23 April 2015
EMA/321083/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lixiana

International non-proprietary name: edoxaban

Procedure No. EMEA/H/C/002629/0000

Note

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

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Table of contents

List of abbreviations

Abbreviation	Definition
ACCP	AmericanCollege of Chest Physicians
ADME	absorption, distribution, metabolism, excretion
AF	Atrial fibrillation
aPTT	activated partial thromboplastin time
AUC	area under the concentration-time curve
$AUC_{0\text{-}inf}$, $AUC_{0\text{-}\infty}$	area under the concentration-time curve from time zero to infinity
$AUC_{0\text{-}t}$	area under the concentration-time curve from time zero to time of the last quantifiable concentration
BA	Bioavailability
BCS	Biopharmaceutic Classification System
BE	Bioequivalence
BID	*Bis in die* (twice daily)
CEC	Clinical Events Committee
CES1	Carboxylesterase 1
$CHADS_2$	Index score for stroke prediction based on the scoring system for Congestive heart failure, Hypertension, Age≥75, Diabetes, previous Stroke/Transient Ischemic Attack (doubled)
CHA_2DS_2-VASc	Congestive heart failure or left ventricular dysfunction, Hypertension, Age≥75 (doubled), Diabetes, Stroke (doubled) - Vascular disease, Age 65-74, Sex category (female)
CHF	Congestive heart failure
CI	confidence interval
CLcr or CrCL	creatinine clearance
CLr or CL_R/F	renal clearance
CL_{NR}/F	non-renal clearance
CLT	total body clearance
CLT/F or CL/F	apparent clearance
CMAs	critical material attributes
Cmax	maximum concentration
Cmin	trough concentration
CPPs	critical process parameters
CQAs	critical quality attributes
CRF	Case report form
CRNM	Clinically relevant non-major (bleed)
CSED	Common study end date
CSR	Clinical Study Report
CT/CAT	Computed tomography
CV	coefficient of variation
CYP	cytochrome P-450
DDI	Drug-drug interaction
DMC	Data Monitoring Committee
DOE	design of experiments
DVT	Deep vein thrombosis

Abbreviation	Definition
eg	*exampli gratia* (for example)
EOT	End of treatment (date)
F	absolute bioavailability
FDA	Food and Drug Administration
FEIBA	Factor eight inhibitor bypassing activity
FXa	Factor Xa
GC	gas chromatography
HAS-BLED	Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly
HPLC	high-performance liquid chromatography
HPLC/MS/MS, HPLC-MS/MS	high-performance liquid chromatography with mass spectroscopy detection
HR	Hazard ratio
ICH	International Conference of Harmonization
ICH	Intracranial hemorrhage
IDMC	Independent Data Monitoring Committee
ie,	*id est* (that is)
INR	international normalised ratio
IPC	In-process control
IR	Infrared
ISS	Integrated Summary of Safety
ISTH	International Society of Thrombosis and Hemostasis
ITT	Intent-to-treat
IXRS	Interactive voice/web response system
JP	Japanese Pharmacopoeia
KF	Karl Fischer
LLQ or LLOQ	lower limit of quantitation
LMWH	Low molecular weight heparin
LSLV	Last subject last visit
LSM	Least squares mean
MS	Mass Spectrometry
NIR	Near Infrared Spectroscopy
NMR	Nuclear Magnetic Resonance
MACE	Major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial infarction
mITT	Modified intent-to-treat
mPT	modified prothrombin time
MS	mass spectrometry
NA	Not applicable
NC	Not calculated
ND	Not determined
NOAC	Novel oral anticoagulant
NVAF	Non-valvular atrial fibrillation

Abbreviation	Definition
OATP	Organic anion transporting peptide
PARs	proven acceptable ranges
PAT	Process Analytical Technology
PCC	Prothrombin complex concentrate
PD	pharmacodynamics
PE	Pulmonary embolism
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PO	*per os* (oral)
PopPK	Population pharmacokinetics
PP	Per Protocol
PT	prothrombin time
PT	Preferred Term
PVC	Polyvinyl chloride
RH	Relative Humidity
RP-HPLC	reversed phase High Performance Liquid Chromatography
RTRT	real time release testing
RV	Right ventricular
QbD	Quality by Design
QD	*Quaque diem* (once daily)
QID	Four times daily
QTc	Corrected QT interval
QTPP	quality target product profile
SA	Scientific Advice
SAE	Serious Adverse Event
SC	Subcutaneous
SD	standard deviation
SEE	Systemic embolic event
SLP	slope of linear proportionality
SmPC	Summary of Product Characteristics
SMQ	Standard MedDRA query
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
THR	total hip replacement
TIA	Transient ischemic attack
TID	Three times daily
$t_{1/2}$	half-life
TKR	total knee replacement
Tmax	time of maximum observed concentration
TTR	Time in therapeutic range (refers to INR values)
UFH	Unfractionated heparin
ULN	upper limit of normal

Abbreviation	Definition
UV	Ultraviolet
VKA	Vitamin K antagonist
Vss	Apparent volume of distribution at steady state
VTE	Venous thromboembolism

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Daiichi Sankyo Europe GmbH submitted on 7 January 2014 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lixiana, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 September 2011.

The applicant applied for the following indication:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

- Treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonaryembolism (PE), and prevention of recurrent VTE in adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that edoxaban was considered to be a new active substance.

The application submitted is 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 tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0028/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0028/2014 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance edoxaban contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

Scientific Advice from the EMEA was sought on 24 April 2008, 22 January 2009 and 14 April 2011 for the development of the NVAF indication. As a result of these meetings, a number of approaches were agreed and changes to the Phase 3 pivotal study made. Some of the key points are summarized hereafter: a) The doses for Phase 3 were agreed to be acceptable; b) The primary efficacy and safety endpoints were acceptable and a focus on cardiovascular and all-cause mortality was established; c) The inclusion and exclusion criteria were clarified and in particular subjects with AF secondary to severe valvular disease were excluded while subjects with bioprosthetic valves were permitted; d) The justification for the non-inferiority margin and the statistical testing to support a single pivotal study were not fully agreed. It was agreed that the primary analysis for the EU would be the per-protocol population and the overall study period and the results would need to be consistent across the endpoints.

For the development of the VTE indication, scientific advice was sought from the CHMP on 24 September 2009: a) The doses for Phase 3 were agreed to be acceptable; b)The primary efficacy and safety endpoints were acceptable and a focus on cardiovascular mortality was established; c)The justification for the non-inferiority margin and the statistical testing to support a single pivotal study were not fully resolved. In response to regulatory feedback, the non-inferiority margin of the study was made more stringent so that a minimum of 70% of the efficacy of the heparin and warfarin regimen was maintained; d) A point of concern for the CHMP was the decision for duration of treatment could be taken after randomization. The applicant has been mindful of this concern in analyzing and presenting the results; e) It was agreed that the primary analysis for the EU would be the per-protocol population and the period from randomization to 30 days after the last dose and the results would need to be consistent across the endpoints.

During the current clinical development, the *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014*) has been drafted and came into effect on 26th December 2014. The compliance of the pivotal study in NVAF to the available Guideline is discussed under the efficacy endpoints. In addition, a revision of the *EMA Note for Guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease (CPMP/EWP/563/98)* is currently ongoing.

Licensing status

Lixiana has been given a Marketing Authorisation in Japan on 21 April 2011 and in the US on 8 January 2015.

1.2. Manufacturers

Manufacturer responsible for batch release

Daiichi Sankyo Europe GmbH
Luitpoldstrasse 1,
Pfaffenhofen, Bayern, 85276, Germany

1.3. Steps taken for the assessment of the product

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

Rapporteur: Concepcion Prieto Yerro

Co-Rapporteur: Martina Weise

- The application was received by the EMA on 7 January 2014.
- The procedure started on 26 February 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 23 May 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 May 2014 .
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 13 June 2014.
- During the meeting on 26 June 2014, 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 27 June 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 September 2014.
- The summary report of the inspection carried out at the following site Daiichi Sankyo Europe GmbH Luitpoldstrasse 1, Pfaffenhofen, Bayern, 85276, Germanybetween 26/09/2014 and 01/10/2014 was issued on 16/12/2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 November 2014 .
- PRAC RMP Advice and assessment overview, adopted on 6 November 2014.
- During the CHMP meeting on 20 November 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 December 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 12 January 2015 .
- During the CHMP meeting on 22 January 2015, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 26 January 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 9 February 2015.
- The Rapporteurs circulated the Joint updated Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 20 February 2015.
- During the CHMP meeting on 24 February 2015, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- PRAC Rapporteur's Risk Management Plan (RMP) Assessment Report as endorsed by PRAC on 10 April 2015.
- During the meeting on 23 April 2015 , the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Lixiana.

2. Scientific discussion

2.1. Introduction

Atrial fibrillation (AF) represents the most common sustained cardiac arrhythmia, affecting more than 6 million people in Europe[1]. AF, particularly when it is persistent/permanent, predisposes patients to the development of atrial thrombi, which may embolize to the systemic circulation, being associated with a 4- to 5-fold increase in the risk of ischemic stroke and systemic embolic events (SEE)[2]. Vitamin K antagonists (VKA; coumarins, like warfarin and acenocoumarol) have been the only oral anticoagulants available over the last 60 years. These agents are effective to prevent stroke in patients with AF, but their management remains problematic due to their narrow therapeutic index and variability in drug exposure, necessitating routine coagulation monitoring, clinical surveillance, and continuous patient education[3]. Such monitoring is inconvenient for patients and medical staff, and costly for healthcare payers. As a result, approximately only half of eligible patients with AF receive oral anticoagulation with VKA.

Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading mortality cause due to circulatory diseases, only behind of myocardial infarction and stroke. Current guidelines recommend treating patients with acute VTE with an oral VKA for at least 3 months[4]. As VKA have a slow onset of action, overlapping with a parenteral anticoagulant [e.g.: low molecular weight heparin (LMWH) or unfractionated heparin (UFH)] is needed for the initial 5–10 days of acute VTE, until appropriate anticoagulation with VKA is achieved [i.e.: international normalized ratio (INR) between 2.0 and 3.0]. LMWH are effective and safe also for the long-term treatment of VTE. However, they still require daily parenteral subcutaneous (SC) administration, which may be problematic for many patients. On the other hand, the VKA have several limitations, as mentioned in previous paragraph.

Direct oral anticoagulants (DOAC) are currently available in the EU and other regions for several indications, including prevention of stroke/SEE in NVAF and/or treatment of VTE: the direct thrombin inhibitor dabigatran (as etexilate) and the direct factor Xa inhibitors rivaroxaban and apixaban. Unlike VKA, these new compounds exhibit a predictable dose response and do not require routine coagulation monitoring, but their anticoagulant effect declines quickly in case of poor compliance and no widely available coagulation monitoring tests or specific antidotes are currently available[5]. The pivotal studies conducted with the DOAC in prevention of stroke/SEE in NVAF or treatment of VTE were mainly large non-inferiority event-driven clinical trials recruiting heterogeneous populations in different geographic regions and with different quality of oral anticoagulation with warfarin. The potential influence of differences in clinical, geographic factors and quality of oral anticoagulation across studies on the relative efficacy and safety of the NOAC, as well as the clinical relevance of these differences, may be significant, particularly in NVAF indication[6].

Edoxaban is a novel, orally active, selective, direct, reversible inhibitor of the coagulation factor Xa (FXa). The prefix “edo” is a tribute to the old imperial city called “Edo” (now Tokyo), while the suffix “xaban” is the common family name of the direct factor Xa inhibitors. Factor Xa plays a pivotal role in the coagulation cascade because it sits at the junction of the intrinsic and extrinsic pathways of the coagulation system. Inhibition of FXa is exerting anticoagulant and antithrombotic effects by decreasing the conversion of prothrombin to active thrombin, thereby diminishing thrombin-mediated activation of the coagulation process, including fibrin formation and platelet activation.

[1] Camm AJ, et al. Eur Heart J. 2010; 31: 2369-429.
[2] Camm AJ, et al. Eur Heart J. 2010; 31: 2369-429.
[3] Ansell J, et al. Chest. 2008;133:160S-198S.
[4] Kearon C, et al. Chest. 2012;141(2 Suppl):e419S-e494S.
[5] Gómez-Outes A, et al. Curr Drug Discov Technol. 2012;9:83-104.
[6] Gómez-Outes A, et al. Thrombosis. 2013:640723.

Currently, edoxaban is approved in Japan for prophylaxis of venous thromboembolism (VTE) in subjects undergoing orthopedic surgeries and in the US to reduce the risk of stroke and systemic embolism (SE) in patients with NVAF and treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).

The CHMP granted the positive opinion for the following indications:

Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ⩾ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).

For *the prevention of stroke and systemic embolism*, the recommended dose is 60 mg Lixiana once daily. For *the treatment of VTE including DVT and PE*, *and prevention of recurrent VTE*, the recommended dose is 60 mg Lixiana once daily following initial use of heparin. For NVAF and VTE the recommended dose is 30 mg Lixiana once daily in patients with one or more of the following clinical factors: a) moderate or severe renal impairment (creatinine clearance: 15-50 ml/min); b) low body weight ≤60 kg; c) concomitant use of the following P-glycoprotein (P-gp) inhibitors: ciclosporine, dronedarone, erythromycin, ketoconazole.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as immediate release tablets containing 15 mg, 30 mg or 60 mg of edoxaban tosilate as active substance.

Other ingredients are:

Tablet core: mannitol (E421), pregelatinised starch, crospovidone, hydroxypropylcellulose, magnesium stearate (E470b);

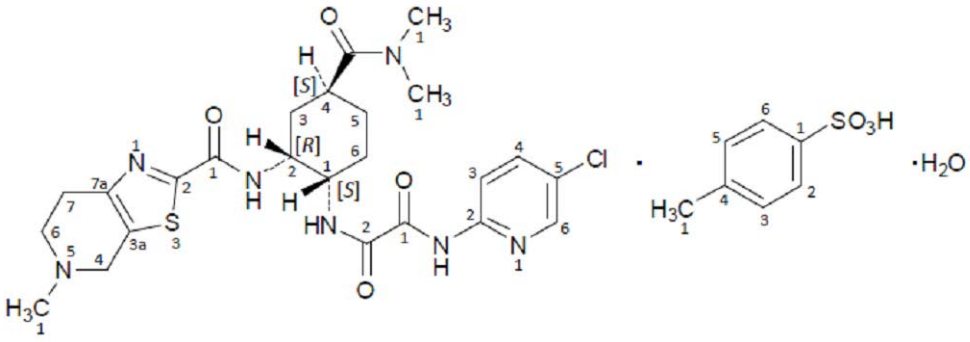
Film-coat: hypromellose (E464), macrogol 8000, titanium dioxide (E171), talc, carnauba wax, iron oxide yellow (E172), iron oxide red (E172).

The product is available in PVC/aluminium blisters.

2.2.2. Active Substance

General information

The chemical name of edoxaban tosilate is *N*-(5-chloropyridin-2-yl)-*N*'-[(1*S*,2*R*,4*S*)-4 (*N*,*N*-dimethylcarbamoyl)-
2-(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-c]pyridine-2-carboxamido)cyclohexyl]oxamide mono(4-methylbenzenesulfonate) monohydrate and it has the following structure:



The chemical structure of edoxaban tosilate has been confirmed by elemental analysis, spectroscopic techniques (UV, IR, ^{1}H and ^{13}C NMR), mass spectrometry and single X-ray structure analysis.

The active substance is a white to pale yellowish-white non-hygroscopic crystalline powder which is practically insoluble in isopropanol and ethyl acetate, slightly soluble in water, ethanol and acetonitrile, soluble in methanol and freely soluble in DMSO and *N*,*N*-dimethylformamide.

Edoxaban exhibits stereoisomerism due to the presence of three chiral centres. The chirality of edoxaban is determined by the synthesis of the relevant starting material and is controlled by the specification of this starting material.

Edoxaban tosilate exists in two polymorphic forms, form I (thermodynamically most stable form) and form II. The crystalline form consistently produced by the proposed synthetic route is form I. In addition, the results from the stability studies conducted on edoxaban tosilate show no evidence of conversion between form I to form II.

Manufacture, characterisation and process controls

Edoxaban tosilate is synthesized by two manufacturers in a three arm convergent synthesis comprising six main stages using well-defined starting materials with acceptable specifications, followed by crystallization and milling. However, at the time of opinion the HPLC method developed to test one of the starting materials was not capable of identifying its oxalate counter ion. Therefore, the applicant is recommended to develop a specific test for the identification of the oxalate in this starting material. The stereocentres introduced in this starting material are stable to epimerization in subsequent synthetic steps.

The particle size of edoxaban tosilate affects its dissolution and is therefore a critical quality attribute (CQA) of the finished product. Several design of experiments (DOEs) were conducted to determine the optimal crystallization process and milling conditions leading to the desired particle size distribution. These included the evaluation of three critical process parameters: pulverization hammer revolution, separator rotor revolution and flow rate. Based in these studies, proven acceptable ranges (PARs) were defined for these parameters. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. A potentially genotoxic reagent is used in the final synthetic step. It was stated that this reagent converts to a non-mutagenic compound under the subsequent acidic crystallisation conditions, and also in the acidic stomach environment when orally administered. However, no specific analytical method for quantification of this reagent is available. The applicant provided data demonstrating that the reagent is genotoxic *in vitro*, but not in a series of *in vivo* studies and therefore, no further *in vivo* mutagenicity studies are required and this reagent can be considered as a class 4 impurity according to ICH M7.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable with the exception of potential benzene in some organic solvents. The applicant is recommended to develop a GC method to test potential benzene levels in ethanol, methanol, isopropyl alcohol and *n*-hexane and update their specifications if required.

Specification

The active substance specification includes tests for appearance, identity (IR, RP-HPLC), assay (RP-HPLC), impurities (RP-HPLC, chiral HPLC), residual solvents (GC), water content (KF), heavy metals (JP), residue on ignition (Ph. Eur.), particle size distribution (Ph. Eur.) and microbial limits (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

The method from the Japanese Pharmacopeia (JP) used for the determination of heavy metals was cross validated against Ph. Eur. monograph, confirming the applicability of both methods as a limit test method for heavy metals in edoxaban tosilate drug substance.

Batch analysis data on fifteen pilot scale batches manufactured during the development program and five commercial scale batches of the active substance were provided. The results were within the specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches of active substance from a development site and three commercial scale batches from one of the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 36 months (pilot scale batches) or up to 6 months (commercial scale batches) months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The following parameters were tested: appearance, colour, optical rotation, identification, assay, related substances, residual solvents, water content, particle size distribution, crystallinity, thermal analysis and microbial purity. The analytical methods used were the same as for release and are stability indicating. For the additional tests performed as part of primary stability studies, which are not part of the release/shelf-life specification, (colour, optical rotation, some related substances, crystallinity, thermal analysis and microbial purity), adequate validation data have been provided. All results were within the proposed specification, and no differences were observed in stability behaviour between the pilot and the commercial scale batches.

Forced degradation studies were performed by exposing solutions of active substance to acid, base, oxidant and solid samples to heat and humidity (25 ºC /33% RH, 25 ºC /93% RH, 40 ºC /75% RH), heat (60 ºC) or light. The results from these studies demonstrated that the active substance is stable to all tested conditions in the solid state but degrades in solution.

In addition, one pilot-scale batch was exposed to light as defined in the ICH Guideline on photostability testing of new drug substances and products. The appearance of the drug substance remained as “white powder” following exposure to the light conditions. There was no observed change in the impurity profile throughout the study, specifically no new degradation products were observed and no change enantiomeric and stereoisomeric content was detected, confirming that edoxaban tosilate is photostable.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The drug product is presented as film-coated, immediate-release tablets available in three strengths: 15 mg, 30 mg and 60 mg.

The quality target product profile (QTPP) was defined as immediate release film-coated tablets containing 15 mg, 30 mg or 60 mg of edoxaban, which can be discriminated visually (by size, film-coating colour and debossed information), and meet compendial and other relevant quality standards.

The critical quality attributes identified were assay, uniformity of dosage units, dissolution, appearance, identity and impurities. Prior knowledge, DOE and mathematical models were applied to identify critical material attributes (CMAs) and critical process parameters (CPPs).

Since edoxaban tosilate is a low solubility compound, studies were conducted to evaluate the impact of its particle size on the drug product dissolution rate and content uniformity. The results from these studies showed that the particle size of the active substance had an impact on the dissolution rate, but not on the content uniformity. Therefore, edoxaban tosilate particle size is reduced during the last step of the manufacturing process of the active substance by milling. X-ray powder diffraction studies confirmed that the polymorphic form I is not changed during the drug product manufacturing process.

The selection of excipients and their target concentrations was conducted using a computer system that identified the initial formulation, followed by a diluent selection study, a disintegrant selection study and DOE to determine the final target concentration for the binder, disintegrant and lubricant based on their impact on dissolution performance and tablet hardness. Additionally, a compatibility study using binary mixtures of excipient-drug substance was performed to evaluate the stability of the potential formulations. Based on these studies, mannitol and pregelatinised starch were selected as diluents, crospovidone as disintegrant, hydroxypopyl cellulose as binder and magnesium stearate as lubricant.

Optimisation of the film coating was next undertaken. Colouring agents were incorporated to differentiate the tablet strengths for commercial use.

All excipients used are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The pharmaceutical development was conducted using Quality by Design (QbD) principles. The applicant proposed some “in-house” terminology which slightly deviated from that one included in ICH guidelines. This is not acceptable and was clarified during the assessment process.

In particular, according to ICH guidance, design spaces are built from CPPs and CMAs of the input materials. However, the applicant instead proposed design spaces for three drug product CQAs, (content uniformity, assay and dissolution), built from CMAs of the output materials (in this case, intermediates) so that they were scale independent. Since the applicant defines the design spaces based on CMAs of intermediates in the manufacturing process and not on input parameters, the ICH definition is not met. However, no regulatory flexibility in terms of process parameters as described in ICH Q8-Q10 was claimed.

Prior knowledge and preliminary hazard analysis (PHA) and failure mode and effects analysis (FMEA) risk assessments were applied to identify CMAs of the API, excipients and in-process materials, and the impact of the manufacturing process unit operations (granulation, blending, tableting and film-coating) on the CQAs. PHA and FMEA risk assessments were also performed to identify the CPPs

which need to be controlled to ensure that the CMAs remain within their target ranges, which in turn ensure that the CQAs of the finished product are attained.

The design spaces were developed at pilot scale. The verification of the design space for content uniformity and assay was performed at commercial scale, but only with the 15 mg strength. The verification of the design space for dissolution was performed with all three strengths, but only at one third of commercial scale. Taking into account that the CMAs of the design spaces are scale independent the verification is considered sufficient.

The formulation used during clinical studies is the same that the used for marketing.

With regards to dissolution method development, a study was conducted to evaluate which pH medium had the best discriminatory capability when varying typical CMAs. The results from these studies demonstrated that the selected pH had adequate discriminatory capability whilst maintaining sink conditions.

The primary packaging is a PVC/aluminum blister. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process of Lixiana tablets consists of four main steps: fluid bed granulation; blending; tableting; film-coating. The tablets are manufactured from a common granulate and are quantitatively proportional. The process is considered to be a standard manufacturing process

As described under the pharmaceutical development section the CQAs of Lixiana tablets are ensured by controlling CMAs within defined design spaces. The control strategy for commercial batches uses process analytical technology (PAT) to ensure the intermediate CMAs are met. It has been demonstrated that these CMAs act as surrogates for Lixiana CQAs which in turn allows a real time release testing (RTRT) strategy to be employed. In addition, some traditional in-process controls (IPCs) are also conducted to verify that each unit operation is carried out as planned.

A hybrid approach for process validation as described in the “Guideline on process validation for finished products - information and data to be provided in regulatory submissions (EMA/CHMP/CVMP/QWP/BWP/70278/2012-Rev1)” has been followed. Traditional process validation has been followed for non-critical manufacturing steps, and a continuous process verification approach for critical steps. A process validation scheme has been provided. To demonstrate and verify that the CQAs meet the specification, extensive in-line and at-line controls including PAT have been established.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product specifications include appropriate tests for this kind of dosage form and comprise appearance, identification (NIR, UV-Vis, HPLC), assay (NIR/gravimetry, HPLC), related substances (HPLC), uniformity of dosage units (NIR/gravimetry, Ph. Eur.), dissolution (NIR/laser diffraction/gravimetry/ thickness, Ph. Eur.), water content (KF), and microbial control (Ph. Eur.).

The absence on a test for enantiomer and stereoisomers content has been adequately justified based on the results from the stability studies.

The finished product is released onto the market through a combination of end product testing and RTRT. The strategy for RTRT has been described in detail, and verification tests against secondary

methods have been adequately described. Parallel data comparing RTRT with equivalent end product release testing at commercial scale has also been provided.

Relevant information regarding chemometric model development, data collection, model calibration, method verification and model maintenance was provided. RTRT has been established for all the CQAs. Content uniformity, assay and dissolution would be monitored by the design spaces developed.

Batch analysis results are provided for batches of 15 mg (8 pilot, 1 commercial scale), 30 mg (6 pilot, 1 commercial scale) and 60 mg (8 pilot, 1 commercial) tablets confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Analytical procedures have been adequately described and validated according to the ICH QR2 guideline and the EMA guideline on the use of Near Infrared Spectroscopy (NIRS) by the pharmaceutical industry.

Stability of the product

Stability data on three pilot scale batches of finished product of each strength stored under long term (25 ºC / 60% RH) and intermediate (30 ºC /75% RH) conditions for up to 24 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. The batches of medicinal product are representative of those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, related substances, enantiomeric impurity, stereosisomer, dissolution, water content and microbial purity. The analytical procedures used are stability indicating.

Stress stability studies were also conducted on Lixiana bulk tablets for all three dosage strengths. Bulk tablets were stored at 60 °C in amber glass bottles closed and tested at the initial time-point and after 1 and 2 months. Bulk tablets of all three dosage strengths were stored in an open dish at 40 °C/75% RH and tested after 1, 2 and 3 months.

No significant changes in the tested parameters appearance, assay, related substances and dissolution were reported under any of the conditions described above. An increase of the water content was observed but had no influence on the quality of the drug product.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products showing that the product is photostable and no special protection from light is required.

In order to simulate short term temperature excursions during transportation, Lixiana tablets packed in the primary packaging material as well as in bulk containers were stored at 60 ºC for 7 days, and were subjected to a temperature cycling study over a period of 12 days. No significant changes in the tested parameters were observed.

A freeze-thaw stability study on tablets stored in double aluminium blisters or aluminium/PVC blisters as well as in bulk containers was also conducted. Samples were stored under thermal cycling conditions for 12 days at alternating temperatures of 40 ºC (12 hours) and -20 ºC (12 hours). No significant changes in the tested parameters were observed, and the proposed transport conditions are therefore supported.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

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

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Lixiana is presented as an immediate-release film-coated tablets containing 15, 30 or 60 mg of edoxaban tosilate as active substance. Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The applicant has applied QbD principles in the development of the finished product and their manufacturing process. Design spaces based on critical material attributes have been proposed for assay, content uniformity and dissolution. The design spaces have been adequately verified. The applicant has applied for Real Time Release Testing (RTRT) for the drug product using Near Infra-Red (NIR) method for identification, assay and uniformity of dosage units. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

-The applicant is recommended to introduce either a IR or HPLC identification test for oxalic acid in the relevant starting material.

-The applicant is recommended to develop a GC method to test potential benzene levels in ethanol, methanol, isopropyl alcohol and n-hexane and update their specifications.

2.3. Non-clinical aspects

2.3.1. Introduction

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro and in vivo primary pharmacology studies with edoxaban tosilate hydrate were conducted by the Applicant in order to elucidate its mechanism of action and assess its anticoagulant effect. In the primary pharmacology studies, inhibitory activities of edoxaban tosilate hydrate on factor Xa and the prothrombinase complex and its selectivity for factor Xa were examined in vitro to elucidate the mechanism of action. Edoxaban tosilate hydrate inhibited human factor Xa with a Ki value of 0.561 nM, and it also inhibited rabbit or cynomolgus monkey factor Xa with similar Ki values of 0.457 and 0.715 nM, respectively, whereas inhibition of rat factor Xa had an about 10-fold higher Ki value of 6.98 nM.

Detailed analysis of enzyme kinetics demonstrated that edoxaban tosilate hydrate is a competitive inhibitor of factor Xa. Although edoxaban, rivaroxaban and apixaban have different chemical

structures, X-ray analysis demonstrated that the binding sites for all three substances on factor Xa involve 2 distinct sites (S1 and S4), i.e. that the binding sites for these substances are at least overlapping if not identical. These observations might be of relevance for the development of antagonists for factor Xa inhibitors.

The anticoagulant effect of the product (prolongation effect on clotting time) was assessed in vitro, as well as the inhibition of activity of factor Xa derived from mutant factor X and the pharmacological activities of several metabolites. Metabolites D21-1402-0201 and D21-2135-0101 prolonged PT in human and rat plasma, with CT2 values similar to those of edoxaban tosilate hydrate.

Antithrombotic effects of the drug were examined in vivo using five rat thrombosis models. In rat models of venous thrombosis and venous stasis thrombosis, pre-treatment with a single oral dose of edoxaban tosilate hydrate dose-dependently inhibited venous thrombosis and exerted anti-Xa activity in plasma at a minimum effective dose of 2.5 and 0.5 mg/kg, respectively, whereas the dose required for PT prolongation was 12.5 mg/kg. In the rat A-V shunt model, the drug inhibited thrombosis in a dose-dependent manner at single oral doses of 2.5 mg/kg or more, and in a rat DIC model, the drug showed a dose-dependent anticoagulant effect at single oral doses of 0.1 mg/kg or more, along with inhibition of platelet consumption, the increase of thrombin-antithrombin III complex, and the decrease of fibrinogen.

It is remarkable that edoxaban inhibited factor Xa activity in rats with an IC50 value of 7 nM, whereas much higher concentrations (in the micromolar range) were required to inhibit thrombus formation in rat thrombosis models. Similar observations have been made previously (Hara et al. 1995), that the factor Xa inhibitor DX-9065a potently inhibited human factor Xa, but that a much higher dose was required to inhibit thrombus formation in a rat thrombosis model. The higher potency for edoxaban regarding inhibition of factor Xa activity when compared to inhibition of thrombus formation in rat thrombosis models was explained by the Applicant by the higher amount of factor Xa generated during thrombus formation in the in vivo thrombosis models.

Edoxaban tosilate hydrate was compared to anticoagulant drugs warfarin and enoxaparin in a rat model of venous thrombosis, showing that edoxaban tosilate hydrate significantly prevents venous thrombosis, like warfarin sodium and enoxaparin sodium, although the onset of action was more rapid after treatment with edoxaban tosilate hydrate than with warfarin sodium in these models. In addition, in a rat model of venous thrombosis treatment, edoxaban tosilate hydrate, enoxaparin sodium and fondaparinux sodium reduced the thrombus weight in a dose-dependent manner.

In conclusion, orally administered edoxaban tosilate hydrate has the potential to treat venous thrombosis similar to warfarin, enoxaparin and fondaparinux, which have different mechanisms of action.

Secondary pharmacodynamic studies

Several in vitro and in vivo secondary pharmacology studies were conducted by the Applicant. In vitro pharmacological activity of 10 µM edoxaban tosilate hydrate was tested on 63 receptors, channels, transporters and enzymes. Edoxaban showed significant affinity for histamine H_2 and opioid binding sites, although the concentration evaluated in the study (10 µM) was about 16 times the exposure in patients given edoxaban at dose of 60 mg, and no clinical relevance is expected.

In the secondary pharmacology studies conducted by the Applicant, edoxaban tosilate hydrate at 100 µM had no effect on aggregation of human platelets induced by collagen, the thromboxane A2 receptor agonist U46619 or ADP. It inhibited thrombin-induced aggregation of human washed platelets. In addition, in a rat bleeding model, edoxaban tosilate hydrate prolonged the bleeding time to a lesser extent than warfarin sodium and enoxaparin sodium, achieving a higher therapeutic index (BT2/ED50). In human plasma or whole blood, anticoagulant activities of edoxaban tosilate hydrate

were significantly suppressed by coagulants recombinant factor VIIa, Feiba™ and PPSB®-HT. Lastly, in a rat plantar bleeding model, tranexamic acid did not affect the prolonged bleeding time and PT induced by a supratherapeutic dose of edoxaban tosilate hydrate. However, the CHMP was concerned whether there is progress in the development of specific antidotes which are able to antagonize the effects of edoxaban tosilate hydrate on blood coagulation (e.g. factor Xa mutants lacking enzymatic activity). This was discussed further in the clinical section (Pharmacodynamic interactions with other medicinal products or substances).

Safety pharmacology programme

The potential adverse effects of edoxaban tosilate hydrate on vital functions have been investigated in a battery of safety pharmacology studies on the central nervous, cardiovascular, respiratory systems and on renal function. The highest dose of 200 mg/kg or the highest concentration of 20 µg/mL used in these studies correspond to 200-times or 58-times, respectively, the recommended clinical dose of a 60 mg of edoxaban tosilate hydrate or its corresponding Cmax value of 0.347 µg/mL. One safety pharmacology study (Study 20020556) was performed in conscious cynomolgus monkeys in order to investigate the effects of edoxaban tosilate hydrate on the central nervous system, the respiratory system and on the cardiovascular system. In addition, one study was performed in order to investigate the effects of edoxaban tosilate hydrate on the central nervous system in mice, one study was performed in order to investigate the effects of edoxaban tosilate hydrate on renal function in rats, and two in-vitro studies (hERG, action potential assay in ventricular papillary muscles from guinea pig) were performed in order to investigate the effect of edoxaban tosilate hydrate on cardiac electrophysiology. No clinically relevant effects were observed in these studies. Edoxaban tosilate hydrate at oral doses of 200 mg/kg did neither affect the function of the central nervous system of mice and monkeys, the respiratory system of monkeys nor the renal function of rats. Edoxaban tosilate hydrate at concentrations of up to 20 µg/ml had no effect on hERG currents or on action potential (AP) parameters in right ventricular guinea pig papillary muscles. Edoxaban tosilate hydrate at oral doses of up to 200 mg/kg did not affect blood pressure, heart rate or ECG parameters in conscious unrestrained cynomolgus monkeys.

Pharmacodynamic drug interactions

No nonclinical studies of pharmacodynamic drug interactions were conducted because clinical interaction studies with aspirin, naproxen and warfarin were undertaken.

2.3.3. Pharmacokinetics

In-vivo nonclinical pharmacokinetic (PK) studies of edoxaban tosilate hydrate were performed primarily in rats and cynomolgus monkeys, which were also used in the toxicology studies. PK were evaluated using oral or intravenous doses of unlabelled or 14C-labelled edoxaban tosilate hydrate, which were dissolved in a solution in 0.5% methylcellulose aqueous solution. In-vitro nonclinical PK studies were performed with 14C-edoxaban tosilate hydrate using animal and human plasma/blood. For D21-2393, a human specific metabolite, the nonclinical PK studies were also performed to assess protein binding and tissue distribution using 14C-labeled D21-2393.

After single oral administration of edoxaban tosilate to rats and cynomolgus monkeys, edoxaban was absorbed with a bioavailability of about 40% in rats and 55% in monkeys, and the plasma edoxaban concentration increased rapidly. After reaching Cmax, edoxaban concentration declined in a biphasic manner with elimination t½ of 0.67 to 5.05 h in rats and 1.55 to 6.59 h in cynomolgus monkeys. Repeat dosing for 2 weeks in rat and 4 weeks in cynomolgus monkeys did not markedly increase edoxaban exposure, although rats treated daily with edoxaban for 4 weeks showed an increase in Cmax and AUC0-24h. However, according to the Applicant, in the clinical studies there is no evidence

that repeated dosing altered the exposure to edoxaban, indicating that steady state exposure is attained within 3 days in humans.

Tissue distribution of edoxaban tosilate hydrate was evaluated in albino and pigmented rats and cynomolgus monkeys. Edoxaban showed a broad tissue-distribution of radioactivity except for central nerve system in all species tested. In pigmented rats and monkeys, higher levels of radioactivity were found in the eyeball and skin than in other tissues, with a t½ for radioactivity in the eyeball of pigmented rats of approximately 260 h. These data indicate that edoxaban and/or its metabolites may have an affinity to melanin-containing tissues. However, the in vitro phototoxicity studies and the 39-week or 52-week repeated-dose oral toxicity studies in cynomolgus monkeys did not show any photosafety issue.

For the investigation of paediatric population, the tissue distribution of radiolabelled edoxaban tosilate was studied in infant, juvenile and adult rats. Infant albino rats exhibited higher radioactivity concentrations in blood and tissues than those in juvenile and adult rats after a single oral dose of ^{14}C-edoxaban tosilate hydrate.

The plasma protein binding of edoxaban in animals and humans (31.6%-56.6%) suggests that edoxaban is unlikely to interact with other drugs via this mechanism.

In vitro metabolism studies conducted by the Applicant are included in the clinical dossier.

Quantitative metabolite profiles of edoxaban in rats and cynomolgus monkeys were investigated with ^{14}C-edoxaban label B, so the labelled position would not be released by metabolism. After an oral dose of ^{14}C-edoxaban to rats and monkeys, unchanged edoxaban was the major radioactive compound in plasma, and it was primarily excreted as unchanged in both species. These data indicate that metabolism makes a minor contribution to the clearance of edoxaban so that any inhibition of drug-metabolizing enzymes is unlikely to affect its PK. The main metabolite in human plasma, D21-2393, was not detected in rat or cynomolgus monkey plasma.

Edoxaban and its metabolites were excreted into urine, bile (tested only in rats) and faeces in rats and cynomolgus monkeys. In rats, at least 24% of the radioactivity excreted into the bile was reabsorbed, suggesting that enterohepatic circulation may occur. Radioactivity was secreted into milk in rats.

A study using *mdr1a/1b* knock-out mice showed that edoxaban is a substrate for mouse P-gp mdr1a/1b, which plays a role in the restricted brain uptake of edoxaban. In consistency with that, an in vitro transcellular transport study using Caco-2 cells demonstrated that edoxaban is a substrate of human P-gp MDR1.

The tissue distribution of D21-2393, the main metabolite in human plasma, was investigated using infant (PND4), juvenile (3 weeks old) and adult (6 weeks old) rats of albino (male Wistar) and pigmented (male Brown Norway) strains. Adult rats exhibited rapid elimination of ^{14}C-D21-2393-derived radioactivity in blood and tissues; the radioactivity concentrations in the blood and tissues in infant and juvenile rats were higher than that in adult rats. The remaining radioactivity in the eyeball and skin observed at 24 h post-dose in infant and juvenile pigmented rats suggested an affinity of D21-2393 to melanin-containing tissues; however, the affinity seems to be less potent compared to edoxaban, which showed long retention of radioactivity in melanin-containing tissues.

The higher blood and tissue concentrations of both edoxaban and its main human metabolite D21-2393 in infant and juvenile compared to adult rats have been explained by the Applicant by the immature development of drug metabolizing enzymes (cytochrome P450 3A4 for edoxaban) and transporters (P-glycoprotein for edoxaban, organic anion transporting peptides (OATP) and other hepatic transporters for D21-2393.

In conclusion, the nonclinical PK studies indicate that edoxaban is absorbed rapidly, has a broad tissue distribution with a high affinity for melanin-containing tissues and is eliminated mainly as a parent compound via hepatic/renal excretion and with limited metabolic elimination.

2.3.4. Toxicology

The toxicology of edoxaban tosilate hydrate has been evaluated in single- and repeated-dose toxicity studies in rats and cynomolgus monkeys, genotoxicity studies, carcinogenicity studies in mice and rats, reproductive and developmental toxicity studies in rats and rabbits, a juvenile toxicity study in rats, and other special toxicity studies including photosafety, ocular toxicity (eye function test), haemolysis and vascular irritation studies. Potential toxicity of the human specific metabolite D21-2393 was also evaluated in repeated-dose oral toxicity studies in rats, in-vitro and in-vivo genotoxicity studies, embryo-fetal developmental toxicity and juvenile toxicity studies in rats.

Single dose toxicity

In single-dose toxicity studies performed in rats, edoxaban tosilate hydrate did not show toxic changes at doses of up to 2000 mg/kg. In single-dose toxicity studies performed in cynomolgus monkeys, prolongations of PT and APTT and a decrease in factor X activity were observed at doses of 200 and 400 mg/kg, and the lethal dose of edoxaban tosilate hydrate was above 400 mg/kg.

Repeat dose toxicity

In repeated dose oral toxicity studies in rats, a small number of focal hemorrhagic lesions were observed in the pancreas, lung and thymus given edoxaban tosilate hydrate at doses ≥ 20 mg/kg/day. These focal incidences were considered to be an extension of the pharmacological activity of edoxaban. In the 26-week repeated dose oral toxicity study in rats, the death of a female animal in the highest dose group was considered by the Applicant not related to the treatment.

Since pharmacological activity of edoxaban tosilate hydrate for the cynomolgus monkey was comparable to that for the human, cynomolgus monkey was considered as an appropriate species for toxicological assessment. In repeated dose oral toxicity studies in cynomolgus monkeys, hemorrhagic findings and anaemia were noted in some animals at ≥15 mg/kg/day, leading to a deteriorated animal condition or animal deaths. According to the Applicant, these findings related to the exaggerated pharmacological action of edoxaban tosilate hydrate are considered the primary adverse effect and the only dose-limiting toxicity for this compound. This conclusion was acknowledged by the CHMP.

Intravenous toxicity studies to support a clinical study for absolute bioavailability were conducted in rats and cynomolgus monkeys. The hemorrhagic findings in these studies were consistent with the findings observed after oral administration.

Genotoxicity

A standard battery of genotoxicity tests has been perfomed with edoxaban tosilate hydrate. Although edoxaban tosilate hydrate caused numerical chromosome aberrations in vitro studies using Chinese hamster lung cells and human lymphocytes at 1250 µg/mL or more and 313 µg/mL or more, respectively, the drug did not show any genotoxic potential in an in vitro micronucleus test using human lymphocytes and in three in vivo studies with different tissues (bone marrow micronucleus test in rats and cynomolgus monkeys, liver micronucleus test in rats, unscheduled DNA synthesis in rat liver).

The doses in these in vivo studies are similar to those administered to rats in single dose toxicity studies and higher than those in repeated dose toxicity studies, thus, it is considered that the plasma exposure is sufficient. In addition, in distribution studies in rats the peak levels of radioactivity in the

liver and bone marrow were about 6 and 2 times higher than in the plasma, respectively. Taken together, edoxaban is not considered to have a relevant in-vivo genotoxic potential.

Carcinogenicity

The carcinogenic potential of edoxaban tosilate hydrate was evaluated in medium-term liver carcinogenesis bioassay in rats, and standard 2-year mouse and rat carcinogenicity studies. The dose selection and study design elements for the 2-year carcinogenicity studies in mice and rats were based on 13 week repeated-dose toxicity studies performed in mice and rats.

The carcinogenicity studies in mice and rats did not reveal any increase in neoplastic effects. The deviation from GLP in the rat study AN07-C0020-R01 (some tissues fixed in expired modified Davidson's fixative) is not considered relevant for the scientific validity of the study. In addition, the medium term liver carcinogenesis bioassay in rats showed that edoxaban is not associated with tumor promotion potential in the liver.

Reproduction Toxicity

Reproductive toxicity studies have been performed in rats and rabbits. Edoxaban showed no effects on fertility and early embryonic development in rats at doses of up to 1000 mg/kg/day. The embryo-foetal development study in rats did not reveal any malformations in the foetuses, although a slight increase in post-implantation loss was observed at 300 mg/kg/day (approximately 49 times the MRHD). The study in rabbits also showed an increase in post-implantation losses, and an increase in the incidence of variations in the gall bladder at ≥200 mg/kg/day (approximately 65 times the MRHD) and increases in the incidence of 13th full ribs and 27 presacral vertebrae at 600 mg/kg/day. According to literature, the presence of gall bladder variations in rabbits is a species characteristic, and it is attributed to a paternal contribution. Regarding the incidence of 13th full ribs and 27 presacral vertebrae, the usefulness of these endpoints in predicting risk for the human population is complex and has not been well studied or validated, and it has been suggested that these findings might simply reflect species-specific anatomic variations, without detrimental effects on salubrity.

In the final report of the fertility and early embryonic development study in rats (20030552) atrophy of the testis and epididymis was observed in several animals (1 in the control group, 1 in the 100 and 300 mg/kg/day group and 2 in the 1000 mg/kg/day group). This finding was also detected in one animal in the highest dose group in the preliminary study 20030165. However, literature data produced both by Charles River Inc. and by other researchers show that there is a large variation of the testis and epididymis weights in Crj:CD(SD)IGS rats, as well as spontaneous seminiferous tubular atrophy, leading to atrophy of the testis and epididymis. The incidence of atrophy of the testis and epididymis in the fertility and early embryonic development studies in rats are comparable to that of the published data.

The margin of safety at the NOAEL derived from the embryo-fetal development studies (rats and rabbits), based on the maximum recommended clinical dose of 60 mg per total body surface area in mg/m^2, is about 16 – 19. Although no AUC data were obtained in these studies, this is not considered an issue because the margin of safety based on dose is appropriate. In addition, in the study in rabbits (2004002) the achieved Cmax is much higher than the Cmax in humans (5830 vs 347 ng/mL).

In an oral study for effects on prenatal and postnatal development including maternal function in rats, vaginal bleeding in dams was observed at 30 mg/kg/day. Lower avoidance response in the shuttle box test was observed on the first day of examination in female offspring, but disappeared afterwards. In the juvenile toxicity study in rats, edoxaban tosilate hydrate did not induce any toxicologically significant effect on postnatal development and growth, organ development, skeletal development, or sexual maturation. The observation that in the embryo-fetal development study pharmacodynamic effects occurred after 10 days, while in the fertility and development study no effects occurred after

an even longer and higher dosing scheme has been explained by the Applicant by the timing of dosing during pregnancy. In conclusion, there is a potential for reproductive toxicity and an intrinsic risk of bleeding exists for humans. Consequently a contraindication for use during pregnancy was included in the SmPC.

Toxicokinetic data

Regarding toxicokinetics, some safety margins are low (repeated dose toxicity in monkeys, reproductive and maternal toxicity in rats have a margin of safety based on the AUC of 1.6). However, this was not considered an issue because the toxicity findings are mostly produced by an exacerbated pharmacological effect.

Local Tolerance

To support a clinical study for absolute bioavailability, local tolerance of edoxaban tosilate hydrate lyophilized product for injection was evaluated in the in-vitro hemolysis and rabbit vascular irritation tests. The local tolerance studies conducted by the Applicant showed no haemolytic action on human blood nor irritation potential on the rabbit auricular vasculature.

Other toxicity studies

Phototoxicity studies

Phototoxicity NRU and photochromosomal aberration tests did not show a potential phototoxic potential for edoxaban tosilate hydrate. In addition, there was no evidence of adverse effects on eye function or morphology of the eye in cynomolgus monkeys after a 39-week repeated dosing of edoxaban tosilate hydrate at 15 mg/kg/day.

Studies with human specific metabolite D21-2393

The Applicant has conducted general toxicity, genotoxicity, reproductive toxicity and juvenile toxicity studies with human specific metabolite D21-2393. The exposures achieved in all studies are much higher than the ones in humans treated with the maximum recommended dose of 60 mg (data from study DU176b-PRT019. In the general toxicity, genotoxicity, embryofoetal development and juvenile toxicity studies in rats no treatment related changes were noted. Regarding metabolite D21-3231, a study conducted by the Applicant showed that rats are exposed to D21-3231 and the potential toxicity of the metabolite has been assessed in the toxicity studies conducted with edoxaban tosilate hydrate.

2.3.5. Ecotoxicity / environmental risk assessment

As required by the given guidelines the applicant provided an environmental risk assessment (ERA) for the active ingredient edoxaban tosylate in accordance with the *Guideline on environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00)*. Since in Phase I of the procedure the action limit of 0.01 µg/L is exceeded, a detailed Phase II Tier A and Tier B assessment was performed to assess the potential risk to surface water, the sewage treatment plant, water-sediment system, groundwater and micro-organisms. Laboratory studies on the environmental fate and effects of edoxaban tosylate were conducted following appropriate OECD Guidelines and under GLP conditions. On the basis of the obtained study results and the calculated PEC/PNEC values it can be concluded that the medicinal product Lixiana is unlikely to represent a concern for daphnids and fishes. However, it was assessed that edoxaban is persistent in the environment. The environmental risk assessment could not be finalized since an adsorption-desorption study in

accordance with OECD106 and a valid OECD 201 growth inhibition test for algae were still not available.

Table 1. Summary of main study results

Substance (INN/Invented Name): edoxaban tosylate					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107				no study was provided
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				no study was provided
	BCF				not assessed
Persistence	DT50 or ready biodegradability	DT50 (12°C) = 126 days in sediment			P
Toxicity	NOEC or CMR	OECD201 is not valid			not assessed
PBT-statement :	The compound is considered as P				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.3 µg/l	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OPPTS 835.1110	K_{oc} = 14			value only acceptable in Phase II Tier A
Ready Biodegradability Test	OECD 301	23% (28d)			not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water(20°C)}$ = 1.1d $DT_{50, sediment (20°C)}$ = 59.1d $DT_{50 sediment (12°C)}$ = 126.1d $DT_{50, whole system (20°C)}$ = 6.1d % shifting to sediment = 60.7 (day 14) TP: D21-3231-0101 > 10%			P, significant shifting to the sediment, test on sediment organism is required
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Daphnia sp. Reproduction Test	OECD 211	NOEC	5570	µg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	2320	µg/L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	*remained questions*
Phase IIb Studies					
Sediment dwelling organisms	OECD 218	NOEC	704 (real conc.)	mg/L	*Chironomus riparius*
Substance (INN/Invented Name):					
CAS-number (if available):					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …				Potential PBT (Y/N)

PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}				B/not B
	BCF				B/not B
Persistence	DT50 or ready biodegradability				P/not P
Toxicity	NOEC or CMR				T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB The compound is considered as vPvB The compound is considered as PBT				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC surfacewater , default or refined (e.g. prevalence, literature)		µg/L			> 0.01 threshold (Y/N)
Other concerns (e.g. chemical class)					(Y/N)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106 or …	K_{oc} =			List all values
Ready Biodegradability Test	OECD 301				
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = % shifting to sediment =			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC		µg/L	species
Daphnia sp. Reproduction Test	OECD 211	NOEC		µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC		µg/L	species
Activated Sludge, Respiration Inhibition Test	OECD 209	EC		µg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/kg	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC		mg/ kg	
Earthworm, Acute Toxicity	OECD 207	NOEC		mg/	

Tests				kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/kg	
Sediment dwelling organism		NOEC		mg/kg	species

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed: (1) to provide an adsorption study for soils in accordance with OECD 106, (2) to submit a valid OECD 201 study for algae.

2.3.6. Discussion on non-clinical aspects

The Applicant conducted *in vitro* and *in vivo* pharmacology studies with edoxaban tosilate to elucidate its mechanism of action and assess its anticoagulant effect. Edoxaban tosilate and some metabolites were able to prolong PT in human and rat plasma. Antithrombotic effects of edoxaban tosilate were examined *in vivo* in several rat thrombosis models, showing anti-Xa activity in plasma and thrombosis inhibition in a dose-dependent manner.

Edoxaban tosilate hydrate was compared to anticoagulant drugs warfarin, enoxaparin and fondaparinux in several rat models, although the mechanism of action of edoxaban is more similar to that of authorized new oral anticoagulants: apixaban and rivaroxaban. In these models, edoxaban tosilate hydrate significantly prevented venous thrombosis, like warfarin sodium and enoxaparin sodium, although the onset of action was more rapid after treatment with edoxaban tosilate hydrate than with warfarin.

The safety pharmacology studies on central nervous, cardiovascular and respiratory systems, and on renal function, did not reveal any clinically relevant effects. Several *in vitro* and *in vivo* secondary pharmacology studies were conducted by the Applicant. In vitro pharmacological activity of 10 μM edoxaban tosilate hydrate was tested on 63 receptors, channels, transporters and enzymes. Edoxaban showed significant affinity for histamine H2 and opioid binding sites, although the concentration evaluated in the study (10 μM) was about 16 times the exposure in patients given edoxaban at dose of 60 mg, and no clinical relevance is expected.

PK studies were conducted in rats and cynomolgus monkeys treated orally or intravenously with edoxaban tosilate hydrate. After single oral administration of edoxaban tosilate to rats and cynomolgus monkeys, edoxaban was absorbed with a bioavailability of about 40% in rats and 55% in monkeys, and the plasma edoxaban concentration increased rapidly. After reaching Cmax, edoxaban concentration declined in a biphasic manner with elimination t½ of 0.67 to 5.05 h in rats and 1.55 to 6.59 h in cynomolgus monkeys. Repeat dosing for 2 weeks in rat and 4 weeks in cynomolgus monkeys did not markedly increase edoxaban exposure. In distribution studies, edoxaban showed a broad tissue distribution except for central nervous system. High levels of radioactivity were found in the eyeball and skin in pigmented rats and monkeys, although phototoxicity and general toxicity studies did not show any photosafety issue.

The main metabolite in human plasma, D21-2393, was not detected in rat or cynomolgus monkey plasma; therefore, specific PK and toxicity studies were conducted with this metabolite. In infant and juvenile rats, concentrations of both edoxaban and this main metabolite D21-2393 were much higher than those in adults. This fact was explained by the immature development of drug metabolizing enzymes and transporters.

