrCI < 30ml/min), potentially putting him at unnecessary risk. In addition, at the Greek site a major finding related to transcription errors for INR-control was identified for 5 out of approximately 50 patients. From a clinical point of view, the Greek findings had the potential to disfavour warfarin vs. DE. The MAH was asked for further clarifications. On D180 the CHMP considered the quality of INR control in the RELY study questionable due to transcription errors leading to inclusion of patients in the analyses as having INR-values "in therapeutic range" despite being in fact "below therapeutic range" (below 2-3). In the response to the D180 LoOIs data were provided to reassure the CHMP on the quality of the INR-control in the RE-LY study: the transcription errors identified at the Greek site 901 did not affect the source data. Thus, warfarin treatment adjustments were not based on wrong INR values. The transcription errors were therefore not believed to have had impact on the primary efficacy- and safety endpoints. However, it was felt that the MAH had not adequately addressed the issue of INR transcription errors in patients on warfarin experiencing major events. Therefore, the MAH was requested to provide a review of the chain of INR transcriptions (source – CRFs – clinical database) in all warfarin treated subjects who experienced thromboembolic events, myocardial infarction, and intracranial haemorrhage as quality of the INR control in RELY study may not have been as good as reported by investigators. At the end the CHMP was of the opinion that the level of severity of the identified Greek findings was not expected to impact the overall study results and that the issue of INR transcriptions from source (CRFs) to the clinical database had been adequately addressed by the MAH.

- Tabular overview of clinical studies

The following Table 1 summarises the overview of new clinical studies conducted for this extension of indication.

Table 1 New studies conducted with dabigatran - assessing clinical pharmacology of dabigatran

Study No.	**Study Objective, Population**	**N**	**Treatment Duration Design**	**Medication dose/day**
Studies in healthy volunteers				
	Biopharmaceutics			
1160.60 U09-1050-01	BE of two DE polymorphs Healthy subjects	66	Single dose Double blind	DE polymorph 1, 150 mg po x 1 DE polymorph 2, 150 mg po x 1
1160.70 U09-1051-01	BE of first and second generation drug product Healthy subjects	66	Single dose Double blind	DE capsule gen 1, 150 mg po x 1 DE capsule gen 2, 150 mg po x 1
1160.87	Relative BA, DE as pellets on	30	Single dose	DE 150 mg, pellets on food;

U09-1839-01	food vs powder resolved in reconstitution solution Healthy subjects		Open label	DE 150 mg, powder for reconstitution into solution; Dabigatran 150 mg capsule
	Clinical Pharmacology			
PK/PD studies				
1160.61 U06-3420	Safety, PK, and PD Healthy Japanese or Caucasian males	48	Multiple dose 6 days Open label	DE 110 mg bid or 150 mg bid
Drug-Drug interaction studies				
1160.74 U09-1052-01	Drug-drug interaction potential between **verapamil** and DE Healthy subjects	40	Single dose Open label	DE 150 mg ± verapamil 120 mg or 240 mg, 1 or 13 days
1160.75 U08-3299-01	Relative BA, with and without **quinidine** sulfate; Effect of quinidine on the absorption of **fexofenadine** Healthy subjects	42	Multiple dose 2.5 days Open label	DE 150 mg bid ± quinidine 600 mg, single dose Fexofenadine 120 mg, single dose
1160.78 U09-1230-01	Relative BA, after switching from 40 mg enoxaparin Healthy subjects	23	Single dose Open label	DE 220 mg Enoxaparin 40 mg, SC x 3 days
1160.82 U08-2188-01	Relative BA with and without **clarithromycin** Healthy subjects	20	Single dose Open label	DE 150 mg ± clarithromycin 500 mg, bid or single dose
1160.83 U09-1547-01	Safety of coadministration of DE and **clopidogrel** and PK interaction Healthy subjects	43	Multiple dose 1 month Open label	DE 75 mg or 150 mg + Clopidogrel 75 or 300 or 600 mg
1160.90 U09-3246-01	Safety of coadministration of DE and **quinidine** and PK interaction Healthy subjects	42	Multiple dose 23-25 days Open label	DE 150 mg, for 6 doses +/- quinidine 200 mg, every 2 hours up to 5 doses

1160.100 U09-1349-01	Relative BA, with and without **rifampicin** Healthy subjects	24	Multiple dose 23 days Open label	DE 150 mg ± rifampicin 600 mg, multiple dose
1160.101 U09-1350-01	Relative BA, with and without with **ketoconazole** Healthy subjects	24	Multiple dose 16 days Open label	DE 150 mg, ± ketoconazole 400 mg, multiple doses
Studies in atrial fibrillation				
Phase II				
PETRO 1160.20 U06-1615-02	Exploratory efficacy and safety; PK and PD; net clinical cost Patients with nonrheumatic AF and at least one risk factor for stroke	502	Multiple dose 12 weeks Double blind (DE), open-label (ASA and warfarin)	DE 50, 150 or 300 mg, bid ± ASA 81 or 325 mg, qd (3 x 3 factorial design), Warfarin (INR 2.0 to 3.0), qd
1160.42 **PETRO-EX** U09-3247-01	Long term safety Extension of PETRO	361	extension 5 years	DE 150 mg or 300 mg, qd or bid
1160.49 **U07-3126**	Exploratory efficacy and safety; PK and PD Japanese patients with	174	Multiple dose 12 weeks Open-label	DE 110 mg bid or 150 mg bid Warfarin (INR 2.0 to 3.0), qd

Japan AF	nonvalvular AF and at least one risk factor for stroke			
Phase III				
RELY 1160.26 U09-3249-01	Efficacy and safety PK and PD Patients with nonvalvular AF and at least one risk factor for stroke	18113	Multiple dose Max 36 months Double blind (DE), open-label warfarin (PROBE)	DE 110 mg bid or 150 mg bid Warfarin (INR 2.0 to 3.0), qd
Studies in various populations				
PK0747E **U07-3471**	PK and PD between Japanese and Caucasians in 18 Phase I and II trials Healthy volunteers ; Patients with non-valvular AF ; Patients undergoing elective total hip or total knee replacement	-	Various (Meta-analysis)	DE various doses
1160_meta-analysis_pk1 **U09-1363-02**	PK between patients with total hip or knee replacement, AF patients and healthy volunteers in Phase I and II studies	-	Various (combined analysis)	DE various doses
1160_combined_popPK_PD **U09-1399-02**	PK and PD between patients with total hip or knee replacement, AF patients and healthy volunteers in Phase I and II studies	-	Various (PK pop study + stimulation study)	DE various doses

2.4.2. Pharmacokinetics

Main Pharmacokinetic data (from initial marketing authorisation application)

Dabigatran etexilate (DE) has a low solubility in water and a high permeability. The absolute bioavailability of DE was low i.e 5-8 %. The administration of DE with a high fat high caloric breakfast resulted in a slight increase in Cmax (8%) and in a moderate increase in AUC (27%). Food was also shown to slow the rate of absorption (approximately 2 hours delay). After oral administration of DE, 7.3% and 85.5% (total 91.3%) of the dose were recovered in the urine and the faeces over 7 days, respectively. The mean terminal half-life of dabigatran was approximately 9-11 hours. The renal clearance (≈ 90 ml/min) accounts for about 82% of its total clearance (110 ml/min) following an IV infusion of dabigatran.

Bioequivalence study 1160.66

DEM exhibits polymorphism (modifications I and II). Bioequivalence had been demonstrated between drug product batches manufactured with pure form I drug substance and pure form II drug substance. Therefore, drug substance batches were considered comparable whatever the route of synthesis and the composition in modification I and II.

Bioequivalence study 1160.70

The solubility of the compound was shown to be significantly pH dependent with increased solubility at acidic pH, and limited solubility at alkaline pH values. Active ingredient layered pellets including a tartaric acid core as a solubilizer filled into hard capsules were developed as the final clinical trial and

commercial dosage form. Bioequivalence was also demonstrated between the product used in the clinical studies and the future commercial product.

Bioavailibility study 1160.87

The integrity of the HPMC capsules should always be preserved in clinical use to avoid unintentionally increased bioavailability of DE. Therefore, patients are advised not chewing the capsules before swallowing and also not to open the capsules and taking the pellets alone (e.g. sprinkled over food or into beverages). Adequate recommendations were proposed in the SmPC.

Dose and time dependency

Dabigatran Cmax and AUC increased linearly with dose from 10 to 400 mg. Analysis of dabigatran trough plasma concentrations indicated that steady state conditions were attained on Day 2 post-administration. Dabigatran displayed moderate accumulation. The accumulation ratios for AUCss and Cmax ss were about 1.8 – 1.5.

Variability

In healthy volunteers, the intraindividual variability was close to 36-39% for Cmax and AUC. In healthy volunteer, the interindividual variabilility of Cmax and AUC was much higher in single dose studies (62-72%) than in multiple dose administration (19-26%).

Target population

Several covariates were found to have a relevant effect on dabigatran pharmacokinetics in AF patients: CrCL, age, sex, weight, indicationand co-medications with Pg-p inhibitors,PPIs and antacids.

Special populations

After single dose administration, the exposure of dabigatran increased about 3-fold in subjects with moderate renal impairment. Haemodialysis effectively eliminates dabigatran from blood. Moderate hepatic impairment decreases Cmax (30% decrease) but does not affect AUC. The effect of severe hepatic impairment on the pharmacokinetics of dabigatran is not known. There is a marked gender difference in the pharmacokinetics of dabigatran. In female patients, CL/F was lower (12.5%) than in male patients. This decrease in CL/F resulted in 14% higher steady-state exposure ($AUC_{\tau,ss}$) of female patients compared to male patients. All the results suggest that ethnicity is not a factor influencing meaningfully the pharmacokinetics of dabigatran. A trend towards increasing dabigatran exposure with decreasing weight was observed in male and female patients. An across study comparison and the population PK analysis indicate that there was a trend toward increasing exposure with increasing age likely to be due to age related decrease in creatinine clearance.

Drug-drug interactions

In view of its pharmacokinetic profile, dabigatran does not seem to induce, inhibit or be a substrate of the CYP450 enzyme system. In vitro studies have proven that interactions with usual hepatic CYP450 isoenzymes are unlikely.

P-gp inhibitors

Results of the newly provided studies add new information about the influence of P-gp inhibitors on the exposure of dabigatran. Some P-gp inhibitors are contra-indicated (e.g. ketoconazole) whereas the use of others like verapamil, amiodarone, quinidine and clarithromycin should lead to precautionary measures. Using pharmacokinetic and clinical outcome data from the RELY study, the MAH had convincingly argued that the dabigatran dose should be reduced in case of concomitant treatment with verapamil, but not with amiodarone or quinidine. The MAH was also asked to address the dose

recommendations with regard to concomitant treatment with verapamil or amiodarone *and* moderate renal impairment. Although the number of events from the RE-LY study was small, it is justified in the opinion of the CHMP not recommending further dose reduction in case of concomitant treatment with verapamil, amiodarone or quinidine in patients with moderate renal impairment. The MAH's reasoning for not contraindicating treatment with cyclosporine, itraconazole and tacrolimus was not agreed with, and the MAH's accepted to include treatment with these drugs as a contraindication.

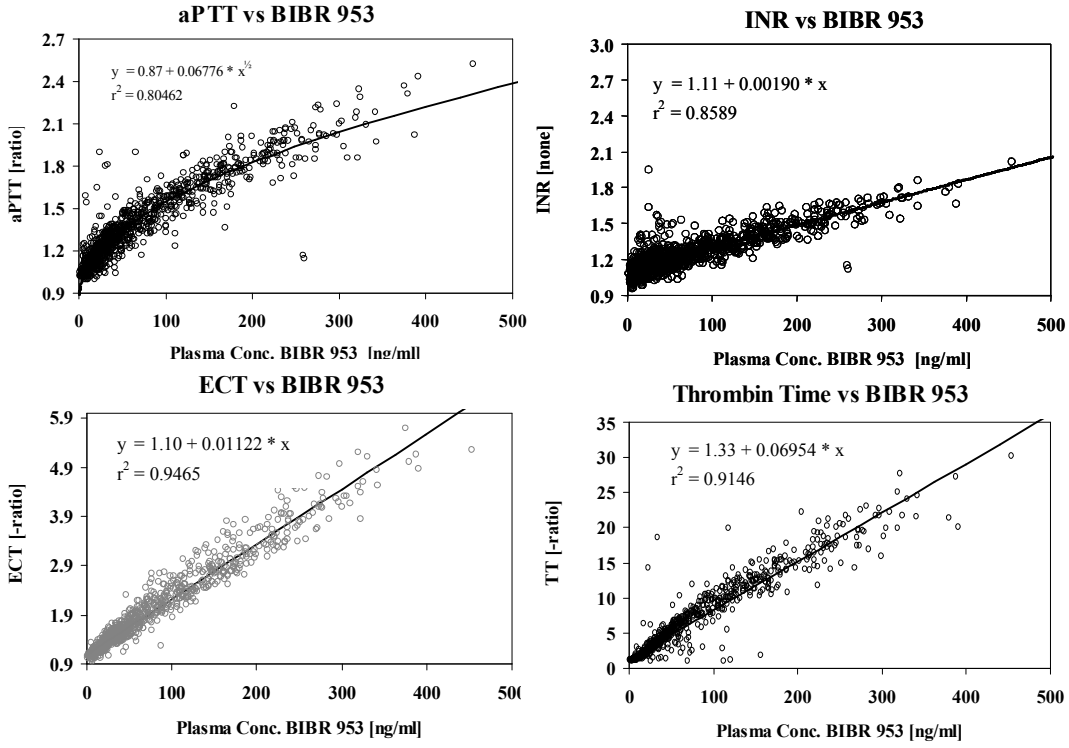
P-gp inducers

The provided study with rifampicine, given as a P-gp inducer, shows that dabigatran exposure is importantly reduced. The combination with strong P-gp inducers such as rifampicine or St John's wort should be avoided.

2.4.3. Pharmacodynamics

Dabigatran etexilate (DE) is a reversible inhibitor of thrombin (direct thrombin inhibitor [DTI]) of relatively low affinity. As for all anticoagulant therapies, its anti-thrombotic effect is counterbalanced by an increased haemorrhagic risk. The effects of dabigatran were assessed using coagulation tests (Figure 1).

Figure 1 Relationship between aPTT, INR, ECT and TT and dabigatran (BIBR 953) plasma concentration



Anticoagulation measurement is necessary to assess the level of anticoagulation of patients:

1/ In the RELY study.

Considering the high dose recommended in the claimed indication, the aPTT was inappropriate to assess the relation between pharmacological and clinical effects in the RELY study. Diluted TT and ECT were considered as the most appropriate tests for measurement of dabigatran effect. Indeed, both

tests displayed a linear relationship with plasma concentrations over the full range of concentrations, with a high level of sensitivity.

2/ In real life, only when judged necessary by physicians (depending on patients characteristics or patients responses to dabigatran).

Measurement of anticoagulant effect is particularly warranted when an overdosing is suspected. Indeed, assessment of exposure/safety relationship highlighted a clear association of longer aPTT (at trough) and the occurrence of major and any bleeding events. Considering the increased drug exposure in special populations and situations such as overdose, patients with moderate renal impairment, elderly, females and patients with low weight, informative coagulation tests should be available. The HYPHEN test, with dabigatran plasma calibrator and control, achieved the CE mark and is now commercially available. Relevant sections of the SmPC have been updated with this information.

PK/PD drug interactions

Despite relatively reassuring PK/PD studies, adequate warnings were added in the SmPC as regards the increased haemorrhagic risk when dabigatran is combined with any drug acting on the coagulation system (e.g. enoxaparin, ASA, clopidogrel). Such combinations are not rare when considering the need to treat coronary artery diseases.

Secondary pharmacology

Potential adverse events such as myocardial infarction and hepatic adverse events, identified in during initial marketing authorisation application as potential secondary adverse events, have been assessed below in Section Clinical Safety.

