European Medicines Agency
Evaluation of Medicines for Human Use

Doc.Ref.: EMEA/174363/2008

CHMP ASSESSMENT REPORT FOR Pradaxa

International Nonproprietary Name:
dabigatran etexilate

Procedure No. EMEA/H/C/829

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

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 85 45
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians
ACS	Acute Coronary Syndrome
AE	Adverse event
aPTT	activated Partial Thromboplastin Time
AUC	area under the curve
b.i.d.; bid (in tables)	Twice daily dosing
BP	Blood Pressure
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human use
CI	Confidence interval
C_{max}	Maximum concentration in plasma
CL_{CR}	Creatinine clearance
CNS	Central nervous system
CRBE	Clinically Relevant Bleeding Events
CT	Computed tomography (also known as: CAT scan)
CTR	Clinical Trial Report
CV	Coefficient of variation
CUS	Compression ultrasound
dabig etex	Dabigatran etexilate
dabig etex 150	Dabigatran etexilate 150 mg
dabig etex 220	Dabigatran etexilate 220 mg
DAB	dabigatran
DE	Dabigatran etexilate
DEM	dabigatran etexilate mesilate
DSC	Differential scanning calorimetry
DTI	Direct Thrombin Inhibitor
DVT	Deep vein thrombosis
ECG	Electrocardiogram
ECT	Ecarin Clotting Time
Emax	maximum effect
EMEA	The European Agency for the Evaluation of Medicinal Products
Enox (in tables)	Enoxaparin
etex	Etexilate
EU	[the] European Union
FAS	Full analysis set
FAS-m	FAS-major; Full analysis set -major
FUM	Follow-up Measure
GC	Gas chromatography
GCP	Good clinical practice
GLP	Good laboratory practice
GMP	Good manufacturing practice
HIT	heparin–induced thrombocytopenia
HPLC	High performance liquid chromatography
INR	International Normalized Ratio
i.v.	intravenous
LMWH	Low molecular weight heparin
MBE	Major bleeding event
MID	Minimum Important Difference
mL	Milliliter
MOS	major orthopedic surgery
n	Number
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drugs

p.o. (po, in tables)	*per os*, oral administration
PD	Pharmacodynamics
PE	Pulmonary embolism
PhEur	European Pharmacopoeia
PK	Pharmacokinetic
PT	prothrombin time
q.d. (qd, in tables)	Once daily dosing
s.c.	Subcutaneous
tDVT	Total deep venous thrombosis
THR	total hip replacement
TKR	total knee replacement
TT	thrombin time
UH	unfractionated heparin
U.S.	United States of America
VKAs	vitamin K antagonists
VTE	Venous thromboembolism

1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 01 February 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Pradaxa, through the centralised procedure under Article 3 (2)(a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 29 June 2006.
The legal basis for this application refers to:

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

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

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

The applicant applied for the following indication: "Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery".

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

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

Rapporteur: Steffen Thirstrup Co-Rapporteur: Pierre Demolis

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 1 February 2007.
- The procedure started on 21 February 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 May 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 May 2007.
- During the meeting 18-21 June 2007, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 June 2007.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 6 September 2007.
- The final Integrated inspection report of the inspection carried out in the investigator sites was issued on 19 September 2007.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 30 October 2007.
- During the CHMP meeting 12-15 November 2007, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.

- During the meeting 21-24 January 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Pradaxa on 24 January 2008. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 22 January 2008.
- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 18 March 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

The need to prevent venous thromboembolism (VTE) in patients undergoing total knee [TKR] or hip replacement [THR] surgery is well established. In the absence of VTE prophylaxis, the absolute risk of VTE ranges from 40-60%; hence, prophylaxis should be administered during the period of highest risk. Heparin and especially the low molecular weight heparins (LMWH) are the most commonly used anticoagulants for the prevention of VTE after major orthopedic surgery (MOS). More recently, fondaparinux has been also recommended. Additionally, vitamin K antagonists (VKAs) are also frequently used in some countries. These drug classes are highly effective therapeutic agents. However, heparin and its derivatives, as well as fondaparinux, must be administered parentally, making self administration both challenging and less desirable. Moreover, unfractionated heparin and, to a lesser extent, the LMWH can cause heparin–induced thrombocytopenia (HIT), a rare but potentially life-threatening adverse event. Warfarin and other VKAs are given orally; however, their use is associated with numerous limitations. These include a high potential for food-drug interactions and drug-drug interactions, which necessitates the need for frequent monitoring of INR and occasional dose adjustments. In addition, VKAs have a slow onset and offset of action, which may limit their effectiveness as prophylactic agents for the prevention of VTE, since the peri-operative period is when the risk of thrombosis formation is greatest. Consequently, bridging therapy with a parenteral agent may be necessary at the initiation of therapy. Given the limitations and inconveniences of currently available agents, many patients do not receive satisfactory anticoagulant therapy or stop it too early. There is a significant need for a fixed dose anticoagulant that is at least as effective as available anticoagulants, which can be given orally, and is free from the challenges of VKAs.

Dabigatran etexilate (DE) is a potent, synthetic, non-peptide competitive, rapidly acting oral direct thrombin inhibitor (oral DTI). DE is the oral pro-drug of the active moiety dabigatran (DAB) and does not possess anticoagulant activity. The pro-drug dabigatran etexilate is used in its salt form dabigatran etexilate mesilate (DEM). That specifically and reversibly inhibits thrombin, the final enzyme in the coagulation cascade. The granted indication is primary prevention of VTE in patients undergoing elective MOS [(THR or TKR)]. The recommended dose is 220mg once daily taken as 2 capsules of 110mg. For patients with moderate renal impairment or aged above 75 years, the recommended dose is 150mg once daily taken as 2 capsules of 75mg. The treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days in knee surgery and 28-35 days in hip surgery. The Phase III DE programme for the primary prevention of VTE consisted of three studies: two European (EU) studies, considered as pivotal, and a supportive North American study. These studies were designed to be as similar as possible. However, the significant differences in practice patterns, registered doses of comparator drugs and differing recommendations for the duration of prophylactic therapy for different types of surgery (hip vs. knee) necessitated some differences in the Phase III study designs, which are discussed in the relevant sections of this document.

A recommended primary endpoint in therapeutic confirmatory trials as written in the CHMP Guideline (CPMP/EWP/ 707/98) is a composite endpoint consisting of clinically relevant and objectively documented events including venographically documented proximal DVT, symptomatic and well-documented non-fatal pulmonary embolism (PE) and VTE related death or death due to any cause. However, despite the total DE development program including over 8000 patients, the individual studies were not thought to be sufficiently powered to reliably assess efficacy for the composite endpoint including proximal DVT, symptomatic VTE and VTE related death (= major VTE and VTE related death).

A meta- analysis was pre-specified in order to evaluate the effects of DE on the composite endpoint specified in the CHMP Guideline (CPMP/EWP/ 707/98). This approach could justify the deviation from the CHMP Guideline if the results of the individual pivotal trials show non-inferiority compared to enoxaparin. This could not be shown in supportive US study. That is why the meta-analysis was considered of exploratory, not of the confirmatory nature.

The introduction of UH and later LMWH as standard prophylactics has reduced the frequency of major VTE and VTE related mortality significantly. Therefore large study populations are needed in order to show non-inferiority. Therefore, a "new" surrogate end-point was proposed which occurs with a higher frequency in order to keep the study population at a reasonable size. Total VTE and all-cause mortality was used during the treatment period as such "new" surrogate marker. Major VTE and VTE related mortality was chosen as one of the secondary endpoints. The MAA for DE was submitted prior to the revision of the CHMP Guideline (CPMP/EWP/ 707/98/Rev 1).

2.2 Quality aspects

Introduction

Dabigatran etexilate has been developed as an orally active anticoagulant for the prevention of venous thromboembolic events in patients who have undergone elective total hip or knee replacement surgery. It is available as 110 mg and 75 mg hard capsules for oral administration presented in aluminium / aluminium blisters or in polypropylene bottles with desiccant.
The recommended dose is 220 mg once daily taken as 2 capsules of 110 mg. For patients with moderate renal impairment the recommended dose of dabigatran etexilate is 150 mg once daily, taken as 2 capsules of 75 mg.
The maximum daily dose for dabigatran etexilate mesilate (DEM) is 300 mg.

Active Substance

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 $C_{35}H_{45}N_7O_8S$. The molecular mass is 723.86 for the salt and 627.75 for the free base.
Dabigatran etexilate is the pro-drug of the active substance, dabigatran which corresponds to the molecular formula $C_{25}H_{25}N_7O_3$ and molecular mass 471.5.
DEM is a yellow-white to yellow non-hygroscopic powder. The partition coefficient of the neutral form (free base) is logP = 3.8, pKa1 = 4.0 ± 0.1 pKa2 = 6.7 ± 0.1. Solubility is strongly pH dependent with increased solubility at acidic pH. The solubility in water is 1.8 mg/ml. DEM is freely soluble in methanol, soluble in ethanol, sparingly soluble in isopropanol, very slightly soluble in acetone and practically insoluble in ethyl acetate.
It has no chiral centers and therefore does not form enantiomers. Geometric isomers (tautomers) are possible.
DEM exhibits polymorphism. Two forms, modification I and II are known. The drug substance is modification I in the anhydrous form and is routinely produced by the commercial method of synthesis. A hydrated form with a stoichiomety close to a hemihydrate also exists.

- Manufacture

The active substance is synthesised in 3 steps and a number of recrystallisation steps on intermediates and the final substance. Protection from humidity is implied during manufacturing and storage to prevent hydrolysis of the pro-drug forming moieties and polymorphic form transformations. Extensive experimental work and scientific evaluation of the potential carryover of these impurities and their derivatives during further process steps were carried out. These experiments prove that the proposed acceptance criteria for the identified impurities in each isolated intermediate are appropriate and ensure that these impurities (as well as their potential derivatives) are removed by extraction and purification procedures of the synthesis process to remain within the levels specified for the drug substance.

Data showing that alkyl methane sulfonates compounds are not formed during drug substance production have been presented which justify why quality controls in the last step of the synthesis are not necessary.
Appropriate controls in the last step of the synthesis are carried out to ensure the formation of the desired crystalline modification I.

- Specification

The specifications for the control of the drug substance includes tests for appearance (visual), identification (IR), colour and clarity of solution (PhEur), purity and polymorphism (DSC), impurities (HPLC), residual solvents (GC), heavy metals (PhEur), water content (PhEur), sulphated ash (PhEur), assay (HPLC and titration), particle size (Laser-beam diffraction).

The specifications have been established based on analytical release data, stability studies and pharmaceutical development studies. In particular, the limits for organic impurities are based on the batch data for 38 representative clinical batches made according to the commercial synthesis process and on the primary stability data. All results meet the proposed regulatory specifications
The proposed specifications for impurities in the active substance are for some specified impurities above the qualification threshold of the ICH guideline *Impurities in new drug substances*, however toxicological qualification has been presented in Module 4 of the application.
The specification limits for two specific impurities of concern may also be considered to be fully qualified, because they are intermediates metabolites of the active substance and are present in vivo.

- Stability

Stability data were presented for three full-scale production batches of dabigatran etexilate mesilate synthesized according to the proposed commercial process at the commercial site of manufacture. These batches were stored for 12 months under long-term storage conditions (25°C/60% RH) and for 6 months under accelerated conditions (40°C/75% RH).
Additional supportive stability data were available for a pilot scale batch stored for 36 months at long-term conditions (25°C/60% RH). This batch was also synthesized according to the proposed commercial process.
Primary stability studies were conducted in accordance with the ICH Q1A(R2) guideline.
All stability testing was performed according to the regulatory analytical procedures and the data evaluated according to the current specification for the drug substance.
After 12 months storage at 25°C/60% RH, the three primary stability batches did not show unexpected degree of decomposition, which in any case was in line with the supportive stability data available for the drug substance over 36 months at 25°C/60% RH.
The retest period is justified based on the stability results available for 24 months of storage.

Stress stability studies of the drug substance were performed on two batches to elucidate the major degradation pathways. DEM was exposed to various stress conditions (Solid state: elevated temperature, humidity and light irradiation and in aqueous solutions: different pH values, elevated temperature and exposure to oxidizing conditions).
In the solid state, DEM is very stable. After storage for 4 weeks at 70 °C in a closed container, not more than 0.50 % total degradation was observed. The degradation rate of the drug substance is markedly accelerated by the presence of moisture. This behaviour provides the rationale for the selection of a container/closure system that protects the drug substance against exposure to moisture.
In aqueous solution at 40 °C, dabigatran etexilate mesilate undergoes considerable hydrolytic degradation.

The results of the stress stability studies show that dabigatran etexilate mesilate predominately undergoes degradation by hydrolytic pathways.
DEM is not sensitive to light irradiation in the solid state.

