Interim Study Report

ETNA-DUS

Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study

DSE-EDO-01-14-EU

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1. SIGNATURES

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GLOSSARY

ADR	Adverse Drug Reaction
AE	Adverse Event
CHF	Congestive Heart Failure
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organisation
DS	Daiichi Sankyo
DSE	Daiichi Sankyo Europe GmbH
DUS	Drug Utilisation Study
DVT	Deep Vein Thrombosis
eCOS	eClinical Operating System
eCRF	Electronic Case Report Form
EU	European Union
EU PAS Register	The European Union electronic Register of Post-Authorisation Studies
FPI	First Patient In
GP	General Practitioner
GVP	Good Pharmacovigilance Practices
ICF	Informed Consent Form
LPI	Last Patient In
NVAF	Non-Valvular Atrial Fibrillation
PASS	Post-Authorisation Safety Study
PE	Pulmonary Embolism
PRAC	Pharmacovigilance Risk Assessment Committee
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SIF	Site Information Form
SmPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack
UK	United Kingdom
US	United States
VTE	Venous Thromboembolism

2. SUMMARY

Study/Registry Title	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study (ETNA-DUS)
Keywords	PASS; Edoxaban; Drug Utilisation Study; Prescription patterns
Rationale and Background	Edoxaban is an orally administered anticoagulant that inhibits coagulation factor Xa. Edoxaban was approved in the European Union (EU) on 19 June 2015 for use in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure (CHF), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA) for prevention of stroke and systemic embolism. In addition, edoxaban is approved for the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and prevention of recurrent VTE in adults. As part of the Risk Management Plan (RMP), Daiichi Sankyo (DS) has developed specific risk minimisation activities to understand the prescription pattern of edoxaban. Standard routine risk minimisation activities include the communication of the information in the Summary of Product Characteristics (SmPC). In order to further optimise the correct use of the medicinal product by the physician, Daiichi Sankyo Europe GmbH (DSE) has implemented additional risk minimisation activities, namely: • Prescriber guide as part of the educational program to make prescribers fully aware of the approved indications and eligible patients for edoxaban, the dosing recommendations and management of safety concerns; • Patient Alert Card. The ETNA drug utilisation study (ETNA-DUS) was designed to gain insight on how edoxaban is used in real practice. The ETNA-DUS will help identify prescription patterns and the effectiveness of the educational programs.
Research Question and Objectives	The study was designed to provide real-world data related to the current prescription patterns of edoxaban. The study objectives are as follows: • To characterize sites and physicians; • To characterize users of edoxaban; • To evaluate the pattern of use of edoxaban;

	• To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization.
Study Design	Multinational, multicentre study involving a retrospective chart review of edoxaban users' medical records. Nested in the study, 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 program.
Setting	Country selection took into account prescription volumes, the number of prescribers per capita, and the regulatory environment to conduct observational studies. The participating countries are Germany, Italy, Switzerland, Belgium, the United Kingdom (UK), Spain and Portugal. Following the identification of the countries, an independent prescription data source was used to identify a representative sample of the prescribers in each country. Based on these sources it was possible to retrieve general information on edoxaban number of prescribers per specialty and geographic region. Physicians participating in any interventional currently ongoing/planned study with edoxaban are not eligible to participate in the DUS and the Educational Material Survey. Approximately 100 hospital- and office-based physicians (General Practitioners [GPs], internal medicine physicians and other specialists) in seven countries (listed above) were foreseen to participate in the study.
Population and Study Size	The study aims to include approximately 1200 medical records of patients who have been treated at least once with one or more dose(s) of edoxaban. For characterization of users including potential off-label use, the level of precision is presented in different scenarios of available number of users of edoxaban for different prevalence of diseases and conditions. In general, the 95% level of confidence is adequate for a prevalence as low as 1% and 1,200 users of edoxaban. In addition, it is estimated that approximately 100 physicians have to complete the survey to allow reasonable precision around estimates of the physicians' awareness and understanding levels. No target thresholds for physicians-reported awareness and understanding have been established in advance. However it is assumed that 85% of physicians demonstrate appropriate awareness and understanding of

	the survey. Given this, the lower bound of the 95% CI is estimated to be above 78% for a sample size of N=100.
Marketing Authorization Holder	Daiichi Sankyo Europe GmbH Zielstattstr. 48 81379 Munich Germany Tel.: +49-89-7808-0
Variables (Observation criteria) and Data Sources	**Site/Physicians' characteristics** To evaluate the diversity of sites the following information are collected for each participating site using the site information form (SIF), within the electronic case report form (eCRF) : • Geographic location of physician site; • Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists); • Patient volume (i.e., number of patients and estimated number of patients using edoxaban). **Edoxaban-treated patients' data** The following data are collected from patient medical chart review: • Demographics and medical history: o Birth year; o Gender; o Ethnic group (where permitted); o Height and body weight; o Smoking status and alcohol consumption. • Diagnosis: o Risk factors and treatment (pharmacological or non-pharmacological) history pertaining to edoxaban treatment o Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities o Relevant familial medical history; o History of haemodialysis