General toxicity studies with edoxaban tosilate hydrate were conducted in rats and cynomolgus monkeys. Since pharmacological activity of edoxaban tosilate hydrate for the cynomolgus monkey was comparable to that for the human, cynomolgus monkey was considered as an appropriate species for toxicological assessment. In both species, all findings were related to the exaggerated

pharmacological action of the test item, such as haemorrhagic lesions in some organs and anaemia. These adverse effects are considered the only dose-limiting toxicity for edoxaban tosilate hydrate. Regarding toxicokinetics, some safety margins are low (repeated dose toxicity in monkeys, reproductive and maternal toxicity in rats have a margin of safety based on the AUC of 1.6). However, this was not considered an issue because the toxicity findings are mostly produced by an exacerbated pharmacological effect.

Although edoxaban tosilate hydrate caused numerical chromosome aberrations *in vitro* studies using Chinese hamster lung cells and human lymphocytes at 1250 µg/mL or more and 313 µg/mL or more, respectively, the drug did not show any genotoxic potential in an *in vitro* micronucleus test using human lymphocytes and in three *in vivo* studies with different tissues (bone marrow micronucleus test in rats and cynomolgus monkeys, liver micronucleus test in rats, unscheduled DNA synthesis in rat liver). In addition, in the carcinogenicity studies no increase in neoplastic effects was found.

The embryo-foetal development study in rats did not reveal any malformations in the foetuses, although a slight increase in post-implantation loss was observed at 300 mg/kg/day (approximately 49 times the MRHD). The study in rabbits showed an increase in post-implantation losses, and an increase in the incidence of variations in the gall bladder at ≥200 mg/kg/day (approximately 65 times the MRHD) and increases in the incidence of 13th full ribs and 27 presacral vertebrae at 600 mg/kg/day. However, the presence of gall bladder variations in rabbits is a species characteristic, and it is attributed to a paternal contribution. Regarding the incidence of 13th full ribs and 27 presacral vertebrae, the usefulness of these endpoints in predicting risk for the human population is complex and has not been well studied or validated, and it has been suggested that these findings might simply reflect species-specific anatomic variations, without detrimental effects on salubrity.

In the juvenile toxicity study in rats, edoxaban tosilate hydrate did not induce any toxicologically significant effect on postnatal development and growth, organ development, skeletal development, or sexual maturation.

The Applicant has conducted general toxicity, genotoxicity, reproductive toxicity and juvenile toxicity studies with human specific metabolite D21-2393. No treatment related changes were noted.

The environmental risk assessment could not be finalized because two studies were still not available.

Assessment of paediatric data on non-clinical aspects

A PIP was agreed for edoxaban tosilate hydrate (EMEA-000788-PIP02-11-M02). The Applicant has conducted all the non-clinical studies required in the PIP, both with edoxaban tosilate hydrate and with metabolite D21-2393.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of edoxaban tosilate hydrate are well characterized and the non-clinical package presented by the Applicant is considered appropriate. However, the environmental risk assessment could not be finalized because two studies were still not available (see List of Recommendations).

2.4. Clinical aspects

2.4.1. Introduction

This submission includes 43 clinical pharmacology studies to characterise the PK and PD profile of edoxaban, while the efficacy and safety in each of the two requested indications is mainly based on two large pivotal Phase III studies: one in NVAF (ENGAGE-AF: 21,105 patients) and one in the treatment of (acute) VTE (Hokusai VTE: 8,292 patients), and supported by 6 phase II studies in NVAF (n= 2045 patients).

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2: Phase 1 Clinical Pharmacology Studies

Study identifier	Type of study	Study objective	Study design and type of control	Test product(s) Dosage regimen, route of administration	No. of subjects	Duration of treatment
PRT001	Healthy subject PK Initial tolerability Comparative BA and BE	Safety, tolerability, assess PK/PD	Single-blind, randomized, placebo-controlled scending single and multiple doses	Single dose: Edoxaban 10 mg, 30 mg, 60 mg, 90 mg, 120 mg, and 150 mg PO; Placebo PO Multiple dose (10 days): Edoxaban 90 mg QD, 60 mg BID, 120 mg QD, PO; Placebo QD PO	Single dose: Edoxaban - 68, Placebo- 17 Multiple dose: Edoxaban - 27, Placebo - 9	1 day (single dose); 10 days (multiple dose)
PRT002	Intrinsic factor PK (effect of age and gender)	Safety, tolerability, assess PK/PD	Single-blind, randomized, placebo-controlled, multiple doses	Edoxaban 90 mg QD PO, Placebo QD PO	Edoxaban: 18 Placebo: 6	9 days (Days 1, 3 to 10)
PRT003	Healthy subject PD PK/PD	Assess PD using shed blood model, PK	Open-label, randomized, parallel group, placebo and active controlled	Edoxaban 30 mg, 60 mg, 120 mg PO; Fondaparinux 2.5 mg SC Placebo PO	Edoxaban: 60 Fondaparinux: 20 Placebo: 20	Single dose
PRT004	BA	Assess PK, regional drug absorption	Open-label, randomized, 4-way pharmacoscintigraphic crossover	Edoxaban: 60 mg tablet PO; 60 mg powder or liquid via Enterion™ capsule PO	8	Single dose x 4
PRT005 (CLN005)	Healthy subject PD PK/PD	Assess PD using an ex vivo model of thrombosis	Open-label, single center, assessor blind, ex vivo study	Edoxaban 60 mg PO	12	Single dose
PRT008	BA	Food effect on PK	Open label, randomized, two-treatment, two-period, two-sequence crossover	Edoxaban 60 mg PO	16 (Japanese) 16 (Caucasian)	Single dose x 2
PRT009	Healthy subject PD PK/PD	Assess PD in ex vivo thrombin generation and platelet activation	Open label, randomized, active-comparator, no-treatment controlled	Edoxaban 60 mg BID PO Dalteparin 5000IU QD SC Ximelagatran 24 mg BID PO	Edoxaban: 10 Dalteparin: 10 Ximelagatran: 10 No treatment: 10	4 days
PRT010 (J02)	Intrinsic factor PK (effect of race)	Safety, tolerability, assess PK/PD	Randomized, single blind, placebo-controlled, repeated dose	Edoxaban 60 mg BID PO, 120 mg QD PO, Placebo BID/QD PO	Edoxaban: 18 Placebo: 6	9 days (Days 1, 3 to 10)

Study identifier	Type of study	Study objective	Study design and type of control	Test product(s) Dosage regimen, route of administration	No. of subjects	Duration of treatment
PRT012	Extrinsic factor PK	Assess PK/PD, interaction with esomeprazole	Randomized, open label, crossover	Edoxaban: 60 mg tablet PO; 60 mg oral solution Esomeprazole: 20 mg capsule QD PO	32 (16 oral tablet, 16 oral solution)	Edoxaban: single dose x 2 Esomeprazole:4 days x 2
PRT013 (CLN013)	BA	Assess PK, colonic permeability	Open-label, randomized, 2-way pharmacoscintigraphic crossover	Edoxaban: 30 mg tablet PO; 30 mg granules with 50 mg fumaric acid granules via Enterion™ capsule PO	10	Single dose x 2
PRT014	Healthy subject PD PK/PD	Assess PK/PD, interaction with digoxin	Open-label, randomized, dual sequence, parallel group	Edoxaban 60 mg QD PO Digoxin 0.25 mg QD PO	48 (24 in each sequence)	7-14 days (7 days monotherapy + 7 days combination)
PRT016	Extrinsic factor PK	Assess PK, interaction with ketoconazole	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg PO Ketoconazole 400 mg QD PO	40	Edoxaban: Single dose x 2 Ketoconazole: 7 days
PRT017	Healthy subject PD PK/PD	Assess bleeding time, PK/PD, interaction with aspirin	Randomized, double blind, 2-cohort, 2-period, 2-way crossover	Edoxaban 60 mg QD PO Aspirin 325 mg QD PO	56 (28 in each cohort) (54 treated w. edoxaban)	5 days in one cohort; 5 days x 2 in another cohort
PRT019	Healthy subject PK Initial tolerability	Assess mass balance (excretion) and metabolite, PK	Open label, nonrandomized	[^{14}C]-Edoxaban 60 mg oral solution, 2.2 MBq (0.57 mSv)	6	Single dose
PRT020 (J01)	Intrinsic factor PK (effect of race) BA	Safety, tolerability, assess PK/PD, food effect on PK in Japanese	Randomized, single blind, placebo controlled, single dose, crossover (food effect)	Edoxaban 30, 60, 90, 120, 150 mg PO Placebo PO	Edoxaban: 45 (Japanese); 27 (Caucasian) Placebo: 15 (Japanese) 9 (Caucasian)	Single dose Single 60 mg dose x 2 for food effect
PRT021	Healthy subject PD PK/PD	Assess effect of therapeutic and supratherapeutic exposure to edoxaban on QTc interval, safety, tolerability	Randomized, placebo and active controlled crossover	Edoxaban 90 mg QD PO; Edoxaban 180 mg QD PO; Placebo PO; Moxifloxacin 400 mg PO	64 (62 treated w edoxaban)	Single dose for each treatment

Study identifier	Type of study	Study objective	Study design and type of control	Test product(s) Dosage regimen, route of administration	No. of subjects	Duration of treatment
A-U120	Intrinsic factor PK	Assess PK, varying degrees of renal impairment versus healthy subjects	Open-label, parallel group,	Edoxaban 15 mg PO	32 (various degrees of renal impairment); 8 (healthy subjects)	Single dose
C-U122	Healthy subject PD PK/PD	Safety, assess PK	Randomized, double blind, placebo-controlled All subjects pretreated with open-label dose adjusted warfarin for 6-16 days, followed by a 24-h washout	Edoxaban 60 mg QD PO Placebo QD PO	Edoxaban: 48 enrolled (43 treated) Placebo: 24 Warfarin pretreatment: 72	5 days
A-A123	Intrinsic factor PK (effect of race)	Safety, tolerability, assess PK/PD	Randomized, single blind, placebo controlled, multiple dose	Edoxaban 60 mg BID PO; Placebo BID PO	Edoxaban: 8; Placebo: 3	9 days (single dose on Days 1 and 10, and BID doses on Days 3 to 9)
A-U127	Healthy subject PD PK/PD	Assess bleeding time, PK, interaction with low-dose aspirin	Open-label, randomized, 3-period, 3-treatment, crossover	Aspirin 100 mg + edoxaban 60 mg QD PO; Edoxaban 60 mg QD PO; Aspirin 100 mg QD PO	36	5 days for each treatment period
A-U128	Healthy subject PD PK/PD	Assess bleeding time, PK, interaction with naproxen	Open-label, randomized, 3-way crossover	Naproxen 500 mg BID PO + edoxaban 60 mg PO; Edoxaban 60 mg PO; Naproxen 500 mg BID PO	34	Edoxaban: single dose x 2; Naproxen: BID for 2 days x 2
A-U129	Extrinsic factor PK	Assess PK interaction with quinidine	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg QD PO; Quinidine 300 mg TID PO	42 (40 treated w. edoxaban)	Edoxaban: a single dose + QD for 4 days; Quinidine: single dose x 3 + TID for 2 days
A-U130	Extrinsic factor PK	Assess PK interaction with verapamil	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg QD PO; Verapamil 240 mg QD PO	34 (33 treated w. edoxaban)	Edoxaban: a single dose + QD for 4 days; Verapamil: a single dose + QD for 11 days
A-U131	Extrinsic factor PK	Assess PK interaction with amiodarone	Open label, one sequence crossover	Edoxaban 60 mg PO; Amiodarone 400 mg QD PO	30	Edoxaban: single dose x 2; Amiodarone: QD for 4 days

Study identifier	Type of study	Study objective	Study design and type of control	Test product(s) Dosage regimen, route of administration	No. of subjects	Duration of treatment
A-E132	Extrinsic factor PK	Assess PK interaction with erythromycin	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg PO; Erythromycin 500 mg QID PO	36 (33 treated w. edoxaban)	Edoxaban: single dose x 2; Erythromycin: QID for 8 days
A-E133	Extrinsic factor PK	Assess PK interaction with atorvastatin	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg PO; Atorvastatin 80 mg QD PO	32 (30 treated w. edoxaban)	Edoxaban: single dose x 2; Atorvastatin QD for 8 days
A-E134	Intrinsic factor PK	Compare PK in subjects with mild or moderate hepatic impairment vs. healthy subjects	Open label, parallel group	Edoxaban 15 mg PO	17 subjects with hepatic impairment; 16 healthy subjects	Single dose
A-J135	BA	Food effect on PK	Open-label, randomized, 2-period, 2-sequence, crossover	Edoxaban 30 mg PO	34	Single dose x 2
A-U136	Extrinsic factor PK	Assess PK interaction with enoxaparin	Open-label, randomized, 4-period, 4-treatment, crossover	Edoxaban 60 mg PO; Enoxaparin 1 mg/kg SC	40 (39 treated w. edoxaban)	Edoxaban: single dose x 3; Enoxaparin: single dose x 3
A-U137	Extrinsic factor PK	Assess PK interaction with rifampin	Open-label, nonrandomized, 2-treatment, 2-period, single sequence	Edoxaban 60 mg PO; Rifampin 600 mg QD PO	34	Edoxaban: single dose x 2; Rifampin QD for 7 days
A-U138	Extrinsic factor PK	Assess PK interaction with ciclosporine	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg PO; Cyclosporin 500 mg PO	34	Edoxaban: single dose x 2; Ciclosporine: single dose
A-U139	BA Extrinsic factor PK	Assess absolute bioavailability; effect of quinidine on edoxaban PK	Open-label, randomized, 3-period, 3-treatment, crossover	Edoxaban 60 mg PO; Edoxaban 30 mg IV Quinidine 300 mg Q8H PO	36	Edoxaban tablet: single dose; Edoxaban single injection x 2; Quinidine: 4 days
A-U140	Comparative BA and BE	Compare bioavailability of 2 formulations of edoxaban	Open-label, randomized, 2-period, 2-treatment, 2-way crossover	Edoxaban (proposed commercial formulation) 60 mg PO; Edoxaban (current formulation) 60 mg PO	44	Single dose x 2 (Single dose x 1 for each formulation)

Study identifier	Type of study	Study objective	Study design and type of control	Test product(s) Dosage regimen, route of administration	No. of subjects	Duration of treatment
A-U141	Extrinsic factor PK	Assess PK interaction with dronedarone under fed condition	Open-label, randomized, 2-period, 2-treatment, crossover	Edoxaban 60 mg PO; Dronedarone 400 mg BID PO	34	Edoxaban: single dose x 2; Dronedarone: BID for 7 days
A-U142	Comparative BA and BE	Assess bioequivalence, round shape tablet versus current tablet formulation	Open-label, randomized, 2-treatment, 4-period, 2-sequence, replicated crossover	Edoxaban (current tablet) 60 mg PO; Edoxaban (round shaped tablet) 60 mg PO	30	Single dose x 4 (single dose x 2 for each formulation)
A-U145	Comparative BA and BE	Compare bioavailability of 4 formulations of edoxaban	Open-label, randomized, 4-period, 4-treatment, crossover	Edoxaban (current tablet) 60 mg PO; Edoxaban (teardrop shaped tablet) 60 mg PO; Edoxaban (oblong shaped tablet) 60 mg PO; Edoxaban (round shaped tablet) 60 mg PO	28	Single dose x 4 (Single dose x 1 for each formulation)
A-U146	Intrinsic factor PK	Evaluate effect of hemodialysis on PK	Open-label, randomized, 2-way crossover	Edoxaban 15 mg PO	10	Single dose x 2
A-U147	BA	Evaluate dose proportionality of edoxaban PK	Open-label, randomized, 3-way crossover	Edoxaban 15 mg, 30 mg, 60 mg PO	48	Single dose x 3 (Single dose x 1 for each dose)
A-U148	BA	Evaluate effect of high-fat meal on edoxaban PK	Open-label, randomized, 2-way crossover	Edoxaban 60 mg PO	36	Single dose x 2
A-U150	Healthy subject PD PK/PD	Effect of prothrombin complex concentrate (PCC) on edoxaban anticoagulation activity	2-cohort, placebo controlled, randomized 3-treatment, 3-way crossover	Edoxaban 60 or 180 mg PO; 25 and 50 IU/kg doses of PCC IV; Placebo IV (PCC and placebo were given in a blinded manner.)	24	Single dose x 3 (Single dose x 1 for each treatment)
A-U151	Healthy subject PD PK/PD	Evaluate PT and aPTT in subjects treated with edoxaban alone or preceded by dabigatran or rivaroxaban	Open-label, randomized, 3-treatment, 3-way crossover	Edoxaban: 60 mg QD PO; Dabigatran 150 mg BID PO; Rivaroxaban 20 mg QD PO	24	Edoxaban: QD for 4 days (Tx A), single dose on Day 4 (Tx B or C); Dabigatran BID or Rivaroxaban QD on Days 1 to 3 (Tx B or C)

Study identifier	Type of study	Study objective	Study design and type of control	Test product(s) Dosage regimen, route of administration	No. of subjects	Duration of treatment
A-E152	Healthy subject PD PK/PD	Evaluate PT in subjects treated with edoxaban alone or preceded by apixaban	Open-label, randomized, 2-treatment, 2-way crossover	Edoxaban 60 mg QD PO; Apixaban 5 mg BID PO	18	Edoxaban: QD for 4 days (Tx A), single dose on Day 4 (Tx B); Apixaban: BID on Days 1 to 3 (Tx B)
A-U153	Healthy subject PD PK/PD	Collect plasma samples to validate the STA-Liquid Anti-Xa assay	Open-label, randomized, parallel group	Edoxaban 15 mg, 60 mg, 90 mg, 180 mg PO	24	Single dose
A-U156	Extrinsic factor PK	Assess PK, interaction with esomeprazole	Open-label, randomized, 2-way crossover	Edoxaban: 60 mg tablet PO; Esomeprazole: 40 mg capsule QD PO	34	Edoxaban: single dose x 2; Esomeprazole: 5 days x 2

Table 3. Phase II clinical studies with edoxaban in patients with NVAF.

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Safety	PRT018 5.3.5.1 NVAF	Safety versus warfarin	Randomized, parallel group, multicenter, double-blind edoxaban, open-label active controlled	Edoxaban: 30 mg QD PO; 30 mg BID PO 60 mg QD PO; 60 mg BID PO Warfarin QD PO	Edoxaban: 30 mg QD – 235; 30 mg BID - 244 60 mg QD - 234; 60 mg BID - 180 Warfarin - 250	Patients with non-valvular AF	3 months (12 weeks)	Completed CSR
Safety	C-J225 5.3.5.1 NVAF	Safety versus warfarin	Randomized, parallel group, multicenter, double-blind edoxaban, open-label active controlled (including a warfarin run-in period to check PT-INR before treatment)	Edoxaban: 30 mg QD PO; 45 mg QD PO; 60 mg QD PO; Warfarin QD PO	Edoxaban: 30 mg QD - 130; 45 mg QD – 134; 60 mg QD – 130 Warfarin_- 125	Patients with non-valvular AF	12 weeks	Completed CSR

Safety	C-J226 5.3.5.1 NVAF	Safety versus warfarin	Randomized, parallel group, multicenter, double-blind edoxaban, open-label active controlled	Edoxaban: 30 mg QD PO; 60 mg QD PO Warfarin QD PO	Edoxaban: 30 mg QD - 79; 60 mg QD - 80 Warfarin - 75	Patients with non-valvular AF	3 months (12 weeks)	Completed CSR
Dose-titration	J03 5.3.5.2 NVAF	Safety	Open-label, multicenter, dose escalation study	Edoxaban: 30 mg BID PO; 45 mg BID PO; 60 mg BID PO	Edoxaban: 32 30 mg BID - 32; 45 mg BID - 29; 60 mg BID - 26	Patients with non-valvular AF	10 weeks: 30 mg BID for 2 weeks, 45 mg BID for 4 weeks, 60 mg BID for 4 weeks	Completed CSR
Dose-titration	J05 5.3.5.2 NVAF	Safety	Open-label, multicenter, dose escalation study	Edoxaban: 5 mg QD PO; 15 mg QD PO; 30 mg QD PO	Edoxaban: 24 5 mg QD - 24; 15 mg QD - 23; 30 mg QD - 23	Patients with non-valvular AF	6 weeks: 5 mg QD for 2 weeks, 15 mg QD for 2 weeks, 30 mg QD for 2 weeks	Completed CSR
Safety	C-J307 5.3.5.2 NVAF	Safety in patients with SRI	Open-label, parallel group	Edoxaban: SRI - 15 mg QD PO; Normal/mild renal impairment - 30 mg (low dose), 60 mg (high dose) QD PO (Dose halved for subject with low body wt (≤60 kg) or on concomitant verapamil or quinidine)	93 SRI: 50 Normal/ mild renal impairment: Low dose – 22 High dose – 21	Patients with non-valvular AF and severe renal impairment	12 weeks	Completed CSR

Table 4. Phase III clinical studies with edoxaban in the requested indications

Type of Study	Study Identifier Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Efficacy and Safety	C-U301 (ENGAGE AF-TIMI 48) 5.3.5.1 NVAF	Efficacy and safety, Non-inferiority versus warfarin	Randomized, multicenter, double-blind, double dummy, parallel group, active controlled	Edoxaban: 30 mg QD PO; 60 mg QD PO Dose halved for subject with moderate renal impairment (CrCL ≥30 and ≤50 mL/min), low body wt (≤60 kg), or on concomitant verapamil, quinidine, dronedarone. Warfarin: QD PO Dose adjusted to maintain INR between 2.0 and 3.0, inclusive.	21,105 enrolled, 21,026 treated Edoxaban: 30 mg QD-7002; 60 mg QD-7012 Warfarin: 7012	Patients with documented AF	From randomization to the common study end date (CSED) visit. Median of 916, 904, and 904 days for edoxaban 30 mg, edoxaban 60 mg, and warfarin, respectively	Completed CSR
Efficacy and Safety	D-U305 (Hokusai VTE) 5.3.5.1 VTE	Efficacy and safety, Non-inferiority versus warfarin	Randomized, multicenter, multinational, double-blind, matching placebo, parallel group, active controlled	LMWH/Edoxaban: LMWH SC for ≥5days, followed by edoxaban 60 mg QD PO; (Edoxaban dose halved for subj. with moderate renal impairment [CrCL ≥30 and ≤50 mL/min], low body wt [≤60 kg], or on concomitant strong P-gp inhibitor [eg, verapamil, quinidine]). LMWH/Warfarin: LMWH SC and warfarin QD PO for ≥5days, followed by warfarin QD PO; (Warfarin dose adjusted to maintain INR between 2.0 and 3.0, inclusive)	8292 enrolled, 8240 treated Edoxaban: 4118 Warfarin: 4122	Patients with symptomatic DVT and/or PE	A minimum of 3 months up to 12 months Median of 267 and 266 days for edoxaban and warfarin, respectively.	Completed CSR

Analytical Methods

Statement on GLP compliance and bio-analytical audits is given.

The validation reports included all validation parameters for full validation of an analytical method according to the FDA Guideline for "Industry, Bioanalytical Method Validation stability. In general, the

pre-study validations of all the bioanalytical methods were consistent and demonstrated an adequate precision and accuracy (both intra- and inter-day) within the calibrated range, which showed an adequate selectivity, matrix effect and carry-over, although in June 2011, the MHRA conducted inspections at the Rushden (UK) laboratory of Quotient and identified irregularities in some of the bioanalytical data. Details of the specific data irregularities identified the affected bioanalytical and clinical studies, and the comprehensive remediation undertaken, are summarized in a Remediation Report (TMBA001). In addition, all amendments were reviewed by GLP or GCP inspectors prior to being sent to the study sponsor. At the end of this process the applicant was satisfied that all relevant data had been assessed and a risk assessment had been carried out which showed minimal impact on study conclusions.

Dilution of samples was necessary (different dilution factors have been validated).

The established long-term stability at -20 °C for all analytes (including analytes in the DDI studies) covers the maximum period of study sample storage with the following exception: for ENGAGE AF-TIMI 48 study (U301), PK samples from subjects were analyzed and reported, even though the collection-to-analysis time could have exceeded validated long-term storage stability period (up to 793 days under -20 ºC, longer storage time not tested).

In general, the analysis of study samples is acceptable and the re-analysis of the study samples were well justified and handled, although some samples reanalysis were carried due to PK reason. For the PK re-assayed, the original values have been reported in the most cases. For the other, the mean concentration was reported. It could be acceptable take into account that these samples do not correspond to values near tmax and it is not a BE study.

All results for ISR samples were within the 20% acceptance limits, although not in all studies the ISR was performed (for BE study the ISR has been performed). This is acceptable as the ISR was performed in others studies using the same analytical methods in the same analytical site.

2.4.2. Pharmacokinetics

The edoxaban has low solubility and low permeability and is classified as Biopharmaceutics Classification System (BCS) Class IV. The formulation strategy focused on developing an oral immediate-release tablet. The proposed commercial formulations are 15, 30, and 60 mg tablets. The 15 and 30 mg tablets were used in the Phase 3 pivotal studies and are the same as the commercial tablets except for a change in the colouring agent. The 60 mg tablet has been demonstrated to be bioequivalent to 2 x 30 mg tablets (U142). The bioequivalence of the 15 mg tablets was not tested *in vivo*, but is assumed as the criteria regarding manufacture process, qualitative composition, ratio between amounts of active substance and excipients and the comparative dissolution profiles are fulfilled according to section 4.1.6 of the *EMA Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **)*.

Absorption

Site of absorption

Edoxaban is absorbed with peak plasma concentrations within 1 - 2 hours. The absolute bioavailability is approximately 62%. Edoxaban is primarily absorbed (approximately 85%) in the upper gastrointestinal tract and is poorly soluble at pH of 6.0 or higher. Compared with oral administration of edoxaban tablets, exposure to edoxaban following delivery in the distal small bowel was about 15% and in the ascending colon about 7%. Administering the compound as a liquid (thus eliminating the limitation of pH dependent solubility) or with an acid (fumaric acid; to reduce pH below 6.0 and thus maximize solubility) did not greatly improve the absorption from the ascending colon. Thus, in subjects with achlorhydria or conditions and concomitant drugs that increase stomach pH higher than

6, edoxaban solubility and dissolution rate may be reduced, thereby affecting total absorption of edoxaban.

Bioavailability

The proposed commercial formulations for the 15 mg and 30 mg tablets have the same composition as the Phase 3 tablets, with the exception of the colorants used in the film coats. Additionally, a 60 mg tablet has been developed for commercial use.

The bioavailability of edoxaban was evaluated in four studies (PRT001, U145, U139 and U147) and is described below.

Study (No. Subjects)	Objectives of the Studies	Dose/Formulation
PRT001	Relative bioavailability, dose-proportionality, food effect	Yellow film coated 60 mg tablet (commercial formulation)
		60 mg/ Oral solution (160 mL 0.375 mg/mL [60 mg])
U145	Pilot bioavailability study of 60 mg tablet formulations	Teardrop, round and oblong 60 mg tablets
		Yellow film coated 30 mg tablet (Phase 3 formulation) (reference)
U139	Absolute bioavailability	Yellow film coated 30 mg tablet (Phase 3 formulation)
		30 mg (IV) Lyophilized product for infusion, 10 mg per vial
U147[1]	Dose proportionality of edoxaban 15, 30 and 60 mg tablets	Yellow film coated 15 mg tablet (Phase 3 formulation)
		Yellow film coated 30 mg tablet (Phase 3 formulation)
		Yellow film coated 60 mg tablet (Commercial formulation)

[1] For assessment of this study, please refer to dose-proportionality section

Oral administration of a 60 mg dose to a fasting subject results in peak plasma concentrations of 309±97 ng/mL (arithmetic mean±standard deviation [SD]) occurring within 1 to 2 h (study U151); this C_{max} was slightly higher on average than after the same dose in study U147.

The absolute bioavailability of edoxaban is about 62% (geometric mean, study U139).

Under fasting conditions, the relative bioavailability of edoxaban from a tablet formulation (white uncoated tablet) is almost 100% with respect to a solution (study PRT 001).

The PK profile of edoxaban is similar for single and multiple dosing (study PRT 001). Steady-state is achieved within 3 days of dosing, with minimal accumulation upon once daily dosing (less than 2-fold). At steady-state, a 60 mg dose results in peak concentrations of 303±88 ng/mL at median (range) 1.5 h (0.5 to 4.00 h). The steady-state exposure is 1990±403 ng•h/mL (AUC_{tau}) with trough concentrations of 15.5±3.98 ng/mL (study U151). At the 60 mg bid dose level, the pre-dose and 4 hours post-dose concentrations after the evening dose on Day 9 were similar to after the morning dose, suggesting no diurnal variation in the pharmacokinetics of DU-176.

Influence of food

The effect of food on the rate and extent of exposure of single doses of edoxaban has been examined in several studies. In the pivotal food effect study (study U148) administration of a high-fat meal did not significantly affect the total exposure of edoxaban (approx. 10%; upper bound 90% CI<125% of fasted from the 60 mg tablets; however, the maximum concentration (C_{max}) of edoxaban increased by 40%, when dosed with a high-fat meal. In general, a variable food effect (4% to 77% increase) was observed in C_{max}, but no significant effect was seen on total exposure. The high-fat meal also delayed the time to peak concentration by about 0.5h; however, in the pivotal Phase 3 clinical studies edoxaban was dosed without regards to food as the observed PK differences were not expected to have a significant impact on PD of edoxaban. Therefore no recommendation is made for edoxaban to be taken with or without food.

Effect of gastric pH

The effect of gastric pH on edoxaban pharmacokinetics was evaluated in a drug-interaction study with esomeprazole 40 mg QD, which elevates the mean 24-hour gastric pH to 4.33. Single dose administration of oral 60 mg edoxaban 2 hours after the fifth dose of esomeprazole 40 mg QD resulted in a 33% decrease in peak concentrations of edoxaban, with 90% CI falling below the 80 to 125% limit, and the total exposure decreased by 12% with 90% CI completely within the 80 to 125% limit (study U156).

Distribution

Distribution of edoxaban appears to be biphasic, probably due to enterohepatic circulation, with a steady-state volume of distribution of 107±19.9 L (study U139). While the intravenous (IV) half-life is about 7 h (U139), the oral half-life is between 10 to 14 h, suggesting a higher terminal phase volume (Vz). This indicates that the gut distribution and redistribution phases contributing to V_z following oral administration result in a longer oral apparent half-life which could be due to enterohepatic recirculation. The inter- and intra-subject variability for clearance and volume of distribution of edoxaban is low (<30%). *In vitro* plasma protein binding was approximately 54-57% (study 20040272). In addition, plasma protein binding of edoxaban was measured at 2 h, 6 h and 12 h after a single dose of 90 mg and 120 mg of edoxaban (study PRT001). At the 90-mg and 120-mg doses, the plasma protein binding ranged from 40% to 59%, and remained relatively constant over time and individual values at 2 hours post-dose ranged between approximately 37 to 59% across the two dose levels.

Elimination

The elimination of endoxaban includes both renal and non-renal pathways. In healthy volunteers both pathways contribute equally (~50%) to the total clearance of edoxaban after iv dosing (U139). Edoxaban is primarily eliminated unchanged in urine and through biliary secretion (PRT019); with metabolism contributing to a lesser extent towards total clearance of edoxaban. In healthy subjects, edoxaban is the predominant excreted component in urine, accounting for 35% (range 27.4% to 46%) of the administered dose indicating that the renal excretion is a significant component of the total clearance. The renal clearance for total radioactivity was 9.69 ± 0.997 L/h, which is higher than glomerular filtration rate suggesting active secretion in kidney. In feces, 62% (range 55.2% to 73.0%) total radioactivity is detected; 49% of the administered dose appears to be as parent drug. As the absolute bioavailability is approximately 61.8% (Study U139). Therefore the unchanged edoxaban detected in the feces was a result of both unabsorbed drug and hepatobiliary excretion of systemically absorbed drug. The total clearance of edoxaban is 21.8±3.03 L/h and the renal clearance of edoxaban was 14.2 ± 3.4 L7H. An *in vitro* uptake study in suspended fresh human hepatocytes provides suggests that edoxaban is not a substrate for the OATP class of uptake transporters, including OATP1B3.

Metabolism

Unchanged edoxaban is the predominant form in plasma. Edoxaban is metabolised via hydrolysis (mediated by carboxylesterase 1), conjugation or oxidation by CYP3A4/5 (< 10%). A total of 7 metabolites have been detected in plasma; 3 have anticoagulant activity (D21-2393 [human specific metabolite], D21-1402, D21-2135). In healthy subjects, D21-2393 (M4) is the most abundant metabolite (approximately 10% of parent drug exposure), followed by D21-3231 (< 10%), D21-1402 (<5%), and D21-2135 (low amounts). D21-1402, D21-2135, D21-2393 and edoxaban inhibited human FXa with IC_{50} values of 6.9, 2.7, 1.8 and 3.0 nM, respectively.

The amount of total metabolites detected in urine and feces was approximately 5 and 4%, respectively, indicating further metabolism of these metabolites and/or small volumes of distribution

corresponding to higher plasma concentrations relative to those in urine and feces. Overall, metabolism appears to play a modest role in the elimination of edoxaban.

Dose proportionality and time dependencies

Based on the studies submitted, the increases in peak and total exposures were slightly less than dose proportional between 15 and 60 mg but this lack of dose proportionality was not considered of relevant magnitude. Hence it can be concluded that edoxaban displays approximately dose-proportional pharmacokinetics for doses of 15 mg to 60 mg in healthy subjects. Population PK modelling (TMPP014) of pooled Phase 1 data from 5 studies, for doses of 10, 15, 30, 60, 90, 120, 150 and 180 mg indicates a slightly less than dose-proportional dose-exposure relationship. The population estimate of F1 (model-based relative bioavailability) was found to remain constant for the dose range of 10 mg to 30 mg, but decreased with increasing doses at higher dose levels. For doses above 30 mg, every 30-mg increase in dose was associated with a 6.7% decrease in F1, presumably due to a decreased dissolution rate.

In study PRT001, the PK profile of edoxaban is similar for single and multiple dosing. Steady-state is achieved within 3 days of dosing, with minimal accumulation upon once daily dosing (less than 2-fold). The mean accumulation ratio at steady-state for maximum (peak) concentration (C_{max}) is 1.07 and for area under the concentration-versus-time curves AUC_{tau} (over tau, the dosing interval of 24 h), is 1.14. At the 60 mg bid dose level, the pre-dose and 4 hours post-dose concentrations after the evening dose on Day 9 were similar to after the morning dose, suggesting no diurnal variation in the pharmacokinetics of DU-176.

Intra- and inter-individual variability

In study PRT001 it was stated, that inter-subject variability in the pharmacokinetics of edoxaban was low for AUC0-∞ and moderate for Cmax. Similar variability was assumed for the intra-subject variability. The inter- and intra-subject variability for clearance and volume of distribution of edoxaban is low (<30%).

Pharmacokinetics in target population

Population PKs indicates very similar PK of edoxaban in healthy subjects and in patients. The PopPK simulations did not indicate clinically relevant differences.

Special populations

Impaired renal function

Results from a targeted study in renal impairment show that edoxaban $AUC_{0\text{-}inf}$ increased by approximately 32%, 74% and 72% in subjects with mild, moderate and severe renal impairment but not on dialysis, respectively, compared to healthy subjects. Edoxaban $AUC_{0\text{-}inf}$ increased by approximately 93% in subjects with ESRD on peritoneal dialysis. A study in ESRD patients on intermittent hemodialysis suggests that hemodialysis does not significantly remove edoxaban from the blood. The PopPK modelling based on data from the Phase 3 study in AF showed that $AUC_{0\text{-}24,ss}$ increase on average by 25%, 57% and 97% in subjects with mild, moderate and severe renal impairment. The following posology is recommended in the proposed SPC: subjects with normal renal function and mild renal impairment (CrCL > 50 mL/min) are recommended to receive edoxaban doses of 60 mg once daily, while for subjects with moderate or severe renal impairment (CrCL 15-50 mL/min) a 50% dose reduction is recommended. In patients with ESRD (CrCL <15 mL/min) or on dialysis, the use of edoxaban is not recommended. Based on the results from the renal impairment study and the PopPK modelling based on data from the Phase 3 study in AF the dosing recommendations in renal impairment seem adequate.

Impaired hepatic function

The targeted phase I study in patients with hepatic impairment suggest that administering a single dose of 15 mg of edoxaban to subjects with mild or moderate hepatic impairment (Child-Pugh A and B) is unlikely to affect edoxaban exposure to a clinically relevant extent. Subjects with severe hepatic impairment have not been studied. It should be however noted that 15 mg is not the proposed therapeutic dose (60 mg). Therefore definitive conclusions regarding the need for dose adjustment in subjects with hepatic impairment can not be concluded from this study. The following posology in hepatic impairment is recommended in the proposed SPC: No dose adjustment is proposed in patients with mild or moderate hepatic impairment and edoxaban is not recommended in patients with severe hepatic impairment. Edoxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk.

Weight

The effect of body weight has been evaluated using Population PK analyses. Allometrically scaled body weight was included on all disposition parameters for edoxaban in the Population PK analyses based on phase I data, characterizing an increase in disposition parameters with increasing body weight. In the phase 2 study C-J225 Japanese subjects with body weight ≤ 60 kg treated with edoxaban had higher incidence of bleeding than those with body weight >60 kg. Therefore, it was decided that patients with low body weight ≤ 60 kg would receive half of the dose in the phase 3 studies. The population PK analysis based on data from the phase 3 study in AF shows that total exposure is predicted to be 13% higher and peak exposure is predicted to be approximately 40% higher in a typical non-asian patient with normal renal function weighing 55 kg with respect to a patient weighing 84 kg. With the proposed dosing, subjects weighing < 60 kg seems under exposed compared to subjects > 60 kg (almost half exposure). Despite lower exposures, the Applicant has shown that both the ENGAGE AF and Hokusai VTE studies did not reveal any clinically relevant increases in stroke/SEE event rates relative to warfarin for subjects randomized to a reduced dose of edoxaban due to body weight ≤ 60 kg. Furthermore, predicted PK data in different body weight groups show that the 25th to 75th percentiles from the subgroups ≤ 60 kg, ≤ 50 kg and ≤ 40 kg overlap. It worth mentioning that the majority of the target population in standard clinical practice will have in addition some degree of impairment in renal function and associated risk factors for bleeding. Therefore, in the low body-weight population, the main concern is bleeding due to potential overexposure rather than a potential lack of efficacy. Therefore the Applicant's conclusion not to change the weight cut off for dose adjustment is accepted. . For 60 mg QD the plasma concentrations of edoxaban in patients with Body weight > 140 kg in relation to all patients in ENGAGE AF-TIMI 48 was reduced to ~60% for C_{max}, ~65% for $AUC_{0-24,ss}$ and ~70% for C_{min}. A weak trend to a reduced efficacy of edoxaban 60 mg OD versus warfarin in heavy patients weighing >100 kg is visible (stroke/SEE, HR: 1.12; 95%CI: 0.70 to 1.78; mITT, overall study period) compared with patients weighing ≤ 100 kg (stroke/SEE, HR: 0.83; 95%CI: 0.70 to 0.98; mITT, overall study period). However, the HR in heavy patients is based on a small number of primary events (38 vs 33) and the efficacy of edoxaban 60 mg compared with warfarin appears to be maintained even in heavy patients (interaction p-value = 0.24).

Gender and Age

Regarding gender and age, a phase I study was performed to assess the PK profiles of edoxaban in healthy females and healthy elderly males. Although it is not possible to draw definitive conclusions from this study due to the reduced sample size, edoxaban pharmacokinetics does not appear to be markedly affected by gender, when differences in body weight are taken into account. Regarding age, the small increase in AUC and the decrease in clearance observed in this study in elderly males are probably due to the decrease in renal function with age. The effect of gender has been further evaluated using population PK analyses. After accounting for body weight, gender does not appear to have a relevant effect on edoxaban PK. Thus, no dose modification is proposed based on gender. The effect of age has also been further evaluated using PK data from pivotal studies and from Population PK analyses. These analyses suggest that, after accounting for renal function, age does not have a

clinically significant effect on edoxaban PK. The analyses were consistent in the subgroups 65-74 years, 75-84 years and older than 85 years. As such, no dose reduction is recommended based upon age alone.

Race

There are very limited data originating from phase I / PK studies. Japanese and Caucasian male subjects were examined in the studies PRT020 and PRT008. Additional information is provided in PopPK-analyses/modelling. PK is sufficiently characterised for Caucasian subjects. Minor differences to Japanese subjects are considered of no clinical relevance. Descriptive PK-data provided for races other than Caucasians or Japanese from pivotal trials suggest that race has no significant impact on the edoxaban exposure.

Table 4: Summary of Predicted C_{max} in Different Dose and Subject Groups [a] (TMPP008 Addendum)

Exposure group	Mean	Median	25th percentile	75th percentile	Min	Max	Observation
Observations with non-dose-adjusted 60 mg QD	216.9	216.8	188.3	245.7	74.87	382.4	10272
Age subgroup							
< 65 years	196.3	196.8	169.7	221.8	74.87	349.9	3362
≥ 65 and < 75 years	220.8	220.8	193.9	247.8	77.12	353.0	3787
≥ 75 and < 85 years	233.7	233.8	207.8	260.4	115.3	382.4	2955
≥ 85 years	247.4	247.7	225.1	273.1	144.6	335.0	168
Body weight subgroup							
≥ 100 kg	230.7	229.0	207.7	254.3	95.18	382.4	7860
> 100 and ≤ 120 kg	181.2	183.5	169.8	194.8	81.37	255.8	1721
> 120 and ≤ 140 kg	155.9	157.2	147.2	166.7	85.83	209.4	485
> 140 kg	132.0	131.1	123.0	141.5	74.9	178.2	206
Race subgroup							
White/Caucasian	216.2	215.7	187.4	245.2	74.87	382.4	8818
Black/African American	205.4	196.6	167.3	239.6	90.69	328.0	125
Native Hawaiian or Other Pacific Islander	203.1	203.6	202.7	207.7	175.3	225.0	9
Other	234.5	236.7	208.7	263.9	93.35	348.3	335
Asian (ENGAGE AF study)	219.0	220.8	195.3	244.9	89.14	332.5	978
Missing	169.6	138.6	123.1	225.6	110.0	241.2	7

Table 5: Summary of Predicted C_{min} in Different Dose and Subject Groups [a] (TMPP008)

Exposure group	Mean	Median	25th percentile	75th percentile	Min	Max	Observation
Observations with non-dose-adjusted 60 mg QD	28.13	27.26	21.99	33.68	5.672	67.58	10272
Age subgroup							
< 65 years	22.94	22.02	18.66	26.20	7.243	61.85	3362
≥ 65 and < 75 years	28.53	27.83	23.21	33.31	5.672	63.33	3787
≥ 75 and < 85 years	32.98	32.76	27.65	37.87	11.16	67.58	2955
≥ 85 years	37.75	38.42	33.33	42.54	13.87	58.53	168
Body weight subgroup							
≤ 100 kg	29.37	28.83	23.30	34.93	8.083	67.58	7860
> 100 and ≤ 120 kg	25.03	23.88	19.95	29.15	5.672	57.06	1721
> 120 and ≤ 140 kg	22.36	21.62	18.93	25.09	8.361	48.42	485
> 140 kg	20.45	20.17	17.07	23.69	8.963	31.43	206
Race subgroup							
White/Caucasian	28.00	27.05	21.91	33.54	5.672	67.58	8818
Black/African American	27.92	26.17	23.48	32.38	13.85	59.60	125
Native Hawaiian or Other Pacific Islander	23.55	21.92	18.05	29.36	17.29	32.91	9
Other	29.73	29.32	23.15	35.63	9.698	52.43	335
Asian (ENGAGE AF study)	28.88	28.64	22.39	34.42	8.713	60.03	978
Missing	19.39	18.70	18.22	22.40	11.50	24.26	7

Table 6: Summary of Predicted $AUC_{0\text{-}24,ss}$ in Different Dose and Subject Groups [a] (TMPP008)

Exposure group	Mean	Median	25th percentile	75th percentile	Min	Max	Observation
Observations with non-dose-adjusted 60 mg QD	2055	2035	1771	2323	946.1	3862	10272
Age subgroup							
< 65 years	1795	1764	1575	1981	946.1	3713	3362
≥ 65 and < 75 years	2088	2074	1845	2309	1002	3394	3787
≥ 75 and < 85 years	2283	2267	2042	2525	1320	3862	2955
≥ 85 years	2490	2496	2263	2664	1911	3468	168
Body weight subgroup							
≤ 100 kg	2175	2151	1924	2409	1096	3862	7860
> 100 and ≤ 120 kg	1746	1714	1579	1900	1002	2896	1721
> 120 and ≤ 140 kg	1522	1495	1394	1628	1073	2296	485
> 140 kg	1327	1330	1200	1445	946.1	1754	206
Race subgroup							
White/Caucasian	2036	2014	1754	2296	946.1	3862	8818
Black/African American	1964	1918	1641	2246	1215	3255	125
Native Hawaiian or Other Pacific Islander	1822	1734	1664	2100	1585	2127	9
Other	2195	2173	1941	2499	1262	3144	335
Asian (ENGAGE AF study)	2194	2192	1950	2461	1260	3134	978
Missing	1543	1326	1297	1949	958.1	2027	7

Pharmacokinetic interaction studies

Effects of other substances on edoxaban:

The potential for other drugs to affect edoxaban exposure seems to be primarily related to the inhibition of P-gp. In vivo DDI studies with drugs known to inhibit P-gp have been conducted. Ketoconazole, ciclosporine, quinidine, verapamil, erythromycin and dronedarone, increased edoxaban AUC by 87%, 73%, 77%, 53%, 85% and 85%, respectively. C_{max} increased by 89%, 74%, 85%, 53%, 68% and 46%. Based on these results, a 50% dose reduction was initially recommended by the Applicant when edoxaban is co-administered with P-gp inhibitors. However, in respect to the clinical efficacy and safety data gained with verapamil or amiodarone comedication (see Discussion on Clinical Pharmacology) and the similarity of the influence of verapamil, amiodarone and quinidine on edoxaban PK, it is considered appropriate to administer edoxaban at a dose of 60 mg once daily when these drugs are a concomitant medication unless additional factors such as impaired renal function or low body weight have to be taken into account.

An in vivo study with the P-gp inducer rifampicin showed that edoxaban AUC decreased by 34% and C_{max} was comparable. In spite of the decrease in edoxaban total extent of exposure, the pharmacodynamic effect was not significantly influenced by the co-administration with rifampicin. This finding is likely due to the observed increase in the total exposure to active metabolites D21-2393 and D21-1402, which can be explained by the OATP1B1 inhibition and by the strong CYP3A induction produced by rifampicin. Based on these results, no dose modification is proposed by the Applicant when edoxaban is administered with rifampicin.

Effects of edoxaban on other substances:

Enzyme inhibition potential has been studied in vitro and the results suggest that a clinically relevant inhibition by edoxaban of the CYP enzymes most commonly involved in drug metabolism is not likely. Predictions based on the PBPK model suggest that a clinically relevant drug-drug interaction via edoxaban CYP3A4 induction is unlikely. A *in vitro* study was considered negative for CYP2B6 induction.

Regarding inhibition of efflux transport proteins, edoxaban effect on P-gp mediated transport of digoxin has been investigated. The results in vitro show that the net flux ratio of digoxin decreases with increased concentrations of edoxaban. However, results from an in vivo study with digoxin show that a clinically relevant effect of edoxaban on the PK of digoxin is not likely.

Results of the AM14-C0053-R01 “in vitro” study showed no effect of edoxaban on BCRP transport.

2.4.3. Pharmacodynamics

Mechanism of action

Edoxaban is a highly selective, direct and reversible inhibitor of factor Xa, the serine protease located in the final common pathway of the coagulation cascade. Edoxaban inhibits free factor Xa, and prothrombinase activity. Inhibition of factor Xa in the coagulation cascade reduces thrombin generation, prolongs clotting time and reduces the risk of thrombus formation.

Primary and Secondary pharmacology

In vitro, edoxaban inhibits the human FXa in a concentration-dependent and competitive manner. In human studies, it has rapid onset of action with anticoagulant effects, as measured by biomarkers such as Factor Xa activity, thrombin generation (TG) parameters, prothrombin time (PT) and activated partial thromboplastin time (aPTT), observed soon after first dose administration.

Inhibition of FXa in the coagulation cascade reduces thrombin generation and prolongs clotting time and reduces thrombus formation. The inhibitory effects of edoxaban on human FXa and prothrombinase complex were evaluated in several studies. Anticoagulant activity of edoxaban was measured in human plasma through activated partial thromboplastin time (aPTT), prothrombin time (PT), expressed as International Normalised Ratio (INR), and thrombin time (TT).

The biomarkers measured during clinical development include D-dimer, anti-FXa activity, PT, aPTT, Intrinsic FX activity, prothrombin fragments F1 and F2 (F1+2), prothrombinase-induced clotting time (PiCT), thrombin generation, thrombin-antithrombin III complex (TAT) and β-thromboglobulin (β-TG). PT and aPTT were measured in most of the clinical pharmacology studies as part of PD or safety assessment. Additional biomarkers were measured in specific clinical pharmacology studies to further characterize the PD effects of edoxaban.

The PD biomarkers of edoxaban have been characterized in many Phase 1 clinical pharmacology studies from healthy subjects (PRT001, PRT003, PRT005, PRT009) to characterize the biological effects of edoxaban.

Edoxaban has a concentration dependent response on PT, aPTT, anti-FXa, TGA, D-dimer and F1+2.

PRT001: In this randomized, single-blind, placebo-controlled two part study, single ascending doses (SAD) of 10 mg, 30 mg, 60 mg, 90 mg, 120 mg, and 150 mg of edoxaban were administered to 85 healthy adult males aged 18-51 years to evaluate the PK and PD of edoxaban (PRT001-SAD and PRT001-MAD). In part two of the study, 36 healthy male subjects received 90 mg QD, 60 mg BID, or 120 mg QD for 10 days. Single oral doses of edoxaban from 10 mg to 150 mg resulted in rapid increase in anti-FXa activity and rapid prolongation of PT and aPTT.

For all dose levels, the median time at which maximal activity was observed was between 1.0 to 3.0 h postdose. On average, maximum observed activity for PT, aPTT and anti-FXa increased in a dose-dependent manner over the dose range studied. Recovery to predose values was dose-dependent with return to baseline by 24 to 36 h postdose in all subjects.

Table PD-01: Pharmacodynamic Parameters after Single Oral Administration of Edoxaban or Placebo (PRT001-SAD)

Biomarker	PD Parameter	Placebo (N=17)	Edoxaban Dose[a]					
			10 mg (N=10)	30 mg (N=10)	60 mg[a] (N=10)	90 mg (N=9)	120 mg (N=9)	150 mg (N=9)
PT	A_{max} (s)	14.7 ± 1.20	15.5 ± 1.13	21.9 ± 2.02	28.2 ± 4.70	33.8 ± 7.71	31.8± 5.77	39.5 ± 8.29
	t_{Amax} (h)[b]	6.00 (0.00, 48.00)	3.00 (0.50, 6.02)	1.00 (1.00, 2.00)	1.02 (0.50, 3.00)	1.00 (0.50, 2.02)	1.00 (0.50, 2.00)	1.02 (0.50, 2.00)
	ΔA_{max} (s)	0.741 ± 0.600	1.91 ± 0.458	7.20 ± 2.04	14.0 ± 4.40	19.0 ± 7.07	18.0 ± 5.44	24.4 ± 7.84
aPTT	A_{max} (s)	33.6 ± 4.03	38.0 ± 4.03	45.7 ± 8.50	54.3 ± 15.2	52.6 ± 7.97	56.2 ± 6.52	58.0 ± 8.64
	t_{Amax} (h)[b]	6.00 (0.00, 48.00)	3.00 (0.50, 6.02)	1.00 (1.00, 2.00)	1.03 (1.00, 3.00)	3.00 (1.00, 3.02)	2.00 (0.50, 3.00)	2.00 (1.00, 3.00)
	ΔA_{max} (s)	1.96 ± 2.12	3.27 ± 0.835	10.7 ± 3.97	18.2 ± 8.15	20.4 ± 5.45	22.1 ± 4.26	24.1 ± 7.11
Anti-FXa activity[c]	A_{max} (IU/mL)	–	0.435 ± 0.160	2.09 ± 0.384	3.80 ± 0.971	8.14 ± 4.86	9.14 ± 3.30	10.7 ± 4.94
	t_{Amax} (h)[b]	–	2.00 (0.50, 6.02)	1.00 (0.50, 3.00)	1.02 (0.50, 3.00)	1.00 (1.00, 2.00)	1.00 (0.50, 2.00)	2.00 (0.50, 3.00)

Source: PRT001-SAD Table 12.1, Table 12-4 and Table 12.8.
Data presented as arithmetic mean ± SD.
a: Includes subjects from Group C only (participated in 2 treatment periods and received a single dose of 60 mg of edoxaban or placebo as tablet in the fasted state)
b: Median (Min, Max)
c: Little or no activities were observed at baseline or postdose in subjects who received placebo.
anti-FXa = anti factor Xa; aPTT = activated partial thromboplastin time;
A_{max} = maximum observed activity value; ΔA_{max} = maximum observed activity value change from baseline;
PT = prothrombin time; t_{Amax} = time of maximum observed activity value.