Medicinal Product

- Pharmaceutical Development

Based on these physicochemical and biopharmaceutical properties of dabigatran etexilate mesilate, and the clinical requirements for a reliable drug release a multilayer pellet was selected. Active ingredient layered organic acid containing pellets filled into hard capsules were developed as dosage form. Other formulation approaches were evaluated during early development, but were inferior to the selected formulation in terms of drug load, stability and *in vivo* performance.
DEM has low solubility in water and high intrinsic passive permeability, and is considered a Class II compound according to the biopharmaceutical classification system.
The active substance is susceptible to hydrolysis in presence of humidity under acidic conditions, which is why a manufacturing process limiting water and acidic conditions is chosen. Drug substance particle size limits are established to ensure consistent drug product manufacturability.
All of the selected excipients, including HPMC capsule shell, are commonly used in oral commercial pharmaceutical dosage forms and are compendial materials. The selection of excipients and their corresponding levels was based on in vitro dissolution, stability, and in vivo bioavailability studies using various prototype formulations.
The compatibility tests results indicate that all tested active-excipient mixtures are sufficiently stable for selection as an excipient in the intended commercial formulation
HPMC capsule shells were selected because DAB is sensitive to hydrolysis and because of the minimum brittleness of the capsule material, when desiccants used in primary packaging.. Dissolution profiles of gelatine and HPMC capsules demonstrate that the release from the HPMC capsules is delayed from about 25% in 15 min but that no difference is observed at 30min. This difference has no impact on in vivo release. This was confirmed by a relative bioavailability study performed on 150mg strength capsules of HPMC and gelatine.
In the drug product, alkyl methanesulfonates were controlled during development, as these alkyl methane sulfonates might be formed during manufacture and storage of dabigatran etexilate capsules.
The analysis was performed with dabigatran etexilate pellets final stage, either prior to encapsulation or with the final drug product, dabigatran etexilate capsules.
Batch analysis results confirm that alkyl methane sulfonates that could potentially be formed during manufacturing are not formed at detectable levels during the manufacturing of the finished product.

The manufacturing process has been validated during the manufacture of the drug product intermediates and for three batches of 75mg capsules and three batches of 110mg capsules at the production site. Retrospective validation data have been provided for the manufacture of the intermediate products. Holding times of the drug product intermediates have been established.

- Adventitious Agents

None of the excipient used is of animal or human origin.

- Manufacture of the Product

The commercial manufacturing process of dabigatran etexilate capsules 75 mg / capsule and 110 mg / capsule includes the following operations:

- manufacture of drug product intermediates
- final blending resulting in dabigatran etexilate pellets final stage
- encapsulation
- packaging of capsules into blisters or bottles

A standard process is used to produce the pellets to be filled in the HPMC capsules.
The same manufacturing process has been utilised for the primary stability batches and the Phase III clinical batches for dabigatran etexilate capsules which were all manufactured at full commercial batch size with respect to the dabigatran etexilate pellets final stage.

The data gathered during process validation and the provided batch analyses demonstrates that the manufacturing process is robust and consistently yields drug product, which meets the predetermined quality characteristics. The chosen in-process controls have been shown to be suitable for monitoring the manufacturing process.

- Product Specification

The specification for batch release and shelf-life include the following tests: appearance (visual), loss on drying for pellets (gravimetry), loss on drying for capsule shell (gravimetry), identification (at release only) (HPLC, UV), active ingredient content (HPLC), degradation products (HPLC), uniformity of dosage units (at release only) (PhEur), dissolution (PhEur), microbiological purity (Ph.Eur)
Residual solvents are controlled in the intermediate product, dabigatran etexilate pellets final stage, according to the requirements of ICH Q3C(R3).

Batch analysis results of nine batches plus results from three other batches (used for clinical trials) were presented. Supportive batch analysis data for batches manufactured during the different stages of development are also provided. The results comply with the specification and confirm consistency of the product.

- Stability of the Product

Three pilot scale 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 packaging. Batches were of same formulation as proposed for commercial batches, except that the capsules were not imprinted.
Parameters investigated: Appearance, Loss on drying (pellets and shell), degradation products, assay, dissolution, microbial contamination.
No significant changes have been observed after storage at either condition in *PP container*. However, in *alu/alu blister* an increase in all degradation products are observed, most markedly for BIBR1154 at both accelerated and long term conditions. This behaviour is due to the drying capacity of the desiccant in the PP container. Statistical evaluation of BIBR1154, total degradation products and assay, has been presented for the 3 primary stability batches of each strength. Results reveal no marked trend, therefore the proposed shelf life is considered acceptable.

Supportive stability results from one pilot scale 150mg capsule batch were also provided, stored in Alu/alu-blister (with equivalent protective properties as the proposed blister) for 36 months at 25°C/60% RH and 30°C/70%RH, and for 6 months at 40°C/75%RH. No significant changes were observed for any of the tested parameters (appearance, loss on drying, dissolution, degradation and assay) and the proposed shelf life specifications were met after 36 months storage under long-term conditions.

Stability results on formation on methane sulfonic acid alkyl esters impurities in the drug product were presented. These results show there is no risk of the formation of these substances at release and at stability conditions/period of 6 month at 40°C/75%RH and 12 months at 30°C/70%RH.

Stability results on formation of polymorphic form II during storage is presented in separate report. No further conversion to From II is observed even if high amounts of From II was present from t=0. Form II is limited in the drug substance.

In-use stability: The in-use study was carried out on one batch of each strength in proposed PP container. Results support the proposed in-use shelf life for capsules stored in the polypropylene bottle container system with desiccant. Batches used had first been stored for 12 months at 25°C/60%RH, and then simulated use was carried out by periodically opening and closing (twice a day) and removing capsules from the bottle (but still stored at 25°C/60%RH). Testing points were after 0, 14 and 30 days. No change in degradation products is observed.
The in-use study supports the proposed in-use shelf life for capsules stored in the polypropylene bottle container system with desiccant.

Photostability: Light stability study of filled capsules revealed no relevant changes (appearance, dissolution, assay and related substances), which is why no further investigation in primary packaging was carried out which is in agreement with the ICH Q1B guideline.

Stress testing: after one day stored open at 40°C/75%RH loss on drying of pellets and of capsule shell increased for the two strengths, as did the hydrolysis degradation products. After 85 days at 60°C (uncontrolled humidity) no significant changes were observed apart from declining loss on drying results and an increase change in total degradation products. These results were however expected as the finished product is sensitive to moisture.

Based on the stability data obtained and their statistical evaluation the proposed shelf-life and storage condition are accepted, as defined in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Pradaxa hard capsules is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of all the important product quality characteristics. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product. The applicant submitted a Letter of Undertaking dated on 22 January 2008 and committed to resolve these as Follow Up Measures after the opinion, within an agreed timeframe.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.
It can be safely concluded that the product should have a satisfactory and uniform performance in the clinic.

2.3 Non-clinical aspects

Introduction

Pradaxa contains 75 mg or 110 mg of DE, the oral pro-drug of the active moiety dabigatran (DAB). The pro-drug DE is present in its salt form dabigatran etexilate mesilate (DEM). The marketing authorization application dossier for Pradaxa contains data from the preclinical studies performed with DEM.

Pharmacology

- Primary pharmacodynamics

DAB is a novel, 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. DAB also inhibits free thrombin, fibrin-bound thrombin and thrombin induced platelet aggregation. DAB is a specific inhibitor of thrombin that demonstrates anticoagulant and antithrombotic activity both *in vitro* and *in vivo*. *In vivo* it has a relatively wide safety window between antithrombotic efficacy and bleeding side effects. In addition according to general/safety pharmacological profiling, it has no proarrhythmic potential based on *in vitro* and *in vivo* assays and is generally well tolerated. DAB is a synthetic non-peptide compound, which acts as a competitive inhibitor at the active site of thrombin. It inhibits human thrombin with a Ki of 4.5 nM. In contrast to heparin, which acts by augmenting the activity of anti-thrombin, DTIs also inhibit fibrin-bound thrombin, as is observed in a blood clot. DAB is poorly absorbed following oral dosing thus it is orally administered in the form of the pro-drug DEM. Administration of i.v. DAB and p.o. DEM, produces a dose- and time-dependent prolongation of coagulation time in various species. The effect of i.v. pre-treatment with DAB on venous clot formation was investigated in a rat and a rabbit model of venous thrombosis. A 50% reduction in clot size (ED_{50}) was observed following i.v. administration of 33 μg/kg and 66 μg/kg DAB in the rat and rabbit, respectively. DAB did not inhibit platelet aggregation in human plasma following the introduction of various platelet activating factors.

- Secondary pharmacodynamics

DAB exhibited low affinity (Ki>3.5 μM) towards the serine proteases factor Xa, factor XIa, factor VIIa/tissue factor complex, plasma kallikrein, plasmin, urokinase, tissue-type plasminogen activator, activated protein C, granulocyte elastase and C1 esterase. DAB inhibited trypsin with a Ki of 50.3 nM, however the digestive enzyme trypsin does not normally occur in the blood and is not involved in haemostasis. The lack of a broader receptor screen was considered acceptable based on the large battery of safety pharmacology and toxicological studies performed.

- Safety pharmacology programme

Safety pharmacology studies applying i.v. administration of DAB or p.o. administration of DEM revealed no special hazard for acute effects on the function of the cardiovascular system, central nervous system, respiratory system, and renal and gastrointestinal system.

- Pharmacodynamic drug interactions

No non-clinical pharmacodynamic (PD) drug interaction studies were performed that was considered acceptable by the CHMP.

Pharmacokinetics

Absorption

DEM was identified as a medium-affinity substrate for the efflux transporter P-glycoprotein in the human colon carcinoma derived cell line Caco-2. Moreover, DEM inhibited the apical-to-basolateral transport of the P-glycoprotein substrate digoxin in a concentration-dependent manner with an IC_{50} of 25 µM (50-fold clinical C_{max}). A clinical study confirmed that no pharmacokinetic (PK) interactions occur when DEM is co-administered with digoxin. Following single administration, the oral bioavailability of [^{14}C]-DEM was 16% in rat, 5% in rabbit, 8% in Rhesus monkey and 7% in man. The clearance was 4.5 to 6-fold higher in rat, rabbit and monkey when compared to man and consequently the half-life was lower in these species. T_{max} was obtained 0.5 h following p.o. dosing in mouse and rat, at 1.3 h in rabbit and monkey and at 1.5 h in man. No gender differences were observed with respect to absorption following repeated dosing of mice, rats and monkeys. No consistent trend towards lower plasma exposure levels with repeated dosing was observed in the species tested.

Distribution

DEM related radioactivity distributed into most tissues 30 minutes following oral dosing in rats whereas only very limited levels of radioactivity were detected in the CNS. Besides the gastrointestinal tract, DEM related radioactivity was predominantly detected in liver, urinary tract, artery wall and adrenal medulla. Minor levels of radioactivity were detected in skin and bone marrow. 24 hours following oral dosing, traces of radioactivity were only detected in the liver. DEM and DAB displayed no affinity for melanin containing tissues. The distribution of [^{14}C]-DAB from plasma into blood cells was negligible. Only very low levels of radioactivity were detected in foetal tissues following p.o. dosing to rats thus DEM exhibits low placental transfer. The plasma protein binding of [^{14}C]-DAB was low in plasma of mice (22-26%), rat (29-33%), rabbits (32%), Rhesus monkeys (38 - 39%) and humans (29-30%).

Metabolism

The metabolism of DEM was investigated in mice, rats, rabbits and Rhesus monkeys. Following DEM administration, the two intermediate pro-drugs BIBR 1087 SE (most predominant) and BIBR 951 CL are formed. This intermediate BIBR 951 CL is pharmacologically active however due to the intermediate nature of BIBR 1087 SE and BIBR 951 CL, they constitute only trace amounts in human plasma samples. Subsequently, these pro-drugs are converted into DAB. Only traces of BIBR 1087 SE undergo further oxidative metabolism. Cytochrome P450 (CYP450) enzymes did not contribute to the metabolism of DEM, DAB nor of the two intermediate pro-drugs BIBR 1087 SE and BIBR 951 CL. Instead, the metabolism of DEM is catalysed by esterases, such as soluble esterases and also microsomal carboxylesterases. More than 20 metabolites were detected in the investigated animal species but DAB was the predominant compound in all samples of matrices investigated. The chemical structure of DAB contains a carboxyacid functional group which is metabolically converted to the 1-*O*-acyl glucuronide. Due to non-enzymatic isomerization of the 1-*O*-acyl glucuronide, several positional isomers are formed. The 1-*O*-acyl glucuronide as well as its isomers prolonged the APTT to the same extent as the parent compound DAB. All acyl glucuronides present in man are also generated in significant amounts in the main animal species (rats and Rhesus monkeys) used in preclinical studies thus they are considered qualified. There were no human-specific metabolites.

Excretion

Following p.o. administration of [^{14}C]-DEM, excretion of radioactivity is predominantly via faeces in mice, rats, rabbits and Rhesus monkeys (87-93%). DAB is secreted into the bile. However,

enterohepatic circulation of DAB occurs only to a very limited extent (0.4% of the administered radioactivity within 6 hrs) due to the fact that DAB cannot readily be reabsorbed by the gut. The excretion of radioactivity into milk was in the range of 0.08 to 0.13% of the dose administered to the dams.

Pharmacokinetic drug interaction

DEM and DAB neither induced the activity of major CYP450 enzymes in primary human hepatocytes nor in vivo in rat liver microsomes. However, the potential for induction of CYP2C9, 2C19 and 2C8 enzymes have not been investigated. DEM, DAB, BIBR 951 CL and BIBR 1087 SE had no effect on the activity of major CYP450 enzymes at clinically relevant concentrations. DEM absorption is not significantly affected by P-glycoprotein-mediated efflux. Altogether, the risk for CYP450 and P-glycoprotein mediated PK drug interactions following DEM administration are considered very limited.