	o History of past use of other anticoagulants o Pregnancy and lactation status at the time of prescription o Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban o Presence of mechanical heart valves o Pertinent lab tests upon availability including liver function test, CrCl test and/or glomerular filtration rate pertaining to possible hepatic or renal impairment. • Drug utilisation: o Edoxaban prescription(s): ▪ start and end date/ongoing treatment; (including repeated prescriptions, if any); ▪ daily dose (30 mg, 60 mg, other) at the beginning of the treatment and afterwards; ▪ reason for use; ▪ reason of discontinuation (if applicable). o Concomitant medications (including if patient is using dual antiplatelet therapy). • Health Care Professional Educational Material knowledge assessments o Survey administration variables; o Description of survey participants; o Assessment of knowledge of the key messages of the educational program. The ETNA-DUS is a retrospective chart review. The identified and trained local site staff reviews the medical charts of all patients that have been prescribed edoxaban, over the given time period, and extracts the desired data elements. The data are entered pseudonymised into the eCRFs via a secure web-based electronic data capture (EDC) system. Independently, the physicians access a de-identified system to answer the Physician's survey, to assess their level of awareness and understanding of the content of the Educational Material/SmPC.

	All information collected during the course of the survey are kept strictly confidential.
Results	• Most of the patients (91.0%) were initially prescribed edoxaban for at least one of the two labelled indications. • No patient aged less than 18 years-old was reported as being prescribed edoxaban. On average, the edoxaban users were elderly, with a mean age of 72.6 years. • Approximately a fourth of the patients (23.0%, 95% CI: 17.4%, 29.5%) had a contraindicated use of edoxaban. • Twenty six patients (13.0%, 95% CI: 8.7%, 18.5%) were using edoxaban outside of the labelled indications or for an unknown indication, for either initial or follow-up prescription. • One hundred and four patients (52.0%, 95% CI: 44.8%, 59.1%) were using a different dose or dosing regimen, as the ones recommended by the SmPC, including patients who could not be identified as such due to missing data. • One patient (0.5%, 95% CI: 0.0%, 2.8%) used edoxaban concomitantly with a drug increasing the risk of bleeding. • Dosing regimen and previous use of a parenteral anticoagulant therapy were incompletely reported and need further investigation, to allow for reliable interpretation of data. Additional emphasis will be put on data review and cleaning, to ensure data quality and accuracy for the final report.
Discussion	The physicians prescribing edoxaban as per the report from the QuintilesIMS data assets and the physicians participating in the DUS appeared to be mainly practicing in private offices, and were represented by a variety of specialties, such as general practice, cardiology, neurology, angiology, internal medicine and others. The physicians had a specific geographical distribution in Switzerland, with a higher proportion of prescribers in the German speaking area, as well as in the UK, where edoxaban prescribers were mostly located in England and Northern Ireland (country reports are appended in Section 13.6). The edoxaban users in first wave countries were 70% to be initially prescribed edoxaban for the NVAF indication, 21% for VTE indication, and in 9% of the patients the indication for initial prescription of edoxaban was either outside the recommendations

	from SmPC or unknown. The study population appeared to be elderly, which is consistent with the NVAF indication, and no particular trend was found for gender distribution. The use as per the recommendations from the SmPC shows a relatively high number of deviations, such as a contraindicated use of edoxaban in 23% of patients, use outside of the labelled indications in 13% of patients, and use with a different dose or dosing regimen as the ones recommended by the SmPC in 52% of patients. However, due to missing and inaccurate data, no specific conclusion can currently be drawn. Additional effort will be enforced to ensure data completeness and accuracy, to allow for a full description of the edoxaban user population in the targeted European countries.
Names and affiliation of principal investigators	The list of participating sites is appended in Section 13.1.
Study progress report / interim report(s)	Planned date: Q3 2017 Actual date: 27 September 2017 upon data extracted on 29 June 2017
Final report of study results	Planned date: Q2 2019 (latest 6 months after data base lock)
Other important milestones	End of data collection: Q4 2018

3. RESPONSIBLE PARTIES

Below is a list of the main responsible parties involved in the study.

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3.1. List of participating sites/investigators

The list of participating sites is appended, please refer to Section 13.1.

4. MILESTONES

Table 1 below displays planned and actual dates for study milestones.