PRT003: An open label, randomised, placebo and positive controlled (Fondaparinux). The primary objective of this study was to investigate the effect of administration of different doses (30, 60 and 120 mg) of oral edoxaban on inhibition of thrombin generation and platelet activation by using the shed blood model. Edoxaban caused a rapid and marked reduction in the thrombin generation markers, F1+2 and TAT in shed blood, at dose levels of 30 to 120 mg. The maximum inhibition appeared to be reached at the 120 mg dose level. There was no apparent drug-related effect of edoxaban on venous F1+2 levels, and edoxaban caused a rapid and variable reduction in venous TAT levels at dose levels of 30 to 120 mg. High between-subject variability in venous F1+2 and TAT data confounded the interpretation. Edoxaban caused a rapid and marked reduction in the marker of platelet activation, â-TG in shed blood, at dose levels of 30 to 120 mg. The between-subject variability in venous â-TG data was high for edoxaban. Edoxaban caused a rapid and marked dose-related prolongation of the venous blood coagulation parameters, APTT, PT and PT-INR, and induction of venous Anti FXa activity at dose levels of 30 to 120 mg. There was no apparent drug-related effect of edoxaban on shed blood volume. Furthermore, high between-subject variability was observed.

PRT005:an open label, single center, assessor blind, ex vivo study. The primary objective of this study was to investigate the antithrombotic effects following a single oral dose of 60 mg edoxaban using a human model of thrombus formation. The secondary objective of the study was to analyze the pharmacological effects of edoxaban using thrombin generation measurement, anti-factor Xa activity, and standard coagulation parameters (PT/INR and aPTT). Pharmacological effects were assessed in relation to plasma concentrations of edosaban at time 0 (pre-dosing), 1.5, 5 and 12 h (post-dosing). Edoxaban 60 mg oral dose reduced ex vivo thrombus formation under high-and low shear rate conditions, prolonged clotting time in subjects´ plasma, and inhibited clotting factor Xa.

PRT009 and PRT018: Two studies investigated both, QD and BID dosing (study PRT009 in elderly healthy subjects and study PRT018 in patients with NVAF). In both studies through levels of pharmacodyamic parameters (especially anti-FXa activity) were markedly higher after BID dosing. Therefore, the effect on pharmacodynamic parameters does not seem to be maintained throughout the dosing interval after QD dosing, at least at the 30 mg dose level. Overall, the low anticoagulant action after about 12 hours after QD dosing has to be discussed in the clinical context, also taking into account the higher bleeding rates with BID dosing.

TMCP-Peds-001 (DSNER1): This study tested the effect on plasma biomarkers of coagulation of ex-vivo treatment with edoxaban (6 concentrations: 12.5, 25, 50, 100, 200 and 500 ng/ml) and rivaroxaban (5 concentrations: 12, 36, 108, 216 and 540 ng/ml) using blood samples from umbilical

cord (n=10) and healthy adult volunteers (n=5). The PD performance of edoxaban in plasma from ex-vivo-treated cord blood was not significantly different from that in plasma from ex-vivo-treated adult blood for any parameter investigated, which included Prothrombin time (PT), activated partial thromboplastin time (aPTT), Anti-Factor Xa (Anti-FXa), Intrinsic Factor X (Intrinsic FX) Thrombin Generating Activity (TGA): Peak (TGA-Peak); lag time (TGA-lag), time to peak (TGA-time to peak), endogenous thrombin potential (TGA-ETP) and velocity index (TGA-VI). In summary, there was no significant difference in the anticoagulant activity of edoxaban in cord and adult plasma. In an addendum to this study, it was reported that the percentage increase of INR following ex-vivo treatment with edoxaban did not differ significantly in samples derived from adult versus cord blood treated.

Secondary pharmacology

PRT021: A phase 1, randomized, single-dose, placebo and active controlled crossover (moxifloxacin 400 mg) study to evaluate a thorough QTC study with edoxaban in healthy subjects.

The primary objective of this study was to assess the effect of therapeutic and supratherapeutic plasma exposures of edoxaban on the QTc interval duration after administration of single oral doses of 90 mg and 180 mg. Blood was collected for the determination of plasma concentrations for edoxaban for up to 48 hours post-dose in each period. The primary endpoint for this study was the time-matched difference in QTcI (individual correction method) interval of each active treatment group (edoxaban 90 mg, edoxaban 180 mg dose, and moxifloxacin) and placebo after baseline adjustment. The main objective of the QTc analysis was to determine whether edoxaban has a threshold pharmacologic effect on cardiac repolarization, as detected by QT/QTc prolongation.

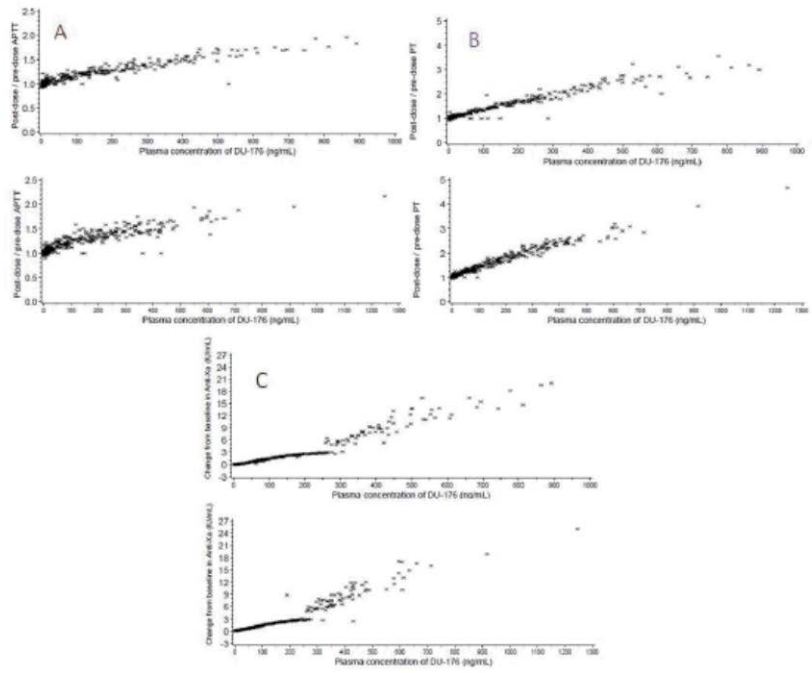
Since the positive control (moxifloxacin) met the criteria for the QTc prolongation of greater than 5 msec at the specified time points, the thorough QTc study is valid to detect conclusively the potential edoxaban to cause changes in ΔQTcI intervals. Edoxaban did not have a threshold pharmacologic effect on cardiac repolarization. The upper bounds of 95% one-sided CIs for the least-squares mean of the placebo-corrected QTcI change from time-matched baseline did not exceed 4 msec at any time point after dosing for either dose level (90 mg and 180 mg). The results showed no relationship between plasma concentrations of edoxaban and ΔQTcI values up to DU-176b concentrations of 857 ng/mL.

In summary, doses of edoxaban had no clinically relevant QTc effect as compared to placebo, and this can be considered a negative thorough QT/QTc study.

Relationship between plasma concentration and effect

In healthy volunteers: In study PRT001, A linear correlation was observed between edoxaban plasma concentrations and PT, aPTT and anti-FXa activity (Figure 2.1).

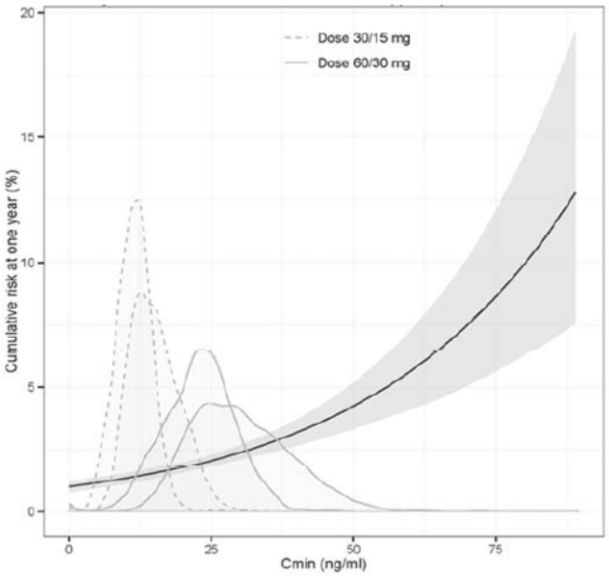
Figure PD-01: Relationship Between Plasma Concentrations of Edoxaban and pharmacodynamic Endpoints (PRT001)



Source: PRT001-MAD Figure 11-19 to Figure 11-24.
(A) Relationship between plasma concentrations of edoxaban and pre/post dose aPTT on Day 1 and Day 10 (B) Relationship between plasma concentrations of edoxaban and pre/post dose PT on Day 1 and Day 10. (C) Relationship between plasma concentrations of edoxaban and change from baseline in anti-FXa activity on Day 1 and Day 10. In each case the Day 1 is the upper figure and Day 10 the lower one.

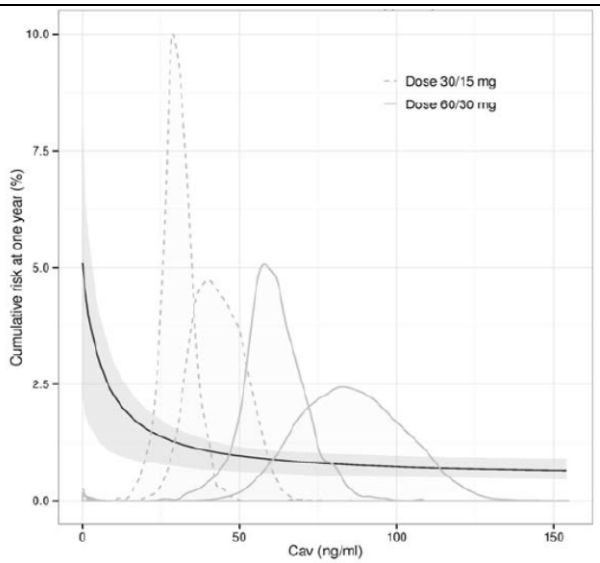
In patients: There are two Phase 3 pivotal studies of efficacy and safety, one of them in NVAF (ENGAGE-AF) and the other one in patients with VTE (Hokusai-VTE), in which plasma samples were obtained and therefore a relationship between plasma and efficacy/safety could be tempted. The first substudy (TMPP009) describes the plasma exposure response of edoxaban and efficacy (time to first occurrence of stroke or SEE, ischemic stroke or SEE and hemorrhagic stroke) and safety endpoints (time to first occurrence of major bleeding) (Figures PD-02 and PD-03). This substudy demonstrated statistically significant exposure response relationships using a median model prediction for major bleeding (minimum concentration), stroke or SEE (average concentrations), and ischemic stroke or SEE (average concentration), but not for hemorrhagic stroke. By appliying a logistic regression model, the period of time that intrinsic factor Xa was maintained at 15% or less was the most significant factor for bleeding. As such, the duration of factor FXa suppression exceeding a certain threshold value seems to be more accountable for bleeding risk than the magnitude of suppression. This may explain the observed increase in bleeding after the 30 mg and 60 mg BID dosing regimens compared to QD dosing of edoxaban in phase II trials.

Figure PD-02: Probability of a Major Bleeding Event Within 1 Year in an Edoxaban Subject Versus Minimum Exposure (Cmin) of Edoxaban (TMPP009)	**Figure PD-03_ Probability of a Stroke or SEE Within 1 year in an Edoxaban Subject Versus Average Exposure (Cav) of Edoxaban (TMPP009)**



Source: TMPP009, Figure 6.8

Note: The solid line represents the median model prediction for a typical edoxaban patient (age 72 years and no other risk factors). The gray shaded area shows the 90th prediction interval. The four distributions represent the predicted distributions of Cmin in the high (solid lines) and low (dashed lines) exposure groups. For each exposure group, the distribution to the right represents non-dose reduced observations and the distribution to the left the dose-reduced observations

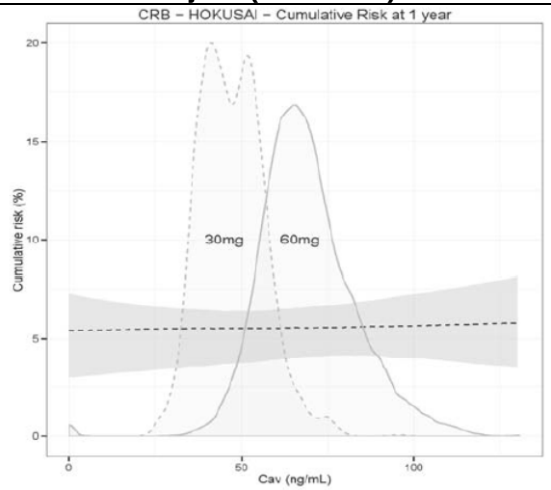


Source: TMPP009, Figure 6.16

Note: The solid line represents the median model prediction for a typical edoxaban patient (age 72 years and no other risk factors). The gray shaded area shows the 90th prediction interval. The four distributions represent the predicted (from the full PopPK model) distributions of Cav in the high (solid lines) and low (dashed lines) exposure groups. For each exposure group, the distribution to the right represents non-dose reduced observations and the distribution to the left the dose-reduced observations.

The second substudy (TMPP011) describes the plasma exposure response of edoxaban and efficacy endpoint of symptomatic recurrent venous thromboembolic event (recurrent VTE) and safety endpoint of clinically relevant bleeding (CRB). This study identifieda statistically significant exposure response relationship using a median model prediction for recurrent VTE (average concentration), but no statistically significant exposure response relationship was detected for CRB (Figures PD-04 and PD-05).

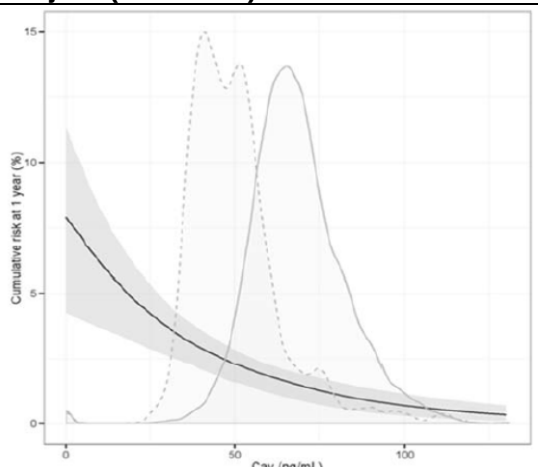
Figure PD-04: Probability of Clinically Relevant Bleeding (CRB) Event Occurring Within 1 Year as a Function of Average Edoxaban Concentration (Cav) in a Typical Edoxaban Subject (TMPP011)



Source: TMPP011, Figure 6.22

The solid line represents the median model prediction

Figure PD-05: Probability of a Symptomatic Recurrent VTE Event Occurring Within 1 Year as a Function of Average Plasma Concentration (Cav) in a Typical Edoxaban Subject (TMPP011)



Source: TMPP011, Figure 6.21

The solid line represents the median model prediction

for a typical edoxaban subject (no risk factors). The gray shaded area shows the 90% prediction interval. The distributions represent the predicted (from the PopPK model) distributions of Cav in the 60 mg (solid lines) and 30 mg (dashed lines) exposure groups.	for a typical edoxaban subject (no risk factors). The gray shaded area shows the 90% prediction interval. The two distributions represent the predicted (from the full PopPK model) distributions of Cav following 60 mg (solid line) and 30 mg (dashed line) dosing.

Pharmacodynamic interactions with other medicinal products or substances

As an anticoagulant, edoxaban has the potential to interact with other drugs that influence the coagulation system. Co-administration of edoxaban with acetylsalicylic acid, naproxen, or digoxin showed additive effects on bleeding time prolongation compared to the administration of edoxaban alone, without additionally affecting platelet aggregation.

The interaction studies with aspirin (high and low doses), naproxen or digoxinare:

PRT014:A phase I, randomized, open-label, dual sequence, parallel group study assessing the pharmacodynamic effects of the co-administration of digoxin and edoxaban in healthy volunteers. The objective of this study was to evaluate the pharmacodynamics (PD) of multiple daily 60 mg edoxaban doses for seven days followed by its co-administration with multiple 0.25 mg digoxin dose for the subsequent seven days. lood samples for PD parameters, were collected over 24 hours on Day 7 (monotherapy) and on Day 14 (combination therapy). Maximal increases in coagulation parameters were noted at approximately 2 hours after the last dose following concomitant administration of edoxaban and digoxin. The maximum decrease in the rate of thrombin generation and the maximum anti-factor Xa activity occurred 2 hours after the last dose. PT, INR, aPTT, all CAT-TGT parameters, and anti-factor Xa (FXa) activity were summarized with descriptive statistics. The combination therapy of digoxin and edoxaban increased the maximal plasma concentration of digoxin by 28% and increased the maximal plasma concentration of edoxaban by 16%, without affecting the total extent of exposure. The combination therapy (edoxaban and digoxin) and the monotherapy with edoxaban resulted in a similar increase of the standard coagulation parameters (INR, PT and aPTT). The thrombin generation was slightly decreased, and the induction of anti-factor Xa activity slightly increased. A strong positive correlation was observed between plasma concentrations of edoxaban and anti-Factor Xa activity. These results were not unexpected based on previous non-clinical pharmacology studies that showed edoxaban to be a potent and direct inhibitor of Factor Xa (FXa) that prolongs clotting (PT and aPTT) in plasma.

U128: A phase I, open-label, randomized, 3-way crossover study to assess the effect of naproxen on the pharmacodynamics of edoxaban. The objective of this study was to determine the effect of co-administration of naproxen (500 mg BID) and edoxaban (60 mg) on bleeding time, and on global coagulation variables (aPTT, PT/INR, and Intrinsic Factor Xa), compared to when each drug was administered alone. Serial blood samples were collected on Day 1 at pre-dose (baseline for each respective period) and on Day 2, measured at various time points up to 24 hours postdose.

Bleeding Time: Both edoxaban and naproxen had an effect on prolongation of bleeding time was most pronounced when both drugs were administered together.

Pharmacodynamic Markers: Graphical data analysis demonstrated correlations between the peak plasma concentrations of edoxaban, administered with or without naproxen, and PT, INR, aPTT and Intrinsic FXa. Similar prolongation effects from baseline were observed for the coagulation biomarkers PT, INR, aPTT and Intrinsic FXa, measured at various time points up to 24 hours postdose on Day 2, when edoxaban was administered with or without naproxen. The prolongation effect of edoxaban on the coagulation biomarkers PT, INR, aPTT and Intrinsic FXa was not significantly influenced by co-administration with naproxen.

PRT017: A phase I, two-cohort, double-blind, randomized, 2-way crossover study in healthy subjects to assess the effect of high dose aspirin on pharmacodynamics of edoxaban. The objectives of this study were to assess the effect of co-administration of high dose aspirin (325 mg) and edoxaban (60 mg) on bleeding time, and the effect of co-administration of aspirin on the pharmacodynamics (PD) edoxaban. Serial blood samples were collected on Day 1 (baseline) and on predose on Day 5 until 24 hours post dose.

Bleeding Time: These results showed that both edoxaban and high dose aspirin have an effect on prolongation of bleeding time was generally most pronounced when both drugs were administered together. Results for changes in bleeding time from baseline were consistent with an additive effect for the prolongation of bleeding time between edoxaban and aspirin.

Pharmacodynamics: The effects of edoxaban and aspirin (administered alone or as a combination therapy) on coagulation were measured using activated partial thromboplastin time (aPTT), prothrombin time (PT), anti-factor Xa (FXa) activity, prothrombinase induced clotting time (PiCT), and calibrated automated thrombogram-thrombin generation time (CAT-TGT) for thrombin generation. In all treatments that included edoxaban either as a monotherapy or as a combination therapy with aspirin, similar increases from baseline were noted for most coagulation parameters following dose administration on Day 5. The pharmacodynamics of edoxaban do not appear to be influenced by the co-administration of aspirin.

U127:A phase I, randomized, 3-way crossover, open-label study in healthy subjects to assess the effect of low dose aspirin on pharmacodynamics of edoxaban. The objectives of this study were to assess the effect of co-administration of low dose aspirin (100 mg) and edoxaban (60 mg) on bleeding time, and the effect of co-administration of aspirin on PT, aPTT, INR and anti-FXa activity of edoxaban. Serial blood samples were collected on Day 1 (baseline) and measured at various time points up to 24 hours post-dose on Day 5, when edoxaban was administered with or without aspirin.

Bleeding Time: concomitant administration of 100 mg aspirin and edoxaban results in greater prolongation of bleeding time, comparing with either drug administered alone. Results for changes in bleeding time from baseline were consistent with an additive effect for the prolongation of bleeding time between edoxaban and aspirin.

Pharmacodynamics: PD analyses were performed in order to determine the effect of co-administration of edoxaban and low dose aspirin on the coagulation parameters aPTT (Time), aPTT (Ratio), PT (Time), PT Rate (%), INR and Intrinsic FXa. No significant difference was observed in coagulation effects when edoxaban was administered with low dose aspirin (Treatment A) compared to its administration alone (Treatment B). Aspirin had no apparent effect on coagulation biomarkers after 5 days of once daily doses of 100 mg. These results were consistent with the similar prolongation effects observed relative to baseline, based on the peak change and percent change from baseline results, for both treatments. These results supported the hypothesis that the effect of edoxaban on the coagulation biomarkers would not be significantly influenced by co-administration with aspirin. The effect of edoxaban on the coagulation biomarkers PT, INR, aPTT and Intrinsic FXa was not significantly influenced by co-administration with aspirin.

Effects of coagulation markers when switching from rivaroxaban, dabigatran, or apixaban to edoxaban:

U122:A phase I, randomized, double blind study to assess the pharmacodynamics of edoxaban in healthy subjects who have recently discontinued warfarin. The objectives of this study were to

determine the effect of warfarin on biomarkers of anticoagulation in healthy subjects who were dosed to achieve an INR of 2 to 3, and to compare the effect of edoxaban to placebo on biomarkers of anticoagulation in healthy subjects who have recently discontinued warfarin. Serial blood samples for PD markers were collected at baseline (predose on Day 1) and from predose up to 12 hours post dose on the last day of warfarin dosing (prior to administration of edoxaban or placebo). The administration of a single edoxaban 60 mg dose 24 hours after the last warfarin dose prolonged the lag time to thrombin formation or clotting time. A positive correlation was observed between plasma concentrations of edoxaban and clotting time as measured by the clotting time factors PT, INR and PICT. A strong positive correlation was observed between plasma concentrations of edoxaban and anti Factor Xa activity.

U151:A phase I, open-label, randomized, crossover study to assess the pharmacodynamics edoxaban (60 mg) in healthy subjects after switching from dabigatran (150 mg BID) or rivaroxaban (20 mg). The objectives of this study were to evaluate the prothrombin time (PT) and the activated partial thromboplastin time (aPTT) profile in healthy subjects treated with edoxaban alone or preceded by rivaroxaban or dabigatran, and to assess the effect of edoxaban alone or preceded by rivaroxaban and dabigatran on additional pharmacodynamic (PD) assays. PD assessments were based on the following biomarkers: PT, aPTT, anti-FXa, TGA parameters, bleeding time, and ecarin clotting time (ECT). Serial blood samples were collected during each treatment edoxaban switching on Day 4, and also during treatment edoxaban only on Day 1, for assessment of PD parameters related to edoxaban. The PD parameters for PT, aPTT, anti-Fxa, ETP peak thrombin after a single edoxaban dose preceded by rivaroxaban were comparable to those parameters after 4 consecutive daily doses of edoxaban. The PD parameters for anti-FXa, ETP, peak thrombin after a single edoxaban dose preceded by dabigatran were comparable to those parameters after four consecutive daily doses of edoxaban, but for PT was higher. Switching from rivaroxaban to edoxaban 24 h after the last rivaroxaban dose resulted in similar anticoagulant effects of edoxaban in all PD assays upon switching as upon multiple dosing of edoxaban. Switching from dabigatran to edoxaban resulted in higher anticoagulant effects of edoxaban for aPTT, PT, and the thrombin generation parameters most sensitive to dabigatran (TGA lag time, TGA time to peak) when dosed 12 h after a dabigatran dose.

E152: A phase I, open-label, 2-treatment, 2-way crossover study to assess the pharmacodynamics edoxaban (60 mg) in healthy subjects after switching from apixaban (5 mg BID). The objectives of this study were to evaluate the prothrombin time (PT) in healthy volunteers treated with edoxaban alone or preceded by apixaban, and to assess the effect of edoxaban alone or preceded by apixaban on additional pharmacodynamic (PD) assays: activated partial thromboplastin time (aPTT), anti-factor Xa (anti-FXa) activity, thrombin generation assay (TGA) parameters. The prothrombin time (PT) observed for apixaban BID followed by edoxaban was comparable to that observed for edoxaban alone on day 4. The other biomarkers anti-FXa, INR, ETP, peak thrombin after edoxaban were comparable across study days in Treatment edoxaban alone (Days 1 and 4) and across treatments switching from apixaban. Switching from apixaban to edoxaban at the next scheduled dosing time of apixaban should be feasible, as anticoagulant effects of edoxaban upon switching are similar to multiple dosing of edoxaban.

Reversal of anticoagulant effects

Study U150 investigated the potential of two concentrations of a 3-factor PCC (factors FII, IX and X) as reversal agents for edoxaban. Both doses of edoxaban (60 and 180 mg) inhibited endogenous thrombin potential (ETP, one of the TGA parameters), an effect that was rapidly reversed (within 0.5 h after administration of PCC) by both doses of PCC (25 and 50 IU/kg). The effect was more pronounced for the 60 mg dose group. At 0.5 h after administration of PCC, the LSM values for change

from baseline for TGA-ETP were -1047, -546 and -611, respectively for 60 mg edoxaban dose alone, or edoxaban with 25 or 50 IU/kg PCC. For the 180 mg edoxaban dose, the change from baseline in TGA-ETP was -1644, -975 and - 1970, respectively with edoxaban alone, or edoxaban with 25 or 50 IU/kg PCC. Both doses of PCC resulted in a more rapid return to baseline for both doses of edoxaban (~3h), than for edoxaban alone (>72h). However, PCC did not substantially reverse the effect of edoxaban on PT, INR or aPTT prolongation relative to placebo. Both doses of PCC did not appear to have any effect on change from baseline for anti-FXa.

Hence, administration of 25 or 50 IU/kg 3-factor PCC with edoxaban 60 or 180 mg did not substantially accelerate reversal of PT, INR or aPTT prolongation relative to placebo. A reversal was demonstrated for ETP. No dose-dependency with respect to the effect on ETP (between 25 IU/ kg and 50 IU/ kg) was observed.

Genetic differences in PD response

Exploratory pharmacogenomics analyses demonstrate that there is no demonstrable effect of *VKORC1* or *CYP2C9* genotype on bleeding events in edoxaban treated subjects, although in warfarin treated subjects, the*VKORC1* 1639 AA subjects appeared to have a higher frequency ofbleeding events that the GG or GA genotypes. Common genetic variants in the *VKORC1* and *CYP2C9* genes that are known to affect warfarin sensitivity had no effect on bleeding in subjects treated with edoxaban.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

A large amount of PK data was generated, as PK-data were not only available from the 43 phase 1 studies but from phase 2 and phase 3 studies as well. In general, PK was considered characterised properly. This includes absorption, distribution, metabolism and excretion (ADME), influence of food and gastric pH, renal and hepatic insufficiency.

Time dependency of edoxaban PK in general was characterised properly. There is a bi-exponential decline of the plasma profile. The half-life estimates were variable across studies. A pooled population PK (PopPK) analysis of 8 Phase 1, 1 Phase 2 and 2 Phase 3 studies of edoxaban characterized the PK of edoxaban using a two-compartment model, giving an estimated half-life of about 12.5 h. In some studies, sparse sampling after 12 hours may have led to a shorter calculated half-life (e.g. t1/2 = 5.5 – 7.5 h in study U147). When edoxaban is dosed 60 mg QD, C_{max} is about 20 - fold the value of C_{trough}. As a linear correlation is observed between edoxaban plasma concentrations and PT, aPTT, and anti-FXa activity the QD dosing was considered not justified from the PK point of view. A BID or even three times a day (TID) dosing scheme could be more favourable. The chosen QD-dosing was addressed as well in the PD, clinical efficacy and safety sections of this assessment report.

The targeted phase I study in patients with hepatic impairment suggested that administering a single dose of 15 mg of edoxaban to subjects with mild or moderate hepatic impairment (Child-Pugh A and B) is unlikely to affect edoxaban exposure to a clinically relevant extent. In light of the results obtained in this study and considering the importance of renal clearance in edoxaban elimination, the Applicant's conclusion regarding no need for dose adjustment in subjects with mild or moderate hepatic impairment was considered acceptable.

In general, the PK interactions profile is characterised properly. Though amiodarone and verapamil show comparable modifications of edoxaban PK, a dose reduction of edoxaban by 50 % was initially suggested if co-administered with verapamil but not when co-administered with amiodarone, a decision mainly based on Cmin calculations. However, clinical phase III data indicate that efficacy of edoxaban was unsatisfactory with dose reduction by 50 % in patients receiving verapamil or

quinidine. In ENGAGE AF-TIMI 48, subgroup analyses for these patients indicated a numerically better efficacy of warfarin. The concern is supported by the POP PK analyses. C min ss values were 28.13 ng/ml (n = 10272) for the 60 mg qd dose and 16.24 ng/ml (n = 335) for the 30 mg qd dose in the presence of a P-gp inhibitor. In respect to the clinical efficacy and safety data gained with verapamil or amiodarone co-medication and the similarity of the influence of verapamil, amiodarone and quinidine on edoxaban PK, it was considered appropriate to administer edoxaban at a dose of 60 mg once daily when these drugs are a concomitant medication unless additional factors such as impaired renal function or low body weight have to be taken into account. The SmPC section 4.5 was modified accordingly. Co-administration of edoxaban with the p-gp inducer rifampicin led to a decrease in mean edoxaban AUC and a shortened half-life, with possible decreases in its PD effects. Therefore, edoxaban should be used with caution when co-administered with P-gp inducers.

Population pharmacokinetics

In general, the population PK analysis was considered acceptable. Presented goodness of fit plots was not easy to interpret since scaling was not optimal. Prediction-corrected Visual Predictive Checks (pcVPCs) were considered acceptable and bootstrap (n=100) results show good agreement. Compared to the results of the non-compartmental analysis (NCA), clearance was underestimated in the normal renal function group and overestimated in the severely renally impaired group. This might indicate an underprediction of the influence of CrCl on edoxaban clearance (CL). Edoxaban seems to undergo an enterohepatic recirculation. A second peak can be seen in the concentration-time profiles. The second peak was more pronounced in patients with mild or moderate renal function compared to those with normal or severe renal function. The model seems to underestimate the influence of renal function since compared to NCA values which ranged from 34.8 to 17.9 L/h from normal to severe renal function; the final model only predicted a range between 31.4 and 20.5 L/h.

Influence of P-gp inhibitors was discussed with the Phase 1 POPPK model. It was mentioned that taking into account the relation of each P-gp inhibitor separately was more adequate than including a class effect of P-gp inhibitors. In the Phase 3 POPPK model, P-gp inhibitors were introduced as a class and the effect on absolute bioavailability (F) and CL remains unclear. A more differentiated conclusion on the necessity of dose adjustment and its extent with the different P-gp inhibitors was not possible with the actual data. The following recommendations were finaly agreed to be included in the SmPC with regards to the concomitant use of edoxaban and P-gp inhibitors: (1) in patients concomitantly taking edoxaban and the following P-gp inhibitors: ciclosporine, dronedarone, erythromycin, or ketoconazole, the recommended dose was agreed to be 30 mg of edoxaban once daily (50% reduction as compared to the usual recommended edoxaban dose of 60 mg once daily); (2) no dose reduction was recommended for concomitant use of amiodarone, quinidine or verapamil; (3) the use of Lixiana with other P-gp inhibitors including HIV protease inhibitors has not been studied. The effect of P-gp inhibitors, pre-specified for dose-adjustment on the PK of edoxaban, differed to the effect of P-gp inhibitors with no dose-adjustment on the PK of edoxaban. The applicant considered the slight non-proportionality of the PK of edoxaban not relevant for a different influence of different P-gp inhibitors on edoxaban exposure, especially because dose reduction was only done by 50% and not from 60 mg to 15 mg.

Eta-shrinkage values were high in the Phase 3 studies. This has to be kept in mind when evaluating the exposure – response relation since estimated exposure values for individual persons will be shrunk to the typical population parameters. Thus, the variability in the exposure will not be adequately captured, but will be lower than real.

Summarizing the results of the population PK analyses, the relevance of the influence of concomitant P-gp inhibitors could not be finally assessed.

Pharmacodynamics

The effect of edoxaban on anti-Xa activity was assessed in multiple clinical trials. The PD effects of edoxaban include induction of venous anti-FXa activity at dose levels of 30 to 120 mg, the prolongation of clotting tests such as PT/INR, and aPTT, as well as edoxaban 60 mg reduced ex vivo thrombus formation. Edoxaban has no apparent direct effect on platelet activation or on endothelial activation.

A linear correlation was observed between edoxaban plasma concentrations and PT, aPTT and anti-FXa activity in healthy subjects (study PRT001). In patients with NVAF, there was a statistically significant exposure response relationship for major bleeding (minimum concentration), stroke or SEE (average concentrations), and ischemic stroke or SEE (minimum concentration), but not for hemorrhagic stroke (TMPP009). In patients with acute VTE, there was a statistically significant exposure response relationship for recurrent VTE (average concentration), but no statistically significant exposure response relationship was detected for CRB (TMPP011).

As an anticoagulant, edoxaban has the potential to interact with other drugs that influence the coagulation system. Co-administration of edoxaban with acetylsalicylic acid, naproxen, or digoxin showed additive effects on bleeding time prolongation compared to the administration of edoxaban alone, without additionally affecting platelet aggregation. The prolongation effect of edoxaban on the coagulation biomarkers PT, INR, aPTT and intrinsic FXa was not significantly influenced by co-administration with these drugs.

Available data support that edoxaban does not affect the QTc interval: the lower bound of the 95% CI for the placebo-adjusted change in QTc after treatment with moxifloxacin was >5 msec, confirming assay sensitivity. The upper bound of the 95% CI for the placebo-adjusted differences for both edoxaban doses were < 4 msec, indicating that edoxaban had no relevant effect on the QTc interval.

The effect on PD parameters seems not to be maintained throughout the dosing interval after QD dosing (e. g. study PRT003). Two studies investigated both, QD and BID dosing (study PRT009 in elderly healthy subjects and study PRT018 in patients with NVAF, please refer to clinical part of this AR). In both studies through levels for PD parameters (especially anti-FXa activity) were markedly higher after BID dosing. Overall, the low anticoagulant action beyond 12 hours after QD dosing has to be discussed in the clinical context, also taking into account the higher bleeding rates with BID dosing. Overall, the choice of the QD dosing regimen is considered justified with regard to the increase in bleeding risk observed after BID dosing. The impact of lower doses than 30 mg BID, which might have exhibited the most favourable B/R profile, cannot be assessed since such doses were not investigated. Further discussion on this issue was not considered necessary given the clinical study data available.

PD interaction studies have been performed with edoxaban and digoxin, naproxen and low- and high-dose ASA. The results from these studies did not reveal any unexpected PD interactions. Adequate warnings were included in the SmPC with respect to co-administration of agents with anti-haemostatic properties (e. g. naproxen). The present wording recommends against the *chronic* concomitant use of naproxen but permits short term treatment, which is acceptable. Since high dose ASA (325 mg) increased the steady state C_{max} and AUC of edoxaban by 35% and 32%, respectively, and was not permitted in the phase III trials, the wording in section 4.5 has been amended as follows: *""The concomitant chronic use of high dose ASA (325 mg) with edoxaban is not recommended. Concomitant administration of higher doses than 100 mg ASA should be only performed under medical supervision*".

Switching from various anticoagulants to edoxaban was examined in healthy subject studies, trough effects on PD markers of coagulation. Based on the study results, switching from enoxaparin, warfarin, rivaroxaban and apixaban can be initiated at the next scheduled dosing time of the preceding anticoagulant. The proposal to start warfarin when the INR is <2.5 was accepted. Switching from the factor II inhibitor (dabigatran) to edoxaban is recommended at the next scheduled dosing time of dabigatran (12 h after the last dose of dabigatran). Switching from dabigatran to edoxaban resulted in higher anticoagulant effect of edoxaban as evidenced by aPTT when dosed 12 hours after dabigatran dose (this effect normalized at about 24 hours). Section 5.1 of the SmPC was updated to reflect that when switching from dabigatran to edoxaban in clinical pharmacology studies, higher aPTT activity was observed after edoxaban administration with prior dabigatran treatment compared to that after treatment with edoxaban alone. This was considered to be due to the carry-over effect of dabigatran treatment, however, this did not lead to a prolongation of bleeding time.

Development of the reversal agent for edoxaban
Study U150 investigated the potential of two concentrations of a 3-factor PCC (factors FII, IX and X) as a reversal agent for edoxaban. This study showed differential effects on PT prolongation, anti-FXa (no reversal) and endogenous thrombin potential (ETP) (reversal). No dose-dependency with respect to the effect on ETP (between 25 IU/ kg and 50 IU/ kg) was observed. Furthermore, unlike warfarin, it is unclear which biomarker correlates best with clinical anticoagulation status and bleeding.
Overall, further investigations on other potential reversal agents and biomarkers for monitoring are considered necessary. Study U158 was a 2-part study, that was performed in healthy subjects to assess the use of a punch-biopsy to evaluate edoxaban effects on bleeding (Part 1), and then to evaluate the reversal effects of a 4-factor PCC (Part 2). Results of study U158 are promising in that a 4- factor PCC (licensed in the EU) could be useful to reverse the anticoagulant effect of edoxaban. PER977 is a small, synthetic molecule designed to bind to factor Xa inhibitors (edoxaban, rivaroxaban and apixaban) and to the oral thrombin inhibitor dabigatran through non-covalent hydrogen bonding and charge-charge interactions. Study PER977 was a first in human study which assessed the safety and the effect on anticoagulation reversal of PER977 when administered alone and after a 60 mg dose of the factor X inhibitor edoxaban. Results from this phase 1 study are also promising. Two phase 2 studies, investigating the reversal of anticoagulant effect of edoxaban with: (1) aripazine (CSR planned for July 2015) and (2) andexanet alfa (sponsored by another company, supported by the applicant), are currently underway. All studies are included in the agreed RMP. Overall, the development program for a reversal agent was considered comprehensive.

Polymorphisms in the genes associated with the determinants of PD (variants in the *VKORC1* and *CYP2C9* genes), that are known to affect warfarin sensitivity had no effect on bleeding in subjects treated with edoxaban.

2.4.5. Conclusions on clinical pharmacology

The PK properties of edoxaban have been generally well characterised. Regarding interaction of edoxaban with other drugs, the overall PK, efficacy and safety data indicates that a dose-adjustment of edoxaban 60 mg is not required when coadministered with verapamil, quinidine or amiodarone.

The PD properties of edoxaban are adequately characterized and are within expected for a direct FXa inhibitor. Overall, the development program for a reversal agent was considered reasonable and comprehensive and has to be followed as specified in the agreed RMP.

2.5. Clinical efficacy

2.5.1. Dose response studies

A total of 6 phase-II studies (3 controlled and 2 uncontrolled studies) were conducted in patients with NVAF. Overall, the studies included 2045 patients receiving at least one dose of study drug (safety population). Of them, 1595 were treated with several oral dosing regimes of edoxaban, ranging from 5 mg OD to 60 mg BID, and 450 patients received warfarin as active control. The Phase 2 studies in subjects with NVAF were not designed to evaluate efficacy; they were safety studies of short term treatment (up to 3 months) and relatively small sample size, with the exception of study PRT-018 (n=1146), which is described below.

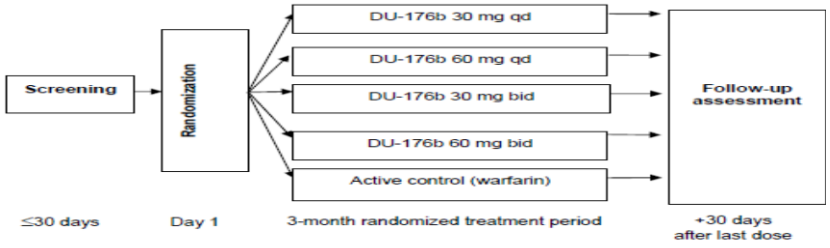
Study PRT-018: A Phase 2, randomized, parallel group, multi-center, multi-national study for the evaluation of safety of four fixed dose regimens of DU-176b in subjects with non-valvular atrial fibrillation

Study Period: First subject first visit date: 02 Jul 2007; Last subject last follow-up date: 10 Jun 2008
Study Center(s): A total of 107 investigative sites randomized subjects in this study. This study was conducted (randomized subjects) at 23 investigative sites in North and South America, 18 investigative sites in Eastern, Western, and Central Europe, 32 investigative sites in Russia, and 34 investigative sites in Ukraine.
Phase of Development: Phase 2
Study objectives: The primary objective was to evaluate the safety of four fixed dose regimens of DU-176b (30 mg once daily [qd], 30 mg twice daily [bid], 60 mg qd, and 60 mg bid) in subjects with non-valvular atrial fibrillation (NVAF). Warfarin was included as an active control. Evaluation of bleeding events and liver enzyme/bilirubin abnormalities were the primary focus of the safety evaluation.
Secondary objectives included the following:

- Evaluation of the incidence of major adverse cardiovascular events (MACE): stroke (ischemic or hemorrhagic), SEE, myocardial infarction (MI), cardiovascular death, and hospitalization for any cardiac condition
- Evaluation of the effects on biomarkers of thrombus formation: D-dimer and prothrombin fragments 1 and 2 (F1 and F2).
- Evaluation of the PK of DU 176 including known metabolites in subjects receiving DU-176b.
- Evaluation of the effects on PD biomarkers (anti FXa activity, endogenous FXa activity, prothombin time [PT], international normalized ratio [INR], prothrombinase induced clotting time [PiCT], and thrombin generation using the calibrated automated thrombogram [CAT-TG]) in subjects receiving DU-176b.

Study Design/Methodology: This was a randomized, double-blind (DU-176b) and open-label (warfarin), parallel group, multi-center, multi-national study. Male and female subjects, 18 to 85 years of age, inclusive, with NVAF and at least a moderate yearly risk of stroke (based on the CHADS2 index score) were randomly assigned to 1 of 5 treatment groups (4 fixed doses of DU-176b or warfarin) in a 1:1:1:1:1 ratio. The Investigator, all subjects, and the Sponsor were blinded to the exact DU-176b dose regimen, but not to whether the assigned treatment was DU-176b or warfarin. Subjects randomized into the study received 1 of the following active treatments: DU-176b 30 mg qd; DU-176b 30 mg bid;DU-176b 60 mg qd; DU-176b 60 mg bid (only subjects randomized before 14 Jan 2008); Warfarin tablets (open-label) qd with dose adjusted to maintain an INR between 2.0 and 3.0, inclusive. Treatments were administered for 3 months (see figure below).

Figure E01. Schematic diagram of PRT-018 study design.



Abbreviations: qd = once daily; bid = twice daily.
Note: DU-176b 60 mg bid dose regimen was terminated by IDMC recommendation on 14 Jan 2008.

An Independent Data Monitoring Committee (IDMC) of external experts was organized to monitor the study data in an unblinded manner while the study was ongoing. The purpose of the IDMC was to protect the safety of the subjects and to advise the Sponsor in case of any signals of safety concern. In addition, an independent Clinical Events Committee (CEC) was organized to evaluate and adjudicate all bleeding events based upon review of blinded data. The CEC adjudicated all bleeding events and categorized them as major, clinically relevant nonmajor, or minor bleeding based on pre-specified definitions.

Table E02. Disposition of subjects in study PRT-018

	DU-176b Daily Dose				
Number of subjects	**30 mg qd**	**30 mg bid**	**60 mg qd**	**60mg bid**	**Warfarin**
Randomized	235	245	235	180	251
Safety analysis set, n (%)	235 (100.0)	244 (99.6)	234 (99.6)	180 (100.0)	250 (99.6)
Per protocol analysis set, n (%)	235 (100.0)	243[a] (99.2)	234 (99.6)	180 (100.0)	250 (99.6)
n (%) with major protocol deviations	0 (0.0)	1[a] (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Pharmacodynamic analysis set, n (%)	230 (97.9)	236 (96.3)	228 (97.0)	170 (94.4)	244 (97.2)

a: Subject (ID#: 4001/0002) was excluded from the per protocol analysis set for a major protocol deviation (randomized dose and treated dose were not the same per CRF); however, after unblinding, it was found that this subject did receive the randomized dose. In any case, per protocol analyses were not conducted.
Note: Percentages are based on the number of randomized subjects.
Source: Table 15.1.1.

Results:

A total of 1146 patients were enrolled. Of them 1143 patients received at least one dose of study drug (safety population). The mean age ranged from 64.7 to 66.0 years. The mean weight ranged from 87.75 kg to 88.95 kg. Most subjects were male (~60%). Most of the subjects (~60%) were warfarin-naïve and approximately half of the subjects were on aspirin therapy at study entry. The majority of subjects were Caucasian (~98.0%) and from Eastern Europe (over 90%). Across all treatment groups, ~36% of subjects had a CHADS2 score ≥ 3, ~20% of subjects had diabetes, ~95% of subjects had hypertension, ~65% of subjects had ischemic heart disease, ~90% of subjects had heart failure, and ~20% had a past stroke or TIA.

Major Adverse Cardiovascular Events (Efficacy): The incidence of MACE was 2.4% for warfarin-treated subjects and 2.5% across all DU-176b treated subjects.

Safety: Overall, DU-176b 30 mg qd and 60 mg qd dosage regimens were well tolerated with lower or similar incidences of bleeding compared with warfarin therapy (see table). Subjects treated with DU-30 mg bid and 60 mg bid regimens had higher bleeding incidences compared with subjects on warfarin therapy. The DU-176b 60 mg bid regimen was considered unsafe by the IDMC due to an unfavourable benefit/risk ratio, and was terminated early. Subjects treated with DU-176b 30 mg qd

and 60 mg qd regimens had lower bleeding incidences than those treated with the 30 mg bid or 60 mg bid regimens.

Table E03. Bleeding events in study PRT-018

Bleeding Category	DU-176b Daily Dose				Warfarin (N = 250)
	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	
All Bleeding, n (%)	13 (5.5)	31 (12.7)	17 (7.3)	33 (18.3)	20 (8.0)
p-value	0.367	0.104	0.864	0.002	
Major or CR non-major bleeding, n (%)	7 (3.0)	19 (7.8)	9 (3.8)	19 (10.6)	8 (3.2)
p-value	1.000	0.029	0.807	0.002	
Major bleeding, n (%)	0 (0.0)	5 (2.0)	1 (0.4)	6 (3.3)	1 (0.4)
p-value	1.000	0.119	1.000	0.023	

The overall incidence of liver enzyme and bilirubin abnormalities was low in this study and there was no significant difference between treatment groups.

Table E04. Liver abnormalities in study PRT-018

Laboratory Test	DU-176b Daily Dose				Warfarin (N = 250)
	30 mg qd (N = 235)	30 mg bid (N = 244)	60 mg qd (N = 234)	60 mg bid (N = 180)	
Any Elevation	5 (2.1)	4 (1.6)	8 (3.4)	7 (3.9)	8 (3.2)
ALT, N	230	235	229	172	245
Total ≥3 x ULN	3 (1.3)	2 (0.9)	6 (2.6)	3 (1.7)	3 (1.2)
AST, N	230	235	229	172	245
Total ≥3 x ULN	2 (0.9)	2 (0.9)	3 (1.3)	2 (1.2)	2 (0.8)
TBL, N	230	235	229	172	245
Total ≥2 x ULN	2 (0.9)	3 (1.3)	1 (0.4)	5 (2.9)	4 (1.6)
ALT and/or AST, N	230	235	229	172	245
ALT or AST ≥ 3 x ULN	3 (1.3)	2 (0.9)	7 (3.1)	3 (1.7)	4 (1.6)
(ALT or AST) and TBL, N	230	235	229	172	245
(ALT/AST ≥ 3 x ULN) and (TBL ≥2 x ULN)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.6)	0 (0.0)

There were two subjects (Subject IDs: 20060002 and 40290006 [1 in each of the DU-176b bid groups]) who experienced concomitant but not persistent elevations of ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN. At the same time as the elevated ALT/AST and TBL, both subjects also had ALP > 2 x ULN, suggesting cholestasis rather than drug-induced hepatocellular injury. Independent hepatologists' review of these cases concluded that one subject had acute cholecystitis and the other had a dilated bile duct confounded by chronic heart failure, intermittent hypotension, and anemia.

Deaths: Fourteen subjects (6 [2.6%] in the 30 mg qd DU-176b group, 4 [1.6%] in the30 mg bid DU-176b group, 1 [0.4%] in the 60 mg qd DU-176b group, 0 in the 60 mg bid DU-176b group, and 3 [1.2%] in the warfarin group) died during the study: 8 deaths occurred while the subject was on study drug, 5 occurred as a results of events during the post-treatment follow-up period, and 1 occurred during the follow-up period as a result of an event that began the day after the last dose of study drug (i.e., on the last day of the treatment period). All deaths resulted from cardiovascular conditions such as MI, coronary artery disease, cardiac failure, stroke, pulmonary embolism, or sudden death.

PK: The pharmacometric analyses were conducted to better understand the PK across the study population, the relationship between PK parameters and bleeding incidence relationship and the differences in bleeding incidences (DU-176b bid regimens vs. DU-176b qd regimens). These pharmacometric analyses confirmed similar total exposure expressed as AUCss between the DU-176b

60 mg qd and 30 mg bid regimens. In addition, logistic regression analyses indicated that the steady state minimum (trough) concentrations (Cmin,ss) best predicted the probability of bleeding.

Overall, the edoxaban 30 mg and 60 mg once daily regimes were safe and well tolerated by subjects with AF treated for 3 months in this Phase 2 study. There was a higher bleeding risk with twice-daily administration. The DU-176b 60 mg bid regimen was considered unsafe by the IDMC due to an unfavourable benefit/risk ratio, and had to be terminated early as a consequence. Logistic regression analyses indicated that the steady state minimum (trough) concentrations (Cmin,ss) best predicted the probability of bleeding.

Dose selection for phase III:

Three elements were considered by the applicant to support the proposed dose. Firstly, to select doses for the Phase 3 pivotal study that were likely to have a 10 to 20% reduction in bleeding when compared to warfarin at no potential cost of efficacy (no numerical increase in thrombotic events and similar effect on PD biomarkers). The second step was to identify a priori subjects who would have increased drug exposure and potentially increased risk of bleeding and hence benefit from dose reduction. The final step was to use the Phase 3 data to identify the optimal dose regimen, validate the dose reduction criteria and identify any other groups who may be at high risk of bleeding who would benefit from a lower dose.

A large Phase 2 study (PRT018) in NVAF subjects compared edoxaban 30 mg QD, 30 mg BID, 60 mg QD, and 60 mg BID and warfarin. All the regimens showed the potential for adequate efficacy based on PD biomarkers but the once daily regimens showed a similar or better bleeding profile when compared with warfarin. The DU-176b 60 mg BID regimen was considered unsafe by the IDMC due to an unfavourable benefit/risk ratio, and had to be terminated early as a consequence. The findings were supported by PK/bleeding modeling which showed that Cmin rather than AUC or Cmax was the driver of bleeding events. Based on these data, both 30 mg QD and 60 mg QD were taken forward in the NVAF Phase 3 pivotal study.

To identify factors for dose reduction, data from two Phase 2 NVAF studies in subjects (PRT018 and J225) plus DDI studies were evaluated by clinical assessment and pharmacometric modeling (TMPP004). In univariate analysis, age and sex had a significant effect but dropped out of multivariate analysis, which identified three independent factors (moderate to severe renal impairment, weight < 60 kg and concomitant use of P-gp inhibitors) that would increase exposure to edoxaban and also potentially increase the risk of bleeding compared with warfarin. Looking at these factors individually and in combination, a 50% dose reduction was selected so that in subjects with one or more of these factors the bleeding risk would be similar to the overall population while efficacy would be maintained. Supporting data with regard to weight was obtained from the subsequently completed study J226. The rationale for the Phase 3 dose section in NVAF was discussed with the CHMP and accepted.

The dose justification for edoxaban in VTE is essentially the same as for NVAF except that there were no dose finding studies in VTE and the clinical considerations of use with heparin and the increased risk of under anticoagulation that could lead to fatal pulmonary embolism. The standard of care for comparison was parenteral heparin with concomitant warfarin titrated to an INR of 2 to 3. For VTE, only the 60 mg dose was selected because of the increased thrombotic load in VTE and the need for intensive anticoagulation in a treatment setting rather than in NVAF, where the aim is prevention of thromboembolic events. Therefore weight was given to ensuring a dose was selected that would ensure efficacy while still being able to demonstrate a 10% reduction in bleeding.

This bridging approach, using principally data from NVAF and VTE prophylaxis subjects for dose selection of VTE treatment, was discussed with CHMP, as was the rationale for the dose reduction and the selection of the single 60 mg dose for VTE.

The study C-J307 in 93 patients with several degrees of renal function, showed that the administration of 15 mg of DU-176b for 12 weeks in Japanese patients with SRI did not result in a marked increase in bleeding compared to the low dose or high dose of DU-176b (30 mg OD and 60 mg OD, respectively) in patients with Normal/MiRI. The plasma concentrations in the subjects with SRI (15 mL/min ≤ CLCR < 30 mL/min) receiving 15 mg of DU-176b overlapped considerably with those concentrations in the subjects with Normal/MiRI receiving the 30 mg OD dose or 60 mg OD dose of DU-176b. These data support the use of halved doses of edoxaban in patients with moderate-severe renal impairment (CrCL 15 – 50 mL/min).

With respect to hepatic safety, in at least two phase II studies (PRT-018 and J225) there was at least one subject on edoxaban that showed concurrent elevations of AST (GOT) or ALT (GPT) ≥3 times the ULN and total bilirubin ≥2 times the ULN, with no corresponding cases reported in the warfarin control group.