Toxicology

- Single dose toxicity

Single-dose p.o. administration of DEM did not give rise mortalities in mice and rats at doses up to 2000 mg/kg and up to 600 mg/kg in Rhesus monkeys.

- Repeat dose toxicity (with toxicokinetics)

The pivotal studies consisted of 26-week studies performed in rats and monkeys and a 52-week study conducted in monkeys. The toxicity observed in the repeat-dose toxicity studies conducted in mice, rats, dogs and Rhesus monkeys was associated to the exaggerated pharmacological activity of DEM. The clinical and biochemical findings consisted of bruising, pallor, decreased activity, swelling of limbs and tail (in rodents) or lips and cheeks (monkeys), blood in faeces, mildly increased fibrinogen levels, increased aPTT, PT and TT values and regenerative anaemia. Histopathological findings in rats consisted predominantly of signs of recurrent haemorrhage in thymus, heart and pancreas. These organs were possibly particularly susceptible to haemorrhage due to the mechanical forces exerted on these tissues during gavage. In monkeys, the site of haemorrhage varied from the urinary bladder, subcutaneous tissue on the head, thymus, uterus, vagina, and to the skin. All treatment-related findings were reversible. Mortalities due to excessive bleeding possibly induced by the exertion of mechanical forces during gavaging were observed at 300 mg/kg in rats. Similarly, a single female monkey administered 200 mg/kg died due to excessive menstrual bleeding. Subsequently, the female monkeys were not dosed during the menstrual period. Altogether, the major safety concern with DEM is the risk for bleeding effects in humans. No signs of hepatotoxicity were observed in the repeat-dose toxicity studies conducted with DEM.

- Genotoxicity

The pro-drug DEM and the active moiety DAB were non-genotoxic in Ames tests, in the *in vitro* mouse lymphoma L5178Y $tk^{+/-}$ assay and in the *in vivo* rat bone marrow micronucleus assay.

- Carcinogenicity

No carcinogenicity studies have been submitted since DEM will not be regularly administered over a substantial part of patient's lifetime. Moreover, there are no causes for concern suggesting a carcinogenic potential for DEM.

- Reproduction Toxicity

Male fertility was not adversely affected in rats following p.o. treatment with doses of up to 200 mg/kg DEM. A decrease in implantations was observed in females with a NOAEL of 15 mg/kg which approximately corresponds to clinical exposure levels. Moreover, the incidence of early resorptions was increased at 200 mg/kg. At maternotoxic and lethal doses (200 mg/kg), a decrease in viable foetuses was observed along with an increase in early, late and total resorptions in the rat embryo-foetal study. Moreover, the foetal weight was decreased in the 200 mg/kg group. A slightly increased incidence of variations was observed in high-dose foetuses. The NOAEL for foetal effects was 70 mg/kg, which gives rise to a safety margin of around 5. In a dose-range finding study, embryo-lethality (increased resorption rate) was observed in pregnant rabbits administered 200 mg/kg.

However, in the pivotal embryo-foetal study, treatment of rabbit with up to 200 mg/kg DEM had no effect on corpora lutea, implantations, viable foetuses, resorptions or resorption rate. The increased incidence of foetal variations was not increased. The NOAEL for foetal effects was 200 mg/kg, which gives rise to an AUC-based safety margin of 2. Maternal toxicity was observed at doses ≥30 mg/kg in the rat pre- and post-natal study and maternal mortality caused by bleeding to death during resorption of the embryos and parturition was observed at 70 mg/kg. The post-implantation loss and the number of dead offspring were significantly increased in the 70 mg/kg group. However, treatment had no negative effects on body weight, developmental landmarks, CNS parameters and on fertility of the pups. Consequently, pre-parturition, the NOAEL for foetal mortality was 30 mg/kg whereas post-parturition, the NOAEL for developmental effects in the offspring was 70 mg/kg. These values correspond to AUC-based safety margins of 1.6 and 3.9, respectively. Since the milk excretion of DAB only constitutes less than 0.13% of the dose administered to the rat dams, the lack of post-natal developmental effects are not unexpected. Small weights of the testes, epididymides, seminal vesicles and prostate gland were observed in monkeys treated with DAB for 52 weeks, but also in untreated control animals, and therefore no relationship to treatment is established

- Other toxicity studies

DEM was well-tolerated by rabbit skin and eyes and did not have a skin sensitisation potential in rabbits. Even though a weak phototoxic signal was detected in the 3T3 NRU assay, a review of the extensive safety database for DEM showed no evidence of a phototoxic potential in patients. 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. The potential presence of the genotoxic impurities methyl mesylate, ethyl mesylate, isopropyl mesilate and n-hexyl mesilate at a level up to 1 ppm each does not represent a significant safety risk. It is unlikely that DAB use will result in an environmental risk.

Ecotoxicity/environmental risk assessment

The PEC_{SW} for DAB was calculated for total Europe as well as for the country with the highest expected market penetration (France). The Fpen values were based on current sales forecasts which might be estimated based on the expected number of patients. The resulting PEC_{SW} values were 0.0036 µg/L and 0.0057 µg/L for EU and France, respectively. These values were below the Phase II trigger value but Phase II assessment was performed. Log K_{ow} for DAB was below 4.5 thus a screening for persistence, bioaccumulation and toxicity was not needed. The adsorption/desorption coefficient K_{OC} was 5758 L/kg (OECD 106) thus an assessment of the drug substance in the terrestrial compartment was not required. It was expected that DAB will disappear rapidly from aerobic aquatic systems mainly via binding to sediment and formation of several minor metabolites (OECD 308). The level of ^{14}C-DAB in the sediment reached a plateau between days 3 and 14 with a maximal detected value of 5.7%. However, due to the structural resemblance to not ready biodegradable substances, a tier B study on transformation in aquatic sediment systems was performed (OECD 308). The calculated PEC/PNEC ratios were all below 1. In summary, due to the low risk further testing in for effects on the aquatic environment, microorganisms and the terrestrial compartment were not required. In addition, due to the low K_{ow} a bioaccumulation study was not needed. $PEC_{sediment}$ values were obtained for EU (0.453 µg/kg) and the "worst-case scenario" France (0.718 µg/kg). Since the PEC/PNEC ratio for the sediment was clearly below 1, it was concluded that with the present use pattern, DAB constitutes an insignificant risk for the sediment compartment. In conclusion, it is unlikely that DAB use will result in an environmental risk.

Discussion on the non-clinical aspects

DAB is a synthetic non-peptide compound, which acts as a competitive inhibitor at the active site of thrombin. DAB is poorly absorbed following oral dosing. Thus it is orally administered in the form of the pro-drug: DEM. Administration of i.v. DAB and p.o. DEM, produces a dose- and time-dependent prolongation of coagulation time in various species. Safety pharmacology studies revealed that treatment with DEM caused an increase in respiratory rate and minute volume and an inhibition of gastric emptying. However, no adverse events have been reported clinically that could be associated to these effects.

Following single administration, the oral bioavailability of DEM was 12% in rat, 5.4% in rabbit, 7.7% in Rhesus monkey and 7.2% in man. The clearance was 4.5 to 6-fold higher in rat, rabbit and monkey when compared to man and consequently the half-life was lower in these species. A less than dose-proportional increase in the exposure parameters C_{max} and AUC were generally observed in mice and monkeys following repeated dosing. DAB plasma exposure in rats and rabbits was generally dose proportional with no consistent effect of gender or repeated dosing. DEM related radioactivity was distributed into most tissues with very limited levels in the CNS. The metabolism of DEM was investigated in mice, rats, rabbits and Rhesus monkeys. Following its administration, the two intermediate pro-drugs were formed. These intermediate pro-drugs are pharmacologically active however they constitute only trace amounts in human plasma samples. Subsequently, they were converted into DAB. The metabolism of DEM is catalysed by esterases and the metabolites are excreted predominantly via faeces in mice, rats, rabbits and Rhesus monkeys. DAB is secreted into the bile. However, enterohepatic circulation of DAB occurs only to a very limited extent.

Single-dose oral administration of DEM did not give rise mortalities in mice and rats at doses up to 2000 mg/kg and up to 600 mg/kg in Rhesus monkeys. The toxicity observed in the repeat-dose toxicity studies conducted in mice, rats, dogs and Rhesus monkeys was associated with exaggerated pharmacological activity of DEM. The findings made in rats consisted predominantly of recurrent haemorrhage, fibrosis, fibrin deposition and haemosiderosis in the thymus, heart and pancreas. In monkeys, the site of haemorrhage varied from the urinary bladder, subcutaneous tissue on the head, thymus, uterus, vagina, and to the skin. In both rats and monkeys, haemorrhage was observed without safety margins to the clinical DAB plasma AUC level. Altogether, the major safety concern with DEM is the risk for bleeding effects in humans. No signs of hepatotoxicity were observed with DE which was of particular concern because it was observed with other DTIs. The pro-drug DEM and DAB were non-genotoxic. No carcinogenicity studies have been submitted since DEM will not be regularly administered over a substantial part of the patient's lifetime. Male fertility was not adversely affected in rats but reduced weights and atrophy of the testis, the epididymides, the seminal vesicles and prostate were observed in DAB-treated monkeys. Although these effects might in part be due to seasonal sexual inactivity at the time of the necropsy, a relationship to treatment cannot be excluded. 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).

2.4 Clinical aspects

Introduction

DE is the orally bioavailable prodrug of DAB, a novel, non-peptidic, reversible inhibitor of thrombin. The primary objective of this application is to review data demonstrating the efficacy of DE 150 mg and 220 mg once daily dosing (q.d.) for the prevention of VTE following MOS. Evidence to support the claimed indication consists of data from two large EU Phase III therapeutic confirmatory clinical trials. These trials were performed in patients undergoing either elective TKR surgery (study 1160.25) or elective THR surgery (1160.48). These studies compared two doses of DE (150 mg and 220 mg, given orally as capsules once daily) against the standard comparator drug, enoxaparin (40 mg, given once daily subcutaneously). Consistent with medical practice and labelling in the EU, the initial dose of enoxaparin was given prior to surgery. In addition, Phase III TKR study (study 1160.24) was performed in parallel in North America using a higher daily dose of the same comparator, enoxaparin (given subcutaneously 30 mg injection twice daily), consistent with labelling in the US. Prior to the Phase III programme, dose-ranging studies were performed in patients undergoing joint replacement. The doses and administration schedule used in Phase III were developed based on the PK database collected during the Phase II programme.

Table 1: Overview of controlled clinical studies pertinent to the claimed indication

Study ID (Phase)	Study design	Key endpoints	Treatment groups	Number of patients randomised
Pivotal				
1160.25 (III)	Randomised, double-blind, parallel group	Total VTE[a] and all-cause mortality Major VTE[b] and VTE related mortality	DE 220 mg qd DE 150 mg qd Enoxaparin 40 mg qd	n = 693 n = 708 n = 699 N = 2101
1160.48 (III)	Randomised, double-blind, parallel group	Total VTE[a] and all-cause mortality Major VTE[b] and VTE related mortality	DE 220 mg qd DE 150 mg qd Enoxaparin 40 mg qd	n = 1157 n = 1174 n = 1162 N = 3494
Supportive				
1160.24 (III)	Randomised, double-blind, parallel group	Total VTE[a] and all-cause mortality Major VTE[b] and VTE related mortality	DE 220 mg qd DE 150 mg qd Enoxaparin 30 mg bid	n = 862 n = 877 n = 876 N = 2615
Dose-ranging				
1160.19 (II)	Randomised, double-blind, parallel group	Total VTE[a]	DE 300 mg qd DE 225 mg bid DE 150 mg bid DE 50 mg bid Enoxaparin 40mg qd	n = 392 n = 398 n = 393 n = 393 n = 393

[a] Total VTE includes at least one of the following: confirmed PE, confirmed symptomatic DVT, or DVT detected by venography

[b] Major VTE includes at least one of the following: confirmed PE, confirmed symptomatic proximal DVT, or proximal DVT detected by venography

GCP

The main dose response study and the phase III studies were performed in accordance with GCP as claimed by the applicant.

Pharmacokinetics

A total of 31 studies enrolling approximately 3100 subjects have been conducted with DAB to evaluate dose-response, PK/PD relationship, mode of action and potential for drug-drug interactions. DE is an oral prodrug. This prodrug is present in a salt form (methane sulfonate or mesilate). It contains the active moiety DAB and an ethyl-ester group. After oral administration, DE is rapidly and completely converted to DAB, which is the active form in plasma. The cleavage of the prodrug DE by esterase-catalysed hydrolysis to the active principle DAB is the predominant metabolic reaction. The absolute bioavailability of DAB following oral administration of DE was approximately 6.5 %. After oral administration of DE in healthy volunteers, the PK profile of DAB in plasma is characterized by a rapid increase in plasma concentrations with Cmax attained within 0.5 and 2.0 hours post administration.

