EU Risk Management Plan for Edoxaban

RMP version to be assessed as part of this application:

Data lock point for this RMP	31 Dec 2022	RMP Version number	18.0
Date of final sign off	31 Mar 2026		

Rationale for submitting an updated RMP:

Update to adapt Annex 6 to the template wording of the RMP template following the guidance on the format of risk management plan (RMP) in the EU, in an integrated format (Rev. 2.0.1), and to align to the wording of the current Product Information (PI) Annex IID.

Summary of significant changes in this RMP:

Changes versus the current approved edoxaban EU RMP version (17.0):

- Annex 6

Details of the currently approved RMP for Roteas and Lixiana:

RMP Version number: 17.0

Approval date 12 Oct 2023

Procedure number:

Lixiana: EMEA/H/C/002629/WS2483/0045

Roteas: EMEA/H/C/004339/WS2483/0032

Daiichi Sankyo Europe
Qualified Person Responsible for Pharmacovigilance (QPPV) name: _____

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

Berlin Chemie QPPV name:

QPPV signature: _____

European Qualified Person for Pharmacovigilance Deputy (on behalf of the QPPV)

QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV.

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PART I PRODUCT(S) OVERVIEW

The following table (Table Part I.1) presents an overview of the edoxaban product characteristics, indications and dosage. In this table and throughout this Risk Management Plan (RMP) the common name (edoxaban) and invented name (Lixiana and Roteas) are used interchangeably depending on the context.

Table Part I.1: Product Overview

Active substance(s) (INN or common name):	**Edoxaban**
Pharmacotherapeutic group(s) (ATC Code):	B01AF03
Name of Marketing Authorisation Holder or Applicant:	Daiichi Sankyo Europe GmbH Berlin-Chemie AG
Medicinal products to which this RMP refers:	edoxaban
Invented name(s) in the EEA:	Lixiana®; Roteas®
Marketing authorisation procedure:	Centralised procedure
Brief description of the product:	Chemical class: Edoxaban tosylate is an anticoagulant agent, an orally active, selective, direct, and reversible inhibitor of FXa, manufactured by Daiichi Sankyo Co., Ltd., Japan.
	Summary of mode of action: Edoxaban does not impair platelet aggregation. Inhibition of FXa in the coagulation cascade prolongs clotting time and reduces the risk of thrombus formation.
	Important information about its composition: The molecular formula of edoxaban tosylate is $C_{24}H_{30}ClN_7O_4S \cdot C_7H_8O_3S \cdot H_2O$. Its molecular mass is 738.27 (548.06 as edoxaban, the anhydrous free base of edoxaban tosylate). The chemical abstracts registry numbers for edoxaban and the anhydrous form of edoxaban tosylate are 480449-70-5 and 480449-71-6, respectively. Edoxaban refers to the anhydrous free base of edoxaban tosylate. Patients are given edoxaban tosylate (a monohydrate salt), but all doses and plasma concentrations are expressed in terms of edoxaban, the anhydrous free base.
Hyperlink to the Product Information:	SmPC Note: In text, references to sections of the SmPC are italicised.

Indication(s) in the EEA: Approved	Current approved **SmPC (SmPC) 4.1 Therapeutic Indications:** Prevention of stroke and systemic embolism in adult patients with NVAF with 1 or more risk factors, such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (see *section 4.4* for haemodynamically unstable PE patients)
	Proposed: Not applicable.
Dosage in the EEA	Current: *Prevention of stroke and systemic embolism* The recommended dose of edoxaban is 60 mg once daily. Therapy with edoxaban in NVAF patients should be continued long term. *Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE (VTE)* The recommended dose is 60 mg edoxaban once daily following initial use of parenteral anticoagulant for at least 5 days (*see section 5.1*). Edoxaban and initial parenteral anticoagulant should not be administered simultaneously. The duration of therapy for treatment of DVT and PE (venous thromboembolism, VTE), and prevention of recurrent VTE should be individualised after careful assessment of the treatment benefit against the risk for bleeding (see section 4.4). 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. For NVAF and VTE the recommended dose is 30 mg edoxaban once daily in patients with one or more of the following clinical factors: • Moderate or severe renal impairment (creatinine clearance (CrCL) 15 - 50 mL/min) • Low body weight ≤ 60 kg • Concomitant use of the following P--glycoprotein (P-gp) inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.

	(**SmPC 4.2 Table 1** provides a summary of Posology in NVAF and VTE [DVT and PE]) *Missed dose* If a dose of Lixiana/Roteas is missed, the dose should be taken immediately and then be continued the following day with the once-daily intake as recommended. The patient should not take double the prescribed dose on the same day to make up for a missed dose. *Switching to and from Lixiana/Roteas* Continued anticoagulant therapy is important in patients with NVAF and VTE. There may be situations that warrant a change in anticoagulation therapy. (**SmPC 4.2 Table 2** provides detailed switching strategies to and from Lixiana/Roteas) *Special populations* *Elderly patients* No dose reduction is required (see *section 5.2*). *Renal impairment:* Renal function should be assessed in all patients by calculating the CrCl prior to initiation of treatment with edoxaban to exclude patients with end stage renal disease (i.e. CrCl < 15 mL/min), to use the correct edoxaban dose in patients with CrCl 15 – 50 mL/min (30 mg once daily), in patients with CrCl > 50 mL/min (60 mg once daily) and when deciding on the use of edoxaban in patients with increased CrCl (see section 4.4). Renal function should also be assessed when a change in renal function is suspected during treatment (eg hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products). The method used to estimate renal function (CrCL in mL/min) during the clinical development of Lixiana was the Cockcroft-Gault method. The formula is as follows: • For creatinine in μmol/L: $\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]}\ (\times 0.85 \text{ if female})}{\text{serum creatinine [μmol/L]}}$

	• For creatinine in mg/dL: $\frac{(140\text{-age [years]}) \times \text{weight [kg]} (\times 0.85 \text{ if female})}{72 \times \text{serum creatinine [mg/dL]}}$ This method is recommended when assessing patients' CrCL prior to and during Lixiana/ Roteas treatment. In patients with mild renal impairment (CrCl > 50 – 80 mL/min), the recommended dose is 60 mg edoxaban once daily. In patients with moderate or severe renal impairment (CrCl 15 – 50 mL/min), the recommended dose is 30 mg edoxaban once daily (see section 5.2). In patients with end stage renal disease (ESRD) (CrCl < 15 mL/min) or on dialysis, the use of edoxaban is not recommended (*see sections 4.4 and 5.2*). *Hepatic impairment* Lixiana/Roteas is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see *section 4.3*). In patients with severe hepatic impairment, Lixiana/ Roteas is not recommended (see *sections 4.4 and 5.2*). In patients with mild to moderate hepatic impairment the recommended dose is 60 mg Lixiana /Roteas once daily (see *section 5.2*). Lixiana/Roteas should be used with caution in patients with mild or moderate hepatic impairment (see *section 4.4*). Patients with elevated liver enzymes (ALT/AST >2 × ULN) or total bilirubin ≥1.5 × ULN were excluded in clinical trials. Therefore, Lixiana/Roteas should be used with caution in this population (see *sections 4.4 and 5.2*). Prior to initiating Lixiana/Roteas, liver function testing should be performed. *Body weight* For patients with body weight ≤60 kg, the recommended dose is 30 mg Lixiana/Roteas once daily (see *section 5.2*).

	Gender No dose reduction is required (see *section 5.2*). *Concomitant use of Lixiana with P-gp inhibitors* In patients concomitantly taking Lixiana /Roteas and the following P-gp inhibitors: cyclosporine, dronedarone, erythromycin, or ketoconazole, the recommended dose is 30 mg Lixiana/Roteas once daily (see *section 4.5*). No dose reduction is required for concomitant use of amiodarone, quinidine, or verapamil (see *section 4.5*). The use of Lixiana /Roteas with other P-gp inhibitors including HIV protease inhibitors has not been studied. *Paediatric population* The safety and efficacy of Lixiana/Roteas in children and adolescents less than 18 years of age have not been established. No data are available. *Patients undergoing cardioversion* Lixiana/Roteas can be initiated or continued in patients who may require cardioversion. For TEE guided cardioversion in patients not previously treated with anticoagulants, Lixiana/Roteas treatment should be started at least **2 hours** before cardioversion to ensure adequate anticoagulation (see *sections 5.1* and *5.2*). Cardioversion should be performed no later than 12 hours after the dose of Lixiana /Roteas on the day of the procedure. **For all patients undergoing cardioversion:** Confirmation should be sought prior to cardioversion that the patient has taken Lixiana/Roteas as prescribed. Decisions on initiation and duration of treatment should follow established guidelines for anticoagulant treatment in patients undergoing cardioversion. <u>Method of administration</u> For oral use. Lixiana /Roteas can be taken with or without food (see *section 5.2*). For patients who are unable to swallow whole tablets, Lixiana/Roteas tablets may be crushed and mixed with water or apple puree and immediately administered orally (see section 5.2). Alternatively, Lixiana/Roteas tablets may be crushed and suspended in a small amount of water and immediately delivered through a gastric tube after which it should be flushed with water (see section 5.2). Crushed Lixiana /Roteas tablets are stable in water and apple puree for up to 4 hours.

	Proposed: *Paediatric population* Edoxaban is not recommended for use in children and adolescents from birth to 18 years of age with confirmed VTE (PE and/or DVT) event as the efficacy has not been established. Available data in VTE patients are described in sections 4.8, 5.1 and 5.2.
Pharmaceutical form(s) and strengths	Current: Film-coated tablet, 15 mg, 30 mg, 60 mg Orange, round-shaped film-coated tablets (6.7 mm diameter) debossed with "DSC L15". Pink, round-shaped film-coated tablets (8.5 mm diameter) debossed with "DSC L30". Yellow, round-shaped film-coated tablets (10.5 mm diameter) debossed with "DSC L60".
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

ALT = alanine transaminase; AST = aspartate transaminase; ATC = anatomical therapeutic chemical; CrCL = creatinine clearance; DVT = deep vein thrombosis; EEA = European Economic Area; ESRD = end-stage renal disease; EU = European Union; FXa = activated coagulation factor X; HIV = human immunodeficiency virus; INN = international non-proprietary name; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism; P-gp = P-glycoprotein; RMP = Risk Management Plan; SmPC = Summary of Product Characteristics; TEE = transoesophageal echocardiogram; TIA = transient ischaemic attack; ULN = upper limit of normal; VTE = venous thromboembolism

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Indications:

The initial market authorisation application for edoxaban in European Union (EU) encompassed 2 indications:

- Prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with 1 or more risk factors, such as congestive heart failure (CHF), hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA)
- Treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults

Following European Commission (EC) decision in Jun 2015, edoxaban became available for patients with NVAF and patients with VTE (DVT and/or PE) for the treatment and prevention of potentially life-threatening recurrent thromboembolic events.

The search methodology for the epidemiology of each indication included searching large registries, databases, and observational studies. Search results focused on publications of human subject data that were published in English language between 2000 and 2018.

If there was no incidence rate provided within the article, it was calculated using the following equation:

$$\text{Incidence rate} = \frac{\text{total number of new cases during time at risk}}{\text{sum of person} - \text{time at risk}} \times 1000$$

Information is presented by indication and comorbidities in the target population presented. Much of the data presented hereafter, arises from population studies of different designs and diagnostic thresholds for diseases of interest. Therefore, the figures provided for incidence, prevalence, and mortality can differ significantly from one study to another, and direct comparisons are not appropriate; typically, higher frequencies for a given parameter suggest broader diagnostic criteria.

SI.1 Nonvalvular Atrial Fibrillation

SI.1.1 Epidemiology of the Disease

Note that data are provided for atrial fibrillation (AF) as opposed to NVAF to provide the most complete dataset available.

AF, the most common cardiac rhythm disorder, affects approximately 4.5 million adults in the EU and about 2.3 million adults in the United States of America (USA). Over the past 3 decades, the incidence of AF has been increasing.

The incidence, prevalence, mortality, and demographic profile of the NVAF population are shown in the table below.

Indication	**Nonvalvular atrial fibrillation**

Incidence:

The variability and uncertainty about the incidence and prevalence of AF is in part related to case definitions and/or inclusion of different types of AF (eg, permanent, persistent, and paroxysmal) or the inclusion/exclusion of AF related to particular underlying pathologies. Older studies tended to include only patients with permanent AF, which constitute a minority of all patients with AF. The lifetime risk of developing AF is about 25% (1 in 4) among those who have reached the age of 40 years.

World: Age-adjusted incidence of AF in 2010 was estimated to be 77.5 and 59.5 per 100,000 person-years for men and women, respectively. Incidence of AF has increased from 1990 to 2010 in both genders.

Netherlands: In a population-based prospective cohort study among individuals aged ≥55 years (n = 6808, time period 1990 to 1999): 9.9 cases (95% CI = 9.0 to 10.9) per 1000 person-years over a mean follow-up period of 6.9 years.

Iceland: In a population-based study in Reykjavik (n >100,000, 1991 to 2008): 2.4 cases per 1000 person-years (age and sex standardised) in 2008.

Denmark: In a registry-based study, the 1999 incidence of hospital diagnosis of AF was 4.38 cases per 1000 person-years in a population aged 40 to 89 years.

UK: In a study using the GPRD database, the incidence of chronic AF was estimated at 1.7 cases per 1000 person-years. In a prospective, population-based study in Western Scotland, the incidence was 0.54 cases per 1000 person-years.

USA: In a population-based study in Olmsted County, Minnesota (n >100,000, 1980 to 2000): 3.68 cases (95% CI = 3.42 to 3.95) per 1000 person-years (age and sex adjusted) in 2000. In the elderly Medicare population aged ≥65 years, the incidence of AF remained stable at around 28.3 cases per 1000 person-years during the 14-year study period between 1993 and 2007.

The overall incidence of AF was estimated to be 9.03 (95% CI = 9.00 to 9.06) per 1000 person-years in a database study in California.

Canada: Based on a study using linkage of 5 databases maintained by the Ministry of Health and Wellness in Alberta (n = 46, 440): 3.5 cases per 1000 person-years (age- and sex-adjusted population) (2000 to 2005).

Indication	Nonvalvular atrial fibrillation

Prevalence:

The prevalence of AF has increased over time and is projected to increase further in the next 50 years. In a recent pooled analysis of published studies, AF prevalence was estimated at 2.8%.

World: In 2010, estimated prevalence rates of AF per 100,000 population were 596.2 (95% uncertainty interval [UI] = 558.4 to 636.7) in men and 373.1 (95% UI = 347.9 to 402.2) in women worldwide.

EU and Netherlands: Based on data from the Rotterdam Study, the 2010 prevalence of AF was estimated at 1.6%. Extrapolating data from the known EU populations, it was estimated that 8.8 million adults over 55 years had AF in Europe in 2010 (95% CI = 6.5 to 12.3). This is projected to double by 2060 to 19.9 million (95% CI = 13.5 to 23.7) if the AF prevalence remains stable.

UK: In a 1972 population-based ECG screening study from Western Scotland, the prevalence of AF was 0.65%. In a retrospective GPRD study, the 1998 prevalence was estimated at 1.2%. In a UK-based study, age- and sex-standardised AF prevalence increased from 2.14% (95% CI = 2.11% to 2.17%) in 2000 to 3.29% (95% CI = 3.27% to 3.32%) in 2016.

Germany: In a 2007 random population sample of 5000 individuals with a mean age of 52.2 years, ECG-confirmed prevalence of AF was 2.5%.

Italy: In a 2000 chart review-based study, the prevalence of AF was 1.75% (70% chronic AF). In a 2009 to 2011 chart review study of adults in Naples, the crude prevalence of AF was 1.3%.

Sweden: The prevalence of clinically diagnosed AF in adults in the national Swedish Patient Registry was reported to be 2.9% (2005 to 2010). In a population-based study that relied on web-based general practitioner reporting, the AF prevalence in 2010 was 2.5%, with 75% of subjects with chronic AF.

Portugal: In a random sample of >10,000 individuals aged ≥40 years, the prevalence of ECG-confirmed AF was 2.5%.

Iceland: In a population-based study in Reykjavik (n = 4905, 1991 to 2008): 1.9% (age and sex standardised) in 2008.

USA: Within the Northern California Kaiser Permanente healthcare system, the 1997 crude prevalence of AF was 0.95%. In a population-based study in Olmsted County, Minnesota (n > 100,000, 1980 to 2000), prevalence was 2.5% (95% CI = 2.4 to 2.7). US nationally (2004 to 2005): 1.03%. **Japan:** In a population-based survey on Kurashiki city residents aged ≥40 years, prevalence was 1.6% in 2006.

Indication	**Nonvalvular atrial fibrillation**

Demographics of the target population (eg, age, sex, and race/ethnic origin):

Age:

The incidence and prevalence of AF increase with age. Using systematically reviewed data from population-based studies of AF in 21 Global Burden of Disease regions, the incidence of AF (per 100,000 person years) was estimated to be about 4.7 (95% CI = 3.6 to 6.5) in individuals 30 to 34 years compared to 368.1 (95% CI = 302.1 to 462.5) in those aged 70 to 74 years.

Netherlands:

The incidence of AF in a population-based prospective cohort study in adults aged ≥55 years (1990 to 1999) was as follows:

Age range	Incidence per 1000 person-years (95% CI)
55 to 59	1.1 (0.3 to 2.9)
60 to 64	3.3 (2.2 to 4.7)
65 to 69	5.5 (4.2 to 7.1)
70 to 74	11.5 (9.5 to 14.0)
75 to 79	14.7 (12.0 to 17.7)
80 to 84	20.7 (16.8 to 25.3)
≥85	18.2 (14.0 to 23.3)

Prevalence: 0.7% (95% CI = 0.4 to 1.4) in ages 55 to 59 years, rising to 17.8% (95% CI = 14.5 to 21.7) in ages ≥85 years

Sweden: The AF prevalence increased with age from 6.3% in patients over 55 years of age to 13.8% in those over 80 years.

Iceland: A linear increase in AF prevalence with increasing age in both sexes was observed in a population-based study (trends during 1998 to 2008).

USA: The AF incidence (per 1000 person-years) by age and gender in a population-based study (period of 1995 to 2000) was as follows:

Index age (years)	Men	Women
<55 years	0.6	0.2
55 to 64	4.6	2.4
65 to 74	12.9	7.3
75 to 84	26.3	17.7
≥85	40.1	28.7

Sex:

In the majority of regions, men had a higher reported incidence of AF than women.

International, UK, Sweden, Iceland, France, and Sweden large population studies: Prevalence is higher in men than in women. In a recent pooled analysis of published studies, AF prevalence was estimated at 3.3% in men and 2.4% in women.

Indication	Nonvalvular atrial fibrillation

Netherlands: The incidence of AF in a population-based prospective cohort study was 11.5 cases per 1000 person-years for men and 8.9 cases per 1000 person-years for women (period of 1990 to 1999).

UK: Incidence in men was higher than in women, especially in younger ages, with an overall age-adjusted relative risk of 1.4.

Denmark: In a series of ECG-based cross-sectional studies in Copenhagen, age-standardised prevalence of ECG-confirmed AF changed from 1.4% (1976 to 1978) to 3.3% (1991 to 1994) in men and from 1.5% (1976 to 1978) to 1.1% (1991 to 1994) in women.

USA: In 11,806 participants from the REGARDS study, over a median follow-up of 9.0 years, 588 (11.1%) men and 428 (6.6%) women ($P < 0.001$) developed AF. Men had a higher risk of AF than women (age- and race-adjusted OR [95% CI] = 1.61 [1.26, 1.75]).

Race/ethnic origin:

In limited data, Whites had a higher reported risk of AF than other individuals with different races or ethnic origins.

Although studies evaluating the prevalence and incidence of AF in non-White populations are limited, a study evaluating the risk of AF based on data from the Age, Gene/Environmental Susceptibility Reykjavik Study, the CHS, and the Framingham Heart Study demonstrated that the risk of AF varies by study cohort and ethnicity, and the incidence of AF was 22.7 cases per 1000 person-years among Whites and 18.4 cases per 1000 person-years among African-Americans in the CHS cohort.

USA: In the CHS (prospective cohort study), the risk of AF was 45% lower (HR 0.55, 95% CI = 0.35 to 0.88) in blacks compared to Whites. In a hospital-based database study in California, Whites had a higher AF risk compared to the AF risk of Blacks, Hispanics, or Asians.

UK: In a cross-sectional study recruiting South Asian and African-Caribbean ethnic groups aged 45 years and over in residents of Birmingham in the UK, the prevalence of AF was 1.4% in African-Caribbean's and 0.7% in South Asians.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

AF is an important marker of future morbidity with major consequences for the healthcare delivery systems and imposes a substantial burden on increased morbidity and mortality-associated therapeutic interventions.

UK: Patient hospitalisation data from the Information and Statistics Division of the Scottish National Health Service from 2004 to 2008 were analysed to estimate trends in hospital episodes in the 5.2 million population of Scotland. Over the 5-year period, AF-related hospital discharges increased by 33% compared with 20% for all cardiovascular discharges (29 and 37 cases per 1000 person-years, respectively). There were increases of 21% in the number of patients hospitalised, 27% in AF-related hospital admissions, and 15% in total patient bed days. The mean length of inpatient stay for AF remained higher than for total cardiovascular conditions (10.9 vs. 8.7 days).

Indication	Nonvalvular atrial fibrillation

Canada: From 1998 to 2009, a random sample of 64,157 Canadian patients with newly diagnosed AF and at least 1-year follow-up was derived from a health claims database and analysed as a cohort for survival and changes in comorbidities and medical resource use after diagnosis. Compared to the year prior to diagnosis, medical resource used increased significantly the year after diagnosis. Patients were hospitalised more frequently (1.5 vs. 1.1 hospitalisations, P <0.01), for longer durations (5.6 vs. 3.3 days, P <0.01), and with more visits to specialists (8.1 vs. 6.7 visits, P <0.01) as opposed to general physicians (4.8 vs. 5.1 visits, P <0.01).

Mortality

Death rates are doubled by AF independently of other known predictors of mortality. Only antithrombotic treatment has been shown to reduce AF-related deaths.

World: In 2010, the age-adjusted mortality rate (per 100,000 population) for AF was 1.6 (95% UI = 1.0 to 2.4) for men and 1.7 (95% UI, 1.4 to 2.2) for women. Mortality rates from AF increased by 2-fold (95% UI, 2.0 to 2.2) and 1.9-fold (95% UI, 1.8 to 2.0) in men and women, respectively, from 1990 to 2010.

International: In the observational Euro Heart Survey (n = 3182) with 1-year follow-up, all-cause mortality was 5.3% (3.5% for paroxysmal AF, 3.0% for persistent AF, and 8.2% for permanent AF). The mean ages of the patients with paroxysmal AF, persistent AF, and permanent AF at baseline were 64, 66, and 71 years, respectively.