2.4.4. Discussion on clinical pharmacology

PK characteristics of dabigatran display some advantages compared to warfarin: lower terminal half-life (9-11 hours), lower intra and inter individual variability, no drug interaction with CYP450 enzyme system, no interaction with food. However, exposure may be increased principally with impaired renal function, age and co-medication with P-gp-inhibitors, which leads potentially to increased risk of bleeding in these situations. Furthermore, contrary to VKAs, there is no antidote to dabigatran. Some drug-drug interactions have been highlighted with P-gp inhibitors. Indeed, dabigatran exposure appears to be increased with amiodarone, quinidine and verapamil. Based on further analyses of the RELY study, the MAH had convincingly argued in favour recommending dose reduction of dabigatran in case of concomitant treatment with verapamil, but not with amiodarone or quinidine. Also, the proposal of not recommending further dose adjustments in patients with moderate renal impairment in case of concomitant treatment with the aforementioned P-gp inhibitors (other than the one already mentioned in case of co-treatment with verapamil) was considered by the CHMP acceptable. The wording of the SmPC includes contraindications against the concomitant use of the strong P-gp inhibitors itraconazole, tacrolimus, and cyclosporine along with ketoconazole as requested by the CHMP. Regarding P-gp inducers, study with rifampicine showed that dabigatran exposure was importantly reduced. Such combination should therefore be avoided. Pharmacodynamic interactions when DE is combined with other antithrombotic agents should also be of concern. Follow up of such bitherapies (clopidogrel + dabigatran or AAS + dabigatran) and tritherapy (clopidogrel + AAS + dabigatran) by prescribers is of relevance as an increased risk of bleeding cannot be eliminated in some patients. No dose adjustment had been judged necessary but a warning related to the bleeding risk was also added in section 4.4 of the SmPC. Dabigatran is a reversible inhibitor of thrombin (direct thrombin inhibitor [DTI]) of relatively low affinity. As for all anticoagulant therapies, its anti-thrombotic effect is counterbalanced by an increased haemorrhagic risk. Anticoagulation measurement has been

requested at the time of the initial marketing authorisation application: (1) to better assess the drug during its clinical development, (2) to provide tools to manage patients in real life in situations of increased bleeding risks, when event is observed or when it is foreseen to occur (drug interactions, overdoses, surgery, special populations). In the context of the claimed indication, the availability of such test is of importance. Indeed, in specific situations known to be associated with a higher risk of bleeding (e.g. overdose), such test could become necessary. The MAH initially proposed aPTT for such monitoring. aPTT was not considered the most appropriate test as values were not linearly correlated to concentrations. Appropriate test should display a linear relationship with plasma concentrations, with a high level of sensitivity, such as ECT or diluted TT, but should also be normalised in order to allow comparisons between laboratories. The MAH demonstrated that an association between high anticoagulation activity, represented as greater ECT or TT levels, and the occurrence of major or any bleeding events exists. In contrast, no relationship to either ECT or TT became obvious for efficacy related events such as the occurrence of stroke/SEE (primary endpoint) or secondary composite endpoints. Therefore, anticoagulation tests can only be used to define the theoretical risk of bleeding at a certain PD measure, but not to define a therapeutic range for the prevention of stroke. These tests can be used to decrease the dose in case of increased exposure but never to increase the dose in case of lower exposure. The MAH identified dabigatran concentrations not to be exceeded because of the increased risk of bleeding or in some special situations such as pre-surgical situations. The 200 ng/mL concentration is the value at trough (10-16 hours after the previous dose), not to be exceeded because of the increased risk of bleeding. Dabigatran concentration under 48 ng/mL is equivalent to elimination of at least 75% of dabigatran and should be recommended before special intervention such as surgery. The Hemoclot assay is a diluted thrombin time (TT) coagulation assay which can be calibrated with lyophilised dabigatran standards for quantitative assessment of dabigatran concentrations in plasma. The MAH has established cooperation with the manufacturer, HYPHEN BioMed. The HYPHEN test, with dabigatran plasma calibrator and control, achieved the CE mark and is now commercially available.

2.4.5. Conclusions on clinical pharmacology

The CHMP was of the opinion that all the issues regarding clinical pharmacology were positively solved.

2.5. Clinical efficacy

2.5.1. Dose response studies

Dose-response was evaluated in the PETRO study (1160.20) and the 5 years extension study to PETRO, PETRO-EX (1160.42).

PETRO study (1160.20)

The PETRO study was a 12 week randomised, parallel group, double-blind (for DE), open-label (for ASA and for warfarin) trial. It was a three-by-three factorial study design, testing 3 doses of DE, either alone (no ASA) or in combination with one of two different doses of ASA. In addition, a tenth treatment group of warfarin alone was chosen as reference treatment. The objective was to determine the safety and efficacy of DE in patients with non-rheumatic atrial fibrillation (AF), (paroxysmal, persistent, or permanent {chronic}) with or without concomitant treatment with acetylsalicylic acid (ASA).

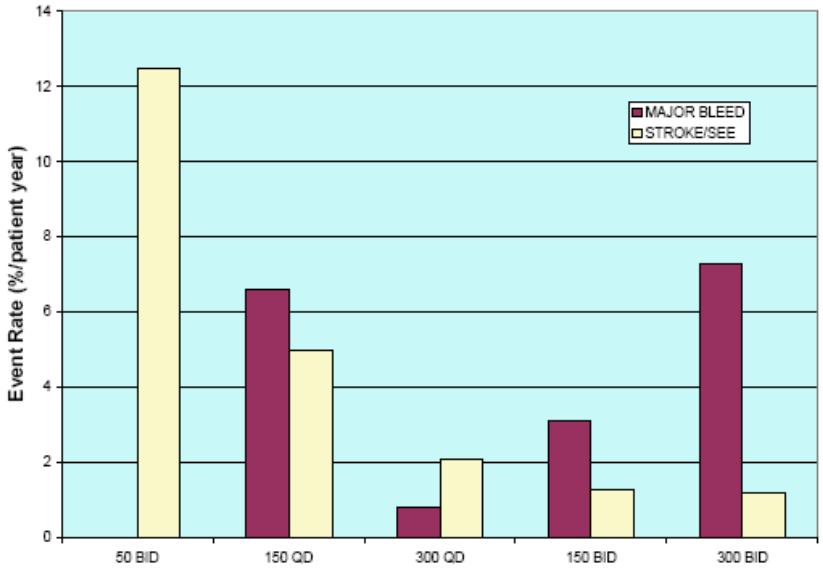
PETRO-EX study (1160.42)

The PETRO-EX study was a long-term, open-label follow-up treatment of patients with AF who had been previously treated with BIBR 1048 in the PETRO trial. The primary objective was to study the

long-term safety and efficacy of DE, with or without concomitant chronic treatment with ASA, in patients with AF, and at least one additional risk factor for thromboembolic events. The dosages applied in these 2 dose-finding-studies were based on data from the BISTRO studies in patients with DVT, indicating safe and effective dosage of BIBR 1048 for the prevention of venous thromboembolism between 100 and 300 mg per day. In addition, due to the fact that patients not undergoing major surgery were at lower risk of bleeding, a dose range of DE between 50 mg bid and 300 mg bid in combination with ASA (0mg, 81mg or 325 mg) was used in the studies. Studies PETRO and PETRO-EX do not contribute to the efficacy of DE in the sought indication due to the short duration and the uncontrolled nature, respectively.

Anticoagulation therapy has to balance prevention of thromboembolic events and risk of bleedings. In PETRO and PETRO-EX doses of DE below 150 mg per day had high rates of thromboembolic events and low bleeding rates, whereas DE doses of 600 mg per day produced unacceptable bleeding. The stroke incidences with a 300mg daily dose appeared to compare with historical trials with warfarin. The use of ASA in PETRO-EX, which included exposure up to 5 years, approximately doubled bleeding rates. Based on the findings in the PETRO and PETRO-EX studies it was agreed by the CHMP that the most appropriate daily dose of DE should be above 150mg but below 600mg daily.

Figure 2 Major Bleed and Stroke/SEE rates, combined data from PETRO (1160.20) and PETRO-EX (1160.42), by dose group



2.5.2. Main study

The single pivotal trial was the RELY study (1160.26).

RELY study (1160.26)

Randomized Evaluation of Long term anticoagulant therapY

Methods

The single large pivotal RELY study was a prospective, randomised, multi-centre (44 countries), parallel-group, non-inferiority trial evaluating long term anticoagulant therapy by comparing the efficacy and safety of two blinded doses of DE with open label warfarin for the prevention of stroke and systemic embolism (SEE) in patients with non-valvular AF.

The duration of treatment was a minimum of 12 months' treatment after the last subject was randomized and a maximum treatment of approximately 3 years. Patients were assigned to 1 of the 3 treatment groups in a 1:1:1 ratio: 1) DE 150 mg bid (blinded); 2) DE 110mg bid (blinded); 3) warfarin od, targeted therapeutic level of INR 2-3 (open-label). The dosage of DE was based upon the phase II PETRO trials suggesting that daily doses of DE seem to be above 150mg but below 600mg daily.

The quality of warfarin management was expressed by the time INR was in the therapeutic range between 2 and 3 (TTR). The TTR for warfarin reached a mean of 64.2%, and a median of 67%. As can be expected, the TTR was higher in the VKA experienced group compared to the VKA naïve group. Furthermore, there was a considerable difference of INR control between regions with Western Europe having the best INR control (TTR mean 68.7%, median 71.8%) and Asia having the worst control (TTR mean 54.3%, median 56.3%). In terms of countries, Sweden, followed by Finland, Australia, Denmark and the UK had the highest TTR, and Taiwan, Mexico, Romania, Peru and India the lowest TTR. The applicant has argued, that the TTR is comparable to the warfarin groups in contemporary trials (SPORTIF-V (68%), SPORTIF III (66%), ACTIVE-W (64%), AMADEUS (63%) and AFFIRM (62%). Admittedly, in these 5 trials the rate of VKA naïve patients, i.e. those with a less favourable TTR, was substantially lower compared to RELY, where VKA experienced and VKA-naïve patients were balanced.

Study Participants

With the chosen in-and exclusion criteria an appropriate and relevant patient population was included in the RELY study. The included patients suffered from symptomatic or asymptomatic paroxysmal or persistent AF. In addition, the patients had one of the following additional risk factors for stroke: a) Previous stroke, TIA or SEE (21.8%); b) LVEF ≤ 40% (10.7%); c) age ≥ 75 years (40.0%); d) age ≥65 years and one of the following additional risk factors: i) DM (19.3%); ii) CAD (24.2%); iii) Hypertension (67.3%). Approximately 31% of subjects had one stroke risk factor, 33% had two risk factors and 33% had three or more risk factors. Exclusion of patients was based on a history of heart valve disorder and severe, disabling stroke as well as conditions associated with an increased risk of bleeding. Patients with severe renal impairment and active liver disease were also excluded.

Treatments

Patients were assigned to 1 of the 3 treatment groups in a 1:1:1 ratio:

-dabigatran etexilate 150 mg bid (blinded)

-dabigatran etexilate 110mg bid (blinded)

-warfarin od, targeted therapeutic level of INR 2-3 (open-label)

The duration of treatment was expected to be a median of 20-24 months, with a minimum of 12 months' treatment after the last subject was randomized and a maximum treatment of approximately 3 years.

Recruitment of 15,000 subjects (for the first 2 years of the trial, closing Dec. 2007) was completed in 1.5 years. The target enrolment was achieved approximately 6 months earlier than expected and it

was predicted that the number of subjects randomized would be increased to approximately 18,000 (see below- amendments)

Concomitant drug therapy (fibrinolytics, the need for antiplatelet therapy, anticoagulation other than warfarin/dabigatran) or surgery/intervention may have required the temporary discontinuation of study warfarin or dabigatran. Due to the ongoing risk of stroke and systemic embolism, the subjects eligible for the study usually required bridging anticoagulation as soon as possible. If the continuation of anticoagulation was indicated, strong consideration was given to resuming the assigned study medication (warfarin or dabigatran) as soon as medically justified.

Following study drug discontinuation due to AEs (e.g., bleeds), the subjects were to be treated according to local clinical practice wherever possible. For subjects who required resumption of oral anticoagulant therapy after resolution of a bleeding event, strong consideration was given to resuming assigned study medication unless absolutely contraindicated.

Objectives

The primary objective is to demonstrate that the efficacy and safety of 2 blinded doses (110 mg bid and 150 mg bid) of dabigatran etexilate are non-inferior to adjusted dose warfarin (target INR 2-3) for the prevention of stroke and systemic embolism in subjects with non-valvular AF with at least 1 additional risk factor for stroke.

Outcomes/endpoints

Relevant primary and secondary endpoints were chosen in the opinion of the CHMP that mirror endpoints chosen in other trials with warfarin in AF.

- The primary endpoint was incidence of stroke (including hemorrhagic) or non-Central Nervous System (CNS) systemic embolism, hereafter referred to as systemic embolism (SEE).
- Secondary endpoints were the composite endpoints of 1) Incidence of stroke (including hemorrhagic), SEE, and all cause death; 2) Incidence of all stroke (including hemorrhagic), SEE, pulmonary embolism (PE), myocardial infarction (MI), vascular death (including deaths from bleeding).
- Other endpoints were 1) individual occurrence or composites of any ischemic stroke (fatal and non-fatal), SEE, PE, acute MI, TIA, vascular death (including deaths from bleeding), all deaths, and hospitalisations; 2) Net Clinical Benefit (NCB) as measured by the composite of the clinical endpoint of stroke, SEE, PE, acute MI, all cause deaths, and major bleeds.
- Safety endpoints were bleeding events (major and minor), intracerebral haemorrhage, other intracranial haemorrhage (ICH), hepatobiliary events and other adverse events (AEs).

Sample size

A total of 18113 subjects were randomised, 6015 to DE110 mg bid, 6076 to DE150 mg bid and 6022 to warfarin.

A yearly event rate of 1.6% was assumed for both dabigatran and warfarin. 5,000 subjects per treatment group were to be recruited in 2 years and followed up for 1 additional year to achieve 150 events per treatment group. Within these parameters, each comparison had approximately 90% power to conclude the non-inferiority of dabigatran to warfarin at a one-sided α=0.025 level (without adjusting for multiple comparisons) based on the derived non-inferiority margin of 1.46. With a total

of 15,000 subjects randomized to the 2 dabigatran doses and warfarin at a 1:1:1 ratio, to achieve a total of 450 events, using the Hochberg procedure to compare each dabigatran dose to warfarin, the trial had approximately 84% power to conclude the non-inferiority of both dabigatran doses to warfarin using the non-inferiority margin of 1.46. A total of 15,000 subjects were recruited in less than 2 years (18 months). If the recruitment was stopped at that time, the last randomized subject would have had to be followed up for more than 1 year to achieve the planned total number of events, if the actual event rate was as expected. In addition, based on the results from other published studies, the actual event rate could be less than 1.6%. Because of these concerns, the operational committee decided to continue the recruitment as planned. As a result, a total of 18,113 subjects were randomized. It was expected that if the actual event rate was as planned, the statistical power would be increased. In the opinion of the CHMP the sample size calculation was adequate.

Randomisation

There were three randomized treatment groups. Randomization was performed via an interactive voice-response system (IVRS) with an allocation ratio of 1:1:1. Randomisation was performed in blocks.

Blinding (masking)

Patients and investigators were not blinded to warfarin or DE treatments. However, blinding was kept as regards the two doses of DE treatment. Though a double-blind study is clearly preferable the difficulties related to a double-blind warfarin study of this size is acknowledged (close monitoring, dose-adjustments, food and medication interactions). An Adjudication Committee blinded to treatment was used for blindly adjudicating outcome events. Also, the sponsor, the Operations Committee and the Steering Committee, remained blinded to all treatments. In addition, the outcome events were mainly objective outcomes whereby the risk of bias was minimised. In view of the difficulties related to a double-blind study, this approach is deemed acceptable. The acceptability of the unblinded study design is also at least partially supported by the retrospectively obtained assay sensitivity as indicated by a clear dose-response relationship between DE 110bid and 150bid on primary endpoint.

Statistical methods

The RE-LY study was a non-inferiority study. The protocol specified non-inferiority margin (NIM) for the hazard ratio was 1.46, based on the meta-analysis of 6 placebo-controlled studies (62% relative risk reduction of stroke by warfarin vs. placebo (95% CI 48-72%) (Hart et al, 1999)). The non-inferiority margin preserved 50% of the benefit of warfarin therapy based on the lower bound of the 95% confidence interval of the VKA effect compared to placebo. The primary analysis compared the upper bound of the 95% confidence interval of the hazard ratio for each DE dose compared to warfarin to assess whether the individual DE doses met the protocol pre-specified NIM of 1.46, using the Hochberg procedure to adjust for multiple testing. It could be argued that the non-inferiority margin was too wide however, in view of the clear benefit of warfarin vs. placebo in primary prevention of thromboembolic events as demonstrated in historical warfarin atrial fibrillation trials (the AFSAK, SPAF, BAATAF and SPINAF trials; Arch Intern Med. 1994; 154: 1449-1457), this is considered acceptable. This view is futher supported retrospectively by the proven superiority of DE 150bid vs. warfarin as well as the proven dose-response relationship for the two DE dosages on the primary endpoint. The primary efficacy statistical analysis was performed on the "randomised set" including all randomised patients whether or not any randomised treatment was received.

In the light of "death" as a competing risk (not a seldom event vs. stroke/SEE) an analysis of "time to event" as such is considered difficult. Therefore, the use of the Cox regression model as the statistical model (with treatment as the only factor in the model) for the analyses of the primary and secondary efficacy variables with subsequent presentation of hazard ratios is considered appropriate. The Hochberg procedure was applied for adjustment for multiplicity when evaluating the 2 dosages of DE for the primary endpoint. No method was pre-specified to adjust for multiplicity when evaluating the secondary endpoints. As the endpoints included in the pre-specified secondary analyses are "natural" extensions of the primary endpoint, this may be acceptable.

Results

Primary endpoint: Time to the first occurrence of stroke/SEE.

The yearly event rate for stroke/SEE was lowest for DE 150bid (134 patients, 1.11%), followed by DE 110bid (183 patients, 1.54%) and warfarin (202 patients, 1.71%) (Table 2), and was driven by strokes. SEE was rare in all treatment groups. The Kaplan-Meier estimates are shown in figure 3.

Mainly ischemic strokes accounted for the primary endpoint with a yearly event rate of 1.28% (152 patients), 0.86% (103 patients) and 1.14% (134 patients) for DE 110bid, DE150 and warfarin. The yearly event rate for hemorrhagic strokes was 0.12% (14 patients), 0.10% (12 patients) and 0.38% (45 patients).

The stroke/SEE rates for warfarin appeared thus roughly comparable to the rates for warfarin in other AF trials (AMADEUS 1.3%, SPORTIF III 2.3%, SPORTIF V 1.2%, ACTIVE W stroke 1.4%).

For the risk of stroke/SEE both dosages of DE were non-inferior to warfarin with absolute and relative risk reductions amounting to 0.17% and 10% for DE 110bid and 0.60% and 35% for DE 150bid, respectively in comparison to warfarin (Table 3). The HRs were 0.90 (95% CI: 0.74, 1.10; p<0.0001) and 0.65 (95% CI: 0.52, 0.81; p<0.0001. Thus, the upper bound of the 95% CI was below 1.46, the protocol specified non-inferiority margin, for both doses. DE 150bid was in addition statistically significantly superior to warfarin (p=0.0001).

The DE 150mg Kaplan-Meier curve seemed to separate from the other two curves continuously during the whole trial (Figure 3).