- Absorption

A study evaluating post-operative absorption of DE, 1-3 hours following surgery, demonstrated relatively slow absorption compared with that in healthy volunteers, showing a smooth plasma concentration-time profile without high peak plasma concentrations. Peak plasma concentrations were

reached at 6 hours following administration in a postoperative period due to contributing factors such as anesthesia, gastrointestinal paresis, and surgical effects independent of the oral medicinal product formulation. It was demonstrated in a further study that slow and delayed absorption is usually only present on the day of surgery. On subsequent days absorption of dabigatran is rapid with peak plasma concentrations attained 2 hours after medicinal product administration. Food does not affect the bioavailability of dabigatran etexilate but delays the time to peak plasma concentrations by 2 hours.

- Distribution

Low (34-35 %) concentration independent binding of DAB to human plasma proteins was observed. The volume of distribution of DAB of 60 – 70 L exceeded the volume of total body water indicating moderate tissue distribution of DAB. Cmax and the area under the plasma concentration-time curve were dose proportional. Plasma concentrations of DAB showed a biexponential decline with a mean terminal half-life of 12 - 14 hours in healthy volunteers and 14 – 17 hours in patients undergoing major orthopaedic surgery. The half-life was independent of dose.

- Metabolism and elimination

Metabolism and excretion of DAB were studied following a single intravenous dose of radiolabeled DAB in healthy male subjects. After an intravenous dose, the DAB-derived radioactivity was eliminated primarily in the urine (85 %). Faecal excretion accounted for 6 % of the administered dose. Recovery of the total radioactivity ranged from 88 - 94 % of the administered dose by 168 hours post dose. DAB is subject to conjugation forming pharmacologically active acylglucuronides. Four positional isomers, 1-O, 2-O, 3-O, 4-O-acylglucuronide exist, each accounts for less than 10 % of total dabigatran in plasma. Traces of other metabolites were only detectable with highly sensitive analytical methods. DAB is eliminated primarily in the unchanged form in the urine, at a rate of approximately 100 ml/min corresponding to the glomerular filtration rate.

- Dose proportionality and time dependencies

DAB Cmax and AUC increased linearly with dose from 10 to 400 mg. Repeat dose study was performed with t.i.d. dosing (50 to 400 mg). Steady-state was achieved on day 2 of administration. DAB displayed moderate accumulation. The accumulation ratios for AUCss and Cmax ss were about 1.6 – 2.5. No PK study was performed with the posology recommended in the SPC i.e. 220 mg q.d.. Variability: in healthy volunteers and in patients, the interindividual variability of Cmax and AUC expressed as CV was high i.e. approximately 80%. In healthy volunteers the intraindividual variability was close to 30%.

- Special populations

Renal insufficiency

The exposure (AUC) of DAB after the oral administration of DE is approximately 2.7 fold higher in volunteers with moderate renal insufficiency (CrCL between 30 – 50 ml/min) than in those without renal insufficiency. In a small number of volunteers with severe renal insufficiency (CrCL 10 - 30 ml/min), the exposure (AUC) to DAB was approximately 6 times higher and the half-life approximately 2 times longer than that observed in a population without renal insufficiency. An observational cohort study will be conducted to evaluate efficacy and safety of DAB in patients with moderate renal impairment as part of the FUMs. This will better describe the benefit/risk profile of the 150 mg dose of DAB in patients with moderate renal impairment.

Elderly patients

Specific PK studies with elderly subjects showed an increase of 40 to 60 % in the AUC and of more than 25 % in C_{max} compared to young subjects. Population-based PK studies have evaluated the PKs of DAB after repeated doses in patients (up to 88 years). The observed increase of DAB `exposure correlated with the age-related reduction in creatinine clearance.

Hepatic insufficiency

No change in DAB exposure was seen in 12 subjects with moderate hepatic insufficiency (Child Pugh B) compared to 12 controls.

Body weight

Population PK studies have evaluated the PKs of DAB in patients of 48 to 120 kg body weight. Body weight had a minor effect on the plasma clearance of dabigatran resulting in higher exposure in patients with low body weight.

Gender

Active substance exposure in female patients is about 40 % to 50 % higher than in male patients and no dose adjustment is recommended.

Ethnic origin

The PKs of DAB was investigated in Caucasian and Japanese volunteers after single and multiple doses. Ethnic origin does not affect the PKs of DAB in a clinically relevant manner. No PK data in black patients are available.

- Pharmacokinetic interaction studies

In vitro interaction studies did not show any inhibition or induction of the principal isoenzymes of CYT P450. This has been confirmed by in vivo studies with healthy volunteers, who did not show any interaction between this treatment and the following active substances: atorvastatin (CYP3A4), digoxin (P-glycoprotein transporter interaction) and diclofenac (CYP2C9). DAB exposure in healthy subjects was increased by 60 % in the presence of amiodarone. A drug-drug interaction study with steady state concentrations of a specific P-gp inhibitor (clarithromycin) will be performed as part of the FUM.

Pharmacodynamics

- Mechanism of action

DE is a small molecule prodrug which does not exhibit any pharmacological activity. After oral administration, DE is rapidly absorbed and converted to DAB by esterase-catalysed hydrolysis in plasma and in the liver. DAB is a potent, competitive, reversible direct thrombin inhibitor and is the main active principle in plasma. Since thrombin enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of thrombus. DAB also inhibits free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. There is a clear correlation between plasma DAB concentration and degree of anticoagulant effect. DAB is a reversible inhibitor of thrombin of relatively low affinity (4.5 nM) compared to hidurin and heparin. However, no data have been presented on the interest of inhibiting bound thrombin, contrary to what was usually presented for previously developed DTI. These previous DTI were characterized by a higher affinity for thrombin.

- Primary and Secondary pharmacology

As for all other DTI developed until now the effects of DAB were assessed using coagulation tests which are known to be non adapted for accurate and sensitive evaluation of DTI: activated partial thromboplastin time (aPTT), prothrombin time (PT), expressed as International Normalized Ratio (INR), thrombin time (TT), and one test which is better adapted but not of current practice in clinical laboratories: ecarin clotting time (ECT).

The maximum effect (Emax) of DAB on PD parameters occurred at the same time as Cmax, indicating that thrombin inhibition by DAB is a direct effect, linked to the DAB plasma concentration. INR, TT and ECT increased in direct proportion to the plasma concentration of DAB, whereas aPTT prolongation was linearly related to the square root of the DAB plasma concentration. PK/PD analyses confirmed marked differences between the various assays used in terms of sensitivity and precision with varying DAB plasma concentrations.

A curvilinear relationship was shown between DAB plasma concentrations and **aPTT**. It is the reason for which the measurement of aPTT may provide a qualitative indication of anticoagulant activity, but it may not be suitable for the precise quantification of anticoagulant effect.

The data suggest a linear relationship between plasma concentration and **INR** (<2.0); however, this assay lacked sensitivity within the clinically-relevant DAB plasma concentration range and showed high variability. Therefore, INR is not considered a suitable tool for monitoring the anticoagulant effects of DE.

The **TT** assay exhibited a linear relationship with plasma concentration with a high level of sensitivity. TT might be too sensitive to DAB plasma concentrations in the clinically relevant plasma concentration range. At DAB concentrations greater than 600 ng/mL, the TT frequently exceeded the maximum measurement time of the coagulometer. TT assay is only presented as a sensitive method for determining if any DAB is present. Additionally, since the reagents used for determining TT at different laboratories are not standardized, the clinical utility of this test during DAB dosing was questioned. Nevertheless, it should be mentioned that an adaptation of the test to allow sensitivity and an effort of standardization among the clinical labs should allow seeing a modified TT as an easy and inexpensive test to monitor DAB and will be done as part of the FUM.

The **ECT** assay displayed a linear relationship with drug plasma concentrations over the full range of concentrations, and did not plateau at higher concentrations. Furthermore, ECT was more sensitive to DAB than, for example, aPTT, as evidenced by an 8-fold maximum ECT prolongation, compared with a 2.5-fold maximum aPTT prolongation at the 400 mg multiple doses of DE. ECT is also a more precise parameter than aPTT. Overall, the ECT may provide a more accurate measurement of DAB anticoagulation than the other PD parameters. However, it should be mentioned that the ECT assay is not regularly used in clinical lab and has never been the object of any tentative of standardization. Therefore, its routine use cannot be recommended. But again this test could be standardized among clinical lab and as such be used in routine even if more expensive than a TT.

To conclude, at the today's standards of the clinical lab there is no assay sufficiently sensitive and standardized to assess routinely the anticoagulant status of patients following DAB administration. But this situation could be improved if an assay allowing DAB plasma concentration monitoring when thought necessary would be developed. A cross-validation of chronometric TT measurements at local laboratories will be performed as part of the FUM . Commercially available TT test kits developed for measurement of TT following administration of DTIs (i.e. hirudin) will be validated for measurement of TT of DAB.

Clinical efficacy

There were 4 multi-center, double blind, double-dummy, randomised, parallel group, controlled clinical studies submitted pertinent to the claimed indication. In all studies, enoxaparin, a recognized and widely used LMWH for this indication, was used as an active control.

- Dose response study

In the phase II dose ranging study 1160.19 there were 5 parallel groups: DE 300 mg q.d., DE 225 mg b.i.d., DE 150 mg b.i.d., DE 50 mg b.i.d. and enoxaparin 40mg q.d.. DE was administered orally, enoxaparin subcutaneously. As in the 2 pivotal studies, DE was administered 1-4 hours post surgery and enoxaparin was administered on the evening before surgery. Patients undergoing THR and TKR were included, which is acceptable for a dose-finding study, however, stratification according to the type of surgery would have been preferred. The primary endpoint was rate of VTE events which included DVT (proximal and distal) as detected by routine bilateral venography on Day 8 ±2, plus symptomatic DVT occurring during the treatment period and confirmed by venography, or PE confirmed by objective testing (chest X-ray, ventilation/perfusion scintigraphy, pulmonary angiography, spiral CT). This endpoint is acceptable for a therapeutic exploratory trial and in accordance with the 'Guideline on clinical investigation of medicinal products for prophylaxis of high intra-and post-operative venous thromboembolic risk '(CPMP/EWP/707/98 Rev. 1).

A total of 1973 patients were randomised, of these, 1921 patients were treated and operated (1306 THR, 615 TKR).

Different analyses sets were defined: the Safety Population (all randomised patients who were treated and who had any available data), the Full Analysis Set (FAS) (which consisted of all randomised patients who had at least one s.c. injection and one oral dose of study medication, with confirmed VTE data available after surgery) and the Per Protocol data Set (PPS) (FAS minus patients with major protocol deviations). The FAS was used for the analysis of efficacy variables. Treatment duration was 5-10 days, which was not according to the newest standards for THR but acceptable for the time (2002/2003) the study was conducted.

The results of the primary endpoint showed a dose-dependent effect of treatment with DE on the VTE rate. The VTE rate for each treatment group (50 mg b.i.d., 150 mg b.i.d., 300 mg q.d. and 225 mg b.i.d.) was 28.5%, 17.4%, 16.6%, and 13.1%, respectively, and 24.0 % for enoxaparin. Treatment with 50 mg dab b.i.d. was not significantly different from 40 mg enoxaparin q.d. with respect to VTE

rate (p=0.2446). Patients treated with 150 mg and 225 mg DAB b.i.d. had statistically significantly less VTE events than patients in the active control group enoxaparin (p=0.0401 and p=0.0007, respectively). No significant difference in VTE rate was observed for b.i.d. or q.d. dosing for a daily dose of 300mg of DE. Subgroup analyses showed that patients >70 years, females, and patients with BMI ≥35 kg/m², as well as patients undergoing TKR and those with intake of the drug >4 h after surgery had a higher VTE rate.

In approximately 350 patients from dedicated Scandinavian centres a PK/PD sub-study was conducted. Plasma concentration-time profiles of DAB were obtained after administration of the first dose of DE on the day of surgery and on Day 4 or 5 of treatment. The number of sub-study patients per dose group was similar. Steady state trough plasma concentrations of DAB measured from Day 4 onwards were obtained from all patients. Linear PK data were observed. In general very high coefficients of variation were observed for all PK parameters. Oral absorption on the day of surgery was delayed by approximately 2 hours compared to steady state and the drug exposure after the first dose varied extremely. The majority of the data for PK evaluation are derived from non-general anaesthesia. The exposure in steady state was comparable for the 150mg b.i.d. and the 300mg q.d. dosing. Lower creatinine clearance increased drug concentrations; this appeared to be more distinct in female patients. Furthermore, a higher exposure to the drug was observed in females compared to males, potentially due to lower average creatinine clearance in females. The prolongation of ECT was linearly related to DAB plasma concentrations. The major bleeding rates in all dose regimens but the 50 mg b.i.d. regimen were higher than for enoxaparin. Therefore, none of these doses was finally chosen for the phase III studies but it was concluded that therapeutic doses must lie between 100 and 300mg daily.

- Main studies

Three phase III studies were conducted. They are summarised in the table below. All were randomised, double-blind, parallel group. All phase III studies were non-inferiority studies and their margin justified according to guidelines. There was one pivotal study (1160.25) conducted in patients with primary elective TKR surgery and one pivotal study (1160.48) in patients with primary elective THR surgery (both conducted predominantly in Europe) as well as one supportive study (1160.24) (conducted in North America) in patients with TKR. The latter study applied the North American dosing recommendations for enoxaparin which differ from the European ones, randomised patients post surgery and administered DE with a delay compared to the other phase III studies and what is proposed in the SPC.