France: A total of 3646 patients with AF or atrial flutter were examined in a single institution between 2000 and 2007. In 2.6 years of follow-up, mortality was reported to be 15%. The mean age of the patients was 71 years.

Sweden: Patients with diagnosis of AF or flutter (n = 1981) were included in a cohort study identified from local hospital or primary care registries. Over 3.6 years of follow-up, all-cause mortality was 35%. In a recent nationwide study, the relative risk of death following AF diagnosis was higher in women than in men in all ages and was highest in the youngest patients. For example, among individuals aged <65 years at AF diagnosis, the relative risk of death within the first year of diagnosis was 7.67 times higher in women and 4.99 times higher in men than in controls. In individuals aged 75 to 85 years at AF diagnosis, the relative risk of death within the first year of diagnosis was 2.81 times higher in women and 2.33 times higher in men.

USA: In the Women's Health Study (n = 34,722), AF was associated with an increased risk of all-cause (HR = 1.7), cardiovascular (HR = 2.57), and non-cardiovascular mortality (HR = 1.42). In the ARIC study (n = 15,439), AF was associated with an increased risk of both sudden and non-sudden deaths, with HRs of 3.26 (95% CI = 2.17 to 4.91) and 2.43 (95% CI = 1.60 to 3.71), respectively.

AF = atrial fibrillation; ARIC = Atherosclerosis Risk in Communities; CHS = Cardiovascular Health Study; CI = confidence interval; ECG = electrocardiogram; EU = European Union; GPRD = General Population Research Database; HR = hazard ratio; OR = odds ratio; UI = uncertainty interval; UK = United Kingdom; US = United States; USA = United States of America

SI.1.2 Main existing treatment options:

European Society of Cardiology Guidelines on the Management of AF:

- Antithrombotic management for the prevention of stroke
- Acetylsalicylic acid, antiplatelet agents
- Vitamin K antagonists (VKAs)
- Direct thrombin inhibitors

- Factor Xa inhibitors
- Rate and rhythm control
- Beta blockers (eg, metoprolol, atenolol, bisoprolol, and nebivolol)
- Calcium channel blockers (eg, diltiazem and verapamil)
- Cardiac glycosides: digoxin
- Pharmacological cardioversion: (eg, amiodarone, dronedarone, procainamide, dofetilide, ibutilide, propafenone, or flecainide)
- Electrical cardioversion
- Radiofrequency ablation

SI.1.3 Concomitant Medication(s) in the Target Population: Atrial Fibrillation

Once cardioversion to sinus rhythm is unsuccessful and AF is recurrent or continuous, the principal aim of medication is to control the ventricular rate rather than to achieve sinus rhythm through the use of beta blockers, calcium-channel blockers, and cardiac glycosides; pharmacological cardioversion is attempted with amiodarone and other antiarrhythmic drugs. Anticoagulation to prevent stroke is employed with either single or combination therapy of antiplatelet agents and oral anticoagulants (VKAs, direct thrombin inhibitors, or factor Xa inhibitors).

Patients with AF often are treated with additional medications for the following comorbidities as discussed in the next section: stroke or TIA, hypertension, cardiac failure, ischemic myocardial disease, diabetes mellitus, malignancy, and renal failure. Complex polypharmacy such as the following is frequent and complicates individual patient management: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, antihyperglycaemic and insulin-sensitising agents, beta-blockers, calcium-channel blockers, and more. Consequently, the potential for drug-drug interactions in the AF population is high and one of the driving factors for the development of novel oral anticoagulants (NOACs). Traditional oral VKAs present a particularly challenging interaction potential with high risk of clinically relevant changes to exposure and resulting adverse effects (particularly bleeding) or lack of effect. Edoxaban's interaction potential and profile has been well studied in the extensive development programme.

SI.1.4 Important Comorbidities Found in the Target Population: Atrial Fibrillation

There are several known risk factors that can be attributed to the development of AF and constitute important comorbidities for AF. Concomitant medical conditions play a role in the perpetuation of AF. The prevalence of these comorbidities is much higher in patients with AF than in patients without. AF is an independent risk factor for stroke, which increases a patient's risk of stroke 4- to 5-fold. The incidence, prevalence, and mortality of well-known comorbidities of the AF population (CHF, hypertension, diabetes mellitus, stroke or TIA, coronary artery disease/myocardial infarction [MI], renal failure, and malignancy) are shown in the table below.

Comorbidities found in target population with atrial fibrillation	
Stroke or TIA	**Incidence:** **UK:** In a 1990 to 2008 cohort study (n = 20,837) using the GPRD, the average annual incidence rate of stroke was 1.0, 3.7, and 8.3 cases per 100 person-years in patients with low, moderate, and high CHF, hypertension, age >75 years, diabetes mellitus, and prior stroke or TIA (CHADS2) scores, respectively. **International:** In an observational Euro Heart Survey (n = 3182), the incidence of ischemic stroke was 1.6% during 1 year of follow-up. **Sweden:** In a hospital-based cohort study with over 3.6 years of follow-up (n = 1981), the incidence of stroke was similar in paroxysmal and permanent AF (26 to 29 events per 1000 person-years). In a large (n = 182,678) nationwide cohort study, the overall incidence of stroke/TIA/peripheral emboli was 7 cases per 100 person-years among patients who never used warfarin, and the incidence increased with increasing risk scores. Women with AF may have a 47% higher risk of stroke than men with AF. There was a decrease in risk of ischemic stroke in patients with AF over time, from 8.7% in 1987 to 1991 to 6.6% in 2002 to 2006. **Denmark:** Patients discharged from the hospital with a diagnosis of AF had a 2.4- to 3-fold higher risk of stroke. The incidence of stroke and death was highest early after AF diagnosis. At 1 year following AF diagnosis, crude incidence of stroke and death was 3.4 and 13.6 cases per 100 person-years, respectively. In a 1991 to 1998 nationwide study, the incidence of stroke was around 30 cases per 1000 person-years. AF is a very pronounced risk factor for stroke. In the Copenhagen City Heart Study, women who had AF had a much higher risk of stroke than women who did not have AF (cumulative incidence in 5 years of follow-up 20% vs. 1.5%, HR = 9.1, 95% CI = 5.8 to 14.2, adjusted for age). Likewise, men who had AF were also at increased risk of stroke compared with men who did not have AF (cumulative incidence in 5 years of follow-up: 7.8% vs. 2.8%, HR = 2.0, 95% CI = 1.1 to 3.5, adjusted for age), but the effect of AF on the risk of stroke was 4.5 times greater in women than in men (HR = 4.5, 95% CI = 2.2 to 9.2). The effect of AF on the risk of stroke and cardiovascular death was 4.6- and 2.5-fold greater in women than in men, respectively. **USA:** In a large observational study, the incidence of ischemic stroke among warfarin users and non-users with NVAF was 0.05 and 0.15 cases per 100 person-years, respectively.Women may have a higher risk of stroke off warfarin therapy than men. Post-AF ischemic stroke incidence decreased significantly by 3.4% per year from 1980 to 2000, during which time there was a substantial increase in the use of antithrombotic therapy. In a pooled analysis, 4 clinical features (prior stroke/TIA, advancing age, hypertension, and diabetes) were found to be consistent independent risk factors for stroke in patients with AF. The Women's Health Study showed that AF was a strong risk factor for stroke. Compared to women without AF, new onset AF cases were more likely to develop stroke over the median observation period of 15.4 years (HR = 4.17; 95% CI = 3.04 to 5.71).

Comorbidities found in target population with atrial fibrillation	
	Prevalence: **International**: 6% of patients had events of stroke, and 5.7% of patients had TIA in the observational Euro Heart Study. **Denmark:** 17.6% of patients had an event of stroke in the national patient registry (NVAF). **UK:** In patients with documented AF in GPRD, 18% had an event of stroke. Another analysis showed 12.8% stroke in patients with incident AF, and 8.0% in patients without AF. **France:** In patients with AF or atrial flutter from a single institution, 4.2% had an event of stroke. **Italy:** Among >6000 patients with AF, 18% had a history of stroke/TIA, and 29.3% had ≥3 comorbidities. **Mortality:** **Denmark:** Mortality within the first year of AF diagnosis was 13.6 cases per 100 person-years, which declined to 5.6 cases per 100 person-years in later years. Survival after AF-associated stroke seems to have improved from 1980 to 2002. **Europe:** In a prospective European rehabilitation cohort study, the 5-year cumulative mortality post-stroke was reported to be 29.12% (95% CI = 22.86 to 35.38), and AF was an independent predictor of mortality (HR = 1.52, 95% CI = 1.08 to 2.14). **Australia:** In patients hospitalised with a TIA (n = 22,157) compared to the age- and sex-matched general population (adjusted for significant comorbid conditions, sex, age, and year of discharge), AF remained an independent predictor of excess mortality (relative risk of 2.04; 95% CI = 1.56 to 2.67; P < 0.001). **Japan:** In a nationwide prospective cohort study of stable outpatients with high-risk cardiovascular diseases (n = 7513), the 1-year mortality due to stroke in patients with AF (n = 2506) was 0.15 events (95% CI = 0.03 to 0.45) per 100 person-years.
Coronary artery disease/MI	**Incidence:** **Canada:** In a random sample of 64,157 patients with newly diagnosed AF selected from a health claims database (1998 to 2009), 8.8% had new cases of MI within 1 year of follow-up. **Japan:** In a nationwide prospective study (n = 7513), 1-year event rate data revealed that the incidence of nonfatal MI among patients with AF was 0.15 events (95% CI = 0.03 to 0.45) per 100 person-years. **Sweden:** In a large observational cohort of patients with AF, MI was an independent risk factor for ischemic stroke, with an HR of 1.09. **USA:** In the Women's Health Study, 33,840 women participating underwent prospective follow-up. Compared to women without AF, new onset AF cases were more likely to experience MI over the median observation period of 15.4 years (HR = 3.14; 95% CI = 2.06 to 4.78).

Comorbidities found in target population with atrial fibrillation	
	Prevalence: **International:** In the observational Euro Heart Survey, the prevalence of coronary artery disease was 33.8%. **Iceland:** The prevalence of ischemic heart disease in a population-based study was 39%. **UK:** In a cohort of patients from GPRD, the prevalence of ischemic heart disease at study baseline was 27.1%. **France:** In a study conducted at a single hospital, 20% of the patients had coronary artery disease, and 11% of the patients had previous MI at baseline. **Canada:** In a random sample of patients diagnosed with AF from a health claims database, the prevalence of acute MI was 8.8% at baseline. **Mortality:** **International:** In a pooled analysis of 19 studies, history of MI was a significant predictor of stroke and mortality risk in patients with AF. **USA:** Warfarin was associated with a reduced mortality risk following stroke in patients with AF (OR: 0.64; 95% CI = 0.45 to 0.91). In a population-based cohort of 3220 patients hospitalised with incident (first-ever) MI from 1983 to 2007 in Olmsted County, Minnesota, AF was associated with a 3.77-fold increased risk of death, independent of clinical characteristics at the time of MI and HF. This risk differed markedly according to the timing of AF and was the greatest for AF occurring >30 days post-MI (HR = 1.63 [95% CI = 1.37 to 1.93] for AF ≤2 days, HR = 1.81 [95% CI = 0.45 to 2.27] for AF between 3 and 30 days, and HR = 2.58 [95% CI = 2.21 to 3.00] for AF >30 days post-MI). A total of 304 patients had AF prior to incident MI, and the HR for death in those with prior AF was 1.46 (95% CI = 1.26 to 1.70). **Japan:** In a nationwide prospective study, 1-year event rate data revealed that the incidence of fatal MI was 0.05 events (95% CI = 0.01 to 0.28) per 100 person-years among patients with AF.

Comorbidities found in target population with atrial fibrillation	
Hypertension	**Prevalence:** **International:** In the observational Euro Heart Survey, the prevalence of hypertension was 65.3%. In the international cross-sectional registry, the prevalence of hypertension was 72.2%. **US:** The Women's Health Study showed 43.8% prevalence of hypertension in women with incident AF, higher than 25.9% in women without incident AF at baseline. **Netherlands:** In a population-based prospective cohort study, the prevalence of hypertension was 21.4%. **Denmark:** In the NVAF, the prevalence of hypertension was 39.7%. **UK:** In a GPRD cohort study, the prevalence of hypertension was 50.2%. Another case–control analysis showed that the prevalence of hypertension was 67.1% in patients with incident AF, and 45.9% in patients without AF. **Mortality:** Mortality rate was higher among adults with hypertension compared to non-hypertensive adults (NHANES I and III). All-cause mortality among hypertensive adults was approximately 42% higher than among non-hypertensive adults (18.8 vs. 13.3 per 1000 person-years) in NHANES I and 57% (14.3 vs. 9.1 per 1000 person-years) in NHANES III. Furthermore, all-cause mortality among White hypertensive adults was higher than among non-hypertensive Whites for both cohorts (NHANES I: 18.1 vs. 12.9; NHANES III: 13.7 vs. 8.8). Similarly, black hypertensive adults had a higher all-cause mortality rate than their non-hypertensive counterparts (NHANES I: 24.5 vs. 19.2; NHANES III: 19.1 vs. 14.3).
CHF	**Incidence:** **Canada:** In a study based on linkage of 5 databases maintained by the Ministry of Health and Wellness in Alberta (n = 46,440), the incidence of new onset HF in the first year of AF diagnosis was 3.7%. **USA:** Among participants in the Women's Health Study, 33,840 women underwent prospective follow-up. Compared to women without AF, new onset AF cases were more likely to experience HF (HR = 14.67; 95% CI = 11.18 to 19.24). In the Framingham Heart Study, the incidence of HF in patients with AF was 33 cases per 1000 person-years, and the incidence of AF in HF patients was 54 cases per 1000 person-years. **Prevalence:** **International:** In the observational Euro Heart Survey, the prevalence of CHF was 36.3%. In the international cross-sectional registry, the prevalence of CHF was 45.8% (15% were categorised as New York Heart Association class III/IV.) **Denmark:** In the NVAF, the prevalence of CHF was 18.8%. **UK**: In the GPRD cohort study, the prevalence of CHF was 29.2%. A case control analysis of patients showed that the prevalence of CHF was 18.2% in patients with incident AF, much higher than 5.7% in patients without AF. **Sweden:** In a cohort of patients identified from local hospital or primary care registries, the prevalence of CHF was 50.2%.

Comorbidities found in target population with atrial fibrillation	
	Italy: Among >6000 patients with AF, 24.8% had HF. **Mortality:** **Denmark, Sweden, and Norway:** Data from HF cohort studies with 6 to 8 years follow-up are as follows: • In a multivariate analysis, AF at baseline was a significant predictor of mortality (HR = 1.09; 95% CI = 1.02 to 1.16; P = 0.0083). • AF remained an age-dependent predictor of mortality in the population 75 years and older (HR = range: 1.11 to 1.30; P <0.05). **USA:** Among HF patients with preserved ejection fraction, prior or concurrent AF (combined HR = 1.3; 95% CI = 1.0 to 1.6) and incident AF modelled as a time-dependent covariate (HR = 2.1; 95% CI = 1.4 to 3.0) were independently associated with death when compared to those without AF. In the Framingham Heart Study, pre-existing HF adversely affected survival in patients with AF, but pre-existing AF was not associated with adverse survival in patients with HF.
Diabetes mellitus	**Incidence:** There is lack of data on the incidence rate of diabetes mellitus in patients with pre-existing AF. There is published data on the incidence rate of AF among patients with diabetes mellitus. **USA:** In a cohort study based on a health maintenance organisation diabetes registry in the USA, diabetic patients without AF developed AF at an age- and sex-adjusted rate of 9.1 cases per 1000 person-years (95% CI = 8.6 to 7.9) compared to a rate of 6.6 cases per 1000 person-years (95% CI = 6.2 to 7.1) among non-diabetic patients. **Prevalence:** **International:** In the observational Euro Heart Survey, the prevalence of diabetes mellitus was 18.2%. In the international cross-sectional registry, the prevalence of diabetes mellitus was 21.3%. **USA:** The Women's Health Study showed 5.5% prevalence of diabetes in women with incident AF, higher than 2.6% in women without incident AF at baseline. **Denmark:** In the NVAF, the prevalence of diabetes mellitus was 9.1%. **UK:** In a GPRD cohort study, the prevalence of diabetes mellitus was 16.6%. **Mortality:** **International (including EU):** In a randomised study in patients with type 2 diabetes, AF was associated with a 61% (95% CI = 31 to 96; P < 0.0001) greater risk of all-cause mortality.

Comorbidities found in target population with atrial fibrillation	
Renal failure	**Prevalence:** **International:** In a cross-sectional registry, 3.9% of patients with a history of AF had chronic advanced renal failure. **Denmark:** In the NVAF, the prevalence of renal disease was 6.2%. **Sweden:** The prevalence of renal failure was 2.9% in a cohort of patients identified from local hospital or primary care centre registries. Renal failure was associated with increased risk of stroke in patients with AF. **Italy:** Among >6000 patients with AF, 26.8% had renal failure. **USA:** In a population-based US study of over 26,000 adults 45 years or older, 2.5% of 361 ECG-detected AF cases had evidence of end-stage renal failure. In subjects with chronic kidney disease who were not on dialysis from the Chronic Renal Insufficiency Cohort, 18% of all patients and >25% of patients ≥70 years of age had evidence of AF. **Mortality:** **USA:** In patients on dialysis with newly diagnosed AF, the all-cause mortality exceeded 40 deaths per 100 person-years.
Malignancy	**Prevalence:** **International:** In both an international cross-sectional survey and the observational Euro Heart Survey, the prevalence of malignancy was 4.6%. **Sweden:** In a cohort of patients identified from local hospital or primary care centre registries, 7.7% of patients had cancer of <3 years. **Denmark:** In the NVAF, the prevalence of malignancy was 14.5%. **Canada:** Based on a study using linkage of 5 databases maintained by the Ministry of Health and Wellness in Alberta (n = 46,440), the prevalence differed according to location where AF was diagnosed, as follows: 16.2% (hospital), 7.7% (emergency department), 5.9% (primary care outpatient clinic), and 6.7% (specialty outpatient clinic). **Mortality:** Cancer was the cause of 23% of all deaths during 2008 in the USA, with 565,469 cancer deaths reported.

AF = atrial fibrillation; $CHADS_2$ = CHF, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA; CHF = congestive heart failure; CI = confidence interval; ECG = electrocardiogram; EU = European Union; GPRD = General Population Research Database; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; NHANES = National Health and Nutrition Examination Survey; NVAF = nonvalvular atrial fibrillation; OR = odds ratio; TIA = transient ischemic attack; UK = United Kingdom; US = United States; USA = United States of America

SI.2 Venous Thromboembolism

SI.2.1 Epidemiology of the Disease

DVT and PE are manifestations of a single pathophysiological process collectively referred to as VTE. DVT and PE often present together, share the same risk factors, and are associated with high morbidity that may progress to a fatal outcome if left untreated. VTE is the third most common cardiovascular illness after acute coronary syndrome and stroke.

The table below presents the incidence, prevalence, mortality, and demographic profile of the VTE population and differentiates between DVT and PE where data are available.

Indication: Venous thromboembolism

Incidence:

The reported incidence of VTE vary widely due to differences in the study populations, the coding or classification of the diagnoses, the settings under which VTE is diagnosed (eg, hospitals, outpatient clinics, etc), and study methodologies.

Denmark: In the Copenhagen Heart Study (random, age-stratified sample of individuals aged ≥20 years old, first sampled in 1976 with re-examination and additional individuals enrolled in 1976 to 1978, 1981 to 1983, 1991 to 1993, and 2002 to 2003), the crude incidence rate of VTE was 2.69 VTE events (95% CI = 2.52 to 2.86) per 1000 person-years. In the Danish prospective study Diet, Cancer and Health (1993 to 2006), which enrolled males and females aged 50 to 64 years old, the overall incidence rate of VTE was 1.15 events (95% CI = 1.07 to 1.25) per 1000 person-years. The incidence rates for DVT and PE were 0.65 events (95% CI = 0.58 to 0.72) per 1000 person-years and 0.51 events (95% CI = 0.45 to 0.57) per 1000 person-years, respectively.

Norway: In a population-based study conducted between 1995 and 2001, the incidence of first VTE, DVT, and PE events were 1.43, 0.93, and 0.50 per 1000 person-years, respectively.

France: In a community-based study, the incidence of VTE was 1.83 events (DVT 1.24 and PE 0.60) per 1000 person-years. For those over the age of 75 years, the incidence reached 1 per 100.

USA: Within the combined cohort of >21,000 participants from the ARIC study and the CHS, the age-standardised incidence of first-time VTE was 1.92 events per 1000 person-years. First-time occurrence of VTE in the USA is estimated to be around 100 persons per 100,000 each year in the USA. The incidence of VTE ranges from 1.6 to 2.69 cases per 1000 person-years in the EU, and US studies have shown incidence ranging from 3.54 to 4.04 cases per 1000 person-years over 3- and 19-year follow-up periods, respectively.

Korea: (General population, 2004 to 2008): 13.8, 5.31, and 7.01 per 100,000 (age- and sex-adjusted annual incidence for DVT alone, PE with DVT, and PE without DVT, respectively)

Germany: (Trauma patients, 2005 to 2007): 1.8% developed VTE during hospitalisation.

US: (Oncology patients, 2004 to 2009): 2.87% developed a PE (12.90% among patients with CNS malignancies and,1.16% among patients with hematologic malignancies).

US: (Neurosurgical patients, 2003 to 2006): 9.7% experienced a DVT during hospitalisation over a 4-year period.

UK: A study in active cancer patients estimated that the incidence rate for first VTE was 5.8 (95% CI = 5.7 to 6.0) per 100 person-years.

Recurrent VTE:

International: In an ongoing international observational registry of consecutive patients with symptomatic and objectively confirmed acute VTE (enrolled in Registro Informtizado su la Enfermedad TromboEmbolica [RIETE]), 14,480 patients with symptomatic DVT were included in a study to investigate fever and DVT and their association with worsening outcomes during the first month of treatment (where 96% of the patients received initial therapy with LMWH). During the 30-day study period, the proportion of patients who experienced recurrent DVT was 1.2% and recurrent PE was 2.6%.

Netherlands: In a cohort of 1303 patients with VTE, the incidence of recurrence was 27.1 cases per 100 person-years among those with malignancies and 9 cases per 100 person-years among non-malignant patients.

Spain: In a retrospective cohort study on patients with acute symptomatic PE (2003 to 2010) conducted in a single institution (n = 1291), 9.9% were found to have had a previous VTE at presentation.

UK: In a small cohort of VTE patients, recurrence at 2 years was 11%. Incidence rate for recurrence was 9.6 (95% CI = 8.8 to 10.4) per 100 person-years among active cancer patients.