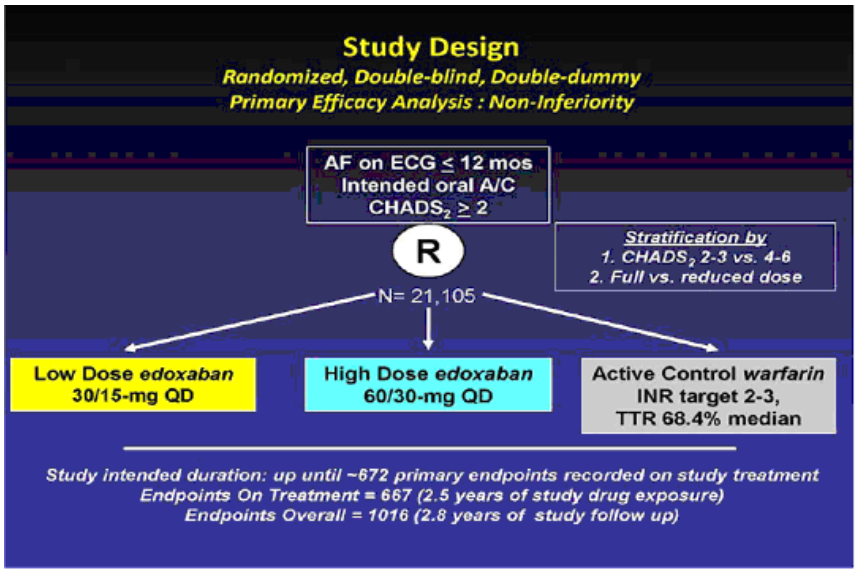
2.5.2. Main studies

ENGAGE AF: Prevention of stroke and SEE in patients with non-valvular atrial fibrillation

Methods

The efficacy data supporting the use of edoxaban for reducing the risk of stroke and SEE in subjects with NVAF are provided by the pivotal Phase 3 ENGAGE AF study (n=21,105 randomized patients; 21,006 received at least one dose) in which 7002 subjects were treated with edoxaban 30 mg (15 mg reduced), 7012 subjects were treated with edoxaban 60 mg (30 mg reduced) and 7012 with warfarin. ENGAGE AF was an event-driven, randomized, double-blind, double-dummy, multinational, multicenter, parallel-group study.

Figure E-02. ENGAGE-AF TIMI 48 study design



Study Participants

Inclusion/exclusion criteria: ENGAGE AF enrolled male or female subjects ≥21 years of age with documented NVAF (including paroxysmal, persistent, or permanent AF) within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for the duration of the study. Subjects who were receiving or had received prior anticoagulant (e.g.: VKA experienced) and/or antiplatelet therapies were eligible, as well as subjects who were naive to anticoagulant and/or antiplatelet therapy. In addition, eligible subjects were required to have a CHADS2 index score ≥ 2. - VKA experienced was defined as current users as well as former users who took VKA for greater than 2 months. VKA naïve were those subjects who received ≤ 2 months of VKA therapy before study entry. Given that these definitions are not homogeneous across trials in NVAF, current *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and SEEs in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014)* recommends sensitivity analyses using different definitions of VKA-naïve users in order to be able to compare with other studies. In this regard, the applicant was requested to show the main efficacy and safety results using other previous definitions of VKA naïve: a) VKA use for < 6 weeks immediately before entry into the trial; b) patients not on a VKA at randomization; c) patients who had never been on a VKA. Subjects with mitral valve stenosis (moderate to severe), unresected atrial myxoma or a mechanical heart valve were not allowed in the study. The intention of the sponsor/investigators was to represent "the typical NVAF population encountered in clinical practice" at the time in which the study was designed (clinical overview; module 2.5). However, this statement contrasts with the 25 exclusion criteria applied in the ENGAGE AF study. It is recognised that many of these exclusion criteria are standard for clinical trials, while others are known general contraindications for anticoagulation. However, some exclusion criteria may deserve specific commentaries. Patients with a mechanical heart valve were excluded from ENGAGE AF, but subjects with bioprosthetic heart valves and/or valve repair could have been included. The applicant proposes a warning stating that "Edoxaban has not been studied in patients with mechanical heart valves. Therefore, use of edoxaban is not recommended in these patients." It is implicit in the proposed warning that edoxaban could therefore be used in patients with bioprosthetic heart valves and/or valve repair. The applicant was requested to describe the efficacy and safety data available from patients with bioprosthetic heart valves and/or valve repair from ENGAGE AF. If the data are not robust, the warning should be extended to "prosthetic heart valves" in line with the wording approved for Xarelto (rivaroxaban). Subjects with severe renal insufficiency (calculated CrCL <30 mL/min) were excluded. In the proposed SmPC the non-recommendation of use was for patients with end-stage renal disease (calculated CrCL <15 mL/min). Despite patients with CrCl between 15 and 30 were not included in the ENGAGE study, the applicant had additional data in these patients from study C-J307 (see dose-finding studies). The results of this study supported a recommendation of use for edoxaban in patients with severe renal impairment not in end-stage renal disease. At the end the it was agreed that in patients with moderate or severe renal impairment (CrCL 15 – 50 mL/min), the recommended dose is 30 mg Lixiana once daily while in patients with end stage renal disease (ESRD) (CrCL < 15 mL/min) or on dialysis, the use of Lixiana is not recommended

Thromboembolic risk stratification: Current guidelines recommend the use of CHA_2DS_2-VAS_C instead of $CHADS_2$ score. Compared with the $CHADS_2$ score, the CHA_2DS_2-VAS_C score markedly increases the number of AF patients for whom OAC is recommended. Therefore it is important to determine by randomized trials if this major paradigm shift to greater use of OAC using the CHA_2DS_2-VAS_C scoring improves patient outcomes. The CHMP has agreed the wording of the indication in NVAF for other NOACs, which includes patients with a $CHADS_2$ index score ≥ 1 (approximately equivalent to current CHA_2DS_2-VAS_C score ≥ 2, in which anticoagulation is indicated as per current ESC guidelines) (de Caterina et al. Eur Heart J. 2012; 33:2719-47). The CHMP approach has accepted to widen the target population from $CHADS_2$ index score ≥ 2 (at least 2 points in $CHADS_2$ tested in pivotal clinical trials) to $CHADS_2$ index score ≥ 1 ("with one or more risk factors" generally not tested in clinical trials) in previous applications for NOACs. Therefore the wording of the

requested indication for edoxaban was also accepted, as it is identical to that of the other compounds. However, as patients with $CHADS_2$ index score=1 were excluded from the single pivotal study ENGAGE-AF but are already included in the wording of the indication (e.g.: patients with only one of the following risk factors: age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II), the applicant justified why the extrapolation of the available data from high risk $CHADS_2$ score ≥2 to $CHADS_2$ score =1 could be acceptable and discussed whether further studies are planned with edoxaban to generate clinical data in these patients at lower risk of stroke. The CHMP accepted the justification.

Treatments

In ENGAGE-AF, Eligible subjects were randomized to edoxaban 30 mg, edoxaban 60 mg, or warfarin (1:1:1 ratio) using stratified randomization. Within each $CHADS_2$ stratum, subjects were further stratified with respect to factors requiring edoxaban dosage reduction. In both edoxaban treatment groups, the dosage regimen was halved for subjects with one or more of moderate renal impairment (CrCL ≥ 30 mL/min and ≤ 50 mL/min as calculated using the Cockroft-Gault formula), low body weight (≤ 60 kg) or for subjects on specified concomitant medications (verapamil, quinidine, dronedarone). Each enrolled subject was to be treated with the study drug from randomization to the Common Study End Date (CSED) visit; this visit had to be within 90 days of the announced CSED (determined by the accrual rate of primary endpoint events), and it was the final dose day for all subjects. At the end, a total of 21105 subjects were randomized, and median duration of treatment exposure was 2.5 years and median duration of follow-up in the study was 2.8 years. Warfarin was the active blinded control and was provided by the Sponsor. International Normalized Ratio (INR) measurements were to be performed using uniform Point-of-Care (POC) devices supplied to all study sites. Warfarin doses were to be adjusted to maintain an INR of 2.0 to 3.0, inclusive. A Japan specific amendment was created to allow Investigator's in Japan to comply with Japanese guidelines for warfarin management in subjects age 70 years or older. In those Japanese subjects, the dose of warfarin was to be adjusted to maintain an INR of 2.0 to 2.5. Treatment regimes tested in the ENGAGE AF study are deemed appropriate.

Objectives

Outcomes/endpoints

Primary endpoint: as in other similar trials, the primary efficacy endpoint in ENGAGE-AF was a net clinical endpoint mixing thromboembolic events (ischemic/undefined stroke, SEE) and haemorrhagic stroke. As a result, there has been double-counting of primary efficacy/safety events (thromboembolism/major bleeding) regarding haemorrhagic stroke (included in both main efficacy and safety endpoints). Current *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and SEEs in patients with non-valvular atrial fibrillation* (EMA/CHMP/341363/2014) stresses the importance of excluding haemorrhagic stroke from the main efficacy endpoint. In this regard, the applicant provided the results of the primary endpoint with the thromboembolic events excluding haemorrhagic strokes. On the other hand, the definition of ischemic stroke/TIA used in ENGAGE-AF is unclear. In recent years, there has been a change in the diagnostic approach of TIA and ischaemic Stroke (from a time-based definition to a tissue-based definition), depending on the absence or presence of signs of brain infarction on neuroimaging. In current EMA Guideline (EMA/CHMP/341363/2014), it is recommended to adjudicate suspected strokes and TIAs as a group and to follow a tissue-based definition. A suspected TIA should be adjudicated as stroke if there is positive neuroimaging confirming a cerebral infarction, even if the duration of symptoms is of less than 24 hours [American Heart Association (AHA) and American Stroke Association (ASA) definition of TIA; Standardized Data Collection for Cardiovascular Trials (SDCCT) Initiative definition]. The occurrence of a TIA (transient episode of focal neurological dysfunction without positive neuroimaging) should not be part of the composite stroke endpoint, instead it is recommended to

assess this as a secondary efficacy endpoint. In this regard, the applicant clarified the approach used in ENGAGE AF to differentiate between ischaemic stroke and TIA (time-based definition or tissue-based definition) and provided with appropriate sensitivity analysis with different definition of ischaemic stroke (including or excluding TIA with positive neuroimaging as being an ischaemic stroke) (tissue-based and time-based definitions, respectively).

Secondary variables: A number of secondary variables were included (each of the components of the main outcome; composite of stroke, SEE, and CV mortality; MACE, which is the composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding; Composite of stroke, SEE, and all-cause mortality). These endpoints are considered acceptable.

Sample size

Randomisation

An Interactive voice/web response system (IXRS) was used. Eligible subjects in ENGAGE-AF were stratified by $CHADS_2$ risk score (2 and 3 versus ≥4). Within each CHADS2 stratum, subjects were stratified further for factors (calculated CrCL ≥50 mL/min and ≤30 mL/min, low body weight ≤60 kg], concomitant verapamil or concomitant quinidine) that required dosage reduction of edoxaban. Randomisation methods in ENGAGE-AF are deemed appropriate.

Blinding (masking)

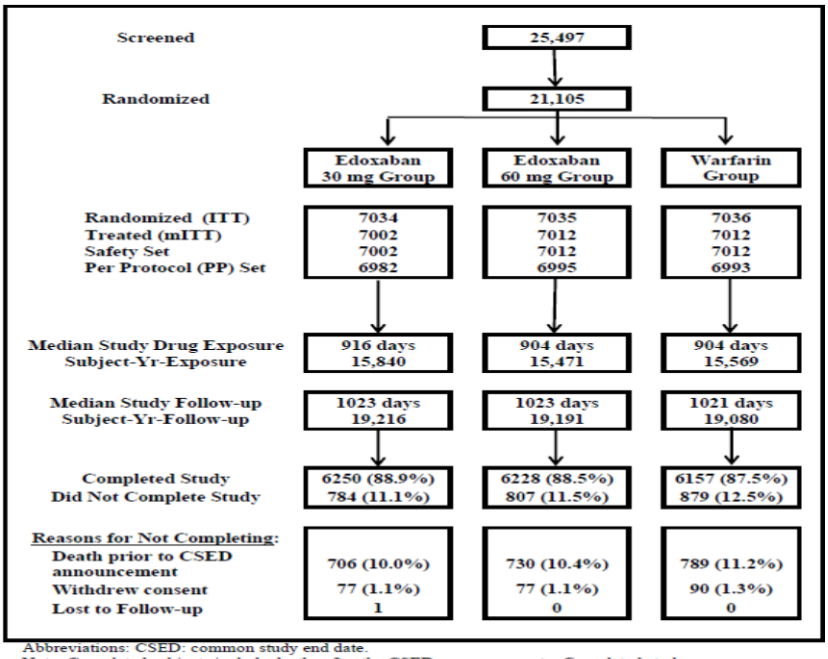
The ENGAGE study used a double-blind design, which is the one recommended by the guideline EMA/CHMP/341363/2014. Blinding/masking methods are deemed appropriate.

Statistical methods

Statistical methods applied in the ENGAGE AF study are considered acceptable. ENGAGE AF was event driven. A total of at least 448 events were required. Sample size calculation is endorsed. The non-inferiority margin (HR <1.38) is comparable to that used in ARISTOTLE study with apixaban and more restringing than the 1.46 used in the RE-LY and ROCKET-AF study with dabigatran and rivaroxaban. The time to first stroke/SEE event (primary endpoint) in ENGAGE-AF was analyzed using the Cox proportional hazards model including treatment groups and 2 dichotomized stratification factors as covariates ($CHADS_2$ 2-3 versus 4-6; full dose versus reduced dose in a given treatment group). The applicant focused its main analysis (non-inferiority) in a modified ITT population during the "on-treatment period". However, the applicant also tested non-inferiority in the PP population during the overall study period according to CHMP recommendations during scientific advice, as well as in the PP population "on-treatment", which is in agreement with the recent *CHMP Guideline on clinical investigation of medicinal products for prevention of stroke and SEEs in patients with NVAF (EMA/CHMP/341363/2014)* that states that "the analysis to show non-inferiority should include the primary endpoint events while taking study drug including a period of 3 days after study drug discontinuation (on-treatment analysis). Sensitivity analyses should include events occurring 1 week and 1 month after study drug discontinuation in order to investigate a possible early rebound increase in thromboembolism after treatment cessation."In order to control the studywise type-I error rate of two-sided $\alpha=0.05$ for non-inferiority, each of these 2 comparisons (60 mg or 30 mg versus warfarin) were performed at the statistical significance level of two-sided $\alpha=0.025$, respectively, which is endorsed. The analysis of superiority was only planned for the comparison between the 60 mg edoxaban dose and warfarin and only if non-inferiority was first established for that group. The significance level of $\alpha=0.01$ for superiority was selected by the sponsor because this was a single pivotal study. This was endorsed by the CHMP. The planned applicant's analysis to show superiority (ITT, overall study period) was consistent with the approach stated in the EMA Guideline (EMA/CHMP/341363/2014). Exploratory analyses of subgroups were conducted depending on at least 14 patient/study characteristics. These analyses are discussed under "ancillary analyses" subsection.

Results

Participant flow



Abbreviations: CSED: common study end date.
Note: Completed subjects include deaths after the CSED announcement. Completed study means completed CSED Visit.
Source data: Tables 14.1.1.1, 14.1.1.5, 14.1.1.7, and 14.1.5.2.

A total of 21,105 subjects who were randomized (7034, 70135, and 7036 in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups, respectively) (ITT). 21,026 subjects were treated with study drug (7002, 7012, and 7012 in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups, respectively) (mITT). 20,970 subjects who were treated with study drug and had no major protocol violations (6982, 6995, and 6993 in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups, respectively) (PP set).

Conduct of the study

A total of 46 countries from 6 regions (North America, Latin America, Western Europe, Eastern Europe, Asia Pacific and South Africa, and Japan) randomized subjects in this study. A total of 1420 investigational study sites screened at least 1 subject and 1393 study sites randomized at least 1 subject in this study. The rate of screening failures was relatively low (17%). There were few differences between the ITT, mITT and PP populations, with a difference between populations of less than 50 subjects per group. Only one patient was lost to follow-up, which is a signal of good quality of study oversight. There were 7 amendments with extensive major changes in the protocol of the ENGAGE-AF study. In particular, amendment 3 could have implications on the quality of management in warfarin control group and dosing errors. As a result, it was unknown if the changes made in the protocol before and after amendment 3 could have had implications on study results. The applicant showed the analyses of the main efficacy and safety outcomes in the ENGAGE AF study (edoxaban 60 mg vs. warfarin) in the subgroup of patients recruited before and after amendment 3 (29-Jul-2010). On the positive side, it seems that these amendments were based on gained experience from other contemporary studies in AF (e.g.: RE-LY, ROCKET-AF, ARISTOTLE). For example, in amendment 1, transition from blinded study drug to open-label warfarin was clarified and added explanation/instruction for use of transition study drug kit. This issue may have resulted in less tromboembolic events during the transition from edoxaban to warfarin after the end of study.

Baseline data

Population included in ENGAGE AF was an old population (mean 72 years; 40% > 75 years; 17% > 80 years) at high risk of stroke (mean CHADS2 score of 2.8; 53% of subjects had a $CHADS_2$ score ≥ 3).

There was no representation of patients with CHADS2 score 0-1.The majority of subjects were Caucasian (81%) and male (62%). Overall, mean body weight was 84 kg and 10% of subjects had body weight ≤60 kg. Approximately 18% of subjects had a body weight >100 kg. Overall, the mean BMI was 29.5 kg/m2, with approximately 60% of subjects having a BMI ≤ 30 kg/m2.

In all 3 treatment groups, CrCL was ≤50 mL/min in approximately 19% of subjects. The percentage of VKA naive subjects was 41% overall. Overall, 52% of subjects had permanent, 23% had persistent, and 25% had paroxysmal AF.

The percentage of subjects from each region was comparable among the treatment groups. Approximately half of the subjects were from Europe (Eastern Europe 34% and Western Europe 15%), 22% from North America, 13% from Latin America, 11% from Asia/Pacific and South Africa (excluding Japan), and 5% from Japan.

More than 65% of subjects were receiving ACE inhibitors or ARBs, or beta blockers, and about 60% were taking diuretic agents. Other more frequent medications used included lipid lowering agents (approximately 48%), aspirin (approximately 30%), calcium channel blockers (approximately 31%), and amiodarone (approximately 12%). Quinidine/verapamil was used by <4% of subjects at randomization.

Table E-19: Demographic and Baseline Characteristics – mITT (safety) analysis set

	Edoxaban 30 mg (15mg DosAdj) (N=7002)	Edoxaban 60 mg (30mg DosAdj) (N=7012)	Warfarin (N=7012)
Age (years), n	7002	7012	7012
Mean	70.6	70.6	70.5
SD	9.31	9.51	9.44
Median	72.0	72.0	72.0
Minimum	27	25	27
Maximum	95	96	95
>= 65 years n(%)	5218 (74.5)	5182 (73.9)	5143 (73.3)
>= 75 years n(%)	2789 (39.8)	2838 (40.5)	2805 (40.0)
>= 80 years n(%)	1197 (17.1)	1177 (16.8)	1195 (17.0)
Gender, n (%)	7002	7012	7012
Male	4284 (61.2)	4353 (62.1)	4383 (62.5)
Female	2718 (38.8)	2659 (37.9)	2629 (37.5)
Race, n (%)[a]	7001	7012	7012
Caucasian	5650 (80.7)	5679 (81.0)	5679 (81.0)
Black	94 (1.3)	96 (1.4)	88 (1.3)
Asian	975 (13.9)	956 (13.6)	963 (13.7)
Other	282 (4.0)	281 (4.0)	282 (4.0)
Edoxaban/Placebo Dose Adjusted at Randomization, n (%)	7002	7012	7012
Yes	1774 (25.3)	1776 (25.3)	1780 (25.4)
No	5228 (74.7)	5236 (74.7)	5232 (74.6)
CrCL (mL/min), n (%)[b]	6961	6954	6973
< 30	42 (0.6)	70 (1.0)	51 (0.7)
30 - <= 50	1274 (18.2)	1287 (18.4)	1297 (18.5)
> 50 - < 80	3034 (43.3)	2985 (42.6)	3030 (43.2)
>= 80	2611 (37.3)	2612 (37.3)	2595 (37.0)
Weight (kg), n (%)[c]	6996	7007	7007
<= 50	148 (2.1)	158 (2.3)	172 (2.5)
<= 60	692 (9.9)	681 (9.7)	697 (9.9)
> 60	6304 (90.0)	6326 (90.2)	6310 (90.0)
Mean (SD)	83.9 (20.11)	84.2 (20.40)	83.7 (20.09)
BMI, n (%)[c]	6976	6985	6984
<= 30	4160 (59.4)	4116 (58.7)	4238 (60.4)
> 30	2816 (40.2)	2869 (40.9)	2746 (39.2)
Mean (SD)	29.5 (5.93)	29.6 (6.05)	29.3 (5.89)
Verapamil or Quinidine Use at Randomization, n (%) [d]	7002	7012	7012
Yes	259 (3.7)	257 (3.7)	241 (3.4)
No	6743 (96.3)	6755 (96.3)	6771 (96.6)
$CHADS_2$, n (%)[e]	7002	7012	7012
2 - 3	5437 (77.6)	5401 (77.0)	5422 (77.3)
4 - 6	1559 (22.3)	1606 (22.9)	1585 (22.6)
>= 3	3705 (52.9)	3784 (54.0)	3686 (52.6)
0	0 (0.0)	0 (0.0)	1 (<0.1)
1	6 (<0.1)	5 (<0.1)	4 (<0.1)
2	3291 (47.0)	3223 (46.0)	3321 (47.4)
3	2146 (30.6)	2178 (31.1)	2101 (30.0)
4	1077 (15.4)	1123 (16.0)	1072 (15.3)
5	399 (5.7)	397 (5.7)	424 (6.0)
6	83 (1.2)	86 (1.2)	89 (1.3)
VKA Use, n (%)[f]	7001	7012	7012
Naive	2857 (40.8)	2879 (41.1)	2888 (41.2)
Experienced	4144 (59.2)	4133 (58.9)	4124 (58.8)
Type of Atrial Fibrillation, n (%)	7001	7012	7010
Paroxysmal	1827 (26.1)	1747 (24.9)	1774 (25.3)
Persistent	1581 (22.6)	1645 (23.5)	1624 (23.2)
Permanent	3593 (51.3)	3620 (51.6)	3612 (51.5)
Region, n (%)	7002	7012	7012
North America	1550 (22.1)	1559 (22.2)	1556 (22.2)
USA	1308 (18.7)	1288 (18.4)	1297 (18.5)
Latin America	882 (12.6)	884 (12.6)	885 (12.6)
Western Europe	1075 (15.4)	1075 (15.3)	1070 (15.3)
Eastern Europe	2369 (33.8)	2374 (33.9)	2378 (33.9)
Asia/Pacific and South Africa (Excluding Japan)	789 (11.3)	784 (11.2)	786 (11.2)
Japan	337 (4.8)	336 (4.8)	337 (4.8)

Abbreviations: DosAdj = Dose Adjusted, CHADS = Scoring system for stroke risk stratification (Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/Transient ischemic attack), CrCL = creatinine clearance, VKA = Vitamin-K antagonist, BMI = body mass index.
[a]: Subjects could only select 1 race. 'Other' was chosen if none of the other prespecified categories applied, or if the subject was multiracial.
[b]: CrCL is derived from information recorded in Central Lab or Local Lab results.
[c]: Weight and BMI are derived from information recorded in the eCRF.
[d]: Verapamil/Quinidine use at randomization is derived from information recorded in both the IXRS and the eCRF. If at least 1 source indicates Verapamil/Quinidine use, then the subject is counted as 'Yes', else 'No'.
[e]: $CHADS_2$ = derived index score for stroke prediction per information recorded in the eCRF
[f]: VKA Experienced is defined as 'Current Users' as well as 'Former Users' who took VKA for greater than 2 months. VKA Naive is defined by the complement of VKA Experienced for those subjects with eCRF data present.
Source data: Table 14.1.3.1

Numbers analysed

Table E-14: Disposition of Subjects and Study Completion Status, ITT Analysis Set

	Edoxaban 30 mg (15 mg DosAdj) (N=7034) n (%)	Edoxaban 60 mg (30 mg DosAdj) (N=7035) n (%)	Warfarin (N=7036) n (%)	Overall (N=21105) n (%)
Treated[a]	7002 (99.5)	7012 (99.7)	7012 (99.7)	21026 (99.6)
Completed CSED Visit [b]	6250 (88.9)	6228 (88.5)	6157 (87.5)	18635 (88.3)
Death On or After CSED Announcement	9 (0.1)	14 (0.2)	20 (0.3)	43 (0.2)
Did Not Complete CSED Visit[b]	784 (11.1)	807 (11.5)	879 (12.5)	2470 (11.7)
Death (Prior To CSED Announcement)	706 (10.0)	730 (10.4)	789 (11.2)	2225 (10.5)
Withdrew Consent	77 (1.1)	77 (1.1)	90 (1.3)	244 (1.2)
Lost to follow up[c]	1 (<0.01)	0 (0.0)	0 (0.0)	1 (<0.01)

Abbreviations: DosAdj = Dose Adjusted, CSED = common study end date
[a]: 'Treated' represents randomized subjects who received 1 or more doses of study drug.
[b]: Completed and Did Not Complete (and reasons) come from the Final Status eCRF. Completed subjects include deaths on or after the CSED announcement but prior to the CSED Visit.
[c]: Subject 1014-0003, from a USA site and randomized to Edoxaban 30mg not dose adjusted, is included in this row. The subject did not complete CSED-Visit and information on the Final Status eCRF page is missing. Site closed and then the subject refused to transfer to another site prior to the CSED announcement.
Source data: Tables 14.1.1.5 and 14.1.1.7

Outcomes and estimation

Edoxaban (or matching edoxaban placebo for the warfarin group) **compliance** was assessed by percentage of doses taken (≥80% versus <80%) at each compliance visit (every 3 months). Treatment compliance (more than 80% of tablets taken; i.e.: 6 or less tablets missed per month) was > 98% in almost all timepoints with the exception of Month 45 (98% and 93% for edoxaban 30 mg OD and 60 mg OD, respectively).Warfarin compliance was assessed by the percentage of time subjects INR was within the range of 2.0 – 3.0. The mean time in therapeutic range (TTR) (INR: 2-3) was 64.9% (median 68.4%), which is comparable to contemporary studies like RE-LY (mean: 64.4%; median 67%) or ARISTOTLE (mean: 62.2%; median: 66%) and higher than in ROCKET-AF (mean: 55.2%; median: 58%) (*Gómez-Outes, et al. Thrombosis. 2013; 640723*). As expected, the more frequent deviation was undercoagulation, with a 22.8% of the time below therapeutic range (INR<2). The percent time above therapeutic range (INR>3) was 12.4% (mean values). By regions, North America, Western Europe and Japan had a mean TTR of 70.2%, 68.3% and 70.3% respectively. Eastern Europe had a mean of 62.5%, Latin America had a mean TTR of 61.5%, and Asia/Pacific and South Africa (excluding Japan) had a mean TTR of 58.10%. These data indicate that quality of anticoagulation with warfarin was relatively good in western Europe, North America and Japan, and of a poorer quality in eastern Europe, Latin America, Asia/Pacific (excluding Japan) and South Africa. The correlation between quality of anticoagulation and efficacy is further discussed under "ancillary analyses".

Non-inferiority of edoxaban 60 mg was shown in the primary sponsor's analysis of all strokes/SEE (mITT, on-treatment) as well as in the sensitivity analysis for ischemic stroke/SEE according to CHMP guideline on NVAF (PP, on-treatment), but superiority was not shown for the previous mentioned endpoints in the ITT population in the overall study period (see below). On the contrary, although the main sponsor's analysis suggested non-inferiority of edoxaban 30 mg versus warfarin on all strokes/SEE, the sensitivity analysis using ischemic stroke/SEE (CHMP guideline) showed inferiority of the low edoxaban dose versus warfarin:

a) **Stroke and SEE -Non-inferiority, mITT, on-treatment (study protocol):** In the mITT on-treatment period (main sponsor's analysis), adjudicated stroke or SEE occurred in 253 subjects in the edoxaban 30 mg group (1.61% per year), 182 subjects in the edoxaban 60 mg group (1.18% per year), and 232 subjects in the warfarin group (1.50% per year). Compared to warfarin-treated subjects, the HR in the edoxaban 60 mg group was 0.79 (97.5% CI: 0.632, 0.985, p<0.0001 for non-inferiority) and in the edoxaban 30 mg group was 1.07 (97.5% CI: 0.874, 1.314, p=0.0055 for non-inferiority).

Table E-29: Adjudicated Primary Endpoint (Stroke or SEE), mITT Analysis Set – On-Treatment (Non-Inferiority) and Overall Study Period

Primary Endpoint	Edoxaban 30 mg (15mg DosAdj) (N=7002)		Edoxaban 60 mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DosAdj) vs Warfarin		Edoxaban 60 mg (30mg DosAdj) vs Warfarin	
First Stroke or SEE	# of events	Event Rate (%/yr) [a]	# of events	Event Rate (%/yr) [a]	# of events	Event Rate (%/yr) [a]	HR (97.5% CI)	p-value[b]	HR (97.5% CI)	p-value[b]
mITT Analysis Set On Treatment Period	253	1.61	182	1.18	232	1.50	1.07 (0.874, 1.314)	0.0055	0.79 (0.632, 0.985)	<0.0001
mITT Analysis Set Overall Study Period	382	2.04	292	1.55	336	1.80	1.13 (0.955, 1.336)	0.0074	0.86 (0.719, 1.029)	<0.0001

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, mITT = Modified Intent-to-Treat, SEE = Systemic Embolic Event, yr = year.
[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure.
[b]: The two-sided p-value is based on the non-inferiority margin of 1.38
Source data: Tables 14.2.1.1 and 14.2.1.2

Highlighted in yellow: main analysis set to show non-inferiority included in the protocol (ITT, on-treatment)

Table E-33: Components and Select Subcomponents of the Primary Endpoint, mITT Analysis Set – On-treatment Period

Event	Edoxaban 60 mg		Warfarin		Edoxaban 60 mg vs Warfarin	
	n	% per year [a]	n	% per year [a]	HR (95% CI)	p-value
mITT Analysis Set	N=7012		N=7012			
On-Treatment Period						
First Stroke	174	1.13	219	1.41	0.80 (0.655, 0.975)	0.0273
Ischemic Stroke	135	0.87	144	0.93	0.94 (0.746, 1.193)	0.6258
Hemorrhagic Stroke	40	0.26	76	0.49	0.53 (0.362, 0.778)	0.0012
Fatal Stroke	45	0.29	43	0.28	1.05 (0.694, 1.602)	0.8038
Disabling Stroke	35	0.23	41	0.26	0.86 (0.548, 1.349)	0.5107
First SEE	8	0.05	13	0.08	0.62 (0.257, 1.497)	0.2884
First SEE/Ischemic Stroke	143	0.93	157	1.01	0.92 (0.730, 1.149)	0.4495

[a]: The event rate (% per yr) is calculated as number of events/subject-year exposure.
Note : Disabling is based on the Rankin score (3 to 5) supplied by the Investigator as well as taking into account if the stroke event was adjudicated as fatal. Rankin score 3 = Moderate disability requiring some help, but able to walk without assistance; 4 = Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance; 5 = Severe disability, bedridden, incontinent, and requiring constant nursing care and attention.
Source: U301, Table 14.2.1.13; U301, Table 14.2.1.18; U301, Table 14.2.1.10; U301, Table 14.2.1.15

b) **Ischemic Stroke/SEE – Non-inferiority, PP, on-treatment (endpoint and population set recommended to show non-inferiority in the NVAF Guideline EMA/CHMP/341363/2014):**the event rate for ischemic stroke and SEE was the similar in both the edoxaban 60 mg group and the warfarin group (0.93% vs. 1.01% per year), with an HR of 0.92 (95% CI: 0.73 to 1.15) (97.5% CI: 0.71 to 1.23). More subjects in the edoxaban 30 mg group experienced ischemic stroke/SEE compared with the warfarin group (event rate of 1.49% and 1.01% per year, respectively), with an HR of **1.47 (95% CI: 1.20 to 1.80)**.

c) **Stroke and SEE - Superiority, ITT, overall study period (study protocol):** In the ITT population (Overall Study Period), fewer subjects in the edoxaban 60 mg group experienced stroke or SEE than the warfarin group (1.57% and 1.80% per year, respectively), with an HR of 0.87 (99% CI: 0.709, 1.068, 95% CI: 0.744, 1.017) but the p-value (p=0.0807) was not below the protocol-specified value of statistical significance for superiority (p< 0.01).

Table E-31: Adjudicated Primary Endpoint (Stroke or SEE), ITT Analysis Set - Overall Study Period (Superiority)

First Stroke/SEE	Edoxaban 30 mg (15mg DosAdj) (N=7034)	Edoxaban 60 mg (30mg DosAdj) (N=7035)	Warfarin (N=7036)
# of Events	383	296	337
Subject Year Exposure	18779.79	18874.84	18690.95
Event Rate (%/yr) [a]	2.04	1.57	1.80
HR (99% CI)	1.13 (0.933, 1.371)	0.87 (0.709, 1.068)	
(97.5% CI)	(0.957, 1.337)	(0.728, 1.040)	
(95% CI)	(0.977, 1.310)	(0.744, 1.017)	
Log rank p-value	0.0980	0.0807	

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, ITT = Intent-to-Treat, SEE = Systemic Embolic Event, yr =year.
[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure.
Source data: Table 14.2.1.7

Highlighted in yellow: main analysis to show superiority (study protocol and EMA/CHMP/341363/2014). The applicant chose a 99%CI for the main analysis given that this was a single pivotal trial.

d) **Ischemic Stroke/SEE - Superiority, ITT, overall study period (endpoint and population set recommended to show superiority in the NVAF Guideline EMA/CHMP/341363/2014):**the event rate for ischemic stroke and SEE was the similar in both the edoxaban 60 mg group and the warfarin group (1.33% vs. 1.36% per year), with an HR of 0.98 (99% CI: 0.78 to 1.23; p = 0.7903). More subjects in the edoxaban 30 mg group experienced ischemic stroke/SEE compared with the warfarin group (event rate of 1.89% and 1.36% per year, respectively), with an **HR of 1.39 (99% CI: 1.12 to 1.72; p < 0.0001)**.

Stroke/SEE during temporary interruptions: The percentage of subjects with 1 or more study drug interruptions (> 3 consecutive days during which the subject did not take study drug) was 62.5%, 61.8%, and 65.5%, respectively, among the edoxaban 60 mg, edoxaban 30 mg, and the warfarin treatment groups. Thromboembolic events occurring during temporary interruptions (starting Day 4 of each interruption period to resumption of study drug after each interruption)were not included in the “on-treatment analysis” of non-inferiority. There were 117 stroke/SEE events on edoxaban 60 mg and 112 stroke/SEE events on warfarin during temporary interruptions (starting Day 4 of each interruption period to resumption of study drug after each interruption). However, when corrected by exposure, the yearly event rate was quite similar (edoxaban 3.06 %/yr vs. warfarin 3.04 %/yr). All-cause, cardiovascular mortality events, hemorrhagic strokes and intracranial bleed events were lower in the edoxaban 60-mg group compared with the warfarin group during temporary interruptions.

Stroke/SEE after the end of study (study drug discontinuation): The percentage of subjects with adjudicated events after 3 days was low and similar in the three treatment groups (0.2%). From day 4 to 30 after end of study, the percentage of patients with stroke was 1.3%, 1.8% and 1.4% in the edoxaban 60 mg OD, edoxaban 30 mg OD and warfarin, respectively. These data indicate that the management of oral anticoagulation after study drug discontinuation in ENGAGE AF was appropriate. Edoxaban dose reduction was only one of the 4 key components for the transition plan from edoxaban to VKA. There were 4 key components: 1) selection of the oral anticoagulant (VKA or an NOAC) by the treating physician and patient; 2) a 14-day transition kit of modified-dose edoxaban for patients randomized to edoxaban (30 mg once daily for patients in whom the edoxaban dose was not reduced before the end-of-trial visit and 15 mg once daily for patients in whom the edoxaban dose had been reduced before the end-of-trial visit, regardless of randomized edoxaban drug assignment) or matching placebo for patients randomized to warfarin; 3) early and frequent INR testing (≥3 tests during the first 2 weeks); and 4) use of a VKA titration algorithm [Ruff et al. J Am Coll Cardiol. 2014;64:576-84].
Control of INR during transition from edoxaban to warfarin was optimal in ENGAGE AF, and this is likely to be the main cause of the low rate of stroke and bleeding seen during the transition procedure. Frequent international normalized ratio (INR) testing and algorithm directed warfarin dosing allowed an INR ≥ 2 to be achieved promptly without giving a loading dose of warfarin. Median time to INR ≥

2.0 was 9 days in patients transitioned from edoxaban to warfarin in ENGAGE-AF. By 30 days after the end of the trial, 98% of patients transitioned from edoxaban to warfarin had ≥ 2.0 therapeutic INR value in ENGAGE AF. In spite of the limitations of across study comparisons, these data compare favourably to those in contemporary trials (i.e.: ROCKET-AF). In order to ascertain the contribution of edoxaban in this process, the applicant modelled factor Xa activity over the 24-hour dosing period for the doses used in the ENGAGE AF study (TMPP008) and showed that even the 15 mg dose has some antithrombotic effect, although lower than that of a full therapeutic dose, as expected. The offset of activity lags the fall in plasma edoxaban concentration and hence there is more sustained activity of edoxaban over the 24-hour period than the pharmacokinetics would suggest. Simulations made by the applicant suggest that the projected incidence in ischemic stroke for the 15-mg dose in monotherapy (≈2%/yr), although higher than that of warfarin (≈1%/yr), may retain some clinical effectiveness in absolute terms, as the estimated background risk untreated is 6 %/year ($CHADS_2$ score 3). However, it is worth mentioning that edoxaban 15 mg is not to be administered in monotherapy, but concomitantly with warfarin during the switching procedure. One of the problems for the other DOACs transition regimens was not only a lack of ischemic protection, but, importantly, of an increased rate of bleeding. This is the reason for the ENGAGE AF protocol to include provisions intended to mitigate the risk of bleeding expected for those patients who were taking two oral anticoagulants concomitantly. On the other hand, SmPC information has been amended to reflect more accurately the switching process used in ENGAGE-AF. An additional warning has been deemed necessary to prevent from treatment with suboptimal 15 mg dose in monotherapy and to make clear that the 15 mg dose isonly indicated in the process of switching from Lixiana 30 mg to VKA (patients with presumed increased exposure), together with an appropriate VKA dose (SmPC).

Secondary outcomes: analyses of composite (first-event) endpoint of stroke, SEE, and CV mortality, the endpoint of MACE, and the composite endpoint of stroke, SEE, and all-cause mortality were generally consistent with the analysis of the main endpoint of all strokes/SEE.

Dose-response in efficacy: The trend for superiority of the high edoxaban dose (60 mg OD) versus warfarin for the primary endpoint is supported by secondary analyses of patients with fatal strokes (80 vs. 86) disabling strokes (54 vs. 57), recurrent stroke/SEE events (5 vs. 8; mITT analysis set on-treatment period) and analysis of the composite of stroke, SEE and TIA (edoxaban 60 mg 1.69% per year vs. warfarin 1.92% per year; HR: 0.88; 95%CI: 0.746 to 1.042; mITT on-treatment period; main sponsor's analysis). On the contrary, the edoxaban 30 mg dose shows a trend for inferiority versus warfarin in the analysis of pure thromboembolic events (ischemic stroke/SEE as well as in MI). The trend for inferior efficacy of edoxaban 30 mg OD versus warfarin is also supported by the higher number of disabling strokes (82 and 57 subjects in edoxaban 30 mg group and the warfarin group, respectively), in the number of patients with who had ≥ 2 occurrences of the primary efficacy endpoint (21 and 8 subjects in edoxaban 30 mg group and the warfarin group, respectively; mITT analysis set on-treatment period) as well as by the high number of events when TIA was added to stroke and SEE (edoxaban 30 mg event rate 2.28% per year vs warfarin 1.92% per year; HR: 1.19; 95%CI: 1.021 to 1.389; mITT on-treatment period; primary sponsor's analysis). However, there was a trend for superiority of edoxaban 30 mg versus warfarin in the reduction of haemorrhagic stroke and CV mortality (mainly due to the reduction in fatal bleedings), which might be of interest in patients at high risk of bleeding.

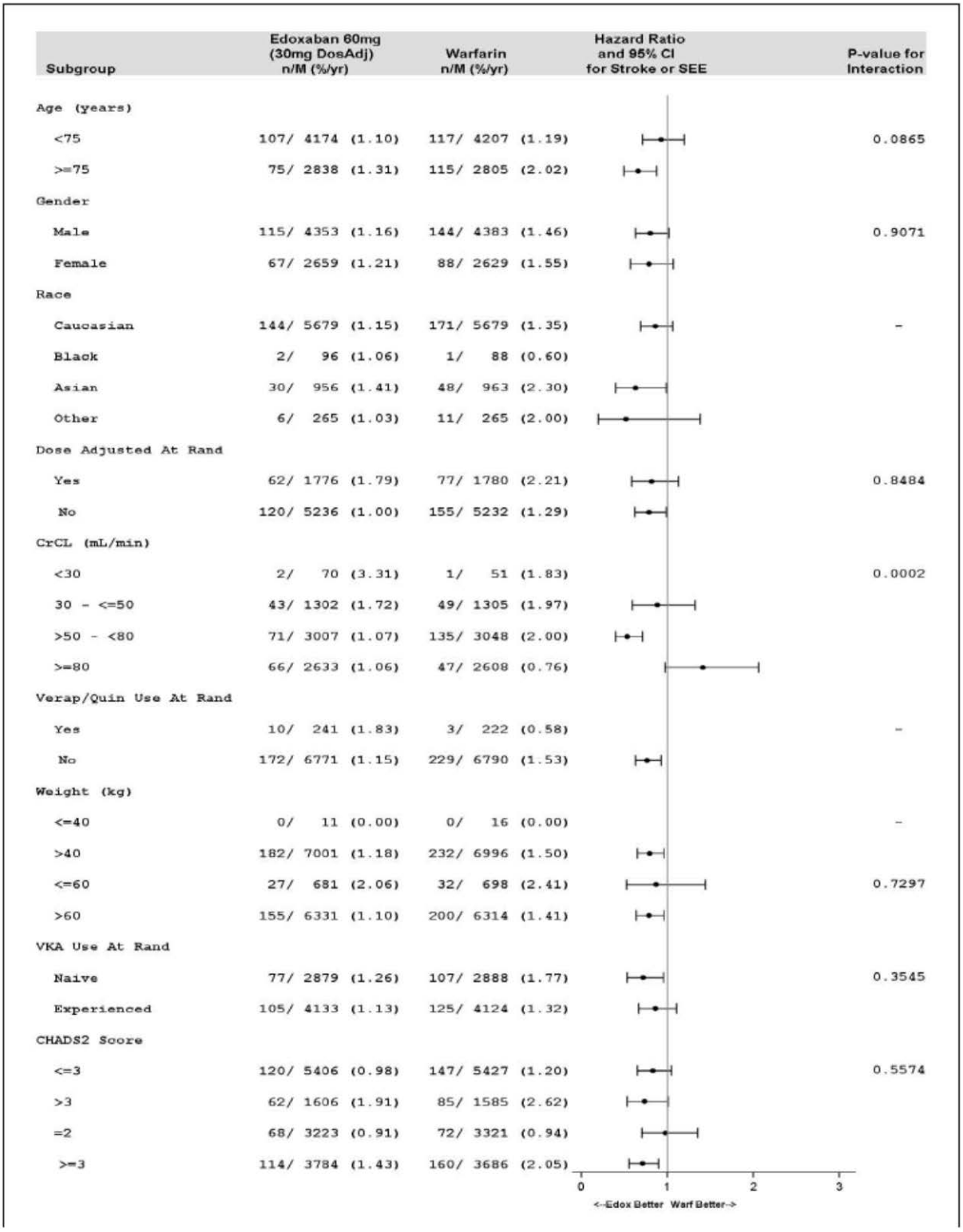
Potential for dose adjustment in patients at high risk of bleeding: At the time of balancing efficacy and safety, the 60 mg edoxaban dose (with reduction to 30 mg in case of increased exposure) was considered the edoxaban dose with the best benefit-risk balance in NVAF. However, given the significant reduction of bleeding with the 30 mg edoxaban dose, the applicant discussed whether a dose reduction to 30 mg OD (in addition to those patients with moderate renal impairment and/or low

body weight ≤ 60 kg and/or concomitant verapamil, quinidine or dronedarone) should also be considered in patients at high risk of bleeding (please see Discussion on Clinical Efficacy section).

Exploratory analyses of subgroups in ENGAGE-AF were conducted by INR/TTR level by centre and quartiles as well as by at least 14 patient/study characteristics. Efficacy data in subgroups are difficult to interpret by the inclusion of haemorrhagic stroke in the analyses. In this respect, the applicant was requested and provided the analyses of subgroups of efficacy by INR/TTR level (center and quartiles) and by patient/study characteristics excluding haemorrhagic stroke (i.e.: including only ischemic stroke and SEE) using the same analysis sets as in the ENGAGE study report. Subgroup analyses by patient/study characteristics showed a generally consistent effect of edoxaban in most subgroups, with the exception of subgroups by renal function and geographic region in which the interaction p-values were significant for both edoxaban doses versus warfarin. The HR for the edoxaban 60 mg group compared with the warfarin group for Western Europe was 1.47 (95%CI: 0.89-2.45; mITT, on-treatment) and for the subgroup with CrCL ≥ 80 mL/min was 1.41 (95%CI: 0.97-2.06). The main primary endpoint results in ENGAGE-AF study seem to be driven by an increased stroke/SEE rate with warfarin in Asia/Pacific/South Africa and Latin America (2.33% and 2.60%, respectively), which contrasts with the 1.13% yearly rate of stroke/SEE found in western Europe. In general, subgroup analyses of ENGAGE-AF for INR level and geographic region are consistent with a recent meta-analysis of subgroups of RE-LY (dabigatran vs. warfarin), ROCKET-AF (rivaroxaban vs. warfarin) and ARISTOTLE (apixaban vs. warfarin) (Gómez-Outes et al. Thrombosis. 2013; 640723). In all these studies, the good results of the new anticoagulants were mainly at expenses of increased stroke/SEE rates with warfarin in Asia and Latin America. However, the interaction by region seems more pronounced in the ENGAGE-AF study than in the other studies.

In addition, the poorer results of edoxaban in the group of normal renal function versus impaired renal function for the primary endpoint was a novel finding (see also "Efficacy data and additional analyses" in the Discussion).

Figure E-08: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for Edoxaban 60 mg Group Versus Warfarin, mITT Analysis Set - On-Treatment Period

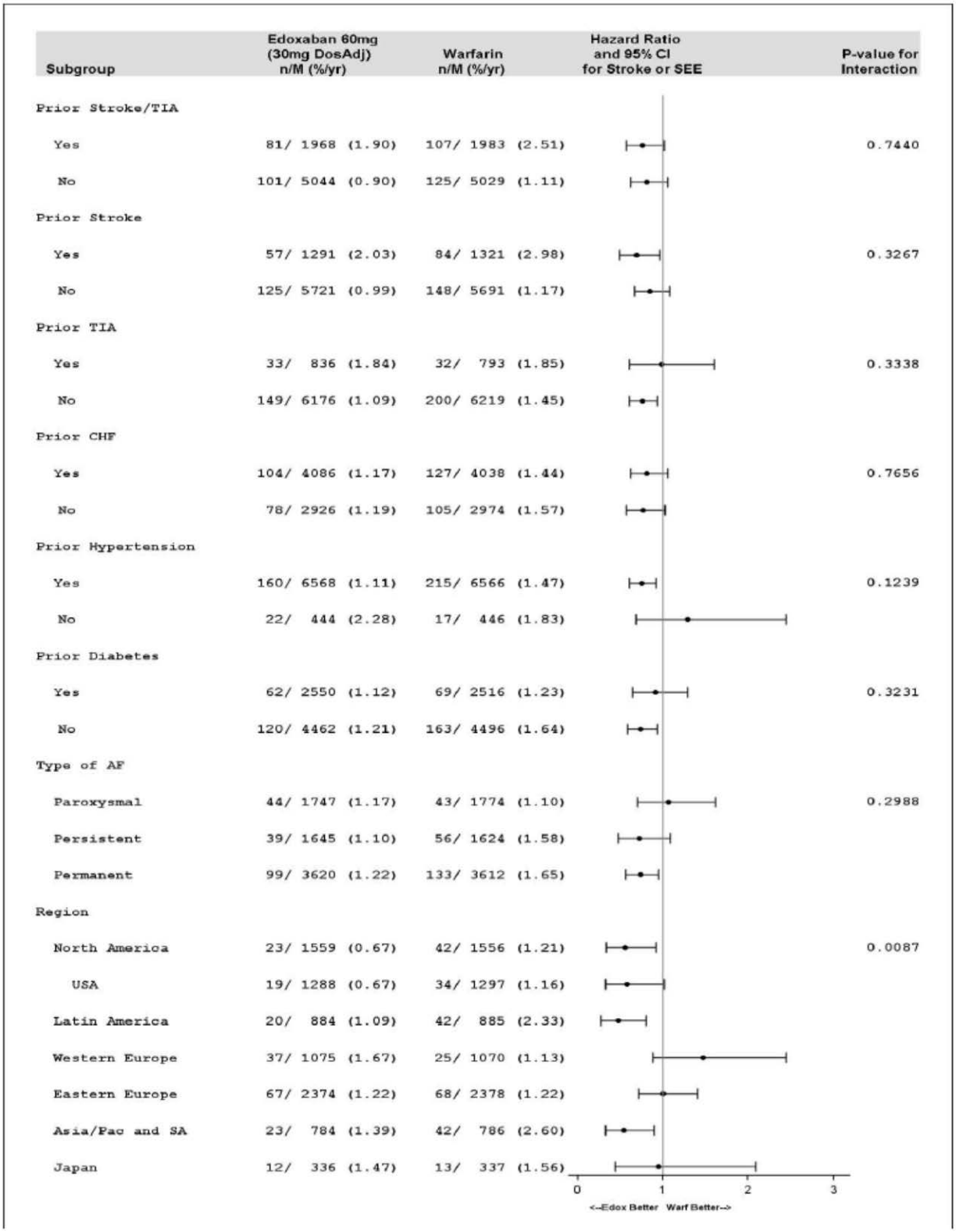


Note: Need at least 5 subjects with events in a group for a forest plot and p value.

Note: Native Hawaiian/Pacific Islander and American Indian/Alaskan Native are not presented under Race because the numbers are small.

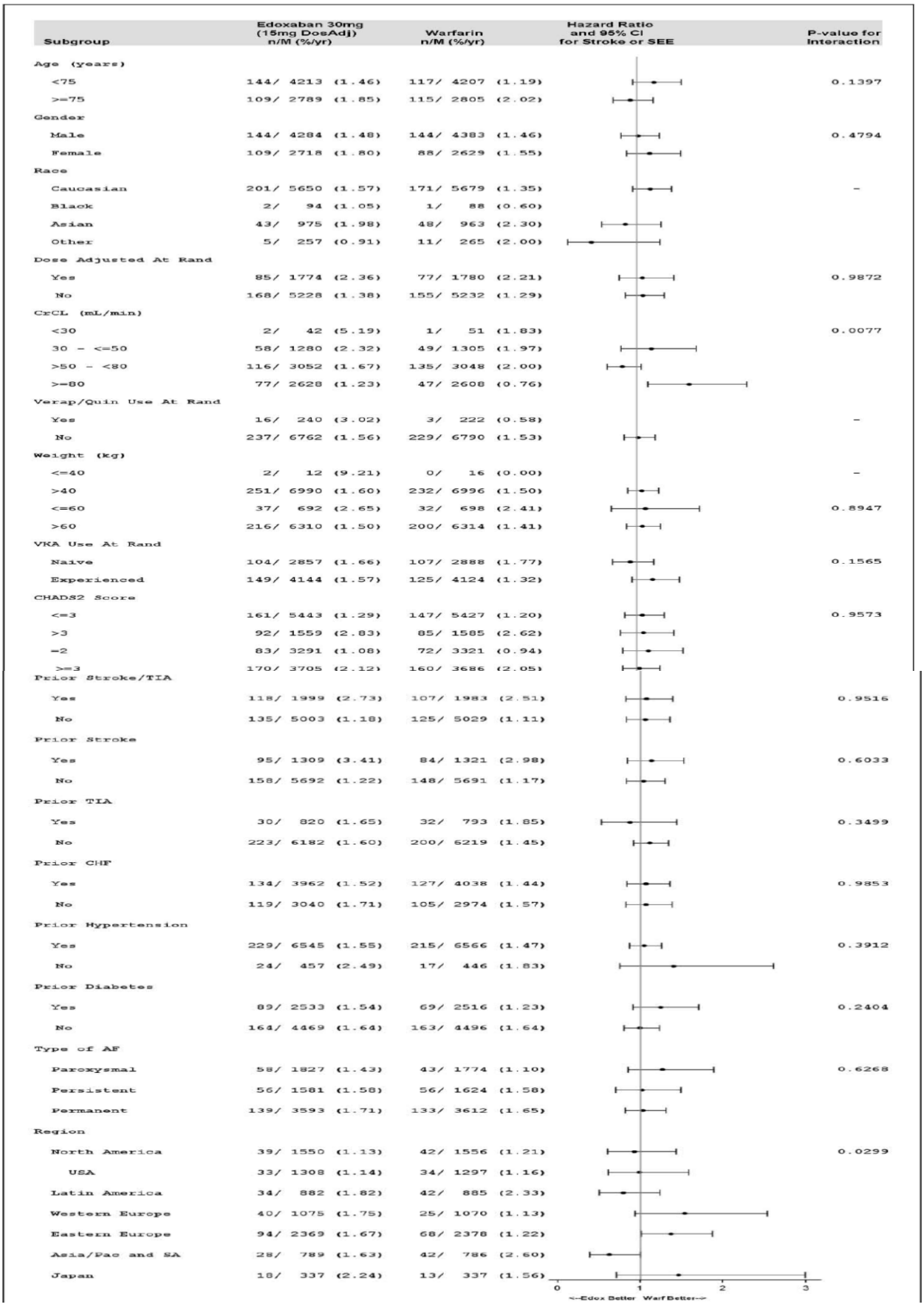
Source: Table 14.2.5.1

Figure E-08: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for Edoxaban 60 mg Group Versus Warfarin, mITT Analysis Set - On-Treatment Period (Continued)



Note: Need at least 5 subjects with events in a group for a forest plot and p value.
Source: Table 14.2.5.1

Figure E-09: Forest Plot of Primary Endpoint (Stroke or SEE) by Baseline Characteristics for the Edoxaban 30 mg Group Versus Warfarin, mITT Analysis Set - On-Treatment Period



Subgroup analyses of stroke/SEE by INR/TTR level suggest that the effect size (reduction of stroke/SEE by edoxaban) decreases as the quality of anticoagulation in the control group increases (i.e.: in centers with TTR > 60% and when INR/TTR is above the fourth quartile, >73.9%). When the TTR data are examined by quartiles for the edoxaban 60 mg group compared to warfarin, the HR for the primary endpoint in the 1st, 2nd, and 3rd quartile was 0.80, 0.73, and 0.74, respectively, and for the 4th quartile was 1.07 (95%CI: 0.65-1.75). For the edoxaban 30 mg group compared to warfarin, the HR for 1st, 2nd, 3rd, and 4th quartiles were 0.82, 1.02, 1.22, and 1.30 (95%CI: 0.81-2.09), respectively. These data are within expected on the light of previous studies with novel oral anticoagulants in NVAF.