Study ID (Phase)	Study design	Type of surgery	Key endpoints	Treatment groups	Number of patients randomised
Pivotal					
1160.25 (RE-MODEL)	Randomised, double-blind, parallel group	Total knee replacement	1ºTotal VTEa and all-cause mortality 2ºMajor VTE[b] and VTE related mortality	Dabigatran etexilate 220 mg q.d. Dabigatran etexilate 150 mg q.d. Enoxaparin 40 mg q.d.	n = 693 n = 708 n = 699 N = 2101
1160.48 (RE-NOVATE)	Randomised, double-blind, parallel group	Total hip replacement	1ºTotal VTE[a] and all-cause mortality 2ºMajor VTE[b] and VTE related mortality	Dabigatran etexilate 220 mg q.d. Dabigatran etexilate 150 mg q.d. Enoxaparin 40 mg q.d.	n = 1157 n = 1174 n = 1162 N = 3494
Supportive					
1160.24 (RE-MOBILIZE)	Randomised, double-blind, parallel group	Total knee replacement	1ºTotal VTE[a] and all-cause mortality 2ºMajor VTE[b] and VTE related mortality	Dabigatran etexilate 220 mg q.d. Dabigatran etexilate 150 mg q.d. Enoxaparin 30 mg b.i.d.	n = 862 n = 877 n = 876 N = 2615

[a] primary endpoint: Total VTE includes at least one of the following: confirmed PE, confirmed symptomatic DVT, or DVT detected by venography

[b] secondary endpoint: Major VTE includes at least one of the following: confirmed PE, confirmed symptomatic proximal DVT, or proximal DVT detected by venography

METHODS

Studies 1160.25 and 1160.48

Study Participants

There were 2101 patients randomised in study 1160.25 and 3494 patients in study 1160.48. In- and exclusion criteria were consistent across the phase III studies. The baseline characteristics of patients were well matched. Surgery was performed in general anaesthesia in 37.9% of patients in study 1160.25 and in 30.5% of patients in study 1160.48. Also patients with risk factors have been entered into the studies: in studies 1160.25 and 1160.48, 19.6% and 14.1% of patients, respectively were >75 years of age, 26.5% and 18.5% of patients, respectively, had a weight >90 kg, 45% and 28% of patients, respectively, had a BMI >30kg/m^2. Approximately one third of patient in each of the two studies had mild renal insufficiency based on calculated creatinine clearance and 5.4% of patients in study 1160.25 and 6.6% of patients in study 1160.48 had moderate renal insufficiency with creatinine clearance 30 -50 ml/min. However, a large portion of patients, more than 70% in study 1160.25, and 63% in study 1160.48 were never-smokers and more than 90 % were abstinent at the time of surgery. This fact does not corresponded with the "real world" and raises concerns regarding selection of population and introduction of bias. It is a well known fact that smokers have higher morbidity and mortality and when the primary endpoint include all cause mortality this introduces bias. In addition, a rather limited percentage of patients with concomitant diseases, being consistent with an increased risk for the patients, have been included. This was true and generally more emphasised in study 1160.48, for patients with CAD, CHF, history of VTE, history of malignancy (active malignancy was an exclusion criterion). As concerns concomitant medication, drugs influencing the coagulation system were excluded, including ASA >160 mg/d or NSAIDs with t½ > 12 h within 7 days prior to surgery.. Overall, NSAIDs were used concomitantly of 55.2% and 63.7% and ASA of 4.1% and 3.3% of patients in studies 1160.48 and 1160.25, respectively.

Treatments

Patients were randomised to DE 220 mg q.d., DE 150 mg q.d. or Enoxaparin 40 mg q.d.. As mentioned previously none of these doses had been tested previously. For the chosen doses a population PK model was used to predict plasma concentration time profiles. Half dose was administered on the day of surgery. Study 1160.48 is one of the first studies where treatment duration of prophylaxis is extended to 28-35 days as recommended in the EMEA Guideline (CPMP/EWP/707/98 Rev.1) for THR surgery. Duration of prophylaxis in study 1160.25 was 6-10 days and thus suboptimal considering that at least 10 days treatment were recommended at the time the study was conducted.

Objectives

The primary objective of these studies was to demonstrate the noninferiority of DE 150 mg and 220 mg once daily dosing (q.d.) per comparison to Enoxaparin 40 mg bid for the prevention of VTE following MOS (separately for THR and TKR). The primary efficacy endpoint of these studies was a composite endpoint of total VTE and all-cause mortality during the treatment period. Total VTE included proximal and distal DVT based on mandatory venography at the end of the treatment period, symptomatic DVT confirmed by venous compression ultrasound, venography or autopsy and objectively confirmed PE. The primary and secondary efficacy endpoints were independently assessed by blinded adjudication committees according to guidelines. The routine venography was to be performed within 24 hours of last oral study medication dose, i.e. Day 28-35 in study 1160.48 and Day 8±2 in 1160.25. This means that venographies were performed on out-patient basis in study 1160.48 (Re-Novate) and study 1160.24 (Re-Mobilize) and just prior to discharge in study 1160.25 (Re-Model). According to a protocol amendment, VTE observed until 3 days after the last administration of trial drug were considered as events occurring "during treatment" and therefore included in the primary efficacy endpoint and secondary endpoints of events occurring during treatment. There were approximately 25% of unevaluable venograms which is comparable with other studies performed in this indication.

Sample size

In study 1160.25, 2101 patients were randomised and in study 1160.48 3494 patients. These were approximately equally distributed on the 3 parallel groups DE 220 mg q.d., DE 150 mg q.d. and enoxaparin 40mg q.d.

Randomisation and blinding (masking)

All phase III studies were randomised and double-blind.

Statistical methods

All phase III studies were non-inferiority studies and their margins were justified according to guidelines.

For evaluation, different analysis sets were defined:
Safety population or Safety Set: All randomized and treated patients. A patient was regarded as treated if he or she received at least 1 dose of trial medication, i.e. DAB, enoxaparin, or placebo.
FAS-op population: All randomized, treated patients who underwent surgery. A patient was regarded as treated if he or she received at least 1 dose of trial medication,
FAS population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram or confirmed symptomatic DVT, PE, or death) during the treatment period.
FAS-major population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram for proximal DVT or confirmed symptomatic DVT, PE, or death) during the treatment period.
FAS-pDVT population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram for proximal DVT or confirmed symptomatic DVT) during the treatment period.
FAS-tDVT population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram for distal and proximal DVT or confirmed symptomatic DVT) during the treatment period.
Per-protocol set or PP or PPS population: Comprised of those patients who were randomised, received at least one subcutaneous injection or one oral dose of study medication, went through surgery, and had had confirmed VTE data (i.e. evaluable venogram or confirmed symptomatic DVT, PE, or death) during the treatment period without relevant protocol deviations.

According to the statistical plan the primary analysis was based on the FAS, whereas the PPs analysis was foreseen to be used additionally only if this population fell below 90% of the primary efficacy analysis population. In the opinion of the Rapporteur this approach is not completely in accordance with the guideline “statistical principles for clinical trials” (CPMP/ICH/363/96) which states that in a “non-inferiority trial use of the full analysis set is generally not conservative and its role should be considered very carefully.” The ”Points to Consider for switching between Superiority and Non-Inferiority” (CPMP/EWP/482/99) assigns equal importance to the Full Analysis Set and the PP analysis Set. Both the FAS and the PP analysis in the pivotal trials provided similar results.

RESULTS

Outcomes and estimation

Comparative analysis of total VTE and all-cause mortality during treatment period based on the FAS population

	Dabigatran 220 mg N(%)		Dabigatran 150 mg N(%)		Enoxaparin N(%)	
Study	**1160.25**	**1160.48**	**1160.25**	**1160.48**	**1160.25**	**1160.48**
FAS	503	880	526	874	512	897
Incidence, N (%)	183 (36.4)	53 (6.0)	213 (40.5)	75 (8.6)	193 (37.7)	60 (6.7)
95% CI*	(32.2, 40.6)	(4.5, 7.6)	(36.3, 44.7)	(6.7, 10.4)	(33.5, 41.9)	(5.1, 8.3)
Risk difference vs. Enoxaparin (%)*	-1.3	-0.7	2.8	1.9	-	-
95% CI*	(-7.3, 4.6)	(-2.9, 1.6)	(-3.1, 8.7)	(-0.6, 4.4)	-	-
p-value*	0.6648	0.5648	0.3553	0.1339	-	-
Relative risk over Enoxaparin (%) #	0.97	0.90	1.07	1.28	-	-
95% CI	(0.82, 1.13)	(0.63, 1.29)	(0.92, 1.25)	(0.93, 1.78)	-	-
Odds ratio over Enoxaparin @	0.9	0.9	1.1	1.3	-	-
95% CI	(0.7, 1.2)	(0.6, 1.3)	(0.9, 1.4)	(0.9, 1.9)	-	-

* based on normal approximation of independent binomial distribution without stratification
p-value tested the hypothesis of no difference between two treatment groups (superiority test)
based on normal approximation of log relative risk without continuity correction
@ based on logistic regression including the main factor of treatment derived from contrast that compared the two treatments

Summary of individual components contributing to the primary endpoint based on the FAS population

	Dabigatran 220 mg		Dabigatran 150 mg		Enoxaparin	
Study	**1160.25**	**1160.48**	**1160.25**	**1160.48**	**1160.25**	**1160.48**
FAS, N (%)	503 (100.0)	880 (100.0)	526 (100.0)	874 (100.0)	512 (100.0)	897 (100.0)
Total VTE or death N (%) during treatment period #,	183 (36.4)	53 (6.0)	213 (40.5)	75 (8.6)	193 (37.7	60 (6.7)
asymptomatic DVT	181 (36.0)	40 (4.5)	208 (39.5)	63 (7.2)	184 (35.9)	56 (6.2)
symptomatic DVT	1 (0.2)	5 (0.6)	3 (0.6)	9 (1.0)	8 (1.6)	1 (0.1)
non-fatal PE	0 (0.0)	5 (0.6)	1 (0.2)	0 (0.0)	0 (0.0)	3 (0.3)
death VTE cannot be ruled out	0 (0.0)	1 (0.1)	1 (0.2)	3 (0.3)	1 (0.2)	0 (0.0)
death not associated with VTE	1 (0.2)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Localisation of DVTs						
distal DVT	169 (33.6)	23 (2.6)	193 (36.7)	37 (4.2)	175 (34.2)	24 (2.7)
proximal DVT¶	13 (2.6)	22 (2.5)	18 (3.4)	35 (4.0)	17 (3.3)	33 (3.7)
during follow- up #@ Symptomatic DVT, PE, or death (N)	4	1	2	3	2	2

Treatment period: from administration of first dose of study medication and ending 3 days after administration of last dose of study medication. Follow-up is from the end of treatment period to the conclusion of subject participation.
@ Study 1160.25: For Dabigatran 220mg: 1 symptomatic DVT, 2 PE, and 1 death; for Dabigatran 150 mg: 2 symptomatic DVTs, 0 PE, and 0 death; for Enoxaparin: 0 symptomatic DVT, 0 PE, 2 deaths.
@ Study 1160.48: For Dabigatran 220 mg: 1 symptomatic DVT, 0 PE, 0 death, for Dabigatran 150 mg: 1 symptomatic DVT, 0 PE, 2 death, for Enoxaparin: 0 symptomatic DVT, 1 PE, 1 death.
¶ Study 1160.25: Includes patients with confirmed proximal DVT as well as 1 patient with a distal and a proximal DVT.
Note: patients were counted only once in the most severe category in subcategories of DVT, PE and death

Major VTE and VTE-related mortality during the treatment period based on the FAS-major population

	Dabigatran 220 mg		Dabigatran 150 mg		Enoxaparin	
Study	**1160.25**	**1160.48**	**1160.25**	**1160.48**	**1160.25**	**1160.48**
FAS-major, N	506	909	527	888	511	917
Incidence, N (%)	13 (2.6)	28 (3.1)	20 (3.8)	38 (4.3)	18 (3.5)	36 (3.9)
95% CI*	(1.2, 3.9)	(2.0, 4.2)	(2.2, 5.4)	(2.9, 5.6)	(1.9, 5.1)	(2.7, 5.2)
Risk difference vs. Enoxaparin (%)*	-1.0	-0.8	0.3	0.4	-	-
95% CI*	(-3.1, 1.2)	(-2.5, 0.8)	(-2.0, 2.6)	(-1.5, 2.2)	-	-
Relative risk over Enoxaparin#	0.73	0.78	1.08	1.09	-	-
95% CI	(0.36, 1.47)	(0.48, 1.27)	(0.58, 2.01)	(0.70, 1.70)	-	-
Odds ratio over Enoxaparin @	0.7	0.8	1.1	1.1	-	-
95% CI	(0.4, 1.5)	(0.5, 1.3)	(0.6, 2.1)	(0.7, 1.7)	-	-

* Based on normal approximation of independent binomial distribution without stratification, p-value is for testing no difference between two treatment groups.

Based on normal approximation of log relative risk without continuity correction.

@ Based on logistic regression including the main factor of treatment, derived from contrast that compared the two treatments.