USA: Based on the review of medical records of residents from Worcester, Massachusetts, with possible VTE (from 1999, 2001, or 2003) from hospitals serving the region, the 3-year cumulative incidence rates of subsequent PE and overall VTE in patients who presented with PE (with or without DVT) and isolated DVT were found to be similar (recurrent PE: 5.9% vs. 5.1%; recurrent VTE: 15% vs. 17.9%). In a

Indication: Venous thromboembolism
population-based cohort in Olmsted County, Minnesota, the cumulative percentages of VTE recurrence at 6 months, 1 year, and 10 years were 10.1%, 12.9%, and 30.4%, respectively. The RR was greatest in the first 6 to 12 months after the initial event. In a claims database study, the cumulative incidence of recurrent VTE events over 3 and 6 months was 9.0% and 10.9%, respectively. Taiwan: (VTE patients, 2001 to 2002): 5.1% per person-year (crude incidence of VTE recurrence); 5.1% among men and 5.2% among women. **Spain, France, Italy, Israel, and Argentina:** (VTE and active cancer, most treated with LMWH, until 2007): 4.6% of women and 5.3% of men had a recurrent VTE after 3 months (recurrent PE: 2.3% in women and 2.4% in men; recurrent DVT: 2.3% in women and 2.9% in men). **US:** In VTE patients, 5.3% had recurrent PE, and 15.2% had recurrent DVT. **Canada:** In acutely ill hospitalised patients from 2002 to 2006, 0.9% developed a DVT in a 3-month period (69% within 30 days), 55% experienced a VTE while hospitalised, and half were diagnosed post-discharge. In an adjusted Cox model, previous VTE predicted 3-month VTE (HR = 5.0).
Prevalence: Many of the large epidemiology studies on VTE in European countries reported the cumulative incidence or incidence rate of VTE rather than prevalence data. **USA:** A retrospective analysis of healthcare claims data in the USA reported an annual prevalence of VTE of 317 cases per 100,000 patients in 2002 and 422 cases per 100,000 patients in 2006.
Demographics of the target population (eg, age, sex, and race/ethnic origin): **Age:** The incidence of VTE steadily increases with age, particularly after age 40 years. In a retrospective analysis of healthcare claims data in the USA, the annual prevalence of VTE (cases per 100,000) was reported to increase with age: 1382 in patients aged ≥65 years versus 231 in patients aged <65 years (2006 data). In Japan, the incidence of VTE steadily increases with age, and increased age is associated with a higher risk of PE. When compared to persons less than 20 years old, the relative risk increases from 160.5 among those aged 70 to 74 years to 417.8 among those more than 79 years old. **Sex:** No consistent differences in the incidence of VTE among men and women have been observed. Some studies have reported higher incidence of VTE in men, while others have reported higher incidence in women. RR may be higher in men than in women. **Ethnicity:** There is a 2.5- to 4-fold lower risk of VTE in Asians/Pacific Islanders and Hispanics compared to Caucasians. White et al reported an annual incidence of VTE in persons ≥18 years of 104 per 100000 among Caucasians, 141 among African-Americans, 55 among Hispanics, and 21 among Asian-Pacific Islanders and an annual incidence of idiopathic VTE of 23 per 100,000 among Caucasians, 29 per 100,000 among African American, 14 per 100000 among Hispanics, and 6 per 100,000 among Asia-Pacific Islanders. The above findings were supported by another study that reported a lower adjusted risk of VTE among Hispanics (RR = 0.7, 95% CI = 0.3 to1.5) and Asians (RR = 0.2, 95% CI = 0.1 to 0.5) than among Whites in a large cohort followed prospectively in the Kaiser Health System in Northern California. **Taiwan:** In VTE patients in 2002, the incidence of VTE was 4 per 100,000 in patients <40 years and 108 per 100,000 in patients ≥80 years. **India:** (DVT patients, 1996 to 2005): 48% were men, the mean age was 45.1 years, and patients with a secondary DVT were older (36.8 vs. 51.8 years).

Indication: Venous thromboembolism
Natural history of the indicated condition in the untreated population, including mortality and morbidity **Morbidity:** **EU:** Based on an epidemiological model constructed to study community- and hospital–acquired cases of VTEs in the EU (France, Germany, Italy, Spain, Sweden, and the UK), the total number of symptomatic VTE events per annum across the 6 countries was estimated to be 761,697 non-fatal VTE events (465,715 cases of DVT and 295,982 cases of PE) and 399,808 associated complications (395,673 patients with post-thrombotic syndrome and 4135 with pulmonary hypertension) in 2004. **USA:** Based on the National Hospital Discharge Survey (2007 to 2009), the estimated average annual rate (per 100,000 population) of hospitalisations with a diagnosis for DVT, PE, or VTE in the USA is 152 (95% CI = 127 to 177), 121 (95% CI = 98 to 144), or 239 (95% CI = 199 to 279), respectively. **Mortality:** Case fatality rates are difficult to interpret, as studies may differ with regard to the inclusion of autopsy data to identify patients with VTE or the practice of conducting autopsies for deaths of unexplained causes. Early mortality after VTE is strongly associated with presentation as PE, advanced age, cancer, and underlying cardiovascular disease. Survival after PE is much rarer than after DVT alone. **International:** In a cohort of 14,480 patients from the RIETE observational registry, 3.1% of patients with acute DVT died within the first 30 days. **International:** In a VTE population followed for 54 months after discontinuing anticoagulant therapy, the annual risk for any fatal PE was 0.49 cases per 100 person-years, with 14% all-cause fatality. **Netherlands:** In a large cohort study, VTE was associated with a 4-fold increased risk of death compared with controls, and the risk remained increased up to 8 years after the event. **EU:** Based on an epidemiological model constructed to study community- and hospital-acquired cases of VTEs in Europe (France, Germany, Italy, Spain, Sweden, and the UK), the total number of symptomatic VTE-related deaths per annum was estimated to be 370,012 (300,193 to 483,108). Of these deaths, 7% were diagnosed as being antemortem, 34% were sudden fatal PE, and 59% followed undiagnosed PE. **Spain:** In a study that recruited patients with acute symptomatic PE from the emergency department of a single hospital (2003 to 2009), the all-cause mortality in the first month of follow-up was 9.9% (95% CI = 8.2 to 11.5). In a study on patients with symptomatic DVT or PE initially treated with LMWH (included in RIETE), mortality was 7.8% over 3 months. **USA:** Based on the review of medical records of residents from Worcester, Massachusetts, from 1999 to 2001 or 2003 from hospitals serving the region, all-cause mortality was higher for patients with PE compared to those with isolated DVT at the following time periods: 30 days (13.0% vs. 5.4%), 1 year (26.0% vs. 20.3%), and 3 years (35.3% vs. 29.6%).

ARIC = Atherosclerosis Risk in Communities; CHF = congestive heart failure; CHS = Cardiovascular Health Study; CI = confidence interval; CNS = central nervous system; DVT = deep vein thrombosis; EU = European Union; HR = hazard ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; PE = pulmonary embolism; RIETE = Registro Informtizado su la Enfermedad TromboEmbolica; RR = risk of recurrence; UK = United Kingdom; US = United States; USA = United States of America; VTE = venous thromboembolism

SI.2.2 Main Existing Treatment Options

The following list the main existing treatment options for VTE

- Initial anticoagulation/prophylaxis:
  - Unfractionated heparin (UFH), low molecular weight heparin (LMWH), fondaparinux
  - Novel agents: rivaroxaban
  - In patients with suspected heparin-induced thrombocytopenia, a direct thrombin inhibitor (argatroban, lepirudin, bivalirudin)
- Long-term anticoagulation/prophylaxis:
  - VKA: warfarin
  - Novel agents: rivaroxaban, dabigatran
- Other treatments, including surgical interventions (less commonly used):
  - Inferior vena cava filters, fibrinolysis, pulmonary embolectomy, pulmonary thromboendarterectomy

SI.2.3 Concomitant Medication(s) in the Target Population: Venous Thromboembolism

When compared with the AF population, patients presenting with VTE arise from diverse populations. Patients with short-term increased risk of thromboembolic events (such as peri-operatively or during significant periods of immobilisation) will have different concomitant medications than patients with chronic comorbid conditions as discussed in the following section: hypertension, cardiac failure, ischemic myocardial, diabetes mellitus, malignancy, chronic obstructive pulmonary disease (COPD) and renal failure. For patients with chronic comorbid conditions, complex polypharmacy is frequent and complicates individual patient management: angiotensin converting enzyme inhibitors, angiotensin receptor blockers, diuretics, antihyperglycaemic and insulin-sensitising agents, beta-blockers, calcium-channel blockers, and more. Furthermore, for COPD bronchodilators and betamimetics, as well as the treatment of renal disease and impairment with consequent anaemia, lead to potentially complex multifactorial ongoing treatment plans. Particularly, patients with a history of or active cancer will also have related antitumor therapies including cytostasis, radiation, and surgical intervention, which all contribute to significant immobility and raising the risk for thromboembolic events both in the short and long term.

SI.2.4 Important Comorbidities Found in the Target Population: Venous Thromboembolism

Comorbidities that the AF population and the VTE population have in common are stroke/TIA, coronary artery disease/MI, CHF, hypertension, diabetes mellitus, malignancy, COPD, and renal failure, albeit their incidence, prevalence, and mortality/morbidity typically differ. Malignancy is an associated risk factor for VTE but not for AF. Many of a patient's predisposing risk factors for VTE are comorbid conditions, such as MI, COPD, and cancer. The available data on incidence, prevalence, and mortality for all these comorbidities are presented in the following table.

Comorbidities found in target populations with venous thromboembolism	
Stroke/TIA	**Prevalence:** **Denmark:** In a population-based case-control study, 7% of the patients (cases: 9190) with incident VTE had a previous hospital diagnosis of stroke compared to 4.8% of the population controls (controls: 91,800). **UK:** In a case-control study (GPRD dataset: 11,557 DVT cases, 5162 PE cases selected), the prevalence of stroke was 2.6% in patients with DVT (controls: 1.4%) and 2.5% in patients with PE (controls: 1.3%). **Mortality:** **International:** In an ongoing observational registry of patients with acute VTE (RIETE), 0.2% of 14,480 patients with symptomatic DVT died from ischemic stroke during the initial 30-day follow-up period.
Coronary artery disease/MI	**Prevalence:** **Denmark:** In patients identified with a hospital diagnosis of VTE (n = 97,558) from a nationwide cohort study, 8.3% of the patients had a record of previous MI. In a population-based case-control study, previous MI remained an independent predictor of all 3 VTE events (PE, PE with DVT, and DVT alone) in an adjusted polytomous logistic regression (OR = 43.5 [95% CI = 39.6 to 47.8], 19.7 [95% CI = 16.0 to 24.2], and 9.6 [95% CI = 8.6 to 10.7], respectively). **UK:** In a case-control study (GPRD dataset), the prevalence of angina pectoris was 8.5% in patients with DVT (controls: 6.1%) and 12.9% in patients with PE (controls: 6.0%). The prevalence of MI was 2.9% in patients with DVT (controls: 2.0%) and 5.7% in patients with PE (controls: 2.1%). **Mortality:** **International:** In patients with symptomatic DVT (RIETE), 0.1% of patients died from MI in the initial 30-day study period. Of the patients in the study, 7.5% had a history of chronic heart disease at baseline.
CHF	**Prevalence:** **Denmark:** In a population-based case-control study, 6.6% of patients (cases: 9190) with incident VTE had a previous hospital diagnosis of HF compared to 3.6% of the population controls (controls: 91,800). In a population-based case-control study, previous CHF in the preceding 3 months conferred high risks of isolated PE (OR = 32.4 [95% CI = 29.8 to 35.2]), PE and DVT (OR = 22.1 [95% CI = 18.7 to 26.0]), or isolated DVT (OR = 12.7 [95% CI = 11.6 to 13.9]). **Spain:** In a retrospective cohort study on patients with acute symptomatic PE (2003 to 2010) in a single institution (n = 1291), 6.6% of the patients had HF at presentation. **Italy:** Based on data on VTE patients in Italy enrolled in RIETE (n = 896), 5.4% had pre-existing CHF. **Mortality:** **International:** In patients with symptomatic DVT (RIETE), 0.2% of the patients died due to HF in the initial 30-day study period. Of the patients in

Comorbidities found in target populations with venous thromboembolism	
	the study, 7.5% of the patients in the study had a history of chronic heart disease at baseline. **Spain:** In a retrospective cohort study on patients with acute symptomatic PE (2003 to 2010) in a single institution (n = 1291), 5.5% of all deaths (total number of deaths = 127) were due to HF. As indicated above, 6.6% of the patients in the total cohort had a history of HF.
Hypertension	**Prevalence:** **Denmark:** In a longitudinal follow-up population study (data from Copenhagen Heart Study), 50% of VTE patients (n = 969) had a history of hypertension. In a nationwide cohort study, 10.0% of VTE patients (n = 97,558) had a record of hypertension. **UK:** In a case-control study (GPRD dataset), the prevalence of hypertension was 25.6% in patients with DVT (controls: 22.0%) and 27.3% in patients with PE (controls: 23.0%).
Diabetes mellitus	**Prevalence:** **Denmark:** In a longitudinal follow-up population study (data from Copenhagen Heart Study), 3.1% of patients with VTE (n = 969) had diabetes mellitus. In a nationwide cohort study, 6.7% of VTE patients (n = 97,558) had a record of diabetes. **UK:** In a case-control study (GPRD dataset), the prevalence of diabetes was 7.8% in patients with DVT (controls: 5.1%) and 6.8% in patients with PE (controls: 5.3%).
Renal failure	**Prevalence:** **Denmark:** In a nationwide cohort study (n = 97,558), 2.1% of patients with a hospital diagnosis of VTE had a record of renal failure. **Italy:** Based on data on VTE patients in Italy enrolled in RIETE (n = 896), 4.7% of patients had CrCL <30 mL/min. **Mortality:** **International:** In patients with symptomatic DVT (RIETE), 0.1% of deaths were due to renal insufficiency in the initial 30-day study period. **Spain:** In a retrospective cohort study on patients with acute symptomatic PE (2003 to 2010) in a single institution (n = 1291), 0.8% of all deaths (total number of deaths = 127) were due to renal failure. There were no data on the proportion of patients with pre-existing renal failure at presentation.

Comorbidities found in target populations with venous thromboembolism	
Malignancy	**Incidence:** Active cancer accounts for 20% of incident VTE events. The incidence of VTE in cancer patients depends on the type, location, and stage of the malignancy. A meta-analysis concluded that there is a 3-fold excess risk of occult cancer in patients with VTE. The risk varies according to tumour site and is highest for cancers of the ovary, pancreas, and liver. **Netherlands:** In a case-control study on women with a first breast cancer hospitalisation during 2000 to 2007 (n = 11,473) and matched 1:10 by age to cancer-free women (cohort of patients selected from the Dutch National Medical Registry of PHARMO Record Linkage System), breast cancer patients experienced an extreme high risk of PE in the first 6 months after diagnosis (HR = 23.5, 95% CI = 11.1 to 49.7 compared to controls), which declined gradually to a 4 times increased risk (HR = 3.6, 95% CI = 2.4 to 5.5) more than 12 months after breast cancer hospitalisation. However, the incidence rate was low: less than 5 events per 1000 person-years during all time periods – 4.7 (95% CI = 3.1 to 6.9) PE/1000 person- years in the first 6 months after first hospitalisation, which declined to 1 (95% CI = 0.7 to 1.4) PE/1000 person- years at 1 year. In the controls, the incidence rate was 0.3 (95% CI = 0.2 to 0.5) PE/1000 person-years in the first 6 months with no change at 1 year. **UK:** In a case-control study (GPRD dataset), 9.2% of patients with DVT (controls: 2.7%) and 11.3% of patients with PE (controls: 2.7%) were reported to have cancer within the past year. **International:** In patients with symptomatic DVT (RIETE), 21.3% of patients had cancer, and 9.3% had disseminated cancer at study baseline. **Switzerland:** Prevalence of cancer among 236 idiopathic DVT patients without known cancer was 4.7%. **Spain:** Prevalence of cancer among 864 acute DVT patients was 5.4%. **Italy:** Based on data on VTE patients in Italy enrolled in RIETE (n = 896), 28% had cancer at registration. **Korea** (VTE patients, 2007): 4% (cancer detected after VTE diagnosis). **Prevalence:** **Denmark:** In patients identified with a hospital diagnosis of VTE (n = 97,558) from a nationwide cohort study, the incidence of patients with malignancies diagnosed before or within 90 days of VTE diagnosis was 17.7%. In a population-based case-control study, 16.7% of VTE patients had cancer (within 3 months after VTE/first hospital admission for VTE). In another registry-based study, the occurrence of cancer was 2.5-fold higher the first year following a superficial thromboembolic event, 2.8-fold higher following a DVT event, and 3.3-fold higher following a PE event. **Korea** (VTE patients, 2007)**:** 24% **UK** (VTE population, 2005 to 2008)**:** 13.6%; the peak incidence of cancer-associated VTE occurred earlier in women than in men in the sixth and seventh decade of life but was more frequent in males in the eighth and ninth decade; cancer was reported in only 2.6% of VTE patients younger than 31 years old.

Comorbidities found in target populations with venous thromboembolism	
	Mortality: **International:** In patients with symptomatic DVT (RIETE), 0.8% died from malignancy in the 30-day study period. **Austria:** In a retrospective analysis on medical records of patients with a history of VTE in 1 outpatient department (1994 to 2008), there were 169 deaths reported out of 3209 enrolled patients. Of the 169 deaths, cause of deaths due to malignancy was reported to be 34.3%. (The study excluded patients with active cancer at the time of referral, patients with asymptomatic PE, and those with isolated visceral vein thrombosis.) **Spain:** In a single-institution registry, patients with acute PE were followed for 30 days for all-cause mortality (n = 1291), and 23% of the patients had active cancer or were under treatment in the last year at presentation. Twenty-five (19.7%) out of a total of 127 deaths reported in the study were caused by cancer. In an unadjusted model, cancer predicted all-cause mortality (OR = 2.37; 95% CI = 1.40 to 4.02) after study entry (*P* <0.01). **Korea** (Lung cancer patients, 2003 to 2009): 3-month onset of PE was a significant predictor of mortality (HR = 1.5).
COPD	**Prevalence:** **Belgium, France, and Switzerland:** Based on data from 3 prospective cohort studies, in 773 patients with confirmed PE, the prevalence of COPD was 6.1%. **UK:** In a case-control study (GPRD dataset), 4.0% of patients with DVT (controls: 2.3%) and 5.0% of patients with PE (controls: 2.3%) were reported to have COPD. **International:** In patients with symptomatic DVT (RIETE), 3.9% had unspecified chronic lung disease. **Spain:** Based on a study in patients with symptomatic DVT or PE treated initially with LMWH (included in RIETE), 11.5% had chronic lung disease at study baseline. **Mortality:** **Spain:** In a single-hospital registry, patients with acute PE were followed for 30 days for all-cause mortality (n = 1291), and 101 (7.8%) patients had unspecified chronic lung disease recorded at presentation. There was a total of 127 deaths reported in the study, and of these, 5 deaths (3.9%) were related to COPD.

CHF = congestive heart failure; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CrCL = creatinine clearance; DVT = deep vein thrombosis; GPRD = General Population Research Database; HF = heart failure; HR = hazard ratio; LMWH = low molecular weight heparin; MI = myocardial infarction; OR = odds ratio; PE = pulmonary embolism; RIETE = Registro Informtizado su la Enfermedad TromboEmbolica; TIA = transient ischemic attack; UK = United Kingdom; VTE = venous thromboembolism

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The toxicity profile of edoxaban has been well characterised in a comprehensive battery of non-clinical studies, including toxicology studies in the rat and monkey. The table below

outlines the main elements of the programme and highlights any safety concerns that may be relevant to human usage from the non-clinical programme.

The table below includes key safety findings from non-clinical studies and relevance to human usage.

Key safety findings (from non-clinical studies)	**Relevance to human usage**
Toxicity **Single- and repeat-dose toxicity:** In general toxicity studies, haemorrhage was identified as the primary adverse effect and the lone dose-limiting toxicity. The single oral dose toxicity studies in rats at doses up to 2000 mg/kg HED, 12,000 mg/m^2; 324 times higher than the maximum recommended human dose of 60 mg/day) and in monkeys at 400 mg/kg (HED, 4800 mg/m^2; 130 times) indicated a relatively low acute toxicity potential for edoxaban. In repeat oral dose toxicity studies, haemorrhagic findings were observed in rats at 20 mg/kg/day (HED, 120 mg/m^2; 3.2 times) or higher doses and in monkeys at 15 mg/kg per day (HED, 180 mg/m^2; 4.9 times) or higher doses.	The toxicity at high dose reflects the dose-related pharmacological action of edoxaban. At therapeutic doses, edoxaban prolongs clotting time. In overdose or in patients with additional risk factors for bleeding, an increased risk of haemorrhage with edoxaban may be expected.
Reproductive and developmental toxicity: Reproductive performance was unaffected in both rats and rabbits. Edoxaban was shown to cross the placenta in rats. In embryo-foetal development studies in rats and rabbits, both maternal toxicity (vaginal haemorrhage, abortion, and death) and embryo-foetal toxicity (post-implantation loss, gallbladder variations, and low foetal weights) were observed in rats at 300 mg/kg/day (HED, 1800 mg/m^2; 48.6 times) and in rabbits at 200 mg/kg/day (HED, 2400 mg/m^2; 64.9 times). No teratogenicity was observed. In pre- and postnatal development studies in rats, maternal toxicity (vaginal haemorrhage) and a lower avoidance response rate in learning test in female offspring were observed at 30 mg/kg/day (HED, 180 mg/m^2; 4.9 times) but not in male offspring. Animal studies have shown that edoxaban is excreted in the breast milk of lactating rats.	No human data are available on fertility. No studies in pregnant subjects have been conducted. There were 10 incident pregnancies during the large Phase 3 programme (all from the Hokusai VTE study). There were 6 live births: 4 full-term delivery; 2 preterm deliveries. In one preterm case, the subject had a history of a prior preterm delivery and in the other, the subject had antiphospholipid antibodies. There was 1 spontaneous abortion (first trimester miscarriage) and 3 elective terminations. There were no congenital anomalies reported. The relevance of edoxaban crossing the placenta in rats is unknown in humans. No studies in lactating human subjects have been conducted. Edoxaban is excreted into the breast milk of lactating rats.