Table 2 Yearly event rate (%) for composite endpoint of stroke/SEE

	DE 110mg bid N (%)	DE 150mg bid N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-years	11899	12033	11794
Subjects with stroke/SEE	183 (1.54)	134 (1.11)	202 (1.71)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
Ischemic stroke	152 (1.28)	103 (0.86)	134 (1.14)
Haemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
Stroke of uncertain classifications	7 (0.06)	9 (0.07)	10 (0.08)
SEE	15 (0.13)	13 (0.11)	21 (0.18)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint. In case of recurrent events, the first event was considered.
Subject-years = sum(date of study termination - date of randomization +1) of all randomized subjects / 365.25.
Yearly event rate (%) = # of subjects with event / subject-years * 100.
Source data: Appendix 16.2.6, Listing 1, 3, Appendix 16.2.7, Listing 1.1

Figure 3 1 Kaplan-Meier estimate of time to first stroke/SEE

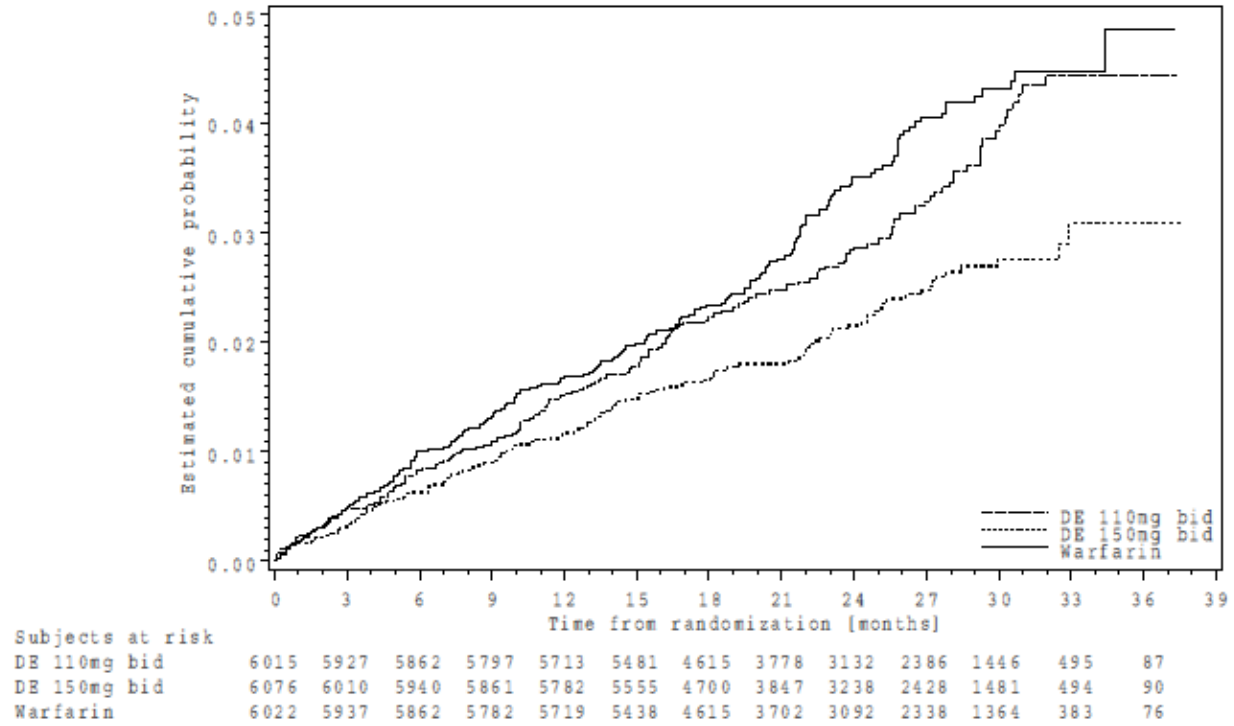


Table 3 Hazard ratios and CIs for composite endpoint of stroke/SEE

	DE 110 vs Warfarin	DE 150 vs Warfarin
Non-Inferiority Analysis		
Hazard ratio (SE)	0.90 (0.09)	0.65 (0.07)
95% CI	0.74, 1.10	0.52, 0.81
97.5% CI	0.71, 1.13	0.51, 0.83
P-value for non-inferiority using 1.46	<.0001	<.0001
P-value for non-inferiority using 1.38	<.0001	<.0001
Superiority Analysis		
P-value for superiority	0.2943	0.0001

Secondary endpoints:

The results for the two secondary endpoints: 1) composite of stroke, SEE and all cause death, and 2) composite of stroke, SEE, PE, MI and vascular death are shown below.

Analysis for stroke, SEE, and all cause death:

Table 4 Yearly event rate (%) for composite endpoint of stroke/SEE/all cause death

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Randomized	6015	6076	6022
Subject-years	11900	12039	11797
Subjects with Stroke/SEE/death	577 (4.85)	520 (4.32)	613 (5.20)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
SEE	15 (0.13)	13 (0.11)	21 (0.18)
Death	446 (3.75)	438 (3.64)	487 (4.13)

Table 5 Hazard ratios and 95% CIs for composite endpoint of stroke/SEE/death

	DE 110mg bid vs Warfarin	DE 150mg bid vs Warfarin
Hazard ratio (SE)	0.93 (0.05)	0.83 (0.05)
95% CI	0.83, 1.045	0.74, 0.93
P-value	0.2206	0.0015

Analysis for stroke, SEE, PE, MI and vascular death:

Table 6 Yearly event rate (%) for composite endpoint of stroke/SEE/PE/MI and vascular death

	DE 110 N (%)	DE 150 N (%)	Warfarin N (%)
Subjects randomized	6015	6076	6022
Subject-year	11900	12039	11797
Subjects with composite endpoint	496 (4.17)	435 (3.61)	504 (4.27)
Stroke	171 (1.44)	122 (1.01)	186 (1.58)
SEE	15 (0.13)	13 (0.11)	21 (0.18)
PE	14 (0.12)	18 (0.15)	12 (0.10)
MI	87 (0.73)	89 (0.74)	66 (0.56)
Vascular death	289 (2.43)	274 (2.28)	317 (2.69)

Each subject with an event was counted once for the composite endpoint and once for each component of the composite endpoint.
Subject-years = sum (date of study termination – date of randomization +1) of all randomized subjects / 365.25. Yearly event rate (%) = # of subjects with event / subject-years * 100.

Table 7 Hazard ratios and 95% CIs for composite endpoint of stroke/SEE/PE/MI and vascular death

	DE 110 vs Warfarin	DE 150 vs Warfarin
Hazard ratio (SE)	0.98 (0.06)	0.84 (0.06)
95% CI	0.86, 1.10	0.74, 0.96
P-value	0.6972	0.0096

Analyses of the two pre-specified secondary composite endpoints showed the same pattern as for the primary endpoint. The risks of "stroke, SEE and all cause death" and "stroke, SEE, PE, MI and vascular death" were similar for DE 110bid vs. warfarin whereas DE 150bid was superior to warfarin for both endpoints. As regards the individual components of endpoints, the event stroke was driven by ischemic stroke in all treatment groups (yearly event rates for DE 110bid, DE 150bid and warfarin were 1.28%, 0.86% and 1.14%, respectively). Haemorrhagic strokes were rare, but less than one third for DE compared to warfarin (yearly event rates for DE 110bid, DE 150bid and warfarin were 0.12%, 0.10% and 0.38%, respectively. Despite low absolute numbers of ICH, the benefit of both DE dosages vs. Warfarin was remarkable consistent across a large variety of subgroups (i.e. age, body weight, centre INR, +/- use of concomitant ASA).

The yearly event rates for MI (including silent MI) were numerically higher for DE 110bid and 150bid vs. warfarin (0.82% and 0.81% vs. 0.64%) (table 8).

Table 8 Hazard ratios and 95% CI for myocardial infarction (including silent MI)

	DE 110 vs Warfarin	DE 150 vs Warfarin
Hazard ratio (SE)	1.29 (0.20)	1.27 (0.19)
95% CI	0.96, 1.75	0.94, 1.71
p-values	0.0929	0.1240

Despite small absolute differences vs. warfarin (DE 110bid: 0.18%; DE 150bid: 0.17%) a separation of the DE 150bid Kaplan-Meier curve from warfarin was observed after 3 months of treatment, and after 23 months the separation increased continuously. Thus, an overall risk of MI associated with dabigatran treatment in the proposed indication seems to exist. No dose-response relationship was identified. The highest risk of MI was found in subjects with a previous MI, those with CAD, HF, reduced LVEF, diabetes and moderate renal function. The relative risk for DE vs. warfarin was not significantly different in these subgroups. Otherwise, a particular subgroup of patients being particularly at risk of MI could not be identified. The pathophysiological mechanism is still unclear and markers that could reveal rebound anticoagulation have not been collected, but the generation of hypotheses is expected from a further sub-study of RELY which is pending. The results and conclusions of this study will be provided as a post-authorisation commitment. The risk of MI does not change the overall benefit of DE vs. Warfarin, However, careful wording in the SmPC is needed and MIs are covered in the RMP as a potential risk.

Also for the pulmonary embolism (PE) the yearly event rates were numerically higher for DE 110bid (0.12%) and 150bid (0.15%) vs. warfarin (0.10%). The issue was discussed by the MAH in the

response to the D120 LoQs however; no conclusion can be drawn on the potential association of PE and DE treatment. The very low overall number of PE during the study is acknowledged still, the signal of an increased risk of PE in DE treated patients should be covered in the RMP as a potential risk.

The yearly event rate for all cause death was 3.75%, 3.64% and 4.13% for DE 110bid, 150bid and warfarin, corresponding to absolute reductions of 0.38% and 0.49% vs. warfarin. The Kaplan-Meier curves for DE 110bid and 150bid separated from warfarin 16 months after randomisation. The HR for all cause death for DE 150bid vs. warfarin was 0.88 (95% CI: 0.77, 1.00; p=0.0475), however, after inclusion of additional outcome events identified after data base lock, the risk of all cause death for DE 150bid vs. warfarin shifted to not statistically different (p=0.0517; please see section below on ancillary analyses). Most deaths were of vascular origin. The vascular death HR for DE 150bid vs. warfarin was 0.85 (95% CI: 0.72, 0.99; p=0.0430).

Participant flow

A total of 20,377 subjects were screened (enrolled), and 18,113 were randomized (entered). There were 2,264 subjects not randomized after screening; almost 70% of these subjects did not meet inclusion/exclusion criteria. The randomized subjects were equally distributed across the three treatment groups. Approximately 36% of the subjects were from the United States and Canada, 25.7% from Western Europe, 15.4% from Asia, 11.7% from Central Europe, 5.9% from Australia, Israel, and South Africa and 5.3% from Latin America. The number of subjects randomized to the three treatment regimens was equally distributed across each geographic region. All except 73 randomized subjects received study medication (99.6%). Overall, 17,360 (96.2%) of the treated subjects completed the study; 78.1% completed on study medication and 18.1% completed follow up but stopped study medication prematurely. A higher frequency of subjects completed the study on medication in the warfarin group compared to the dabigatran 110 mg bid and 150 mg bid dose groups (80.8% vs. 77.1% and 76.4%, respectively). The three most common reasons for discontinuing study drug were other, patient preference and outcome events, all more common on dabigatran. A total of 680 (3.8%) of the 18,042 treated subjects were prematurely discontinued from the study and did not complete the trial follow-up; there were no significant differences across treatment groups. The majority of these subjects withdrew consent (412; 2.3%).

Recruitment

A total of 18113 subjects were randomised, 6015 to DE110 mg bid, 6076 to DE150 mg bid and 6022 to warfarin.

Conduct of the study

Study period: December 2005 – March 2009, conducted at 951 sites across 44 countries (Europe, North America, Latin America, Asia, South Africa, Australia). The protocol changes put in place in order to provide a balance between VKA naïve and VKA experienced subjects as well as the changes increasing the sample size from 15,000 to 18,000 patients were considered by the CHMP the most important ones. A negative impact on the study conduct is not expected in the opinion of the Committee. Most other amendments are clarifications or are put in place for safety reasons.

Baseline data

The groups were generally well balanced with respect to demographic and disease characteristic information:

The mean age was 71.5 years. Overall, 16.4% of subjects were < 65 years of age, 43.6% were in the range 65-75 years, and 40.0% were ≥ 75 years old. Males comprised 63.6% of the subjects. The majority of patients recruited came from North America (36.1%), followed by Western Europe (25.7%), Asia (15.4%) and Central Europe (11.7%).

VKA use: The randomization of this trial was balanced by VKA use (VKA naïve and VKA experienced).

Pacemakers and implantable defibrillators were present in 10.7% and 2.2% of the subjects in this trial, respectively. Approximately 28% of the overall population in this study had a previous cardioversion and 2.1% had an atrioventricular (AV) node ablation

Renal status: Concordant with a high percentage of elderly ≥ 75 years of age patients with mild or moderate renal impairment were reasonably represented (45.8% and 18.5%, respectively).

Baseline stroke risk factors where also well balanced in between treatment groups.

The mean CHADS2 score was 2.1, median 2, corresponding to an intermediate stroke risk (approx 3-5% per year; ACC/AHA/ESC 2006 guideline). Approximately one third of subjects had CHADS2 scores of 3 or higher.

Concomitant medications: Medication at baseline was wide and corresponded to what can be expected from a patient population with cardiovascular comorbidity. Approximately 40% of the subjects used ASA at least once during the study while 20.5% of the subjects received ASA throughout the study. Clopidogrel was used at least once by 7.4% of subjects (slightly higher than the use at baseline), while 2.4% of the subjects received clopidogrel throughout the study. Approximately 1% of the subjects received ASA plus clopidogrel throughout the study. A slightly higher use of PPI during the study was noted in the DE groups (DE 110mg: 24.6%; DE 150mg: 24.7%) compared to the warfarin group (21.1%), probably due to the higher rate of gastrointestinal adverse events including GI bleedings,with DE Overall, it can be resumed that a relevant patient population with AF was enrolled in the pivotal RELY trial (1160.26) constituting those patients typically encountered in clinical practice, with considerable CV comorbidity as reflected in their advanced age with reduced renal function, stroke risk profiles, and concurrent medications (antihypertensives, antiarrhytmics and other drugs used in AF, antithrombotic therapies, cholesterol lowering drugs, anti-inflammatory drugs).

Numbers analysed

Data analysis sets:

A total of 5 data sets (a randomized set, safety set, treated set, per protocol set and PK/PD set) were defined for the analyses in this study and the number of patients analysed in each set are described in table below. The randomized data set included all 18,113 randomized subjects.

Table 9 Subjects in each analysis data set

	DE 110	**DE 150**	**Warfarin**	**Total**
Randomized set	6015	6076	6022	18113
Safety set	5983	6059	5998	18040
Treated set	4995	4988	5283	15266
Per protocol set	4821	4797	5112	14730
PK/PD set	4995	5007	N/A	10002

Outcomes and estimation

The yearly event rate for the primary endpoint stroke/SEE was 1.54% (183 patients) for DE 110bid, 1.11% (134 patients) for DE 150bid and 1.71% (202 patients) for warfarin. Mainly ischemic strokes accounted for the primary endpoint with yearly event rates of 1.28% (152 patients), 0.86% (103 patients) and 1.14% (134 patients) for DE 110bid, DE 150bid and warfarin. The yearly event rates for hemorrhagic strokes were 0.12% (14 patients), 0.10% (12 patients) and 0.38% (45 patients).The stroke/SEE rates for warfarin appeared thus roughly comparable to the warfarin rates in other AF trials (AMADEUS 1.3%, SPORTIF III 2.3%, SPORTIF V 1.2%, ACTIVE W stroke 1.4%). For the risk of stroke/SEE both dosages of DE were non-inferior to warfarin with absolute and relative risk reductions amounting to 0.17% and 10% for DE 110bid and 0.60% and 35% for DE 150bid, respectively in comparison to warfarin (Table 3). The HRs were 0.90 (95% CI: 0.74, 1.10; p<0.0001) and 0.65 (95% CI: 0.52, 0.81; p<0.0001. Thus, the upper bound of the 95% CI was below 1.46, the protocol specified non-inferiority margin, for both doses. DE 150bid was in addition statistically significantly superior to warfarin (p=0.0001). The DE 150bid Kaplan-Meier curve seemed to separate from the other two curves continuously during the whole trial. In view of the easier administration of DE (no monitoring and no dose-adjustments) the efficacy is considered of clinical benefit. The efficacy of DE was not affected when analysed by baseline demographic subgroups (age, gender, ethnicity, region, weight, BMI and CrCL) – data not presented above. Several sensitivity analyses for stroke/SEE were performed to support the efficacy results using the safety- and the per protocol set, investigator reported events and stratified analyses by baseline VKA use, ASA use and history of stroke/SEE/TIA. The analyses seemed to support the efficacy of DE.

Subgroup analyses

Age: The rates of events on the primary endpoint stroke/SEE generally increased with age across all treatment groups. In the three sub-groups of age (< 65, 65-75 and ≥75 years of age), DE 110 seemed of less benefit than DE 150.

Renal function: Stroke rates increased with decreasing renal function in all treatment groups.

Gender: Females had higher rates of stroke/SEE than males. They also experienced a slightly better efficacy of DE 150, which can be explained by a higher exposure to dabigatran in correlation with slight decreased CL/F.

Body weight: Stroke rates increased with decreasing body weight in all treatment groups.

Ethnic groups: There were no obvious differences in hazard ratios for the primary endpoint observed across different ethnic groups, but it is difficult to conclude for black subjects due to the small number of patients.

Regions: There was high difference in stroke rates by region. DE 150 consistently had a lower stroke rate compared to warfarin. DE 110 provided point estimates > 1 in some regions (the highest hazard ratios being in Central Europe), where the warfarin rate was also the lowest.