In both studies, a clear dose-response for DAB was observed. The results in the DAB 220 mg dose group were consistently numerically slightly better than in the DAB 150 mg group. Statistical analysis of the primary endpoints and the secondary endpoints showed non inferiority compared to Enoxaparin for both high and low dose of DAB. Superiority was not shown (superiority testing was foreseen in the statistical analysis plan in case non-inferiority was confirmed). Mainly distal DVTs account for total VTE in the TKR surgery study 1160.25. In the THR surgery study 1160.48 proximal DVT account for roughly half of the DVTs, independent of the treatment group.The vast majority of DVT in both types of surgery were asymptomatic. The total VTE results for TKR are in the range of those seen with other oral DTI whereas those for THR are considerably lower, probably due to an extended prophylaxis period. The incidence of proximal DVTs was comparable in both types of surgery.

Ancillary analyses

Exploratory subgroup analyses were performed which showed an increased risk in patients with moderate renal insufficiency, patients with general anaesthesia, older patients, females, patients with weight >110 kg (only in study 1160.25) and in patients who received the first oral dose of study medication <4 hours after surgery.

A routine inspection was carried out of study 1160.25 at two sites in South Africa and Hungary. A critical finding was that in approximately one third of patients a starch derivative was used which potentially may affect both the efficacy and the safety of the investigational product. Further analyses have therefore been provided by the Applicant. These findings indicate that in both of the European pivotal studies (1160.25 and 1160.48) the rates of total VTE and all cause mortality are lower in patients who received colloidal starch therapy (roughly one third of patients in study 1160.25 and half of patients in 1160.48) than in those patients who did not. The secondary endpoint major VTE and VTE related mortality confirmed that trend. Bleeding was slightly increased. These results were consistent in both DAB and enoxaparin treatment groups, and DAB results by subgroups are homogeneous with overall results.

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

A meta- analysis was pre-specified in order to evaluate the effects of DE and enoxaparin on the composite endpoint of major VTE and VTE related mortality (proposed primary endpoint in the CHMP guideline CPMP/EWP/ 707/98). A meta- analysis was pre-specified in order to evaluate the effects of DE on the composite endpoint specified in the CHMP Guideline (CPMP/EWP/ 707/98). This approach was only acceptable for justifying the deviation from the CHMP Guideline “if all results of the individual trials point all in the same direction”. This was not the case since only the pivotal EU studies showed non inferiority compared to enoxaparin, this could not be shown in supportive US study. Although it was stated that the studies are very similar and only differ due to clinical practice there are major differences in key areas between Europe and US. These comprise types of surgeries (hip/knee), duration of treatment (short/long), selection of patients by time of randomization (pre-/postsurgery), 1st oral dosing time (0-4 h post surgery vs. 6-12 h post surgery), dose regimen (enoxaparin 40mg vs. 30mg b.i.d.), and time span between surgery and venography. It

was also questioned whether data on VTE can be pooled from two different surgical procedures where mechanical properties (etc. use of tourniquet during knee surgery and therefore no blood flow in the lower leg at all) have different impact on the anatomical regions in question. One would expect that this factor had a greater influence on distal DVT than on proximal DVT. In the view of the CHMP these differences makes it highly unlikely that a meta-analysis can be performed in two so different populations. In phase III studies it is rather unusual to perform "no confirmatory statistical hypothesis testing". No Delta value was prespecified. These analyses were not specified in the protocol and therefore not "lege artis" and unacceptable from a statistical point of view. The above mentioned points were serious faults and concerns regarding the way the meta-analysis was performed. That is why the metaanalysis was considered of exploratory, not of confirmatory nature.

- Supportive study

Supportive study (1160.24) differed from the pivotal studies in the timing of the study medication and the dosing of enoxaparin. The enoxaparin dose schedule was 30 mg b.i.d. and the first dose was given 12-25 h post surgery. The first DE dose was administered 6-12h after surgery (instead of 1-4 h after surgery as in the pivotal studies). More importantly, patients were randomised post surgery, provided that haemostasis was present, and it must be assumed that bias was introduced by this method. Those patients with complications during surgery and long surgery time were most likely excluded and those patients would most likely also be at higher risk for VTE. The incidence of the primary endpoint in the DE 220 mg group was 31.1% (95%CI 27.4, 34.8), in the DE 150 mg group 33.7% (30.1, 37.4) and in the enoxaparin group 25.3% (22.0, 28.7). The risk difference vs. enoxaparin for the DE 220 mg group was 5.8 ((0.8, 10.8), and for the DE 150mg group 8.4 (3.4, 13.3). The non-inferiority margin of 9.2% was thus exceeded and non-inferiority not demonstrated.

- Discussion on clinical efficacy

A recommended primary endpoint in therapeutic confirmatory trials as written in the CHMP Guideline (CPMP/EWP/ 707/98) is a composite endpoint consisting of clinically relevant and objectively documented events including venographically documented proximal DVT, symptomatic and well-documented non-fatal pulmonary embolism (PE) and VTE related death or death due to any cause. However, despite the total DE development program including over 8000 patients, the individual studies were not thought to be sufficiently powered to reliably assess efficacy for the composite endpoint including proximal DVT, symptomatic VTE and VTE related death (= major VTE and VTE related death).

A meta- analysis was pre-specified in order to evaluate the effects of DE on the composite endpoint specified in the CHMP Guideline (CPMP/EWP/ 707/98). This approach was only acceptable "if the results of the individual trials point all in the same direction". This was not the case since only the pivotal EU studies showed non inferiority compared to enoxaparin. This could not be shown in supportive US study. That is why the meta-analysis was considered of exploratory, not of the confirmatory nature.

The introduction of UH and later LMWH as standard prophylactics has reduced the frequency of major VTE and VTE related mortality significantly. Therefore large study populations are needed in order to show non-inferiority. Therefore, a "new" surrogate end-point was proposed which occurs with a higher frequency in order to keep the study population at a reasonable size. Total VTE and all-cause mortality was used during the treatment period as such "new" surrogate marker. Major VTE and VTE related mortality was chosen as one of the secondary endpoints. The MAA for DE was submitted prior to the revision of the CHMP Guideline (CPMP/EWP/ 707/98/Rev 1).

Clinical safety

- Patient exposure

A total of 10.084 patients were treated in 4 actively controlled VTE prevention trials with at least one dose of the medicinal product. Of these 5419 were treated with 150 mg or 220 mg daily of DE, while 389 received doses less than 150 mg daily and 1168 received doses in excess of 220 mg daily.

The most commonly reported adverse reactions are bleedings occurring in total in approximately 14 % of patients; the frequency of major bleeds (including wound site bleedings) is less than 2 %.

	Dabigatran etexilate				Enoxaparin	Total
Treatment period	< 150 mg	150 mg	220 mg	> 220 mg		
Number of treated patients (N [%])	389 (100.0)	2737 (100.0)	2682 (100.0)	1168 (100.0)	3108 (100.0)	10084 (100.0)
Exposure days (N [%])						
≥1	389 (100.0) 0	2737 (100.0)	2682 (100.0)	1168 (100.0) 0	3108 (100.0) 1043 (33.6)	10084 (100.0)
≥18		1038 (37.9)	1044 (38.9)			3125 (31.0)
≥43	0	67 (2.4)	64 (2.4)	0	63 (2.0)	194 (1.9)
Summary statistics						
Mean	8.0	19.8	20.0	7.8	18.4	17.6
SD	2.0	12.2	12.2	2.1	12.1	12.0
Median	8.0	15.0	15.0	8.0	14.0	13.0
Minimum	1	1	1	1	1	1
Maximum	13	52	69	13	49	69
Total exposure years	8.5	148.5	146.9	25.0	156.5	485.4

- Adverse events

The AEs in the 2 pivotal trials as well as the 4 active controlled VTE prevention studies were largely comparable, also between the treatment groups. The most frequent AEs in the pivotal studies were nausea (21.2% / 20.5% / 25% for DE 150mg /220 mg /enoxaparin), vomiting (16.0% / 16.8% / 16.8%), constipation (11.0% / 11.9% / 12.3%) , deep vein thrombosis (9.3% / 6.4% / 7.3%), insomnia (8.2% / 7.8% / 8.1%), oedema peripheral (7.3% / 6.4% / 5.9%), wound secretion (6.9% / 7.0% / 4.7%). There were no marked differences between DAB and the enoxaparin groups with regards to treatment emergent AEs classified by system organ class for the 2 pivotal studies, neither was any marked dose effect evident. Slight differences in the unfavour of DE were noted for the following AEs: hypokalemia (1.2% in the DAB 150mg group, 1.6% in the DAB 220mg group, 0.9% in the enoxaparin group), oedema peripheral (7.3% in the DAB 150mg group, 6.4% in the DAB 220mg group, 5.9% in the enoxaparin group), and wound secretion (6.9% in the DAB 150mg group, 7.0% in the DAB 220mg group, 4.7% in the enoxaparin group). Furthermore, deep vein thrombosis was more frequent in the DAB 150 mg group (but not in the 220mg group) compared to enoxaparin (9.3% vs. 7.3%). The same pattern was observed when taking the 4 VTE active controlled trials together. Most AEs were mild and moderate in severity. The severe AEs were comparable between treatment groups. In all treatment groups, AEs increased with increased age group, increased with decreasing creatinine clearance, and were more frequent in females.

Bleeding events

Bleeding events were classified as Major Bleeding Events (MBE), Clinically Relevant Bleeding Events (CRBE) and Minor Bleeding Event. The latter were defined as all other bleeding events that did not fulfil the criteria of MBE or CRBE. The clinical safety evaluations by MBE are in accordance with the CHMP/EMEA guideline. The evaluation of CRBE has been proposed by the Applicant but has not been validated. Many of the criteria are not well defined and one would expect a large variation between centres causing interpretation to be difficult. Data are presented according to the time of randomization (study 1160.24 post operative randomization and 1160.19, 1160.25, and 1160.48 pre operative randomization). The table below shows frequencies of patients experiencing a bleeding event by category of bleeding severity in the four active-controlled VTE prevention trials.

	Dabigatran etexilate				
	<150 mg	150 mg	220 mg	>220 mg	Enoxaparin
			Number (%)		
Post-operative randomisation[a]					
Treated patients	NA	871 (100.0)	857 (100.0)	NA	868 (100.0)
Most severe bleeding					
Major bleeding	--	5 (0.6)	5 (0.6)	--	12 (1.4)
Clinical relevant bleeding	--	22 (2.5)	23 (2.7)	--	21 (2.4)
Minor bleeding	--	45 (5.2)	46 (5.4)	--	51 (5.9)
No bleeding	--	799 (91.7)	783 (91.4)	--	784 (90.3)
Pre-operative randomisation[b]					
Treated patients	389 (100.0)	1866 (100.0)	1825 (100.0)	1168 (100.0)	2240 (100.0)
Most severe bleeding					
Major bleeding	1 (0.3)	24 (1.3)	33 (1.8)	49 (4.2)	35 (1.6)
Clinical relevant bleeding	9 (2.3)	103 (5.5)	88 (4.8)	48 (4.1)	87 (3.9)
Minor bleeding	16 (4.1)	131 (7.0)	130 (7.1)	91 (7.8)	168 (7.5)
No bleeding	363 (93.3)	1608 (86.2)	1574 (86.2)	980 (83.9)	1950 (87.1)

a Included Trial 1160.24.
b Included Trial 1160.19, 1160.25, and 1160.48.
Note: For Phase III Trials 1160.24, 1160.25, and 1160.48, bleeding events with onset between study drug initiation and 3 days after the last study drug administration were considered treatment emergent. For the Phase II Trial 1160.19, treatment-emergent bleeding events included those with onset up to 1 day after the last dose of study drug.

There was a difference in bleeding frequency observed between pre- and post-operative randomizations. As expected, the orthopaedic surgical site was the most frequently reported site of major bleeding in all of the VTE prevention trials. A clear dose response with respect to bleeding was seen for DAB. For any bleeding event, there was no statistical difference between DE 150 mg and enoxaparin and between DE 220 mg and Enoxaparin. Patients with MBE who required transfusion in the pivotal studies (> 2units or more) were more frequent in DAB 220mg than in enoxaparin and much less in DAB 150mg (1.58% , 1.13% and 0.75% respectively). The use of transfusions in the pivotal studies is difficult to assess since no strict rules on when to transfuse are given. In a clinical setting most transfusions are given based on haemodynamic parameters, but these are missing all together. Discontinuation due to bleeding in the pivotal studies occurred similarly and less frequently in DAB 150mg and enoxaparin than in DAB 220mg (0.05% vs 0.16%). Re-operation due to bleeding was slightly more frequent in DAB 220mg, and similar in DAB 150mg and enoxaparin (0.27% vs 0.21% respectively). A large proportion of patients with mild renal impairment (less with moderate renal impairment) was included in order to provide safety data in this subpopulation. Impaired renal function causes increased blood concentration and a raise in bleeding events. The bleeding frequency decreased with increasing creatinine clearance. Patients >75 years and patients with decreased renal function were especially at higher risk of bleeding.

The use of ASA and derivatives increases bleeding frequency although it remained lower than with the use of Enoxaparin. Very few patients used concomitant ASA or derivatives and the effect on bleeding events can not be evaluated from these studies.