Table 1. Study Milestones

Milestone	Planned date	Actual date	Comments
Date of first IEC approval	Q3 2016	29 November 2016	First approval was obtained in Germany
Start of data collection	Q3 2016	09 December 2016	
End of data collection	Q4 2018	NA	
Registration in the EU PAS Register®	Q3 2016	04 January 2017	EU PAS Register® Number: EUPAS17062
Interim report	Q3 2017	27 September 2017	
Final report of study results	Q2 2019	NA	Latest 6 months after database lock

Notes: NA: Not Applicable; Q: Quarter; IEC: Independent Ethics Committee; EU PAS Register: The European Union electronic Register of Post-Authorisation Studies.

Table 2 below displays planned and actual dates for study milestones per country.

Table 2. Milestones per Country

Country	Planned First Patient In (FPI)	Actual First Patient In (FPI)	Wave
Switzerland	Q3 2016	17 January 2017	I
Germany	Q3 2016	09 December 2016	I
United Kingdom	Q3 2016	08 May 2017	I
Belgium	Q3 2017	NA	II
Italy	Q3 2017	NA	II
Spain	Q3 2017	NA	II
Portugal	Q1 2018	NA	II

Notes: NA: Not Applicable; Q: Quarter.

5. RATIONALE AND BACKGROUND

Edoxaban is an orally administered anticoagulant that inhibits coagulation factor Xa.

In the European Union (EU) it was approved on 19 June 2015 for the following indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one 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 deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults.

This approval was based on the results of two pivotal studies: the ENGAGE AF-TIMI 48 study (Giugliano et al, 2013) and the Hokusai-VTE study (Büller et al, 2013).

The clinical development program was undertaken to support marketing authorisation submissions for edoxaban in the above indications. However, as it is the case with any medicinal product, real-life use of edoxaban may differ from the use studied in phase 3 trials or extend beyond the patient population that was studied or is included under the approved indication. The results of observational studies on edoxaban have not been published yet, as the studies are still recruiting patients. Limited information is available on the use of edoxaban in real life (Almutairi et al, 2017).

With regards to edoxaban, Daiichi Sankyo (DS) addressed this concern in the Risk Management Plan (RMP) in order to anticipate necessary risk minimisation activities and understand the prescription pattern of edoxaban. Standard risk minimisation activities include the communication of appropriate information in the Summary of Product Characteristics (SmPC). In order to further optimise the correct use of the medicinal product by the physicians, Daiichi Sankyo Europe GmbH (DSE) has implemented additional risk minimisation measures:

- Distribution of the Prescriber Guide, as part of the educational program, is aimed at improving the knowledge of the prescribing physicians about the approved indications and eligibility criteria for the edoxaban treatment, the dosing recommendations and management of safety concerns.
- Patient Alert Cards have been distributed. The Patient Alert Card is included in every edoxaban package in the EU.

The Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study (ETNA-DUS) aims to gain insight on how edoxaban is used in real practice, identify prescription patterns, the effectiveness of the educational programs and promptly detect any safety concern, so that pharmacovigilance planning and risk management for edoxaban could be effectively refined, if necessary, on an ongoing basis.

The ETNA-DUS is performed on a voluntary basis by DSE as part of the pharmacovigilance plan included in the edoxaban RMP. The observation plan was reviewed by the Pharmacovigilance Risk Assessment Committee (PRAC) prior to start the data collection.

The analyses presented in this Interim Study Report are based on the data collected for the first wave countries (Germany, Switzerland and United Kingdom [UK]) from 09 December 2016 to 29 June 2017. As an interim analysis of an ongoing study, results included in this report are not considered final and may change until the final study report planned for the second quarter 2019.

The analyses presented in this Interim Study Report are descriptive results of sites and physicians participating in the study; edoxaban users and pattern of use of edoxaban; and descriptive response to the Physician's survey.

6. RESEARCH QUESTION AND OBJECTIVES OF THE OBSERVATION

The aim of the ETNA-DUS is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows:

- To characterize sites and physicians;
- To characterize users of edoxaban;
- To evaluate the pattern of use of edoxaban;
- To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimisation.

Detailed objectives are described in the Observational Plan appended (Section 13.2)

7. AMENDMENTS AND UPDATES TO THE OBSERVATIONAL PLAN

Protocol for this DUS was revised, according to the timelines listed below in Table 3. The first revision made in May 2017 was performed upon the PRAC review and request.

The following updates were made to:

- The list of participating countries: France and the Netherlands were excluded, and Belgium, Spain and Portugal were added.