Prior VKA use: Subgroup analyses of the primary endpoint by prior VKA use did not seem to influence the overall efficacy of both DE dosages on the primary endpoint. The difference between DE 150bid vs. warfarin, however, was smaller in the VKA experienced group than in the VKA naïve group.

Baseline stroke risk factors: DE 110bid was unaltered non-inferior to warfarin when analysed by baseline stroke risk factors.

No altered efficacy was observed when the primary endpoint was analysed by CHADS2-score. As could be expected, the primary endpoint event rate increased with increasing CHADS2 score for all treatment groups.

INR time in therapeutic range (2-3; TTR): Extensive analyses on the association between quality of INR and outcomes were requested by CHMP and provided in the response to the D120 LoQ.

For the overall RE-LY trial the mean TTR (time in therapeutic range) was 64.4% and the median was 67.3%. The mean TTR in the EU countries was 66.9%, with Sweden, Finland, Denmark and the UK having the highest TTR and Romania, Poland, France and Slovakia the lowest.

Not unexpectedly, the outcome of warfarin treatment improved with increasing TTR. The presented analyses clearly demonstrated that the benefits observed in the comparison of DE to warfarin diminished if INR control was good with TTR >70%. Still, for the overall population as well as for patients ≥ 75 years of age, DE 150 appeared more attractive with respect to the primary endpoint (prevention of stroke/SEE) when compared to warfarin at centres with TTR ≥70%. DE 110 appeared comparable to warfarin in this case. This information is included in section 5.1 of the SmPC.

Ancillary analyses

After data base lock 27 new events were identified by the sponsor (by routine site closeout visits) and the data coordinating center, PHRI. Of the 27 events 22 events were adjudicated as outcome events. Sensitivity analyses on primary endpoint, all cause death, vascular death, major bleeds and intracranial haemorrhage have been performed including the new adjudicated outcome events. Only for all cause death a shift was observed for DE 150 mg: HRs (DE 150mg vs. warfarin) were unaltered 0.88 (old and new data) with unaltered 95% CIs of 0.77, 1.00. However, the p-value moved from statistically significantly superior (p=0.0475) to not statistically significantly superior (p=0.0517). For NCB the HR for the comparison DE150 vs. warfarin was 0.90 (95%CI 0.82, 0.99), p= 0.0254. For the other outcome events the results were unaltered. Overall, the conclusions on efficacy and safety for DE vs. warfarin are unaltered despite the inclusion of the additional adjudicated outcome events.

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 10 Summary of Efficacy for Trial 1160.26

Title: Randomized Evaluation of Long term anticoagulant therapy (RE-LY®) comparing the efficacy and safety of two blinded doses of dabigatran etexilate with open label warfarin for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: prospective, multi-centre, parallel-group, non-inferiority trial (RE-LY® study).		
Study identifier	1160.26	
Design	Prospective, randomized, open label, blinded endpoint evaluation (PROBE), controlled, parallel group, non-inferiority trial with open-label warfarin or two double-blind doses of dabigatran etexilate	
	Duration of main phase:	Maximum 36 months, median 24 months

	Duration of Run-in phase: Duration of Extension phase:		not applicable not applicable
Hypothesis	Non-inferiority		
Treatments groups	Dabigatran 110 (DE 110)		Dabigatran etexilate 110 mg twice daily. Max. 36 months, N=6,015
	Dabigatran 150 (DE 150)		Dabigatran etexilate 150 mg twice daily. Max. 36 months, N=6,076
	Warfarin		Warfarin (target INR 2-3). Max. 36 months, N=6,022
Endpoints and definitions	Primary endpoint:	Stroke/SEE	incidence of stroke (including hemorrhagic) or systemic embolic events
	Safety endpoint	MBE	Incidence of major bleeds
	Secondary endpoint	Stroke/SEE/ death	Incidence of stroke (including hemorrhagic), systemic embolic event, and death
	Secondary endpoint	Stroke/SEE/ PE/MI/death / major bleed	Incidence of stroke (including hemorrhagic), systemic embolic event, pulmonary embolism, myocardial infarction, death, and major bleeding
	Other endpoint	Ischemic stroke	Incidence of ischemic stroke
	Other endpoint	Haemorr-hagic stroke	Incidence of haemorrhagic stroke
	Other endpoint	All-cause mortality	Incidence of all-cause mortality
	Other endpoint	Vascular mortality	Incidence of vascular mortality
	Other endpoint	ICH	Incidence of ICH
Database lock	June 16, 2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat: all randomized patients Kaplan-Meier analysis of time to first event (median time in trial=24 months)			
Descriptive statistics and estimate variability	Treatment group	DE 110	DE 150	warfarin
	Number of subjects	6,015	6,076	6,022
	Stroke/SEE (% per year)	1.54	1.11	1.71
	<variability statistic>	n/a	n/a	n/a
Analysis description	**Safety endpoint**			
Descriptive statistics and estimate variability	Major Bleeding (% per year)	2.87	3.32	3.57
	<variability statistic>	n/a	n/a	n/a
Analysis description	**Secondary Analyses**			
Descriptive statistics and estimate variability	Stroke /SEE/death (% per year)	4.85	4.32	5.20
	Stroke/SEE/PE/ MI/death/ major bleed (% per year)	7.25	7.05	7.84
	Ischemic stroke (% per year)	1.28	0.86	1.14
	Haemorrhagic stroke (% per year)	0.12	0.10	0.38
	All-cause mortality (% per year)	3.75	3.64	4.13
	Vascular mortality (% per year)	2.43	2.28	2.69
	ICH (% per year)	0.23	0.32	0.76

Effect estimate per comparison	Primary endpoint	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.90
		95% confidence interval	0.74-1.10
		P-value, non-inferiority P-value, superiority	P <0.0001 P =0.2943
	Primary endpoint	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.65
		95% confidence interval	0.52-0.81

		P-value, non-inferiority P-value, superiority	P <0.0001 P =0.0001
	Safety endpoint (major bleeding)	Comparison groups	DE 110 vs. warfarin
		Hazard Ratio	0.80
		95% confidence interval	0.70-0.93
		P-value, superiority	P=0.0026
	Safety Endpoint (major bleeding)	Comparison groups	DE 150 vs. warfarin
		Hazard Ratio	0.93
		95% confidence interval	0.81-1.07
		P-value, superiority	P =0.3146
	Secondary endpoint: stroke /SEE/death	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.93
		95% confidence interval	0.83-1.045
		P-value, superiority	P =0.2206
	Secondary endpoint: stroke /SEE/death	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.83
		95% confidence interval	0.74-0.93
		P-value, superiority	P =0.0015
	Secondary endpoint: Stroke/SEE/PE/ MI/death/ major bleed	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.92
		95% confidence interval	0.84-1.01
		P-value, superiority	P=0.0852
	Secondary endpoint: Stroke/SEE/PE/ MI/death/ major bleed	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.90
		95% confidence interval	0.82-0.99
		P-value, superiority	P=0.0254
	Other endpoint: Ischemic stroke	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	1.13
		95% confidence interval	0.89-1.42
		P-value, superiority	P=0.3139
	Other endpoint: Ischemic stroke	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.75
		95% confidence interval	0.58-0.97
		P-value, superiority	P=0.0296
	Other endpoint: Haemorrhagic stroke	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.31
		95% confidence interval	0.17-0.56
		P-value, superiority	P <0.001
	Other endpoint:	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.26

	Haemorrhagic stroke	95% confidence interval	0.14-0.49
		P-value, superiority	P <0.001
	Other endpoint: All-cause mortality	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.91
		95% confidence interval	0.80-1.03
		P-value, superiority	P=0.1308
	Other endpoint: All-cause mortality	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.88
		95% confidence interval	0.77-1.00
		P-value, superiority	P=0.0517
	Other endpoint: Vascular mortality	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.90
		95% confidence interval	0.77-1.06
		P-value, superiority	P=0.2081
	Other endpoint: Vascular mortality	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.85
		95% confidence interval	0.72-0.99
		P-value, superiority	P=0.0430
	Other endpoint: ICH	Comparison groups	DE 110 vs warfarin
		Hazard Ratio	0.30
		95% confidence interval	0.19-0.45
		P-value, superiority	P<0.0001
	Other endpoint: ICH	Comparison groups	DE 150 vs warfarin
		Hazard Ratio	0.41
		95% confidence interval	0.28-0.60
		P-value, superiority	P<0.0001
Notes	The annualized rates of events were computed from the total patient years of exposure and the number of patients with at least one event. Treatment comparisons were based on hazard ratios of the different treatments. The high dose was superior to warfarin in stroke/SEE reduction and similar to warfarin in the rate of major bleeds. The low dose was similar to warfarin in efficacy (stroke/SEE) and superior to warfarin for major bleeds. Both doses significantly reduced intracranial hemorrhage compared to warfarin. Addition of death to the primary endpoint, as a competing risk, did not change the efficacy compared to warfarin.		
Analysis description	The statistical model for the primary efficacy analysis was the Cox proportional hazard model including treatment as a factor in the model. The hazard ratio and its confidence limits were determined for evaluating the non-inferiority of dabigatran over warfarin. The Cox regression model was also used for other time-to-event analyses.		

2.5.3. Discussion on clinical efficacy

Antithrombotic therapy for patients with AF is currently recommended for patients with a high risk factor (stroke/SEE/TIA) or patients with one or more moderate risk factors (age >75 years, hypertension, HF, LVEF <35%, diabetes mellitus) whereas anticoagulation in patients with weaker risk

factors (females, age 65-74, CAD, thyreotoxicoxis) is debatable. A strengthening of the treatment recommendations has been proposed recently (ESC 2010 guideline[2]) with the recommendation to provide anticoagulation to patients with one 'major' risk factor or more than 2 'clinically relevant non-major' risk factors and the option to treat if one 'clinically relevant non-major' risk factor is present. The major risk factors are prior stroke/TIA/SEE and age ≥75 years. 'Clinically relevant non-major' risk factors are HF, hypertension, diabetes mellitus, females, age 65–74 years, and vascular disease. Thus, a relevant patient population with AF was enrolled in the pivotal RELY trial (1160.26) constituting those patients typically encountered in clinical practice, with considerable cardiovascular co-morbidities as reflected in their advanced age with reduced renal function, stroke risk profiles, and concurrent medications. In contrast to recent AF trials (SORTIF III and IV, ACTIVE-W, AMADEUS) patients were balanced as regards their previous VKA use.

The yearly event rate for the primary endpoint stroke/SEE was 1.54% (183 patients) for DE 110bid, 1.11% (134 patients) for DE 150bid and 1.71% (202 patients) for warfarin. DE 110bid was non-inferior and DE 150bid superior when compared to warfarin. The absolute and relative risk reductions amounted to 0.17% and 10% for DE 110bid and 0.60% and 35% for DE 150bid, respectively. The DE 150 mg Kaplan-Meier curve seemed to separate continuously from the other two curves during the whole trial indicating a consistent and increasing effect. Approximately half of all strokes were disabling including fatal, with no significant differences between treatment groups. Mainly ischemic strokes accounted for the primary endpoint with yearly event rates of 1.28% (152 patients), 0.86% (103 patients) and 1.14% (134 patients) for DE 110bid, DE 150bid and warfarin. The yearly event rates for hemorrhagic strokes were 0.12% (14 patients), 0.10% (12 patients) and 0.38% (45 patients).

Subgroup analyses of the primary endpoint: Prior VKA use did not seem to influence the overall efficacy of both DE dosages on the primary endpoint. Analyses by "baseline medication use", "medication use during study" and by different demographic subgroups indicated overall consistent efficacy as the point estimate for HR was below 1 for most groups for both DE 110mg and 150mg. Further analyses of D150 by weight cut-off at 60kg indicated that the benefit of DE 150mg bid was preserved also in this low weight category and a dose reduction seems not indicated in these patients. Stroke rates increased with decreasing renal function and decreasing body weight as well as with increasing age in all treatment groups. When the primary endpoint was analysed by baseline stroke risk factors (LVEF <40%, symptomatic HF, age >65 years with concomitant diabetes or hypertension or CAD) DE 150bid was still more favourable compared to warfarin.

Two secondary endpoints were specified in the protocol: composite endpoints of "stroke, SEE and all cause death" and "stroke, SEE, PE, MI and vascular death": the event rates for "stroke, SEE and all cause death" and "stroke, SEE, PE, MI and vascular death" were similar for DE 110bid (4.85% and 4.17%) and warfarin (5.20 % and 4.27%) whereas DE 150bid (4.32% and 3.61%) was superior to warfarin for both endpoints. Subgroup analyses of the secondary endpoint by VKA use did not affect the efficacy of DE 110mg and 150mg vs. warfarin. Also for other endpoints the efficacy of DE vs. warfarin was similar to the efficacy on primary- and secondary endpoints: The yearly event rates for composite endpoint of "ischemic stroke, SEE, PE, MI, TIA, hospitalisation or all cause deaths" were 20.80%, 21.61% and 22.27% for DE 110bid, DE 150bid and warfarin respectively. The yearly event rates for the "net clinical benefit" endpoint (composite endpoint of "stroke, SEE, PE, MI, all cause death and major bleed") were 7.25%, 7.05% and 7.84% for DE 110bid, DE 150bid and warfarin respectively. The HR was superior for DE 150mg vs. warfarin for the "Net clinical benefit" endpoint, however, the upper limit of the 95% CI contained 1 (0.91 (95% CI: 0.82, 1.00; p=0.0393). In view of additional outcome events (identified after data base lock) shifting the superior effect of DE150 mg vs. warfarin

[2] European Heart Journal (31):2369-2429 - doi:10.1093/eurheartj/ehq278

on "all cause death" to not significantly different, the applicant re-analysed NCB, the HR was then 0.90 (95%CI 0.82, 0.99; p=0.0254).

Analyses of the individual components of endpoints: The yearly event rates of strokes were lower for DE 110bid and DE 150bid compared to warfarin (1.44%, 1.01% and 1.58% respectively). Absolute reductions for DE 110mg and 150 mg vs. warfarin: 0.14% and 0.57%, respectively). Likewise the number of subjects with 1-, 2- or ≥3 strokes was lower for both DE dosages vs. the warfarin group. The frequency of ischemic strokes for DE 110 bid was numerically higher than for DE 150bid and warfarin (1.28%, 0.86% and 1.12% respectively). The difference for all strokes in favour of DE 110bid vs. warfarin was mainly driven by haemorrhagic strokes (0.12% and 0.38%). However, the Kaplan-Meier curves for ischaemic strokes separated early for DE 150bid and by month 30 also for DE 110bid when compared to warfarin. As regards" time to first haemorrhagic stroke" and "time to first intracranial haemorrhage" both DE curves separated early (month 1-3) from warfarin. The severity of the strokes as evaluated by the Modified Rankin Score (score from 0-2; disabling stroke: score form 3-6, 6= fatal outcome) was similar for all three treatment arms. The yearly event rate for SEE was very small in all treatment groups being lower for DE treated patients compared to warfarin (0.13%, 0.11% and 0.18% for DE 110bid, DE 150bid and warfarin; absolute reductions vs. warfarin amounted to 0.05% and 0.07%). The yearly event rates for MI were lowest in the warfarin group and similar in the DE treatment groups (warfarin 0.64%, DE 110 0.82%, DE 150 0.81%). The risk of MI was numerically higher for either dose of DE vs. warfarin (HRs were 1.29 (95% CI: 0.96, 1.75; p=0.0929) for DE 110bid and 1.27 (95% CI: 0.94, 1.71; p=0.1240) for DE 150bid compared to warfarin) substantiated by a separation of the DE 150bid Kaplan-Meier curve from warfarin after 3 months of treatment. After 23 months the separation increased continuously. No clear pattern was observed when analysed by baseline demographic characteristics, stroke risk factors, CHADS2 score, AF type, "baseline medication use" or by "medication use during study period". Further analyses on the MI risk were provided in the response to the D120 LoQ and D180 LoOIs. A dose-dependency for the increased risk of MI could not be confirmed. The highest risk of MI was found in subjects with a previous MI, those with CAD, HF, reduced LVEF, diabetes and moderate renal function. The relative risk for DE vs. warfarin was not significantly different in these subgroups. Thus, a particular subgroup of patients being particularly at risk of MI could not be identified. The overall benefit risk of dabigatran is not considered to be affected by this finding, however, strong warnings have been inserted in the SmPC and MI was included as a potential risk in the RMP.

According to the EMA guideline: *Points to consider on application with 1. meta-analyses; 2. one pivotal study" (CPMP/EWP/2330/99)*, the confirmatory evidence provided by one pivotal study only has to be exceptionally compelling. The internal validity should be high, thus there should be no indications of a potential bias. As discussed above the latter has not been fulfilled in the present application. However, in view of the relatively rare nature of the outcome events in the primary endpoint (stroke /SEE) it seems unreasonable to require an additional study of the same magnitude. To confirm the internal validity an inspection was conducted. In addition, extensive analysis on the association between quality of INR and outcomes were requested by CHMP and provided in the response to the D120 LoQ and D180 LoOIs.

For the overall RELY trial the mean TTR (time in therapeutic range) was 64.4% and the median was 67.3%. The mean TTR in the EU countries was 66.9%, with Sweden, Finland, Denmark and the UK having the highest TTR and Romania, Greece, Poland, France and Slovakia the lowest. Not unexpectedly, the outcome of warfarin treatment improved with increasing TTR. The presented analyses clearly demonstrated that the benefits observed in the comparison of DE to warfarin diminished if INR control was good with TTR >70%. Still, for the overall population as well as for patients ≥ 75 years of age DE 150 appeared more attractive with respect to the primary endpoint

(prevention of stroke/SEE) when compared to warfarin at centres with TTR ≥70%. DE 110 appeared comparable to warfarin in this case. For a discussion on major bleeding events and TTR please refer to the safety section below. The yearly event rates for PE were overall low but also numerically higher for both DE dosages vs. warfarin albeit the absolute differences were low amounting to 0.02% for DE 110mg and 0.05% for DE 150mg. PE is addressed in the RMP as a potential risk. It is reassuring that patients randomised to any of the DE doses had lower rates of all-cause death than warfarin (DE 110mg: 3.75%; DE 150mg: 3.64%; warfarin: 4.14%), although a statistically significance difference could no longer be proven for DE 150 after the new analyses. The HR for DE 150mg vs. warfarin was 0.88 (95% CI: 0.77,1.00; p= 0.0517). 16 months after randomization the "all cause death" Kaplan-Meier curves for DE 110mg and 150mg separated from warfarin indicating a consistent effect. Most deaths were of vascular origin. The vascular death HR for DE 150mg vs. warfarin was 0.85 (95% CI: 0.72, 0.99; p=0.0430). Subjects treated with DE 110 had the lowest rate of hospitalisation, which was significantly lower when compared with warfarin (p=0.0209).