Table E-42: Primary Endpoint (Stroke or SEE) by Center Level INR TTR, mITT Analysis Set – On-Treatment Period

Primary Endpoint	Edoxaban 30 mg (15mg DosAdj) (N=7002)		Edoxaban 60 mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DosAdj) vs Warfarin	Edoxaban 60 mg (30mg DosAdj) vs Warfarin
First Stroke or SEE	n/M[a]	Event Rate (%/yr)[b]	n/M[a]	Event Rate (%/yr)[b]	n/M[a]	Event Rate (%/yr)[b]	HR (95% CI)	HR (95% CI)
Centers with TTR > 66.4% (Median)	110/3273	1.46	73/3277	1.00	94/3402	1.19	1.24 (0.944, 1.639)	0.85 (0.623, 1.148)
Centers with TTR <= 66.4% (Median)	134/3509	1.72	107/3517	1.39	138/3602	1.82	0.93 (0.737, 1.185)	0.77 (0.595, 0.986)
p value for the interaction							0.1243	0.6275
Centers with TTR >= 60%	175/4990	1.54	120/4960	1.09	155/5191	1.30	1.19 (0.955, 1.472)	0.84 (0.661, 1.065)
Centers with TTR < 60%	69/1792	1.77	60/1834	1.51	77/1813	2.14	0.81 (0.584, 1.119)	0.71 (0.503, 0.989)
p value for the interaction							0.0559	0.4114

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, yr = year, INR = International Normalized Ratio, mITT = Modified Intent-to-Treat, TTR = Time in Therapeutic Range, SEE = Systemic Embolic Event.
[a]: n is the number of events, M is the total number of subjects on whom the information is available for that subgroup.
[b]: The event rate (%/yr) is calculated as # of events/subject-year exposure.
Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Source data: Table 14.2.5.10

Table E-43: Primary Endpoint (Stroke or SEE) by Quartiles of INR TTR, mITT Analysis Set – On-Treatment Period

Primary Endpoint	Edoxaban 30 mg (15mg DosAdj) (N=7002)		Edoxaban 60 mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg (15mg DosAdj) vs Warfarin	Edoxaban 60 mg (30mg DosAdj) vs Warfarin
Quartiles of INR TTR	n/M[a]	Event Rate (%/yr)[b]	n/M[a]	Event Rate (%/yr)[b]	n/M[a]	Event Rate (%/yr)[b]	HR (95% CI)	HR (95% CI)
1st Quartile (<= 57.7%)	54/1406	1.78	51/1413	1.68	57/1406	2.07	0.82 (0.563, 1.183)	0.80 (0.547, 1.164)
2nd Quartile (>57.7% to <= 66.4%)	80/2103	1.69	56/2104	1.21	81/2196	1.68	1.02 (0.747, 1.387)	0.73 (0.516, 1.020)
3rd Quartile (>66.4% to <= 73.9%)	71/1906	1.63	42/1908	0.99	63/2038	1.35	1.22 (0.871, 1.717)	0.74 (0.500, 1.090)
4th Quartile (>73.9%)	39/1367	1.23	31/1369	1.02	31/1364	0.95	1.30 (0.814, 2.092)	1.07 (0.648, 1.751)
p value for the interaction							0.3384	0.6372

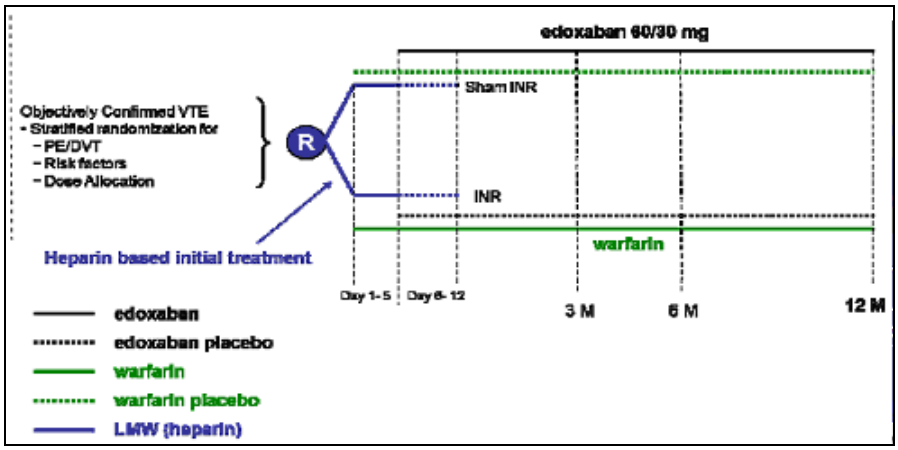
Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, yr = year, INR = International Normalized Ratio, mITT = Modified Intent-to-Treat, TTR = Time in Therapeutic Range, SEE = Systemic Embolic Event.
[a]: n is the number of events, M is the total number of subjects on whom the information is available for that subgroup.
[b]: The event rate (%/yr) is calculated as # of events/subject-year exposure.
Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Source data: Table 14.2.5.10

HOKUSAI VTE: Treatment of VTE including DVT and PE, and prevention of recurrent VTE

Methods

The efficacy and safety of edoxaban in reducing the risk of symptomatic recurrent VTE in subjects with documented acute symptomatic DVT and/or PE is primarily based upon the large Phase 3 Hokusai VTE study in which 4118 subjects were treated with edoxaban 60 mg (30 mg reduced) and 4122 with warfarin for 3-12 months (all patients received heparin-based initial treatment for 5-12 days). Hokusai VTE was an event-driven, Phase 3, multinational, multicenter, randomized, double-blind, matching placebo, parallel-group, event-driven non-inferiority study to evaluate the benefits and risks of edoxaban in reducing the risk of symptomatic recurrent VTE in subjects with documented acute symptomatic DVT and/or PE. At least 40% of subjects had to present with PE.

Figure E-03. Hokusai-VTE study design



Study Participants

Inclusion/exclusion criteria: HOKUSAI-VTE enrolled male or female adult subjects with symptomatic DVT and/or PE documented by objective methods. Exclusion criteria were similar to other contemporary trials. Patients with active cancer (in which LMWH treatment instead of VKA is recommended), active liver disease, severe renal impairment or pregnancy were excluded, as well as those with contraindications to anticoagulation (e.g.: active bleeding) or treatment with potent P-gp inhibitors. Patients could have temporary risk factors only (such as trauma, surgery, immobilization, estrogen therapy, etc.) for which a 3-month treatment may suffice, or all others (e.g.: intrinsic factors), for which a longer treatment may be needed.

Treatments

In HOKUSAI-VTE, eligible subjects were randomized to (LMW)heparin/edoxaban or (LMW)heparin/warfarin using stratified randomization. All patients received initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days. Edoxaban or warfarin was administered in a double-blind, double-dummy fashion. Edoxaban (or placebo) was started after discontinuation of initial heparin. Edoxaban was administered at a dose of 60 mg orally once daily, taken with or without food, or at a dose of 30 mg once daily in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. The study was designed with the aim of broadening applicability to real-world practice and encouraging the enrolment of all patients, including those with extensive disease, by specifying that treatment should be initiated with the proven, global standard of parenteral heparin; that the dose of the study drug should be halved in patients perceived to be at higher risk for bleeding (e.g., those with renal impairment or low body weight); and that physicians should be allowed to adjust the duration of treatment after 3 months according to their clinical judgment or in keeping with evolving evidence. Dosing in the experimental group (heparin lead-in followed by edoxaban) is similar to the dosing selected for dabigatran trials in acute VTE (RE-COVER I and II), but different from the single drug approach (no need for heparin lead-in, using higher doses of the new anticoagulant during the first weeks and followed by a lower maintenance dose) used in rivaroxaban trials (EINSTEIN DVT and PE) and apixaban pivotal trial in acute VTE (AMPLIFY). This is an important difference in dosing between edoxaban and the other Factor Xa inhibitors. In order to avoid medication errors, it should be stated in section 4.2 of the SmPC that Lixiana is to be started

following initial use of heparin (subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin) for at least 5 days.
Treatment regimes tested in the HOKUSAI-VTE study are in general deemed appropriate. However, study duration was left to the investigator. Although it was endorsed that this approach may mimic standard practice, it was considered unfortunate that a second randomisation, or a second study was not performed in patients having received anticoagulation after 3-6 months, in order to generate randomised clinical data versus placebo or active comparator in the setting of extended treatment of VTE (i.e.: as conducted in the EINSTEIN-ext with rivaroxaban, RE-MEDY and RE-SONATE study with dabigatran or the AMPLIFY-ext study with apixaban). However, the design and analysis (mITT Overall versus On-Treatment) of the study allowed for assessment of the extension of therapy/the secondary prevention of VTE without the need for a formal “extension” study. Furthermore this “extension” study within Hokusai was performed with an active comparator-warfarin rather than placebo allowing a more robust comparison as to the real world risk benefit if continued therapy. As such the indication for both the active treatment of acute VTE and secondary prevention of recurrent VTE were demonstrated with the Hokusai VTE study with up to 12 months of therapy. Therefore, it was agreed that a separate "extension" study was not warranted.

Objectives

Outcomes/endpoints
The primary efficacy outcome in HOKUSAI-VTE was symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE). The secondary efficacy outcome added was the same but adding all-cause mortality. The main analysis set was the mITT during the overall study period (12 months). CEC adjudication results was the basis of the analyses. The objective criteria used to confirm recurrent VTE are in line with those used in contemporary studies in the acute treatment of VTE and are considered acceptable. In this regard, the *CHMP Guidance on clinical investigation of medicinal products for the treatment of venous thromboembolic disease [CPMP/EWP/563/98] published in 2000* (now in revision), states that if, in exceptional cases, recurrent VTE events diagnosed only by clinical symptoms are followed by acute, new antithrombotic therapy, such events could be considered for inclusion in the endpoint only after adjudication by the clinical events committee. The applicant has confirmed that approximately 8% of primary efficacy events were adjudicated events without confirmatory imaging. These events mainly included VTE-related deaths. However, the events were equally distributed in both groups and sensitivity analysis excluding these events (HR: 0.90: 95%CI: 0.69-1.16) yielded very similar results than the main analysis (HR: 0.89; 95%CI: 0.70-1.13), thus supporting non-inferiority of edoxaban under different assumptions.

Randomisation
Randomisation in HOKUSAI-VTE study was stratified by presenting diagnosis (PE and DVT only), Baseline risk factors (temporary risk factors vs. all others), and need for edoxaban dose reduction to 30 mg (yes, no). An Interactive voice/web response system (IXRS) was used. Randomisation methods in HOKUSAI-VTE study are considered acceptable.

Blinding (masking)
The HOKUSAI-VTE study used a double-blind design, which is in line of the one used in the recent RE-COVER studies with dabigatran and AMPLIFY study with apixaban (EINSTEIN studies with rivaroxaban followed an open-label design). Blinding/masking methods are deemed appropriate.

Statistical methods
HOKUSAI-VTE was event driven. A total of at least 220 events were required. Sample size calculation is endorsed. The primary efficacy analysis of the HOKUSAI-VTE study was based on a modified Intent-to-Treat (mITT) Analysis Set (subjects who are randomized and received at least one dose of

study drug) using all primary efficacy events (symptomatic recurrent VTE) that occurred in the 12-month study period. The time to the first event of the composite primary efficacy outcome was analyzed using a Cox proportional hazards model including treatment and the stratification factors as covariates. The experimental regime was considered non-inferior to the comparator if the upper limit of the 95%CI for the HR was less than 1.5. The non-inferiority margin (HR <1.50) is the more restrictive one use in recent studies with novel oral anticoagulants in the treatment of VTE (1.80 in AMPLIFY; 2.0 in EINSTEIN studies; 2.75 in RE-COVER studies). During discussion with the CHMP SA procedure, it was advised that the preferred assessment for non-inferiority of the primary endpoint, recurrent VTE (the composite endpoint of DVT, non-fatal PE and fatal PE), was the treatment period plus 30 days tested using the PP analysis set; although the mITT analysis for the overall study period was also important. The sponsor decided to maintain the main analysis of non-inferiority in the mITT in the overall study period but planned sensitivity analyses for non-inferiority and superiority in the mITT and PP population at different study time points (on-treatment period; treatment +30 days period; first 90 days). In the CHMP view, primary analysis of non-inferiority should have been focused on recurrent VTE in the PP population on-treatment. However, this analysis has been provided at least as sensitivity analysis, which is endorsed. The superiority analysis should have focused on recurrent VTE + all-cause mortality in a pure ITT population (randomized patients) in the overall study period. However, as the proportion of randomized patients that were excluded from the mITT population was less than 1% (see “participant flow”), the mITT analysis conducted by the applicant was considered appropriate for the analysis of superiority. Superiority was tested for the secondary endpoint of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality (mITT, overall study period). An α=0.01 two-sided was chosen and the analysis was based on the mITT Analysis Set using the same proportional hazard model as for the primary efficacy analysis. Exploratory analyses of subgroups were conducted depending on at least 16 patient/study characteristics.

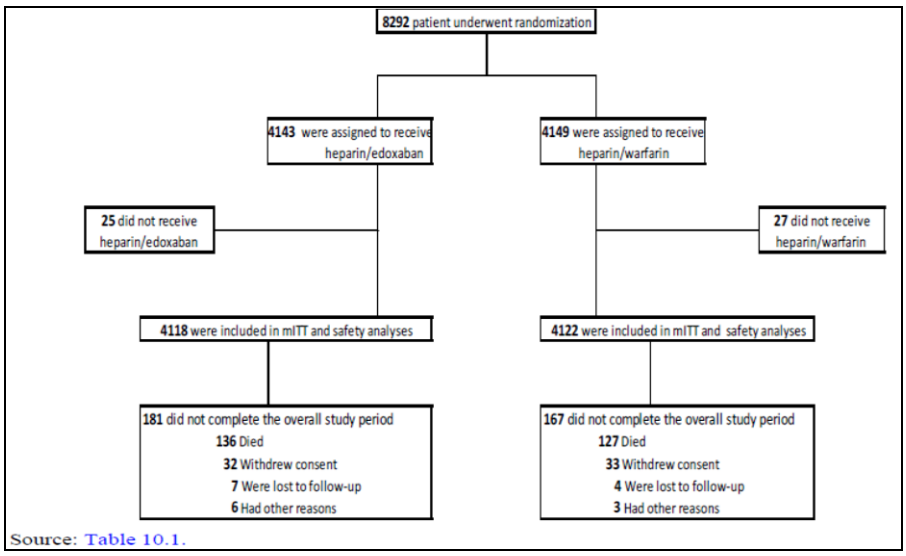
Results

Participant flow

Populations analysed: A total of 8292 subjects were randomized and assigned to the edoxaban (N=4143) or warfarin (N=4149) treatment groups, and a total of 8240 subjects were treated with edoxaban (N=4118) or warfarin (N=4122) (mITT set).

There was no screening period in Hokusai VTE, which is consistent with the acute and serious nature of the event to be treated. The critical study qualification work-up was conducted outside of the study as a matter of routine for the management of VTE. These procedures were deemed acceptable if done within 48 hours before randomization. . Of the 8,240 mITT subjects, 65 (0.8%) subjects withdrew consent and 11 (0.1%) were lost to follow up.

Figure E-05: Enrollment and Study Completion Outcomes



Source: Table 10.1.

Recruitment

Conduct of the study

A total of 439 investigational study sites in 37 countries randomized at least one subject in this trial. The countries were classified into 10 regions (South Europe, Central Europe, Nordic, Eastern Europe, China/Japan, Western Europe, Other Asian, Australia-New Zealand, South Africa/South America, and United States and Canada).

There were 4 amendments to the original protocol of the HOKUSAI-VTE study dated 24 Aug 2009. It is unlikely that the amendments had impact the integrity of the study.

Baseline data

The baseline characteristics of the patients included in the HOKUSAI-VTE study were similar in the two study groups. The mean age was 56 years and the majority of subjects were males (57%). Approximately 41% of patients presented PE as index event. Risk factors for VTE were transient in 28% of patients. Intented treatment duration was 3 months in 6% of patients, 6 months in 37% of patients and 12 months in 57% of patients.

Table E-24: Demographic and Baseline Characteristics, mITT Analysis Set

	Edoxaban N=4118 n (%)	Warfarin N=4122) n (%)	Overall N=8240 n (%)
Age (years)			
Mean (SD)	55.7 (16.28)	55.9 (16.17)	55.8 (16.23)
Median	57.0	57.0	57.0
Minimum	18	18	18
Maximum	106	95	106
<65 years	2784 (67.6)	2752 (66.8)	5536 (67.2)
>=65 years	1334 (32.4)	1370 (33.2)	2704 (32.8)
>=75 years	560 (13.6)	544 (13.2)	1104 (13.4)
>=80 years	252 (6.1)	265 (6.4)	517 (6.3)
Gender	4118	4122	8240
Male	2360 (57.3)	2356 (57.2)	4716 (57.2)
Female	1758 (42.7)	1766 (42.8)	3524 (42.8)
Race	4109	4115	8224
Caucasian	2867 (69.6)	2895 (70.2)	5762 (69.9)
Black	156 (3.8)	144 (3.5)	300 (3.6)
Asian	866 (21.0)	861 (20.9)	1727 (21.0)
Other	220 (5.3)	211 (5.1)	435 (5.3)
Presenting Diagnosis (IXRS)			
Pulmonary Embolism	1671 (40.6)	1679 (40.7)	3350 (40.7)
with DVT	611 (14.8)	560 (13.6)	1171 (14.2)
without DVT	1060 (25.7)	1119 (27.1)	2179 (26.4)
DVT Only	2447 (59.4)	2443 (59.3)	4890 (59.3)
Risk Factors (IXRS)			
Temporary	1132 (27.5)	1140 (27.7)	2272 (27.6)
Other	2986 (72.5)	2982 (72.3)	5968 (72.4)
Intended Treatment Duration			
3 Months	221 (5.4)	245 (5.9)	466 (5.7)
6 Months	1555 (37.8)	1502 (36.4)	3057 (37.1)
12 Months	2339 (56.8)	2371 (57.5)	4710 (57.2)
Edoxaban 30 mg dose at Randomization (IXRS)			
Yes	733 (17.8)	719 (17.4)	1452 (17.6)
No	3385 (82.2)	3403 (82.6)	6788 (82.4)
Weight at Randomization (IXRS) (kg)			
<=60	524 (12.7)	519 (12.6)	1043 (12.7)
> 60	3594 (87.3)	3603 (87.4)	7197 (87.3)
Creatinine Clearance at Randomization (IXRS) (mL/min)			
>=30 to <=50	268 (6.5)	273 (6.6)	541 (6.6)
>50	3850 (93.5)	3849 (93.4)	7699 (93.4)
Verapamil or Quinidine Use at Randomization (IXRS)			
Yes	26 (0.6)	25 (0.6)	51 (0.6)
No	4092 (99.4)	4097 (99.4)	8189 (99.4)
Region			
Western Europe	680 (16.5)	679 (16.5)	1359 (16.5)
South Europe	586 (14.2)	590 (14.3)	1176 (14.3)
Central Europe	468 (11.4)	464 (11.3)	932 (11.3)
Eastern Europe	483 (11.7)	485 (11.8)	968 (11.7)
Nordic	174 (4.2)	180 (4.4)	354 (4.3)
China/Japan	349 (8.5)	344 (8.3)	693 (8.4)
Japan	106 (2.6)	103 (2.5)	209 (2.5)
Other Asian	501 (12.2)	503 (12.2)	1004 (12.2)
Australia/New Zealand	145 (3.5)	145 (3.5)	290 (3.5)
South Africa/South America	316 (7.7)	312 (7.6)	628 (7.6)
USA/Canada	416 (10.1)	420 (10.2)	836 (10.1)

Abbreviations: DVT = deep vein thrombosis, IXRS = Interactive voice/web response system, N = number of subjects in analysis set, n = number of subjects meeting event criteria, SD = standard deviation.
Note: Dose allocation, creatinine clearance, and verapamil/quinidine use is derived from information recorded in the IXRS at randomization.
Note: Risk Factors and Presenting Diagnosis are per the Investigator at Randomization. Risk Factors are categorized temporary (e.g., trauma, surgery, immobilization, estrogen therapy, etc.) vs all others.
Source: Table 14.1.1.3, Table 14.1.3.1, and Table 14.1.5.4.

The regions throughout Europe enrolled the majority of subjects. Approximately 17% of subjects required the 30 mg edoxaban at randomization due to body weight ≤ 60 kg (10%), CrCL 30-50 mL/min (4%), or for the use of quinidine/verapamil (0.5%). Post- randomization requirement for 30 mg edoxaban/edoxaban placebo occurred in 123 subjects (68 for edoxaban and 55 for edoxaban placebo (active warfarin), respectively. Approximately 17.6% of subjects had their dose adjusted at randomization. Approximately 8% of the dose reductions were due to concomitant medication with P-gp inhibitors. However, only 0.8% is due to concomitant treatment of with the examples given in the protocol (verapamil, quinidine or dronedarone). The numerically more important subgroup was

the group of azole antifungals, macrolides and "other" (4.6% including captopril, carvedilol, diltiazem, felodipine, ticagrelor, and ranolazine, among others).

Numbers analysed

Table E-17: Number of Subjects in Analysis Sets – All Randomized Subjects

	Edoxaban N=4143 n (%)	Warfarin N=4149 n (%)
Randomized	4143	4149
Never Received Study Drug	25 (0.6)	27 (0.7)
mITT (Treated)	4118 (99.4)	4122 (99.3)
Dosed But Excluded From Per Protocol	61 (1.5)	44 (1.1)
Subjects Experiencing Treatment Misallocation	0 (0.0)	0 (0.0)
Index Event Not Confirmed by CEC Adjudication	61 (1.5)	44 (1.1)
Per Protocol	4057 (97.9)	4078 (98.3)
Safety [a]	4118 (99.4)	4122 (99.3)

Abbreviations: mITT=modified Intent-to-Treat (treated subjects), N = number (overall), n = number within a subset of subjects.
[a] Based on actual treatment received. There were no treatment misallocations in Hokusai VTE
Source: Table 14.1.1.5

Major protocol deviations were reported in 23% of patients (Table 14.1.2.1 of the HOKUSAI-VTE study report). Most of them (16%) corresponded to the use of disallowed medications (mainly disallowed NSAIDs) that impacts the evaluation of main efficacy/safety endpoints, followed by pretreatment for more than 48 hours with therapeutic dosages of anticoagulant treatment before randomisation (4%). However, it was not endorsed that patients with major protocol deviations were excluded from the PP analysis. Only patients for whom the index DVT or PE event at baseline could not be confirmed by the CEC were excluded from the PP population. This was considered inconsistent with the criteria followed in the ENGAGE-AF study, in which patients with all major protocol violations were excluded from the PP population. In summary, the original PP analysis of the applicant (not excluding all major protocol violations) favoured the demonstration of non-inferiority of edoxaban versus warfarin in efficacy. However, non-inferiority was also demonstrated after conducting a "true" PP analysis (excluding all major protocol violations).

Outcomes and estimation

Treatment compliance: Compliance with edoxaban or matching placebo was analyzed as the percentage of doses taken (≥ 80% to ≤ 120% of the planned number of doses) during the study treatment period. In the edoxaban and edoxaban placebo groups, 93.6% and 93.3% of subjects in the mITT Analysis Set On-Treatment period were within the compliance range of ≥ 80% to ≤ 120%). This analysis suggests that the definition of compliance was quite insensitive to detect differences that could be of relevance (e.g.: a patient could have been declared compliant missing 5 consecutive doses per month). In this regard, sensitivity analyses were requested by narrower intervals of percentaje of doses taken (5-10% intervals), but could not be provided by the Applicant as the data as collected did not have sufficient granularity. The Applicant noted that compliance was high in both studies and it cannot be refuted with the data available. Compliance with warfarin was analyzed by using the subjects'duration of time in the INR therapeutic range (2.0 to 3.0) during the study treatment period. The mean time in the therapeutic range (TTR) was 63.5% (median: 65.6%). The overall mean percent of reported INR measurements that were < 2.0 was 18.9% and > 3.0 was 17.6%, respectively. The mean TTR in HOKUSAI-VTE (63.5%) was above the upper range of TTRs reported in contemporary studies (from 57% in RE-COVER II to 62.7% in EINSTEIN PE). Therefore, in the overall study population, quality of anticoagulation was reasonable good.The correlation between quality of anticoagulation by region/center and efficacy is further discussed under "ancillary analyses".

Non-inferiority of edoxaban 60 mg was shown in the primary sponsor's analysis of symptomatic recurrent VTE (mITT, overall study period) as well as in the sensitivity analysis for symptomatic

recurrent VTE (PP, on-treatment), but superiority was not shown for the secondary endpoint of symptomatic recurrent VTE and all-cause death (mITT, overall study period. In addition, there was a huge difference in the number of VTE events "on-treatment" and "overall study period" (approximately half of total primary events occurred post-treatment) (see below):

- **Recurrent VTE, mITT, overall study period (main non-inferiority analysis):** Symptomatic recurrent VTE occurred in a total of 130 subjects (3.2%) in the edoxaban group, compared to 146 (3.5%) subjects in the warfarin group, during the Overall Study Period. The Hazard Ratio (HR) for the edoxaban group vs. the warfarin group was 0.89 (95% CI: 0.703, 1.128). The upper bound of the 95% CI is 1.128, which was below the pre-specified non-inferiority margin of 1.5, and the difference between edoxaban and warfarin in the time to first occurrence of adjudicated symptomatic recurrent VTE was statistically significant for non-inferiority (p<0.0001) (Table 11.2).

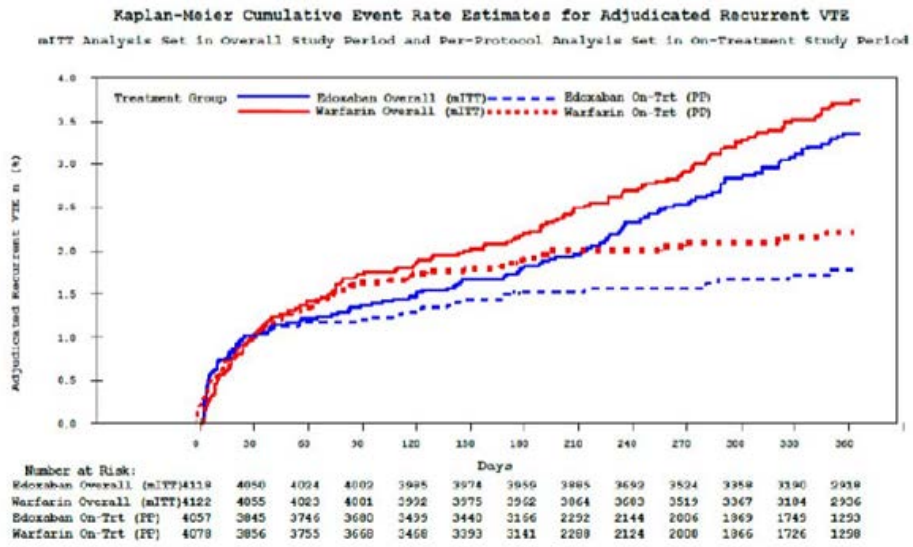
Table E-38: Primary Endpoint (Adjudicated Symptomatic Recurrent VTE), mITT Analysis Set – Overall Study Period

Primary Endpoint [a]	Edoxaban N=4118	Warfarin N=4122
All Subjects with Recurrent VTE, n (%)	130 (3.2)	146 (3.5)
HR Edoxaban vs. Warfarin (95% CI) [b]	0.89 (0.703, 1.128)	
p-value (for non-inferiority) [b, c]	<0.0001	
p-value (for superiority) [b]	0.3362	
Type of First Recurrent VTE, n (%)		
PE With/Without DVT	73 (1.8)	83 (2.0)
PE-Related Deaths	24 (0.6)	24 (0.6)
Fatal PE	4 (<0.1)	3 (<0.1)
Unexplained Death (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Non-Fatal PE	49 (1.2)	59 (1.4)
With DVT	2 (<0.1)	2 (<0.1)
Without DVT	47 (1.1)	57 (1.4)
DVT Only	57 (1.4)	63 (1.5)

Abbreviations: DVT = deep vein thrombosis, HR = Hazard Ratio vs. warfarin, CI = confidence interval, mITT = modified Intent-to-Treat, N = number of subjects in mITT analysis set, n = number of subjects with events, PE = pulmonary embolism, VTE = venous thromboembolic event.
[a] The primary efficacy endpoint is symptomatic recurrent VTE (i.e., the composite endpoint of DVT, non-fatal PE, and fatal PE). Only CEC adjudication results are considered for this summary.
[b] The HR, two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT; DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes/no).
[c] The p-value is for the pre-defined non-inferiority margin of 1.5.
Note: Events are included in the Overall study period if they occurred on or after the randomization date up to Day 365.
Source: Table 14.2.1.1.

The Kaplan-Meier curves (figure below) provide further support that continued exposure, remaining on therapy (Ontreatment versus Overall population) is associated with decreased recurrence and both analyses (ontreatment and overall population) favors edoxaban versus warfarin. The main issue during HOKUSAI-VTE regarding duration of therapy, looking at post-treatment recurrences, was that many patients would have been benefited from longer treatment durations of anticoagulation. Furthermore, the Kaplan Meier curves are linear data and there is long-term safety data from the ENGAGE AF. Due to the above mentioned reasons, it was agreed not to limit the duration of treatment of VTE to the 1 year tested with edoxaban in HOKUSAI-VTE.

Figure: Kaplan-Meier curves for recurrent VTE in Hokusai VTE



Data Source: U305, Figure 14.2.1.33, Figure 14.2.1.43

- **Sensitivity analyses for non-inferiority:** In the PP Analysis Set, a total of 64 subjects (1.6%) in the edoxaban group vs. 80 (2.0%) subjects in the warfarin group had recurrent VTE during the on-treament study period. The Hazard Ratio (HR) for non-inferiority was 0.80 (95% CI: 0.58, 1.12). The upper bound of the 95% CI was 1.12, which was below the pre-specified non-inferiority margin of 1.5. All of the remaining sensitivity analyses of non-inferiority for the mITT Analysis Set, Overall Study Period and PP analysis set, excluding unexplained deaths for which VTE could not be ruled out and assessing the potential impact of missing data are all consistent with the results of the primary analysis.

Table E-39: Efficacy Analyses Across Multiple Analysis Sets and Study Periods

	Edoxaban	Warfarin	Edoxaban vs. Warfarin	
Recurrent VTE mITT Analysis Set[a]	**N=4118 n (%)**	**N=4122 n (%)**	**HR (95% CI) [b]**	**p-value [c]**
mITT Analysis Set, Overall Study Period (Primary efficacy)	130 (3.2)	146 (3.5)	0.89 (0.703, 1.128)	<0.0001
mITT Analysis Set, Overall Study Period excluding unexplained deaths [d]	110(2.7)	125(3.0)	0.88 (0.682, 1.138)	<0.0001
mITT Analysis Set, Overall Study Impact of Missing Data [e]	132 (3.2)	147 (3.6)	0.90 (0.710, 1.136)	<0.0001
Recurrent VTE PP Analysis Set[a]	**N=4057 n (%)**	**N=4078 n (%)**	**HR (95% CI) [b]**	**p-value [c]**
PP Analysis Set – On-Treatment Study Period	64 (1.6)	80 (2.0)	0.80 (0.577, 1.113)	<0.0001
PP Analysis Set - Treatment+30 Days Study Period	87 (2.1)	102 (2.5)	0.85 (0.642, 1.137)	<0.0001
PP Analysis Set - 1st 90 days	54 (1.3)	71 (1.7)	0.76 (0.536, 1.088)	<0.0001
PP Analysis Set, Treatment+30 Days excluding unexplained deaths [d]	74 (1.8)	89 (2.2)	0.83 (0.611, 1.133)	<0.0001

Abbreviations: CI = confidence interval, HR = hazard ratio, mITT = modified Intent-to-Treat, N = number of subjects in the analysis set, n = number of subjects with events, PP = per protocol, VTE = venous thromboembolism.
[a] Recurrent VTE= recurrent symptomatic DVT, non-fatal PE , fatal PE and unexplained death for which PE could not be ruled out
[b] The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes, no).
[c] The p-value is based for a non-inferiority margin of 1.5.
[d] Recurrent VTE excluding unexplained death for which VTE could not be ruled out; recurrent VTE=recurrent symptomatic DVT, non-fatal PE, fatal PE only.
[e] Imputation for missing data as defined in the statistical analysis plan.
Source: Table 14.2.1.1, Table 14.2.1.2, Table 14.2.1.4, Table 14.2.1.5, Table 14.2.1.12, Table 14.2.1.23, and Table 14.2.1.24.

- **Additional sensitivity analysis to show non-inferiority:** In the original PP analysis (not excluding all major protocol violations but only those patients without confirmed VTE at baseline) there were 4057 patients on edoxaban and 4078 patients on warfarin. The HR for recurrent VTE was 0.85 (0.64 to 1.14; treatment+30 days). In the revised "true" PP analysis (excluding **all** major protocol violations) there are 3116 patients on edoxaban and 3143 patients on warfarin. The HR of edoxaban versus warfarin for recurrent VTE is 0.95 (0.68 to 1.33; treatment+30 days), thus confirming non-inferiority (p-value 0.0040). In summary, the original PP analysis of the applicant (not excluding all major protocol violations) favoured the demonstration of non-inferiority of edoxaban versus warfarin in efficacy. However, non-inferiority was also demonstrated after conducting a "true" PP analysis (excluding all major protocol violations).

- **Time onset of recurrent VTE events:** There was a huge difference in the number of recurrent VTE events between the PP on-treatment analysis (edoxaban 64 events vs warfarin 80 events) and the mITT overall study period analysis (130 events vs 146 events), which indicates that approximately half of the events during overall study period (66 events in each group) occurred after anticoagulant treatment had been stopped. On the one hand, it is reassuring that no differences in rebound thromboembolism were noticed between groups and therefore the non-inferiority of edoxaban vs. warfarin on-treatment was sustained at 12 months. On the other hand, it questions whether duration of anticoagulant therapy was generally insufficient during the trial.

- **Recurrent VTE and all-cause mortality, mITT analysis set, overall study period (main superiority analysis):** The composite endpoint of recurrent VTE and all-cause mortality occurred in 228 of subjects (5.5%) in the edoxaban group and in 228 subjects (5.5%) in the warfarin group (HR: 1.00; 95% CI: 0.832, 1.200, p=0.9933). Although recurrent VTE (DVT or PE) favoured numerically to edoxaban versus warfarin, there was a numerical imbalance in the number of deaths in the overall study period of the HOKUSAI-VTE study (edoxaban 122 vs warfarin 106), thus leading to a hazard ratio of 1.00. Analysing the timecourse of deaths, there was not an imbalance in on-treament deaths (edoxaban 35 vs warfarin 33). The imbalance was attributed to an excess in deaths due to infectious disease in the edoxaban arm after treatment had been stopped. This imbalance was not seen in the ENGAGE-AF study in a population with AF, which may indicate a chance finding. Deaths are also discussed under safety.

Table E-40: Adjudicated Secondary Endpoint (Recurrent VTE and All-cause Mortality), mITT Analysis Set - Overall Study Period

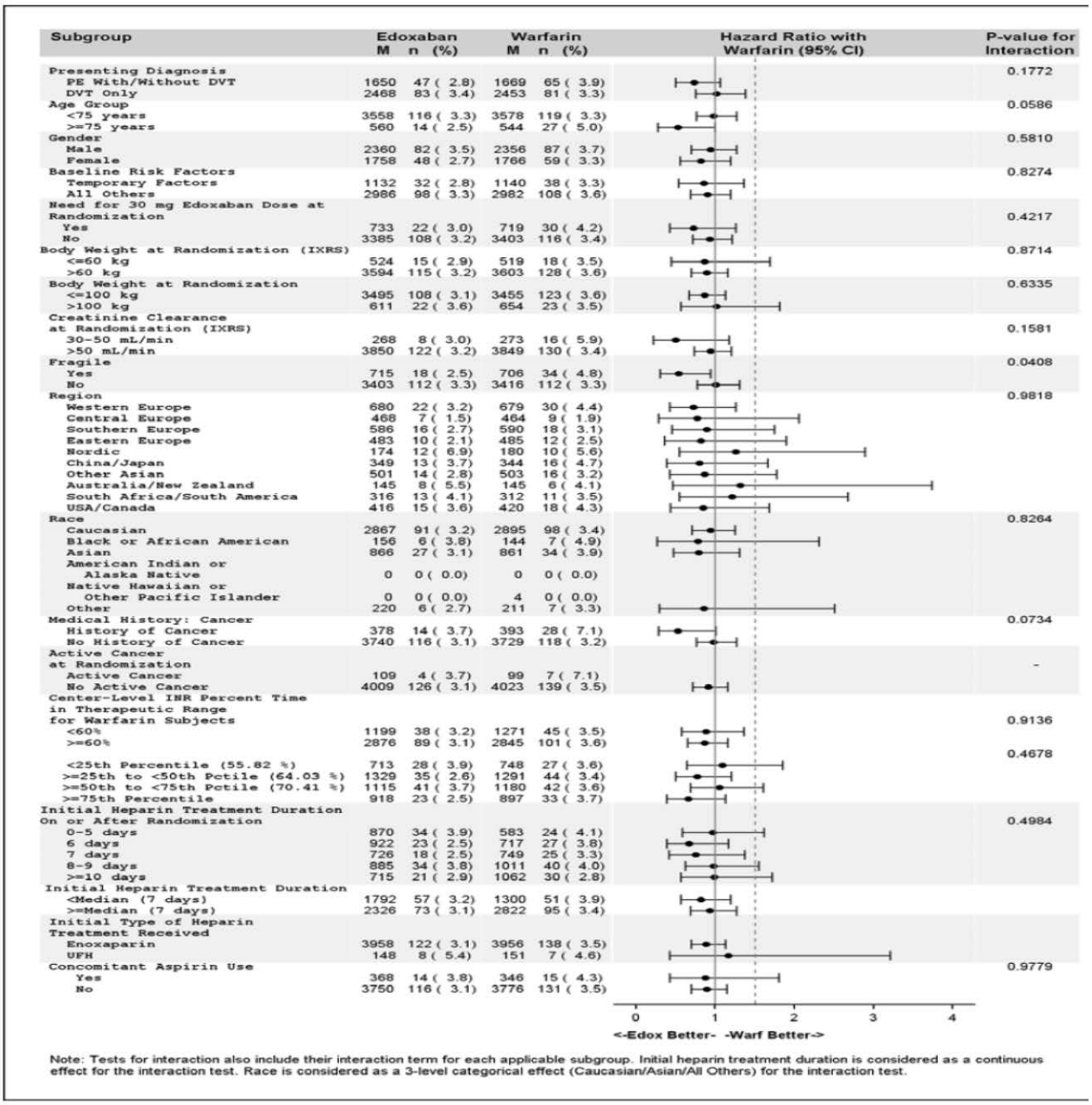
Secondary Endpoint [a]	Edoxaban N=4118	Warfarin N=4122
All Subjects With Recurrent VTE or All-Cause Mortality, n (%)	228 (5.5)	228 (5.5)
HR Edoxaban vs. Warfarin (95% CI) [b]	1.00 (0.832, 1.200)	
p-value [b]	0.9933	
Type of Initial Recurrent VTE or All-Cause Mortality, n (%)		
All-Cause Mortality	122 (3.0)	106 (2.6)
VTE-Related Death	24 (<0.1)	24 (<0.1)
Fatal PE	4 (<0.1)	3 (<0.1)
Unexplained Death (and VTE cannot be ruled out)	20 (0.5)	21 (0.5)
Other Death [c]	98 (2.4)	82 (2.0)
Non-Fatal PE	49 (1.2)	59 (1.4)
With DVT	2 (<0.1)	2 (<0.1)
Without DVT	47 (1.1)	57 (1.4)
DVT Only	57 (1.4)	63 (1.5)

Abbreviations: CI = Confidence Interval, DVT = Deep vein thrombosis, HR = Hazard Ratio vs. Warfarin, N = number of subjects in analysis set, n = number of subjects meeting event criteria, PE = Pulmonary embolism, VTE = Venous thromboembolic event.
[a] The secondary efficacy endpoint is symptomatic recurrent VTE (i.e., the composite endpoint of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality).
[b] The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo at randomization (yes, no), p-value α =0.01 [two-sided].
Note: Events are included in the Overall study period if they occurred on or after the randomization date up to Day 365.
[c] Of "Other Deaths", infectious disease was the cause of death in 25 (0.6%) subjects in the edoxaban group vs. 12 (0.2%) in the warfarin group (Table 12.21)
Note: CEC adjudication results only are considered for this summary.
Source: Table 14.2.2.1.

Net clinical outcome (composite of symptomatic recurrent DVT, nonfatal symptomatic recurrent PE, Major bleeding, and All-cause mortality) occurred in 138 subjects (3.4%) in the edoxaban group and 158 subjects (3.9%) in the warfarin group (HR: 0.87; 95% CI: 0.696, 1.099; p = 0.2515). However, these results correspond to a secondary PP analysis on-treatment, and not to the main analysis in the mITT, overall study period, which may have biased the results in favour of edoxaban, as post-treatment deaths were not included. For the shake of consistency, the applicant was requested to show the results of net clinical outcome in HOKUSAI-VTE using the same approach as in the main analysis of the primary endpoint (i.e.: in the mITT population, overall study period). The HR and 95% CIs for the net clinical outcome using this approach (HR: 1.00; 95%CI: 0.85-1.18) suggest that both edoxaban and warfarin (both with lead in parenteral anticoagulant) are equivalent strategies for VTE treatment. The SmPC, section 5.1, has been amended accordingly**.**

Subgroup analyses in HOKUSAI-VTE: The effect of edoxaban was generally consistent across subgroups tested in the HOKUSAI-VTE study. Overall, of the 55 comparisons presented from 18 subgroup analyses, most (45) resulted in a point estimate favouring edoxaban. Statistically significant interaction was only found for fragile vs. non-fragile patients. Edoxaban effect was better in fragile than in non-fragile patients. In general, the effects of edoxaban were also better (although not statistically significant interaction was found) in index PE, age > 75 years and history of cancer, which is reassuring.
Regarding the quality of oral anticoagulation, the edoxaban group had a relative reduction in risk for recurrent VTE compared to warfarin for subjects at centers TTR < 60% (HR: 0.89; 95% CI: 0.574, 1.364) and also at centers with TTR ≥60% (HR: 0.87; 95% CI: 0.653, 1.153). The Hazard Ratio for the edoxaban group for centers with INR-TTR >55.8 ≤64.0% was 0.77 (95% CI: 0.496, 1.205).

Figure E-10: Forest Plot of Primary Endpoint (Recurrent VTE) by Subgroup, mITT Analysis Set – Overall Study Period



Fragile population = at randomization: age ≥75 years and/or body weight ≤50 kg and/or CrCL 30-50 mL/min
Source: Table 14.2.5.1, Table 14.2.5.7.

Subgroups by renal function: In the subgroup of patients with normal renal function (CrCL ≥ 80 mL/min), no significant differences between edoxaban and warfarin were found in recurrent VTE (3.3% vs. 3.2%), major bleeding (0.8% vs. 1.0%) or all-cause mortality (1.8% vs. 2.1%). Looking at the overall benefit-risk in terms of the net clinical outcome (recurrent VTE, major bleeding and all-cause mortality) there is considerable overlap between the CrCL subgroups and no statistical difference is apparent between the treatments, including the subgroup of patients with CrCL ≥ 80 mL/min (3.1% vs. 3.2%; HR: 0.96; 95%CI: 0.71 to 1.29).

Subgroups by treatment duration: There was significant disagreement between planned and actual treatment duration. Of the subjects intended for treatment of 3 months 55.7% received 3 months of treatment, whereas 24.4 % received 3-6 months of treatment, 19.9% received >

6-months of treatment and 10.0% received a full 12-months of treatment. Edoxaban demonstrated non-inferiority to warfarin for the 6- and 12-month intended treatment duration subjects. The HR for the primary efficacy endpoint, recurrent VTE (HR; 95%CI; mITT, overall study period) was 1.34 (0.52-3.41) in the 3-month intended treatment duration, 0.80 (0.57-1.12) in the 6-month intended treatment duration (edoxaban 62/1555 vs warfarin 75/1502) and 0.94 (0.66-1.34) in the 12-month intended treatment duration (edoxaban 58/2339 vs. warfarin 63/2371). In the 3-month intended treatment duration the HR was 1.34 but was associated with a small sample size and numerically very few events (edoxaban 10/221 vs. warfarin 9/245).

Summary of main studies

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

Table E-45. Summary of efficacy for trial ENGAGE-AF TIMI 48

Title: A Phase 3, Randomized, Double-blind, Double-dummy, Parallel-group, Multi-center, Multi-national Study for Evaluation of Efficacy and Safety of DU-176b (Edoxaban) Versus Warfarin in Subjects with Atrial Fibrillation, Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48)		
Study identifier	DU176b-C-U301 (ENGAGE AF-TIMI 48)	
Design	This was an event-driven, Phase 3, multi-national, multi-center, randomized, double-blind, double-dummy, parallel-group study in subjects with documented AF within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for the duration of the study.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Event-driven (until approximately 672 targeted primary endpoint events were collected). Median duration of treatment: 2.5 years Median subject-year follow-up: 2.8 years. First subject randomized: 19 Nov 2008 Start of study close-out procedures: 22 January 2013. Last subject completed: 24 May 2013 not applicable not applicable
Hypothesis	Non-inferiority (both edoxaban doses vs. warfarin; HR <1.38), then superiority (only edoxaban high dose vs. warfarin)	
Treatments groups	Edoxaban 60 mg OD (experimental)	Randomized (ITT analysis set): 7035 Treated (mITT, safety analysis): 7012 Per-protocol: 6995
	Edoxaban 30 mg OD (experimental)	Randomized (ITT analysis set): 7034 Treated (mITT, safety analysis): 7002 Per-protocol: 6982
	Warfarin dose-adjusted (INR: 2.0-3.0) (control)	Randomized (ITT analysis set): 7036 Treated (mITT, safety analysis): 7012 Per-protocol: 6993

Endpoints and definitions	Primary endpoint	Stroke/SEE	The primary efficacy endpoint was the composite of stroke (ischemic or haemorrhagic) and systemic embolic events (SEE) (Time to first event).
	Secondary:	Several composite endpoints	• Composite of stroke, SEE, and CV mortality; • Major adverse cardiovascular event (MACE), which is the composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding; • Composite of stroke, SEE, and all-cause mortality.
	Other:	Components of primary endpoint	• Ischemic stroke • Haemorrhagic stroke • SEE
Database lock	07 Aug 2013		

Results and Analysis

Analysis description	**Primary Analysis of non-inferiority (study protocol)**			
Analysis population and time point description	Modified intention-to-treat, on-treatment (time to first event)			
Descriptive statistics and estimate variability	Treatment group	Edoxaban 60 mg OD	Edoxaban 30 mg OD	Warfarin (dose-adjusted)
	Number of subjects	7012	7002	7012
	Primary endpoint All strokes/SEE *(r*ate per 100 patient-years)	1.18% per year (182 subjects)	1.61% per year (253 subjects)	(1.50% per year (232 subjects)
	Hazard ratio versus warfarin (97.5%CI)	0.79 (0.632 to 0.985, p<0.0001 for non-inferiority)	1.07 (0.874 to 1.314, p=0.0055 for non-inferiority).	-

Analysis description	**Primary Analysis of non-inferiority (CHMP guideline*)**			
Analysis population and time point description	Per-protocol, on-treatment (time to first event)			
Descriptive statistics and estimate variability	Treatment group	Edoxaban 60 mg OD	Edoxaban 30 mg OD	Warfarin (dose-adjusted)
	Number of subjects	6995	6982	6993
	Ischemic stroke/SEE (rate per 100 patient-years)	0.93% per year (143 subjects)	1.49% per year (235 subjects)	(1.01% per year (157 subjects)
	*Hazard ratio versus warfarin (95%CI)***	0.92 (0.73 to 1.15)	1.47 (1.20 to 1.80)	-

Analysis description	**Primary Analysis of superiority (study protocol)**			
Analysis population and time point description	Intention-to-treat, overall study period (time to first event)			
Descriptive statistics and estimate variability	Treatment group	Edoxaban 60 mg OD	Edoxaban 30 mg OD	Warfarin (dose-adjusted)
	Number of subjects	7035	7034	7036
	Primary endpoint All strokes/SEE(rate per 100 patient-years)	1.57% per year (296 subjects)	2.04% per year (383 subjects)	(1.80% per year (337 subjects)
	Hazard ratio versus warfarin (99%CI)	0.87 (0.709, 1.068, p=0.0807 for superiority)	1.13 (0.933 to 1.371, p=0.0980 for superiority)	-
Analysis description	**Primary Analysis of superiority (CHMP guideline)***			
Analysis population and time point description	Intention-to-treat, overall study period (time to first event)			
Descriptive statistics and estimate variability	Treatment group	Edoxaban 60 mg OD	Edoxaban 30 mg OD	Warfarin (dose-adjusted)
	Number of subjects	7035	7034	7036
	Ischemic stroke/SEE (rate per 100 patient-years)	1.33% per year (251 subjects)	1.89% per year (356 subjects)	(1.36% per year (255 subjects)
	Hazard ratio versus warfarin (99%CI)	0.98 (0.78 to 1.23, p=0.7903)	1.39 (1.12 to 1.72, p<0.0001)	-
Analysis description	**Secondary variables (ITT, overall study period)**			
Descriptive statistics and estimate variability	Treatment group	Edoxaban 60 mg	Edoxaban 30 mg	warfarin
	Number of subject	N = 7035	N= 7034	N = 7036
	Stroke, SEE or CV mortality(rate per 100 patient-years)	3.85% per year (728 subjects)	4.23% per year (796 subjects)	4.43% per year (831 subjects)
	Hazard ratio versus warfarin (95%CI)	0.87 (0.79 to 0.96)	0.95 (0.87 to 1.05)	-
	MACE (rate per 100 patient-years)	4.41% per year (827 subjects)	4.90% per year (913 subjects)	4.43% per year (926 subjects)

	Hazard ratio versus warfarin (95%CI)	0.89 (0.81 to 0.97)	0.98 (0.90 to 1.08)	-
	Stroke, SEE or all-cause mortality (rate per 100 patient-years)	5.01% per year (949 subjects)	5.23% per year (985 subjects)	4.57% per year (1046 subjects)
	Hazard ratio versus warfarin (95%CI)	0.90 (0.82 to 0.98)	0.94 (0.86 to 1.02)	-

*Ischemic stroke/SEE, Per-protocol, on-treatment (*EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014*)) (excluding haemorrhagic stroke).

**97.5% CI was not calculated by the sponsor for this outcome.

Table E-46. Summary of efficacy for trial Hokusai VTE

Title:A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multi-Center, Multi-National Study for the Evaluation of Efficacy and Safety of (LMW) Heparin/Edoxaban versus (LMW)Heparin/Warfarin in Subjects with Symptomatic Deep-Vein Thrombosis and/or Pulmonary Embolism		
Study identifier	DU176B-D-U305 (HOKUSAI VTE)	
Design	This was an event-driven, Phase 3, multi-national, multicenter, randomized, double-blind, matching placebo, parallel-group, non-inferiority study to evaluate the benefits and risks of edoxaban in reducing the risk of recurrent venous thromboembolism (VTE) complications in subjects with documented acute symptomatic DVT and/or PE.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Event driven: The study continued until ≈ 220 primary efficacy endpoint events (i.e., recurrent VTE) were recorded (mITT set). Treatment: maximum of 12 months. First subject, first visit date: 28-Jan-2010. Last subject, last follow-up date: 12-Jun-2013. not applicable not applicable
Hypothesis	Non-inferiority (recurrent VTE, mITT, overall study period; HR < 1.5), then superiority (recurrent VTE+all-cause death, mITT, overall study period).	
Treatments groups*	Edoxaban (60 or 30 mg OD)†	Randomized: 4143 Treated: 4118 patients (60 mg OD: 3385; 30 mg OD: 733) Treatment duration (median): 265 days.
	Warfarin (dose-adjusted)	Randomized: 4149. Treated: 4122. Treatment duration (median): 261 days.