  In France, Daiichi Sankyo faced issues regarding the reimbursement of Lixiana® (edoxaban). Up to the date, it remains uncertain if and when Lixiana® (edoxaban) will be launched in France, therefore, France was taken out from the list of participating countries. In the Netherlands, the sales volume showed a very low market penetration 12 months after edoxaban launch, so operationally the implementation of the ETNA-DUS in this country would have been challenging. To replace these two countries and still manage to achieve a sufficient number of patients' data Belgium, Spain and Portugal were included.
- The study milestones to take into consideration unexpected edoxaban launch delays, study long start-up time and slow recruitment in the first wave countries.
- The wording of section 11.2 of the Observational Plan, Reporting of Suspected ADRs by the investigators, which was considered confusing, and was aligned with the Good Pharmacovigilance Practices (GVP) Module VI (C.1.2.1.b.) and reporting rules in non-

interventional post-authorisation safety study (PASS) based on secondary use of data, such as medical chart reviews.

The last revision made in Jun 2017 was performed to update the end of data collection timelines per country and the last patient in (LPI) milestone for all countries.

The last two amendments are documented in the last version of the study protocol, but were not submitted to the PRAC for review as they had been considered as non-substantial, as defined in the GVP Module VIII (B.3.2.).

Table 3. Summary of Protocol Amendments

Number	Date	Section of study protocol	Amendment or update	Reason
1	24 November 2015	Full protocol	Amendment to V 1.0; new version 2.0	PRAC request
2	09 May 2016	Full protocol	Amendment to V 2.0; new version 3.0	PRAC request
3	05 August 2016	Full protocol	Amendment to V 3.0; new version 4.0	PRAC request
4	17 May 2017	Full protocol	Amendment to V 4.0; new version 5.0	Changes of: - the participating countries list: France and the Netherlands excluded and Belgium, Spain and Portugal added - the study milestones - wording of Section 11.2 Reporting of suspected ADRs by the Investigator
5	08 June 2017	Full protocol	Amendment to V 5.0; new version 6.0	Changes of: - end of data collection per country: from “6 to 9 months” to “approximately 12 months”; - LPI milestone for all countries.

Notes: ADR: Adverse Drug Reaction; LPI: Last Patient In; PRAC: Pharmacovigilance Risk Assessment Committee.

8. RESEARCH METHODS

8.1. Study design

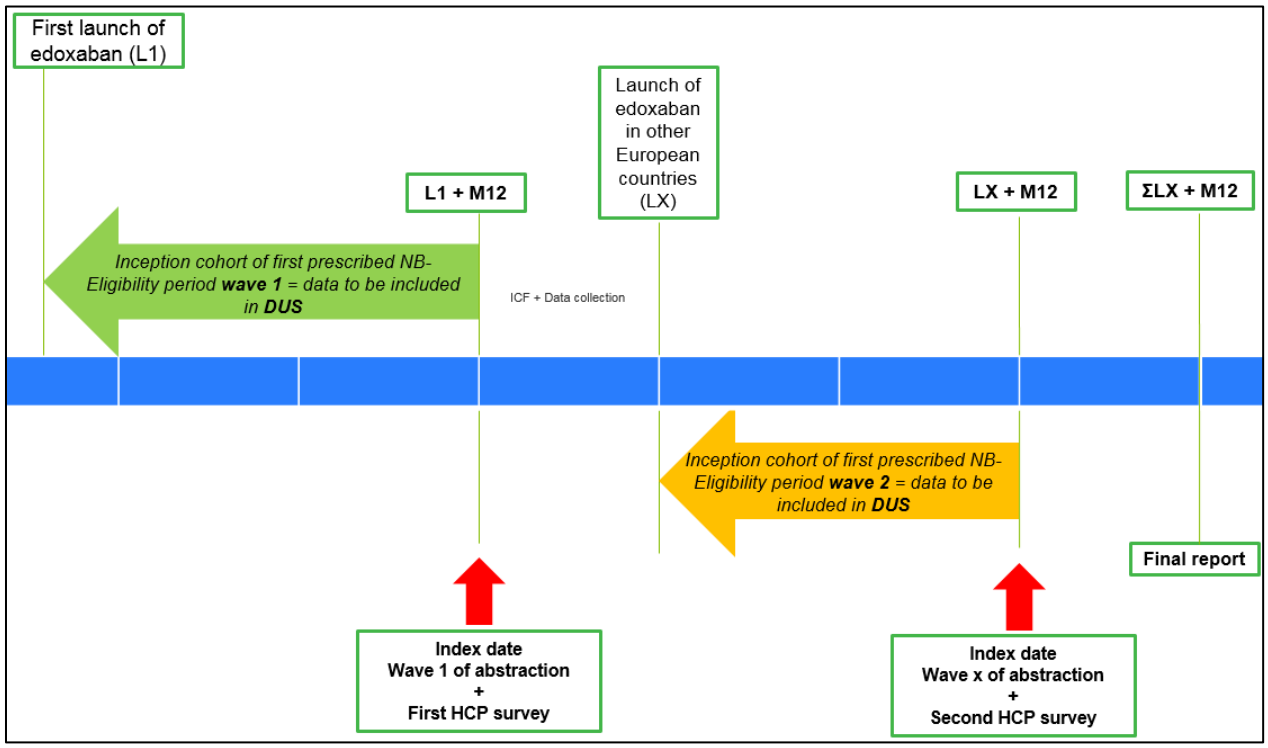
The ETNA-DUS is a multinational, multicentre study involving a retrospective chart review of edoxaban users' medical records. A cross-sectional survey of all participating prescribing physicians is nested in the study. This survey is repeated over the course of the study to evaluate the effectiveness of the physician educational program.