2.5.4. Conclusions on the clinical efficacy

DE 110bid was non-inferior and DE 150bid was superior when compared to warfarin for the primary outcome (time to the first occurrence of stroke/SEE). Also for the two secondary outcomes (composite of "stroke, SEE and all cause death", and "stroke, SEE, PE, MI and vascular death") and the "other" endpoint Net Clinical Benefit DE 110bid was non-inferior and DE 150bid was superior when compared to warfarin. The effect of DE seemed consistent across the components of the composite endpoints. In view of the easier administration of DE (no monitoring and no dose-adjustments) and from a pure efficacy point of view the consistent efficacy of both dosages of DE is considered a clinical benefit. One exception however was MI. Although small in absolute numbers, the risk of MI was numerically higher for DE 110mg and 150mg vs. warfarin, substantiated by continuously diverging Kaplan-Meier curves throughout study duration. A dose-response for MI could not be confirmed. Extensive analysis on the association between quality of INR and outcomes were requested by CHMP and provided in the response to the D120 LoQ and D180LoOIs. Not unexpectedly, the outcomes associated with warfarin improved with increasing TTR. The presented analyses clearly demonstrated that the benefits observed in the comparison of DE to warfarin diminished if INR control was good with TTR >70%. Still, for the primary endpoint DE 150mg bid compares favourably to warfarin treated patients from centres with TTR ≥ 70%.

2.6. Clinical safety

Patient exposure

Safety data are derived from the combined SPAF Phase II/III trials (1160.20, 1160.42, 1160.49 and 1160.26) but are mainly based on results from the phase III RE-LY study A total of 18 042 patients were included in the safety analysis of RELY (5 983 in DE 110 bid, 6 059 in DE 150 bid and 5 998 in warfarin). The mean total exposure to study drug was similar across treatment groups (20.5 months in DE 110 bid, 20.3 months in DE 150 bid and 21.3 months in warfarin).

The primary safety endpoint

The primary safety endpoint was major bleeding events (MBE) adjudicated by an Adjudication Committee blinded to treatment. Overall the definition of MBEs and life-threatening bleeding events used in the RE-LY study are considered acceptable.

Adverse events

Bleeding events

In the RELY study the yearly rate of major bleedings, the primary safety endpoint, was 2.87% for DE 110mg bid, 3.32% for DE150 mg bid and 3.57% for warfarin (table 11). The MBE risk was significantly lower for DE 110 bid compared to warfarin (HR = 0.80 (95% CI: 0.70, 0.93; p=0.0026), whereas it was numerically lower for DE 150 bid compared to warfarin, but the difference was not statistically significant (HR = 0.93 (95% CI: 0.81, 1.07; p=0.3146)). The risk of life-threatening bleeds, hemorrhagic strokes and ICHs was significantly lower in DE treated patients vs. warfarin (all p values ≤0.0001, except for p=0.0305 for life-threatening bleeds for DE 150 mg bid vs. warfarin). The yearly rates for life-threatening bleedings were 1.24% 1.49% and 1.85%, for haemorrhagic strokes 0.12%, 0.10% and 0.38% and for ICH 0.23%, 0.32% and 0.76% for DE 110bid, DE150 bid, and warfarin, respectively (table 11). Despite low absolute numbers of ICH, the benefit of both DE dosages vs. Warfarin was remarkable consistent across a large variety of subgroups (i.e. age, body weight, centre INR, +/- use of concomitant ASA).

Table 11 Yearly event rate of major bleeding events and other bleeding events in Study 1160.26 (randomized set (the RE-LY study)

	DE 110 bid	DE 150 bid	Warfarin
	N (%)	N (%)	N (%)
Adjudicated Bleeds			
Number of subjects	6,015	6,076	6,022
Subject-years	11,899	12,033	11,794
Major bleeds	342 (2.87)	399 (3.32)	421 (3.57)
Life threatening MBEs	147 (1.24)	179 (1.49)	218 (1.85)
Other MBEs	218 (1.83)	248 (2.06)	226 (1.92)
Haemorrhagic stroke	14 (0.12)	12 (0.10)	45 (0.38)
ICH	27 (0.23)	38 (0.32)	90 (0.76)
Minor bleeds	1,566 (13.16)	1,787 (14.85)	1,931 (16.37)
Any bleeds	1,754 (14.74)	1,993 (16.56)	2,166 (18.37)

In case of recurrent event of the same category, the first event was considered. Minor bleeds were not adjudicated. Subject-years = sum (date of study termination - date of randomization +1) of all randomized subjects / 365.25. Yearly event rate (%) = # of subjects with event / subject-years * 100. ICH consists of adjudicated hemorrhagic stroke and subdural and/or subarachnoid hemorrhage.

As regards MBE analysed by bleeding criteria "symptomatic bleedings in critical areas/organs", these were approximately halved for each dose of DE compared to warfarin. The main bleeding localisation was intracranial for warfarin" and constituted 18.7% of the MBE in the warfarin group and 8.6% and 7.5% in the DE 150bid and the DE 110 bid treatment groups, respectively (table 12). Fatal bleeds were also more frequent with warfarin compared to DE 150bid and DE 110bid (8.3% vs. 5.9% and 6.1%). Intracranial fatal bleedings were reported more frequently for warfarin than for DE110 and DE150 (N= 23, 10 and 9 respectively) whereas GI fatal bleedings were more frequent for DE150 than for DE110 and warfarin (N= 10, 4 and 6 respectively). Gastrointestinal MBEs constituted a large part of

all MBEs and were noticeably higher with both DE doses (table 12). The yearly event rates for any GI bleeds was 5.41%, 6.13% and 4.02% and for GI major bleeds 1.14%, 1.57% and 1.07% for DE 110mg bid, DE 150mg bid and warfarin, respectively. The risk of GI major bleeds was significantly higher for DE 150 bid compared to warfarin (HR = 1.47 (95% CI: 1.17, 1.85; p=0.0008]), including GI life threatening bleeds (HR = 1.62 (95% CI: 1.17, 2.26; p=0.0038), and was also significantly lower for DE110 bid vs. DE 150 bid. There was a significant interaction of major GI bleed for age and certain stroke risk factors. Thus, the risk of GI bleeding is an issue of concern for patients ≥ 75, For all treatment groups an increased risk of GI bleeding was also associated with concomitant medication with ASA, clopidogrel and NSAIDs. In addition, for patients "on PPI only during treatment" an increased frequency of major GI bleed was observed.

Table 12 Major bleeds by bleeding criteria in Trial 1160.26 (randomized set1)

	DE 110 bid	DE 150 bid	Warfarin
Total number of major bleeds	426(100.0)	525 (100.0)	518 (100.0)
Hospitalized for the event	300 (72.9)	390 (77.8)	385 (76.5)
Bleeding criteria,			
-Drop of Hemoglobin >=20 g/L	276 (64.8)	347 (66.1)	301 (58.1)
-Required transfusion >= 2 units	248 (58.2)	330 (62.9)	252 (48.6)
-Symptomatic bleeding in critical area/organ	63 (14.8)	79 (15.0)	154 (29.7)
Intraocular	17 (4.0)	12 (2.3)	19 (3.7)
Intraspinal	0	0	0
Intramuscular	8 (1.9)	8 (1.5)	18 (3.5)
Retroperitoneal	2 (0.5)	9 (1.7)	12 (2.3)
Intra-articular	5 (1.2)	5 (1.0)	7 (1.4)
Pericardial	2 (0.5)	4 (0.8)	4 (0.8)
Symptomatic intracranial	32 (7.5)	45 (8.6)	97 (18.7)
Subdural	14 (3.3)	25 (4.8)	41 (7.9)
Intracerebral	16 (3.8)	19 (3.6)	54 (10.4)
Gastrointestinal	162 (38.0)	222 (42.3)	144 (27.8)
Other area/organs	44 (10.3)	40 (7.6)	49 (9.5)
Associated with hypotension	19 (4.5)	35 (6.7)	23 (4.4)
Required surgical intervention	37 (8.7)	58 (11.0)	68 (13.1)

Death	26(6.1)	31 (5.9)	34 (8.3)

MBEs by subgroup analyses

Age: A statistical significant interaction for the risk of major bleeds with treatment was observed for age (p<0.0001). For subjects <75 years of age, the DE groups had lower rates of MBEs vs. warfarin (<65 years: DE 110bid vs. warfarin, HR = 0.33 (95% CI: 0.19, 0.59); DE 150 bid vs. warfarin, HR = 0.36 (95% CI: 0.21, 0.62); 65-<75 years: DE 110bid vs. warfarin, HR = 0.70 (95% CI: 0.56, 0.89); DE 150bid vs. warfarin, HR = 0.80 (95% CI: 0.64, 1.00)). However subjects ≥75 years of age on DE 150bid had a higher rate of MBE compared to warfarin (DE 110: 4.44%; DE 150: 5.12%; warfarin: and 4.39%; DE 110 vs. warfarin HR 1.01 (CI 0.83, 1.23), DE 150 vs. warfarin 1.18 (CI 0.98, 1.43)). The increased rate of MBEs in the elderly population ≥ 75 years is worrisome due to the fragility of this population compared to the population below 75 years of age. Please refer to discussion on dosing in elderly in discussion on clinical safety.

ASA use during the study had a strong effect on bleeding risk. Subjects who took ASA at least once during the study almost doubled the risk of a major bleed (hazard ratio = 1.91, p-value<0.001) compared with those who did not use ASA during the study. However, no statistical significant interaction for the risk of MBE with treatment was observed for ASA.

Renal dysfunction was associated with a higher risk of bleeding, for all treatments, thus the rates of MBEs increased with decreasing renal function. In the sub-group of moderate renal impairment (CrCL 30-50 ml/min), the yearly event rate of MBEs was comparable for DE 110 vs. warfarin (5.65% vs. 5.68%) however, lower for DE 150 vs. Warfarin (5.27% vs. 5.68%).

In the sub-group with mild renal impairment (CrCL 50-80 ml/min) treatment with DE 150 caused higher MBEs rates than DE 110 (but lower rates vs. warfarin), confirming the overall relationship between increased dose and bleeding risk in this population, in spite of the paradoxical results in the moderate renal impairment sub-group.

In the response to the D120 LoQs subgroup analyses supported the use of the DE 150 mg dosage in patients with moderate renal failure (i.e. lowering the dosage of DE did not decrease the rate of bleedings), however caution should be envisaged for patients in concomitant high risk of bleeding.

Body weight: Increased rates of MBEs by decreasing body weight were observed in all treatment groups. The interaction was however, insignificant. In the response to the D120 LoQ sub-group analyses were provided supporting the use of DE150 also in patients with bodyweight below 60 kg.

Gender: the risk of MBEs was not influenced by gender.

INR control: Not surprisingly the yearly MBE rate in warfarin treated patients was higher if INR was poorly controlled. When MBE rates where further analysed by centre time in therapeutic range (TTR) the yearly MBE rate was higher for DE150 mg bid vs. Warfarin for centres with TTR ≥ 70%. Please refer to safety section for further discussion.

Other adverse events

The most frequently occurring AEs (in MedDRA preferred terms) for DE 110 bid, DE 150 bid, and warfarin subjects were dyspnoea (8.3%, 8.7%, and 9.2%, respectively), dizziness (7.6%, 7.6%, and 9.3%), and oedema peripheral (7.5%, 7.3%, and 7.6%), in which warfarin subjects had the highest incidence in all cases.

DE 110bid and 150bid treated subjects had the highest incidence of gastrointestinal AEs (34.6% and 34.5%, vs. 24.1% for warfarin). Diarrhoea, dyspepsia, and nausea were the most frequently reported GI AEs, all of which were reported at a higher frequency with the DE groups, particularly for dyspepsia (6.2%, 5.7%, and 1.4% for DE 110bid, DE 150bid, and warfarin, respectively). There was no consistent dose-response relationship with respect to GI AEs. A thorough discussion was provided by the MAH in the response to the D120 LoQs on the increased risk of GI AEs as well as of GI bleedings associated with DE treatment. Though, the rates of dyspepsia were higher in both DE groups vs. the warfarin group, this finding seemed not associated with an increased risk of GI bleedings in the DE groups vs. the warfarin group. In contrast, the risk of GI bleeding seemed disproportionately higher for DE150 bid vs. Warfarin in patients on "on PPI only during study". Caution should be given for patients on PPI and H2-blockers upon initiation of DE treatment as well as for patients on DE who experience symptoms or signs necessitating initiation of PPI or H2-blocker treatment. The lower dose of DE may be appropriate in these cases.

Currently, based on the available data no specific conclusions can be drawn on the causal relation between DE treatment and GI AEs and GI bleedings. Further data analysis regarding dyspepsia will be implemented in the ongoing RELY-ABLE trial. This was considered acceptable by the CHMP.

The severity of AEs was comparable between treatment groups with the majority of AEs being classified as mild or moderate. However, a greater percentage of subjects in the DE groups had GI AEs that were considered severe in intensity compared with warfarin (5.0%, 5.5%, and 4.2% for DE 110bid, DE 150bid, and warfarin, respectively).

Serious adverse event/deaths/other significant events

In the RE-LY study, all outcomes of death were adjudicated for cause of death. Dabigatran treated subjects had the lowest incidence of deaths (7.4%, 7.2%, and 8.1% for DE 110 bid, DE 150 bid, and warfarin, respectively). Approximately 60% of deaths were vascular in nature. Within the category of vascular deaths, slightly more than half were cardiovascular deaths (sudden/arrhythmic death or pump failure death). The overall rate of other vascular deaths was slightly higher for warfarin compared to both dabigatran groups (1.7%, 1.5%, and 2.1% for DE 110 bid, DE 150 bid and warfarin, respectively). Non-vascular deaths were balanced across treatment groups. These included cancer, respiratory failure, trauma, infection and other. Of the 1371 deaths observed in the trial (randomized set), 366 subjects had an adverse event with a fatal outcome (safety set). The incidence of fatal AEs was generally similar between treatment groups (2.0%, 1.8%, and 2.3% for DE 110, DE 150, and warfarin, respectively). Pneumonia and cardiac failure were the most frequent fatal AEs during the study (0.1% to 0.2%). Sudden cardiac death was slightly more frequent in DE 110 than in the remaining groups and 4 fatal hepatic failures (N=3 for warfarin; N=1 for DE 110bid) were reported. The reported incidence of SAEs was similar across all treatment groups (21.2%, 21.3%, and 22.6% for DE 110 bid, DE 150 bid, and warfarin, respectively). SAEs were generally similar for dabigatran and warfarin subjects. The most frequently reported SAEs were cardiac failure congestion (1.4%, 1.0%, and 1.2% for DE 110 bid, DE 150 bid, and warfarin groups, respectively), pneumonia (1.2%, 1.2%, and 1.0%), AF (1.1%, 0.9%, and 1.2%), and cardiac failure (0.9%, 1.0%, and 1.1%). Two hepatic lesions (one in each DE groups) were reported, however, based on data provided in the response to the D120 LoQs no association to DE treatment seemed evident. In terms of SOCs the most frequently occurring were cardiac disorders, infections and infestations, and GI-disorders.

Laboratory findings

Treatment with DE did not seem to be associated with any statistical significant or clinically relevant alteration in liver function tests. In the response to the D120 LoQs the low hepatotoxicity potential of dabigatran was confirmed. Changes in haematological parameters were consistent with bleeding events in the three treatment arms.

Other findings related to safety

The incidence of MI was numerically increased for dabigatran treated subjects compared to warfarin treated subjects. The higher frequency of MI compared to warfarin persisted regardless of at least one use of ASA, clopidogrel, ASA+clopidogrel, verapamil, diltiazem and beta blocker. The incidence of MI did not differ by age, gender, weight or region, except in Asia. However, the incidence of MI was low and similar across all treatment groups. There was a higher incidence of MI for Blacks treated with warfarin (2.47%) or dabigtran 150 mg bid (2.49%) compared with those treated with dabigatran 110 mg bid (0%); however, the sample size in these groups was low (N= 52-67) in the treatment arms.

Safety related to drug-drug interactions and other interactions

Anticoagulants and antiplatelet aggregation agents

The following treatments have not been studied and may increase the risk of bleeding when used concomitantly with dabigatran: UFH, low molecular weight heparins (LMWH), and heparin derivatives (fondaparinux, desirudin), thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, prasugrel, dextran, sulfinpyrazone, rivaroxaban, and vitamin K antagonists. UFH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

Clopidogrel: In a phase I study in young healthy male volunteers, the concomitant administration of dabigatran etexilate and clopidogrel resulted in no further prolongation of capillary bleeding times compared to clopidogrel monotherapy. In addition, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ and the coagulation measures for dabigatran effect or the inhibition of platelet aggregation as measure of clopidogrel effect remained essentially unchanged comparing combined treatment and the respective mono-treatments. With a loading dose of 300 mg or 600 mg clopidogrel, dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased by about 30-40 %.