Endpoints and definitions	Primary endpoint	Symptomatic Documented recurrent VTE	The composite of DVT, non-fatal PE, and fatal PE, documented by objective methods during the 12-month study period. CEC adjudication results were the basis for the final analyses.
	Secondary endpoint	Symptomatic documented recurrent VTE + all-cause mortality	The composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study period.
	Secondary endpoint	Net clinical outcome	The composite of symptomatic (non-fatal) recurrent VTE, (non-fatal) major bleeding and all-cause mortality.
Database lock	26 Jun 2013		

Results and Analysis

Analysis description	**Primary Analysis for non-inferiority**		
Analysis population and time point description	mITT, overall study period		
Descriptive statistics and estimate variability	Treatment group	Edoxaban	Warfarin
	Number of subject	4118	4122
	Symptomatic recurrent VTE(%)	3.2% (130 subjects)	3.5% (146 subjects)
	Hazard ratio versus warfarin (95%CI)	0.89 (0.70 to 1.13; p < 0.0001 for non-inferiority)	-

Analysis description	**Primary analysis for superiority**		
Analysis population and time point description	mITT, overall study period		
Descriptive statistics and estimate variability	Treatment group	Edoxaban	Warfarin
	Number of subject	4118	4122
	Symptomatic (non-fatal) recurrent VTE + all-cause mortality(%)	5.5% (228 subjects)	5.5% (228 subjects)
	Hazard ratio versus warfarin (95%CI)	1.00 (0.83 to 1.20; p = 0.9933 for superiority)	-

Analysis description	**Net clinical endpoint (PP analysis set, on treatment)**		
Descriptive statistics and estimate variability	Treatment group	Edoxaban	Warfarin
	Number of subject	4057	4078

	Symptomatic (non-fatal) recurrent VTE + (non-fatal) major bleeding + all-cause mortality (%)	3.4% (138 subjects)	3.9% (158 subjects)
	Hazard ratio versus warfarin (95%CI)	0.87 (0.70 to 1.10)	-

*All patients received initial parenteral treatment with LMWH or UFH for at least 5 days.

†Edoxaban 60 mg OD in most patients. Dose was halved to 30 mg OD in any of the following cases: Body weight ⩽ 60 kg; CrCL between 30-50 mL/min; and/or concomitant use of P-glycoprotein (P-gp) inhibitors (e.g.: verapamil or quinidine).

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

N/A

Clinical studies in special populations

A clinical study in 93 patients with several degrees of renal function, including severe renal impairment (study C-J307) has already been described and discussed under section 3.3 (dose-finding studies). No other studies in special populations have been submitted. For available efficacy data in special populations see also ancillary analyses subsection (subgroup analyses of the pivotal studies).

Supportive studies

N/A

2.5.3. Discussion on clinical efficacy

2.5.3.1. Phase II studies

The totality of the data from the edoxaban clinical development program support the selection of the edoxaban 60 mg dose for phase III studies in NVAF and treatment of acute VTE, the dose reduction criteria and the magnitude of the dose reduction to 30 mg in subjects with reduced renal function, low weight and some of the identified P-gp inhibitors. In ENGAGE AF the primary efficacy endpoint (stroke + SEE) was superior for the 60 mg QD as compared to the 30 mg QD regimen albeit the rate of haemorrhagic strokes was lower in the 30 mg QD group. On the other hand, for the secondary "net clinical benefit endpoint" (stroke, SEE, major bleeding events, mortality) the 30 mg QD dose was better than the 60 mg group due to the lower bleeding rates despite of lower efficacy.

Efficacy and B/R of a BID vs. a QD dosing regimen were further requested by the CHMP during the procedure however lacking data on efficacy for a BID regimen, modelling of B/R of an adapted bid dose were not possible to be provided post hoc.

2.5.3.2. ENGAGE AF: Prevention of stroke and SEE in patients with non-valvular atrial fibrillation

ENGAGE AF enrolled male or female subjects ≥21 years of age with documented NVAF (including paroxysmal, persistent, or permanent AF) within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for the duration of the study.

- *VKA naïve/VKA experienced patients*

Subjects who were receiving or had received prior anticoagulant (e.g.: VKA experienced) and/or antiplatelet therapies were eligible, as well as subjects who were naive to anticoagulant and/or antiplatelet therapy. In addition, eligible subjects were required to have a CHADS2 index score ≥ 2. **VKA experienced** was defined as current users as well as former users who took VKA for greater than 2 months. **VKA naïve** were those subjects who received ≤ 2 months of VKA therapy before study entry. Given that these definitions are not homogeneous across trials in NVAF, current *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014)* recommends sensitivity analyses using different definitions of VKA-naïve users in order to be able to compare the studies. Ancillary analyses provided by the applicant using different definitions of VKA experienced patients yielded very similar results to those of the primary analysis.

- *Bio-prosthetic heart valves*

Patients with a mechanical heart valve were excluded from ENGAGE AF, but subjects with bioprosthetic heart valves and/or valve repair could have been included. A total 321 subjects with a history of **bio-prosthetic heart valves** or valve surgery were treated with study drug (either edoxaban or warfarin) in ENGAGE AF with 277 to 286 subject-year follow-up. Rates of stroke/SEE and major bleeding (main outcomes) in this subgroup were similar than in the overall study population. A further clarification whether patients with bioprosthetic heart valves were included in the first 3 months after surgery for valve implantation was requested, as during the first 3 months, the tissue valve is in contact with the blood and cannot be treated like native valve disease. The Applicant was unable to identify the proportion of subjects with a recent history of bioprosthetic heart valve surgery and a non-recommendation of edoxaban use during the first 3 months after implantation of a bio-prosthetic heart valve was included in the SmPC accordingly.

- *Patients $CHADS_2$ score = 1*

Patients with $CHADS_2$ index score=1 were excluded from the single pivotal study ENGAGE-AF but were included in the wording of the indication (e.g.: patients with only one of the following risk factors: age≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (NYHA Class ≥ II), the applicant was requested to justify why the extrapolation of the available data from high risk $CHADS_2$ score ≥2 to $CHADS_2$ score =1 could be acceptable. It could not be confirmed nor ruled out that the effect of edoxaban is different from that of warfarin in **patients $CHADS_2$ score = 1** using CHA_2DS_2VASc= 2 as a proxy, due to the limited amount of patients and events in this pos-hoc subgroup. However, compared with no treatment in patients with $CHADS_2$ = 1, edoxaban 60 mg is still projected to reduce the rate of ischemic stroke/SEE by 2.5%/yr at a cost of a 0.7%/yr increase in major bleeding. The benefit in mortality versus no treatment is projected to be > 10%/yr. However, the results were hampered by its exploratory nature and by the combination of data from different studies/sources. The CHMP agreed that anticoagulation with edoxaban may provide additional benefit versus no treatment in patients with $CHADS_2$ =1, and that the extrapolation is acceptable, as it has been accepted for similar compounds. With respect to the optimal dose to be used in this subgroup, considering that the edoxaban 60 mg dose was more effective than the 30 mg dose in preventing ischemic stroke/SEE in ENGAGE and that a significant proportion of patients with $CHADS_2$ =1 has normal renal function and edoxaban exposure is consequently decreased, it seems reasonable to recommend the 60 mg dose over the 30 mg dose in these patients, as in the overall population. The applicant clarified that no further studies are planned with edoxaban to generate clinical data in these patients at lower risk of stroke. This was considered acceptable.

- *Treatment regimes tested in the ENGAGE AF*

In ENGAGE-AF, eligible subjects were randomized to edoxaban 30 mg or 60 mg, or warfarin (1:1:1 ratio) using stratified randomization. Within each $CHADS_2$ stratum, subjects were further stratified with respect to factors requiring edoxaban dosage reduction[moderate renal impairment (CrCL ≥ 30

mL/min and ≤ 50 mL/min as calculated using the Cockroft-Gault formula), low body weight (≤ 60 kg) or for subjects on specified concomitant medications (verapamil, quinidine, dronedarone)]. **Treatment regimes tested in the ENGAGE AF study were deemed appropriate**. The ENGAGE study used a double-blind design, which is the one recommended by the *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014)*.

- *Results of the primary endpoint with the thromboembolic events excluding haemorrhagic strokes*

As in other similar trials, the primary efficacy endpoint in ENGAGE-AF was a net clinical endpoint mixing thromboembolic events (ischemic/undefined stroke, SEE) and haemorrhagic stroke. As a result, there has been double-counting of primary efficacy/safety events (thromboembolism/major bleeding) regarding haemorrhagic stroke (included in both main efficacy and safety endpoints). Current *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation (EMA/CHMP/341363/2014*) stresses the importance of excluding haemorrhagic stroke from the main efficacy endpoint. The applicant provided the **results of the primary endpoint with the thromboembolic events excluding haemorrhagic strokes**, in line with the above mentioned guideline. The rates of ischemic stroke/SEE in the PP population, on-treatment was 0.93%/yr with edoxaban 60 mg and 1.01 %/yr with warfarin (HR: 0.92; 95% CI: 0.73 to 1.15; 97.5%CI: 0.71 to 1.23) thus supporting the non-inferiority of edoxaban 60 mg versus warfarin in the prevention of ischemic stroke/SEE (excluding hemorrhagic stroke) at different CIs. The applicant clarified that, in ENGAGE AF, the time-based definition was used to differentiate between ischaemic stroke and TIA. There were few TIA events with abnormal imaging only (25 events: 10 on edoxaban 60 mg and 15 on warfarin) and the analysis of ischemic stroke using time-based definition (excluding TIA with positive neuroimaging as being an ischemic stroke) (HR: 0.99; 95%CI: 0.82-1.18) or using tissue-based definition (sensitivity analysis including TIA with positive neuroimaging) (HR: 0.97; 95%CI: 0.81-1.16) were very similar.

- *Statistical methods applied in the ENGAGE AF study*

ENGAGE AF was an **event driven trial**. A total of at least 448 events were required. Sample size calculation was endorsed by the CHMP. The non-inferiority margin (HR <1.38) was comparable to that used in ARISTOTLE study with apixaban and more strickter than the 1.46 used in the RE-LY and ROCKET-AF studies with dabigatran and rivaroxaban. The time to first stroke/SEE event (primary endpoint) in ENGAGE-AF was analyzed using the Cox proportional hazards model including treatment groups and 2 dichotomized stratification factors as covariates ($CHADS_2$ 2-3 versus 4-6; full dose versus reduced dose in a given treatment group). The applicant focused its main analysis (non-inferiority) in a modified ITT population during the "on-treatment period". However, the applicant also tested non-inferiority in the PP population during the overall study period according to CHMP recommendations obtained during the scientific advice procedure, as well as in the PP population "on-treatment", which is in agreement with the recent *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with NVAF (EMA/CHMP/341363/2014)* that states that "the analysis to show non-inferiority should include the primary endpoint events while taking study drug including a period of 3 days after study drug discontinuation (on-treatment analysis). Statistical methods applied in the ENGAGE AF study were considered acceptable.

- *Protocol Amendments*

There were 7 amendments with extensive major changes in the protocol of the ENGAGE-AF study. In particular, amendments 3 and could have implications in the quality of management in warfarin control group and dosing errors. Ancillary analyses of efficacy and safety suggest that implementation

of **Protocol Amendments 3 and 4** may have led to an improvement in warfarin management. However, for both periods (before and after implementation of protocol amendments), edoxaban was associated with a lower rate of stroke or SEE events compared with warfarin.

- *Non-inferiority of edoxaban 30 mg versus warfarin in sensitivity analysis*

Non-inferiority of edoxaban 60 mg was shown in the primary sponsor's analysis of all strokes/SEE (mITT, on-treatment) as well as in the sensitivity analysis for ischemic stroke/SEE according to *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with NVAF (EMA/CHMP/341363/2014)* (PP, on-treatment), but superiority was not shown for the previous mentioned endpoints in the ITT population in the overall study period. On the contrary, although the main sponsor's analysis suggested non-inferiority of edoxaban 30 mg versus warfarin on all strokes/SEE, the sensitivity analysis using ischemic stroke/SEE (as per above guideline) showed **inferiority of the low edoxaban dose versus warfarin**.

- *Study drug interruptions*

The percentage of subjects with 1 or more **study drug interruptions** (> 3 consecutive days during which the subject did not take study drug) was 62.5%, 61.8%, and 65.5%, respectively, among the edoxaban 60 mg, edoxaban 30 mg, and the warfarin treatment groups. Thromboembolic events occurring during temporary interruptions (starting Day 4 of each interruption period to resumption of study drug after each interruption) were not included in the "on-treatment analysis" of non-inferiority, but off-treatment events on the first 3 days study drug interruption were included in the "on-treatment analysis". Theoretically, temporary interruptions are more dangerous for edoxaban than for warfarin, due to its shorter half-life. There were 117 stroke/SEE events on edoxaban 60 mg and 112 stroke/SEE events on warfarin during temporary interruptions (starting Day 4 of each interruption period to resumption of study drug after each interruption). However, when corrected by exposure, the yearly event rate was quite similar (edoxaban 3.06 %/yr vs. warfarin 3.04 %/yr). All-cause, cardiovascular mortality events, hemorrhagic strokes and intracranial bleed events were lower in the edoxaban 60-mg group compared with the warfarin group during temporary interruptions. Considering various reasons and circumstances for study drug interruptions and varying duration and nature of "off-study drug" antithrombotic therapies that may have been used by the investigators during interruptions, these data may need to be interpreted with caution.

- *Adjudicated events after study drug discontinuation in ENGAGE AF*

After the end of study, the percentage of subjects with adjudicated events within 3 days was low and similar in the three treatment groups (0.2%). From day 4 to 30 after end of study, the percentage of patients with stroke was 1.3%, 1.8% and 1.4% in the edoxaban 60 mg OD, edoxaban 30 mg OD and warfarin, respectively. These data indicate that the management of oral anticoagulation after study drug discontinuation in ENGAGE AF was appropriate.

- *Consistency of the analyses for 60mg OD*

Analyses of composite (first-event) endpoint of stroke, SEE, and CV mortality, the endpoint of MACE, and the composite endpoint of stroke, SEE, and all-cause mortality were generally **consistent with the analysis of the main endpoint of all strokes/SEE**. The trend for superiority of the high edoxaban dose (**60 mg OD**) versus warfarin for the primary endpoint was supported by secondary analyses of patients with fatal strokes (80 vs. 86), disabling strokes (54 vs. 57), recurrent stroke/SEE events (5 vs. 8; mITT analysis set on-treatment period) and analysis of the composite of stroke, SEE and TIA (edoxaban 60 mg 1.69% per year vs. warfarin 1.92% per year; HR: 0.88; 95%CI: 0.746 to 1.042; mITT on-treatment period; main sponsor's analysis).

- *Efficacy of 30mg OD strength*

On the contrary, the edoxaban 30 mg dose showed a trend for inferiority versus warfarin in the analysis of pure thromboembolic events (ischemic stroke/SEE as well as in MI). The trend for inferior efficacy of edoxaban 30 mg OD versus warfarin was also supported by the higher number of disabling strokes (82 and 57 subjects in edoxaban 30 mg group and the warfarin group, respectively), in the number of patients with who had ≥ 2 occurrences of the primary efficacy endpoint (21 and 8 subjects in edoxaban 30 mg group and the warfarin group, respectively; mITT analysis set on-treatment period) as well as by the high number of events when TIA was added to stroke and SEE (edoxaban 30 mg event rate 2.28% per year vs warfarin 1.92% per year; HR: 1.19; 95%CI: 1.021 to 1.389; mITT on-treatment period; primary sponsor's analysis). However, there was a trend for superiority of edoxaban 30 mg versus warfarin in the reduction of haemorrhagic stroke and CV mortality (mainly due to the reduction in fatal bleedings), which might be of interest in patients at high risk of bleeding. In post hoc analyses submitted together with D121 responses in subjects with high risk of bleeding, the edoxaban 30-mg regimen (30 mg with reduction to 15 mg) did not reduce ischemic events with HR more than 1.0 compared with warfarin. Based on the data on ischemic strokes/SEE, it was difficult to justify edoxaban 30-mg regimen (with the exception of those patients with increased exposure where 30mg OD dose is recommended: (1) moderate renal impairment and/or (2) low body weight ≤ 60 kg and/or (3) concomitant use with some P-gp inhibitors) for patients with high risk of bleeding. The analysis by HAS-BLED score did not identify a group who would benefit from the lower dose of 30 mg. Therefore, ancillary analyses did not support the use of the edoxaban 30 mg dose, even in patients at high risk of bleeding.

- *Number of strokes and undefined strokes*

There was an apparent **discrepancy in numbers of primary endpoint** events across tables, which was due to the **inclusion of either first events or all events**. The primary endpoint in the ENGAGE-AF study was time to first stroke/SEE. A total of 292 primary endpoint events were recorded for the edoxaban 60-mg group (made up of 278 strokes and 14 SEE) and 336 primary endpoint events were recorded for the warfarin group (made up of 315 strokes and 21 SEEs) (mITT population, overall study period). However, 18 subjects in the edoxaban 60-mg group and 29 in the warfarin group experienced ≥ 2 adjudicated strokes. Thus more events were counted in the components of the primary endpoint analysis than in the primary analysis where only the first event was counted for a subject. Regarding confirmation of primary events, for all events adjudicated as strokes (either primary ischemic or primary hemorrhagic stroke), the images were available. All primary stroke (efficacy or hemorrhagic) events were adjudicated based on the clinical description of the event accompanied with neuroimaging studies. However, there were also "undefined strokes" during ENGAGE-AF, but these were excluded from the analysis, mainly for not having confirmatory neuroimaging tests available. Numerically, there were more unconfirmed events with edoxaban than with warfarin (113 vs 104). Combining these events to those included in the study reported primary endpoint as sensitivity analysis yields to 324 events in the edoxaban group (event rate of 1.72%/year) vs. 372 (event rate of 2.00%/year) in the warfarin group with a hazard ratio of 0.86 (0.74, 1.00), thus still favouring edoxaban 60 mg versus warfarin. Therefore, the inclusion of unconfirmed non-adjudicated events did not change the primary study results indicating non-inferiority of edoxaban 60 mg versus warfarin.

- *Adjudicated versus investigator-reported events*

With respect to **adjudicated versus investigator-reported events**, the number of Clinical Events Committee (CEC) adjudicated strokes (ischemic or hemorrhagic) was lower than the investigator reported primary events. However, in both cases, the events were lower with edoxaban than with warfarin (adjudicated: edoxaban 278. vs warfarin 316; investigator-reported: edoxaban 288 vs warfarin 329). Of interest, the CEC adjudicated a slightly lower number of ischemic strokes with edoxaban than the investigators (233 vs 235), but a higher number of ischemic strokes with warfarin than the investigator (234 vs 220). The main reason for the discrepancy seems a combination of

chance and a lower number of TIAs that were upgraded to ischemic strokes by the CEC in the edoxaban group than in the warfarin group (13 vs 21). This small imbalance in the adjudication of TIA was considered by the CHMP unlikely to alter the conclusion of non-inferiority of edoxaban versus warfarin. In addition, investigators reported more SEE than the adjudicating committee, because they reported DVT and PE in addition to the arterial embolic events on the SEE form, but in both cases there were less SEE with edoxaban than with warfarin. If primary ischemic stroke and SEE as reported by the investigators are combined, the numbers are similar in both groups: edoxaban 305 (235+70) vs. warfarin 301 (220+81). Therefore, when counting all strokes, or the sum of ischemic stroke + SEE, there are no major discrepancies between investigator-reported and adjudicated primary endpoint events.

Exploratory analyses of subgroups in ENGAGE-AF

Exploratory analyses of subgroups in ENGAGE-AF were conducted by INR/TTR level by centre and quartiles as well as by at least 14 patient/study characteristics. Efficacy data in subgroups were difficult to be interpreted due to the inclusion of haemorrhagic stroke in the analyses. Subgroup analyses of stroke/SEE by INR/TTR level suggest that **the effect size** (reduction of stroke/SEE by edoxaban) **decreases as the quality of anticoagulation in the control group increases** (i.e.: in centers with TTR > 60% and when INR/TTR is above the fourth quartile, >73.9%). When the TTR data are examined by quartiles for the edoxaban 60 mg group compared to warfarin, the HR for the primary endpoint in the 1st, 2nd, and 3rd quartile was 0.80, 0.73, and 0.74, respectively, and for the 4th quartile was 1.07 (95%CI: 0.65-1.75). For the edoxaban 30 mg group compared to warfarin, the HR for 1st, 2nd, 3rd, and 4th quartiles were 0.82, 1.02, 1.22, and 1.30 (95%CI: 0.81-2.09), respectively. These data are within expected on the light of previous studies with novel oral anticoagulants in NVAF.

Subgroup analyses by patient/study characteristics showed a generally **consistent effect of edoxaban in most subgroups, with the exception of subgroups by renal function** and **geographic region** (for both edoxaban doses versus warfarin). The HR for the edoxaban 60 mg group compared with the warfarin group for Western Europe was 1.47 (95%CI: 0.89-2.45; mITT, on-treatment) and for the subgroup with CrCL ≥ 80 mL/min was 1.41 (95%CI: 0.97-2.06).

- *Results by geographical region in the ENGAGE-AF study*

The main primary endpoint results in ENGAGE-AF study seem to be driven by an increased stroke/SEE rate with warfarin in Asia/Pacific/South Africa and Latin America (2.33% and 2.60%, respectively), which contrasts with the 1.13% yearly rate of stroke/SEE found in Western Europe. In general, subgroup analyses of ENGAGE-AF for INR level and geographic region were consistent with a recent meta-analysis of subgroups of RE-LY (dabigatran vs. warfarin), ROCKET-AF (rivaroxaban vs. warfarin) and ARISTOTLE (apixaban vs. warfarin) (*Gómez-Outes et al. Thrombosis. 2013; 640723*). In all these studies, the good results of the new anticoagulants were mainly at expenses of increased stroke/SEE rates with warfarin in Asia and Latin America. However, **the interaction by region seems more pronounced in the ENGAGE-AF study** than in the other studies. Although the interpretation of the results in Western Europe is hampered by the limitations of subgroup analyses and the low event rates, additional information provided by the Applicant suggest that the cause of the poorer results of edoxaban in Western Europe than in other regions could be multifactorial, due to a combination of increased ischemic stroke/SEE rates in the edoxaban arms (a result of decreased exposure due to good renal function and increased body weight in many Western Europe patients in comparison with other regions), and a low rate of ischemic/hemorrhagic stroke and SEE in the warfarin arm, due to a good quality of oral anticoagulation in Western Europe centres in comparison with other regions. Nevertheless, it should be taken into account that ENGAGE AF demonstrated non-inferiority of edoxaban 60 mg versus a well-controlled warfarin regime in the overall population.

All-cause and CVS mortalities were broadly similar in the overall vs. on-treatment analysis in both the edoxaban and warfarin groups in Western Europe, with point estimates of HR close to 1. Therefore, no safety signal was apparent in Western Europe. In addition, when the analysis was made in the region of the EEA + Switzerland, the results on ischemic stroke/SEE were broadly similar in the edoxaban and warfarin groups (HR 0.94 and 0.99 point estimates in the overall study period and on-treatment analyses, respectively). In summary, although the hazard ratios for the on-treatment and overall periods may show some variability, given in excess of 100 combinations of regions and endpoints this minor level of inconsistency in ischemic stroke/SEE is considered to be due to a combination of chance due to the extreme multiplicity of testing and probably due to a trend towards a better control of warfarin treatment in Western Europe and North-America than in other regions. The overal study results are deemed representative for the EEA.

- *Poorer results of edoxaban in the group of normal renal function*

In addition, the **poorer results of edoxaban in the group of normal renal function** versus impaired renal function for the primary endpoint is a novel finding. Sub-group analysis of ENGAGE-AF identified the increase in renal function as a significant predictor for increase in risk of stroke/SEE with edoxaban 60 mg versus warfarin (interaction p = 0.0002) and edoxaban 30 mg versus warfarin (interaction p = 0.0077). Patients with normal renal function (CrCl ≥ 80 mL/min) in the edoxaban 60 mg tended to have a higher risk of stroke/SEE than warfarin-treated patients (HR: 1.41, 95% CI: 0.97-2.06). The interpretation of that finding is hampered by the exploratory nature of subgroup analyses and the relatively low number of events and patients with normal renal function. Comparing the within-treatment groups, there was no indication that a better creatinine clearance was associated with a higher rate of events with edoxaban, as the events rates of stroke/SEE, CV mortality and MACE were lower in the normal renal function patients than in patients with impaired renal function in both treatment groups. In the edoxaban group, stroke/SEE rates were 1.26%/yr in patients with normal renal function, lower than the 1.49%/yr stroke/SEE rate in mild renal insufficiency and 2.29%/yr in patients with moderate renal insufficiency (see Table 1 below). However, the lower event rates in patients with normal renal function could also be due to differences in demographic characteristics as patients with normal renal function tend to be younger and with a lower thrombotic risk as shown by lower CHADS2 scores than patients with renal impairment.The finding may also be due, at least in part, to a surprisingly low event rate with warfarin in patients with normal renal function, with strokes rates of less than 1%/yr, while in contemporary AF trials (ARISTOTLE, RELY, ROCKET-AF), the rate of stroke/SEE in patients with normal renal function was always above 1%/yr (1.05%/yr to 1.42%/yr). This finding could be related to the fact that the quality of anticoagulation with warfarin in ENGAGE was best compared to other contemporary AF trials.

Table 1: Key Efficacy Endpoints by CrCL Category for Edoxaban 60 mg vs Warfarin in ENGAGE AF, mITT Overall Study Period

CrCLsubgroup (mL/min)	Edoxaban 60 mg (N = 7012)			Warfarin (N = 7012)			Edoxaban 60 mg vs Warfarin
	M	n	%/yr [a]	M	n	%/yr [a]	HR (95% CI)
Stroke/SEE							
CrCL ≥30 to ≤ 50	1302	76	2.29	1305	87	2.68	0.86 (0.632, 1.169)
CrCL > 50 to < 80	3007	121	1.49	3048	176	2.18	0.68 (0.538, 0.854)
CrCL ≥ 80	2633	91	1.26	2608	70	0.97	1.31 (0.958, 1.787)
Ischemic Stroke/SEE							
CrCL ≥30 to ≤ 50	1302	63	1.89	1305	67	2.05	0.93 (0.660, 1.314)
CrCL > 50 to < 80	3007	105	1.29	3048	129	1.59	0.80 (0.622, 1.041)
CrCL ≥ 80	2633	76	1.05	2608	55	0.76	1.39 (0.983, 1.968)
Ischemic Stroke							
CrCL ≥30 to ≤ 50	1302	58	1.74	1305	59	1.81	0.97 (0.677, 1.398)
CrCL > 50 to < 80	3007	99	1.22	3048	121	1.49	0.81 (0.620, 1.055)
CrCL ≥ 80	2633	73	1.01	2608	52	0.72	1.41 (0.990, 2.018)
Hemorrhagic Stroke							
CrCL ≥30 to ≤ 50	1302	13	0.38	1305	23	0.70	0.54 (0.276, 1.071)
CrCL > 50 to < 80	3007	19	0.23	3048	51	0.62	0.37 (0.220, 0.631)
CrCL ≥ 80	2633	16	0.22	2608	16	0.22	1.00 (0.501, 2.008)
Myocardial Infarction							
CrCL ≥30 to ≤ 50	1302	32	0.95	1305	34	1.03	0.92 (0.567, 1.494)
CrCL > 50 to < 80	3007	63	0.77	3048	63	0.77	1.00 (0.707, 1.422)
CrCL ≥ 80	2633	35	0.48	2608	40	0.55	0.88 (0.557, 1.381)
CV Mortality							
CrCL ≥30 to ≤ 50	1302	165	4.79	1305	204	6.02	0.80 (0.654, 0.985)
CrCL > 50 to < 80	3007	193	2.32	3048	259	3.10	0.75 (0.620, 0.900)
CrCL ≥ 80	2633	155	2.10	2608	134	1.82	1.16 (0.920, 1.462)
MACE							
CrCL ≥30 to ≤ 50	1302	239	7.23	1305	273	8.42	0.86 (0.727, 1.028)
CrCL > 50 to < 80	3007	317	3.93	3048	427	5.32	0.73 (0.635, 0.849)
CrCL ≥ 80	2633	247	3.44	2608	210	2.93	1.18 (0.982, 1.419)

[a]: The event rate (% per yr) is calculated as number of events/subject-year exposure.
Note: The HR and two-sided CI for pairwise comparisons versus warfarin are based on the Cox proportional hazard model including treatment and the two stratification factors as covariates: dichotomized CHADS2 score and dichotomized dose adjustment factor.
Source: Table R55-007

Table 7: Key Safety Endpoints by CrCL Edoxaban 60 mg vs Warfarin in ENGAGE AF, Safety Analysis Set

CrCL (mL/min)	Edoxaban 60 mg (N = 7012)			Warfarin (N = 7012)			Edoxaban 60 mg vs Warfarin
	M	n	%/yr [a]	M	n	%/yr [a]	HR (95% CI)
On-Treatment Period							
Major Bleed							
CrCL ≥ 30 to ≤ 50	1302	96	3.91	1305	128	5.23	0.75 (0.575, 0.975)
CrCL > 50 to < 80	3007	209	3.20	3048	237	3.55	0.90 (0.747, 1.084)
CrCL ≥ 80	2633	109	1.77	2608	154	2.52	0.71 (0.552, 0.903)
Major or CRNM Bleed							
CrCL ≥ 30 to ≤ 50	1302	304	13.74	1305	404	19.18	0.72 (0.625, 0.841)
CrCL > 50 to < 80	3007	725	12.40	3048	802	13.71	0.91 (0.820, 1.004)
CrCL ≥ 80	2633	490	8.68	2608	547	9.91	0.88 (0.779, 0.995)
Overall Study Period							
Fatal Bleed							
CrCL ≥ 30 to ≤ 50	1302	10	0.30	1305	29	0.87	0.34 (0.166, 0.704)
CrCL > 50 to < 80	3007	21	0.25	3048	40	0.48	0.53 (0.310, 0.891)
CrCL ≥ 80	2633	17	0.23	2608	19	0.26	0.90 (0.466, 1.722)
All-Cause Mortality							
CrCL ≥ 30 to ≤ 50	1302	229	6.64	1305	280	8.27	0.81 (0.683, 0.968)
CrCL > 50 to < 80	3007	306	3.68	3048	352	4.21	0.87 (0.748, 1.017)
CrCL ≥ 80	2633	215	2.92	2608	187	2.55	1.15 (0.948, 1.404)

[a]: The event rate (% per yr) is calculated as number of events/subject-year exposure.
Note : The HR and two-sided CI for pairwise comparisons versus warfarin are based on the Cox proportional hazard model including treatment and two stratification factors as covariates: dichotomized CHADS2 score and the dichotomized dose adjustment factor.
Source: Table R55-008, Table R55-009, Table R55-010

The CHMP agreed that in NVAF, although the overall benefit risk in the AF indication is considered positive across the continuum of renal function at the population level, there are indications of reduced efficacy of edoxaban compared to well-managed warfarin therapy that could be of relevance at the individual level in patients with increased creatinine clearance. The data in patients with normal renal function appear to be sufficiently robust, making a chance adverse finding unlikely. They may be explained by a combination of a lower exposure to edoxaban 60 mg in patients with normal renal function (in comparison with the exposure to 60 mg in patients with mild renal impairment) and a well-managed warfarin therapy resulting in a low stroke/SEE rate in the control group, particularly in patients with high creatinine clearances. **In this respect, a warning has been included in section 4.4 of the SmPC that a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk. In addition, a warning was also included in the SmPC that CrCL should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated.** The applicant has also been committed to further evaluate post-marketing whether a higher QD dose would provide a further improvement of the benefit-risk relationship in patients with high creatinine clearance

- *Monitoring of anti-Xa activity*

Monitoring of anti-Xa activity may be helpful to individualise the treatment and dose in certain circumstances (e.g.: at the beginning of the treatment in patients with cumulative risk factors for decreased exposure, such as high renal clearance combined with high body weight or in case of emergency or overdose). The Applicant has submitted a plan for developing a validated anti-Xa test to measure edoxaban's anticoagulant activity.

- *Additional subgroups analyses*

During the procedure, the Applicant was requested to show the analyses of subgroups of efficacy in ENGAGE-AF by subgroups excluding haemorrhagic stroke (i.e.: including only ischemic stroke and SEE). The event rate for composite of ischemic stroke and SEE was lower in the edoxaban 60-mg group than in the warfarin group for most subgroups, with the HR less than 1.0 for the overall study period, but in some of the sub-groups the HR was more than 1.0. However, there were several significant ($p<0.05$) interactions:

(1) for the type of atrial fibrillation: The HR was 0.79 and 0.85 for subjects with persistent and permanent AFs and **1.73 for subjects with paroxysmal AF**. However, this finding was based on a relatively low number of events and patients in this subgroup. The variations in stroke/SEE rates in the warfarin group was the main responsible for the interaction (1.23%/yr in paroxysmal AF versus 2%/yr for other types of AF). This also holds true for contemporary AF studies, in which stroke/SEE with warfarin was lower in patients with paroxysmal AF than in those with permanent/persistent AF. No safety signal was apparent in this subgroup, and CV mortality numerically favoureds edoxaban. In the subgroups by type of AF there was no question of differences in exposure as the renal function of each subgroup was essentially the same. The interaction by type of AF is probably multifactorial, more related to variations in stroke/SEE rates with warfarin (unexpectedly low stroke/SEE rates in some subgroups) than corresponding variations with edoxaban, in line with the interactions reported by treatment region and by renal function.

(2) for the VKA-naïve versus VKA experienced subjects: The HR was 0.75 for VKA naïve subjects and 1.17 for VKA experienced subjects. VKA-experienced patients comprise the majority of patients enrolled in ENGAGE-AF (59%) and suggest that switching from warfarin to edoxaban was not associated woth a benefit in efficacy. Considering the primary endpoint of stroke/SEE, a significant interaction was found for the overall study period for prior VKA use ($p=0.0253$) but this was not observed for the on-treatment period ($p=0.3545$). The most important patient characteristics of the VKA-experienced subjects was the increased TTR which at 70% is very high in the ENGAGE AF study. None-the-less for the primary endpoint of stroke/SEE, edoxaban 60 mg did show similar efficacy and even for ischemic stroke, any gap in efficacy was less than 0.5%/year and is offset by a clinically significant decrease in major bleeds, and demonstrating similar net clinical outcome and all-cause mortality. Therefore, edoxaban 60 mg showed a positive benefit-risk balance in absolute terms and a similar benefit-risk balance to VKA with very good TTR control, which was the rule in VKA-experienced patients and is not expected to be the rule in many EU countries in standard practice (a poorer INR is expected), with some exceptions in specific centers and/or countries. Therefore, the CHMP was of the opinion that there is no need to include the information about this finding in the label, especially given its similar performance to other direct oral anticoagulants (DOACs) when the differences in background risk and TTR are taken into account;

(3) for the verapamil subgroup: The HR was 0.92 for subjects without concomitant verapamil and 2.59 for subjects who took concomitant verapamil. Verapamil use was very low (<5% of total population) and number of events were low (18 vs. 7). Notwithstanding, it suggests that the edoxaban 30 mg dose used in these patients was insufficient. Consequently, the applicant proposed not to reduce the edoxaban 60 mg to 30 mg when edoxaban is coadministered with verapamil or quinidine, which was endorsed.

Other issues that were discussed during the procedure regarding the ENGAGE AF study are following:

a) There were 728 subjects for whom treatment allocation was unblinded because of SUSARs. Ancillary analysis indicated that there is no indication that unblinding of the data to the independent Data Analysis Group and the Data Monitoring Committee had an impact on the overall study results;

b) Dose adjustment rules for patients ≤ 60 kg came into place in Protocol Amendment 7. However, none of the 66 patients randomized before amendment 7 had a body weight ≤60 kg, and therefore none of them received the unadjusted 60 mg edoxaban dose;

c) Ancillary analyses suggested that for those patients with the best quartile for center based results for INR numerically efficacy was slightly better for warfarin than for edoxaban 60 mg (ischaemic stroke, SEE, myocardial infarction). For haemorrhagic strokes, CV mortality, "net clinical outcome", MACE and all cause mortality numerically the effects were still in favour of Edoxaban 60 mg. For major bleeds, major bleeds, CRNM bleeds and fatal bleeds the results were inconsistent. Taken the data together the CHMP agreed that edoxaban performs better, when compared to a suboptimal therapy with warfarin;

d) All cause mortality and CV mortality rates were numerically lower with the 30 mg regimen as compared to the 60 mg treatment. Therefore, the CHMP agrees that where the risk of bleeding events outweighs the risk of ischaemic strokes and SEEs the 30 mg QD dose might be an option. This could be the case for patients with a low CHADS2 score and/or patients with contraindications for VKA therapy. However, no data comparing low dose edoxaban e.g. with aspirin or aspirin/clopidogrel are available for patients with contraindications for VKA therapy and the issue could not be answered within this procedure;

e) Overall, the number of strokes, SEE and particular disabling strokes was higher in the 30 mg QD group as compared to warfarin, but the number of fatal strokes was lower. Haemorrhagic strokes are more likely to be fatal than ischaemic strokes. In the edoxaban 60 mg group more haemorrhagic strokes occurred and haemorrhagic strokes were even more likely to be fatal than in the edoxaban 30 mg group. The net effect was a lower rate of disabling strokes (53 vs. 81) in the 60 mg group at the expense of a higher rate of fatal strokes (79 vs. 73). In about 7000 patients 81 additional strokes, of these 28 disabling strokes, could be prevented at the cost of 6 additional fatal strokes with the 60 mg compared to the 30 mg dose;

f) The event rate in the edoxaban group decreased with increasing TTR INR. The Applicant provided a potential explanation to this observation. On one hand, a better center specific INR control for warfarin may indicate a better overall level of care that is per se associated with a lower event rate in the edoxaban group. Such factors may contribute to the association between outcome in the edoxaban group and control of INR values in the warfarin group. In addition, center specific characteristics of patients included influenced INR control on one hand and the outcome on the other hand. e.g. center specific previous VKA use and region were highly correlated with INR control and may be relevant for the outcome.

g) For edoxaban 60 mg group, non-inferiority vs. warfarin can be assumed at least for those patients with TTR INR up to about 74%. However, for the highest quartile, the point estimate of the HR was in favour of warfarin (1.07; 95%CI: 0.65, 1.75). The data support the impression that non-inferiority of efficacy of edoxaban 60 mg vs. warfarin is questionable for those centers with optimal warfarin INR control. Ischaemic strokes, ischaemic strokes or SEE and all strokes + SEE were numerically in favour of warfarin in the highest quartile group. For bleeding events, MACE, MI and "net clinical outcome" the event rates were largely similar and the rate of haemorrhagic strokes and CV deaths were numerically in favour of edoxaban. INR control may relate to two factors: I) general level of medical support and II) patient characteristics that may not be changeable. Albeit the primary statistical analysis was not based on quartiles of INR control, for individual treatment decisions it was agreed to briefly summarize the key data per quartile in the SmPC to provide reassurance to the physician that no benefit can be expected by switching a well controlled patient on warfarin to edoxaban.

2.5.3.3. HOKUSAI VTE: Treatment of VTE including DVT and PE, and prevention of recurrent VTE

The efficacy and safety of edoxaban in reducing the risk of symptomatic recurrent VTE in subjects with documented acute symptomatic DVT and/or PE is primarily based upon the large Phase 3 Hokusai VTE study in which 4118 subjects were treated with edoxaban 60 mg (30 mg reduced) and 4122 with warfarin for 3-12 months (all patients received heparin-based initial treatment for 5-12 days). Hokusai VTE was Phase 3, multinational, multicenter, randomized, double-blind, matching placebo, parallel-group, non-inferiority study to evaluate the benefits and risks of edoxaban in reducing the risk of symptomatic recurrent VTE in subjects with documented acute symptomatic DVT and/or PE. At least 40% of subjects had to present with PE.

- *Dosing in the experimental group in HOKUSAI-VTE*

HOKUSAI-VTE enrolled male or female adult subjects with symptomatic DVT and/or PE documented by objective methods. In HOKUSAI-VTE, eligible subjects were randomized to (LMW) heparin/edoxaban or (LMW) heparin/warfarin using stratified randomization. All patients received initial therapy with open-label enoxaparin or unfractionated heparin for at least 5 days. Edoxaban or warfarin was administered in a double-blind, double-dummy fashion. Edoxaban (or placebo) was started after discontinuation of initial heparin. Edoxaban was administered at a dose of 60 mg orally once daily, taken with or without food, or at a dose of 30 mg once daily in patients with a creatinine clearance of 30 to 50 ml per minute or a body weight of 60 kg or less or in patients who were receiving concomitant treatment with potent P-glycoprotein inhibitors. Dosing in the experimental group (heparin lead-in followed by edoxaban) was similar to the dosing selected for dabigatran trials in acute VTE (RE-COVER I and II), but different from the single drug approach (no need for heparin lead-in, using higher doses of the new anticoagulant during the first weeks and followed by a lower maintenance dose) used in rivaroxaban trials (EINSTEIN DVT and PE) and apixaban pivotal trial in acute VTE (AMPLIFY). This was considered to be an important difference in dosing between edoxaban and the other Factor Xa inhibitors. Consequently, a statement was included in section 4.2 of the SmPC that Lixiana is to be started following initial use of a parenteral anticoagulant for at least 5 days.

- *Treatment duration in HOKUSAI-VTE*

Study duration was left to the investigator. Although it was endorsed that this approach may mimic standard practice, it would be preferable to plan for a second randomisation, or a second study in patients having received anticoagulation after 3-6 months, in order to generate randomised clinical data versus placebo or active comparator in the setting of extended treatment of VTE (i.e.: as conducted in the EINSTEIN-ext with rivaroxaban, RE-MEDY and RE-SONATE study with dabigatran or the AMPLIFY-ext study with apixaban). However, the design and analysis (mITT Overall versus On-Treatment) of the study allowed for assessment of the extension of therapy/the secondary prevention of VTE without the need for a formal “extension” study. Furthermore this “extension” study within Hokusai was performed with an active comparator-warfarin rather than placebo allowing a more robust comparison as to the real world risk benefit if continued therapy. As such the indication for both the active treatment of acute VTE and secondary prevention of recurrent VTE were demonstrated with the Hokusai VTE study with up to 12 months of therapy. Therefore, it is agreed that a separate "extension" study is not warranted. The Kaplan-Meier curves of recurrent VTE provided further support that continued exposure, remaining on therapy (on treatment versus overall population) is associated with decreased recurrence and both analyses (on treatment and overall population) favored edoxaban versus warfarin. The main issue during HOKUSAI-VTE regarding duration of therapy, looking at post-treatment recurrences, is that it seems that many patients would have benefited from longer treatment durations of anticoagulation. Furthermore, the Kaplan-Meier curves are linear data and there is long-term safety data from ENGAGE AF. Due to the above

mentioned reasons, it was agreed not to limit the duration of treatment of VTE to 1 year tested with edoxaban in HOKUSAI-VTE.

Optimal treatment duration with edoxaban after acute VTE is unclear. According to clinical practice guidelines, the duration of therapy for treatment of VTE including DVT and PE, and prevention of recurrent VTE should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE. This information was included in the SmPC.

The HOKUSAI-VTE study used a double-blind design, which is in line of the one used in the recent RE-COVER studies with dabigatran and AMPLIFY study with apixaban (EINSTEIN studies with rivaroxaban followed an open-label design). HOKUSAI-VTE study was stratified by: (1) diagnosis at presentation (PE and DVT only), (2) baseline risk factors (temporary risk factors vs. all others), and (3) need for edoxaban dose reduction to 30 mg (yes, no). The primary efficacy outcome in HOKUSAI-VTE was symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE). The applicant confirmed that approximately 8% of primary efficacy events were adjudicated events without confirmatory imaging. These events mainly included VTE-related deaths. However, the events were equally distributed in both groups and sensitivity analysis excluding these events (HR: 0.90: 95%CI: 0.69-1.16) yielded very similar results than the main analysis (HR: 0.89; 95%CI: 0.70-1.13), thus supporting non-inferiority of edoxaban under different assumptions.

- *Statistical considerations in HOKUSAI-VTE*

HOKUSAI-VTE was event driven study. A total of at least 220 events were required. Sample size calculation was endorsed. The primary efficacy analysis of the HOKUSAI-VTE study was based on a modified Intent-to-Treat (mITT) Analysis Set (subjects who are randomized and received at least one dose of study drug) using all primary efficacy events (symptomatic recurrent VTE) that occurred in the 12-month study period. The time to the first event of the composite primary efficacy outcome was analyzed using a Cox proportional hazards model including treatment and the stratification factors as covariates. The experimental regime was considered non-inferior to the comparator if the upper limit of the 95%CI for the HR was less than 1.5. The non-inferiority margin (HR <1.50) is the most restrictive one compared to recent studies with novel oral anticoagulants in the treatment of VTE (1.80 in AMPLIFY; 2.0 in EINSTEIN studies; 2.75 in RE-COVER studies).

- *Study conduct*

A total of 8292 subjects were randomized and assigned to the edoxaban (N=4143) or warfarin (N=4149) treatment groups, and a total of 8240 subjects were treated with edoxaban (N=4118) or warfarin (N=4122) (mITT set). There was no screening period in Hokusai VTE, which is consistent with the acute and serious nature of the event to be treated. The critical study qualification work-up was conducted outside of the study as a matter of routine for the management of VTE. These procedures were deemed acceptable if done within 48 hours before randomization. Of the 8,240 mITT subjects, 65 (0.8%) subjects withdrew consent and 11 (0.1%) were lost to follow up. Major protocol deviations were reported in 23% of patients (Table 14.1.2.1 of the HOKUSAI-VTE study report). Most of them (16%) corresponded to the use of disallowed medications (mainly disallowed NSAIDs) that impacts the evaluation of main efficacy/safety endpoints, followed by pretreatment for more than 48 hours with therapeutic dosages of anticoagulant treatment before randomisation (4%). The applicant was requested to show the main efficacy/safety analyses, on-treatment, conducting a “pure” per-protocol analysis (i.e.: excluding the 23% of patients with major protocol deviations, in addition to those already excluded for not having a baseline VTE event confirmed by the CEC). In the revised "true" PP analysis (excluding all major protocol violations) there were 3116 patients on edoxaban and 3143 patients on warfarin. The HR of edoxaban versus warfarin for recurrent VTE was 0.95 (0.68 to

1.33; treatment+30 days), thus confirming non-inferiority (p-value 0.0040). In summary, the original PP analysis of the applicant (not excluding all major protocol violations) favoured the demonstration of non-inferiority of edoxaban versus warfarin in efficacy. However, non-inferiority was also demonstrated after conducting a "true" PP analysis (excluding all major protocol violations). Only 11 patients (0.1%) were lost to follow-up. However, a total of 24 patients (16 patients in the edoxaban group and only 8 patients from warfarin group) were excluded at sites for which subject data authenticity was suspect and could not be confirmed. Ancillary analyses provided by the Applicant supported in conclusion that the inclusion/exclusion of these patients did not change study results. Approximately 17% of subjects required the 30 mg edoxaban at randomization due to body weight ≤ 60 kg (10%), CrCL 30-50 mL/min (4%), or for the use of quinidine/verapamil (0.5%). Post-randomization requirement for 30 mg edoxaban/edoxaban placebo occurred in 123 subjects (68 for edoxaban and 55 for edoxaban placebo (active warfarin), respectively. Approximately 17.6% of subjects had their dose adjusted at randomization. Approximately 8% of the dose reductions were due to concomitant medication with P-gp inhibitors.

- *Main study results*

Non-inferiority of edoxaban 60 mg was shown in the primary sponsor's analysis of symptomatic recurrent VTE (mITT, overall study period) as well as in the sensitivity analysis for symptomatic recurrent VTE (PP, on-treatment), but superiority was not shown for the secondary endpoint of symptomatic recurrent VTE and all-cause death (mITT, overall study period. In addition, there was a huge difference in the number of VTE events "on-treatment" and "overall study period" (approximately half of total primary events occurred post-treatment).

Net clinical outcome (composite of symptomatic recurrent DVT, nonfatal symptomatic recurrent PE, Major bleeding, and All-cause mortality) occurred in 138 subjects (3.4%) in the edoxaban group and 158 subjects (3.9%) in the warfarin group (HR: 0.87; 95% CI: 0.696, 1.099; p = 0.2515). However, these results correspond to a secondary PP analysis on-treatment, and not to the main analysis in the mITT, overall study period. For the shake of consistency, the applicant was requested to show the results of net clinical outcome in HOKUSAI-VTE using the same approach as in the main analysis of the primary endpoint (i.e.: in the mITT population, overall study period). The HR and 95% CIs for the net clinical outcome using this approach (HR: 1.00; 95%CI: 0.85-1.18) suggest that both edoxaban and warfarin (both with lead in parenteral anticoagulant) are equivalent strategies for VTE treatment. The SmPC, section 5.1, has been amended accordingly**.**

- *Subgroup analyses*

The efficacy of edoxaban was generally consistent across subgroups tested in the HOKUSAI-VTE study. Overall, of the 55 comparisons presented from 18 subgroup analyses, most (45) resulted in a point estimate favouring edoxaban. Statistically significant interaction was only found for fragile vs. non-fragile patients. Edoxaban effect was better in fragile than in non-fragile patients. In general, the effects of edoxaban were also better (although not statistically significant interaction was found) in index PE, age > 75 years and history of cancer, which was reassuring. Regarding the quality of oral anticoagulation, the edoxaban group had a relative reduction in risk for recurrent VTE compared to warfarin for subjects at centers TTR < 60% (HR: 0.89; 95% CI: 0.574, 1.364) and also at centers with TTR ≥60% (HR: 0.87; 95% CI: 0.653, 1.153). The Hazard Ratio for the edoxaban group for centers with INR-TTR >55.8 ≤64.0% was 0.77 (95% CI: 0.496, 1.205).

- *DMS, SMCC, and CEC*

DMS, SMCC, and CEC: The large difference between peak and trough values and the close relation between plasma concentration and factor Xa activity raiseed a question, whether a lower dose bid dose (e.g. 15 or 20 mg BID) would have been preferable over a qd dosing. However, it may not be

possible to draw final conclusions from the phase 3 Hokusai VTE study, whether a lower bid dose adapted to a similar overall duration of suppression of FXa activity to 15% or less would have changed the B/R ratio. The DMC but not the SMCC had access to INR measurements that could have led to partial unblinding. A high risk patient that dies due to any reason will not have an index event of the primary endpoint. The applicant provided a competing risk analysis upon request with non-VTE related deaths as competing risk. The overall result was similar to the result of the primary analysis and did not change the conclusions.

- *Transition between LMW heparin and edoxaban treatment*

The excess of index recurrent VTE events in the edoxaban group during the first 30 days raised a question, whether the transition between LMW heparin and edoxaban treatment could be improved (intensified to achieve a more potent anticoagulation; e.g. by an overlapping treatment initiation with a reduced dose or an initial parenteral therapy longer than 5 days). However, subgroup analyses did not show a consistent better efficacy in patients initially treated with LMWH for more than 5 days than in those treated for 5 days or less. Therefore, the recommended posology (Lixiana 60 mg once daily following initial use of parenteral anticoagulant for at least 5 days) was considered acceptable.

- *Possibility of a rebound effect*

There was a slight increase in recurrent VTE rates in the edoxaban group after Day 360, especially after Day 390. This is mainly due to the low number of subjects at these timepoints. The change in the curve after Day 390 in the edoxaban group is due to 3 events which occurred after the subjects had stopped study drug. The data do not indicate a general rebound effect on MACE or VTE events after cessation of edoxaban.

- *Asymptomatic patients with DVT*

Asymptomatic patients with DVT (e.g. with malignant disease) were not included in the study. The transferability of Hokusai VTE to patients with asymptomatic DVT is difficult to establish. However, as the indication should include the population studied in pivotal trials (symptomatic patients only, in Hokusai VTE) and on the other hand, asymptomatic patients with incidental extensive thrombosis are usually anticoagulated according to established clinical practice guidelines (Kearon et al. Chest. 2012; 141(2 Suppl): e419S-e494S), there is no reason to include in the SmPC neither a recommendation or a non-recommendation of use in asymptomatic patients with VTE.

2.5.3.4. Both pivotal studies

Only few black patients were included in both pivotal trials. The sparse data do not indicate concerns for efficacy and safety but the low number of black patients included in the studies has been reflected in the SmPC.

Cox's proportional hazards model was used for primary analysis of the pivotal trials for both indications, which assumes a constant HR over time. The applicant provided further clarifications that were accepted by the CHMP.

2.5.4. Conclusions on the clinical efficacy

In NVAF, the ENGAGE AF study provided evidence of non-inferiority for edoxaban 60 mg QD versus warfarin for the composite of all strokes and SEE (primary endpoint recommended in SA) and for the composite of ischemic strokes and SEE (primary endpoint recommended currently in the *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with NVAF [EMA/CHMP/341363/2014]*). On the contrary, although the low edoxaban dose (30 mg QD) showed non-inferiority versus warfarin for all strokes/SEE (study endpoint), it was inferior to warfarin for the composite of ischemic stroke/SEE. Therefore, the

Applicant's proposal of recommending the edoxaban 60 mg dose for prevention of stroke and SEE in patients with NVAF was endorsed.