Key safety findings (from non-clinical studies)	Relevance to human usage
Nephrotoxicity: Edoxaban did not affect renal function in rats at doses up to 200 mg/kg (HED, 1200 mg/m^2; 32.4 times). No renal histopathological findings were revealed in the carcinogenicity studies, including dose-range finding studies up to 1500 mg/kg in mouse and rat.	No concern has been identified.
Hepatotoxicity: No hepatotoxicity was observed at any dose evaluated in repeat-dose toxicity studies in rats or monkeys.	No concern has been identified.
Genotoxicity: No genotoxic potential was identified in the bacterial reverse mutation assay (Ames test). Numerical chromosomal aberrations observed in Chinese hamster lung cells and in human lymphocytes after exposure to high concentrations (1250 µg/mL and 313 µg/mL, respectively) at which edoxaban precipitated. There was no genotoxic potential in bone marrow micronucleus tests in rats and monkeys, the liver micronucleus test in rats, and unscheduled deoxyribonucleic acid synthesis test in rat liver.	No concern has been identified.
Carcinogenicity: No evidence of carcinogenic effect was observed in the 2-year carcinogenicity studies in mice and rats at doses up to and exceeding the maximum tolerated dose. There was no evidence of carcinogenic effect observed in a medium-term liver carcinogenesis bioassay in rats at 20 mg/kg/day (HED, 120 mg/m^2; 3.2 times).	No concern has been identified.
General safety pharmacology: No clinically relevant changes were seen in the cardiovascular, central nervous, respiratory, or renal systems.	General safety pharmacology has not raised any signal to indicate potential toxicity in humans.
QT risk assessment: At concentrations up to 20 µg/mL, edoxaban did not affect the peak tail current human ether-a-go-go-related gene (hERG) potassium channel current in hERG-transfected human embryonic kidney 239 cells or the action potential duration of an isolated guinea pig ventricular papillary muscle preparation. No edoxaban-related changes were observed in ECG parameters, including QT interval, in monkeys at doses up to 200 mg/kg (HED, 2400 mg/m^2; 64.9 times), indicating that edoxaban has a low potential for QT-interval prolongation even at relatively higher doses.	The effect of edoxaban on cardiac polarisation was evaluated in an active- and placebo-controlled thorough corrected QT interval (QTc) study at supratherapeutic doses of 90 mg and 180 mg edoxaban in healthy subjects (Study PRT021). Edoxaban did not have a threshold pharmacologic effect on cardiac repolarisation. The absolute value of QTc interval did not exceed 450 ms for any subject on either dose of edoxaban. No clinically relevant changes in ECG waveforms were noted on edoxaban treatment.

Key safety findings (from non-clinical studies)	Relevance to human usage
Phototoxicity: Edoxaban was shown to bind to ocular and skin tissues in pigmented rats and monkeys and showed some light absorption at a wavelength of more than 290 nm. Subsequent photo safety studies showed that edoxaban did not affect any eye function parameters in a 9-month electroretinography test in monkeys given 15 mg/kg/day (180 mg/m^2; 4.9 times) and was negative in in vitro photocytotoxicity and photo-chromosomal aberration tests. Consequently, edoxaban is considered not to have any significant phototoxicity risk.	No concern has been identified.
Haemolysis or vascular irritation: Edoxaban has neither haemolytic action on human blood nor irritation potential on the rabbit auricular vasculature at concentrations up to 1 mg/mL.	No concern has been identified.
Ocular toxicity: No ocular toxicity was observed at any dose evaluated in repeat-dose toxicity studies in rats or monkeys.	No concern has been identified.
<u>Mechanisms for drug interactions</u> **Metabolism:** Edoxaban is a substrate of the efflux transporter P-gp. Edoxaban is cleared by both renal and non-renal pathways. There is a small fraction that is metabolised, and this is via cytochrome P450 (CYP). Edoxaban has a low potential for CYP inhibition. Neither edoxaban nor its human metabolite D21-2393 is an inducer of CYP1A2, CYP3A4, or P-gp. Edoxaban has low potential to be an inhibitor of MDR1, OAP1, OAT3, OCT1, OATP1B1, and OATB1B3. *Cyclosporine:* Concurrent administration of a single dose of cyclosporine 500 mg with a single dose of edoxaban 60 mg increased edoxaban area under the curve to infinite time ($AUC_{0-\infty}$) and maximum serum concentration (Cmax) by 73% and 74%, respectively. *Dronedarone:* Dronedarone 400 mg twice daily for 7 days with a single concomitant dose of edoxaban 60 mg on Day 5 increased edoxaban $AUC_{0-\infty}$ and Cmax by 85% and 46%, respectively. *Erythromycin:* Erythromycin 500 mg 4 times daily for 8 days with a single concomitant dose of edoxaban 60 mg on Day 7 increased edoxaban $AUC_{0-\infty}$ and Cmax by 85% and 68%, respectively. *Ketoconazole:* Ketoconazole 400 mg once daily for 7 days with a single concomitant dose of edoxaban 60 mg on	In healthy subjects, edoxaban is cleared by both renal and non-renal pathways, each of which contributes approximately 50% to the total clearance (A-U139). Concomitant use of P-gp inhibitors may increase plasma levels of edoxaban and hence may increase bleeding risk if the dose of edoxaban is not reduced (PRT016, A-U129, A-U130, A-U131, A-E132, A-U138, A-U139, and A-U141). Rifampicin (P-gp inducer) 600 mg once daily for 7 days with a single dose of edoxaban 60 mg on Day 7 decreased the area under the curve (AUC) of edoxaban by 34% without an apparent effect on Cmax. CYP3A4 induction by rifampicin resulted in an increase in the active metabolite, therefore mitigating the reduced exposure to edoxaban. No effect was seen on prothrombin time (PT) or activated partial thromboplastin time (aPTT) when edoxaban was co-administered with rifampicin (A-U137). The Summary of Product Characteristics (SmPC) provides guidance and information on the effects of concomitant use of P-gp inhibitors and inducers (*sections 4.2, 4.5*, and *5.2*).

Key safety findings (from non-clinical studies)	**Relevance to human usage**
Day 4 increased edoxaban $AUC_{0-\infty}$ and Cmax by 87% and 89%, respectively. *Quinidine:* Quinidine 300 mg once daily on Days 1 and 4 and 3 times daily on Days 2 and 3, with a single concomitant dose of edoxaban 60 mg on Day 3, increased edoxaban AUC_{0-24h} by 77% and Cmax by 85%. *Verapamil:* Verapamil 240 mg once daily for 11 days with a single concomitant dose of edoxaban 60 mg on Day 10 increased edoxaban AUC_{0-24h} and Cmax by approximately 50%.	Drugs that are inhibitors or inducers of CYP3A4 without concomitant P-gp activity are unlikely to have a significant effect on the edoxaban pharmacokinetics (PK), as CYP3A4 metabolism represents a minor metabolic pathway.
Pharmacodynamics (PD): In well-characterised in vitro and in vivo non-clinical studies, edoxaban is an orally active, selective, reversible FXa inhibitor with a consequent effect on coagulation. The main risk of edoxaban is an exaggerated PD effect resulting in bleeding.	Other drugs affecting haemostasis (anticoagulants, nonsteroidal anti-inflammatory drugs [NSAIDs], and antiplatelet agents) may increase the risk of bleeding through a PD interaction. The SmPC provides warnings and guidance on the use of concomitant medications affecting haemostasis (*sections 4.4 and 4.5*).
Other toxicity-related information or data **Evaluation in juvenile rats:** Repeat-dose juvenile toxicity studies of edoxaban did not induce any toxicologically significant effect on postnatal development and growth, organ development, skeletal development, or sexual maturation in juvenile rats.	Evaluation for paediatric use completed according to the PIP.
Absorption, distribution, metabolism, and excretion studies in juvenile rats: After oral doses of ^{14}C-labelled edoxaban or intravenous doses of ^{14}C-labelled D21-2393, more radioactivity was observed in the blood and tissues of juvenile rats than those of adult rats. The distribution of radioactivity into the eyes and skin of pigmented rats indicated an affinity of edoxaban and D21-2393 for melanin-containing tissues in juvenile rats as well as adult rats. The exposure levels in juvenile rats given 20 mg/kg/day from Day 4 (HED 1.2 mg/kg) to Day 14 (HED 1.7 mg/kg) were approximately 30 times higher on an AUC basis than those in adult rats given the same dose.	The juvenile rat exposure findings indicate that in very young children under the age of 2 years, the PK profile may be non-linear. Exposure will be carefully observed as part of the PIP PK study.
Factor X polymorphism: In vitro studies on FXa activated from mutant FX showed similar effects to wild-type FXa, suggesting that there is likely to be negligible variability due to polymorphisms of FX.	There is no evidence to suggest any altered effect in patients with genetic polymorphisms.
Reversing edoxaban anticoagulant effect: Reversal effects of PCC (PPSB-HT, Japan), activated prothrombin complex concentrate (Feiba®), and rFVIIa, (NovoSeven©) were evaluated in vitro and in rats. PPSB-	In a clinical study in healthy subjects, a 3-factor prothrombin complex concentrate (PCC) resulted in a statistically significant reversal of

Key safety findings (from non-clinical studies)	**Relevance to human usage**
HT, Feiba, and rFVIIa shortened PT prolongation in a concentration-dependent manner. Feiba (100 U/kg, IV) and rFVIIa (1 mg/kg and 3 mg/kg, IV) significantly reversed edoxaban (1 mg/kg/hour) (HED 6 mg/m^2/hour) induced prolongation of bleeding time in rats. In a rat venous thrombosis model, no potentiation of thrombus formation was observed when the highest dose (3 mg/kg) of rFVIIa was added to edoxaban (0.3 and 1 mg/kg/hour) (HED 1.8 mg/m^2/hour and 6 mg/m^2/hour) compared with the control. Thus, the non-clinical data suggest that rFVIIa, Feiba, and PPSB-HT have the potential to be reversal agents for edoxaban.	anticoagulant effects of 60 mg and 180 mg of edoxaban, as assessed by the endogenous thrombin potential (ETP) (A-U150). However, PCC did not substantially accelerate reversal of PT, INR, or aPTT prolongation relative to placebo. PCC also did not have an effect on antiFXa relative to placebo. Results of Study DU-176b-U158 have shown that the 50 IU/kg dose of a 4-factor PCC produced complete reversal of the effect of 60 mg edoxaban on bleeding duration, 2.75 hours after administration of the latter and 30 minutes after the end of the infusion. The 25 IU/kg dose produced partial reversal of the edoxaban effect. The 10 IU/kg dose failed to inhibit the effect of edoxaban. Results with ETP were consistent with those in which bleeding duration and volume were measured after punch biopsy. In contrast, edoxaban effects on PT were only partially reversed even at the highest dose of 4-factor PCC, following treatment with a reversal agent. Andexanet Alfa has been approved in Japan as a reversal agent for edoxaban, and further applications (including EMA/FDA) are ongoing. Further clinical studies are underway to determine reversibility strategies in humans (see Section Part III:III.2).
Protein binding: The in vitro plasma protein binding for edoxaban at concentrations from 0.2 to 5 µg/mL is about 55%, which does not change with impaired renal function. Of note, the human specific metabolite D21-2393 (constitutes less than 10% of edoxaban exposure) is about 80% bound to plasma proteins over a concentration range of 0.02 to 2 µg/mL. Specific proteins to which edoxaban or D21-2393 bind have not been identified.	Plasma protein binding does not appear to change appreciably with change in renal function (Study U146). Clinically relevant drug-drug or drug-disease interactions are unlikely to occur due to changes in protein binding of edoxaban.
Metabolite D21-2393 was found in trace amounts in non-clinical animal studies, but in humans, this is the most abundant metabolite (<10% in healthy subjects). Therefore, a specific comprehensive toxicology programme with this metabolite was conducted. No clinically relevant adverse effects were observed in repeat-	No concern was identified to suggest that the human-specific metabolite D21-2393 presents clinically relevant risks to humans in addition to those of the parent molecule.

Key safety findings (from non-clinical studies)	Relevance to human usage
dose toxicity studies in rats, in in vitro and in vivo genotoxicity studies, and in embryo-foetal developmental studies in rats.	

aPTT = activated partial thromboplastin time; AUC = area under the curve; AUC_{0-24h} = area under the curve during 24 hours; $AUC_{0-\infty}$ = area under the curve to infinite time; Cmax = maximum serum concentration; CYP = cytochrome P450; ECG = electrocardiogram; ETP = endogenous thrombin potential; FX = coagulation factor X; FXa = activated coagulation factor X; HED = human equivalent dose; hERG = human ether-a-go-go-related gene; INR = international normalised ratio; NSAIDs = nonsteroidal anti-inflammatory drugs; PCC = prothrombin complex concentrate; PD = pharmacodynamics; P-gp = P-glycoprotein; PIP = paediatric investigational plan; PK = pharmacokinetics; PPSB-HT = prothrombin complex concentrate (Japan); PT = prothrombin time; QTc = corrected QT interval; rFVIIa = recombinant factor VIIa; SmPC = Summary of Product Characteristics

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

SIII.1 Brief Overview of Development

Additional clinical development programmes have been undertaken to support marketing authorisation submissions for edoxaban in 2 indications:

- Prevention of stroke and systemic embolism in adult patients with NVAF with 1 or more risk factors, such as CHF, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA.
- Treatment of VTE including DVT and PE, and prevention of recurrent VTE in adults

The clinical programme in AF included 5 Phase 2 safety studies to evaluate the safety of various dose regimens of edoxaban in subjects with NVAF and 1 large Phase 3 pivotal registration study (DU176b-C-U301, also known as ENGAGE AF - TIMI 48, and referred to as ENGAGE-AF in the text and U301 for cross-references to the clinical study report. This last-mentioned double-blind, double-dummy, randomised, controlled study evaluated the efficacy and safety of 2 doses of edoxaban (60 mg [dose reduced 30 mg], and 30 mg [dose reduced 15 mg]) administered once daily in comparison with warfarin. Subjects with low body weight (<60kg), moderate renal impairment (creatinine clearance [CrCL] 30–50 mL/min) or taking certain medications (P-glycoprotein [P-gp] inhibitors) received half the full dose in order to achieve comparable exposure.

Warfarin was selected as the control as it is the most widely used anticoagulant agent for reducing the risk of systemic embolic events (SEEs) in patients with AF. Approximately 14,000 subjects were randomised to edoxaban and 7,000 to warfarin in ENGAGE-AF. In contrast, the Phase 2 safety studies included just 1952 subjects, of whom 1502 received edoxaban.

The clinical programme for the treatment and prevention of VTE included 1 large Phase 3 pivotal registration study, DU176b-D-U305, hereafter referred to as Hokusai VTE. The Hokusai VTE study was designed to evaluate the benefits and risks of edoxaban in reducing the risk of recurrent VTE in subjects with documented acute symptomatic DVT and/or PE. It was a double-blind, double-dummy, randomised, parallel-group study with 2 treatment groups: Edoxaban group (LMWH or UFH and edoxaban) and Warfarin group (LMWH/UFH and warfarin).

Approximately 4150 subjects were randomised to edoxaban and 4150 to warfarin and treated for up to 12 months in Hokusai VTE.

Edoxaban (Lixiana) Marketing Authorisation was granted by the EC on 19 Jun 2015 for the following indications:

- Prevention of stroke and SEE in adult patients with NVAF with 1 or more risk factors, such as CHF, hypertension, age ≥75 years, diabetes mellitus, prior stroke or TIA
- Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults

On 20 Apr 2017, Roteas® was approved by the European Commission (EC) in the EU as an informed consent product to Lixiana 15 mg, 30mg , 60 mg film-coated tablets and has been transferred to Berlin-Chemie AG on 18 Dec 2019 (EC decision).

Currently, edoxaban is approved in 69 countries and is marketed in 60 countries worldwide.

The following list shows the countries where the drug is approved.

European Economic Area:

Approved and Marketed

Austria	Finland	Liechtenstein	Slovak Republic
Belgium	Germany	Lithuania	Slovenia (Roteas)
Bulgaria (Roteas)	Hungary	Luxembourg	Spain
Czech Republic	Iceland	Netherlands	Sweden
Croatia (Roteas)	Ireland	Norway	
Denmark	Italy	Portugal	
Estonia	Latvia	Romania (Roteas)	

Approved and Not Marketed

Cyprus	Greece	Malta	Poland
France			

Rest of World

Approved and Marketed

Albania (Roteas)	El Salvador	Malaysia	Taiwan
Azerbaijan	Guatemala	Mexico	Thailand
Bahrain	Honduras	Nicaragua	Turkey
Belize	Hong Kong	Panama	UAE
Brazil	Indonesia	Philippines	UK
Canada	Japan	Singapore	USA
China	Kazakhstan	Saudi Arabia	Vietnam
Costa Rica	Kyrgyzstan	South Korea	Israel
Dom. Rep.	Macau	Switzerland	

Approved and Not Marketed

Russia	Oman	Turkmenistan	Kuwait

SIII.2 Clinical Trial Exposure

Cumulatively 46,255 subjects have been treated within the clinical development programme (in ongoing and completed studies) until last DSUR cut-off (21-APR-2022), either as healthy subjects (2,140 healthy subjects) or patients (44,115 patients).

Estimates of overall cumulative subject exposure are provided in Table Part II: Module SIII.1, based upon actual exposure data from completed/open-label studies and the enrolment/randomisation schemes for ongoing studies.

Table Part II: Module SIII.1: Estimated Cumulative Subject Exposure in DU-176b Clinical Studies

Treatment	Number of Subjects
Edoxaban	29,390
Comparator	16,148
Placebo	717
Total	46,255

Table Part II: Module SIII.2: Age Group and Gender

Age group	Patients	
	M	F
<65	8,298	3,935
≥65	9,265	7,837
Total	17,563	11,772

Table Part II: Module SIII.3: Ethnic Origin (Nonvalvular Atrial Fibrillation, Venous Thromboembolism, and Orthopaedic Surgery Indications)

Estimated Cumulative Subject Exposure to DU-176b in Completed Clinical Studies by Racial Group	
Racial Group	**Number of Subjects**
White	20,313
Asian	5,545
Black or African American	1,075
Unknown	284
Native Hawaiian or Other Pacific Islander	2
American Indian or Alaska native	1
Other	874
Total	**28,094**

[a] Missing to the total of 29,390 edoxaban patients: ethnic origin not collected in some studies

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

The edoxaban clinical development programme has been undertaken to support the marketing authorisation submission for 3 indications globally:

- NVAF
- Treatment of VTE, including DVT and PE
- Prevention of VTE in patients undergoing any of the following orthopaedic procedures on the lower limb: total knee replacement, total hip replacement, and hip fracture surgery (Japan only)

Exclusion criteria in pivotal clinical studies within the development programme for NVAF and VTE indications			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Active clinically significant bleeding and conditions associated with a high risk of bleeding (such as history of spontaneous bleeding or intracranial bleeding, gastrointestinal bleeding, active ulcer, recent severe trauma, major surgery or procedure within 10 days, active infective endocarditis, uncontrolled hypertension, or haemorrhagic disorder)	In SmPC *section 4.3*, Contraindications, the use of edoxaban in patients with clinically significant active bleeding is contraindicated.	No	Bleeding occurs due to the pharmacological action of edoxaban and is considered an important identified risk. Edoxaban is contraindicated in patients with active clinically significant bleeding. Bleeding is monitored regularly as part of ongoing pharmacovigilance activities.
Subjects receiving prohibited concomitant medications (non-study anticoagulants, other than those used as a bridge to/from study drug)	These patients were excluded from the study, as the key aim was to study the efficacy of edoxaban and not combination treatment with other anticoagulants except for certain situations such as the lead-in heparin treatment in the Hokusai VTE study or when switching to and from study treatment.	No	Bleeding, an important identified risk with edoxaban, may occur with concomitant use of medicines affecting haemostasis. This is described in the Warning and Precautions and Interactions sections of the SmPC (*section 4.4* and *section 4.5*)

Exclusion criteria in pivotal clinical studies within the development programme for NVAF and VTE indications			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Dual antiplatelet therapy (eg, ASA and thienopyridine such as ticlopidine or clopidogrel)	These patients were excluded from the study, as no data were available, and there is a theoretical risk that concomitant use with edoxaban would increase the risk of bleeding.	Yes	Not applicable
Treatment with ASA at a dose of more than 100 mg/day	Co-administration of edoxaban with ASA (100 mg to 325 mg) resulted in increased bleeding times (Study PRT017).	No	Bleeding, an important identified risk that may result from co-administration of edoxaban with ASA, is monitored regularly as part of ongoing pharmacovigilance activities.
Chronic treatment with NSAIDs	Administration of edoxaban in combination with naproxen resulted in greater bleeding times than observed for edoxaban alone (Study A-U128). The increased bleeding risk with chronic NSAID use is well known. To accurately assess the bleeding risk of edoxaban, chronic NSAID use was an exclusion criterion from the Phase 3 studies.	No	Bleeding, an important identified risk that may result from chronic co-administration of edoxaban with NSAIDs, is monitored regularly as part of ongoing pharmacovigilance activities.
Treatment with potent P-gp inhibitors	Edoxaban is a substrate for P-gp. Data from drug-drug interaction studies show that potent P-gp inhibitors may increase exposure to edoxaban (Studies PRT016, A-U129, A-U130, A-U131, A-E132, A-U138, A-U139, and A-U141). During the large Phase 3 studies, a dose adjustment scheme was used for selected P-gp inhibitors to ensure that exposure to edoxaban remained stable.	No	Co-administration of edoxaban with P-gp inhibitors increases exposure to edoxaban and may increase the risk of bleeding, which is an important identified risk for edoxaban. Bleeding is monitored regularly as part of ongoing pharmacovigilance activities.