ASA: The effect of concomitant administration of dabigatran etexilate and ASA on the risk of bleeds was studied in patients with atrial fibrillation in a phase II study in which a randomized ASA coadministration was applied. Based on logistic regression analysis, co-administration of ASA and 150 mg dabigatran etexilate twice daily may increase the risk for any bleeding from 12 % to 18 % and 24 % with 81 mg and 325 mg ASA, respectively.

NSAIDs: NSAIDs given for short-term perioperative analgesia have been shown not to be associated with increased bleeding risk when given in conjunction with dabigatran etexilate. With chronic use NSAIDs increased the risk of bleeding by approximately 50 % on both dabigatran and warfarin. Therefore, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended.

LMWH: The concomitant use of LMWHs, such as enoxaparin and dabigatran etexilate has not been specifically investigated. After switching from 3-day treatment of once daily 40 mg enoxaparin s.c., 24 hours after the last dose of enoxaparin the exposure to dabigatran was slightly lower than that after administration of dabigatran etexilate (single dose of 220 mg) alone. A higher anti-FXa/FIIa activity was observed after dabigatran etexilate administration with enoxaparin pre-treatment compared to

that after treatment with dabigatran etexilate alone. This is considered to be due to the carry-over effect of enoxaparin treatment, and regarded as not clinically relevant. Other dabigatran related anti-coagulation tests were not changed significantly by the pre-treatment of enoxaparin.

Interactions linked to dabigatran etexilate and dabigatran metabolic profile

Dabigatran etexilate and dabigatran are not metabolised by the cytochrome P450 system and have no *in vitro* effects on human cytochrome P450 enzymes. Therefore, related medicinal product interactions are not expected with dabigatran.

Transporter interactions

P-gp inhibitors

Dabigatran etexilate is a substrate for the efflux transporter P-gp. Concomitant administration of strong P-gp inhibitors (such as amiodarone, verapamil, quinidine, ketoconazole and clarithromycin) is expected to result in increased dabigatran plasma concentrations. If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administered with strong P-gp inhibitors. A coagulation test helps to identify patients with an increased bleeding risk due to increased dabigatran exposure.

Systemic ketoconazole, cyclosporine, itraconazole and tacrolimus are contraindicated. Caution should be exercised with other strong P-gp inhibitors (e.g. amiodarone, quinidine or verapamil). Ketoconazole: Ketoconazole increased total dabigatran $AUC_{0-\infty}$ and C_{max} values by 138 % and 135 %, respectively, after a single dose of 400 mg, and 153 % and 149 %, respectively, after multiple dosing of 400 mg ketoconazole once daily. The time to peak, terminal half-life and mean residence time were not affected by ketoconazole. Concomitant treatment with systemic ketoconazole is contraindicated.

Amiodarone: When dabigatran was coadministered with a single oral dose of 600 mg amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The dabigatran AUC and C_{max} were increased by about 60 % and 50 %, respectively. The mechanism of the interaction has not been completely clarified. In view of the long half-life of amiodarone the potential for drug interaction may exist for weeks after discontinuation of amiodarone.

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg dabigatran if they receive concomitantly dabigatran etexilate and amiodarone. Close clinical surveillance is recommended when dabigatran etexilate is combined with amiodarone and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Quinidine: Quinidine was given as 200 mg dose every 2nd hour up to a total dose of 1000 mg. Dabigatran etexilate was given twice daily over 3 consecutive days, on the 3rd day either with or without quinidine. Dabigatran $AUC_{\tau,ss}$ and $C_{max,ss}$ were increased on average by 53 % and 56 %, respectively with concomitant quinidine.

Patients treated for prevention of VTEs after hip or knee replacement surgery, dosing should be reduced to 150 mg taken once daily as 2 capsules of 75 mg dabigatran if they receive concomitantly dabigatran etexilate and quinidine. Close clinical surveillance is recommended when dabigatran etexilate is combined with quinidine and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

Verapamil: When dabigatran etexilate (150 mg) was coadministered with oral verapamil, the C_{max} and AUC of dabigatran were increased but magnitude of this change differs depending on timing of administration and formulation of verapamil. The greatest elevation of dabigatran exposure was

observed with the first dose of an immediate release formulation of verapamil administered one hour prior to dabigatran etexilate intake (increase of C_{max} by about 180 % and AUC by about 150 %). The effect was progressively decreased with administration of an extended release formulation (increased of C_{max} by about 90 % and AUC by about 70 %) or administration of multiple doses of verapamil (increased of C_{max} by about 60 % and AUC by about 50 %). Therefore, close clinical surveillance (looking for signs of bleeding or anaemia) is required when dabigatran is co-administrered with verapamil. In patients with normal renal function after the hip or knee replacement surgery, receiving dabigatran etexilate and verapamil concomitantly, the dose of dabigatran should be reduced to 150 mg taken once daily as 2 capsules of 75 mg. In patients with moderate renal impairment and concomitantly treated with dabigatran etexilate and verapamil, a dose reduction of dabigatran to 75 mg daily should be considered. Close clinical surveillance is recommended when dabigatran etexilate is combined with verapamil and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment. There was no meaningful interaction observed when verapamil was given 2 hours after dabigatran etexilate (increased of C_{max} by about 10 % and AUC by about 20 %). This is explained by completed dabigatran absorption after 2 hours.

Clarithromycin: When clarithromycin (500 mg twice daily) was administered together with dabigatran etexliate in healthy voluteers, increase of AUC by about 19 % and C_{max} by about 15 % was observed without any clinical safety concern. However, in patients receiving dabigatran, a clinically relevant interaction cannot be excluded when combined with clarithromycin. Therefore, a close monitoring should be exercised when dabigatran etexilate is combined with clarithromycine and particularly in the occurrence of bleeding, notably in patients having a mild to moderate renal impairment.

The following potent P-gp inhibitors have not been clinically studied but from in vitro results a similar effect as with ketoconazole may be expected: itraconazole, tacrolimus and cyclosporine, which are contra-indicated.

Neither clinical nor in vitro test results are available for posaconazole which is not recommended for concomitant treatment with dabigatran. Inadequate clinical data are available regarding the co-administration of dabigatran and dronedarone, and their co-administration is not recommended.

P-gp inducers

Concomitant administration of a P-gp inducer (such as rifampicin, St Johns wort (Hypericum perforatum), carbamazepin, or phenytoin) is expected to result in decreased dabigatran concentrations and should be avoided.

Rifampicin: Pre-dosing of the probe inducer rifampicin at a dose of 600 mg once daily for 7 days decreased total dabigatran peak and total exposure by 65.5 and 67 %, respectively. The inducing effect was diminished resulting in dabigatran exposure close to the reference by day 7 after cessation of rifampicin treatment. No further increase in bioavailability was observed after another 7 days.

Other drugs affecting P-gp

Protease inhibitors including ritonavir and its combinations with other protease inhibitors affect P-gp (either as inhibitor or as inducer). They have not been studied and are therefore not recommended for concomitant treatment with dabigatran.

P-gp substrate

Digoxin: In a study performed with 24 healthy subjects, when dabigatran was coadministered with digoxin, no changes on digoxin and no clinical relevant changes on dabigatran exposure have been observed.

Pantoprazole: When dabigatran was coadministered with pantoprazole, a decrease in the dabigatran area under the plasma concentration-time curve of approximately 30 % was observed. Pantoprazole and other proton-pump inhibitors were co-administered with dabigatran in clinical trials and no effects on bleeding or efficacy were observed.

Ranitidine: Ranitidine administration together with dabigatran had no clinically relevant effect on the extent of absorption of dabigatran.

Discontinuation due to adverse events

Discontinuations due to AEs occurred more frequently in both DE groups (DE150 bid 20.5%, DE 110bid 19.0%) compared to the warfarin group (15.7%). Discontinuations due to GI disorders were most frequent (DE150 bid 6.9%, DE 110bid 6.5%, warfarin 3.9%), followed by cardiac disorders, nervous system disorders and renal and urinary disorders. They were all slightly more frequent in the DE groups. Subjects treated with DE 150 bid had a higher risk of discontinuation due to MBEs compared with DE 110 bid and warfarin subjects for the first 18 months of treatment. After this time, the risk was generally similar, although there were fewer subjects in the study after this time. Subjects treated with DE 110 bid or warfarin had a similar risk of discontinuation due to MBEs for the first 18 months of treatment, after which the risk was higher with warfarin treatment. No antidote is available for neutralisation of the anti-thrombotic properties of DE treatment. Therefore, the risk of bleeding was an issue of concern for patients in need of acute surgical interventions. In the response to the D120 LoQs the MAH provided reassuring data indicating that the rate of outcome events (stroke/SEE, MBE, minor bleedings or death) in subjects with interruption of anticoagulant therapy for emergency surgery and procedures were similar between DE (110mg and 150mg) and warfarin.

2.6.1. Discussion on clinical safety

The safety evaluation is mainly based on the RELY study with approximately 18.000 subjects. The number of subjects exposed to DE and the duration of exposure to DE are considered sufficient for safety evaluation. The primary safety endpoint was major bleeding events (MBE). Overall the definition of MBEs and life-threatening bleeding events used in the RE-LY study are considered acceptable. The yearly event rates of major bleeds (MBE) were 2.87%, 3.32% and 3.57% for DE 110bid, DE 150bid and warfarin, respectively with absolute reductions vs. warfarin of 0.70% and 0.25%, respectively. The risk of major bleeds was significantly lower for DE 110bid and numerically lower for DE 150bid vs. warfarin (HRs of 0.80 (95% CI: 0.70, 0.93; p=0.0026) and 0.93 (95% CI: 0.81, 1.07; p=0.3146). The risk was also significantly lower for DE 110 mg bid compared to DE 150 bid (HR=0.86 (95% CI: 0.75, 1.00; p=0.0429). When MBEs were analysed by baseline demographics, only age had statistical significant impact.

For patients aged ≥ 75 years the risk of a MBE was higher for DE150 bid than for warfarin (4.44%, 5.12% and 4.39%/year for DE110 bid, DE150 bid and warfarin, respectively, HR DE150 bid vs. warfarin = 1.18; 95% CI: 0.98, 1.43). Due to the general fragility of the elderly population the increased rate of MBEs is worrisome. Still, the effect of DE on other endpoints also has to be taken into account: The rates of stroke/SEE were 1.89%, 1.43% and 2.15%/year and the rates of ICH were 0.37%, 0.40% and 1.00%/year for DE110 bid, DE150 bid and warfarin, respectively). The HRs for DE150 bid vs. warfarin and DE110 bid vs. warfarin for net clinical benefit (NCB: composite of stroke, SEE, PE, acute MI, all cause death and MBE were similar for patients ≥ 75 years (both close to 1). A favourable effect of DE110 bid vs. warfarin was observed on stroke/SEE and ICH, in addition, the death rates are similar between treatments (DE 110 5.22%, DE150 5.12% and, warfarin 5.13%/year). However the benefit on stroke/SEE was less pronounced than for DE150 bid. Thus, for patients ≥ 75

years (please refer to discussion on patients ≥ 80 years below) 68 MBE (out of 10000 patients) would be avoided with DE110 bid, but 46 additional strokes/SEEs would be experienced compared with DE150 bid. Thus, DE110 bid should not be systematically recommended to patients between 75-80 years. DE110 bid should be individually envisaged in at risk patients, since the bleeding rates were decreased with this dosage in patients ≥ 75 years. This is reflected in the SmPC.

For patients ≥ 80 years the HRs for both dosages of DE vs. warfarin on NCB were similar and in favour of warfarin (DE110 bid = 1.12 (95% CI: 0.93, 1.36); DE150 bid = 1.13 (95% CI: 0.94, 1.35)). The rates of MBE in DE treated patients ≥ 80 accounted for the unfavourable effect on NCB (DE 110 5.25%, DE150 6.24% and warfarin 4.70%/year). The increased rate of MBE was however not due to an increased rate of devastating ICHs (DE110 bid 0.32%, DE150 bid 0.69% and warfarin 1.31%/year). Based on almost comparable NCB between DE 150 and 110 and a maintained favourable effect on Stroke/SEE (1.88%, 1.78% and 2.72% for DE110 bid, DE150 bid and warfarin) and ICH (0.32%, 0.69% and 1.31% for DE110 bid, DE150 bid and warfarin) the lower dose of DE seems most appropriate for the elderly ≥ 80 years of age in order to bring down the risk of MBEs: 10 additional stroke/SEE would be experienced compared to DE 150bid however, 99 MBE and 37 ICH would be avoided with DE 110bid compared to DE 150bid.

For the elderly patients ≥ 85 years, data being limited (approx. 250 per treatment arm), conclusion should be drawn cautiously. However, the same beneficial pattern seems to exist for the low dosage of DE also for this subgroup.

Based on the MAH's analyses of stroke/SEE and MBE in subjects with different degrees of renal dysfunction, a reduction of the DE dosage seems not necessary. In patients with moderate renal dysfunction (CrCL 30-<50 ml/min) the rates of MBE were higher for DE110 bid vs. DE150 bid group and comparable to warfarin group. Thus, DE150 bid had the lowest MBE rate. As for the primary endpoint, the rates were less for both DE doses vs. warfarin and the corresponding HRs for DE110 bid and DE150 bid vs. warfarin were below 1. However, due to a higher exposure to DE in patients with moderate renal failure, caution is advised for patients at concomitant high risk of bleeding. Patients with severe renal dysfunction with CrCL < 30 ml/min were excluded from the study and the existing contraindication for these patients must therefore also apply to the applied AF indication.

When MBE were analysed by time in therapeutic range (TTR) the rates of MBE associated with warfarin treatment for the overall population decreased with increasing TTR. For centres with TTR ≥ 70% the MBE rates were marginally higher for DE150 bid than for warfarin (2.90%, 3.32% and 3.04% for DE110 bid, DE 150 bid and warfarin, respectively). Still, for this population the rates of stroke/SEE, stroke/SEE/death and ICH (rates for ICH were remarkably reduced in the DE groups (0.19%, 0.21%, 0.77% for DE110 bid, DE 150 bid and warfarin, respectively)) were in favour of DE150 bid when compared to warfarin. Thus, due to the devastating effects of ICH the B/R of DE150 bid vs. warfarin is positive also when compared to well controlled warfarin treated subjects.

For the elderly ≥ 75 years however, the pattern in MBE noted for the overall study population with TTR≥70% appeared even more pronounced (4.26%, 5.14% and 3.58% for DE110 bid, DE150 bid and warfarin respectively), the difference of DE150 bid vs. warfarin being statistically significant. The rates of the secondary endpoints stroke/SEE/death, MBE and NCB were numerically lowest in warfarin treated patients vs. both DE dosages. The rate of the primary endpoint (stroke/SEE) was numerically lowest in the DE150 bid group (1.74%, 1.63% and 1.76% for DE110 bid, DE150 bid and warfarin respectively).

For patients with moderate renal impairment, MBE where lowest in warfarin treated subjects with TTR ≥ 70% (5.44, 5.23 and 4.18% for DE110 bid, DE150 bid and warfarin, respectively). However, for other endpoints (stroke/SEE, stroke/SEE/death, NCB and ICH) the rates were in favour of DE150 bid.

Concomitant use of ASA had a clear influence on the yearly rate of MBE (rate of MBEs was nearly doubled regardless of treatment in all treatment groups). This was also noted for the other antithrombotic therapies, COX 2 inhibitor and other NSAID. Also mild and moderate renal function, decreased body weight and increase number in stroke risk factors (CHADS2 score) increased the risk of MBE regardless of treatment. Thus, the favourable effect of DE150 bid was unaltered for these sub-groups.

Statistically significant risk reductions for both DE110 bid and DE150 bid vs. warfarin were observed for adjudicated haemorrhagic strokes (absolute reductions in yearly rates: 0.26% and 0.28%; relative reductions 69% and 74%, p= 0.0001 and <0.0001), ICH (absolute reductions in yearly rates: 0.53% and 0.44%; relative reductions 70% and 59%, p<0.0001 for both) and life-threatening bleedings (absolute reductions in yearly rates: 0.61% and 0.36%; relative reductions 33% and 20%, p=0.0001 and 0.0305). For" time to first haemorrhagic stroke" and "time to first intracranial haemorrhage" both DE Kaplan-Meier curves separated from warfarin after 1-3 months of treatment. For "time to first life-threatening bleed" the DE110 bid curve separated after 3 months- and the DE150 bid curve separated after approximately 12 months of treatment. The effect of both DE dosages on ICH was remarkably consistent across a wide range of sub-groups ((i.e. age, body weight, centre INR, +/- use of concomitant ASA).

In addition to the generally increased risk of bleeding in the elderly population, the above-mentioned safety outcomes are also somewhat offset by opposing effects on gastrointestinal bleedings. Based on the data provided in the response to the D120 LoQs a clear association between DE-treatment and GI-bleeding seem to exist. The yearly event rates of GI MBEs were higher for DE110 bid (1.14%) and DE150 bid 1.57%) when compared to warfarin (1.07%) resulting in a statistically significant increased risk for DE150 bid vs. warfarin (HR=1.47 (95% CI: 1.17, 1.85; p=0.0008). A clear separation of the DE150 bid Kaplan-Meier curve was apparent after just a few days of treatment. The separation remained throughout the study. This significantly increased risk also included GI life-threatening MBEs and "any GI bleeds". The observed GI MBEs were dose dependent. The risk of GI MBEs is highly correlated to age (please refer to discussion above on dosage in the elderly population).

For the overall population the risk of GI major bleeding while on DE is outweighed by the benefits obtained on stroke/SEE and in particular on ICH. The frequency of ICH is lower for both DE doses for all age groups. Though the absolute difference in ICH was low, the clinical relevance is considered significant due to the most often devastating consequences of ICH. The risk of GI-bleedings is mentioned in the SmPC. For the sub-group of patients on "PPI only during treatment" 6.2%, 10.2% and 8.2% experienced a major GI bleeding on DE 110bid, DE 150bid and warfarin, respectively. It is likely that caution should be given for patients on PPI upon initiation of DE treatment as well as for patients on DE who experience symptoms or signs necessitating initiation of PPI treatment. Data provided in the D180 LoOIs proved reassuring effect of both dosages of DE on stroke/SEE, ICH and deaths for these subgroups. The lower dose of DE may be appropriate in these cases as 400 GI MBE (pr. 10.000 patients) could be avoided on DE 110 bid compared to DE 150 bid.