The effect of edoxaban 60 mg dose was consistent in most subgroups analysed. However, stroke/SEE rates tended to favour warfarin in patients recruited in Western Europe and those with normal renal function. The interpretation of the results in Western Europe was hampered by the limitations of subgroup analyses and the low event rates. These regional variations in the context of the heterogeneous countries of EEA region were discussed by the CHMP, and the CHMP took also into account that ENGAGE AF demonstrated non-inferiority of edoxaban 60 mg versus a well-controlled warfarin regime in the overall population. All-cause mortality and CV mortality were broadly similar in the overall vs. on-treatment analysis in both the edoxaban and warfarin groups in Western Europe, with point estimates of HR close to 1. Therefore, no safety signal was apparent in Western Europe. In addition, when the analysis was made in the region of the EEA and Switzerland, the results on ischemic stroke/SEE were broadly similar in the edoxaban and warfarin groups (HR 0.94 and 0.99 point estimates in the overall study period and on-treatment analyses, respectively). In summary, although the hazard ratios for the on-treatment and overall periods may show some variability, given in excess of 100 combinations of regions and endpoints this minor level of inconsistency in ischemic stroke/SEE was considered to be due a combination of chance due to the extreme multiplicity of testing and a trend towards a better control of warfarin treatment in Western Europe and North-America than in other regions. The overal study results were deemed hence representative for the EEA.

A positive B/R in patients with AF and normal renal function (CrCL ≥ 80 mL/min) was questioned and extensively discussed but at the end considered positive across the continuum of renal function at the population level. More than 2000 patients were included in each arm in this analysis, there was consistency over a wide range of efficacy endpoints, the results were essentially consistent in the 60/30 mg arm and in the 30/15 mg arm, INR control in the warfarin arm was independent of renal function, there was external support since the event rates on edoxaban in ENGAGE AF were higher as compared to the event rates in the respective warfarin arms in additional 2 out of 3 studies, there was replication since also in Hokusai VTE there was a clear correlation between renal function and comparative efficacy with a HR numerically in favour of warfarin in patients with normal renal function. Taken all these considerations together and balancing the apparent robustness of the findings for the clinical endpoints on one hand and the fact that PK considerations cannot entirely explain the findings on the other hand, the level of concern remained high enough to make prescribing physicians clearly aware of the signal in patients with normal renal function. Therefore, a warning was included in section 4.4 of the SmPC that a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. Therefore, edoxaban should only be used in patients with NVAF and high creatinine clearance after a careful evaluation of the individual thromboembolic and bleeding risk.

In the treatment of acute VTE, HOKUSAI VTE provided evidence of non-inferiority of edoxaban 60 mg versus warfarin (both regimes preceded by heparin lead-in treatment). The non-inferiority was consistent in the ITT and PP populations, as well as in the on-treatment and overall study period analysis. No specific VTE extension studies have been conducted with edoxaban. However, the design and analysis of the study allowed the applicant to assess extension of therapy/the secondary prevention of VTE without the need for a formal “extension” study. Furthermore this “extension” study within Hokusai was performed with an active comparator-warfarin rather than placebo allowing a more robust comparison as to the real world risk benefit if continued therapy. As such the indication for both the active treatment of acute VTE and secondary prevention of recurrent VTE were demonstrated with the Hokusai VTE study with up to 12 months of therapy. The main issue during HOKUSAI-VTE regarding duration of therapy, looking at post-treatment recurrences, was that it seems that many patients would benefit from longer treatment durations of anticoagulation. That is

why it was agreed not to limit the duration of treatment of VTE to the 1 year tested with edoxaban in HOKUSAI-VTE.

During pivotal studies, dose reductions were made in patients concomitantly receiving P-gp inhibitors. However, the totality of the data did not support diminishing the dose when edoxaban 60 mg is concomitantly administered with verapamil, quinidine or amiodarone. However in patients concomitantly taking edoxaban and the following P-gp inhibitors: ciclosporine, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30mg of edoxaban once daily.

Finally, the applicant's intention for applying for the authorisation of the 15 mg QD was endorsed but restricted to the process of switching from edoxaban to VKA for patients currently on edoxaban 30 mg. The information in the SmPC has been amended to reflect more accurately the switching process used in ENGAGE-AF study. An additional warning was included in the SmPC to prevent from treatment with suboptimal 15 mg dose in monotherapy and to make clear that the 15 mg dose is only indicated in the process of switching from edoxaban 30 mg to VKA (patients with presumed increased exposure), together with an appropriate VKA dose.

2.6. Clinical safety

Patient exposure

Exposure: The exposure in the Pooled Phase 3 studies amounts to 18,010 patients treated with edoxaban for approximately 1.9 years (more than 34000 subject-years for edoxaban: approximately 18200 subject-years for edoxaban 60 mg and 15800 subject-years for edoxaban 30 mg) and and 11,010 patients treated with warfarin for approximately 1.7 years (approximately 18350 subject-years).

Table S-01: Numbers of Subjects in Analysis Sets in Phase 3 Studies

	Edoxaban Total Exposure	Edoxaban 30 mg	Edoxaban 60 mg	Warfarin
Pooled Phase 3 Studies				
Safety	18010	7002	11008	11010
ENGAGE AF				
Safety	14014	7002	7012	7012
mITT	14014	7002	7012	7012
ITT	14069	7034	7035	7036
Hokusai VTE				
Safety	4118	NA	4118	4122
mITT	4118	NA	4118	4122

NA = not applicable
Source: ISS Appendix 12.6.2, Table S4, U301, Table 14.1.1.5 and U305, Table 14.1.1.5

Exposure to treatment in ENGAGE AF dominates the total exposure, with total subject-years of treatment of >15400 being accumulated on each of edoxaban 30 mg, edoxaban 60 mg and warfarin in this NVAF study. The subjects in ENGAGE AF and Hokusai VTE were enrolled globally. Approximately half of the subjects were recruited from Europe (Eastern and Western). Total exposure to edoxaban is approximately 1.7 times as high in males as in females and more than twice as high in subjects aged over 65 years than in younger subjects. These differences in exposure are largely accounted for by the dominant ENGAGE AF dataset, which comprised a notably older population than the Hokusai VTE set. An appreciable number of patients aged >75 years (edoxaban 6153 vs warfarin 3319) and >85 years (edoxaban 661 vs warfarin 374) were included in the pooled phase III trials. The available exposure to edoxaban is deemed appropriate for the assessment of frequent adverse events in the target population.

The number of overall AEs and patients with at least one AE was initialy unknown as the applicant has only shown disaggregated data of “bleeding” and “non-bleeding AEs”. The applicant provided during the procedure summarized tables of overall adverse events (not disagreggated into “bleeding” and “non-bleeding” adverse events), showing: total adverse events and patients with at least one adverse event; serious and non-serious AEs; related and not related AEs) in the pooled phase III trials and by trial. The rate of patients with TEAEs/SAEs as well as drug-related TEAEs/SAEs favoured edoxaban in most categories, in both pivotal studies, separately and pooled, thus indicating a better safety profile of edoxaban in comparison with warfarin.

Adverse events

Overall adverse events in ENGAGE-AF (NVAF indication): A summary of overall TEAEs is provided in the following table, which includes bleeding events, hepatic events, bone fractures, and malignancies. The rates of patients with TEAE/SAE were lower with edoxaban than with warfarin for most categories and similar for TEAE that caused drug permanent discontinuation.

Table S-02: ENGAGE AF: Overview of All TEAEs (Bleed and Non-Bleed TEAEs), On-treatment Period

	Edoxaban 30 mg (N = 7012)	Edoxaban 60 mg (N = 7002)	Warfarin (N = 7012)
	n (%)		
Subjects With TEAE	5988 (85.5)	6044 (86.2)	6068 (86.5)
Subjects With TESAE	2552 (36.4)	2530 (36.1)	2788 (39.8)
Subjects With Drug-Related TEAE	1654 (23.6)	1974 (28.2)	2251 (32.1)
Subjects With Drug-Related TESAE	230 (3.3)	332 (4.7)	461 (6.6)
Subjects With TEAE Leading to Fatal Outcome	290 (4.1)	311 (4.4)	362 (5.2)
Subjects With TEAE That Caused Study Drug Permanent Discontinuation	889 (12.7)	1059 (15.1)	1054 (15.0)

Source: Table S3.10.13.1

Overall adverse events in Hokusai VTE (VTE treatment indication): A summary of overall TEAEs is provided in the following table, all of which include bleeding events, hepatic events, bone Fractures, malignancies and Investigator-confirmed endpoint events. The rates of patients with TEAE/SAE were lower with edoxaban than with warfarin for most categories and similar for TEAE leading to fatal outcome and TEAT that caused drug permanent discontinuation.

Table S-03: Hokusai VTE: Overview of All TEAEs (Bleed and Non-Bleed TEAEs), On-treatment Period

	Edoxaban (N = 4118)	Warfarin (N = 4122)
Subjects With TEAE	2973 (72.2)	3085 (74.8)
Subjects With SAE	625 (15.2)	698 (16.9)
Subjects With Drug-Related TEAE	1021 (24.8)	1349 (32.7)
Subjects With Drug-Related SAE	106 (2.6)	210 (5.1)
Subjects With TEAE Leading to Fatal Outcome	80 (1.9)	76 (1.8)
Subjects With TEAE That Caused Study Drug Permanent Discontinuation	294 (7.1)	284 (6.9)

Source: U305, Table 14.3.1.152

Bleeding events in ENGAGE-AF (NVAF indication): The risk of bleeding was lower for edoxaban 60 mg than warfarin for all categories. HR were below 1 and p values showed the reductions to be highly statistically significant: major bleeds (HR 0.80, p=0.009), fatal bleeds (HR 0.55, p=0.0059), non-fatal (HR 0.83, p=0.0087), life-threatening (HR 0.51, p < 0.0001), CRNM (HR 0.86, p=0.0001),

major or CRNM (HR 0.86, p < 0.0001), minor (HR 0.84, p=0.0023) and any confirmed bleed (HR 0.87, p < 0.0001). The lower risk of major intracranial hemorrhage (ICH) was particularly marked (HR 0.47, p < 0.0001). A dose-response was apparent for edoxaban, as the rates of adjudicated bleeds were even lower with edoxaban 30 mg than with edoxaban 60 mg, but this advantage with regard to bleeding is offset by the notably lower efficacy of this dose (30 mg OD).

Table S-04: Adjudicated Bleeding Events, Safety Analysis Set – On-Treatment Period (ENGAGE AF)

	Edoxaban 30 mg (N=7002)		Edoxaban 60 mg (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg vs Warfarin		Edoxaban 60 mg vs Warfarin	
Bleeding Category - First Event	n	Event Rate (%/yr)	n	Event Rate (%/yr)	n	Event Rate (%/yr)	HR (95% CI)	p-value	HR (95% CI)	p-value
Major	254	1.61	418	2.75	524	3.43	0.47 (0.406, 0.548)	<0.0001	0.80 (0.707, 0.914)	0.0009
ICH	41	0.26	61	0.39	132	0.85	0.30 (0.215, 0.433)	<0.0001	0.47 (0.344, 0.631)	<0.0001
Non-ICH	214	1.36	359	2.36	398	2.60	0.52 (0.444, 0.619)	<0.0001	0.91 (0.788, 1.049)	0.1906
Fatal	21	0.13	32	0.21	59	0.38	0.35 (0.212, 0.574)	<0.0001	0.55 (0.355, 0.840)	0.0059
ICH[b]	12	0.08	24	0.15	42	0.27	0.28 (0.147, 0.532)	0.0001	0.58 (0.349, 0.951)	0.0312
Non-ICH	9	0.06	8	0.05	17	0.11	0.52 (0.231, 1.162)	0.1105	0.47 (0.204, 1.095)	0.0804
Non-Fatal (Major)	234	1.49	386	2.54	466	3.05	0.49 (0.418, 0.572)	<0.0001	0.83 (0.729, 0.955)	0.0087
ICH[b]	29	0.18	37	0.24	90	0.58	0.32 (0.208, 0.481)	<0.0001	0.41 (0.283, 0.608)	<0.0001
Non-ICH	205	1.30	351	2.31	381	2.49	0.52 (0.443, 0.622)	<0.0001	0.93 (0.803, 1.074)	0.3166
Bleeding Category - First Event	n	Event Rate (%/yr)	n	Event Rate (%/yr)	n	Event Rate (%/yr)	HR (95% CI)	p-value	HR (95% CI)	p-value
Life-Threatening	40	0.25	62	0.40	122	0.78	0.32 (0.225, 0.460)	<0.0001	0.51 (0.377, 0.695)	<0.0001
Clinically Relevant Non-Major	969	6.60	1214	8.67	1396	10.15	0.66 (0.605, 0.712)	<0.0001	0.86 (0.795, 0.927)	0.0001
Major or Clinically Relevant Non-Major	1161	7.97	1528	11.10	1761	13.02	0.62 (0.575, 0.666)	<0.0001	0.86 (0.800, 0.918)	<0.0001
Minor	533	3.52	604	4.12	714	4.89	0.72 (0.647, 0.809)	<0.0001	0.84 (0.758, 0.941)	0.0023
Any Confirmed Bleed	1499	10.68	1865	14.15	2114	16.40	0.66 (0.619, 0.706)	<0.0001	0.87 (0.816, 0.924)	<0.0001

Note: The event rate (%/yr) is calculated as # of events/subject-year exposure.
Note: ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epi/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion. All ICHs reported on the Adjudicated Cerebrovascular and Non-Intracranial bleed eCRF forms confirmed by the Adjudicators are included in ICH counts.
Note: Life-threatening bleeds are defined as all non-fatal ICH and non-fatal non-intracranial major bleeds with hemodynamic compromise requiring intervention.
Note: 'Any Confirmed Bleed' includes those that the adjudicator defined as clinically overt.
Note: A subject can be included in multiple sub-categories. The first event of each category is included in the analysis.
Source: Module 2.7.4 Table 2.1

Major bleeding was lower in most locations in the edoxaban groups compared with the warfarin group. However, there were more Major GI bleeds in the edoxaban 60 mg group than in the warfarin group (1.51% and 1.23% per year, respectively).

Table S-05: Adjudicated Major Bleeding by Treatment Group and Location, Safety Analysis Set – On-Treatment Period

	Edoxaban 30 mg (N=7002)		Edoxaban 60 mg (N=7012)		Warfarin (N=7012)	
	n	Event Rate (%/yr) [a]	n	Event Rate (%/yr) [a]	n	Event Rate (%/yr) [a]
Any Major Bleed	254	1.61	418	2.75	524	3.43
Gastrointestinal	129	0.82	232	1.51	190	1.23
Upper Gastrointestinal	88	0.56	140	0.91	111	0.71
Lower Gastrointestinal	44	0.28	96	0.62	81	0.52
ICH	41	0.26	61	0.39	132	0.85
Intraocular	16	0.10	30	0.19	37	0.24
Macroscopic Hematuria/Urethral	11	0.07	28	0.18	26	0.17
Cutaneous Soft Tissue	15	0.09	19	0.12	57	0.37
Surgical Site	6	0.04	15	0.10	12	0.08
Intra-Articular	7	0.04	8	0.05	25	0.16
Epistaxis	10	0.06	7	0.05	15	0.10
Other	4	0.03	6	0.04	9	0.06
Retroperitoneal	6	0.04	6	0.04	8	0.05
Pericardial	0	0.00	4	0.03	1	0.01
Intramuscular, No Compartment Syndrome	5	0.03	3	0.02	8	0.05
Puncture Site	2	0.01	3	0.02	6	0.04
Vaginal [b]	2	0.03	3	0.05	2	0.03
Hemoptysis	3	0.02	1	0.01	5	0.03
Oral/Pharyngeal	0	0.00	1	0.01	1	0.01
Intramuscular With Compartment Syndrome	0	0.00	0	0.00	3	0.02
Intraspinal	0	0.00	0	0.00	4	0.03

Note: A subject may be counted in multiple subcategories when multiple events occurred.
[a]The event rate is calculated as n/subject-year exposure based on when the subject is at risk.
[b] For gender specific category (vaginal bleeding), the Event Rate is based on the gender specific subject numbers (2718 for edoxaban 30 mg, 2659 for edoxaban 60 mg and 2629 for warfarin).
Source: U301 Table 12.9

Adjudicated CRNM bleeding was also lower in most locations in the edoxaban groups than the warfarin group. However, again there was more CRNM GI bleeds in the edoxaban 60 mg OD group than in the warfarin group (2.17% and 1.31% per year, respectively).

Table S-06: Adjudicated Clinically Relevant Non-Major Bleeding by Treatment Group and Location, Safety Analysis Set – On-Treatment Period

	Edoxaban 30mg (15mg DosAdj) (N=7002)		Edoxaban 60mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)	
	# of events	Event Rate (%/yr)[a]	# of events	Event Rate (%/yr)[a]	# of events	Event Rate (%/yr)[a]
Any Clinically Relevant Non-Major Bleed	969	6.60	1214	8.67	1396	10.15
Gastrointestinal	232	1.49	328	2.17	201	1.31
Upper Gastrointestinal	46	0.29	52	0.34	34	0.22
Lower Gastrointestinal	187	1.19	282	1.86	169	1.10
Cutaneous Soft Tissue	299	1.93	309	2.04	613	4.13
Macroscopic Hematuria/Urethral	178	1.14	262	1.73	219	1.43
Epistaxis	174	1.11	248	1.63	242	1.58
Other	57	0.36	68	0.44	121	0.78
Oral/Pharyngeal	33	0.21	57	0.37	93	0.60
Hemoptysis	48	0.30	56	0.36	70	0.45
Surgical Site	23	0.15	36	0.23	44	0.28
Vaginal[b]	35	0.58	32	0.58	25	0.44
Intramuscular, No Compartment Syndrome	2	0.01	8	0.05	8	0.05
Puncture Site	11	0.07	3	0.02	15	0.10
Intraocular	0	0.00	2	0.01	0	0.00

Abbreviations: DosAdj = Dose Adjusted, yr = year.
[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure. The subject year exposure is the sum, across subjects, of the number of 'at risk' years up to the event or censoring.
[b]: For gender specific category (vaginal bleeding), the event rate is based on the gender specific subject numbers.
Note: A subject may be counted in multiple subcategories when multiple events occurred.
Note: Events are sorted in descending order of frequency in the Edoxaban 60mg group.
Source data: Tables 14.3.1.1 and 14.3.1.13

The benefit in overall major bleeding risk was consistent in most subgroups analysed, particularly in fragile patients with renal insufficiency, age > 75 yrs or body weight < 60 kg. However, there was no difference between edoxaban 60 mg and warfarin with regard to overall major bleeds when warfarin treatment is optimally managed (i.e.: in centers with TTR > 66.4% or in the 4th quartile of INR/TTR), which is the rule in many European centers.

Table S-07: Adjudicated Major Bleeds by Center-Level INR Control: Safety Analysis Set – On-Treatment Period (ENGAGE AF)

	Edoxaban 30 mg (N=7002)		Edoxaban 60 mg (N=7012)		Warfarin (N=7012)		Edoxaban 30 mg vs Warfarin	Edoxaban 60 mg vs Warfarin
	n/M[c]	Event Rate (%/yr)[a]	n/M[c]	Event Rate (%/yr)[a]	n/M[c]	Event Rate (%/yr)[a]	HR (95% CI)[b]	HR (95% CI)[b]
Centers with TTR > 66.4% (Median)	122/3273	1.62	225/3277	3.15	273/3402	3.51	0.47 (0.377, 0.578)	0.90 (0.752, 1.071)
Centers with TTR ≤66.4% (Median)	116/3509	1.49	177/3517	2.33	251/3602	3.35	0.44 (0.357, 0.554)	0.70 (0.576, 0.847)
p-value for the interaction[b]							0.7559	0.0607

Note: Only INRs taken while on study medication and after the first 7 days of study medication are included.
[a]: The event rate is calculated as n/subject-year exposure
[b]: The HR and two-sided CI for pairwise comparisons versus warfarin are based on the Cox regression model with counting process approach including treatment and the two stratification factors as covariates: the dichotomized CHADS2 score and the dichotomized dose-reduction factor. The p-value for interaction is based on the Cox regression model with counting process approach for on treatment including treatment, the two stratification factors as covariates: dichotomized CHADS2 score and dichotomized dose-adjustment factor, subgroup, treatment and subgroup interaction.
[c]: M is the total number of subjects on whom the information is available for that subgroup.
Source: U301. Table 12.12

Table S-08: Adjudicated Major Bleeds by Quartiles of INR TTR, Safety Analysis Set – On Treatment Period

	Edoxaban 30mg (15mg DosAdj) (N=7002)		Edoxaban 60mg (30mg DosAdj) (N=7012)		Warfarin (N=7012)		Edoxaban 30mg (15mg DosAdj) vs Warfarin	Edoxaban 60mg (30mg DosAdj) vs Warfarin
	n/M[c]	Event Rate (%/yr)[a]	n/M[c]	Event Rate (%/yr)[a]	n/M[c]	Event Rate (%/yr)[a]	HR (95% CI)[b]	HR (95% CI)[b]
1st Quartile (<= 57.7%)	48/1406	1.59	78/1413	2.60	102/1406	3.77	0.42 (0.295, 0.587)	0.69 (0.516, 0.932)
2nd Quartile (>57.7% to <= 66.4%)	68/2103	1.43	99/2104	2.15	149/2196	3.12	0.46 (0.348, 0.617)	0.70 (0.540, 0.898)
3rd Quartile (>66.4% to <= 73.9%)	69/1906	1.59	119/1908	2.84	165/2038	3.59	0.45 (0.337, 0.590)	0.80 (0.628, 1.007)
4th Quartile (>73.9%)	53/1367	1.67	106/1369	3.58	108/1364	3.39	0.50 (0.358, 0.692)	1.05 (0.803, 1.371)
p value for the interaction[d]							0.8941	0.1102

Abbreviations: DosAdj = Dose Adjusted, HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, yr = year, INR = International Normalized Ratio, TTR = Time in Therapeutic Range.
[a]: The event rate (%/yr) is calculated as # of events/subject-year exposure. The subject year exposure is the sum, across subjects, of the number of 'at risk' years up to the event or censoring.
[b]: The HR and two-sided CI for pairwise comparisons versus Warfarin are based on the Cox regression model with counting process approach for on-treatment period including treatment and the 2 stratification factors as covariates: the dichotomized CHADS2 score and the dichotomized dose-adjustment factor.
[c]: M is the total number of subjects on whom the information is available for that subgroup.
[d]: The p-value for interaction is based on the Cox regression model with counting process approach for on treatment period including treatment, the 2 stratification factors: dichotomized CHADS2 score and dichotomized dose-adjustment factor, subgroup, treatment and subgroup interaction
Note: All INRs taken while on-treatment, excluding the initial 7 days of study medication are considered.
Source data: Table 14.3.1.23

Bleeding events in HOKUSAI-VTE: In Hokusai VTE, the reduction in bleeding risk was highly significant for Major/CRNM bleeding (8.5% VS. 10.3%; HR 0.81; 95%CI: 0.71-0.94; p=0.0040) but not for major bleeds (1.4% vs. 1.6%; HR: 0.84; 0.59-1.21; p=0.3521). There were fewer critical site Major/CRNM bleeds on edoxaban than warfarin treatment (13 vs. 32), fewer intracranial bleeds in the edoxaban group than the warfarin group (5 vs. 18) and fewer fatal bleeds (2 vs. 10). It seems that the more important benefit of edoxaban, as with other new anticoagulants, is the reduction in ICH.

Table S-09: Adjudicated Bleeding Events, Safety Analysis Set – On-Treatment Period (Hokusai VTE)

Adjudicated Bleeding	Edoxaban (N=4118)	Warfarin (N=4122)
Major/CRNM Bleeding, n (%)	349 (8.5)	423 (10.3)
HR Edoxaban vs. Warfarin (95% CI) [a]	0.81 (0.705, 0.936)	
p-value [a]	0.0040	
Major Bleeding, n (%)	56 (1.4)	66 (1.6)
HR Edoxaban vs. Warfarin (95% CI) [a]	0.84 (0.592, 1.205)	
p-value [a]	0.3521	
Fatal, n (%) [b]	2 (<0.1)	10 (0.2)
CRNM Bleeding, n (%)	298 (7.2)	368 (8.9)
Nuisance Bleeding, n (%)	663 (16.1)	787 (19.1)
All Bleeding, n (%)	895 (21.7)	1056 (25.6)

[a] The HR (versus warfarin) and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes, no), p-value α =0.01 [two-sided].
[b] Of the 2 fatal bleeding events that occurred in the subjects on the edoxaban arm, neither had yet received edoxaban study drug (ie, event occurred during the initial heparin treatment)
Source: Module 2.7.4 Table 2.7.

On the contrary, there was an increase in major/CRNMB associated with a fall in hemoglobin > 2 g/dL (40 vs. 33) and needing a transfusion ≥ 2 units (28 vs. 22), which was mainly due to an increase in "mucosal bleedings", including major/CRNM gastrointestinal bleedings (2.4% in edoxaban group versus 2.3% of warfarin group) and vaginal bleeds (4.6% in the edoxaban group versus 3.2% in the warfarin group).

Table S-10: Adjudicated Major or Clinically Relevant Non-Major Bleeding Event Characteristics: Safety Analysis Set – On-Treatment Period (Hokusai VTE)

Adjudicated Major or CRNM Bleeding	Edoxaban 60 mg (N=4118) n (%)	Warfarin (N=4122) n (%)
Event Characteristic [a]		
Fatal Bleed	2 (<0.1)	10 (0.2)
Clinically Overt	349 (8.5)	423 (10.3)
Fall in Hemoglobin ≥2 g/dL	40 (1.0)	33 (0.8)
Transfusions ≥2 units	28 (0.7)	22 (0.5)
Hemodynamic Compromise	1 (<0.1)	6 (0.1)
Requiring Surgery	3 (<0.1)	2 (<0.1)

Source: U305, Table 12.8

When all adjudicated confirmed bleeds were considered, gastrointestinal bleeds were recorded for 4.2% and 3.6% in the edoxaban and warfarin groups, respectively, with the majority of these affecting the lower GI tract (3.4% and 3.1% of subjects in each treatment group). The incidence of all vaginal bleeds was 9.0% for edoxaban and 7.1% for warfarin. The increase in GI bleedings with edoxaban 60 mg OD was consistent with the increase in risk of GI bleeding seen in the ENGAGE-AF study and the results obtained with other NOAC. The higher rate of occurrence of vaginal bleeds (mainly menorrhagia) in this study compared with ENGAGE AF may be a reflection of the younger age of the population. The benefit in major bleeding risk was consistent in most subgroups analysed, particularly in fragile patients with renal insufficiency, age > 75 yrs or body weight < 60 kg. However, there was no difference between edoxaban 60 mg and warfarin with regard to MB/CRNMB bleeds at centres with TTR > 60% (HR: 0.91; 95% CI: 0.770, 1.077), which is the rule in many European centers, and in centers with TTR >70.41% (HR: 1.06; 95%CI: 0.79 to 1.44).

Table S-11: Primary Safety Endpoint (Adjudicated Major/CRNM Bleeding) by Center Level Percent Time in Therapeutic Range (TTR), Safety Analysis Set, On-Treatment Study Period

	Edoxaban m/M (%)	Warfarin m/M (%)	Edoxaban vs. Warfarin HR (95% CI) [a]
Adjudicated Major or CRNM Bleeding			
Centers with TTR < 60%	83/1199 (6.9)	139/1271 (10.9)	0.61 (0.468, 0.805)
Centers with TTR >= 60%	265/2876 (9.2)	284/2845 (10.0)	0.91 (0.770, 1.077)
Centers with TTR < 25th Percentile (55.82%)	47/713 (6.6)	92/748 (12.3)	0.52 (0.366, 0.738)
Centers with TTR >= 25th to < 50th Percentile (64.03%)	117/1329 (8.8)	140/1291 (10.8)	0.80 (0.627, 1.024)
Centers with TTR >= 50th to < 75th Percentile (70.41%)	95/1115 (8.5)	109/1180 (9.2)	0.90 (0.686, 1.189)
Centers with TTR >= 75th Percentile	89/918 (9.7)	82/897 (9.1)	1.06 (0.786, 1.439)

Abbreviations: CI = Confidence Interval, CRNM = Clinically Relevant Non Major, HR = Hazard Ratio, M = number of subjects Analysis Set for each individual subgroup, m = number of subjects in each individual subgroup with an event, TTR = Time in Therapeutic Range.
[a] The HR and two-sided CI are based on the Cox proportional hazards regression model including treatment and the following randomization stratification factors as covariates: presenting diagnosis (PE with or without DVT, DVT only), baseline risk factors (temporary factors, all others), and the need for 30 mg edoxaban/edoxaban placebo dose at randomization (yes, no).

Ancillary analyses of bleeding events across studies

Intracranial hemorrhage (ICH): Ancillary analyses provided by the Applicant showed that the benefits of edoxaban versus warfarin in ICH were consistent in the worst case (high TTR and Western European population). It was consistent with results observed with other NOACs. The class benefit seems to be driven by an intrinsically risk of ICH with VKAs, which is seen even at high TTR. The

absolute benefit of edoxaban versus warfarin is difficult to establish due to low number of events, but could be around 3 ICH avoided per 1,000 patients treated per year in the European AF population (edoxaban 3 ICH vs warfarin 6 ICH/1,000/yr). In the overall ENGAGE AF study population, the projected benefit is around 5 ICH per 1,000 patients treated (edoxaban 4 ICH vs. warfarin 9 ICH/1,000/yr). In the overall Hokusai VTE study population, the absolute benefit of edoxaban versus warfarin in ICH may be similar, around 3 ICH avoided per 1,000 patients treated for acute VTE (edoxaban 1 ICH/1,000 vs. warfarin 4 ICH/1,000), but difficult to establish due to low number of events and shorter durations of treatment (usually lasting less than 1 year).

Baseline characteristics of patients with major bleeding: Patients who experienced major bleedings had older age, higher proportion of renal impairment and concomitant ASA use than patients without major bleedings. These patients were more represented in ENGAGE AF than in Hokusai VTE. In both ENGAGE AF and Hokusai VTE, demographic characteristics in subjects with adjudicated major bleeds were generally comparable between treatment groups, except for concomitant aspirin use in Hokusai VTE which was higher in the edoxaban than the warfarin group.

Clinical management of major bleeding: In ENGAGE AF the rate of patients needing hospitalization for major bleeding was less frequent in edoxaban than in warfarin in ENGAGE AF (1.54%/yr vs 1.81%/yr), transfusion ≥ 2 units was similar (1.05%/yr in both groups), as well as need for surgery (0.20%/yr vs 0.29%/yr). Hospitalization with intensive care was lower with edoxaban (0.7%/yr vs 1.4%/yr). In Hokusai VTE, the rate of patients requiring hospitalization for major bleeding (1.2% vs. 1.2%), transfusion ≥ 2 units (0.7% vs 0.5%), need for surgery (<0.1 vs < 0.1% and hospitalization with inensive care unit (0.3 vs 0.4%) was generally comparable between edoxaban and warfarin treatment groups.

Major bleeding outcomes: there was lower 30-day all-cause mortality after major bleeding in the edoxaban 60-mg than the warfarin group (ENGAGE AF: 0.5% vs. 1.0%; Hokusai VTE: 0.1% vs. 0.3%). Major bleed outcome of resolved with sequelae was lower with edoxaban than with warfarin in ENGAGE AF (0.7% vs 1.2%), but not in Hokusai VTE (0.2% vs. 0.1%).

Major and CRNM GI bleeding: In ENGAGE AF, edoxaban 60-mg subjects had a higher rate of Major/CRNM GI bleed than warfarin subjects (3.54%/yr vs. 2.42%/yr), including those requiring hospitalization (1.61%/yr vs. 1.27%/yr) and transfusion (0.97%/yr vs. 0.84%/yr). However, the more severe bleedings, resulting in death of hospitalisation in intensive care unit, are more often reported with warfarin than with edoxaban. The increase in GI bleedings (HR≈ 1.46) mimic those reported with dabigatran 150 mg BID in RE-LY study (HR: 1.52) and rivaroxaban 20 mg OD in ROCKET AF (HR ≈ 1.26) for CRNM GI bleed. Further SmPC changes in sections 4.4 and 4.8 have been included to warn about this increase in risk.

Common non-bleeding TEAEs (pooled Phase III trials): Comparison of total edoxaban and edoxaban 60 mg with warfarin revealed only small differences in incidence for the majority of events (Pooled Phase 3 studies). However, anaemia was reported for a higher proportion of edoxaban subjects (4.2%) than warfarin subjects (2.9%). Gastrointestinal TEAEs (diarrhoea, nausea, gastritis and dyspepsia) was also reported for a higher proportion of edoxaban subjects than warfarin subjects (6.3% vs 6% for diarrhoea; 3.4% vs. 2.8% for nausea; 2.1% vs. 1.9% for gastritis and 1.8% vs. 1.6% for dyspepsia, respectively). The most notable difference was for INR increased which was, as anticipated, much more common on warfarin than edoxaban treatment (4.7% compared with 0.5%).

Treatment-related non-bleeding TEAEs: In the Pooled Phase 3 studies, treatment-related non-bleeding TEAEs were recorded for 11.6% of the edoxaban 60 mg group and 14.6% of the

warfarin group over the modified on-treatment period. “Anaemia” and “hepatic enzyme increased” was more frequent in edoxaban 60 mg group than in the edoxaban 30 mg group or warfarin group (anemia: 0.9% versus 0.8% and 0.6%) (hepatic enzyme increased: 0.8% vs. 0.2% and 0.6%).

Table S-13: Common Treatment-related Non-Bleeding TEAEs in ≥0.5% of Subjects in Pooled ENGAGE AF and Hokusai VTE Studies: Safety Analysis Set; Modified On-Treatment Period

	Edoxaban Total (N=18010) n (%)	Edoxaban 30 mg (N=7002) n (%)	Edoxaban 60 mg (N=11008) n (%)	Warfarin (N=11010) n (%)
Blood and Lymphatic System Disorders	239 (1.3)	86 (1.2)	153 (1.4)	117 (1.1)
Anaemia	156 (0.9)	57 (0.8)	99 (0.9)	62 (0.6)
Gastrointestinal Disorders	358 (2.0)	139 (2.0)	219 (2.0)	211 (1.9)
Diarrhoea	69 (0.4)	32 (0.5)	37 (0.3)	38 (0.3)
Investigations	600 (3.3)	204 (2.9)	396 (3.6)	781 (7.1)
Hepatic Enzyme Increased	101 (0.6)	16 (0.2)	85 (0.8)	67 (0.6)
Creatinine Renal Clearance Decreased	86 (0.5)	40 (0.6)	46 (0.4)	33 (0.3)
International Normalised Ratio Increased	46 (0.3)	15 (0.2)	31 (0.3)	450 (4.1)

Note: Investigator-confirmed bleeding events and efficacy endpoint events such as DVT, PE, MI, SEE, and stroke are excluded. If PT is death, the AE is also excluded.
Note: Table includes PTs with frequency of ≥0.5% in at least one group. SOC represents all TEAE counts for that SOC, including PTs that were reported by <0.5% of subjects.
Source: ISS Appendix 12.6.2, Table S16

Hepatic safety: There was a small imbalance against edoxaban 60 mg versus warfarin (pooled phase 3 studies) in: a) the cases of hyperbilirubinaemia (edoxaban 60 mg 0.3% vs warfarin 0.1%); b) in concurrent elevation of ALT or AST ≥ 3 x ULN & Total Bilirubin ≥ 2 x ULN (edoxaban 60 mg 0.4% vs warfarin 0.3%, corresponding to 43 and 29 cases, respectively; Pooled Phase 3 trials); c) In the percentage of subjects in the edoxaban 60 mg group versus warfarin that were characterized by an independent hepatologist as having a hepatocellular injury (1.1% vs. 1.0%, respectively); d) In the percentage of cases of liver injury possible/probable related to study drug [(edoxaban 60 mg 0.4% (48 of 11008 subjects) versus warfarin 0.3% (30 of 11010 subjects)]; e) in the percentage of liver injury adjudicated as severe (edoxaban 60 mg 0.4% vs warfarin 0.3%); f) and in the number of Hy’s law cases adjudicated as severe hepatocellular liver injury possibly/probably related to study drug (edoxaban any dose 2 vs warfarin 1), which is of concern. A similar concern has been arisen with other factor Xa inhibitors. A definitive association between these novel oral factor Xa inhibitors and risk of hepatic injury has not been definitively confirmed.

Hepatic events: All suspected hepatic events were blindly adjudicated by two hepatologists independently. There were no hepatic events adjudicated as “unassessable”. Of all hepatic events sent for adjudication, there were 4 cases that the adjudicators had insufficient data for severity only; nature of liver injury and causality were determined for all cases. In both ENGAGE AF and Hokusai VTE, an independent adjudication process by expert hepatologists was established to provide an unbiased and systematic assessment of individual cases in a blinded fashion. There were 82 concurrent combination abnormalities (69 from ENGAGE AF: 22 on edoxaban 30 mg, 28 on edoxaban 60 mg, 19 on warfarin; and 11 from Hokusai VTE: 7 on edoxaban 60 mg and 4 on warfarin). From independent adjudication using the CEC Charter definition (consistent with the FDA’s DILI Guidance) and blinded to study drug, there were 8 adjudicated as having hepatocellular injury and probably/possibly related, of which 5 met Hy’s Rule criteria (1 edoxaban 30 mg, 3 edoxaban 60 mg, 2 warfarin-treated). There were 3 additional cases (2 edoxaban 30 mg, 1 edoxaban 60 mg, 0 warfarin) assessed as related per investigator (assessed as unlikely/unrelated per adjudication), all which revealed confounding factors. When adding these 3 additional cases to those already adjudicated by the independent hepatologists, it would result in 3 total Hy's law cases with edoxaban

30 mg, 3 total cases with edoxaban 60 mg and 2 total cases with warfarin. Therefore, the addition of these cases do not change the overall conclusion about hepatic safety of edoxaban, as the overall number of Hy's law cases would still be insufficient for a meaningful conclusion. The observed discrepancies between the investigator-reported and hepatologist-adjudicated Hy's law cases can be judged as within normal variability expected in these kind of assessments, where hepatologists tend to be more strict than investigators by applying pre-defined criteria for Hy's law cases. In addition, both pivotal studies were declared GCP compliant. Therefore, the validity of the adjudication process by the hepatologists was endorsed. There was a numerical excess of adjudicated hepatic events in the edoxaban arm compared with warfarin (15 versus 6) when coadministered with macrolides, with associated event rates of 1.31%/year and 0.53%/year. However, the number of subjects receiving macrolides was low (edoxaban 60 mg 459 subjects versus warfarin 451 subjects). Although the hazard ratio for those taking macrolides was in favour of warfarin, the 95% CI was very wide and included unity, while the p-value for interaction was not significant. The Applicant considered that the imbalance between the two groups (edoxaban 60 mg and warfarin) may be a chance finding, to which the CHMP agreed. The Applicant has not performed specific studies on the effect of edoxaban on mitochondrial extracts. The rationale for this was the lack of evidence from the nonclinical studies, specifically the long-term toxicology studies in which there were no apparent hepatotoxicity-related responses associated with this test compound. The Applicant shared the draft study protocol of the mitochondrial inhibition assay that was endorsed by the CHMP.
The liver function tests (LFTs) evaluated in the various single and repeated dose toxicity studies were consistently not positive for toxicologically significant LFT elevations and histopathology examinations. In addition, female rats at the doses that showed even higher edoxaban exposure did not present liver lesions. Regarding the observed secondary liver degeneration/necrosis in a cohort of dead or moribund/sacrificed male rats in the high dose group in the carcinogenicity study, the Applicant believed that it is associated with well-studied phenomena that hepatocytes are particularly vulnerable to necrotizing insults such as severe metabolic disturbances including hypoxia. Hepatocellular lesion in the high-dose male group is considered related to the moribund condition of animals given 600/400 mg/kg/day which clearly exceeded the MTD. Therefore, the Applicant concluded that hepatocellular finding observed in the rat carcinogenicity study is of no toxicological significance and was not considered relevant to human, which was agreed by the CHMP.

There were no concurrent combination abnormality cases for which a biopsy was performed in ENGAGE AF. In Hokusai VTE, two subjects with combination abnormalities had a liver biopsy, one edoxaban-treated and one warfarin-treated subject. The edoxaban patient had a history of chronic cholecystitis that, on Day 47 of study had adenocarcinoma in the liver tissue. This case was classified as severe cholestasis, unlikely/unrelated to study drug per CEC hepatologists adjudication. The additional case occurred during warfarin treatment. After six months of treatment with warfarin, the patient developed liver enzyme elevations that progressed to fulminant hepatitis requiring liver transplant (post-operative fatality) while off study drug. This event was adjudicated as severe hepatocellular liver injury, probably/possibly related to study drug and meeting Hy’s Rule based on the CEC hepatologists adjudication. Therefore, the very scarce data on liver biopsies were insufficient to draw any meaningful conclusion, but did not raise any major concern on edoxaban.

SmPC changes related to liver safety: It was agreed to add to the SmPC a recommendation of use with caution in patients with mild or moderate hepatic impairment and use with caution in patients with elevated liver enzymes ALT/AST > 2xULN or total bilirubin ≥ 1.5xULN and a recommendation to perform liver function testing prior to initiation of treatment. The Applicant also agreed to add that periodic monitoring of hepatic function is recommended for patients on edoxaban treatment beyond 1 year.

Malignancies and bone fractures: Overall the reporting frequency of events of neoplasms was low and no significant imbalance was observed between groups in both pivotal studies. The percentage of subjects with new bone fractures was comparable among treatment groups in both pivotal studies. The most common bone fracture was hip/pelvis/proximal.

MACE: In ENGAGE, MACE rates and its components (stroke, MI, fatal bleeding and CV death) were consistently lower with edoxaban 60 mg than with warfarin. In HOKUSAI-VTE, MI was numerically more frequent with edoxaban (60 mg/d standard dose) compared to warfarin. Furthermore, overall MACE was numerically increased with edoxaban as were the rare individual events CV death, fatal ischaemic stroke and SEE. Additional analyses showed that the difference in MI between edoxaban and warfarin was numerically larger in the CAD subpopulation (2.9% vs. 0.9%) than in the total study population (0.5% vs. 0.3%), but due to the low number of events (6 vs. 2) firm conclusions are not possible. In the AF study no such imbalance disfavouring edoxaban was observed (edoxaban 60 mg 72 MI vs. warfarin 85 MI in the CAD subpopulation). Mechanistic data supporting or rebutting the assumption that edoxaban might favour development of MI in CAD patients compared to warfarin are not available. In summary, the CHMP agreed that there was no need to exclude CAD patients from treatment with edoxaban.

Other adverse events of interest: For some SMQs, including acute renal failure (both pivotal studies), acute polyneuropathies (ENGAGE-AF), anaphylactic reactions (HOKUSAI-VTE) and interstitial lung disease (ILD) (HOKUSAI-VTE), a small increase is seen for edoxaban in comparison with warfarin:

a) Acute renal failure: the imbalance is noticed in both edoxaban clinical trials with the edoxaban 60 mg OD dose. There is no evidence that edoxaban may be associated to a worsening of acute renal failure or nephrotoxic effect. However, there is evidence that patients with severe bleeding with edoxaban may experience worsening CrCL or even acute renal failure in the overall data from clinical trials and post-marketing experience. This finding has been included in section 4.8 of the SmPC;

b) Acute polyneuropathies: An imbalance has been reported on the incidence of acute polyneuropathies with edoxaban in the ENGAGE-AF study. There was a low incidence of GBS/ALS throughout the edoxaban program with only 1 (serious) ALS case and no GBS case during edoxaban treatment/treatment + 30 days. The small imbalance in the Acute Polyneuropathy Clinical Event group in ENGAGE AF was primarily driven by the PT ‘polyneuropathy’, which is not specific for ALS/GBS as the majority of the reported cases had confounding etiological factors and were unrelated to study medication and the differences are thus not suggestive of neurologic toxicity. No cases for GBS/ALS were found from post marketing data up to 30 June 2014;

c) Allergic reactions: in HOKUSAI-VTE the numbers of anaphylactic reactions on-treament were higher with edoxaban than with warfarin (230 vs 197) as well as the cases of angioedema (48 vs. 38). There are some allergic reactions (hypersensitivity, allergic oedema and anaphylaxis) during pivotal trials with at least possible/probable relationship with edoxaban (Anaphylactic reactions: Hokusai-VTE-61423070, Hokusai-VTE-35004296, ENGAGE-AF-12060006; Angioedema: Hokusai-VTE-10680073, Hokusai-VTE-401115473, ENGAGE-AF-42100001; Severe cutaneous reaction: ENGAGE-AF-10070071) and a post-marketing case of eyelid oedema/angioedema (DSJ-2013-20575). These cases are within reported with other direct oral factor Xa inhibitors (Xarelto, Eliquis) and have been included in section 4.8 of the SmPC in alignment with these compounds. In addition, "pruritus" (common) and "urticaria" (uncommon) were reported with edoxaban in pivotal trials and have been added to "rash" in the subsection of "Skin and Subcutaneous Tissue Disorders" with the said frequencies.

d) Gastrointestinal symptoms: Nausea (common) has been included in section 4.8 of the SmPC, as it was reported as related to edoxaban by the investigators in both pivotal studies. The findings in

both pivotal studies for the remaining GI adverse events (gastritis, dyspepsia, diarrhoea) are not as consistent as for nausea and it is agreed not to include them in section 4.8 of the SmPC.

Serious adverse events and deaths

Deaths: The overall death rate was lowest for edoxaban 60 mg (8.0%) and highest for edoxaban 30 mg (10.4%), with the rate for warfarin being 8.6% (pool analysis of Phase 3 Trials). The majority of deaths were classed as cardiovascular; the rate of cardiovascular deaths was lowest for edoxaban 60 mg (4.6%) and highest for edoxaban 30 mg (6.8%), with the rate for warfarin being 5.1%. The edoxaban 30 mg group included only subjects from ENGAGE AF. The death rate in edoxaban 30 mg was largely driven by ischemic events (suggesting a lack of effective anticoagulation). However, there was heterogeneity in the causes of death in both pivotal studies.

Table S-22: Adjudicated Deaths in Pooled ENGAGE AF and Hokusai VTE Studies: Safety Analysis Set; Overall Study Period

	Edoxaban Total (N=18010) n (%)	Edoxaban 30 mg (N=7002) n (%)	Edoxaban 60 mg (N=11008) n (%)	Warfarin (N=11010) n (%)
Total	1613 (9.0)	731 (10.4)	882 (8.0)	952 (8.6)
Cardiovascular Deaths	984 (5.5)	478 (6.8)	506 (4.6)	559 (5.1)
Non-Hemorrhagic Stroke	98 (0.5)	53 (0.8)	45 (0.4)	47 (0.4)
Systemic Embolic Event	4 (<0.1)	4 (<0.1)	0	3 (<0.1)
Myocardial Infarction	37 (0.2)	20 (0.3)	17 (0.2)	19 (0.2)
Pulmonary Embolism	12 (<0.1)	8 (0.1)	4 (<0.1)	7 (<0.1)
Sudden Death	467 (2.6)	224 (3.2)	243 (2.2)	263 (2.4)
Other Cardiac Death	366 (2.0)	169 (2.4)	197 (1.8)	220 (2.0)
Bleeding	115 (0.6)	54 (0.8)	61 (0.6)	110 (1.0)
Other Deaths	514 (2.9)	199 (2.8)	315 (2.9)	283 (2.6)
Malignancy	230 (1.3)	90 (1.3)	140 (1.3)	136 (1.2)
Infection	182 (1.0)	64 (0.9)	118 (1.1)	91 (0.8)
Other Death	102 (0.6)	45 (0.6)	57 (0.5)	56 (0.5)

Source: ISS Appendix 12.6.2, Table S23

In ENGAGE-AF, a positive trend was found in favour of edoxaban 60 mg for all-cause death and CV death on-treatment and overall study period, mainly at expenses of lower CV death rates (7.5% vs. 8.7%).

Table S-23: Adjudicated Deaths – mITT/Safety Analysis Set, Modified On- Treatment and Overall (ENGAGE AF)

	Edoxaban 30 mg (N=7002) n (%)		Edoxaban 60 mg (N=7012) n (%)		Warfarin (N=7012) n (%)	
	Modified On-Treatment	Overall	Modified On-Treatment	Overall	Modified On-Treatment	Overall
Total	386 (5.5)	731 (10.4)	379 (5.4)	769 (11.0)	432 (6.2)	836 (11.9)
Primary Cause						
Cardiovascular	307 (4.4)	522 (7.5)	296 (4.2)	527 (7.5)	348 (6.2)	608 (8.7)
Sudden/Unwitnessed Death	159 (2.3)	229 (3.3)	167 (2.4)	246 (3.5)	179 (2.6)	269 (3.8)
Congestive Heart Failure/Cardiogenic Shock	59 (0.8)	117 (1.7)	51 (0.7)	129 (1.8)	62 (0.9)	142 (2.0)
Other Cardiovascular	8 (0.1)	48 (0.7)	11 (0.2)	45 (0.6)	6 (<0.1)	50 (0.7)
Ischemic Stroke	38 (0.5)	55 (0.8)	22 (0.3)	43 (0.6)	26 (0.4)	47 (0.7)
Intracranial Hemorrhage	10 (0.1)	16 (0.2)	25 (0.4)	30 (0.4)	44 (0.6)	53 (0.8)
Dysrhythmia	12 (0.2)	20 (0.3)	11 (0.2)	16 (0.2)	9 (0.1)	15 (0.2)
Atherosclerotic Vascular Disease	4 (<0.1)	11 (0.2)	3 (<0.1)	5 (<0.1)	5 (<0.1)	8 (0.1)
Directly Related to CABG or Percutaneous Coronary Intervention	2 (<0.1)	3 (<0.1)	3 (<0.1)	5 (<0.1)	1 (<0.1)	4 (<0.1)
Non-Intracranial Hemorrhage	6 (<0.1)	9 (0.1)	3 (<0.1)	5 (<0.1)	10 (0.1)	12 (0.2)
Pulmonary Embolism	4 (<0.1)	9 (0.1)	0	3 (<0.1)	4 (<0.1)	5 (<0.1)
Systemic Arterial Embolic Event	5 (<0.1)	5 (<0.1)	0	0	2 (<0.1)	3 (<0.1)
Malignancies	23 (0.3)	93 (1.3)	25 (0.4)	94 (1.3)	23 (0.3)	84 (1.2)
Malignancies Clin Evid Before Rand	0	0	0	0	1 (<0.1)	2 (<0.1)
Malignancies Clin Evid After Rand	23 (0.3)	93 (1.3)	25 (0.4)	94 (1.3)	22 (0.3)	82 (1.2)
Non-CV/Non-Malignancy	56 (0.8)	116 (1.7)	58 (0.8)	148 (2.1)	61 (0.9)	144 (2.1)
Infection	30 (0.4)	69 (1.0)	37 (0.5)	94 (1.3)	42 (0.6)	92 (1.3)
Other Non-Cardiovascular/ Non-Malignancy	16 (0.2)	30 (0.4)	14 (0.2)	36 (0.5)	10 (0.1)	30 (0.4)
Accidental/Trauma	4 (<0.1)	5 (<0.1)	3 (<0.1)	10 (0.1)	6 (<0.1)	10 (0.1)
Renal	5 (<0.1)	9 (0.1)	1 (<0.1)	4 (<0.1)	2 (<0.1)	8 (0.1)
Suicide	1 (<0.1)	1 (<0.1)	2 (<0.1)	3 (<0.1)	0	1 (<0.1)
Hepatobiliary	0	2 (<0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)	3 (<0.1)

Source: U301, Table 14.2.6.2 and Table S2.6.15.1

On the contrary, in HOKUSAI-VTE, numerically more deaths were reported with edoxaban than with warfarin on-treatment + 30 days (79 vs 71) and during overall study period (136 vs. 130), including an imbalance in CV deaths on-treatment + 30 days (12 vs 6) and death due to infectious disease in the overall study period (25 vs 12). Among the latter, lung infections constituted a large proportion. These pneumonias were not related to PE but were due to the reduced general condition of the study patients with high co-morbidity. The most likely explanation for the observed difference is therefore a chance finding. For the numerically increased CV events in the VTE study, a causal relationship is difficult to delineate from the individual events but some uncertainty remains. It is reassuring that there is no hint for a higher rate with edoxaban of recurrent PEs or deaths in patients with a more severe index event, i.e. in patients with potentially higher risk for a (severe) recurrent VTE. The all-cause mortality in the safety data set is listed in the SmPC, which is endorsed. Although the patient population is different, it is reassuring that mortality was numerically decreased with edoxaban in the ENGAGE AF trial.