Exclusion criteria in pivotal clinical studies within the development programme for NVAF and VTE indications			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Haemoglobin <10 g/dL or platelet count <100,000 cells/µL or white blood cell count <3000 cells/ µL	Patients with these conditions were excluded to maximise safety, as any occurrence of bleeding would have a greater impact on a patient with lower than normal haemoglobin. Patients with a low platelet count are at increased risk of bleeding. Inclusion of these patients could bias the population and impact the study endpoint evaluation.	No	Bleeding is an important identified risk with edoxaban, and anaemia due to bleeding may occur. Low platelet count may increase the risk of bleeding. Both anaemia and thrombocytopenia are ADRs associated with edoxaban (although not considered important risks).
Subjects with pre-planned invasive procedures in which bleeding could be anticipated	Inclusion of such patients could have impacted the evaluation of the study endpoints due to the increased risk of bleeding events.	No	Appropriate guidance is provided in the SmPC *section 4.4*: "If anticoagulation must be discontinued to reduce the risk of bleeding with surgical or other procedures, Lixiana should be stopped as soon as possible and preferably at least 24 hours before the procedure."
Subjects with severe renal insufficiency (calculated CrCL <30 mL/min)	Patients were excluded due to absence of data to confirm safety prior to the start of Phase 3 studies. However, during the large Phase 3 Study ENGAGE-AF, some patients experienced a decline of CrCL to below 30 mL/min leading to discontinuation of edoxaban.	Yes	Not applicable

Exclusion criteria in pivotal clinical studies within the development programme for NVAF and VTE indications			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Patients with active malignancy, treatment with anticancer therapy in the last 5 years, significant active concurrent medical illness or infection, reduced life expectancy (<12 months) (ENGAGE-AF) Patients with active cancer, reduced life expectancy (<3 months) (Hokusai VTE)	Patients with these conditions were excluded because of the risk of not completing the study and the independent risk of severe and fatal events. Thus, inclusion of such patients could bias the population and impact the study endpoint evaluation.	No	These patients do not represent a continuing safety concern with edoxaban and were excluded from the study to preserve the accuracy of analysis of the study data and reduce bias.
Subjects with active liver disease or persistent elevation of liver enzymes/bilirubin (ALT or AST ≥2 times ULN and total bilirubin ≥1.5 times ULN) Subjects testing positive for hepatitis B or C	Patients with these conditions were excluded because of the independent risk of developing hepatic impairment with associated coagulopathy. Further, it was important to evaluate liver function tests in the clinical studies in patients without overt liver disease. Inclusion of these patients could bias the population and impact the study endpoint evaluation.	Yes	Not applicable
Unresected atrial myxoma Intracardial mass or left ventricular thrombus Acute MI, stroke, acute coronary syndrome, or percutaneous coronary intervention within the previous 30 days	Patients with these conditions were excluded because of the independent and particularly high risk of thromboembolic events, and thus, inclusion of such patients could bias the population and impact the study endpoint evaluation.	No	These patients do not represent a continuing safety concern with edoxaban and were excluded from the study to preserve the accuracy of analysis of the study data and reduce bias.
Moderate to severe mitral stenosis, mechanical heart valve	Study objective was the investigation of edoxaban in patients with NVAF.	Yes	Not applicable

Exclusion criteria in pivotal clinical studies within the development programme for NVAF and VTE indications			
Criteria	**Reason for exclusion**	**Is it considered missing information?**	**Rationale**
Thrombectomy, insertion of a vena cava filter, or use of a fibrinolytic agent to treat the current episode of DVT and/or PE History of left atrial appendage exclusion (either by surgery or by a procedure)	Excluded to allow an adequate evaluation of the study endpoints.	No	These patients do not represent a continuing safety concern with edoxaban and were excluded from the study to preserve the accuracy of analysis of the study data and reduce bias.
Subjects testing positive for HIV	Patients were excluded, as they are likely to be treated with antiretroviral agents (such as ritonavir), which are P-gp inhibitors.	No	Co-administration of edoxaban with P-gp inhibitors increased exposure to edoxaban and may increase the risk of bleeding, which is an important identified risk with edoxaban. These patients do not represent a continuing safety concern with edoxaban and were excluded from the study to preserve the accuracy of analysis of the study data and reduce bias.

ADR = adverse drug reactions; AF = atrial fibrillation; ALT = alanine transaminase; ASA = acetylsalicylic acid; AST = aspartate transaminase; CrCL = creatinine clearance; DVT = deep vein thrombosis; HIV = human immunodeficiency virus; MI = myocardial infarction; NSAIDs = nonsteroidal anti-inflammatory drugs; NVAF = nonvalvular atrial fibrillation; PE = pulmonary embolism; P-gp = P-glycoprotein; SmPC = summary of product characteristics; ULN = upper limit of normal; VTE = venous thromboembolism

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, where applicable by indication of use.

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure, where applicable by indication of use.

Table Part II: Module SIV.1: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of special population	Exposure (subject years)
Pregnant women	10 (NA) All 10 pregnancy reports were received from the Hokusai VTE U305 study.[a]
Breastfeeding women	
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with CHF • Patients with a history of MI/CAD/CABG • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	Hepatic impairment: Mild/moderate: 16 (NA) Renal impairment: CrCL <30mL/min: 953 (621.8)[b] CrCL ≥30 to ≤50 mL/min: 3047 (5187.0)[c] CrCL >50 to ≤80 mL/min: 8437 (14,436.2)[c] CHF: 8048 (17,781.7)[d] History of MI/CAD/CABG: 4685 (10,236.7)[e] Immunocompromised patients: History of malignant disease: 1277 (2202.2)[f] Patients with a disease severity different from inclusion criteria in clinical trials: Not applicable, as the pivotal studies included patients of all disease severities.
Populations with relevant different ethnic origins	During the large Phase 3 study programs, a substantial number of patients in each region in the world with a broad geographical and ethnic distribution participated. No differences in efficacy or safety driven by ethnic differences were observed.
Subpopulations carrying relevant genetic polymorphisms	The frequency of FX polymorphisms is uncommon (based on the National Centre for Biotechnology Information database; data on file). There were 2 missense allele mutations impacting mature FX protein, both of which had a frequency ≤5%. In vitro studies on FXa activated from mutant FXs showed similar effects to wild-type FXa, suggesting that there is likely to be negligible variability due to polymorphisms of FX.

CABG = coronary artery bypass graft; CAD = coronary artery disease; CHF = congestive heart failure; CrCL = creatinine clearance; FX = coagulation factor X; FXa = activated coagulation factor X; ISS = Integrated Sumamry of Safety; MI = myocardial infarction; NA = not available; OS = orthopaedic surgery; VTE = venous thromboembolism

[a] All 10 pregnancy reports arise from the Hokusai VTE U305 study.
[b] Source: U301 Table14.3.1.38. B-J306 and C-J307
[c] Source: Table S8-3A Pooled Phase 2 AF, Phase 3 AF (ENGAGE-AF), Phase 3 VTE (HOKUSAI) and Phase 2/3 VTE prophylaxis-OS studies
[d] Source: ISS Appendix 12.6.2 Table S39 (ENGAGE-AF study)
[e] Source: ISS Appendix 12.6.2 Table S40 (ENGAGE-AF study)
[f] Source: ISS Appendix 12.6.2 Table S33 (Pooled ENGAGE-AF and Hokusai VTE studies)
Note: Table includes VTE post-surgery prophylaxis studies.

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

SV.1 Post-Authorisation Exposure

SV.1.1 Method Used to Calculate Exposure

Patient exposure in the post-marketing setting is estimated based on standard units data retrieved from the IQVIA MIDAS sales data. The following were considered in the cumulative and interval patient exposure calculations:

- For the prevention of VTE in patients undergoing selected orthopaedic surgery (OS) indication: an average duration of 10.2 days and stable use pattern assumed for the duration after Supplement New Drug Application (sNDA) for NVAF and VTE indications in Japan (ie, same number of patients being treated in the current period based on the estimated use, calculated in the 2 years prior to the sNDA in Japan).
- For the NVAF and VTE indications: chronic therapy with 1 tablet per day per patient and exposure is expressed in person-years. This is considered a more appropriate presentation of data, as it is assumed that patients will receive edoxaban for long-term use for these indications.

SV.1.2 Exposure

Cumulatively, from IBD through to the end of second quarter 2022, a total of 906,229 patients are estimated to have received edoxaban for OS indication and 8,556,835 patient-years of edoxaban exposure for NVAF and VTE indications.

Post-marketing data is not available by age group or gender.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1. Potential for Misuse for Illegal Purposes

No studies have been conducted to evaluate the dependence potential of edoxaban. The available data suggest that edoxaban is unlikely to cause dependence. As a class, activated coagulation factor X (FXa) inhibitors are not associated with dependence, and the chemical structure of this molecule differs from central nervous system active drugs associated with dependence. The pharmaceutical characteristics and pharmacokinetic (PK)/pharmacodynamic (PD) characteristics of edoxaban are not characteristic of drugs with high dependence potential (eg, rapid-onset or short-acting active substances).

SVI.2. Potential for Transmission of Infectious Agents

The potential for transmission of infectious agents via ingestion of edoxaban tablets is negligible. There are no materials of animal or human origin used as components in the formulation or aspects of the manufacturing process. The risk of transmission of infectious agents by this product is considered negligible based on product design, manufacturing process, facility design and controls, and current testing programs, as well as an extended history of safe human use of products for this class. European Pharmacopoeia standards have been met.

SVI.3. Potential for Harm from Overdose

The primary concern of accidental or intentional overdose of edoxaban is the potential for haemorrhagic complications as a result of the PD effect. A programme of clinical studies is underway in an effort to identify a reversal strategy (see Section Part III).

The Summary of Product Characteristics (SmPC) *section 4.9*, Overdose, provides the following information for management of bleeding:

Should a bleeding complication arise in a patient receiving edoxaban, the next edoxaban administration should be delayed, or treatment should be discontinued as appropriate. Edoxaban has a half-life of approximately 10 to 14 hours (see *section 5.2*). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

For life-threatening bleeding that cannot be controlled with the measures such as transfusion or haemostasis, the administration of a 4-factor prothrombin complex concentrate (PCC) at 50 IU/kg has been shown to reverse the effects of Lixiana within 30 minutes after completing the infusion.

Recombinant factor VIIa can also be considered. However, there is limited clinical experience with the use of this product in individuals receiving edoxaban.

Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings.

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of edoxaban.

There is no experience with the use of antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving edoxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatics (desmopressin, aprotinin) in individuals receiving edoxaban. Due to the high plasma protein binding edoxaban is not expected to be dialysable.

SVI.4. Potential for Medication Errors

Worldwide reports of medication errors have been discussed in each submitted Periodic Safety Update Report (PSUR). Following review of the data for each PSUR, it was concluded that no safety signal had arisen from the analysis of medication errors during any of the reporting periods. A review of all reports of medication errors (Medication Errors, Standardised MedDRA Queries [SMQ] Narrow) from the post-marketing setting through 31Jul2021 does not suggest a safety concern.

As a result of a request received (Feb 2016) from the Name Review Group (NRG)/CHMP to address a potential for name-related medication error, the sponsor undertook an in-depth review of the potential of this error. The invented names of the 2 medicinal products in question were Lyxumia (a type 2 diabetes mellitus medicine) and Lysanxia (an anxiolytic).

After evaluation of the available information, including global post-marketing data, a detailed response was submitted to the NRG/CHMP in Apr 2016, where the sponsor considered the

invented name Lixiana could continue to coexist with the invented names Lyxumia and Lysanxia. The sponsor committed to proactively monitor for any types of medication errors as part of ongoing safety monitoring and signal detection activities.

The CHMP, upon recommendation by the NRG, decided to allow the coexistence of the medicinal products under the current names and stated that no further action was required at that point in time.

There have been no reports of medication errors related to name confusion (preferred term) between Lixiana and Lyxumia or Lysanxia as of the data lock point (DLP) of this RMP update.

Isolated report of dispensing error:

As of the DLP (21 Apr 2021), there has been 1 fatal report of dispensing error: a spontaneous report of drug dispensing error (DSJ-2017-117431) with fatal gastrointestinal haemorrhage, which occurred in a hospital in Japan. According to this report, Rifxima was to be administered to a patient for hepatic encephalopathy. However, Lixiana 60 mg was administered 3 times daily for 2 and a half days (administered 8 times in total).

Following initial receipt of this report in Jul 2017, Daiichi Sankyo (Japan) voluntarily decided to distribute a leaflet to draw the attention of health care professionals (HCPs) to this potential for error between Lixiana and Rifxima in Japan. Communication with ASKA Pharmaceutical Co. (Marketing Authorisation Holder for Rifxima) and the Pharmaceuticals and Medical Devices Agency (PMDA) was initiated. The PMDA requested to include a cause/factor analysis of the incidence in the leaflet, including whether the event was a "prescription error" or "drug dispensing error." Following investigation of this report by the hospital where the error occurred, it was subsequently confirmed that the incidence was a "drug dispensing error."

The leaflet was posted on both Daiichi Sankyo (Japan) and ASKA websites. Distribution of the leaflet to HCPs in Japan started on 12 Oct 2017. The information was posted on the PMDA website on 25 Oct 2017.

SVI.5. Potential for Off-Label Use

In general, there is an approved, indicated, or well-established treatment alternative available to prescribers and patients for indications of anticoagulant therapy (eg, VKAs or drugs from the heparin group). In recent years, NOACs (direct thrombin inhibitors and direct FXa inhibitors) added a safe, effective, and convenient treatment alternative for the following indications:

- Prevention of VTE in patients with elective hip or knee replacement surgery
- Prevention of SEEs in patients with NVAF
- Treatment of VTE and prevention of recurrent VTE in patients with DVT or PE
- Prevention of atherothrombotic events in patients after an acute coronary syndrome

Edoxaban is approved in the EU for the following indications:

- Prevention of stroke and systemic embolism in adult patients with NVAF with 1 or more risk factors, such as CHF, hypertension, age ≥75 years, diabetes mellitus, prior stroke, or TIA
- Treatment of VTE, including DVT and PE, and prevention of recurrent VTE in adults

The potential for off-label use of edoxaban for unapproved indications in general is considered low due to the availability of approved, indicated, or well-established treatment alternatives.

Similar to all other new anticoagulants, a residual risk for off-label use may be considered in other indications requiring mid- or long-term anticoagulant treatment (eg, in patients with prosthetic valves and in patients with active malignancies, with or without metastasis, with high risk of bleeding), in case of poor compliance of the patient to more complex and less convenient standard treatment regimens or contraindications to the standard treatment regimes.

Daiichi Sankyo monitors off-label use via post-marketing spontaneous and literature reports, in addition to periodic review in aggregate reports (eg, PSUR and Signal Detection Reports), and is conducting drug utilisation studies after sufficient time of marketing in major European markets to gain further insight into real-life prescribing patterns and off-label use. Review of all post marketing reports of Off-label use (PT) through 31Jul r 2021, has not revealed safety concerns.

To prevent off-label use, an educational program is in place to ensure prescribers are fully aware of the approved indications and populations.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

“Use in paediatric population” previously classified as missing information has been removed from the list of safety concerns.

An update has been made on ETNA-AF-Europe (DSE-EDO-04-14-EU) study. The section on the Anticoagulation Reversal Programme has also been updated and the paragraph on Perosphere has been removed.

ETNA-AF PASS has been completed and has been removed from the ongoing Additional Pharmacovigilance Activities.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

No new important identified or potential risks have been added to this RMP update since the previously approved version 11.0 (07 Apr 2020).

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important identified risk: Bleeding or 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)

(Medical Dictionary for Regulatory Activities [MedDRA] Terms: Haemorrhage terms [excluding laboratory terms] [SMQ] and Haemorrhage laboratory terms [SMQ Narrow])

Potential mechanisms:

A variety of mechanisms can increase the risk of bleeding. These relate to the underlying pathology as discussed above.

Edoxaban, by means of its PD effect as a factor Xa inhibitor, has an anticoagulant effect. When used in patients with other bleeding risk factors or in patients who are taking other medications that can increase bleeding risk, there is potential for increased risk of bleeding.

Edoxaban exposure is increased in patients with reduced renal function, with low body weight, and who concomitantly take strong P-gp inhibitors. The clinical studies employed a dose-reduction scheme in patients with 1 or more of those characteristics to achieve comparable exposures and aimed at achieving comparable overall exposure within the dose groups, minimising any excess bleeding risk due to increased exposure, to optimise the benefit/risk balance. The study results show that this dose-reduction scheme has successfully managed any excess risk of bleeding.

Evidence source(s) and strength of evidence:

Oxford Textbook of Medicine

For bleeding definitions: ENGAGE-AF protocol (modified definition from International Society on Thrombosis and Haemostasis [ISTH]), Hokusai VTE protocol, and CEC Charters

For bleeding events: ENGAGE-AF and Hokusai VTE study reports

Characterisation of the risk:

Frequency

In the ENGAGE-AF study, median time on treatment was approximately 2.5 years, and median follow-up period was about 2.8 years. A significant risk reduction in both the edoxaban 60-mg and 30-mg groups compared with the warfarin group in major bleeding was observed (event rate of 2.75%, 1.61%, and 3.43% per year, respectively), with an HR of 0.80 ($P = 0.0009$) in the edoxaban 60-mg group and an HR of 0.47 ($P < 0.0001$) in the edoxaban 30-mg group. Again, across all categories of bleeding, there were significantly fewer reports for edoxaban-treated subjects than for those in the warfarin group: major bleeds (as above), clinically relevant nonmajor (CRNM) bleeding (8.67%, 6.60%, and 10.15%, respectively), and minor bleeds (4.12%, 3.52%, and 4.89%, respectively). Major bleeding events in ENGAGE-AF showed an increased risk for those receiving aspirin and NSAIDs in comparison to those not receiving the same drugs. For the small numbers of subjects receiving P-gp inhibitors, there was no increased risk; note that this group of subjects had a dose reduction.

In the Hokusai VTE study, more than half of all subjects received treatment for 6 months, and 40% of the subjects received treatment for a full 12 months. Major/CRNM bleeding (principal safety endpoint) was 8.5% in the edoxaban group and 10.3% in the warfarin group (HR = 0.81; 95% CI = 0.705 to 0.936; $P = 0.004$), with edoxaban being statistically superior to warfarin with a relative risk reduction of 19%. Major bleeding was 1.4% in the edoxaban group and 1.6% the warfarin group (HR = 0.84; 95% CI = 0.592 to 1.205; $P = 0.3521$). Consistently across all bleeding categories, there were less reports of

major bleeding (1.4% vs. 1.6%), CRNM (7.2% vs. 8.9%), nuisance (16.1% vs. 19.1%), and all bleeds (21.7% vs. 25.6%) reported for edoxaban compared with warfarin during the on-treatment period.

Major/CRNM bleeding in Hokusai VTE was increased by concomitant aspirin use.

Seriousness and outcomes

In ENGAGE-AF, the incidence of fatal bleeds was significantly lower for both the edoxaban 60-mg and 30-mg groups compared with the warfarin group: event rates were 0.21%, 0.13%, and 0.38% per year, respectively, with an HR of 0.55 ($P = 0.0059$) for edoxaban 60 mg and 0.35 ($P < 0.0001$) for edoxaban 30 mg. The difference was primarily due to the smaller number of fatal intracerebral haemorrhage (ICH) bleeding events with edoxaban 60 mg and 30 mg compared with warfarin: events rates were 0.15%, 0.08%, and 0.27% per year, respectively, with an HR of 0.58 ($P = 0.0312$) for edoxaban 60 mg and 0.28 ($P = 0.0001$) for edoxaban 30 mg.

In Hokusai VTE, there were fewer fatal bleeds (2 vs. 10) on treatment, including fewer fatal intracranial bleeds (0 vs. 6), in the edoxaban group compared with the warfarin group. There were fewer critical site bleeds (13 vs. 32) on treatment, including fewer intracranial bleeds (5 vs. 18), in the edoxaban group compared with the warfarin group.

Severity and nature of risk

The severity of bleeding depends on the extent and site of bleeding and includes the outcome. Bleeds of minor extent in critical sites such as the eye or intracranially can lead to significant disabilities or can be fatal. Additionally, the extent of bleeding poses an obvious direct threat to the subject and requires medical intervention, possibly transfusion.

In the clinical studies with edoxaban, bleeding was adjudicated and classified by extent and location.

Bleeding categories:

Major bleeding

ENGAGE-AF definition: Overt bleeding with 1 or more of the following:

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ: retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome
- A clinically overt bleeding event that caused a fall in haemoglobin of at least 2.0 g/dL (or a fall in haematocrit of at least 6.0% in the absence of haemoglobin data), adjusted for transfusions

Hokusai VTE definition: Overt bleeding with 1 or more of the following:

- Fatal bleeding
- Symptomatic bleeding in a critical area or organ: retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome
- Bleeding that caused a fall in haemoglobin level of 2.0 g/dL (1.25 mmol/L) or more, or lead to transfusion of 2 or more units of whole blood or packed red blood cells

Clinically relevant non-major bleeding

ENGAGE-AF definition: A clinically overt bleeding event that required medical attention. An outpatient visit without any of the above or similar diagnostic/therapeutic measures did not satisfy the criteria for “requiring medical attention”.

Hokusai VTE definition: Overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with any other discomfort such as pain, or impairment of activities of daily life.

Minor/nuisance bleeding
ENGAGE-AF: Other overt bleeding events that did not fulfil the criteria of a major bleed or a CRNM bleed (eg, epistaxis that did not require medical attention) were to be classified as a minor bleed.

Hokusai VTE definition: All other overt bleeding episodes not meeting the criteria for Major or CRNM bleeding were to be classified as nuisance bleeding.

In both clinical studies, there was consistently less bleeding across all categories in edoxaban-treated subjects compared to warfarin-treated subjects (see above).

Bleeding site:

In the ENGAGE-AF study, adjudicated major bleeding was lower in all locations in the edoxaban 30-mg group and in most locations for the edoxaban 60-mg group compared with the warfarin group. There was a lower rate of major gastrointestinal bleeds in the edoxaban 30-mg group and a higher rate in the edoxaban 60-mg group than the warfarin group (0.82%, 1.51%, and 1.23% per year, respectively). Similarly, there was a higher rate of CRNM gastrointestinal bleeds in the 30-mg and 60-mg edoxaban groups than the warfarin group (1.49%, 2.17%, and 1.31% per year, respectively).

Other bleeds in critical sites, such as intraocular, were reported less frequently in the edoxaban-treated groups than the warfarin control group (0.10%, 0.19%, and 0.24% per year, respectively).

In the Hokusai VTE study, the percentage of subjects with major or CRNM bleeding was lower for the edoxaban group than the warfarin group for ICH (0.1% and 0.4%, respectively) and comparable for gastrointestinal bleeding (2.4% and 2.3%, respectively). The percentage of female subjects with major/CRNM vaginal bleeding was 4.6% in the edoxaban group compared with 3.2% in the warfarin group. The majority of the vaginal bleeds were reported as menorrhagia in women <50 years of age. Vaginal bleeding was rarer in older (post-menopausal) female subjects. This was likely the same reason why vaginal bleeds were much less frequently reported in the ENGAGE-AF study, as the vast majority of the female subjects in the ENGAGE-AF study were post-menopausal. There was only a single intraocular bleed in the edoxaban 60-mg group compared to 4 in the warfarin group.

Details of bleed events that occurred in the 3 Phase 3/ 3b studies (DU176b-F-E308 [ENSURE-AF], DSE-EDO-01-16-EU [ELIMINATE-AF], and DU176b-D-U311 [Hokusai VTE Cancer Study] which have been completed since initial approval of the Marketing Authorisation are summarised here. All bleeds in all of these studies have been independently adjudicated.

DU176b-F-E308 (ENSURE-AF):

In the ENSURE AF study, 2149 subjects were treated either with edoxaban (N = 1067) or warfarin (N = 1082). In the edoxaban and warfarin groups, the mean treatment duration was 37.8 days and 37.0 days, respectively, and the mean treatment exposure was 37.7 days and 36.3 days, respectively.

All bleed events were adjudicated. A total of 16 subjects (1.5%) in the edoxaban group and 11 subjects (1.0%) in the warfarin group experienced the primary safety endpoint of major or CRNM bleeding during the on-treatment period in the Safety Analysis Set. For the primary safety endpoint, the odds ratio was 1.48, favouring warfarin. This increase was driven by CRNM bleeding events.

The incidence of the first major bleed in the edoxaban and warfarin groups was 3 (0.3%) and 5 (0.5%), respectively, during the on-treatment period and 3 (0.3%) and 6 (0.6%), respectively, during the overall study period. There was no ICH bleeding in either treatment group. During the on-treatment period there was 1 fatal bleed (1 warfarin) and 2 life-threatening bleeds (1 edoxaban, 1 warfarin).