No antidote is available for neutralisation of the anti-thrombotic properties of DE treatment. This is a matter of concern for DE treated patients undergoing acute surgical interventions. In the response to the D120 LoQs the MAH provided reassuring data indicating that the rate of outcome events (stroke/SEE, MBE, minor bleedings or death) in subjects with interruption of anticoagulant therapy for emergency surgery and procedures were similar between DE (110mg and 150mg) and warfarin. With respect to the incidence of AEs in general, the safety of DE 110bid and DE 150bid was comparable to warfarin. The most frequently occurring AEs were dyspnoea (8.3%, 8.7% and 9.2% for DE110 bid, DE150 bid, and warfarin, respectively), dizziness (7.6%, 7.6%, and 9.3%), and oedema peripheral (7.5%, 7.3%, and 7.6%), in which warfarin subjects had the highest incidence in all cases. An

exception was however, GI AEs for which the DE treatment groups had higher frequencies than warfarin (DE110 bid: 34.6%; DE150 bid: 34.5%; warfarin: 24.1%). Diarrhoea, dyspepsia, and nausea were the most frequently reported GI AEs. The risk for dyspepsia with DE appeared during the first few weeks of treatment and remained doubled compared to warfarin throughout the study. Though, the rates of dyspepsia were higher in both DE groups vs. warfarin, this finding as such seemed not associated with an increased risk of GI bleedings in the DE groups vs. the warfarin group. Deaths were slightly higher in the warfarin group (8.1% vs. 7.2% and 7.4% in the DE150 bid and DE110 bid treatment groups), mainly due to a higher frequency of "other vascular deaths", but appeared otherwise overall comparable between the treatment groups. Approximately 60% of all deaths were vascular deaths (the majority hereof CV deaths), the remaining were non-vascular deaths. The incidence of AEs with fatal outcome was overall comparable between the treatment groups.

Serious adverse events occurred with a similar incidence in all treatment groups and were consistent with an elderly AF population. The most frequently reported SAEs were cardiac failure congestion (1.4%, 1.0%, and 1.2% for DE110 bid, DE150 bid, and warfarin groups, respectively), pneumonia (1.2%, 1.2%, and 1.0%), AF (1.1%, 0.9%, and 1.2%), and cardiac failure (0.9%, 1.0%, and 1.1%). As discussed in the efficacy section, patients treated with DE had a numerically increased risk of MIs (DE 150 mg bid vs. warfarin: 1.27 (95% CI: 0.94, 1.71; p=0.1240; DE 110 mg bid vs. warfarin: 1.29 (95% CI: 0.96, 1.75; p=0.0929).). As regards interactions, concerns of increased bleeding risk are raised with concomitant medications with P-gp inhibitors or other antithrombotic therapies (clopidogrel, ASA). Adequate warnings in the corresponding sections of the SmPC (4.2., 4.4., and 4.5.) were introduced on each concomitant drug.

2.6.2. Conclusions on the clinical safety

The risk of major bleeds was significantly lower for patients randomised to DE 110 bid vs. patients randomised to warfarin. A qualitatively similar signal, albeit not statistically significant, was observed for patients randomised to treatment with DE150 bid. The main localisations of MBE were intracranial for warfarin and gastrointestinal for dabigatran. When looking into the components of MBEs both DE dosages significantly decreased the risk for haemorrhagic strokes, life-threatening bleedings and ICH vs. warfarin. Not unexpectedly, the outcome associated with warfarin improves with increasing TTR. The presented analyses clearly demonstrated that the benefits of DE vs. warfarin diminished if INR control was good with TTR >70%. This seemed particularly true for patients > 75 years - in these patients MBE and NCB were numerically highest in the DE treatment groups. Notwithstanding these observations ICH were consistently lowest in the DE treatment groups. Some major safety concerns have been identified in the DE groups, which are mainly related to risk of bleeding in the elderly, the risk of GI bleedings and myocardial infarction. These safety issues have been discussed by the MAH in the response to the D120LoQs and were solved by appropriate SmPC wording: due to the general fragility of the elderly population the increased rates of MBEs and GI-bleedings are worrisome. The NCBs (composite of stroke, SEE, PE, acute MI, all cause death and MBE) of DE110 bid and DE150 bid were not in favour of DE for patients ≥ 80 years. This was primarily due to an increased incidence of GI bleedings. Based on a favourable effect of DE110 bid vs. warfarin on stroke/SEE and in particular on ICH and a reduced risk of MBE for DE110 bid vs. DE 150 bid a dose reduction to 110 mg seems to be appropriate for the elderly ≥ 80 years of age. The same dose recommendation seems acceptable for the very elderly ≥ 85 years though the data are more limited in this sub-group of very elderly. DE110 bid should not be systematically recommended to patients between 75-80 years. DE110 bid should be individually envisaged in at risk patients, since the bleeding rates were decreased with this dosage in those patients.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system has deficiencies that should be addressed as part of the follow up measures.

Risk Management Plan

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

Table 13 Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important identified risk Bleeding	**<u>Routine Pharmacovigilance Activities</u>** **<u>Additional Pharmacovigilance Activities</u>** Two observational studies to investigate the safety and efficacy of Pradaxa for the prevention of venous thromboembolism in patients undergoing elective total hip or knee replacement surgery in: 1) a routine clinical setting (study 1160.85) 2) patients with moderate renal impairment (study 1160.84). Study 1160.71 RELY-ABLE: a long term multi-center extension of dabigatran treatment in patients with AF who completed the RE-LY trial to establish the long term safety of DE. Study 1160.86: An open-label, pharmacokinetic and pharmacodynamic phase IV study to evaluate the effect of DE on coagulation parameters including a calibrated thrombin time test (Hemoclot®)* in patients with moderate renal impairment undergoing elective total knee or hip replacement was initiated. * A test kit for thrombin time measurement (Hemoclot®) developed by HYPHEN BioMed and registered in Europe. Study 1160.136 GLORIA-AF: International multicentre, prospective observational study including patients newly diagnosed with nonvalvular atrial fibrillation at risk of stroke, to increase knowledge on: characteristics of patients with nonvalvular AF at risk of stroke, treatment of patients for prevention of stroke and systemic embolism, mode of prescription and use in a real-world setting including characteristics of prescribing physician / site and influence on outcomes. Events of interest: bleeding events, stroke, systemic embolism, PE, TIAs, MIs, death, and side effect profile of DE. Prescriber/ partient survey will be performed in order to monitor the effectiveness of risk minimisation	**<u>Routine risk minimisation activities</u>** In Sections 4.2 and 4.4 of the SmPC a detailed description of populations potentially at higher risk of bleeding and recommendations for dose reduction is given In Section 4.5 of the SmPC a detailed description of drug-drug interaction that might lead to an increased risk of bleeding events has been included. In Section 4.8 of the SmPC bleeding is listed as an undesirable effect. In Section 4.9 of the SmPC information is given on how to manage overdose situations. **<u>Additional risk minimisation activities</u>** **Educational materials** target to prescribers and patients: a) **Prescriber guide** (one for each indication) focused on recommendations for dose reduction in at risk populations, management of overdose situations and the use of coagulation tests and the interpretation thereof. b) **Patient alert card** to reinforce patient counselling about signs and symptoms of bleeding, the importance of treatment compliance and the necessity to inform Health Care Providers that they are taking Pradaxa in case of any surgery or invasive procedure.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	activities.	
Important identified risk	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities**
Gastrointestinal disorders		Gastrointestinal haemorrhage, abdominal pain, diarrhoea, dyspepsia, nausea, rectal haemorrhage, haemorrhoideal haemorrhage, gastrointestinal ulcer, gastrooesophagitis, gastrooesophageal reflux disease, vomiting, and dysphagia are listed in Section 4.8 of the SmPC as undesirable effects.
Important identified risk	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities**
Hypersensitivity		Drug hypersensitivity, rash, pruritus, urticaria, and bronchospasm are listed in Section 4.8 of the SmPC as undesirable effects.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important potential risk Hepatotoxicity	**Routine Pharmacovigilance Activities** **Additional Pharmacovigilance Activities** Two randomised, double-blind and controlled studies: Study REMEDY 1160.47, trial ongoing; active controlled study to investigate the efficacy and safety of DE compared to warfarin for the secondary prevention of venous thromboembolism, trial size 2,200 patients. Study RECOVER 1160.53, trial completed, phase III study of the efficacy and safety of DE compared to warfarin for 6 months treatment of acute symptomatic venous thromboembolism, 2539 patients treated. Study 1160.71 RE-LYABLE: see above	**Routine risk minimisation activities** 4.3 Contraindication: Treatment in patients with hepatic impairment or liver disease expected to have any impact on survival is contraindicated. 4.4 Special warning: Use is not recommended in patients with elevated liver enzymes > 2 ULN due to the lack of experience. 4.8 Undesirable effects: Increase of hepatic enzymes is listed in Section 4.8 of the SmPC as undesirable effect.
Important potential risk Myocardial infarction	**Routine Pharmacovigilance Activities** **Additional Pharmacovigilance Activities** Study 1160.71 RE-LYABLE: see above Study 1160.136 GLORIA-AF: see above	**Routine risk minimisation activities** 4.4 Precautions and warnings The risk of myocardial infarction in patients treated with Pradaxa compared to that in patients treated with warfarin is described. 4.8 Undesirable effects A statement is provided that the annual MI rate for DE was increased from 0.64% (warfarin) to 0.82% (DE 100 mg bid) / 0.81% (DE 150 mg bid) in the RE-LY study.
Important potential risk Pulmonary embolism	**Routine Pharmacovigilance Activities** **Additional Pharmacovigilance Activities** Study 1160.71 RE-LYABLE: see above Study 1160.136 GLORIA-AF: see above	Not applicable.

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important missing information Renal impairment (CrCl ≤ 30 ml/ min)	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities** 4.3 Contraindications Treatment of patients with severe renal impairment (CrCl ≤ 30 ml/ min) is contraindicated.
Important missing information Patients with liver impairment (liver enzymes > 2 upper limit of normal)	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities** See above: Important potential risk Hepatotoxicity
Important missing information Pregnant and lactating women	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities** 4.6 Fertility, pregnancy and lactation The lack of information on fertility, pregnancy and lactation in humans is described. Breastfeeding should be discontinued during treatment. Pradaxa should not be used during pregnancy unless clearly necessary.
Important missing information Patients under 18 years	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities** 4.2 Posology and method of administration A statement that there is no relevant use in paediatric patients is provided. Not recommended for the use in patients below 18 years due to lack of data on safety and efficacy.
Important missing information Patients with low body weight	**Routine Pharmacovigilance Activities**	**Routine risk minimisation activities** 4.2 Posology and method of administration Recommendations about the use in patients with a body weight < 50 kg are given.

The CHMP, having considered the data submitted in the application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- The MAH shall provide an educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use Pradaxa. This educational pack is aimed at

increasing awareness about the potential risk of bleeding during treatment with Pradaxa and providing guidance on how to manage that risk.

- The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authority prior to distribution of the educational pack. The educational pack must be available for distribution for both therapeutic indications prior to the launch of the new indication (prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors) in the Member State.
- The physician educational pack should contain:
    - The Summary of Product Characteristics
    - Prescriber Guide
    - Patient Alert Cards
- The Prescriber Guide should contain the following key safety messages:
  - Details of populations potentially at higher risk of bleeding
  - Recommendations for dose reduction in at risk populations
  - Management of overdose situations
  - The use of coagulation tests and their interpretation
  - That all patients should be provided with a Patient alert card and be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure.

- The Patient alert card should contain the following key safety messages:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance
    - Necessity to carry the Patient alert card with them at all times
    - The need to inform Health Care Professionals that they are taking Pradaxa if they need to have any surgery or invasive procedure.

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

The pivotal trial, RELY (1160.26), compared dabigatran with the current standard warfarin for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation. A relevant patient population including patients with considerable cardiovascular comorbidities, advanced age, reduced renal function, stroke risk profiles, and concurrent medications has been enrolled. In contrast to recent AF trials (SORTIF III and IV, ACTIVE-W, AMADEUS) patients were balanced as regards their previous VKA use. Superiority of DE150 bid vs. warfarin was demonstrated for the primary endpoint "time to first occurrence of stroke/SEE", and non-inferiority was demonstrated for

DE110 bid vs. warfarin. The Kaplan Meier curves suggest that the effect is consistent over time. The primary endpoint was driven by strokes; systemic embolisms (SSE) were very rare in all treatment groups. Approximately half of all strokes were disabling, with no significant differences between treatment groups. Haemorrhagic strokes and intracranial haemorrhages (ICH), though overall rare, were considerably reduced for either dose of dabigatran compared to warfarin. The benefit of both dabigatran dosages vs. warfarin on ICH was remarkably consistent across a large variety of subgroups (i.e. age, body weight, centre INR, +/- use of concomitant ASA). Also for the secondary endpoints, the composites of "stroke, SEE and all cause death", as well as "stroke, SEE, PE, MI and vascular death" DE150 bid was superior to warfarin. As described below, some of the components of the latter composite were, however, in favour of warfarin. Not unexpectedly, the quality of warfarin treatment as expressed by the time in therapeutic range (TTR) influences the comparisons between dabigatran and warfarin. The outcome of warfarin treatment improved with increasing TTR and the presented analyses clearly demonstrated that the benefits observed in the comparison of dabigatran to warfarin diminished if INR control was good with TTR >70%. This was reflected in Section 5.1 of the SmPC. Still, for the overall population as well as for patients ≥ 75 years of age DE150 bid appeared more attractive with respect to the primary endpoint (prevention of stroke/SEE) when compared to warfarin at centres with TTR ≥70%. DE110 bid appeared comparable to warfarin in this case.

Choice of dabigatran dosages: Two DE dosages of 110 mg bid and 150 mg bid have been proposed by the MAH for this extension of indication. The overall results demonstrated an overall positive benefit for both dosages on the primary composite efficacy endpoint (stroke/systemic embolism) and safety (decrease or similar overall bleedings) compared to warfarin. Age factor is of paramount importance as in real life, elderly patients will certainly constitute the main target population of non valvular AF patients. Despite higher bleeding rates on DE in elderly ≥ 75 years, DE110 bid should not be systematically recommended to patients between 75-80 years as the effect of DE110 bid on stroke/SEE is lower than DE150 bid (but still favourable vs. warfarin). Thus, for patients ≥75 years of age 68 MBE and 3 ICH (out of 10000 patients) would be avoided with DE110, but 46 additional strokes/SEEs would be experienced compared with DE150. It was concluded that DE110 bid can be individually envisaged in at risk patients, since the bleeding rates are decreased with this dosage in patients ≥ 75 years. In contrast for patients ≥ 80 years, DE110 bid seems to be the appropriate dose: ten additional stroke/SEE would be experienced however 99 MBE and 37 ICH would be avoided with DE110 bid compared to DE150 bid. Data for the elderly ≥ 85 years are more limited. With DE110 bid 53 more stroke/SEE would be observed but 128 MBE and 63 ICH would be avoided as compared to DE150 bid. Though the overall death rates were higher in very elderly treated with dabigatran as compared to warfarin (DE110 bid: 11.13%; DE150 bid: 9.25%; warfarin: 7.95%) the frequency of vascular death was similar between the 3 groups (DE110 bid: 5.33%; DE 150 bid: 4.73%; warfarin: 4.64%). The rates of overall death should also been seen in the context of the benefit of DE 110bid on often debilitating strokes and ICH in these very elderly patients.

Despite slightly higher exposure of DE in patients with moderate renal impairment, low body weight or patients of female gender no dose reduction is considered necessary for the overall population.

The risk of major bleeds was significantly lower for DE110 bid treated patients vs. patients treated with warfarin (HR 0.80 (95% CI: 0.70, 0.93; p=0.0026)). No significant difference was observed for DE 150bid treated patients (HR 0.93 (95% CI: 0.81, 1.07; p=0.3146)). Nonetheless, subgroup analyses showed, that patients <75 years of age had a significantly lower risk of major bleedings with either dose of DE compared to warfarin (results on MBEs are based on analyses including outcome events identified after data base lock). The risk of life-threatening bleedings and ICH were statistically significantly reduced for either dose of DE compared to warfarin. Despite low absolute numbers of ICH,

the benefit of both dabigatran dosages vs. warfarin was remarkably consistent across a large variety of subgroups (i.e. age, body weight, centre INR, +/- use of concomitant ASA).

The lack of need for dose adjustments and monitoring during treatment with dabigatran is regarded as a benefit vs. warfarin treatment. In addition to the lack of food interactions, dabigatran has a different interaction profile compared to warfarin, offering a treatment alternative based on patients' co-medication.

- Uncertainty in the knowledge about the beneficial effects.