Table S-24: Adjudicated Primary Cause of Death - Safety Analysis Set, Treatment + 30 days and Overall Study Period (Hokusai VTE)

Cause of Death	Edoxaban 60 mg (N=4118) n (%)	Warfarin (N=4122) n(%)	Edoxaban 60 mg (N=4118) n (%)	Warfarin (N=4122) n(%)
	Treatment + 30 days		Overall	
All Causes	79 (1.9)	71 (1.7)	136 (3.3)	130 (3.2)
VTE-Related Death	18 (0.4)	16 (0.4)	27 (0.7)	28 (0.7)
PE	3 (<0.1)	2 (<0.1)	4 (>0.1)	3 (<0.1)
Unexplained Death (and VTE cannot be ruled out)	15 (0.4)	14 (0.3)	23 (0.6)	25 (0.6)
Cardiovascular Death	12 (0.3)	6 (0.1)	15 (0.4)	13 (0.3)
MI	2 (<0.1)	2 (<0.1)	2 (<0.1)	2 (<0.1)
Ischemic stroke	4 (<0.1)	1 (<0.1)	6 (0.1)	3 (<0.1)
SEE	0	0	0	0
Other Cardiac Death	6 (0.1)	3 (<0.1)	7 (0.2)	8 (0.2)
Other Known Cause	49 (1.2)	49 (1.2)	94 (2.3)	89 (2.2)
Cancer	22 (0.5)	28 (0.7)	51 (1.2)	59 (1.4)
Bleeding (including Hemorrhagic Stroke)	2 (<0.1)	9 (0.2)	6 (0.1)	10 (0.2)
Infectious Disease	17 (0.4)	8 (0.2)	25 (0.6)	12 (0.3)
Other	8 (0.2)	4 <0.1)	12 (0.3)	8 (0.2)

Note: Deaths are included in the Overall Study Period if they occurred on or after the date of first dose of any study drug. All deaths that occurred prior to last study follow-up contact are considered for the Overall Study Period.
Note: Percentages are based on N, the total number of subjects.
Source: U305. Table 12.21 and Table 14.2.6.2

Finally, ancillary analyses of deaths in both pivotal studies show that all-cause mortality and CV mortality are not reduced by edoxaban 60 mg as compared with warfarin, particularly in centres above the median TTR and in original regions with a good quality of warfarin anticoagulation, like in Western Europe. In the overall European population (EEA + Switzerland), the point estimates slightly favour edoxaban in ENGAGE-AF and warfarin in Hokusai VTE, but the CIs for the HRs are wide and no significant differences in all-cause mortality or CV mortality are expected between edoxaban 60 mg and warfarin in AF or treatment of VTE in Europe.

Other serious adverse events: The serious adverse events reported in edoxaban 60 mg and warfarin groups were generally well balanced. Cardiac disorders SOC including atrial fibrillation and cardiac failure were less frequent TESAEs on edoxaban 60 mg than warfarin. The edoxaban 30 mg group had a higher frequency of events of the Cardiac system, particularly of atrial fibrillation, as previously noted for all TEAEs, and cardiac failure. TESAEs of anaemia and iron-deficiency anaemia were more frequent with edoxaban 60 mg (and edoxaban 30 mg) than warfarin treatment. TESAEs of gastritis were also more frequent with edoxaban 60 mg than warfarin treatment (24 vs 11).

Laboratory findings

There was a clear increase with edoxaban versus warfarin in the number of patients with Hb drop from baseline >2 g/dl in the ENGAGE-AF study (edoxaban 20.6% vs. warfarin 16.4%) (Table 3.2 of the Summary of Clinical Safety). The imbalance is also apparent, although of a lesser magnitude, in the HOKUSAI VTE study (6.2% vs 4.2%). From both studies, approximately half of the imbalance in subjects with hemoglobin drop > 2 g/dL is accounted for by increased mucosal bleeds in edoxaban subjects compared with warfarin, which is consistent with the pathophysiology of mucosal bleeding that is associated with higher volume loss over time (compared with ICH). From ENGAGE AF, bleed events with very high volume loss (transfusion ≥ 4 units, ≥ 5 g/dL adjusted hemoglobin loss) were lower (total number of subjects and percentage) in edoxaban 60-mg than warfarin subjects.

No imbalances in creatinine, platelet count or leucocyte count are evident in the pooled phase III studies. Hepatic events have been assessed in previous sections.

Safety in special populations

Non-bleeding adverse events in special populations: Post-hoc analyses of non-bleeding adverse events in subpopulations (by gender, age, race, renal or hepatic impairment, pregnancy and lactation) of pooled phase III trials, with some methodological limitations (e.g.: exclusion of some subpopulations in pivotal trials, low numbers and post-hoc nature of the analysis) did not reveal any safety concern in a particular population.

Elderly: The following table provides a summary of the number of older subjects included in PK, controlled and non-controlled clinical studies bv age ranges.

Table S-25. Summary of Older subjects included in Clinical studies

Clinical studies	Age 65-74 yrs (N Older/N Total)	Age 75-84 yrs (N Older/N Total)	Age≥85 yrs (N Older/N Total)
PK studies [a]	52/1427	2/1427	0/1427
Controlled Studies [b]	10576/34401	9606/34401	1096/34401
Non Controlled Studies [c]	184/662	63/662	5/662
Total studies	**10812**/36490	**9671**/36490	**1101**/36490

[a]: PK Trials include all completed Phase 1 studies.
[b]: Controlled studies include: PRT018, J225, J226, U301 (ENGAGE AF), U305 (Hokusai VTE), PRT011, J302, J303, J04, and J209.
[c]: Uncontrolled studies include J03, J05, and PRT-007.

Source: Table T-Age-pooled

Events of special interest in the elderly: The following tables show non-bleedings AEs of interest in the elderly, by age range, separately for each pivotal study. Data pooling was not deemed appropriate due to differences in study designs, patients' characteristics and different treatment durations. Bleeding events by age subgroups were already included in subgroup analyses shown previously in the corresponding safety section and therefore are not presented here. As anticipated, regarless of treatment group, there was a higher rate of events in the older age groups compared with the younger age groups, but edoxaban compared favourably to warfarin for most types of adverse events and age groups. The exception is the numerical increase in SAEs in Hokusai VTE study in patients 85 years, which is due to increased number of infections (see also assessment of Q143). However, this increase was not seen in ENGAGE-AF and is hampered by the low number of subjects (n= 74) and events (27). Therefore, it is likely to be a chance finding.

Table S-26: Overview of Non-Bleeding TEAEs by Age, Safety Analysis Set; Modified On-Treatment Period: ENGAGE AF

	Edoxaban 30 mg (N = 7002) n (%)				Edoxaban 60 mg (N = 7012) n (%)				Warfarin (N = 7012) n (%)			
	< 65 y M = 1784	65-74y M = 2429	75-84 y M = 2502	≥ 85 y M = 287	< 65 y M = 1830	65-74 y (M = 2344	75-84 y M = 2528	≥ 85 y M = 310	< 65 y M = 1869	65-74 y M = 2338	75-84 y M = 2508	≥ 85 y M = 297
Total with AEs	1434 (80.4)	2046 (84.2)	2179 (87.1)	254 (88.5)	1480 (80.9)	1951 (83.2)	2204 (87.2)	286 (92.3)	1493 (79.9)	1954 (83.6)	2196 (87.6)	280 (94.3)
Serious AEs – Total Subjects	578 (32.4)	960 (39.5)	1030 (41.2)	128 (44.6)	563 (30.8)	855 (36.5)	1012 (40.0)	141 (45.5)	622 (33.3)	901 (38.5)	1089 (43.4)	151 (50.8)
- Fatal	65 (3.6)	123 (5.1)	124 (5.0)	28 (9.8)	76 (4.2)	116 (4.9)	141 (5.6)	25 (8.1)	80 (4.3)	106 (4.5)	159 (6.3)	34 (11.4)
- Hospitalization/prolong existing hospitalization	532 (29.8)	880 (36.2)	980 (39.2)	116 (40.4)	525 (28.7)	793 (33.8)	945 (37.4)	132 (42.6)	564 (30.2)	823 (35.2)	1000 (39.9)	134 (45.1)
- Life-threatening	19 (1.1)	35 (1.4)	33 (1.3)	4 (1.4)	22 (1.2)	28 (1.2)	30 (1.2)	6 (1.9)	18 (1.0)	35 (1.5)	39 (1.6)	14 (4.7)
- Disability/incapacity	8 (0.4)	8 (0.3)	14 (0.6)	3 (1.0)	6 (0.3)	10 (0.4)	16 (0.6)	2 (0.6)	3 (0.2)	9 (0.4)	9 (0.4)	4 (1.3)
- Other (medically significant)	195 (10.9)	322 (13.3)	366 (14.6)	47 (16.4)	198 (10.8)	309 (13.2)	358 (14.2)	46 (14.8)	213 (11.4)	317 (13.60	394 (15.7)	57 (19.2)
AE leading to drop-out [a]	103 (5.8)	220 (9.1)	323 (12.9)	63 (22.0)	114 (6.2)	231 (9.9)	364 (14.4)	75 (24.2)	111 (5.9)	205 (8.8)	370 (14.8)	82 (27.6)
Psychiatric disorders (SOC)	117 (6.6)	179 (7.4)	249 (10.0)	35 (12.2)	115 (6.3)	176 (7.5)	243 (9.6)	27 (8.7)	111 (5.9)	167 (7.1)	219 (8.7)	37 (12.5)
Nervous system disorders (SOC)	290 (16.3)	524 (21.6)	621 (24.8)	91 (31.7)	288 (15.7)	475 (20.3)	656 (25.9)	78 (25.2)	319 (17.1)	478 (20.4)	637 (25.4)	93 (31.3)
Accidents and injuries (SMQ)	210 (11.8)	346 (14.2)	559 (22.3)	90 (31.4)	210 (11.5)	330 (14.1)	545 (21.6)	85 (27.4)	255 (13.6)	396 (16.9)	608 (24.2	100 (33.7)
Cardiac disorders (SOC)	458 (25.7)	647 (26.6)	691 (27.6)	76 (26.5)	461 (25.2)	596 (25.4)	637 (25.2)	95 (30.6)	479 (25.6)	630 (26.9)	673 (26.8)	103 (34.7)
Vascular disorders (SOC)	225 (12.6)	365 (15.0)	397 (15.9)	51 (17.8)	237 (13.0)	330 (14.1)	421 (16.7)	44 (14.2)	219 (11.7)	363 (15.5)	408 (16.3)	57 (19.2)
Cerebrovascular disorders (SMQ)	12 (0.7)	29 (1.2)	20 (0.8)	5 (1.7)	12 (0.7)	27 (1.2)	24 (0.9)	0 (0.0)	9 (0.5)	25 (1.1)	31 (1.2)	7 (2.4)
Infections and infestations (SOC)	721 (40.4)	1097 (45.2)	1239 (49.5)	149 (51.9)	732 (40.0)	1082 (46.2)	1236 (48.9)	154 (49.7)	753 (40.3)	1077 (46.1)	1235 (49.2)	164 (55.2)
Anticholinergic syndrome (SMQ)	170 (9.5)	315 (13.0)	435 (17.4)	67 (23.3)	183 (10.0)	300 (12.8)	446 (17.6)	62 (20.0)	207 (11.1)	308 (13.2)	436 (17.4)	72 (24.2)
Quality of life decreased (PT)	0	0	0	0	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	232 (13.0)	471 (19.4)	663 (26.5)	103 (35.9)	242 (13.2)	420 (17.9)	679 (26.9)	87 (28.1)	265 (14.2)	485 (20.7)	701 (28.0)	105 (35.4)
Other AEs appearing more frequently in older subjects [b]												

[a] AEs leading to drop out = Subjects with non-bleeding TEAE that caused study drug permanent discontinuation.
[b] Please refer to Table 2
Source: Table T-Q147-001, Table T-Q147-002, Table T-Q147-003, Table T-Q147-004, Table T-Q147-005

Table S-27: Overview of Non-Bleeding TEAEs by Age, Safety Analysis Set; Treatment + 30 Days Period: Hokusai VTE

	Edoxaban (N = 4118) n (%)				Warfarin (N = 4122) n (%)			
	< 65 y M = 2784	≥65<75y M = 774	≥75-<85 y M = 486	≥85+ y M = 74	< 65 y M = 2752	≥65<75y M = 826	≥75-<85y M = 463	≥85+ y M = 81
Total with AEs	1882 (67.6)	573 (74.0)	363 (74.7)	61 (82.4)	1972 (71.7)	598 (72.4)	358 (77.3)	61 (75.3)
Serious AEs – Total Subjects	298 (10.7)	134 (17.3)	108 (22.2)	27 (36.5)	350 (12.7)	135 (16.3)	104 (22.5)	21 (25.9)
- Fatal	39 (1.4)	22 (2.8)	19 (3.9)	6 (8.1)	40 (1.5)	22 (2.7)	14 (3.0)	4 (4.9)
- Hospitalization/prolong existing hospitalization	260 (9.3)	118 (15.2)	93 (19.1)	26 (35.1)	279 (10.1)	114 (13.8)	86 (18.6)	19 (23.5)
- Life-threatening	14 (0.5)	10 (1.3)	6 (1.2)	4 (5.4)	7 (0.3)	3 (0.4)	3 (0.6)	0
- Disability/incapacity	2 (< 0.1)	3 (0.4)	3 (0.6)	0	3 (0.1)	1 (0.1)	2 (0.4)	0
- Other (medically significant)	119 (4.3)	42 (5.4)	45 (9.3)	11 (14.9)	169 (6.1)	63 (7.6)	44 (9.5)	7 (8.6)
AE leading to drop-out[a]	105 (3.8)	41 (5.3)	34 (7.0)	15 (20.3)	98 (3.6)	44 (5.3)	40 (8.6)	3 (3.7)
Psychiatric disorders (SOC)	138 (5.0)	60 (7.8)	30 (6.2)	4 (5.4)	121 (4.4)	36 (4.4)	24 (5.2)	6 (7.4)
Nervous system disorders (SOC)	344 (12.4)	105 (13.6)	72 (14.8)	12 (16.2)	333 (12.1)	88 (10.7)	61 (13.2)	11 (13.6)
Accidents and injuries (SMQ)	208 (7.5)	78 (10.1)	58 (11.9)	13 (17.6)	239 (8.7)	90 (10.9)	69 (14.9)	15 (18.5)
Cardiac disorders (SOC)	105 (3.8)	50 (6.5)	39 (8.0)	10 (13.5)	100 (3.6)	45 (5.4)	45 (9.7)	9 (11.1)
Vascular disorders (SOC)	178 (6.4)	62 (8.0)	31 (6.4)	10 (13.5)	204 (7.4)	80 (9.7)	44 (9.5)	7 (8.6)
Cerebrovascular disorders (SMQ)	15 (0.5)	18 (2.3)	9 (1.9)	2 (2.7)	16 (0.6)	16 (1.9)	12 (2.6)	1 (1.2)
Anticholinergic syndrome (SMQ)	161 (5.8)	61 (7.9)	50 (10.3)	9 (12.2)	156 (5.7)	57 (6.9)	51 (11.0)	10 (12.3)
Infections and infestations (SOC)	721 (25.9)	224 (28.9)	138 (28.4)	31 (41.9)	736 (26.7)	221 (26.8)	158 (34.1)	22 (27.2)
Quality of life decreased (PT)	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	128 (4.6)	56 (7.2)	50 (10.3)	10 (13.5)	148 (5.4)	67 (8.1)	57 (12.3)	12 (14.8)
Other AEs appearing more frequently in older subjects[b]								

[a] AEs leading to drop out= Subjects with non-bleeding TEAE that caused study drug permanent discontinuation.
[b] Please refer to Table 4
Source: Table AE100A6575, Table AE100A7585, Table AE100AGE85, Table AE100ALT65, Table AE101A6575, Table AE101A7585, Table AE101AGE85, Table AE101ALT65, Table AE201A6575, Table AE201A7585, Table AE201AGE85, Table AE201ALT65, Table AESA6575, Table AESA7585, Table AESAGE85, Table AESALT65, Table SSAE460LT65, Table SSAE460GE65TO75, Table SSAE460GE75TO85, Table SSAE460GE85, Table ACHOLLT65, Table ACHOLGE65TO75, Table ACHOLGE75T085, Table ACHOLGE85

Renally impaired patients:

The Applicant provided the safety evaluation in renally impaired patients (moderate-severe renal impariment: baseline CrCl ≤ 50 mL/min) separately for the two large phase 3 studies. No relevant imbalances (edoxaban vs, warfarin) were observed. Hence, the data provide no hint that safety and tolerability of edoxaban in renally impaired patients is worse than in the general study population. Pneumonia was more frequent with edoxaban in the VTE study (2.6% vs. 0.7%). This was also true for the general study population as discussed under "Serious Events and Deaths" subsection.

Safety related to drug-drug interactions and other interactions

Concomitant medications and bleeding risk: Subgroup analysis of major bleedings in ENGAGE AF indicated that subjects receiving concomitant aspirin (use was permitted with a dose <100 mg/day), other antiplatelet agents, and thienopyridines had an approximately 2-fold higher annual event rate for major bleeding than those not receiving such medications. Additional SmPC amendments have been implemented in this regard. In most subgroups, the HR for major bleeds for the comparison of the edoxaban 60 mg and edoxaban 30 mg groups with the warfarin group was less than 1. Some small increases above 1 were seen in patients receiving concomitant amiodarone and those not receiving concomitant ACEI/ARB. However, these variations are within expected when many subgroups are analysed.

Discontinuation due to adverse events

Permanent discontinuations: In the ENGAGE-AF, the percentage of subjects who permanently discontinued study drug was comparable among the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups (33.0%, 34.4%, and 34.5%, respectively). The most common reason for permanent discontinuation of study drug in the edoxaban 30 mg, edoxaban 60 mg, and warfarin treatment groups was AE or suspected endpoint event (15.6%, 17.2% and 16.7%, respectively). In HOKUSAI-VTE, the percentage of subjects who permanently discontinued study drug was also comparable between the edoxaban and warfarin treatment groups (16.9% and 17.4%, respectively). The most common reason for permanent discontinuation of study drug in the edoxaban and warfarin treatment groups was non-target endpoint AE (5.7% and 5.4%, respectively). Suspected target endpoints (specified efficacy or safety endpoints) accounted for 3.4% and 3.8%, respectively.

Discontinuations due to bleeding adverse events: In ENGAGE-AF, bleeding leading to study drug interruption was 13.2% in the edoxaban 60 mg group vs. 15.3% in the warfarin group. Bleeds that led to study drug permanent discontinuation were 3.9% in the edoxaban 60 mg group vs. 4.1% in the warfarin group. In HOKUSAI-VTE, bleeding leading to study drug interruption was 2.9% in the edoxaban group vs. 5.2% in the warfarin group. Bleeds that led to study drug permanent discontinuation were 1.4% in both groups.

Discontinuations due to non-bleeding AEs: There were no marked differences between the treatment groups with regard to the TEAEs leading to permanent treatment discontinuation in pooled phase 3 studies (edoxaban 60 mg 8.6% vs warfarin 8.3%). In summary, in phase 3 trials there were no marked differences between the treatment groups with regard to overall permanent discontinuations, or those related to bleeding or non-bleeding AEs.

Post marketing experience

Edoxaban was approved in Japan on 22 Apr 2011 for the prevention of VTE following total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery (HFS). For the purpose of this MAA, a cumulative output from the global safety database was generated from launch of

edoxaban in Japan through to 30 Sep 2013. To obtain the estimated of number of patients exposed to edoxaban, the distribution data between the launch and September 2013 were used. Assuming a dosing period per patient of 14 days regardless of strength, the number of patients exposed to LIXIANA was estimated and the number of total and the most frequent AEs was assessed during post-marketing experience. These events are within expected in patients undergoing major orthopaedic surgery. No specific clinical data have been generated on the use of activated charcoal to reduce absorption in case of edoxaban overdose.

2.6.1. Discussion on clinical safety

The safety database was mainly derived from two Phase 3 studies (ENGAGE-AF in NVAF and Hokusai VTE in patients with acute VTE), which amounts to 18,010 patients treated with edoxaban for approximately 1.9 years. In these studies, edoxaban showed a generally lower rate of adverse events than warfarin, mainly driven by a lower risk of major and CRNMB than warfarin. The benefit in bleedings was consistent across most subgroups analysed, including fragile patients, but was not significant in centers where warfarin was managed optimally. Depending on localisation, edoxaban showed a consistent lower risk of ICH than warfarin but an augmented risk of mucosal bleeding (e.g.: gastrointestinal bleedings and vaginal bleedings), which was associated to a significant number of patients experiencing a drop in Hb > 2 g/dl as compared to baseline.
Major and CRNMB was the more frequent AE with edoxaban (11.1 events per 100 patient-year in NVAF and 8.5% in acute VTE; corresponding MB rates were 2.75 % patient-year and 1.3%, respectively). Anaemia was reported for a higher proportion of edoxaban subjects (4.2%) than warfarin subjects (2.9%).

Intracranial hemorrhages: Ancillary analyses provided by the Applicant showed that the benefits of edoxaban versus warfarin in ICH were consistent in the worst case (high TTR and European, mainly Western Europe, population). This benefit was consistent with those observed with other similar compounds. The class benefit seems to be driven by an intrinsically risk of ICH with vitamin K antagonists, which is seen even at high TTR. The absolute benefit of edoxaban versus warfarin was difficult to be established due to low numbers of events, but could be estimated to be around 3 ICH avoided per 1,000 patients treated per year in the European AF population (edoxaban 3 ICH vs warfarin 6 ICH/1,000/yr). In the overall ENGAGE AF study population, the projected benefit was around 5 ICH per 1,000 patients treated (edoxaban 4 ICH vs. warfarin 9 ICH/1,000/yr). In the overall Hokusai VTE study population, the absolute benefit of edoxaban versus warfarin in ICH may be similar, around 3 ICH avoided per 1,000 patients treated for acute VTE (edoxaban 1 ICH/1,000 vs. warfarin 4 ICH/1,000), but difficult to establish due to low number of events and shorter durations of treatment (usually lasting less than 1 year).

Major bleeding: Patients who experienced major bleedings had older age, higher proportion of renal impairment and concomitant ASA use than patients without major bleedings. These patients were more represented in ENGAGE AF than in Hokusai VTE. In both ENGAGE AF and Hokusai VTE, demographic characteristics in subjects with adjudicated major bleeds were generally comparable between treatment groups, except for concomitant aspirin use in Hokusai VTE which was higher in the edoxaban than the warfarin group. In ENGAGE AF the rate of patients needing hospitalization was less frequent in edoxaban than in warfarin in ENGAGE AF (1.54%/yr vs 1.81%/yr), transfusion ≥ 2 units was similar (1.05%/yr in both groups), as well as need for surgery (0.20%/yr vs 0.29%/yr). Hospitalization with intensive care was lower with edoxaban (0.7%/yr vs 1.4%/yr). In Hokusai VTE, the rate of patients requiring hospitalization (1.2% vs. 1.2%), transfusion ≥ 2 units (0.7% vs 0.5%), need for surgery (<0.1 vs < 0.1% and hospitalization with inensive care unit (0.3 vs 0.4%) was generally comparable between edoxaban and warfarin treatment groups. There was lower 30-day

all-cause mortality after major bleeding in the edoxaban 60-mg than the warfarin group (ENGAGE AF: 0.5% vs. 1.0%; Hokusai VTE: 0.1% vs. 0.3%). Major bleed outcome of resolved with sequelae was lower with edoxaban than with warfarin in ENGAGE AF (0.7% vs 1.2%), but not in Hokusai VTE (0.2% vs. 0.1%).

Gastrointestinal bleedings: In ENGAGE AF, edoxaban 60-mg subjects had a higher rate of Major/CRNM GI bleed than warfarin subjects (3.54%/yr vs. 2.42%/yr), including those requiring hospitalization (1.61%/yr vs. 1.27%/yr) and transfusion (0.97%/yr vs. 0.84%/yr). However, the more severe bleedings, resulting in death of hospitalisation in intensive care unit, are more often reported with warfarin than with edoxaban. The increase in GI bleedings (HR≈ 1.46) mimic those reported with dabigatran 150 mg BID in RE-LY study (HR: 1.52) and rivaroxaban 20 mg OD in ROCKET AF (HR ≈ 1.26) for CRNM GI bleed. Further SmPC changes in sections 4.4 and 4.8 have been implemented to warn about this increase in risk.

Other adverse events: Gastrointestinal TEAEs (diarrhoea, nausea, gastritis and dyspepsia) were also reported for a higher proportion of edoxaban subjects than warfarin subjects (6.3% vs 6% for diarrhoea; 3.4% vs. 2.8% for nausea; 2.1% vs. 1.9% for gastritis and 1.8% vs. 1.6% for dyspepsia, respectively). The most notable difference was for INR increase which was, as anticipated, much more common on warfarin than edoxaban treatment (4.7% compared with 0.5%). The rates of deaths and serious adverse events were similar with edoxaban and warfarin, as where the rates of patients that discontinued study drug. However, some imbalances were found in hepatic events, cases of acute renal failure, acute polyneuropathies and allergic reactions.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Edoxaban was generally associated to a lower risk of adverse events than warfarin, mainly driven by a lower risk of major and CRNMB in pivotal studies. The benefit was consistent across most subgroups analysed, including fragile patients, but was not significant in centers where warfarin was managed optimally. Edoxaban showed a lower risk of ICH than warfarin but an augmented risk of mucosal bleeding (e.g.: gastrointestinal bleedings and vaginal bleedings). Gastrointestinal TEAEs (diarrhoea, nausea, gastritis and dyspepsia) was also reported for a higher proportion of edoxaban subjects than warfarin subjects (6.3% vs 6% for diarrhoea; 3.4% vs. 2.8% for nausea; 2.1% vs. 1.9% for gastritis and 1.8% vs. 1.6% for dyspepsia, respectively). No significant imbalances were found in rates of death or SAEs.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

2.8. Risk Management Plan

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

The PRAC considered that the risk management plan version 5 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The applicant implemented the changes in the RMP as requested by PRAC.

The CHMP endorsed the Risk Management Plan version 6 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Bleeding due to: • drug interaction in combination with other drugs known to increase the risk of bleeding eg, aspirin, NSAIDs, • inappropriate administration of 60 mg dose /inadvertent overdose by use of 60-mg dose, eg in combination with use of strong P-gp inhibitors; in patients with low body weight ≤ 60 kg; and in patients with moderate to severe renal impairment (CrCL 15-50 mL/min).
Important potential risk	Hepatic Dysfunction
Important potential risk	Trend towards decreasing efficacy in NVAF subjects with high Creatinine Clearance
Missing information	Lack of reversal agent
Missing information	Paediatric use
Missing information	Reproductive and development toxicity [Pregnancy and lactation]
Missing information	Patients with hepatic impairment
Missing information	Patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease (CrCL < 15 mL/min or on dialysis)
Missing information	Patients with mechanical heart valves
Missing information	Combination with dual antiplatelet therapy
Missing information	Off-label use in Europe in populations or indications outside the approved indications per European SmPC

Pharmacovigilance plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Drug utilization study: characterize actual prescribing pattern and assess off-label use (category 3)	Prescription patterns, assess off-label use in Europe	Off-label use	[Planned]	Study design: protocol for EMA comments within 3 months of marketing authorization of edoxaban. Study execution and final report within 18 months post-EMA approval of protocol and minimum 1 year post-launch and depending on results may be repeated 1 year later in at least 5 major EEA markets.
PASS: Non-interventional study on **E**doxaban **t**reatment in routi**n**e clinical pra**c**tise for patients with non valvular **a**trial **f**ibrillation (**ETNA-AF-Europe)** (category 3)	To collect real-world safety data on bleeding events including intracranial haemorrhage, drug related adverse events such as liver adverse events, cardiovascular (CV) and all-cause mortality in AF patients treated with edoxaban up to 4 years. Furthermore,	Safety of edoxaban in clinical practice	[Planned]	Execution following approval of protocol by authorities. Submission of full study protocol within 3 months of positive CHMP opinion. Interim reports: Regular interim status reports, yearly data snapshots, pooled safety analysis after 1.5 years (combined with ETNA-VTE-Europe) Final Report: Q4 2021

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	subgroup analyses will be performed in predefined patient populations, such as patients with renal or hepatic impairment.			
Non-interventional study on **E**doxaban **t**reatment in routine cli**n**ical pr**a**ctice for patients with acute **v**enous **t**hrombo**e**mbolism in Europe (**ETNA-VTE-Europe**). (category 3)	The co-primary objective is to collect real world safety safety data on bleeding events, drug related adverse events such as liver adverse events, and mortality (VTE-related and all-cause) in VTE patients treated with edoxaban. Furthermore, safety analyses in pre-specified subpopulations such as patients with renal impairment and patients with hepatic impairment will be performed. Primary objective is the analysis of the overall symptomatic VTE recurrence rate during an overall observational	Safety of edoxaban in clinical practice VTE recurrence in clinical practice.	[Planned]	Execution following approval of protocol by authorities. Submission of full study protocol within 3 months of positive CHMP opinion. Approximate Interim reports: Regular interim status reports, yearly data snapshots, pooled safety analysis after 1.5 years (combined with ETNA-AF-Europe) Final report: Approximately Q2 2020

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
	period of 18 months in unselected patients with acute VTE.			
This study is sponsored by company Portola, supported by the applicant: A Randomized, Double Blind, Vehicle-Controlled Multiple Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Intravenously Administered PRT064445 After Dosing to Steady State with Edoxaban (category 3)	To identify whether PRT064445 can reverse the effect of Factor Xa inhibitors	Reversibility of edoxaban effect in humans	Ongoing	TBD
This study is sponsored by company Perosphere, supported by the applicant: A "Phase II Randomized, Sequential Group, Evaluation of Ascending Reversal Doses of PER977 Administered to Subjects with Steady State Edoxaban Dosing and Re-	To identify whether PER977 can effectively reverse the effect of Factor IIa and Xa inhibitors.	Reversibility of edoxaban effect in humans	Ongoing. Clinical completion is anticipated in December 2014	CSR planned for July 2015

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
anticoagulation with Edoxaban Following PER977 Reversal" (category 3)				
Stago is planning to conduct a for-registration study in March 2015. It is planned to file for CE Marking of the anti-FXa assay in Q1 2016. Commercially available assay planned to be available approximately Q2 2016 (category 3)	To develop a commercial calibrated quantitative anti Factor Xa assay	Measurement of edoxaban levels in humans	Planned	Commercially available anti-FXa assay planned to be available approximately Q2 2016

Risk minimisation measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Bleeding	SmPC/PIL Prescription only medicine (POM)	Educational Package including • Prescriber's guide • Patient Alert card
Hepatic Dysfunction	SmPC/PIL POM	None
Trend towards decreasing efficacy in NVAF subjects with high Creatinine Clearance	SmPC POM	None
Missing information	SmPC/PIL POM	Educational Package including Prescriber's guide

2.9. Product information

2.9.1. User consultation

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

2.9.2. Package leaflet

The Applicant proposed to include a **Quick Response (QR)** code in the Package leaflet that links to a patient website. The home page will require the patient to select their country and whether they are taking Lixiana for NVAF or VTE.

The CHMP considered that the information initialy proposed to be included within the product website via QR code was not acceptable. The CHMP agreed with the inclusion of a QR code as long as it only links to the statutory information approved (i.e. SmPC, Package leaflet or educational material agreed in the RMP).

3. Benefit-Risk Balance

Benefits

Beneficial effects

The ENGAGE AF was a large (n=21,105 patients) double-blinded, event-driven, non-inferiority clinical trial where patients with NVAF were randomised to either edoxaban 30mg once daily treatment group, or edoxaban 60mg once daily treatment group or warfarin.

The study provided evidence of non-inferiority for edoxaban 60 mg OD versus warfarin for the composite of all strokes and SEE (HR: 0.79; 97.5% CI: 0.632, 0.985; non-inferiority margin: 1.38; p<0.0001 for non-inferiority; mITT, on treatment) and for the composite of ischemic strokes and SEE (HR: 0.92; 95%CI: 0.73-1.15; PP, on-treatment) (endpoint recommended in the current *EMA Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with NVAF [EMA/CHMP/341363/2014]*)).

The mean time in therapeutic range (TTR) (INR: 2-3) was 64.9% (median 68.4%), the highest across the contemporary AF studies, and the rate of stroke/SEE event rate in the warfarin arm (1.5%/yr) was the lowest.

Analyses of composite (first-event) endpoint of stroke, SEE, and CV mortality, the endpoint of MACE, and the composite endpoint of stroke, SEE, and all-cause mortality were consistent with the analysis of the primary endpoint. The trend for superiority of the high edoxaban dose (60 mg OD) versus warfarin for the primary endpoint was supported by secondary analyses of patients with fatal strokes (80 vs. 86) disabling strokes (54 vs. 57), recurrent stroke/SEE events (5 vs. 8; mITT, on-treatment period) and analysis of the composite of stroke, SEE and TIA (HR: 0.88; 95%CI: 0.746 to 1.042; mITT on-treatment period).

Given that NVAF population and AF management were heterogeneous, exploratory analyses of subgroups in ENGAGE-AF were conducted by INR/TTR level by centre and quartiles as well as by at least 14 patient/study characteristics. Subgroup analyses by patient/study characteristics showed a generally consistent effect of edoxaban in most subgroups, but not in some relevant ones (see: Uncertainty in the knowledge about the beneficial effects).

HOKUSAI VTE: Treatment of VTE including DVT and PE, and prevention of recurrent VTE

HOKUSAI VTE was a large (n=8292) double-blinded, event-driven, non-inferiority comparative trial (edoxaban 60 mg OD vs warfarin) in patients with acute VTE. Approximately 41% of patients presented with PE as index event. Intended treatment duration was 3 months in 6% of patients, 6 months in 37% of patients and 12 months in 57% of patients. Edoxaban and warfarin regimes were preceded by heparin lead-in treatment for at least 5 days.

The study showed evidence of non-inferiority with regard to the composite endpoint of documented symptomatic recurrent VTE (HR: 0.89; 95% CI: 0.70-1.13; non-inferiority margin = 1.5; p<0.0001 for non-inferiority; mITT, overall study period). For subjects presenting with PE (with or without DVT), 50 (1.2%) edoxaban and 58 (1.4%) of warfarin subjects had a recurrent VTE [HR (95% CI): 0.85 (0.64, 1.14)].

The effect of edoxaban was generally consistent across subgroups tested in the HOKUSAI-VTE study. Overall, of the 55 comparisons presented from 18 subgroup analyses, most (45) resulted in a point estimate favouring edoxaban. Edoxaban effect was (significantly) better in fragile than in non-fragile patients. In general, the effects of edoxaban were also better (although no statistically significant interaction was found) in index PE, age >75 years and history of cancer, which is reassuring.

Regarding the quality of oral anticoagulation, the mean TTR was 63.5%, which is higher than that reported in other contemporary studies with NOACs in this indication (from 57% in RE-COVER II to 62.7% in EINSTEIN PE). The edoxaban group had a relative reduction in risk for recurrent VTE compared to warfarin for subjects at centers TTR < 60% (HR: 0.89; 95% CI: 0.574, 1.364) and also at centers with TTR ≥60% (HR: 0.87; 95% CI: 0.653, 1.153).

Uncertainty in the knowledge about the beneficial effects.

The utility of the **lowest edoxaban dose (15 mg)** was restricted to the process of switching from Lixiana to VKA for patients currently on edoxaban 30 mg (reduced dose in patients with presumed increased exposure). It was unclear whether dose reduction from 30 mg OD to 15 mg was necessary in this process and if the 15 mg dose will provide a sufficient level of anticoagulation. The applicant modelled factor Xa activity over the 24-hour dosing period for the doses used in the ENGAGE AF study and showed that even the 15 mg dose has some antithrombotic effect, although lower than that of a full therapeutic dose, as expected. However, edoxaban 15 mg is not to be administered in monotherapy, but only concomitantly with warfarin during the switching procedure. The ENGAGE AF protocol included 15 mg strength as provision intended to mitigate the risk of bleeding expected for those patients who were taking two oral anticoagulants concomitantly.

ENGAGE AF: Prevention of stroke and SEE in patients with non-valvular atrial fibrillation

Although the **low edoxaban dose** (30 mg OD) showed non-inferiority versus warfarin for all strokes/SEE (HR: 1.07; 97.5% CI: 0.87-1.31; p=0.0055 for non-inferiority; mITT, on-treatment), it was inferior to warfarin for the composite of ischemic stroke/SEE 1.47 (HR: 95% CI: 1.20 to 1.80; PP, on-treatment). The trend for inferior efficacy of edoxaban 30 mg OD versus warfarin was also supported by the analysis of pure thromboembolic events (ischemic stroke/SEE as well as MI), by the higher number of disabling strokes (82 and 57 subjects in edoxaban 30 mg group and the warfarin group, respectively), by the number of patients who had ≥ 2 occurrences of the primary efficacy endpoint (21 and 8 subjects in edoxaban 30 mg group and the warfarin group, respectively; mITT analysis set, on-treatment period) as well as by the high number of events when TIA was added to stroke and SEE (edoxaban 30 mg event rate 2.28% per year vs warfarin 1.92% per year; HR: 1.19; 95%CI: 1.021 to 1.389; mITT on-treatment period).

Exploratory analyses of subgroups in ENGAGE-AF were conducted by INR/TTR level by centre and quartiles as well as by at least 14 patient/study characteristics. However, stroke/SEE rates tended to favour warfarin in patients recruited in **Western Europe** and those with **normal renal function**.

The interpretation of the **results in Western Europe** was hampered by the limitations of subgroup analyses and the low event rates. Whether these regional variations may be acceptable in the context of the heterogeneous countries of EEA region was discussed taking into account the fact that ENGAGE AF demonstrated non-inferiority of edoxaban 60 mg versus a well-controlled warfarin regime in the overall population. In addition, all-cause mortality and CV mortality were broadly similar in the overall vs. on-treatment analysis in both the edoxaban and warfarin groups in Western Europe. In summary, the overal study results were considered representative for the European population.

In NVAF, although the overall benefit risk in the AF indication was considered positive across the continuum of renal function at the population level, there were indications of reduced efficacy of

edoxaban compared to well-managed warfarin therapy that could be of relevance at the individual level in patients with increased creatinine clearance. In general, a trend towards **decreasing efficacy with increasing creatinine clearance** was observed for edoxaban compared to well-managed warfarin. The data in patients with normal renal function were considered to be sufficiently robust, making a chance adverse finding unlikely. They may be explained to a combination of a lower exposure to edoxaban 60 mg in patients with normal renal function (in comparison with the exposure to 60 mg in patients with mild renal impairment) and a well-managed warfarin therapy resulting in a low stroke/SEE rate in the control group, particularly in patients with high creatinine clearances. Therefore, a warning has been included regarding this trend in the SmPC.

Subgroup analyses of stroke/SEE by INR/TTR level suggest that the **effect size (reduction of stroke/SEE by edoxaban) decreases as the quality of anticoagulation in the control group increases** (i.e.: in centers with TTR > 60% and when INR/TTR was above the fourth quartile, >73.9%). When the TTR data were examined by quartiles for the edoxaban 60 mg group compared to warfarin, the HR for the primary endpoint in the 1st, 2nd, and 3rd quartile was 0.80, 0.73, and 0.74, respectively, and for the 4th quartile was 1.07 (95%CI: 0.65-1.75). For the edoxaban 30 mg group compared to warfarin, the HR for 1st, 2nd, 3rd, and 4th quartiles were 0.82, 1.02, 1.22, and 1.30 (95%CI: 0.81-2.09), respectively. These data were expected in the light of similar results in previous studies with novel oral anticoagulants in NVAF and were presented in the SmPC.

The analyses of efficacy in ENGAGE-AF by subgroups excluding haemorrhagic stroke were provided (i.e.: including only ischemic stroke and SEE). The event rate for composite of ischemic stroke and SEE was lower in the edoxaban 60-mg group than in the warfarin group for most subgroups, with the HR less than 1.0 for the overall study period, but in some of the sub-groups the HR was more than 1.0. However, there were several significant ($p<0.05$) interactions:

-for the **type of atrial fibrillation**: The HR was 0.79 and 0.85 for subjects with persistent and permanent AFs and 1.73 for subjects with paroxysmal AF. However, this finding was based on a relatively low number of events and patients in this subgroup. The variations in stroke/SEE rates in the warfarin group was the main responsible for the interaction.

- for the **VKA-naïve versus VKA experienced** subjects: The HR was 0.75 for VKA naïve subjects and 1.17 for VKA experienced subjects. VKA-experienced patients comprised the majority of patients enrolled in ENGAGE-AF (59%). The finding indicated that switching from warfarin to edoxaban was not associated with a benefit in efficacy. Considering the primary endpoint of stroke/SEE, a significant interaction was found for the overall study period for prior VKA use ($p=0.0253$) but this was not observed for the on-treatment period ($p=0.3545$). The most important patient characteristics of the VKA experienced subjects in the ENGAGE AF study was the high TTR at 70%. Nonetheless, for the primary endpoint of stroke/SEE, edoxaban 60 mg did show similar efficacy and even for ischemic stroke, any gap in efficacy was less than 0.5%/year and was offset by a clinically significant decrease in major bleeds, resulting in similar net clinical outcome and all-cause mortality.

- for the **verapamil subgroup**: The HR was 0.92 for subjects without concomitant verapamil and 2.59 for subjects who took concomitant verapamil. Verapamil use was very low (<5% of total population) and number of events were low (18 vs. 7). Nevertheless, it suggests that the edoxaban 30 mg dose used in these patients was insufficient and 60mg dose was recommended for these patients.

No data were available on subjects during the first 3 months after implantation of a **bioprosthetic heart valves**, and therefore a non-recommendation of use was included in the product information.

The extrapolation of the data to patients **with $CHADS_2$ index score=1** (included in the indication) was accepted.

HOKUSAI VTE: Treatment of VTE including DVT and PE, and prevention of recurrent VTE

Although recurrent VTE (DVT or PE) (main efficacy endpoint) favoured numerically edoxaban over warfarin in the overall study period, there was a **numerical imbalance in the number of all-cause deaths** in the overall study period of the HOKUSAI-VTE study (edoxaban 122 vs warfarin 106), thus leading to a hazard ratio of 1.00 in the superiority analysis of recurrent VTE and all-cause death for the overall study period (HR: 1.00; 95%CI: 0.83-1.20; p=0.9933). Analysing the time-course of deaths, the imbalance was not attributed to the on-treatment deaths (edoxaban 35 vs warfarin 33) but to an excess in deaths due to infectious diseases in the edoxaban arm after treatment had been stopped. This imbalance was not seen in the ENGAGE-AF study in a population with AF.

No specific VTE extension studies have been conducted with edoxaban. However, the design and analysis (mITT Overall versus On-Treatment) of the study allowed assessing extension of therapy/the secondary prevention of VTE without the need for a formal extension study. The main issue in HOKUSAI-VTE regarding duration of therapy was that many patients may have benefited from longer anticoagulative treatment durations. Therefore, it was agreed not to limit the duration of treatment of VTE to the 1 year study duration of HOKUSAI-VTE.

During pivotal studies, dose reductions were made in patients concomitantly receiving **P-gp inhibitors**. However, the totality of the data does not support diminishing the dose when edoxaban 60 mg is concomitantly administered with verapamil, quinidine or amiodarone, and this was reflected in the SmPC.

Risks

Unfavourable effects

The safety database is mainly derived from two Phase 3 studies (ENGAGE-AF in NVAF and Hokusai VTE in patients with acute VTE), which amounts to 18,010 patients treated with edoxaban for a mean of approximately 1.9 years. Major and clinically-relevant nonmajor (CRNM) bleeding was the most frequent AE with edoxaban (11.1 events per 100 patient-year in NVAF and 8.5% in acute VTE; corresponding major bleeding (MB) rates were 2.75 % patient-year and 1.3%, respectively). Anaemia was reported for a higher proportion of edoxaban subjects (4.2%) than warfarin subjects (2.9%) in the pooled Phase 3 studies. In these studies, edoxaban showed a generally lower risk of MB and CRNMB than warfarin. The benefit was consistent across most subgroups analysed, including fragile patients, but was not significant in centers where warfarin was managed optimally. Depending on localisation, edoxaban showed a consistently lower risk of ICH than warfarin but an augmented risk of mucosal bleeding (e.g.: gastrointestinal bleedings and vaginal bleedings), which was associated with a significant number of patients experiencing a drop in Hb < 2 g/dl as compared to baseline. Gastrointestinal TEAEs (diarrhoea, nausea, gastritis and dyspepsia) was also reported for a higher proportion of edoxaban subjects than warfarin subjects (6.3% vs 6% for diarrhoea; 3.4% vs. 2.8% for nausea; 2.1% vs. 1.9% for gastritis and 1.8% vs. 1.6% for dyspepsia, respectively). The most notable difference was for INR increased which was, as anticipated, much more common on warfarin than edoxaban treatment (4.7% compared with 0.5%). The rates of deaths and serious adverse events were similar with edoxaban and warfarin, as where the rates of patients that discontinued study drug. However, some imbalances were found in hepatic events, cases of acute renal failure, acute polyneuropathies and allergic reactions, and MACE (Hokusai VTE study only) (see Uncertainty in the knowledge about the unfavourable effects).

Uncertainty in the knowledge about the unfavourable effects

Bleeding events

It seems that an important benefit of edoxaban, as with other NOACs, was the reduction in ICH. However, the projected benefit in ICH may be highly dependent on the expected rate of ICH with warfarin in standard practise. For example, the rates of ICH with warfarin in patients with NVAF in standard practice in North-America and Europe are low (approximately 0.4 per 100 patients-year in both), which is much lower than the 0.85 per 100 patient-year incidence found with warfarin in ENGAGE-AF. In addition, in ENGAGE-AF, there was no difference between edoxaban 60 mg and warfarin with regard to overall major bleedings when warfarin treatment was optimally managed (i.e.: in centers with TTR > 66.4%), which is the rule in many European centers. Similar results were found in Hokusai-VTE with respect to the lack of reduction in bleeding events when warfarin was optimally managed. The consequences of major bleedings seemed more benign with edoxaban than with warfarin as shown by a lower 30-day all-cause mortality after major bleeding in the edoxaban 60-mg than the warfarin group in both trials, and by a lower rate of hospitalization due to major bleeding in AF patients. Ongoing development plans for assay to measure the anticoagulant activity and potential specific reversal agents have been included in the agreed RMP.

Hepatic safety

There were some imbalances against edoxaban 60 mg versus warfarin in pooled phase 3 studies in: a) the cases of hyperbilirubinaemia (edoxaban 60 mg 0.3% vs warfarin 0.1%); b) and concurrent elevation of ALT or AST ≥ 3 x ULN & Total Bilirubin ≥ 2 x ULN (edoxaban 60 mg 0.4% vs warfarin 0.3%, corresponding to 43 and 29 cases, respectively; Pooled Phase 3 trials); c) the percentage of subjects in the edoxaban 60 mg group versus warfarin that were characterized by an independent hepatologist as having a hepatocellular injury (1.1% vs. 1.0%, respectively); d) In the percentage of cases of liver injury possibly/probably related to study drug [(edoxaban 60 mg 0.4% (48 of 11008 subjects) versus warfarin 0.3% (30 of 11010 subjects)]; e) in the percentage of liver injury adjudicated as severe (edoxaban 60 mg 0.4% vs warfarin 0.3%) ; f) and in the number of Hy's law cases adjudicated as severe hepatocellular liver injury possibly/probably related to study drug (edoxaban any dose 2 vs warfarin 1). It was agreed to add important safety information related to hepatic safety to the SmPC. The issue will be further investigated in the non-interventional post-authorization safety study (PASS) in patients with AF.

There were other non-bleeding events reported during phase 3 studies, including: acute renal failure, acute polyneuropathies, anaphylactic reactions, interstitial lung disease, and MACE in which a small numerical increase was seen for edoxaban in comparison with warfarin. It was agreed that some of these numerical imbalances like acute polyneuropathies and MACE, are likely due to chance. Acute renal failure could be associated with some severe bleedings, and allergic reactions were within what has been reported for other NOACs.

Benefit-risk balance

Importance of favourable and unfavourable effects

Strokes in association with AF are often fatal, and those patients who survive are left more disabled by their stroke and more likely to suffer a recurrence than patients with other causes of stroke. Edoxaban 60 mg OD showed at least similar efficacy compared to warfarin in reducing stroke rates in NVAF. This was supported by secondary analyses of patients with fatal strokes, disabling strokes (54 vs. 57) and recurrent stroke/SEE events. Venous thromboembolism (VTE), encompassing deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third leading cause of mortality due to circulatory diseases, only behind myocardial infarction and stroke. Edoxaban 60 mg OD also showed similar efficacy compared to warfarin in preventing recurrent VTE.

With respect to safety, an important benefit of edoxaban, as with other new anticoagulants, is the reduction in ICH. However, the projected benefit in ICH may be highly dependent on the expected

rate of ICH with warfarin in different conditions in standard practise. In addition, edoxaban showed an augmented risk of mucosal bleeding (e.g.: gastrointestinal bleedings and vaginal bleedings), which was associated with a significant number of patients experiencing a drop in Hb > 2 g/dl as compared to baseline. It was reassuring that the most severe bleedings were less frequent with edoxaban than with warfarin. The information about increase in mucosal bleedings was added as warning in the SmPC. Finally, no differences in overall number of deaths were found between warfarin and edoxaban in pivotal studies.

All these data suggest that edoxaban is non-inferior to warfarin in both indications, with some advantages related to ICH but disadvantages related to mucosal bleedings.

Benefit-risk balance

The overall benefit-risk balance of edoxaban was considered positive.

Discussion on the benefit-risk balance

In NVAF, although the overall benefit-risk balance in the NVAF indication was considered positive across the continuum of renal function at the population level, there were indications of reduced efficacy of edoxaban compared to well-managed warfarin therapy that could be of relevance at the individual level in patients with increased creatinine clearance.

In general, a trend towards decreasing efficacy with increasing creatinine clearance was observed for edoxaban compared to well-managed warfarin. A warning has been included in section 4.4 of the SmPC to create awareness about this observation. The applicant agreed to further evaluate post-marketing whether a higher QD dose would provide a further improvement of the benefit-risk relationship in patients with high creatinine clearance This was included in the agreed version of the RMP as MEA to address potential risk: “trend towards decreasing efficacy in patients with high creatinine clearance

Monitoring of anti-Xa activity may be helpful to individualise the treatment and dose in certain circumstances (e.g.: at the beginning of treatment in patients with cumulative risk factors for decreased exposure, in case of high renal clearance combined with high body weight; in case of emergency or overdose). The Applicant has submitted a plan for developing a validated anti-Xa test to measure edoxaban's anticoagulant activity. The anti-Xa assay will be first validated retrospectively by using anti-Xa, efficacy/safety data from pivotal trials, and then prospectively in future clinical trials.

In the treatment of acute VTE, HOKUSAI VTE provided evidence of non-inferiority of edoxaban 60 mg versus warfarin (both regimes preceded by heparin lead-in treatment). No specific VTE extension studies have been conducted with edoxaban. However, the design and analysis (mITT Overall versus On-Treatment) of the study allowed assessing extension of therapy/the secondary prevention of VTE without the need for a formal “extension” study. It was also agreed not to limit the duration of treatment of VTE to the 1 year study duration of HOKUSAI-VTE but to leave the decision to the treating physician taking into account clinical practice guidelines, which recommend that the duration of therapy be individualised.

In both pivotal studies, edoxaban showed a generally lower risk of MB and CRNMB than warfarin. The benefit was consistent across most subgroups analysed, including fragile patients, but was not significant in centers where warfarin was managed optimally. Again, it was debated whether the safety advantage found in these studies can be extrapolated to many European centers in which warfarin treatment is optimal. Depending on localisation, edoxaban showed a lower risk of ICH than warfarin, which was considered a major benefit, consistent with that reported for other NOACs. Edoxaban showed an augmented risk of mucosal bleeding (e.g.: gastrointestinal bleedings and

vaginal bleedings), which was associated with a significant number of patients experiencing a drop in Hb < 2 g/dl as compared to baseline.

There were some imbalances in hepatic events not favouring edoxaban 60 mg versus warfarin. A definitive association between these novel oral factor Xa inhibitors and risk of hepatic injury has not been confirmed. The uncertainties have been solved with SmPC ammendments and an RMP plan to further investigate this potential risk postauthorisation.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lixiana in the
Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ⩾ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see section 4.4 for haemodynamically unstable PE patients).
is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

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

An updated RMP should be submitted:

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

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the

same time.

- **Additional risk minimisation measures**

Prior to launch of Lixiana in each Member State, the Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at mitigating the risk of serious bleeds or haemorrhage in patients treated with Lixiana by ensuring prescriber awareness and providing guidance on appropriate patient selection, correct dosing as well as management of the risk.
The programme is also aimed at ensuring that the healthcare professionals who intend to prescribe Lixiana are aware of the Patient alert card and that the card is to be given to and reviewed with all patients treated with Lixiana.

The MAH shall ensure that in each Member State where Lixiana is marketed, all healthcare professionals who are expected to use Lixiana are provided with the following educational material:

- The Summary of Product Characteristics
- Prescriber Guide for healthcare professionals
- Patient alert card

The Prescriber Guide for healthcare professionals shall contain the following key elements:

- Relevant information on the risk of bleeding
- Details of the population potentially at higher risk of bleeding
- Contraindications
- Recommendations for dose adjustment in at risk populations, including patients with renal or hepatic impairment, low body weight and concomitant use of some P-gp inhibitors
- Guidance on switching from or to Lixiana treatment
- Guidance regarding surgery or invasive procedure, and temporary discontinuation
- Management of overdose situations and haemorrhage
- Use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be counselled about:
  - The signs or symptoms of bleeding and when to seek attention from a healthcare provider
  - Importance of treatment compliance
  - Necessity to carry the Patient alert card with them at all times
  - The need to inform Health Care Professionals that they are taking Lixiana if they need to have any surgery or invasive procedure

The Patient alert card should contain the following key safety messages:

- The signs or symptoms of bleeding and when to seek attention
- Importance of treatment compliance
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Lixiana if they need to have any surgery or invasive procedure

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

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP

considers that edoxaban tosilate is qualified as a new active substance.

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0028/2014and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, assessment of studies significance, in the agreed paediatric investigation plan P/0028/2014 is not applicable, as none of the studies were initiated before entry into force of the Regulation and completed after this.