8.2. Settings

8.2.1. Study schedule and flow chart

The study flow chart per patient is presented in Figure 1.

Figure 1. Study flow chart per patient



Notes: DUS: Drug Utilisation Study. HCP: Health Care Professionals. ICF: Informed Consent Form. L1: Launch date in the first European country participating in the study; LX: Launch date in other European countries participating in the study (Recruitment wave I: Switzerland: May2015; Germany: Aug2015; UK: Jul2015; Recruitment wave II: Belgium: Oct2016; Italy: Sep2016; Spain: Sept2016; Portugal: Mar2017). ΣLX: All medicinal products launched. M12: 12 months later. M18: 18 months later. The launch of edoxaban in other European countries (LX) may also occur before the end of data collection for the first country.

The inception cohort was defined as patients initiating edoxaban during a 12-month period following the launch of the product in each country. Country selection took into account prescription volumes, the number of prescribers per capita, and the regulatory environment to conduct observational studies.

For the first wave countries, study start-up activities were initiated following a study-defined index date, approximately 12 months after the product launch. All study participants within a country have been assigned the same index date and have not been contacted prior to the index date. Initiation of prescriber-specific activities for selection of patient records meeting study selection criteria commenced or will commence on or following the index date, and the data on drug utilisation are censored on the index date, according to the study timelines in each participating country. This approach was enforced to ensure that study procedures do not influence the prescribing practices. The Table 4 summarises the dates of edoxaban launch and index dates in the participating countries.

Table 4. Launch dates and index dates by country

Country	Launch Date	Index Date*	Recruitment Wave
Switzerland	1-May-15	1-Jul-16	I
Germany	1-Aug-15	24-Aug-16	I
United Kingdom	16-Jul-15	10-Nov-16	I
Belgium	1-Oct-16	1-Oct-17	II
Italy	9-Sept-16	9-Sept-17	II
Spain	1-Sept-16	1-Sept-17	II
Portugal	1-Mar-17	1-Mar-18	II

*in Italic appears the planned index date.

Individual edoxaban treatment periods for a single patient can vary between one day and the difference between index date and launch date; and are dependent on when the patient started edoxaban with respect to the index date.

A global European protocol was submitted and reviewed by the EMA. The study could not start before the finalisation of the protocol on 05 August 2016. However in Switzerland the physicians were first contacted for participation on 01 July 2016. For the UK, the sales volume showed a low market penetration 12 months after edoxaban launch, so the observational period was extended to 16 months and physicians were contacted on 10 November 2016 to allow sufficient market penetration.

8.2.2. Site sampling strategy

Available and independent national prescription databases were screened to describe edoxaban prescriber characteristics. On a national level for the targeted countries, the distribution of regional location of the sites as well as the distribution of the prescribers' specialty were provided.

QuintilesIMS proprietary data assets were used *a priori* to refine the sampling strategy for the full study (using regional and specialty distribution of prescribers). A single database for all targeted countries was not available. Therefore, multiple data sources to gather information for prescribers and patients treated with edoxaban in European targeted countries were used, including the following:

- IMS RWD LRx (IMS Real-World Data Longitudinal Prescriptions) database was used for the *a priori* analysis, to identify a representative sample of prescribers in Switzerland, Germany, UK, and the same database will be used for Belgium and Italy.
- MIDAS National Prescription Audit and Medical Audit will be used for Spain and Portugal.

Based on these sources it is possible to retrieve general information on edoxaban prescribers. Data were extracted from appropriate database that are representative for the targeted countries. The information are detailed in the specific statistical analysis plan (SAP) developed for this purpose (Section 13.4).

To refine the sampling strategy for the ETNA-DUS and to identify a representative sample of edoxaban prescribers, for all physicians who prescribed edoxaban at least once during the *a priori* observation period, the following data were summarised for each country:

- Geographical location (region) and/or language region (only for Switzerland);
- Specialty, profession or area of primary practice (e.g., General Practitioners [GPs], cardiologists, other specialists [hospital- vs. office-based, when applicable]).