The incidence of the first CRNM bleed in the edoxaban and warfarin groups was 14 (1.3%) and 7 (0.6%), respectively, during the on-treatment period and 18 (1.7%) and 12 (1.1%), respectively, during the overall study period.

The incidence of the first minor bleed in the edoxaban and warfarin groups was 16 (1.5%) and 26 (2.4%), respectively, and the first all bleed was 32 (3.0%) and 35 (3.2%), respectively, during the on-treatment period.

There were no notable differences in major or CRNM bleeding based on demographic characteristics.

DU176b-C-E314 (Post Authorisation Measure study):

A total of 303 subjects received edoxaban 60 mg and 303 subjects received edoxaban 75 mg once daily. The median treatment duration was 363 days in both edoxaban groups, and the median treatment exposure was 362 days in both groups.

Adjudicated Major and or CRNM bleeding

The number of subjects with adjudicated major and/or CRNM bleeding was 11 (3.6%) in the edoxaban 60 mg group compared to 10 (3.3%) in the edoxaban 75 mg group, during the On-Treatment Study Period.

During the On-Treatment Study Period, adjudicated major bleeding events occurred in 2 (0.7%) subjects in the edoxaban 60 mg group compared to 3 (1.0%) subjects in the edoxaban 75 mg group. Of the 2 major bleeds in the edoxaban 60 mg group, one was in a critical area/organ (intraocular) and the other major bleed was an intramuscular bleed. Of the 3 major bleeds in the edoxaban 75 mg group, 2 occurred in a critical area/organ (intracranial; intracerebral) and 1 was an upper GI bleed. One of the adjudicated intracerebral bleed had a fatal outcome (adjudicated as a CV death) and the other intracerebral bleed was a life threatening bleed. The data for adjudicated major bleeds was identical for On-Treatment and Overall Study Period.

Subjects with any bleeding event were similar between both groups; occurring in 19 (6.3%) subjects in the edoxaban 60 mg group and 20 (6.6%) in the edoxaban 75 mg group.

DSE-EDO-01-16-EU (ELIMINATE-AF):

The incidence of adjudicated major bleeding (ISTH definition) for the mITT analysis set in the period from the date of first intake of study drug to Day 90/EOT was low and comparable for the Edoxaban and VKA groups (2.5% [n = 10] and 1.5% [n = 3], respectively).

- The time to the first major bleeding event was not statistically different between the treatment groups (*P* value = 0.432).
- No subject experienced fatal bleeding during the study.
- One subject (0.2%) in the edoxaban group had intracranial bleeding/intracranial haemorrhage.
- All other major bleeding events were non-intracranial bleeding.

Secondary Safety

<u>ISTH-defined Bleeding Events (Based on Adjudication)</u>

- The incidence of CRNM bleeding events was low, but was numerically higher for the edoxaban group compared to the VKA group (7.9% [n = 32] and 3.6% [n = 7], respectively). The time to

the first CRNM bleeding event was not statistically different between the treatment groups (*P* value = 0.064).

- The incidence of minor bleeding events was low and was comparable for the edoxaban and VKA groups (5.4% [n = 22] and 6.1% [n = 12], respectively). The time to the first minor bleeding event was not statistically different between the treatment groups (*P* value = 0.673).
- When considering all major, CRNM, and minor ISTH-defined bleeding events, the time to first bleeding event was not statistically different between the treatment groups (*P* value = 0.279). When only considering major and CRNM ISTH-defined bleeding events combined, the time to first bleeding event was numerically higher for edoxaban compared to VKA (exploratory *P* value = 0.045).
- All bleeding events that led to study drug withdrawal were experienced by subjects in the edoxaban group: major bleeding (0.2% [n = 1]), CRNM bleeding (1.2% [n = 5]), and minor bleeding (0.2% [n = 1]).
- The most common bleeding location was puncture site with results comparable for the edoxaban and VKA groups (3.5% [n = 14] and 2.5%% [n = 5], respectively).

TIMI-defined Bleeding Events (Based on Adjudication)

- One subject (0.2%) in the edoxaban group had a major bleeding event.
- The incidence of minor bleeding events was low, however was numerically higher for the edoxaban group compared to the VKA group (9.4% [n = 38] and 5.1% [n = 10], respectively). The time to the first minor bleeding event was not statistically different between the treatment groups (*P* value = 0.092).
- The incidence of minimal bleeding events was low and comparable for the edoxaban and VKA groups (5.9% [n = 24] and 6.1% [n = 12], respectively). The time to the first minimal bleeding event was not statistically different between the treatment groups (*P* value = 0.867).
- When considering all major, minor, and minimal TIMI-defined bleeding events, or only major and minor TIMI-defined bleeding events, the time to first bleeding event was not statistically different for between the treatment groups (*P* value = 0.312 and *P* value = 0.077, respectively).

BARC-defined Bleeding Events (Based on Adjudication)

- No subject experienced a BARC type 5 (fatal) bleeding event.
- The incidence of BARC type 3 and type 1 bleeding events was low and was comparable for the edoxaban and VKA groups (1.7% [n = 7] and 1.5% [n = 3]; 5.7% [n = 23] and 6.1% [n = 12], respectively).
- The incidence of BARC type 2 bleeding events was low, however was numerically higher for the edoxaban group compared to the VKA group (8.1% [n = 33] and 3.6% [n = 7], respectively).
- Regardless of the BARC bleeding definition (type 1, 2, or 3), whether analysed alone or in combination with other definitions, the time to the first bleeding event was not statistically different between the treatment groups (*P* value range: 0.053 to 0.822).

DU176b-D-U311 (VTE Cancer study):

The incidence of VTE or major bleeding occurred in 67 (12.8%) of the 522 subjects in the edoxaban group and in 71 (13.5%) of the 524 subjects in the dalteparin group during the Overall Study Period. The Hazard Ratio for the edoxaban group versus the dalteparin group was 0.97 (95% CI = 0.696 to 1.359). The upper bound of the 95% CI is 1.359, which was below the pre-specified non-inferiority margin of 1.5, and the difference between edoxaban and dalteparin in the time to first occurrence of adjudicated VTE or major bleeding was statistically significant for non-inferiority (P = 0.0056).

DU176b-D-U312 (Hokusai VTE Paediatrics Study):

During the Main Treatment Period (randomization until the end of Month 3) and On-treatment (on study drug or within 3 days of interruption or discontinuation) , 3 (2.1%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC experienced at least 1 adjudicated confirmed major/CRNM bleeding event (HR: 0.60, 95% CI: 0.139, 2.597; Module 5.3.5.1 DU176b-D-U312 CSR Table 14.3.1.1).

During the Main Treatment Period and On-treatment, all major/CRNM bleeding events were localised in noncritical sites (upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and "other" bleeding; Module 5.3.5.1 DU176b-D-U312 CSR Table 14.3.1.19). All subjects experienced clinically overt bleeding events; in addition, 1 (0.7%) subject in the edoxaban group had a decrease in haemoglobin level of ≥2 g/dL, and 1 (0.7%) subject in the edoxaban group and 3 (2.1%) subjects in the SOC group had bleeding events that required surgery in an operating room or suite.

During the Main Treatment Period plus Extension Period and On-treatment, 8 (5.5%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudicated confirmed major/CRNM bleeding event (HR: 1.48, 95% CI: 0.484, 4.503; Module 5.3.5.1 DU176b D-U312 CSR Table 14.3.1.7).

During the Main Treatment Period plus Extension Period and On-treatment, 1 bleeding event occurred in a critical site (pulmonary haemorrhage in 1 subject in the edoxaban group), while all other bleeding events were localised in noncritical sites (upper and lower gastrointestinal tract bleeding, vaginal bleeding, epistaxis, and "other" bleeding; Module 5.3.5.1 DU176b D U312 CSR Table 14.3.1.25). All subjects experienced clinically overt bleeding events; in addition, 1 (0.7%) subject in the edoxaban group had a decrease in haemoglobin level of ≥2 g/dL, 1 (0.7%) subject in the edoxaban group required transfusion(s), 4 (2.8%) subjects in the edoxaban group and 3 (2.1%) subjects in the SOC group required surgery in an operating room or suite.

During the Overall Treatment Period, 10 (6.9%) subjects in the edoxaban group and 5 (3.5%) subjects in the SOC group experienced at least 1 adjudicated confirmed major/CRNM bleeding event (HR: 1.85, 95% CI: 0.637, 5.370; Module 5.3.5.1 DU176b-D-U312 CSR Table 14.3.1.14).

DU176b-C-U313 (ENNOBLE-ATE Study):

As shown in Table 2.1, 1 (0.9%) subject in the edoxaban group and 1 (1.7%) in the SOC group experienced a CRNM bleeding event (HR [95% CI]: 1.24 [0.88, 1.73]; p=0.2184; Module 5.3.5.1 DU176b-C-U313 CSR Table 14.3.1.1). Annualised rates were 0.04 for the edoxaban group and 0.07 for the SOC group.

The proportion of subjects with all bleeding event was similar in the edoxaban and SOC groups: 3.7% and 3.4%, respectively.

Table 2.1: Summary of Adjudicated Bleeding Events, Main Treatment Period – Study U313 (Safety Analysis Set)

Adjudicated Bleeding Events	Statistics	Edoxaban (N = 109)	SOC (N = 58)
Major/CRNM bleeding events	n (%)	1 (0.9)	1 (1.7)
	Annualised rate	0.04	0.07
	Rate difference (95% CI)	-0.03 (-0.18, 0.12)	
Major bleeding events	n (%)	0	0
	Annualised rate	-	-
	Rate difference (95% CI)	-	
All bleeding events (Major/CRNM/Minor)	n (%)	4 (3.7)	2 (3.4)
	Annualised rate	0.15	0.14
	Rate difference (95% CI)	0 (-0.24, 0.25)	

CI = confidence interval; CRNM = clinically relevant nonmajor; SAP = Statistical Analysis Plan; SOC = standard of care
Note: Annualised rate = number of subjects with events/total time at risk (years). For each subject, the "at risk" years = (the event or censoring – date of randomization + 1)/365.25. If a subject has multiple events, the time of the first event is used.
Note: 95% CI for rate difference is calculated by using Wald's method.
Note: Percentages are based on the number of subjects in the Safety Analysis Set.
Source: Module 5.3.5.1 DU176b-C-U313 CSR Table 14.3.1.2.

Impact on quality of life

The impact on the individual patient will vary depending upon the site and severity of the bleeding. Small localised superficial bruising may have limited impact. However, a cerebral haemorrhage or a major gastrointestinal bleed may have severe consequences and will lead to hospitalisation, potential long-term disability, and possibly death. Bleeding in critical sites, such as the eye or intra-articular, will also have significant impact on the individual patient.

Risk factors or risk groups:

In patients who have not received anticoagulant treatment, there are a number of risk factors that can predispose patients to bleeding, such as blood vessel abnormalities, haematological disorders, other concomitant pathology (including abscesses and tumours) leading to local haemorrhage, hypertension, and drug treatment.

The risk of haemorrhage associated with anticoagulant therapy varies, and several of the risk factors for stroke are also associated with an increased risk for anticoagulant-associated haemorrhage. It has been shown that bleeding rates increase in parallel with CHADS2 score. Other bleeding risk scores have been developed, such as those used in the ATRIA study and HAS-BLED, to predict patients with increased risk of bleeding while on VKAs.

The risk of bleeding is directly related to the mechanism of action of anticoagulants, and clear dose-responses are observed both in the efficacy of prevention of thromboembolic events as well as in the risk of bleeding. The balance of the effects needs to be carefully managed.

Preventability:

Patients at high risk of bleeding are identified to ensure careful adherence to dose recommendations and to avoid concomitant therapies that affect coagulation.

The SmPC recommends the following:

Section 4.2, Posology and method of administration

For NVAF and VTE the recommended dose is 30 mg edoxaban once daily with one or more of the following factors:

- Moderate or severe renal impairment (creatinine clearance (CrCl) 15–50 mL/min)
- Low body weight ≤60 kg
- Concomitant use of the following P-gp inhibitors: ciclosporin, dronedarone, erythromycin, or ketoconazole.

Section 4.3, Contraindications

The use of edoxaban is contraindicated in the following conditions:

- Clinically significant active bleeding
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
- Lesion or condition, if considered to be a significant risk for major bleeding
- Uncontrolled severe hypertension
- Concomitant treatment with other anticoagulants

Section 4.4, Special warnings and precautions for use

Haemorrhagic risk

Edoxaban increases the risk of bleeding and can cause serious, potentially fatal bleeding. Lixiana, like other anticoagulants, is recommended to be used with caution in patients with increased risk of bleeding. Lixiana administration should be discontinued if severe haemorrhage occurs (see *sections 4.8 and 4.9*).

In the clinical studies, mucosal bleedings (e.g. epistaxis, gastrointestinal, genitourinary) and anaemia were seen more frequently during long term edoxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several subgroups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see *section 4.8*). Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing. A specific anticoagulant reversal agent for edoxaban is not available (see *section 4.9*).

Haemodialysis does not significantly contribute to edoxaban clearance (see *section 5.2*).

Interaction with other medicinal products affecting haemostasis

Concomitant use of drugs affecting haemostasis may increase the risk of bleeding. These include ASA, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs), and chronic NSAIDs (see *section 4.5*).

Section 4.5, Interaction with other medicinal products and other forms of interaction

Anticoagulants, antiplatelets, and NSAIDs (see *section 4.4*)

There is very limited experience on the use of edoxaban with dual antiplatelet therapy or fibrinolytic agents.

Anticoagulants: Co-administration of edoxaban with other anticoagulants is contraindicated due to increased risk of bleeding.

ASA: Co-administration of ASA (100 mg or 325 mg) and edoxaban increased bleeding time relative to either medicine alone. Co-administration of high-dose ASA (325 mg) increased the steady state Cmax and AUC of edoxaban by 35% and 32%, respectively. 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 only be performed under medical supervision.

In clinical studies, concomitant use of low-dose ASA (≤100 mg/day), other antiplatelet agents and thienopyridines was permitted and resulted in approximately a 2-fold increase in major bleeding in comparison with no concomitant use, although to a similar extent in the edoxaban and warfarin groups (see *section 4.4*).

Edoxaban can be co-administered with low-dose ASA (≤100 mg/day). Co-administration of low dose ASA (≤100 mg) did not affect the peak or total exposure of edoxaban either after single dose or at steady-state.

NSAIDs: Co-administration of naproxen and edoxaban increased bleeding time relative to either drug alone. Naproxen had no effect on the Cmax and AUC of edoxaban. In clinical studies, co-administration of NSAIDs resulted in increased clinically relevant bleeding. Chronic use of NSAIDs with edoxaban is not recommended.

SSRIs/SNRIs: As with other anticoagulants, the possibility may exist that patients are at an increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets (see *section 4.4*).

Impact on the risk-benefit balance of the product Overall, edoxaban has an adequately characterised positive benefit-risk ratio in large and representative populations for the NVAF, and VTE indications, demonstrating efficacy in the overall populations and subgroups (with dose reduction as required) in conjunction with a favourable bleed profile and additional advantages of once-daily dosing and no necessity for constant monitoring of therapy. Bleeding is an important identified risk with treatment due to the anticoagulant mechanism of action of edoxaban and has been observed in the edoxaban clinical development programme; however, this important identified risk is not expected to outweigh the demonstrated benefit of treatment with edoxaban.
Public health impact A public health impact is mainly arising in case of major bleeds, as these will present a significant burden on the healthcare system. In the short term, impact arises through hospitalisation and potentially significant diagnostic and treatment efforts. In the long term, outcomes of significant permanent disabilities (depending on the site of bleed) will impact public health burden with rehabilitation, nursing support, and loss of earning capability. However, this is balanced against the public health burden arising from thromboembolic events, which are prevented with effective anticoagulation. An effective anticoagulant without therapeutic monitoring requirement (such as is required for VKA) reduces the ongoing cost of preventative treatment and burden on the healthcare system caused by the prevented VTEs and SEEs.

AF = atrial fibrillation; ASA = acetylsalicylic acid; AUC = area under the curve; CEC = Clinical Event Committee; $CHADS_2$ = CHF, hypertension, age ≥75 years, diabetes mellitus, and prior stroke or TIA; CHF = congestive heart failure; CI = confidence interval; Cmax = maximum serum concentration; CrCL = creatinine clearance; CRNM = clinically relevant non-major; HR = hazard ratio; ICH = intracranial haemorrhage; ISTH = International Society on Thrombosis and Haemostasis; MedDRA = Medical Dictionary for Regulatory Activities; mITT = modified intent-to-treat; NSAIDs = nonsteroidal anti-inflammatory drugs; NVAF = nonvalvular atrial fibrillation; PD = pharmacodynamics; P-gp = P-glycoprotein; SEEs = systemic embolic events; SMQ = Standardised MedDRA Queries; SNRI = serotonin norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; VKA = vitamin K antagonists; VTE = venous thromboembolism

Important potential risk: Hepatic dysfunction **(MedDRA SMQs: Hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; Hepatitis, non-infectious; Cholestasis and jaundice of hepatic origin; and Liver-related investigations, signs, and symptoms)**
Potential mechanisms: Drug-induced liver injury is caused by many different mechanisms, which are poorly understood. These include immune-mediated response against the liver and/or bile duct that may result in a disease with clinical features that can be hepatocellular, cholestatic, or a mixed injury.
Evidence source(s) and strength of evidence: Marketing Authorisation Application Module 2.7.4, clinical study data from ENGAGE-AF and Hokusai VTE, Module 5 Integrated Summary of Safety Appendix 12.6.2 pooled tables.
Characterisation of the risk: <u>Frequency</u> In the 2 large Phase 3 studies, a low rate of abnormalities was observed in all treatment groups, with the incidence being comparable between edoxaban and warfarin groups.

In ENGAGE-AF, concurrent ALT or AST elevations >3 × ULN together with bilirubin elevations >2 × ULN for the edoxaban 30-mg, 60-mg, and warfarin groups were reported for 23 (0.3%), 36 (0.5%), and 25 (0.4%) subjects, respectively, considering the overall study period.

The overall incidences of investigator-reported suspected hepatic events in the ENGAGE-AF study did not differ greatly between edoxaban and warfarin, with 376 (5.4%), 347 (4.9%), and 362 (5.2%) subjects in the edoxaban 30-mg, 60-mg, and warfarin groups, respectively, reporting at least 1 event for the on-treatment + 30 days period; the most commonly reported individual preferred terms were hepatic enzyme increased (50 [0.7%], 57 [0.8%], and 61 [0.9%], respectively) and blood bilirubin increased (65 [0.9%], 43 [0.6%], and 68 [1.0%], respectively).

In Hokusai VTE, concurrent ALT or AST elevations >3 × ULN together with bilirubin elevations >2 × ULN for the edoxaban 60-mg and warfarin groups were reported for 7 (0.2%) and 4 (0.1%) subjects, respectively, considering the overall study period (excluding heparin lead-in).

Investigator-reported suspected hepatic events in Hokusai VTE were recorded for 293 (7.3%) and 273 (6.8%) subjects in the edoxaban 60-mg and warfarin groups, respectively, for the on-treatment + 30 days period (excluding heparin lead-in). The most common individual preferred term reported was hepatic enzyme increased (100 [2.5%] and 93 [2.3%], respectively).

Seriousness and outcomes

Hepatic toxicity was experienced with ximelagatran, an oral anticoagulant in the direct-thrombin-inhibitor class. Other currently marketed NOACs have reported elevated liver function tests, and these are recommended prior to commencing therapy.

Based on preclinical exposure and clinical experience, hepatotoxicity is not likely with edoxaban. The observed liver function test abnormalities in clinical studies of edoxaban had alternative causes identified in the majority of cases.

Thus, even though edoxaban is considered to have low potential for hepatic toxicity, elevation of liver function tests is considered an important potential risk. In the pivotal Phase 3 clinical study programme of edoxaban, hepatic events were events of special interest, and an adjudication process was specified a priori with events meeting criteria being sent to the adjudication committee for adjudication blinded to the treatment arm. The committee would review the adjudication package including laboratory examinations and additional clinical details on the event to establish the type of injury sustained (no hepatic event, hepatocellular, cholestatic, or mixed injury) and the likelihood of a causal relationship with study medication. The adjudication process and criteria as well as the result categories were carefully described in the adjudication process documents established prior to the start of the Phase 3 studies.

In the pivotal Phase 3 studies, liver function test elevations were observed in the edoxaban treatment groups; however, there was no imbalance observed between the warfarin and edoxaban groups for hepatic injury following adjudication.

The percentage of subjects in the edoxaban 30-mg, edoxaban 60-mg, and warfarin groups that were characterised by an independent hepatologist as having a hepatocellular injury was 1.2%, 1.1%, and 1.0%, respectively, considering the on-treatment + 30 days period.

Where assessable, a causal relationship of probably or possible was assigned for 0.2%, 0.4%, and 0.3% of the total number of patients in the edoxaban 30-mg, edoxaban 60-mg, and warfarin groups, respectively.

Overall, 5 cases were adjudicated as meeting Hy’s law criteria, 3 in the edoxaban group and 2 in the warfarin group (1 event in the warfarin group was fatal liver failure).

The majority of these cases recovered without sequelae.

Severity and nature of risk

In the edoxaban Phase 3 clinical studies, hepatic function test elevations were reported in comparable frequencies for the edoxaban and warfarin control groups. Most cases were asymptomatic or clearly part of an ongoing disease process that was the clear cause of the liver function test abnormality (such as viral hepatitis, cholecystolithiasis, pancreatitis, or CHF-related). There were very few cases of suspected drug-induced liver injury, and only 5 cases in over 30,000 Phase 3 study populations were adjudicated as meeting Hy's law criteria.

Hepatotoxicity is a poorly predictable event, and as such, in the post-marketing phase, all reports of hepatic function abnormality are being carefully monitored.

There were no increases in AST or ALT ≥3 × ULN and TBL ≥2 × ULN observed with edoxaban in any of the 3 Phase 3/ 3b studies (DU176b-F-E308 [ENSURE-AF]; DU176b-C-E314 (PAM study); DSE-EDO-01-16-EU [ELIMINATE-AF], and DU176b-D-U311 [Hokusai VTE Cancer Study]) that have been completed since initial approval of the Marketing Authorisation.

Impact on quality of life

Drug-induced hepatotoxicity is the most common cause of acute liver failure in the United States; it is also the most frequently cited reason for withdrawal of an approved drug from the market. Patients may require hospitalisation for the investigation of their symptoms; rarely, may require liver transplant, and may even result in death.