Acute Coronary Syndrome (ACS)

For clinical trials with DAB that were all blinded, ACS events were based on investigator reported SAEs that might represent an ACS event. And for the three ongoing phase III trials, all reported SAEs by the investigator and related to ACS were adjudicated. Similar frequencies of ACS events in orthopaedic surgical clinical trials were observed regarding both adjudicated and non adjudicated events.

- Serious adverse event/deaths/other significant events

In the pivotal VTE primary prevention trials, frequencies of patients who experienced one or more SAEs were similar across treatment groups. Frequencies were 7.2% in the DE 150 mg group, 6.6% in the DE 220 mg group, and 6.8% in the enoxaparin group. The SOCs with the most frequently experienced SAEs were injury, poisoning, and procedural complications (1.7% in the dab 150 mg group, 1.6% in the dab 220 mg group, 2.1% in the enoxaparin group); vascular disorders (1.9% / 1.2% / 1.5%); infections and infestations (0.9% / 1.3% / 1.0%); and cardiac disorders (1.1% / 0.6% / 0.7%). For cardiac disorders, no specific SAE was prominent. For injury, poisoning, and procedural complications, the most frequent specific SAE was wound secretion, which was slightly more frequent in the DE 150 mg group (0.5%) and DE 220 mg group (0.4%) than the enoxaparin group (0.2%). For vascular disorders, the most frequent specific SAE by far was DVT, which was 1.4% in the DE 150 mg group, 0.7% in the DE 220 mg group, and 1.0% in the enoxaparin group. In the active-controlled VTE prevention trials (1160.19, 1160.24, 1160.25, and 1160.48) 31 patients (0.3%) died. During the treatment 11 patients died, 5 patients (0.2%) in the DE 150 mg group, 5 patients (0.2%) in the DE 220 mg group, 1 patient (<0.1%) in the enoxaparin group. No patients from the DE <150 mg group and the >220 mg group died during the treatment. During the post treatment period 12 patients died, and during the post study period 8 patients died. In the pivotal and active-controlled VTE prevention trials, most deaths in DE treatment groups had fatal AEs with onsets during the treatment period and most deaths in the enoxaparin group had fatal AEs with onsets during the post-treatment period. The most frequent treatment-emergent SOC was cardiac disorders, and the most frequent treatment-emergent AE was cardiac arrest. None of the treatment-emergent or post-treatment AEs leading to death were considered by investigators to be related to study medication.

The percentage of patients in the pivotal studies with common comorbidities and/or risk factors for VTE was rather low; there were for instance 2.7% and 2.3% of patients in studies 1160.25 and 1160.48, respectively with heart failure, 11.2% and 8.4% with coronary artery disease, 3.7% and 2.9% with a history of VTE. This concern should also be seen in view of the chosen endpoint which includes all-cause mortality.

- Laboratory findings

No clinically significant haematological or other laboratory abnormalities were consistently identified in the trials within the DE clinical development programme. Decrease in haemoglobin and heamatocrit were reported in all treatment groups and across all clinical trials and approximately 40% of patients had possible clinically significant abnormalities regarding haematocrit and 35% regarding haemoglobin in both Re-Model and Re-Novate trials. This is what to be expected in patients exposed to MOS.

Liver function

During DAB development, additional LFT surveillance was added to all ongoing and planned DAB clinical trial protocols, in order to detect any potential signal of hepatotoxicity. Special attention was paid to increase of ALT, as increased ALT > 3ULN is considered as a specific indicator of liver injury (hepatocyte necrosis) and increased ALT > 3ULN combined to elevated bilirubin above 2xULN within 30 days (in the absence of biliary obstruction) may indicate severe hepatotoxicity. Elevations of ALT occurred primarily in the period up to 10 days post surgery. When precisely, is not known, since no laboratory testing was done earlier. Disregarding the <150 mg and the >220 mg dosage groups in the shorter term trials, no dose response in LFT elevations was noted for DE.

Shorter term VTE prevention trials (1160.19, 1160.24, 1160.25): Elevations >2ULN, >3ULN and >5ULN were slightly more frequent in the enoxaparin groups. Elevations >10ULN occurred in 3 patients in the dab 150mg group (0.2%), 1 patient in the dab 220 mg group (0.1%) (as well as 1 patient in the >220mg group) and 2 patients in the enoxaparin group (0.1%). The elevations in the DAB 150mg group occurred in the periods 11-19 days (2 patients) and 20-56 days (1 patient). There was 1 ALT elevation >20ULN, this occurred in the dab 150 mg group, in the period 20-56 days. Longer term VTE prevention trial (1160.48): all magnitudes of ALT elevations were either more frequent or identically frequent (only in the >20ULN group) in the enoxaparin group compared to the DE groups. Elevated ALT frequencies were higher in the longer term treatment trial 1160.48 compared to the shorter term duration trials.

In summary, the LFT analyses from the VTE prevention trials do not seem to indicate hepatotoxicity. Only few data were provided in the current application from long term ongoing clinical trial in atrial

fibrillation (PETRO-EX) with DAB. Indeed up to September 2006, only 300 patients were exposed to DAB for at least one year. Increased ALT above 3 ULN was reported in eleven patients mostly with DAB 150mg b.i.d.. The causality of DAB is difficult to establish. In two cases, normalised LFTs were observed while patients remained on treatment, in three cases, a negative rechallenge was reported and in four cases a positive dechallenge was reported. The applicant provided also data from a prespecified, interim analysis of RE-LY, a long-term trial of DE in patients with atrial fibrillation. Patients with active hepatic disease or with persistent ALT, AST or alkaline phosphatase >2xULN were excluded. Patients were scheduled to receive a minimum of 1 year of treatment with either one of two blinded doses of DE (110 mg bid or 150 mg bid) or open label warfarin (target INR 2-3) with the goal of preventing strokes and systemic emboli. The overall absolute frequency of transaminase elevations >3xULN was low, approximately 1% at 6 months for both warfarin and DAB.

- Safety in special populations

Bleeding events are the most relevant safety issue in special populations. The table below presents the frequency of bleeding events stratified after special populations in the active-controlled VTE prevention trials (1160.19, 1160.24, 1160.25, and 1160.48).

	Dabigatran etexilate														
	<150 mg			150 mg			220 mg			>220 mg			Enoxaparin		
		Patients with MBE			Patients with MBE			Patients with MBE			Patients with MBE			Patients with MBE	
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
Treated patients	389			2737			2682			1168			3108		
Patient with MBE	389	1	(0.3)	2737	29	(1.1)	2682	38	(1.4)	1168	49	(4.2)	3108	47	(1.5)
Gender															
Male	166	1	(0.6)	1112	16	(1.4)	1119	12	(1.1)	441	16	(3.6)	1234	20	(1.6)
Female	223	0		1625	13	(0.8)	1563	26	(1.7)	727	33	(4.5)	1874	27	(1.4)
Age (years)															
<65	157	0		1193	10	(0.8)	1128	13	(1.2)	464	16	(3.4)	1294	7	(0.5)
65-75	158	1	(0.6)	1116	13	(1.2)	1105	12	(1.1)	483	18	(3.7)	1289	23	(1.8)
>75	74	0		428	6	(1.4)	449	13	(2.9)	221	15	(6.8)	525	17	(3.2)
BMI (kg/m^2)															
Missing	0			1	0		2	0		0			5	0	
<25	117	0		539	9	(1.7)	534	13	(2.4)	330	22	(6.7)	665	16	(2.4)
25-30	170	1	(0.6)	1096	13	(1.2)	1044	17	(1.6)	473	16	(3.4)	1209	17	(1.4)
30-35	73	0		680	3	(0.4)	708	7	(1.0)	258	9	(3.5)	840	10	(1.2)
>35	29	0		421	4	(1.0)	394	1	(0.3)	107	2	(1.9)	389	4	(1.0)
Weight (kg)															
Missing	0			0	0		0			0			1		
<50	2	0		15	0		19	0		18	0		27	1	(3.7)
50-110	380	1	(0.3)	2542	28	1.1	2496	38	1.5	1108	48	4.3	2915	44	1.5
>110	7	0		180	1	0.6	167	0		42	1	2.4	165	2	1.2
Creatinine Clearance (mL/min)															
Missing	5	0		70	1	(1.4)	64	0		16	2	(12.5)	62	0	
<30	1	0		7	0		10	0		6	1	(16.7)	14	1	(7.1)

	Dabigatran etexilate												Enoxaparin		
	<150 mg			150 mg			220 mg			>220 mg					
	Patients with MBE			Patients with MBE			Patients with MBE			Patients with MBE			Patients with MBE		
	N	n	%	N	n	%	N	n	%	N	n	%	N	n	%
30-50	24	0		185	0		199	8	(4.0)	109	8	(7.3)	248	10	(4.0)
50-80	152	1	(0.7)	1011	14	(1.4)	945	12	(1.3)	446	20	(4.5)	1148	17	(1.5)
>=80	207	0		1464	14	(1.0)	1464	18	(1.2)	591	18	(3.0)	1636	19	(1.2)

Note: N = number of treated patients; n = number of patients with MBE events.

The results in the table above remain unchanged even if a patient that were randomized post operative (study 1160.24) is excluded due to the fact that this study introduce bias towards less bleeding events. A clear dose response with respect to bleeding is seen for DAB. Patients >75 years and patients with decreased renal function (well knowing that these factors are related) are especially at risk.

- Safety related to drug-drug interactions and other interactions

Interaction studies have only been performed in adults.

Anticoagulants and platelet aggregation agents: The following treatments are not recommended concomitantly with DE: UHs and heparin derivatives, LMWH, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran, sulfinpyrazone and vitamin K antagonists. It should be noted that UH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

Interactions linked to DE and DAB metabolic profile: DE and DAB are not metabolised by the CYTP450 system and have no *in vitro* effects on human CYTP 450 enzymes. Therefore, related medicinal product interactions are not expected with DAB.

NSAIDs: When DE was coadministered with diclofenac, the plasma exposure of both medicinal products remained unchanged indicating a lack of a PK interaction between DE and diclofenac. However, due to the risk of haemorrhage, notably with NSAIDs with elimination half-lives > 12 hours, close observation for signs of bleeding is recommended.

Transporter interactions: Amiodarone is an inhibitor of the efflux transporter P-glycoprotein and DE a substrate of this transporter. When DE was coadministered with amiodarone, the extent and rate of absorption of amiodarone and its active metabolite DEA were essentially unchanged. The DAB 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. Dosing should be reduced to 150 mg DE daily in patients who received concomitantly DE and amiodarone.

P- glycoprotein inhibitors: Caution should be exercised with strong P- glycoprotein inhibitors like verapamil, clarithromycin, and others. Quinidine is contraindicated.

P- glycoprotein inducers: Potent P- glycoprotein inducers such as rifampicin or St John's wort (Hypericum perforatum), may reduce the systemic exposure of DAB. Caution is advised when co-administering these medicinal products.

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

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

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

- Discontinuation due to adverse events

During the two pivotal VTE primary prevention trials alone, frequencies of patients who discontinued study medication because of AEs were similar across the three treatment groups, with

6.1% in the DE 150 mg group, 5.4% in the DE 220 mg group, and 5.3% in the enoxaparin group. The only SOCs with specific AEs occurring in ≥0.3% of treated patients in any treatment group were cardiac disorders (atrial fibrillation in 0.3% / 0.3% / 0.4% and myocardial infarction in 0.3% / 0.1% / 0.3% in the DAB.150mg/ DAB 220mg/ enoxaparin groups), vascular disorders (DVT 0.6% / 0.3% / 0.4% in the DAB.150mg/ DAB 220mg/ enoxaparin groups), and gastrointestinal disorders (nausea 0.8% / 0.7% / 0.8% and vomiting 0.3% / 0.2% / 0.3% in the DAB.150mg/ DAB 220mg/ enoxaparin groups). The largest difference among treatment groups for any of these SOCs was only 0.5% for cardiac disorders, with 1.2% in the DE 150 mg group, 0.7% in the DE 220 mg group, and 1.1% in the enoxaparin group. No specific AE varied by more than 0.3% across treatment groups. The rates of discontinuation due to AEs did not seem to be clearly dose-dependant for the proposed therapeutic DE doses and seem to be similar to the enoxaparin group. It seems, however, that the discontinuation rate due to AEs in the DAB>220 mg group, was higher. It should be remembered, though, that these higher doses were applied only in study 1160.19. The most common reasons for discontinuation due to AEs were nausea, vomiting, injury, poisoning, and procedural complications, and deep vein thrombosis.

- Discussion on clinical safety

The safety data was based on 7942 subjects who received at least one dose of DE, 6976 of these in the VTE prevention trials. The AEs in the 2 pivotal trials as well as the 4 active controlled VTE prevention studies were largely comparable, also between the treatment groups. The most frequent AEs in the pivotal studies were nausea, vomiting, constipation, deep vein thrombosis, insomnia, oedema peripheral, and wound secretion. There were no marked differences between DAB and the enoxaparin groups with regards to treatment emergent AEs classified by system organ class for the 2 pivotal studies, neither was any marked dose effect evident. Slight differences in unfavour of DE were noted for the following AEs: hypokalaemia, oedema peripheral and wound secretion. The most common reasons for discontinuation due to AEs were nausea, vomiting, injury, poisoning, and procedural complications, and deep vein thrombosis.