Study design: In the RELY study, patients and investigators were not blinded to warfarin or dabigatran treatments. Blinding was only kept as regards the two doses of dabigatran treatment. It cannot be excluded that the unblinded study design may have influenced the outcomes of the study. Appropriate measures have been implemented to minimise bias but considering that all evidence rest on only one pivotal study, inspections of the sponsor, the CRO and of two sites (in USA and Greece) were conducted. Another reason for the inspections was some discrepancies found by the FDA in the database of the RELY study. The two critical findings at the sponsor's site were mainly due to lack of communication between sponsor and the CRO (which was the PHRI = Population Health Research Institute). The PHRI contract did not specify all the tasks transferred from the MAH. As a consequence the data quality was compromised. Excessive error rate on study critical data was identified by the FDA, in particular severe transcription errors for INR values transferred from CRFs to data listings. Implementation of special measures were required to solve these data quality issues resulting in extensive re-checks on CRF accuracy, data plausibility and consistency checks (between the CRF and database). This has been done and this issue was regarded by the CHMP as resolved. While the study was conducted perfectly at the inspected US site, from a clinical point of view one critical and one major finding identified at the Greek investigator site 901 were considered of importance. Large gaps between two consecutive INR controls were identified in some patients despite protocol specified gaps of 4 weeks. In addition, INR transcription errors were identified in 5 patients out of 26 patients revised. These findings had the potential to disfavour warfarin vs. dabigatran due to potential reporting of embolic events in patients with INR values ”out of therapeutic range” despite being reported in the study protocol as being in therapeutic range. In 6 of these 8 cases, the investigators placed the patients in therapeutic range despite being below therapeutic range. In the 2 additional cases, the INR was already within therapeutic range either in the source data or in the transcription. There were no cases of placing the INRs out of range despite being within therapeutic range. Hypothetically, INR measurements might be unreliable. It could be argued that this issue is critical in an unblinded study. However the identified Greek findings did not lead to dose-adjustments of warfarin treatment based on wrong INR values, the findings were thus not considered to influence the primary endpoint Stroke/SEE. In response to the D180 LoOIs the MAH provided clarification on the issue, and no additional inspections of other Greek or European sites or further questioning on this issue were deemed necessary. However, the CHMP concluded that the MAH had not adequately addressed the issue of INR transcription errors in patients on warfarin experiencing major events. Therefore, the MAH was requested to provide a review of the chain of INR transcriptions in all warfarin treated subjects who experienced thromboembolic events, myocardial infarction and intracranial haemorrhage. The MAH has thoroughly described the way of collecting source INR data collection and handling of source- and CRF INR data. Based on these descriptions the CHMP was of the opinion that there is no reason to believe that the errors have biased the results in favour of dabigatran.

For the proposed indication the target population and the pattern of use of dabigatran will completely change. The new indication will include a great majority of elderly patients, with prescriptions mainly made by general practioners or cardiologists outside of hospital environment, with a monitoring that could be softened with the time, due to the long-term duration of treatment. The safety consequences

of these important changes have been sufficiently addressed by the MAH in the clinical program. Appropriate prescriber guides (one for both indications) and patient alert cards have been drafted. Also, a drug utilisation study and post-authorisation studies aiming to evaluate the effectiveness of the risk minimisation activities and to assess potential off-label use outside AF will be conducted as specified in the updated RMP and the LoU.

Risks

- Unfavourable effects

The limitation of effective anti-thrombotic therapy is increased risk of bleedings.

Age: Age was a significant factor for MBE. Whereas patients <75 years had a significantly lower risk of MBE with either dose of DE compared to warfarin , the risk for patients aged ≥ 75 years of a MBE was approximately similar for DE 110bid compared to warfarin (HR 1.01 (95% CI 0.83, 1.23) but was higher for DE 150bid vs. warfarin (HR1.18 (95% CI 0.98, 1.43)). Moreover, in very elderly patients > 85 years of age, an increased risk of MBEs was reported even for the low DE dose compared to warfarin. The risk of bleedings in the elderly is mitigated by dosing recommendations. As for the primary endpoint (stroke/SEE) the benefit of DE vs. warfarin also decreased by improved warfarin treatment and INR-control (TTR≥ 70%). This was particularly true for the elderly patients aged ≥ 75 years. The risk of MBE was markedly higher with DE compared to warfarin (yearly rate for DE110 bid 4.26%, for DE150 bid 5.14% and for warfarin 3.58%). The advantage of well controlled warfarin is also reflected in the NCB (composite of stroke, SEE, PE, acute MI, all cause death and MBE) in patients aged ≥ 75 years. However, a significant advantage of warfarin over DE is not evident in any of the provided subgroup analyses.

GI bleedings and GI AEs: GI bleedings occurred notably more frequent in patients randomised to DE. The yearly event rates of GI MBEs were dose dependent for DE (DE110 bid 1.11%, DE150 bid 1.57% vs. 1.07% for warfarin). The increased risk for DE150 bid vs. warfarin was statistically significant (HR=1.47 (95% CI: 1.17, 1.85; p=0.0008). A clear separation of the DE150 bid Kaplan-Meier curve in favour of warfarin was apparent after just a few days of treatment. The separation remained throughout the study. This significantly increased risk also included GI life-threatening MBEs and "any GI bleeds". For both DE dosages post-hoc sub-group analyses of GI MBE suggested that patients <75 years had lower risk of GI MBEs whereas patients aged ≥75 had a significantly higher risk with DE 150bid when compared to warfarin. The risk of GI bleeding is an issue of concern for patients ≥ 75 years but does not change the overall risk benefit of dabigatran. This safety issue necessitated a strong warning in the SmPC, section 4.4. Gastrointestinal adverse events dominated the adverse event profile of dabigatran in this indication, mainly represented by dyspepsia, nausea, abdominal pain and gastritis.

Myocardial infarctions: Another risk is the numerically increased risk of MI for patients randomised to dabigatran when compared to warfarin, although the risk was small in absolute terms (0.81%, 0.82% and 0.64% for DE110 bid, DE150 bid and warfarin, respectively). The increased risk of MI associated with DE (both dosages) vs. warfarin does not seem to decrease over time. No clear pattern was observed when analysed by baseline demographic characteristics, stroke risk factors, $CHADS_2$ score, AF type, baseline medication use or by medication use during study period. A dose response for the risk of MI could not be confirmed. In order to put MI into perspective of other outcomes, yearly event rates and absolute differences to warfarin for several patient sub-groups with high risk of MIs were provided (previous MI; history of CAD and age ≥65 years; diabetes and age ≥65 years; heart failure; LVEF <40%; moderate renal dysfunction). Based on these analyses the benefit of DE on the ultimate outcome of death, still compares favourably to the increased risk of MI. The pathophysiological

mechanism is still unclear and markers that could reveal rebound anticoagulation have not been collected, but the generation of hypotheses is expected from a further sub-study of RELY which is pending (1Q-2Q of 2011). The numerically increased risk of MI with dabigatran is not considered to change the net benefit of DE vs. warfarin. Adequate warning was introduced in section 4.4 of the SmPC. Furthermore, MI is covered as a potential risk in the RMP.

Hepatic function: Patients with active liver disease (including patients with ALT or AST or Alk. Phosphatase elevations 2x upper limit of normal (ULN)) as well as patients with liver enzyme elevations on ximelagatran were excluded from the RE-LY study. In view of the potentially lifelong treatment the follow-up time in the RELY trial was considered limited. A more detailed analysis was performed by the MAH on the events of severe LFT elevations, Hy's law cases and hepatic AEs of interest (hepatic lesions, fatal hepatic failure and deaths with LFT elevations). The data confirm the low potential of hepatotoxicity of DE.

Patients with GI disorders requiring PPI: For patients "on PPI only during treatment" an increased risk for major GI bleed was observed (6.2%, 10.2% and 8.2% for DE 110bid, DE 150bid and warfarin, respectively). The risk seemed disproportionately higher for DE 150mg bid vs. warfarin for patients "on PPI only during treatment" compared to patients "never on PPI" and "on PPI at baseline". It is likely that caution should be given for patients on PPI upon initiation of DE treatment as well as for patients on DE who experience symptoms or signs necessitating initiation of PPI treatment. The lower dose of DE may be appropriate in these cases.

- Uncertainty in the knowledge about the unfavourable effects

Renal impairment: Patients with severe renal insufficiency have not been studied in RELY. This is already a contraindication for the use of Pradaxa. Patients with moderate renal failure were at increased risk of bleedings in both treatment groups with no evidence of dose-effect relationship, however, based on clinical data, no dose-reduction is considered necessary in the SPAF indication.

Pulmonary embolism: Apart from the increased risk for MIs, there was also a weak signal for an increased risk of PE with DE. PE is covered as a potential risk in the RMP.

Body weight: The rate of MBEs increased by decreasing body weight in all treatment groups however, there was no obvious impact of weight on the benefit risk of dabigatran vs. warfarin in this indication.

Biological monitoring test/antidote: An appropriate biological test that display a linear relationship with plasma concentrations, with a high level of sensitivity and that allows comparisons between laboratories is essential for drug monitoring. The Hemoclot assay is a diluted thrombin time coagulation assay which can be calibrated with lyophilised dabigatran standards for quantitative assessment of dabigatran concentrations in plasma. The Hemoclot assay is now available on the market.

Guidance has also been provided in the SmPC on how to handle DE before and after surgical interventions, in emergency situations and overdosing, and when switching from other anticoagulants to DE.

Benefit-risk balance

- Importance of favourable and unfavourable effects

Systemic embolism and in particular strokes are important outcome parameters in prevention therapy in patients with non-valvular AF due to the most often disabling nature of these events. Estimated annual incidence of stroke in the non-treated AF population ranges from 2-5% per year in moderate risk subjects to 5-10% per year in high risk subjects. In view of these considerations the clearly

favourable efficacy of DE vs. warfarin on strokes across all age groups including both ischaemic (constituted the majority of the strokes) and haemorrhagic strokes is considered clinically meaningful.

The limitation of effective anti-thrombotic therapy is the bleeding risk. Particularly the risk of major- and life-threatening bleedings is of importance, as this can lead to a higher risk of morbidity and death. The increased risk of MBE in the elderly population ≥ 75 years of age for DE vs. warfarin is considered of major clinical relevance due to the fragility of this population. In addition, the risk may potentially affect the sub-populations of patients at high risk of bleeding or with expected higher exposure to DE (e.g. moderate renal failure, female gender, low body weight).

The risk of GI MBE bleedings was significantly higher for DE (150 mg) vs. warfarin. In addition, an increased risk of MIs seems to be associated with DE treatment. These unfavourable findings must be counterbalanced against the beneficial effects.

It should be noted however, that life-threatening bleedings were significantly reduced for either dose of DE compared to warfarin. In addition, the data presented on all-cause mortality (analysed as a secondary efficacy endpoint) are reassuring. For patients allocated to treatment with DE110 bid or DE150 bid the relative risk compared to patients treated with warfarin was 0.91 ((0.80-1.03), p=0.1308) and 0.88 ((0.77-1.00), p=0.051), respectively. The data for vascular death were 0.90 ((0.77-1.06), p=0.2081) and 0.85 ((0.72-0.99), p=0.043), respectively.

- Benefit-risk balance

The overall risk of strokes has decreased in recent AF trials due to improved treatment of risk factors such as hypertension and heart failure. In view of this, the reduced risk of stroke/SEE in DE150 bid treated patients vs. warfarin treated patients is a significant clinical benefit. Also of clinical benefit is the decreased risk of intracranial haemorrhage, the perhaps most serious and devastating bleeding complication with VKA. Although absolute reductions were small, the relative reductions in comparison to warfarin were marked and consistent across a large variety of sub-groups.

Clinically important is also the fact that the favourable outcome on the primary efficacy outcome seemed not counterbalanced by an increased risk of major bleeding, at least in patients aged less than 75 years. The increased risk of bleeding in the elderly ≥ 75 years and in particular ≥ 80 years is worrisome due to the fragility of this population. Specific dosing recommendations are warranted for this population to mitigate this risk. Warnings for patients at high risk of bleeding as well as for patients expected to have higher exposure to DE (female gender, low body weight, moderate renal failure, concomitant use of P-gp inhibitors) have been included in the SmPC.

Dabigatran was associated with an increased risk of gastrointestinal bleedings (including all GI bleedings, GI MBEs and GI life-threatening bleedings). GI bleedings were associated with concomitant medication with ASA, clopidogrel, and NSAIDs, additionally to GI disorders requiring treatment with PPI and H2 blockers. Moreover, a significant interaction of major GI bleed for age ≥ 75 years was observed. The risk of GI bleedings did not change the overall benefit of DE vs. warfarin and specific dosing recommendations for the elderly as well as for certain sub-groups (subjects with known gastritis, esophagitis, or gastroesophageal reflux; subjects experiencing gastritis, esophagitis or gastroesophagial reflux while taking dabigatran; patients treated with proton pump inhibitors or H2 blockers) were implemented in the SmPC.

The pathophysiological mechanism behind the numerically increased risk of MI associated with DE treatment is not understood. Despite the potential serious outcome of such events, the overall benefit risk of DE is not considered affected by this finding due to the beneficial effect on stroke/SEE and in particular ICH. However, strong warnings have been inserted in the SmPC and MI has been included as a potential risk in the RMP.

In addition to the above discussion, the reduced risk for all cause death is reassuring though the difference vs. warfarin for either dose of DE was not statistically significant.

It should also be noted that global INR control in RELY, although being comparable to contemporary trials in this indication, was not optimal from a Northern/Western European standard. When MBE were analysed by time in therapeutic range (TTR) the outcome of warfarin treatment for the overall population improved with increasing TTR. For centres with TTR ≥ 70% the MBE rates were marginally higher for DE150 bid vs. warfarin. Still, for this population the rates of stroke/SEE, stroke/SEE/death and ICH were in favour of DE150 bid when compared to warfarin. Thus, due to the devastating effects of ICH the B/R of DE150 vs. warfarin is positive also when compared to well controlled warfarin treated subjects.

Also GI AEs were considerably more frequent with DE compared to warfarin. These adverse events may result in poorer compliance and risk of under-treatment. GI AEs occurred with approximately the same magnitude in the pivotal VTE prevention trials as in the RELY trial, however, in the VTE program they were not more frequent as for the comparator enoxaparin.

2.8.1. Discussion on the benefit-risk balance

Overall, both efficacy and safety of DE110 bid and warfarin in the prevention of stroke in nonvalvular atrial fibrillation was considered by the CHMP comparable. The superior efficacy of DE 150 bid vs. warfarin on primary endpoint (stroke/SEE) and on ICH was considered of major clinical relevance.

Risk management plan

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

Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns and the following additional risk minimisation activities were required: educational pack for each therapeutic indication, targeting all physicians who are expected to prescribe/use Pradaxa.

2.9. Recommendation

The CHMP, having considered the application, recommended the granting of an extension of the Marketing Authorisation for the above mentioned medicinal product concerning a new strength: 150 mg.

In addition, CHMP recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations requested		**Type**
A.7	Administrative change - Deletion of manufacturing sites	IA
B.I.a.2.b	Changes in the manufacturing process of the active substance - Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product	II
B.I.a.2.b	Changes in the manufacturing process of the active	II

Variations requested		Type
	substance - Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product	
B.I.b.1.b	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	IA
B.I.b.1.b	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	IA
B.I.b.1.c	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	IA
B.I.b.1.c	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	IA
B.I.b.1.d	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	IA
B.I.b.1.f	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the active substance	II

B.I.b.1.z	**Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation**	**IB**
B.I.b.1.z	Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	IB
B.I.b.2.a	Change in test procedure for active substance or starting material/reagent/intermediate - Minor changes to an approved test procedure	IA
B.I.b.2.a	Change in test procedure for active substance or starting material/reagent/intermediate - Minor changes to an approved test procedure	IA
B.II.b.2.a	Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	IA
B.I.c.3.z	Changes in the test procedure for the immediate packaging of active substance - Other variation	IB
B.II.b.1.a	Replacement or addition of a manufacturing site for the FP - Secondary packaging site	IA
B.II.b.1.a	Replacement or addition of a manufacturing site for the FP - Secondary packaging site	IA
B.II.b.1.e	Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.	IB
B.II.b.2.a	Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	IA
B.II.b.3.b	Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	II
B.II.b.4.z	Change in the batch size (including batch size ranges) of the finished product - Other variation	IB
B.II.b.4.z	Change in the batch size (including batch size ranges) of the finished product - Other variation	IB
B.II.b.5.a	Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	IA
B.II.b.5.c	Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	IA

B.II.b.5.z	**Change to in-process tests or limits applied during the manufacture of the finished product - Other variation**	**IB**
B.II.b.5.z	Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	IB
B.II.b.5.z	Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	IB
B.II.d.1.a	Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	IA
B.II.d.2.a	Change in test procedure for the finished product - Minor changes to an approved test procedure	IA
B.II.d.2.z	Change in test procedure for the finished product - Other variation	IB
B.II.e.3.z	Change in test procedure for the immediate packaging of the finished product - other variation	IB
B.II.e.3.z	Change in test procedure for the immediate packaging of the finished product - other variation	IB
B.II.e.5.a.2	Change in pack size of the finished product – Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	IB
B.II.f.1.a.1	Stability of FP – Reduction of the shelf life of the finished product - As packaged for sale	IA
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Update of the SmPC to include a new indication for the new strength (150 mg) and for 110 mg strength: Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more of the following risk factors: Previous stroke, transient ischemic attack, or systemic embolism (SEE); left ventricular ejection fraction < 40 %; Symptomatic heart failure, ≥ New York Heart Association (NYHA) Class 2; Age ≥ 75 years; Age ≥ 65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension.

In addition it concerns changes to the first generation synthesis, and the addition of an alternate routes of synthesis. It further concerns changes to the first generation synthesis related to the specifications and suppliers of starting materials and intermediates, testing of the drug substance and specification of the same. The application also concerns a new drug product manufacturing method and further changes related to manufacture, in-process controls, testing, specifications and shelf-life of the drug product for the registered and the new 150 mg strengths.

Finally, information addressing FUM 005, related to the development of a new in-process control at the isolation step, has been also presented.

As well as the refusal of the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation requested		**Type**
B.II.d.1.e	Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	II

Widening of the shelf-life limits for degradation products in the specification of 75 mg and 110 mg capsules in PP bottles.

Based on batch results and stability results in both packaging materials the proposed changes in shelf-life limits of some related substances are not justified from the presented data on three strengths manufactured according to the 2nd gen DP process and therefore the proposed change is not accepted.