Risk factors or risk groups:

The risk of developing hepatotoxicity involves a complex interplay between the chemical and pharmacological properties of the drug (eg, chemical formula, metabolism, excretion, metabolites, etc), environmental factors (eg, concomitant drugs, alcohol, etc), age, sex, underlying disease (eg, hepatitis B or C, HIV, and diabetes), and genetic factors (those influencing metabolism, transportation, detoxification, as well as those that influence cell injury and repair).

To date, no risk group has been identified; in general, the elderly and those receiving polypharmacy may be considered most vulnerable.

Preventability:

Drug withdrawal is the general standard measure in cases with elevated transaminases that might indicate drug-induced liver injury to prevent worsening and potentially reverse liver damage.

The SmPC recommends the following (hepatic impairment):

Section 4.2, Posology and method of administration:

Lixiana is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see *section 4.3*).

In patients with severe hepatic impairment edoxaban is not recommended (see *sections 4.4 and 5.2*).

In patients with mild to moderate hepatic impairment, the recommended dose is 60 mg edoxaban once daily (see *section 5.2*). Edoxaban should be used with caution in patients with mild to moderate hepatic impairment (see *section 4.4*).

Patients with elevated liver enzymes (alanine aminotransferase (ALT) or aspartate transaminase (AST) > 2 x upper limit of normal (ULN)) or total bilirubin ≥ 1.5 x ULN, were excluded in clinical studies. Therefore, edoxaban should be used with caution in this population (see sections 4.4 and 5.2). Prior to initiating edoxaban, liver function testing should be performed.

Section 4.4 Special warnings and precautions for use:

Edoxaban is not recommended in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Edoxaban should be used with caution in patients with mild or moderate hepatic impairment (see section 4.2).

Patients with elevated liver enzymes (ALT/AST >2 × ULN) or total bilirubin ≥1.5 × ULN were excluded in clinical trials. Therefore, Lixiana should be used with caution in this population (see *sections 4.2* and *5.2*). Prior to initiating Lixiana, liver function testing should be performed. Periodic hepatic monitoring is recommended for patients on Lixiana treatment beyond 1 year.
Impact on the risk-benefit balance of the product: Overall, edoxaban has an adequately characterised positive benefit-risk ratio in large and representative populations for the NVAF, VTE, and OS indications, demonstrating efficacy in the overall populations and subgroups (with dose reduction as required) in conjunction with a favourable bleed profile and additional advantages of once-daily dosing and no necessity for constant monitoring of therapy. A possible link between edoxaban and events of hepatic dysfunction cannot be ruled out. Events in this category were observed in the edoxaban clinical development programme; however, the number of reported events were low. This important potential risk has not outweighed the demonstrated benefit of treatment with edoxaban, since edoxaban received regulatory approval for the NVAF, VTE, and OS indications.
Public health impact: Drug-induced hepatotoxicity is the most common cause of acute liver failure in the United States; it is also the most frequently cited reason for withdrawal of an approved drug from the market. Patients may require hospitalisation for the investigation of their symptoms; rarely, may require liver transplant and may even result in death.

AF = atrial fibrillation; ALT = alanine transaminase; AST = aspartate transaminase; CHF = congestive heart failure; HIV = human immunodeficiency virus; MedDRA = Medical Dictionary for Regulatory Activities; NOAC = novel oral anticoagulants; NVAF = nonvalvular atrial fibrillation; OS = orthopaedic surgery; PAM = Post Authorisation Measure; SmPC = Summary of Product Characteristics; SMQ = Standardised MedDRA Queries; TBL = total bilirubin; ULN = upper limit of normal; VTE = venous thromboembolism

Potential risk: Trend towards decreasing efficacy in NVAF subjects with high creatinine clearance
Potential mechanisms: The trend towards reduced efficacy compared to well-managed warfarin in ENGAGE-AF may be due to reduced edoxaban exposure in NVAF subjects with higher creatinine clearance.
Evidence source and strength of evidence: Clinical study data from ENGAGE-AF; CHMP assessment, Day 180 List of Outstanding issues (dated 26 Feb 2015); Gage BF, Waterman AD, Shannon W, et al., Validation of clinical classification schemes for predicting stroke: results from the national registry of atrial fibrillation. JAMA. 2001; 285: 2864–70 (42).

Characterisation of the risk:

This trend towards decreasing efficacy was observed in subjects with NVAF with increasing CrCL in the ENGAGE-AF study. When analysed across the full range of CrCL, the differences between edoxaban 60 mg and warfarin were very small and were only numerically evident for those patients with very high levels of CrCL. In the 3 highest CrCL subgroups, the observed differences are 1, 3, and 8 events (Table 1).

Table 1: Number of Strokes/SEE by CrCL Category in ENGAGE-AF-Overall Study Period

CrCL subgroup (mL/min)	Edoxaban 60 mg (N = 7012)			Warfarin (N = 7012)			
	n	Number of events	Event rate (%/year)	n	Number of events	Event rate (%/year)	HR (95% CI)
≥30 to ≤50	1302	76	2.29	1305	87	2.68	0.859 (0.632, 1.169)
>50 to ≤70	2093	95	1.69	2106	130	2.35	0.717 (0.550, 0.934)
>70 to ≤90	1661	57	1.25	1703	68	1.47	0.853 (0.600, 1.214)
>90 to ≤110	927	33	1.32	960	32	1.21	1.096 (0.674, 1.781)
>110 to ≤130	497	16	1.15	469	13	1.02	1.117 (0.539, 2.316)
>130	462	11	0.86	418	3	0.25	-*

Source: Table T_EU-CR-001

Abbreviations: N = number of subjects mITT population overall study period, n = number of patients in subgroup

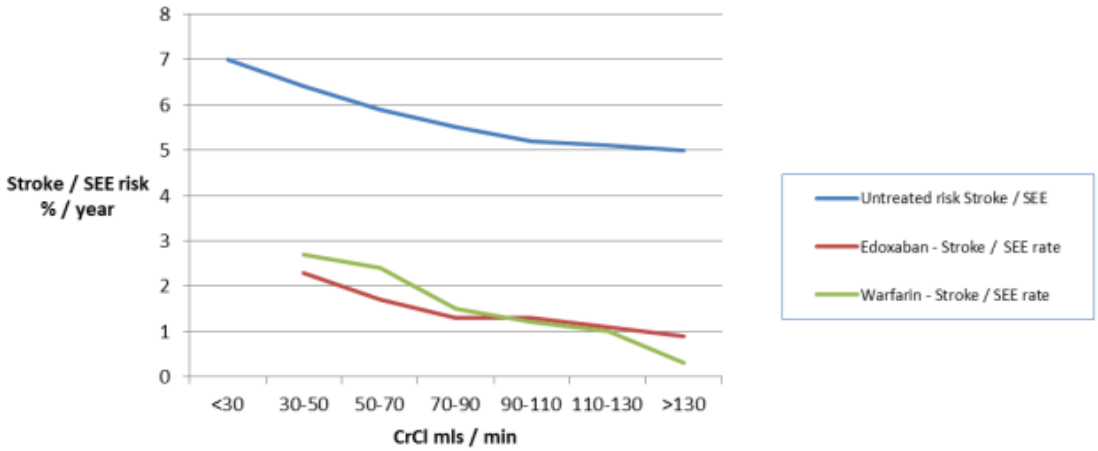
*HR not computed if number of events < 5 in one treatment group.

Seriousness/outcomes: Stroke may have severe consequences and can lead to hospitalisation, potential long-term disability and possibly death.

Background incidence/prevalence:

Incidence: In untreated patients (Figure 1, top curve in blue), the risk of ischaemic stroke/SEE in patients with higher CrCL tended to be lower compared to patients with lower CrCL, although there remains substantial risk (5% to 7% of cases per year) across the entire continuum of CrCL. Data in Figure 1 also show that the post-treatment event rates for stroke/SEE for both edoxaban and warfarin decline in parallel across the renal function continuum with absolute risk reduction reasonably constant at approximately 4% per year vs. untreated.

Figure 1: Stroke/SEE Rates for Edoxaban 60 mg and Warfarin in ENGAGE-AF vs. Untreated



Prevalence: N/A for stroke/SEE. Source: Table T_EU-CR-001, Gage et al

Potential risk: Trend towards decreasing efficacy in NVAF subjects with high creatinine clearance

Risk groups or risk factors:

Risk factors for stroke/SEE may include age, gender, prior stroke or TIA, CrCL/kidney function status, hypertension or blood pressure, a history of vascular disease, a history of AF or a history of heart failure.

Preventability:

The **SmPC** recommends the following:

Section 4.2:

Renal impairment:

Renal function should be assessed in all patients by calculating the CrCL prior to initiation of treatment with Lixiana to exclude patients with end-stage renal disease (ie, CrCL <15 mL/min), to use the correct Lixiana dose in patients with CrCl 15–50 mL/min (30 mg once daily), in patients with CrCL >50 mL/min (60 mg once daily) and when deciding on the use of Lixiana in patients with creatinine clearance (see *section 4.4*).

Renal function should also be assessed when a change in renal function is suspected during treatment (e.g. hypovolaemia, dehydration, and in case of concomitant use of certain medicinal products).

The method used to estimate renal function (CrCL in mL/min) during the clinical development of Lixiana was the Cockcroft-Gault method. The formula is as follows:

For creatinine in µmol/L:

$$\frac{1.23 \times (140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{\text{Serum creatinine [µmol/L]}}$$

For creatinine in mg/dL:

$$\frac{(140\text{-age [years]}) \times \text{weight [kg]} \ (\times 0.85 \text{ if female})}{72 \times \text{Serum creatinine [mg/dL]}}$$

This method is recommended when assessing patients' CrCL prior to and during Lixiana treatment.

In patients with mild renal impairment (CrCl > 50 – 80 mL/min), the recommended dose is 60 mg edoxaban once daily.

In patients with moderate or severe renal impairment (CrCl 15 – 50 mL/min), the recommended dose is 30 mg edoxaban once daily (see section 5.2).

In patients with end stage renal disease (ESRD) (CrCl < 15 mL/min) or on dialysis, the use of edoxaban is not recommended (see sections 4.4 and 5.2).

Section 4.4:

"Renal function in NVAF

A trend towards decreasing efficacy with increasing CrCl was observed for edoxaban compared to well-managed warfarin (see section 5.1, ENGAGE AF-TIMI 48).

Data from additional edoxaban clinical trials which included patients with NVAF and high CrCl (see section 5.1) utilising edoxaban 60 mg is provided to further assess the protection against ischaemic stroke in patients with high CrCl.

Edoxaban should be used in patients with NVAF and high CrCl only after a careful evaluation of the individual thromboembolic and bleeding risk.

Potential risk: Trend towards decreasing efficacy in NVAF subjects with high creatinine clearance
Assessment of renal function: CrCl should be monitored at the beginning of the treatment in all patients and afterwards when clinically indicated (see section 4.2). Additional information on ischaemic strokes/SEE, Major Bleeding, Fatal Bleeding, and Intracranial Bleeding by CrCL category in NVAF patients in ENGAGE AF-TIMI 48 are included in *section 5.1* of the SmPC.
Impact on individual patient: At the patient level, there may be a potential trend for reduced efficacy at the individual level in patients with high CrCL. Stroke may have severe consequences and can lead to hospitalisation, potential long-term disability, and possibly death. At the overall population level, the overall benefit risk in the AF indication was considered positive across the continuum of renal function; there were indications of a trend towards reduced efficacy of edoxaban compared to well -managed warfarin therapy that could be of relevance at the individual level in patients with high CrCL.
Public health impact: A public health impact is anticipated from stroke, as stroke will present a significant burden on the healthcare system. In the short term, impact arises through the need for hospitalisation and potentially significant diagnostic and treatment efforts. In the long-term, outcomes of significant permanent disabilities will impact public health with a need for rehabilitation and nursing support.

AF = atrial fibrillation; Cav = average concentration; CHMP = Committee for Medicinal Products for Human Use; CI = confidence interval; Cmin = minimum concentration in plasma; CrCL = creatinine clearance; CSR = clinical study report; FXa = factor Xa; HR = hazard ratio; mITT = modified intent-to-treat; N/A = not available; NOAC = novel oral anticoagulants; NVAF = nonvalvular atrial fibrillation; PAM = Post Authorisation Measure; QD = once daily; SEE = systemic embolic event; SmPC = Summary of Product Characteristics; TIA = transient ischaemic attack

Important risks are reviewed regularly and are presented in each PSUR. As of DLP of this RMP update, the important identified and potential risks remain unchanged.

SVII.3.2 Presentation of the Missing Information

Missing information: Lack of reversal agent
Evidence source: Bleeding is a known and expected pharmacological action of edoxaban. Reversal of bleeding has been studied in non-clinical and clinical studies.
Anticipated risk/consequence of the missing information: The main concern arises over events of bleeding or situations in which a rapid reversal of an anticoagulant effect is needed to prevent bleeding complications. Non-clinical studies were completed, and several clinical studies have also been completed. Andexanet Alfa has been approved in Japan as a reversal agent for edoxaban, and further applications (including EMA/FDA) are ongoing. The SmPC *section 4.9* states that administration of 4-factor PCC has been shown to reverse the effects of edoxaban during life-threatening bleeding that cannot be controlled with transfusions or haemostasis. rFVIIa) may also be considered; however, use of this product in individuals receiving edoxaban is limited. Protamine sulphate and vitamin K are not expected to affect edoxaban's anticoagulant activity.

PCC = prothrombin complex concentrate; rFVIIa = recombinant factor VIIa; SmPC = Summary of Product Characteristics

Missing information: Reproductive and development toxicity [Use in pregnancy and lactation]
Evidence source: Women who were pregnant or breastfeeding were excluded from the clinical development programme for edoxaban. Non-clinical studies have been conducted.
Population in need of further characterisation: No studies in pregnant subjects have been conducted. There are limited data from the use of edoxaban in pregnant women; there were a number of incidental pregnancies during the large Phase 3 programme. Animal reproductive and development toxicity studies showed maternal and embryo-foetal toxicities in rats and rabbits at higher doses. The SmPC states that Lixiana is contraindicated during pregnancy due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that edoxaban passes the placenta. The SmPC also states that "no specific studies have been conducted with edoxaban in humans to evaluate the effect on fertility." The relevance of edoxaban crossing the placenta in rats is unknown in humans. No studies in lactating human subjects have been conducted. Edoxaban is excreted into the breast milk of lactating rats. The SmPC describes that a "decision must be made whether to discontinue breastfeeding or discontinue edoxaban taking into importance of the drug to the mother."

SmPC = Summary of Product Characteristics

Missing information: Use in patients with hepatic impairment
Evidence source: Edoxaban has not been studied in patients with severe hepatic impairment.
Population in need of further characterisation: Edoxaban is not recommended in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (SmPC *section 4.2*). Patients with mild or moderate hepatic impairment exhibited comparable PK/PD to their matched healthy control group (SmPC *section 5.2*).

PD = pharmacodynamics; PK = pharmacokinetics; SmPC = Summary of Product Characteristics

Missing information: Use in patients with severe renal impairment (CrCL <30 ml/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis)
Evidence source: Subjects with severe renal insufficiency (calculated CrCL <30 mL/min) were excluded from clinical trials.
Anticipated risk/consequence of the missing information: Edoxaban is not recommended in patients with end-stage renal disease (CrCL <15 mL/min) or on dialysis (SmPC *section 4.2*).

CrCL = creatinine clearance; SmPC = Summary of Product Characteristics;

Missing information: Use in patients with mechanical heart valves
Evidence source: Patients with mechanical valve replacements were excluded from clinical studies. Limited data are available from a small number of patients with mild or moderate valvular disease included in the clinical studies.
Anticipated risk/consequence of the missing information: Edoxaban has not been studied in patients with mechanical heart valves. The use of edoxaban in patients with mechanical heart valves is not recommended (SmPC *section 4.4*).

SmPC = Summary of Product Characteristics

Missing information: Combination with dual antiplatelet therapy
Evidence source: Bleeding is considered an important identified risk with edoxaban.
Anticipated risk/consequence of the missing information: The main concern arises over the increased risk of bleeding, as studies have shown an increased bleeding risk also in single combination therapy with other antiplatelet agents. The SmPC (*sections 4.4* and *4.5*) provides special warning and precautions with concomitant use of drugs affecting haemostasis.

SmPC = Summary of Product Characteristics

Missing information: Off–label use in Europe in populations or indications outside the approved indications per SmPC (eg Use in post orthopaedic surgery in Europe)
Evidence source: Use of edoxaban in the European population for any indication outside those approved in the SmPC is considered off-label use.
Anticipated risk/consequence of the missing information: Limited or absence of data concerning use of edoxaban in certain populations (eg pregnant women and children) and contraindications in situations associated with major bleeding are concerns with off-label use. In the EU, edoxaban is contraindicated in conditions considered to present a major risk for bleeding such as gastrointestinal ulceration, malignant neoplasms at high risk of bleeding, recent intracranial haemorrhage, certain vascular abnormalities, and surgery (SmPC *section 4.3*). However, the potential for off-label use of edoxaban in Europe is low due to availability of approved and indicated treatment alternatives.

EU = European Union; SmPC = Summary of Product Characteristics

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table Part II: Module SVIII.1: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding e.g. 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 risks	Hepatic dysfunction
Important potential risks	Trend towards decreasing efficacy in NVAF subjects with high CCL
Missing information	Lack of reversal agent
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

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = glycoprotein; SmPC = Summary of Product Characteristics

PART III PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for any safety concerns:

Questionnaires were implemented for the following important risks:

- Bleeding
- Hepatic dysfunction

These questionnaires were created at the request of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC); however, Daiichi Sankyo has agreed to implement this measure in all regions in which edoxaban is approved for use.

When the follow-up questionnaires were initially implemented for the identified important risk concerning bleeding, this was done for both serious and non-serious cases. However, the MAH noted that the follow-up questionnaire of non-serious cases, did not lead to additional information that improved the case quality. Thus, the MAH will no longer use the follow-up questionnaires in bleeding cases that are non-serious. Bleeding is an identified risk for edoxaban and all bleeding events are considered expected according to the SmPC.

Other forms of routine pharmacovigilance activities for any safety concerns:

Not applicable.

III.2 Additional Pharmacovigilance Activities

Drug Utilisation Study (DSE-EDO-01-14-EU)

Rational and study objectives: To assess prescribing patterns, to assess off-label use in Europe.

Study design: A multinational, multicentre study involving a retrospective chart review of edoxaban users' medical records.

The drug utilisation study is measuring patterns of use/off-label use to ensure HCPs understand and comply with the product information and educational materials. Both studies, the drug utilisation study and the prescription survey have been combined in one protocol and are being conducted at the same sites. The drug utilisation study is a retrospective chart review, whereas the prescription survey directly asks the physicians to assess their level of awareness and understanding of the content of the educational material/SmPC.

PRAC approved the protocol and the CHMP's conclusion was received in Sep 2016. The study started in Dec 2016. A snapshot analysis was submitted to PRAC on 20 Oct 2017. The start of the procedure was on 13 Nov 2017 and the CHMP's conclusion was received on 25 Jan 2018. PRAC requested additional information that was submitted on 14 Mar 2018. The study is clinically completed, and 1219 patients were enrolled. Database was locked on 30 Apr 2019.

Study population: Patients who have been treated at least once with 1 or more dose(s) of edoxaban.

Milestones: Protocol approved in Oct 2016, interim report was submitted in Oct 2017, and final report was submitted in October 2019. The positive CHMP Opinion was received on 26 November 2020.

Prescription Survey

Study design: EU survey of HCPs. Nested in the drug utilisation study is a cross-sectional survey of all participating prescribing physicians is performed, starting from the date of the first data abstraction and repeated over the course of the study to evaluate the effectiveness of the physician educational programme.

Rationale and study objectives: To ascertain the effectiveness of the risk minimisation measures and educational programmes in European countries using edoxaban for its approved indications, Daiichi Sankyo proposed in the approved EU-RMP (version 6.0, dated Apr 2015) to conduct a periodic prescription surveys among representative samples of cardiologists, haematologists, and

other relevant HCPs to examine, recall and have an understanding of key risk minimisation measures associated with the use of edoxaban. The patient aspect of the Prescription Survey is primarily focusing on the use of the patient alert card.

Study population: HCPs who are personally responsible for treatment decisions and initiation of anticoagulation with edoxaban.

Milestones: The Prescription Survey is being conducted approximately 1 year after launch in the respective countries, and depending on results, may be repeated 1 year later in at least 5 European countries. Start of data collection was 09 December 2016, end of data collection was 30 April 2019 (data base lock). The results were submitted together with DSE-EDO-01-14-EU in October 2019 and positive CHMP Opinion was received on 26 November 2020.

ETNA-VTE-Europe (DSE-EDO-05-14-EU): Non-interventional study on Edoxaban Treatment in routine cliNical prActice for patients with acute Venous ThromboEmbolism in Europe.

Rationale and study objectives: This non-interventional study is collecting real-world data using medical records and/or telephone interviews in patients with acute VTE treated with edoxaban outside of clinical trials. Co-primary objectives include assessment of VTE recurrence and safety events (bleeding, drug related adverse events and mortality). ETNA-VTE Europe data will be combined with 18-month safety data from the Edoxaban Treatment in routine cliNical PrActice for patients with nonvalvular Atrial Fibrillation in Europe (ETNA-AF-Europe [DSE-EDO-04-14-EU]) study evaluating the safety and effectiveness of edoxaban in real-world treatment of AF. Subgroup analyses will be performed in predefined patient populations, such as patients with renal or hepatic impairment.

Study design: An 18-month prospective, single-arm, non-interventional, multinational post authorisation safety study (PASS) in 8 European countries (Austria, Belgium, Germany, Ireland, Italy, the Netherlands, Switzerland and the United Kingdom [UK]). Data from patient medical records and/or telephone interviews is being collected at baseline, 1, 3, 6, 12 and 18 months.

Study population: Patients with established acute initial or recurrent VTE treated with edoxaban according to the SmPC.

Milestones: Periodic data reports are presented in the PSURs. 2,826 patients have been registered. Enrolment has stopped and the final study report has been submitted in June 2021.

ETNA-AF-Europe (DSE-EDO-04-14-EU): Edoxaban Treatment in routine cliNical PrActice for patients with nonvalvular Atrial Fibrillation in Europe.

Rationale and study objectives: Daiichi Sankyo is conducting this non-interventional PASS in order to evaluate the safety and effectiveness of edoxaban in real-world treatment of NVAF. The study aims to gain insight into the safety (bleeding, drug related AEs and all-cause mortality) in this setting. Subgroup analyses will be performed in predefined patient populations, such as patients with renal or hepatic impairment.

Study design: A multicentre, prospective, observational study in 10 European countries (Austria, Belgium, Germany, Ireland, Italy, the Netherlands, Portugal, Spain, Switzerland, and the UK). Patient data is documented at baseline, once annually during 4 years of follow-up and during the final assessment.

Study population: Patients with established NVAF treated with edoxaban according to SmPC.

Milestones: Periodic data reports are presented in the PSURs. As of the DLP of this report, 13,980 patients have been registered. Enrollment has stopped and the final study report has been submitted in Mar 2023.