Bleeding events_were classified as Major Bleeding Events (MBE), Clinically Relevant Bleeding Events (CRBE) and Minor Bleeding Event. The latter were defined as all other bleeding events that did not fulfil the criteria of MBE or CRBE. The clinical safety evaluations by MBE are in accordance with the CHMP/EMEA guideline. There was a difference in bleeding frequency observed between pre- and post-operative randomizations. As expected, the orthopaedic surgical site was the most frequently reported site of major bleeding in all of the VTE prevention trials. A clear dose response with respect to bleeding was seen for DAB. For any bleeding event, there was no statistical difference between DE 150 mg and enoxaparin and between DE 220 mg and Enoxaparin. The use of ASA and derivatives increases bleeding frequency although it remained lower than with the use of Enoxaparin. Very few patients used concomitant ASA or derivatives and the effect on bleeding events can not be evaluated from these studies. The possibility of drug monitoring would be valuable, especially for these patients at risk and commercially available TT test kits will be developed for measurement of TT following administration of DTIs (FUM). Also, increased risk of bleeding observed with DE therapy in patients with moderate renal impairment or elderly was the reason for deciding that an observational cohort study on the risk of bleeding to be conducted in the postauthorisation phase. In the pivotal VTE primary prevention trials, frequencies of patients who experienced one or more SAEs were similar across treatment groups in the main studies. The most frequently experienced SAEs were injury, poisoning, procedural complications, vascular disorders, infections and infestations, and cardiac disorders.

The percentage of patients in the pivotal studies with common co-morbidities and/or risk factors for VTE was rather low. No clinically significant haematological or other laboratory abnormalities were consistently identified in the trials within the DE clinical development programme.

During DAB development, additional LFT surveillance was added to all ongoing and planned DAB clinical trial protocols, in order to detect any potential signal of hepatotoxicity. The LFT analyses from the VTE prevention trials do not seem to indicate hepatotoxicity.

Bleeding events are the most relevant safety issue in special populations. Patients >75 years and patients with decreased renal function are especially at risk.

Drug interaction studies have only been performed in adults. The following treatments are not recommended concomitantly with DE: UHs and heparin derivatives, LMWHs, fondaparinux, desirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine, dextran,

sulfinpyrazone and vitamin K antagonists. It should be noted that UH can be administered at doses necessary to maintain a patent central venous or arterial catheter.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified risk: Bleeding	Routine pharmacovigilance activities will be used to monitor the incidence of bleeding.	An updated RMP including a prescriber guide to educate prescribers regarding methods of coagulation testing for dabigatran and its interpretation. An observational cohort study on the risk of bleedings to be conducted in the more general population of patients with an increased risk of bleeding.
Potential risk: Hepatotoxicity	Routine pharmacovigilance activities will be used to monitor for any signs/symptoms of hepatotoxicity. Data from ongoing and to be initiated controlled clinical trials of dabigatran etexilate will be monitored. In particular, there is one large trial underway from which data has already been provided to the member states. This long term study (RELY study [1160.26]) is evaluating the use of dabigatran etexilate (2 blinded doses) compared to open label warfarin in patients with atrial fibrillation. It has so far randomized 18, 114 patients and has a minimum 12-month follow-up period, which is continuing. The primary endpoint is the composite of stroke and systemic embolism. Criteria for safety include: (1) Bleeding events – major and minor bleeds: (2) Hepatobiliary events including clinically relevant changes in liver function tests and hepatic dysfunction; and (3) Other adverse events.	Contraindication for Hepatic impairment or liver disease expected to have any impact on survival in section 4.3 of the SPC. Special warning: Hepatic impairment in section 4.4 of the SPC. Patients with elevated liver enzymes > 2 ULN were excluded in controlled clinical trials. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation. Increase of hepatic enzymes listed as ADR in section 4.8 Undesirable effects of the SPC.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product were investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology 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 in the repeat-dose toxicity studies were due to the exaggerated PD effect of DAB. 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). Carcinogenicity studies have not yet been completed with DAB.

Efficacy

The clinical efficacy of DE in VTE prevention after elective THR or TKR has been demonstrated in four multi-centre, double blind, double-dummy, randomised, parallel group, controlled clinical studies. In all studies, enoxaparin, a recognized and widely used LMWH for this indication, was used as active control. The clinical confirmatory trials were all non-inferiority trials with use of non-inferiority margin in accordance with current CHMP guidance. The chosen endpoint was not in accordance with the current CHMP guidance. The endpoint proposed by the current CHMP guidance was however studied as a secondary endpoint. The proposed therapeutic doses (150 or 220 mg q.d.) were found to be non-inferior to enoxaparin in the pivotal studies.

Safety

The safety data was based on 7942 subjects who received at least one dose of DE, 6976 of these in the VTE prevention trials. The most frequent AEs in the pivotal studies were nausea, vomiting, constipation, deep vein thrombosis, insomnia, oedema peripheral, and wound secretion. There were no marked differences between DAB and the enoxaparin groups with regards to treatment emergent AEs. For any bleeding event, there was no statistical difference between DE 150 mg and enoxaparin and between DE 220 mg and enoxaparin. A clear dose response with respect to bleeding was seen for DAB. From the safety database all the adverse reactions reported in clinical trials have been included in the SPC. Having considered the safety concerns in the RMP, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The Applicant performed a readability testing ("user consultation") and a satisfactory report has been provided.

Risk-benefit assessment

- **Benefits**

In the elective THR or TKR more than 50% of the patients develop DVT in the absence of prophylactic therapy. UH and more recently LMWH have been used as anticoagulants to prevent thromboembolic events in these patients. The advantage of LMHW over UH is no need for blood level monitoring. However, the need for parenteral or subcutaneous administration is a clear disadvantage. Currently the only orally administered alternative is vitamin-K-antagonist which has numerous

limitations such as slow onset of action, a narrow therapeutic range, large inter- and intra-individual variability in PK and PD properties as well as many drug-drug interactions all necessitating frequent laboratory monitoring to adjust the dosage. In these settings an oral anticoagulant like DE not needing laboratory monitoring is therefore highly needed.

The clinical efficacy in VTE prevention after elective THR or TKR has been demonstrated in four multi-centre, double blind, double-dummy, randomised, parallel group, controlled clinical studies. In all studies, enoxaparin, a recognized and widely used LMWH for this indication, was used as active control. Two pivotal phase III studies were conducted in Europe, 1 supportive phase II study in US. Differences between European and US studies relate to time of randomization (pre-/postsurgery, respectively), 1st oral dosing time (0-4 h post surgery vs. 6-12 h post surgery, respectively), and dose regimen (enoxaparin 40mg vs. 30mg b.i.d., respectively). The patient population studied may not fully reflect the target population (exclusion of patients on platelet inhibitors such as ASA and patients with risk factors for VTE.). The prolonged duration of treatment for 28-35 days in hip surgery is considered adequate, being in line with recent guidelines. The duration of treatment in the TKR study was thus suboptimal (6-10 days) At the time of initiation of the study 10 days of thromboprophylaxis were recommended, nowadays it is 10-14 days. The clinical confirmatory trials were all non-inferiority trials with use of non-inferiority margin in accordance with current CHMP guidance. The chosen endpoint (all VTE [=proximal and distal DVT+PE] and all-cause mortality) was not in accordance with the current CHMP guidance. The endpoint proposed by the current CHMP guidance (major VTE [proximal DVT+PE] and VTE related mortality) was however studied as a secondary endpoint. The proposed therapeutic doses (150 or 220 mg q.d.) were found to be non-inferior to enoxaparin in terms of efficacy in the pivotal studies. Superiority was not shown (superiority testing was foreseen in the statistical analysis plan in case of non-inferiority was confirmed). In the US supportive study non-inferiority for both DE doses in comparison with enoxaparin was not met. Mainly distal DVTs accounted for total VTE in the study of TKR surgery. In the EU study, there were less distal DVTs in the DAB 220mg group as compared with the enoxaparin group and more in the DAB 150mg group. In the North-American supportive study, there were more distal DVTs in both DAB groups as compared with the enoxaparin group. DVT rates were lower in the US supportive study than in the EU study in TKR surgery. This may be due to the selection of patients because of post-operative randomisation, but it could also be due to the duration of treatment (not sufficiently long in the pivotal study). In THR surgery, about 50% of all DVTs were distal and about 50% were proximal in the DAB groups. There were as many distal DVTs in the DAB 220mg group as in the enoxaparin group but more distal DVTs in the DAB 150mg group, whereas there were less proximal DVTs in the DAB 220mg group as compared with the enoxaparin groupand a little more in the DAB 150mg group. The vast majority of DVT in both types of surgery were asymptomatic. Regarding the "Major VTE and VTE related mortality", secondary endpoint in both pivotal studies there were numerical fewer events in the DAB 220mg group compared to the enoxaparin group (2.6% vs 3.5% in TKR, 3.1% vs. 3.9% in THR, with no statistically significant difference) and a higher number of events in the DAB 150mg group (3.8% vs 3.5% in Re-Model, 4.3% vs 3.9% in Re-Novate). The number of symptomatic DVTs, PEs, and deaths during the treatment period was low in all three treatment groups of the phase III studies.

- **Risks**

The safety profile of DAB was similar to the one observed with enoxaparin. The most frequent AEs were related to gastrointestinal disorders, vascular disorders, injury and poisoning and procedural complications. Most AE were mild and moderate in severity. In all treatment groups, AEs increased with increased age group, increased with decreasing creatinine clearance, and were more frequent in females. A dose response with respect to bleeding was seen for DE. For the proposed doses of DE bleeding events seem overall comparable to enoxaparin. The rate of major bleeding events in the trials with pre-operative randomisation (116019, 1160.25, 1160.48) was 1.3% (95% CI 0.8; 1.9) in DAB 150mg, 1.8% (95% CI 1.2; 2.5) in DAB 220mg and 1.6% (95% CI 1.1; 2.2) in the enoxaparin groups. Any bleeding event was seen in 13.8% (95% CI 12.3; 15.4) in DAB 150mg, 13.8% (95% CI 12.2; 15.3) in DAB 220mg and 12.9% (95% CI 11.6; 14.3) in enoxaparin groups. Identified risk factors for bleeding were female in general (male patients were at increased risk in Re-Model trial), patients aged over 75 years, patients with moderate renal impairment (creatinine clearance: 50-30ml/min), BMI < 25. As expected the use of ASA and derivatives increases bleeding frequency although it remains lower than with the use of Enoxaparin. Very few patients use concomitant ASA or derivatives and the

effect on bleeding events can not be fully evaluated. The possibility of drug monitoring would be valuable, especially for these patients at risk and commercially available TT test kits will be developed for measurement of TT following administration of DTIs. No objective measures (e.g. Hgb, MAP, CVP, Hct) were used when deciding on whether a patient needed transfusion or not and a non-validated algorithm was used to evaluate bleeding events. These circumstances make it very unlikely that patients across the study sites are classified and treated in the same way when it comes to bleeding. No clinically significant haematological or other laboratory abnormalities were consistently identified in the trials within the DE clinical development programme. Because pre-clinical toxicology studies did not provide any indication of potential hepatic injury, early clinical studies of DE employed only routine surveillance for hepatotoxicity signals. Additional LFT surveillance intended to detect any potential signal of hepatotoxicity was added during all ongoing and planned DE clinical trial protocols. The applicant provided also data from a prespecified, interim analysis of RE-LY, a long-term trial of DE in patients with AF. These data do not seem to indicate hepatotoxicity. DE and DAB are not metabolised by the cytochrome P450 system and have no effects in vitro on human cytochrome P450 enzymes. Therefore, clinically relevant drug-drug interactions are not expected. Towards transport proteins such as P-glycoprotein, an effect of DAB cannot be excluded. Clinical relevant PD interactions must be expected with other drugs acting on the coagulation system and their use is therefore discouraged.

- **Balance**

The use of DE seems to be associated with a clinical efficacy comparable to that seen with the LMWH enoxaparin but with less inconveniency as the therapy can be administered orally instead of by subcutaneous injections. There is a clinical need for this kind of product. The risks are also comparable to that seen with LMWH-therapy. Likewise seems the bleeding risk comparable to that of LMWH therapy, however, with the limitation that the assessment of bleeding was partially based on a non validated algorithm. Hepatotoxicity, which previously was found for another DTI, has not been detected for DAB in the clinical program submitted. Efficacy and safety results in the EU studies show a clear dose-effect of DAB for anticoagulation. The objective of non-inferiority of DAB on total VTE and all-cause mortality was met in comparison with enoxaparin for both dosages 220mg and 150mg. There is a trend to higher efficacy of DAB 220mg compared with enoxaparin, associated with an increased bleeding risk. On the opposite, with DAB 150mg, there is a trend to lower efficacy compared with enoxaparin, associated with a lower bleeding risk, which might be useful for some at risk populations (patients with moderate renal impairment, elderly) which have increased DAB exposure. It is important to underline that the PK characteristics of DAB i.e low bioavailability (6.5%) with a very large interindividual variability, the concentration-effect relationship and the bleeding risks strongly suggest that drug monitoring is needed. Based on the above balance the benefits associated with the proposed use of DE are considered to outweigh the risks.

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

- routine pharmacovigilance was adequate to monitor the safety of the product.

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

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Pradaxa in the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery was favourable and therefore recommended the granting of the marketing authorisation.