The information was provided in Patients and/or Prescriptions and/or Prescribers or Units dispense level (depending of the country).

8.2.3. Participating sites

Approximately 100 hospital- and office-based physicians (GPs, internal medicine physicians and other specialists) in seven Western European countries (Germany, Italy, Switzerland, the UK, Belgium, Spain and Portugal) were foreseen to participate in the study. Additional European country(ies) may be included based upon the actual use of edoxaban.

With the available descriptive information on edoxaban prescribers in each targeted country, as described above, an initial broad list of physicians in the geographical area of interest was created from various sources (QuintilesIMS database, DSE and additional remote desk research). An invitation letter and a study-specific Site Information Form (SIF) was sent to the proposed sites. The electronic SIF identifies physician's interest for the study, potential available resources, start-up information, and also includes patient recruitment-focused questions. For the sites interested, the SIF of each site was reviewed, sites fulfilling the site selection criteria were asked to provide the required documentation for regulatory submission and schedule a site initiation visit.

Participating sites must have met the following criteria:

- Willing to provide a list of patients receiving edoxaban;
- Allowed/had access to the source data of the patients that were being treated with edoxaban;

- Able to complete the study in the electronic data capture (EDC) system (only in exceptional cases, if no access to internet was provided, paper case report forms [CRFs] may be permitted);
- Able to conduct the study adequately with respect to staff and time capacities.

Physicians participating in interventional programs for edoxaban are not eligible to participate in the study.

8.2.4. General study process

During the site initiation, the investigators received all trainings to perform the study and were asked to complete the Physician's survey. The Physician's survey is available through an anonymous on-line system, independent from the electronic CRF (eCRF) to ensure as much as possible physicians' adherence and honesty. The survey is repeated six months after initiation to assess differences over time. Specific reminders are sent to the physicians to complete these surveys, however, as the access to the questions is fully anonymous, the monitoring of the survey completeness is limited.

During site initiation, the investigator or any designee is asked to identify and list all potential eligible patients with at least one edoxaban prescription in the medical chart. All identified patients should be contacted to participate in the study and follow the below steps:

- The investigator explains the study to the patient and/or (in the case of a minor) to his/her parents or legally acceptable representatives, in particular the objectives of the study and its observational nature. The study explanation could be done during a routine visit if one is already planned with the patient or during a phone call, if the remote consent process was agreed with the independent ethics committee.
- The investigator gives an information sheet and consent form. The patient/parents/legal representatives are given adequate time before deciding whether to take part. If the patient, and/or parents/legal representative in the case of a minor, has agreed to take part in the study, the investigator asks them to sign the consent/assent form (if the minor is able, they should always sign the assent form themselves, in addition to their parents/legal representative). For deceased patients and depending on local regulations a next of kin consent signature is asked of any close relatives.
- The investigator documents the Informed Consent Form (ICF) process in the medical file of the patient.
- The investigator completes an eCRF through a secured EDC system at each patient visit during the complete study duration period:
    - For identified eligible patients who are not invited, or refuse to participate in the study, minimal information is collected on the screening log (detailed collected variables can be found in Section 8.4.3).
    - For patients who agree to participate, the relevant data is abstracted from the medical chart and entered into the eCRF. The investigator or any on site designee

who is entering patient data had received a training on eCRF completion and have personal username and password to access the system.

8.3. Population/Patients

In total, the study aims to include approximately 1200 medical records of consecutive patients who have been treated at least once with one or more dose(s) of edoxaban since its launch in Europe.

Inclusion Criteria

Patients can be enrolled when they have:

- At least one edoxaban prescription recorded in their medical records, irrespective of the underlying health condition;
- Signed a written ICF.

Exclusion Criteria

No exclusion criteria for the patients were defined.

Participating sites are required to maintain a patient enrolment log of all eligible patients at their sites. This screening log is captured within the eCRF and it documents how patients come to be included or excluded from the study, in order to assess the representativeness of the study population.

8.4. Variables

The eCRF is appended (Section 13.3).

8.4.1. Cross-sectional Physician's Survey

- Survey administration variables:
    - Number of physicians in the sample, in total and by key characteristic (country, region, type of setting, type of physician, medical specialty, and profession or area of primary practice);
    - Number of physicians attempted to contact;
    - Number of physicians effectively contacted (corresponding to those attempted to contact since all physicians participating to the ETNA-DUS are asked to participate in the survey);
    - Number of contacted physicians who agreed to participate;
    - Of those who agreed to participate, number who completed survey (participating investigators set-responders).
- Description of survey participants:
    - Medical specialty;

- Country;
- Setting (type, geography);
- Experience with edoxaban (yes/no and if yes number of months);
- Patient volume;
- Receipt of Educational Material (yes/no).