A tabulated summary of ongoing and completed pharmacovigilance studies may be found in Annex 2.

Anticoagulation Reversal Programme

Astra Zeneca: Prospective, Open-Label Study of Andexanet Alfa in Patients Receiving a Factor Xa Inhibitor Who Have Acute Major Bleeding (ANNEXA-4)

Rationale and study objectives: The objective of this study is to demonstrate the decrease in anti-FXa activity following andexanet treatment in patients receiving an FXa inhibitor who have acute major bleeding and reduced FXa activity.

To evaluate the haemostatic efficacy of andexanet in patients receiving an FXa inhibitor who have acute major bleeding and reduced FXa activity in the United States, accelerated approval was granted for andexanet alfa on 03 May 2018 as a reversal agent for apixaban and rivaroxaban. Andexanet alfa was not initially indicated for edoxaban, as clinical data from ongoing ANNEXA-4 study are still being accrued to support the edoxaban reversal labelling. Ondexxya (andexanet alfa) has been approved as reversal agent for edoxaban in Japan on 28 March 2022. In the EU, a CHMP positive opinion was received on 28 Feb 2019 for apixaban and rivaroxaban. The EC granted conditional authorisation of andexanet for reversal of the anticoagulant effect of edoxaban and rivaroxaban as of 26 April 2019. Once sufficient edoxaban data has been accrued in ANNEXA-I (Trial of Andexanet Alfa in ICH Patients Receiving an Oral FXa Inhibitor), Astra Zeneca plans to submit a Type II variation seeking approval for reversal of edoxaban in EU.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: On-Going and Planned Additional Pharmacovigilance Activities

Study: **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation: None				
Category 2 – Imposed mandatory additional pharmacovigilance activities that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances: None				
Category 3 - Required additional pharmacovigilance activities: None				

Part IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

IV.1 Applicability of Efficacy to All Patients in the Target Population

Not applicable.

IV.2 Tables of Post-authorisation Efficacy Studies

The Applicant conducted a study post CHMP approval to investigate if further optimisation of the protective effects toward prevention of stroke could possibly be achieved by using a higher dose of edoxaban in the above-mentioned NVAF patients. This study (DU176b-C-E314) was a Post Authorisation Measure (PAM). The study has now been completed and the CSR was submitted in Nov 2019, in line with the post-authorisation measures agreed with CHMP (MEA004, LEG002).

Table Part IV.1: Planned and on-Going Post Authorisation Efficacy Studies That Are Conditions of the Marketing Authorisation or That Are Specific Obligations

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Efficacy studies that are conditions of the marketing authorisation				
Not applicable				
Efficacy studies that are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

Table Part IV. 2: Other Efficacy/Effectiveness Studies

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due Date
Evaluation of LIXIANA® (edoxaban) in Patients with Nonvalvular Atrial Fibrillation and High Creatinine Clearance (Short Title: Edoxaban in Atrial Fibrillation and High Creatinine Clearance; DU176b-C-E314) Completed Category 3	Primary Objective: To compare the exposure (based on Cav, Cmin, and anti-FXa) of an edoxaban 75-mg QD dose in patients with CrCL >100 mL/min to that of an edoxaban 60-mg QD dose seen in the same patients treated for 12 months. Secondary Objectives: Pharmacokinetic (PK)/Pharmacodynamic (PD) and Anti-FXa assay evaluation: Compare the incidence of stroke/systemic embolism, and its components, ischemic stroke, haemorrhagic stroke and systemic embolism as well as net clinical outcome (composite: stroke/systemic embolism, myocardial infarction, cardiovascular death, major bleeding) in AF patients with the CrCL >100 mL/min treated with edoxaban 75 mg QD for 12 months with edoxaban 60 mg QD for 12 months in the same patient population. Compare the incidence of major, intracranial, extracranial and clinically relevant bleeding (major and CRNM) in AF patients with CrCL >100 mL/min treated with edoxaban 75 mg QD for 12 months with edoxaban 60 mg QD for 12 months in the same patient population.	Protective effects toward prevention of stroke in patients with NVAF and high CrCL using a higher dose of edoxaban	Protocol submission	Study start delayed due to ongoing negotiations with EMA. Final protocol approved in Jun 2016.
			Study start	First patient in occurred in Jan 2017
			Study finish	All 607 patients randomised and completed study treatment as per the protocol
			Final report	CSR was submitted in Nov 2019

AF = atrial fibrillation; Cav = average concentration; Cmin = minimum concentration in plasma; CrCL = creatinine clearance; CRNM = clinically relevant nonmajor; CSR = clinical study report; FXa = activated coagulation factor X; NVAF = nonvalvular atrial fibrillation; PD = pharmacodynamics; PK = pharmacokinetics; QD = once daily

PART V RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

V.1 Routine Risk Minimisation Measures

Table Part V.1: Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding e.g. 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)	Routine risk communication: • SmPC *section 4.2* • SmPC *section 4.3* • SmPC *section 4.4* • SmPC *section 4.5* • SmPC *section 4.9* • PIL sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Increase awareness of the risk of bleeding and provide guidance on how to manage the risk of bleeding in SmPC *sections 4.2, 4.3, 4.4, 4.5, 4.8* and *4.9* • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None
Important potential risks	
Hepatic dysfunction	Routine risk communication: • SmPC *section 4.2* • SmPC *section 4.3* • SmPC *section 4.4* • PIL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Increase awareness of the risk of hepatic dysfunction and provide guidance on monitoring of hepatic function and how to manage the risk in SmPC sections 4.2, 4.3 and 4.4. • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None

Important potential risks	
Trend towards decreasing efficacy in NVAF subjects with high creatinine clearance	Routine risk communication: • SmPC *section 4.4* Routine risk minimisation activities recommending specific clinical measures to address the risk: • Advice is given on the trend of decreasing efficacy with increasing CrCL and provide guidance on how to manage the risk in the SmPC *sections 4.2, 4.4* and *5.1* • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None
Missing information • Lack of reversal agent • Reproductive and development toxicity (Pregnancy and lactation) • Patients with hepatic impairment • Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15mL/min or on dialysis) • Patients with mechanical heart valves • Combination with dual antiplatelet therapy • Off-label use in Europe in populations or indications outside the approved indications per European SmPC	Routine risk communication: • SmPC *section 4.2* • SmPC *section 4.3* • SmPC *section 4.4* • SmPC *section 4.6* • SmPC *section 4.9* • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein; PIL = patient information leaflet; SmPC = Summary of Product Characteristics

V.2 Additional Risk Minimisation Measures

The 2 global additional risk minimisation measures for edoxaban, the Prescriber Guide and Patient Alert Card, are described below. Note that although these are global measures, terminology and wording may differ between regions based on local regulations and conventions (ie, Japan's utilisation of different terms for healthcare providers and patients).

Prescriber Guide
Objectives: Educational materials are being provided to HCPs with the objective of providing an additional resource to inform and educate regarding the risks of bleeding. Prompt attention to symptoms of bleeding and appropriate medical attention can minimise the impact of bleeding events. This information is provided in the Prescriber Guide.
Rationale for the additional risk minimisation activity: Educational materials are being provided to HCPs with the objective of being an additional resource to inform and educate regarding the risks of bleeding as a preventive measure for this important identified risk. This additional educational tool serves as a preventive measure for the important identified risk of bleeding to ensure that swift action can be taken in response to any events that may occur.
Plans to evaluate the effectiveness of the interventions and criteria for success: Effectiveness and benefit-risk is analysed for each important risk with each PSUR.

HCP = health care professional; PSUR = Periodic Safety Update Report

Patient Alert Card
Objectives: A Patient Alert Card is also available to the patient in order that the patient is aware of what action they should take if bleeding occurs and the need to keep the card with them at all times so as to inform any other physician that they are taking edoxaban. Prompt attention to symptoms of bleeding and appropriate medical attention can minimise the impact of bleeding events. This information is provided in the Patient Alert Card.
Rationale for the additional risk minimisation activity: A Patient Alert Card is included in the medicine pack, (where national regulations allow) so that the patient is aware of what action they should take if bleeding occurs and the need to keep the card with them at all times so as to inform any other physician that they are taking edoxaban. This additional educational tool will serve as a preventive measure for the important identified risk of bleeding to ensure that swift action can be taken in response to any events that may occur.
Plans to evaluate the effectiveness of the interventions and criteria for success: Effectiveness and benefit-risk is analysed for each important risk with each PSUR.

PSUR = Periodic Safety Update Report

Removal of additional risk minimisation activities

Not applicable.

V.3 Summary of Risk Minimisation Measures

Table Part V.2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Bleeding or 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)	Routine risk communication: • SmPC *section 4.2* • SmPC *section 4.3* • SmPC *section 4.4* • SmPC *section 4.5* • SmPC *section 4.9* • PIL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Increase awareness of the risk of bleeding and provide guidance on how to manage that risk in SmPC *section 4.4* • Prescription-only medicine Additional risk minimisation measures: • Prescriber Guide • Patient Alert Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire (only serious cases) Additional pharmacovigilance activities: • None
Important potential risks		
Hepatic dysfunction	Routine risk communication: • SmPC *section 4.2* • SmPC *section 4.3* • SmPC *section 4.4* • PIL Sections 2 and 4 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Edoxaban is not recommended in patients with severe hepatic impairment (SmPC *section 4.2*)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up questionnaire Additional pharmacovigilance activities: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• Edoxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk (SmPC *section 4.2*) • Prescription-only medicine Other routine risk minimisation measures beyond the Product Information: • None Additional risk minimisation measures: • None	
Trend towards decreasing efficacy in NVAF subjects with high creatinine clearance	Routine risk communication: • SmPC *section 4.4* Routine risk minimisation activities recommending specific clinical measures to address the risk: • Special warnings and precautions for use in NVAF patients with high CrCL and provides guidance on how to manage that risk in the SmPC *sections 4.2* and *4.4* • Prescription-only medicine Other routine risk minimisation measures beyond the Product Information: • None Additional risk minimisation measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Missing information		
Missing information: • Lack of reversal agent • Reproductive and development toxicity	Routine risk communication: • SmPC *section 4.2* • SmPC *section 4.3*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None

Safety concern	Risk minimisation measures	Pharmacovigilance activities
(Pregnancy and lactation) • Patients with hepatic impairment • Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis) • Patients with mechanical heart valves • Combination with dual antiplatelet therapy • Off-label use in Europe in populations or indications outside the approved indications per European SmPC	• SmPC *section 4.4* • SmPC *section 4.6* • SmPC *section 4.9* • PIL Section 2 Routine risk minimisation activities recommending specific clinical measures to address the risk: • Prescription only medicine Other routine risk minimisation measures beyond the Product Information: • None Additional risk minimisation measures: • Prescriber Guide	Additional pharmacovigilance activities: • Anticoagulation reversal programme (to address lack of reversal agent)

CHMP = Committee for Medicinal Products for Human Use; CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; PAM = Post Approval Measure; P-gp = P-glycoprotein; PIL = patient information leaflet; SmPC = Summary of Product Characteristics

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR EDOXABAN

This is a summary of the RMP for edoxaban. The RMP details important risks of edoxaban, how these risks can be minimised, and how additional information will be obtained about edoxaban's risks and uncertainties (missing information).

Edoxaban’s SmPC and its package leaflet give essential information to healthcare professionals and patients on how edoxaban should be used.

Important new concerns or changes to the current ones will be included in updates of edoxaban’s RMP.

I THE MEDICINE AND WHAT IT IS USED FOR

Edoxaban is authorised for prevention of stroke and systemic embolism in adult patients with NVAF and treatment of VTE including DVT and PE, and prevention of recurrent VTE in adults (see the SmPC for the full indication). It contains the anhydrous free base of edoxaban tosylate as the active substance and it is given by oral administration.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of edoxaban, together with measures to minimise such risks and the proposed studies for learning more about edoxaban's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be as follows:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including by PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Important risks of edoxaban are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely orally. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of edoxaban. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table Part II.1: Lists of Important Risks and Missing Information

List of Important Risks and Missing Information (from Part II: Module SVIII)	
Important identified risks	Bleeding or Bleeding due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding eg, aspirin, NSAID • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 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 risks	• Hepatic dysfunction • Trend towards decreasing efficacy in NVAF subjects with high CrCL
Missing information	• Lack of reversal agent • Reproductive and development toxicity (Pregnancy and lactation) • Patients with hepatic impairment • Patients with severe renal impairment (CrCL <30 mL/min) or end-stage renal disease (CrCL <15 mL/min or on dialysis) • Patients with mechanical heart valves • Combination with dual antiplatelet therapy • Off-label use in Europe in populations or indications outside the approved indications per European SmPC

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein; SmPC = Summary of Product Characteristics

II.B Summary of Important Risks

Bleeding or Bleeding Due to: • Drug interaction in combination with other drugs known to increase the risk of bleeding, eg, aspirin, NSAIDs • Inappropriate administration of the 60-mg dose /inadvertent overdose by use of the 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)	
Risk minimisation measures	• SmPC/PIL • Prescription-only medicine • Educational package including: – Prescriber Guide – Patient Alert Card
Additional pharmacovigilance activities	• None
Hepatic Dysfunction	
Risk minimisation measures	• SmPC/PIL • Prescription only medicine
Additional pharmacovigilance activities	• None
Trend Towards Decreasing Efficacy in NVAF Subjects with High Creatinine Clearance	
Risk minimisation measures	• SmPC • Prescription-only medicine
Additional pharmacovigilance activities	• None
Missing Information (including reversibility, pregnancy and lactation, hepatic impairment, renal impairment, mechanical heart valves, combination with antiplatelets and off-label use)	
Risk minimisation measures	• SmPC/PIL • Prescription-only medicine • Prescriber Guide
Additional pharmacovigilance activities	• Anticoagulant reversal programme • None

CrCL = creatinine clearance; NSAID = nonsteroidal anti-inflammatory drug; NVAF = nonvalvular atrial fibrillation; P-gp = P-glycoprotein; PIL = patient information leaflet; SmPC = Summary of Product Characteristics

II.C Post-Authorisation Development Plan

II.C.1 Studies That Are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of edoxaban.

II.C.2 Other Studies in Post-Authorisation Development Plan

Drug Utilisation Study (DSE-EDO-01-14-EU)

Purpose of the study: To assess off-label use in the EU. This study is completed.

Prescription Survey Study

Purpose of the study: To measure the effectiveness of the risk minimisation measures and educational programmes in European countries using edoxaban for its approved indications educational materials for HCP and patients. This study is completed.

PASS: ETNA-AF-Europe (DSE-EDO-04-14-EU)

Purpose of the study: 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. This study is completed.

PASS: ETNA-VTE-Europe (DSE-EDO-05-14-EU)

Purpose of the study: To collect real world 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. This study is completed.

PAM (DU176b-C-E314): Edoxaban in Atrial Fibrillation and High Creatinine Clearance

Purpose of the study: To compare the exposure (based on Cav, Cmin, and Anti-FXa) of an edoxaban 75-mg QD dose in patients with CrCL >100 mL/min to that of an edoxaban 60-mg QD dose seen in the same patients treated for 12 months. This study is completed.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Edoxaban Follow-up Questionnaire
- GENERAL BLEEDING -

Reported Events with Start/Stop Dates			
Date:	**Signature:**	**Daiichi Sankyo ARGUS #:**	
Information provided by:			
Patient Characteristics			
Initials:		Birth Date or Age:	
Gender:		Race/Ethnicity:	
Weight:			
Edoxaban			
Lot Number:		Indication:	
Dose:		Frequency:	
Edoxaban Start date:			
Bleeding Details – General Questions			
Start date of event:			
Bleeding site:		Volume of blood loss:	
Duration of bleed:			
Edoxaban discontinued due to bleeding event?	☐ Yes / ☐ No	Date of edoxaban D/C	
Event resolved after discontinuation?	☐ Yes / ☐ No	Edoxaban restarted?	☐ Yes / ☐ No
Date edoxaban restarted		Bleeding Event reoccurred?	☐ Yes / ☐ No
Causality assessment to edoxaban		Explanation	

Bleeding Details – Event Outcome		
☐ Recovered	☐ Recovered with Sequelae	☐ Recovered after Treatment
☐ Recovering	☐ Not Recovered	☐ Worsened
☐ Unknown	☐ Fatal (if conducted, please provide copy of post-mortem report)	☐ Hospitalized

Other, please describe	
Please provide circumstances of bleeding (for example, ICH due to fall; GI bleeding due to gastric ulcer)	
Cause of bleeding (for example, trauma, menses related)	
Did the patient have more than 1 bleeding episode? If yes, how many	

Medications at Time of Event (enter all that apply, add dose and date)			
Medication (class)	**Medication (drug substance)**	**Daily dose**	**Start Date**
Heparin			
Other platelet aggregation inhibitors excluding heparin; eg clopidogrel, prasugrel			
NSAID			
Other oral anticoagulant e.g, warfarin			
Anti-thrombin therapy			
Fibrinolytic/Thrombolytic therapy			
Proton pump inhibitor			
P-gp inhibitor			
P-gp inhibitor			
P-gp inhibitor			
Other:			
Other:			
Other:			

Relevant Medical History / Risk Factors	
Renal impairment (please specify)	
Hepatic impairment (please specify)	
Bleeding disorders (please specify)	
Alcohol use	
Gastric/duodenal ulcer / Esophageal varices	
Prior bleeding episodes	
Family history (please specify)	
Other	

Laboratory Tests / Investigations				
Relevant Lab Tests	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Latest Value**
		Date:	**Date:**	**Date:**
INR/PT				
Platelet Count				
APTT				
Serum Creatinine				
Hemoglobin				
Hematocrit				
Other				

Relevant Diagnostic Testing (tick all that apply and add results)		
☐ Ultrasound	☐ CT	☐ MRI
☐ Gastroscopy	☐ Angiography	☐ Colonoscopy
☐ Biopsy	☐ Other	

Procedures for bleeding event (specify)	
If the patient was continued or resumed on edoxaban following the bleeding event, was edoxaban discontinued for the above procedures?	☐ Yes / ☐ No

Special Treatment			
Blood transfusion	# of units	Date	
Platelet transfusion	# of units	Date	
FFP/Plasma concentrate	# of units	Date	
Reversal agent	Product	Date	
Other, please specify		Date	

Edoxaban Follow-up Questionnaire
- HEPATIC -

Reported Events with Start/Stop Dates			
Date:	**Signature:**	**Daiichi Sankyo ARGUS #:**	
Information provided by:			
Patient Characteristics			
Initials:		Birth Date or Age:	
Gender:		Race/Ethnicity:	
Weight:			
Edoxaban			
Lot Number:		Indication:	
Dose:		Frequency:	
Edoxaban Start date:			
Hepatic Details			
Primary Diagnosis for Reported Hepatic Events:			
Start date of event:			
Edoxaban discontinued due to hepatic event?	☐ Yes / ☐ No	Date of edoxaban D/C	
Event resolved after discontinuation?	☐ Yes / ☐ No	Edoxaban restarted?	☐ Yes / ☐ No
Date edoxaban restarted		Hepatic Event reoccurred?	☐ Yes / ☐ No
Causality assessment to edoxaban		Explanation	

Hepatic Details – Event Outcome		
☐ Recovered	☐ Recovered with Sequelae	☐ Recovered after Treatment
☐ Recovering	☐ Not Recovered	☐ Worsened
☐ Unknown	☐ Fatal (if conducted, please provide copy of post-mortem report)	☐ Hospitalized
Other, please describe:		

Please indicate if the patient had the following events that may have contributed to hepatic event (liver enzyme elevations)		
☐ Sepsis	☐ Kidney Failure	☐ Bleeding
☐ Hypotension	☐ Renal impairment	☐ Malignancy
☐ Congestive Heart Failure	☐ Myopathy/rhabdomyolysis	☐
☐ Other:	☐	☐

Presenting Signs/Symptoms due to Reported Hepatic Event (tick all that apply)			
☐ Rash	☐ Palmar erythema	☐ Urticaria	☐ Itching
☐ Nausea	☐ Abdominal pain	☐ Vomiting	☐ Diarrhea
☐ Anorexia	☐ Weight loss	☐ Fever/Chills	☐ Fatigue
☐ Dark colored urine	☐ Scleral icterus	☐ Jaundice	☐ Ascites
☐ Edema	☐ Asterixis	☐ Confusion	☐
☐ Other:	☐	☐	☐

Relevant Past Medical History (tick all that apply and give further details)	
☐ No known liver disease	
☐ Chronic Hepatitis (specify type Chronic persistent or chronic active hepatitis)	☐ Cirrhosis (provide etiology, if portal hypertension/esophageal varices present)
☐ Autoimmune hepatitis	☐ Alcohol liver disease
☐ Gall bladder disease	☐ Fatty liver/Steatosis (NASH)
☐ Abnormal liver lab results/Jaundice	☐ Diabetes
☐ Family history (please specify):	
☐ Other (to specify):	

Recent Exposure Within the Past 2 Months	
☐ Alcohol (provide type and quantity):	
☐ Tobacco	☐ Liver toxin exposure
☐ Recent travels to tropical countries:	
☐ Blood transfusions (provide number of units)	
☐ Acetaminophen/paracetamol (provide type and quantity)	
☐ Other medications (prescription, over the counter), nutritional supplements, herbals started in past 2 months (provide name, start date):	
☐ Other:	

Laboratory Tests				
Relevant Lab Tests	**Normal Range**	**Baseline Value**	**Abnormal Value**	**Latest Value**
		Date:	**Date:**	**Date:**
AST (SGOT)				
ALT (SGPT)				
Total Bilirubin				
Direct Bilirubin				
Alk. Phos.				
GGT				
PT-INR				
PT				
Platelet Count				
Other relevant labs (example CPK)				

Serology/Studies		
Other Serology/Study	**Date**	**Results**
Hepatitis serology (A/B/C/E))		
Other serology (e.g. ANA, ASMA, CMV, EBV)		
Abdominal (Hepatic) Ultrasound		
MRI		
CT Scan		
Liver Biopsy		
Other		

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Approved Key Messages of the Additional Risk Minimisation Measures

Prior to launch of Lixiana/Roteas in each Member State, the marketing authorization holder (MAH) must agree about 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 (NCA).

The educational programme is aimed at mitigating the risk of serious bleeds or haemorrhage in patients treated with Lixiana/Roteas 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/Roteas are aware of the patient alert card and that the card is to be given to and reviewed with all patients treated with Lixiana/Roteas.

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

- Summary of Product Characteristics (SmPC)
- Prescriber guide for healthcare professionals
- Patient alert card

Physician educational material:

- SmPC
- Prescriber guide:

  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/Roteas 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 healthcare professionals that they are taking Lixiana/Roteas if they need to have any surgery or invasive procedure

- Patient Alert Card:

  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/Roteas if they need to have any surgery or invasive procedure

The patient information pack:

- Patient information leaflet