- Assessment of knowledge of the key messages of the educational program:
  - Frequency and distribution of correct and incorrect responses to each survey question at site initiation and after six months;
  - Frequency and distribution of changes in response to each survey question from site initiation to six months;
  - Assessment of physicians' opinion/satisfaction on the utility of Educational Material (frequency of answers to the survey questions: "You have not read the Prescriber's Guide, please select the most relevant reason that applies" and "You find the information in the Prescriber's Guide").

8.4.2. Participating patients' data abstracted after medical chart review

The following demographic characteristics and medical history data are collected for all participating patients when available upon medical chart review:

- Demographics, vital signs and life-style factors:
  - Birth year;
  - Gender;
  - If female, child-bearing potential;
  - Ethnic group (where permitted);
  - Height;
  - Body weight;
  - Body Mass Index;
  - Smoking status;
  - Alcohol consumption.
- Diagnosis (i.e., indication for prescription of edoxaban);
- Risk factors and treatment history;
- Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities;
- History of haemodialysis;

- Relevant familial medical history;
- History of past use of other anticoagulants;
- Pregnancy and lactation status at the time of prescription;
- Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban;
- Presence of mechanical heart valves;
- Pertinent lab tests upon availability including liver function test, creatinine clearance (CrCl) and/or glomerular filtration rate pertaining to possible hepatic or renal impairment.

The following drug utilisation data are collected for all participating patients when available upon medical chart review:

- Edoxaban prescription(s):
    - Duration of treatment/ongoing treatment (including repeated prescriptions, if any);
    - Daily dose (30 mg, 60 mg, other) at the beginning of the treatment and afterwards;
    - Reason for use;
    - Type of discontinuation (permanent/suspension; if applicable);
    - Reason of discontinuation (if applicable);
    - Number of prescriptions of edoxaban per patient.
- Concomitant medications (including dual antiplatelet therapy).

The occurrence of adverse drug reactions (ADRs) (yes/no) is collected.

8.4.3. Screened but not participating patients' data

All patients that were identified by the participating sites but were not included regardless of the reason should be logged within a screening log completed as part of the eCRF.

The following data are collected in the screening log:

- Reason for non-inclusion in the study;
- Indication for prescription of edoxaban;
- Birth year;
- Gender.

8.5. Data Sources and Measurements

All data elements are being collected from information routinely recorded in the medical records by the investigator for the purposes of the study. No visits or examinations, laboratory tests, or procedures are mandated as part of this study.

DUS

This study is a retrospective chart review. The participating site staff reviews the medical charts of the specified number of patients that were prescribed edoxaban, over the given time period, and extracts the relevant data elements. The data is entered pseudonymised into eCRFs by the prescribers via a secure web-based EDC system. In sites that do not have the capabilities to access the internet to enter data, a provision was made to collect pseudonymised data recorded on paper CRFs and enter into the study database by the Sponsor or designee (e.g., contract research organization [CRO]) on behalf of the site staff.

Educational Material Evaluation Survey

The 27-question survey (Section 13.2, appended to the Observational Plan) is administered online through a unique web link concomitantly at the time of the site initiation visit, thus minimising the impact of any previous reading of the Educational Material by the physician. Six months later, the same survey is administered *de novo*. This strategy, together with a comparative analysis of respondents and non-respondents' characteristics, is expected to minimise and detect any response bias or trend among the survey population. Physicians are not to be assessed individually. Results are reported in aggregate form only and not linked to any personal identifier. All information collected during the course of the survey is kept strictly confidential.

The Educational Material was distributed to all physicians prior to edoxaban availability and irrespectively of the participation in the DUS. However, only the investigators participating in the DUS can take part in the survey to assess the physicians' level of awareness and understanding of the content of the Educational Material/SmPC.

8.6. Bias

As this study aims at collecting real-world evidence, some limitations common to non-interventional studies apply. In addition to this, the following aspects need to be considered:

Selection bias:

- Although sites were selected to ensure representativeness through the site sampling strategy for the respective country or region as much as possible, sites also needed to have sufficient interest and capacities to participate in the registry.
- Although eligible patients should be consecutively enrolled at a site, it needs to be considered that patients have to give their informed consent for their medical records to be extracted. This can hamper consecutive and exhaustive enrolment at a site.
- To allow for demonstrating representativeness of edoxaban patients included into the trial, an enrolment log is filled by the sites, where all patients treated with edoxaban at the site at discretion of the physician need to be listed and the reason to participate or not to participate has to be documented.
- In addition, an *a posteriori* analysis using available independent longitudinal patient databases will be used to describe edoxaban patients' characteristics and to assess the

representativeness of patients included in the ETNA-DUS. This analysis was not performed on the current report and is planned for the final study report when patient recruitment will be completed.

- No explicit non-eligibility criteria were defined to avoid selection of patients, and thus violation of the "real-life" principle.
- Concerning the evaluation of effectiveness of the educational program, it could be noted that participation in a survey may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more motivated or educated individuals, such as physicians involved in research program.

Information bias:

- As data collected in the study is part of routine medical practice and is not being collected for the purpose of the study, some limitations with regards to data completeness may occur, mainly related to the type and completeness of the information captured in the patients' medical records.
- Measures to ensure the completion of the eCRF in a systematic, professional, and unbiased manner include:
    - eCRF completion guidelines provide consistent instructions on completion of the eCRF.
    - All individuals performing data abstraction from medical records were trained on appropriate data abstraction techniques in order to minimise possible discrepancies between interpretation of the information recorded by the prescriber in the medical records and the individual performing the review and abstraction of the data.
    - Missing or inconsistent data is queried in the eCRF and followed up during remote monitoring contacts.

8.7. Sample Size

In total, the study aims to include approximately 1200 medical records of patients who have been treated at least once with one or more dose(s) of edoxaban since its launch in seven European countries.

For characterization of users including potential off-label use, the level of precision in different scenarios of available number of users of edoxaban for different prevalence of diseases/conditions was presented. In general, the 95% level of confidence was adequate for a prevalence as low as 1% and 1,200 users of edoxaban.

The sample size was estimated based on the precision of a percentage, that is, the width of the 95% confidence interval (CI). Table 5 presents the precision in the estimate of the proportion of use of edoxaban out of the labelled indication for tentative proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) and different sample sizes.

Table 5. Precision of estimation for proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) of off-label use and increasing sample size

	Proportion											
	0.02			0.03			0.04			0.05		
Sample Size	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.030	0.020	0.080
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067
800	0.010	0.010	0.030	0.012	0.018	0.042	0.014	0.026	0.054	0.015	0.035	0.065
1000	0.009	0.011	0.029	0.011	0.019	0.041	0.012	0.028	0.052	0.014	0.036	0.064
1200	0.008	0.012	0.028	0.010	0.020	0.040	0.011	0.029	0.051	0.012	0.038	0.062

Notes: CI: 95% of Confidence Interval (CI); ½ CI: distance from proportion to lower/upper limit of the two-sided 95% CI (equals half of the width of the CI); L95%: Lower Limit of the 95% CI; U95%: Upper Limit of the 95% CI.

Table 5 shows that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients shows additional (though small) effect on the width of the 95% CI. Therefore, the current aim of recruiting 1,200 patients assures to receive reliable results.

A sample size of 600 patients for instance would allow the detection of a rate of 5% of off-label use with a precision of 1.7%, that is, the estimated proportion would be between 3.3% and 6.7%. A sample size of 1,200 patients allows for an even higher precision, as a rate of 5% of off-label use is detected with a precision of 1.2%, that is, the estimated proportion is between 3.8% and 6.2%.

In addition, it was estimated that approximately 100 physicians would need to complete the survey to allow reasonable precision around estimates of the physicians' awareness and understanding levels. In order to achieve robust results from the various statistical validation methods, it was recommended to have at least 10 physicians per questionnaire item/observation. This rule has been adopted as the standard for psychometric (fit for purpose) validation with its origin within the classical test theory of principal component analysis (Hatcher, 1994).

No target thresholds for physicians-reported awareness and understanding were established in advance. However, it was assumed that 85% of physicians would demonstrate appropriate awareness and understanding of the survey. Given this, the lower bound of the 95% CI is estimated to be above 78% for a sample size of N=100 (Center for Drug Evaluation and Research, 2012).

8.8. Data Management

The study is collecting information through an EDC system. The system used for capturing the medical chart data is Merge eClinical Operating System (eCOS). This EDC system comprises the eCOS platform which complies with industry standards and regulatory expectations for software developers and service providers within the global regulatory environment (United States [US] 21 CFR Part 11, EU Commission Directive 2005/28/EC). Merge eCOS is installed on US-based servers provided by Merge, adhering to the EU data protection directive 95/46/EC. The eCOS platform is a secure, easy to use and reliable web-based EDC platform for the collection and reporting of clinical data. This project was built on eCOS Version 2016.8.1.

During patient enrolment within eCOS Merge, patients are automatically assigned a 4-digit and sequential patient number unique by site. Patient enrolment in Merge eCOS should ideally follow the sequence/order of the data abstraction performed at the site. The sites need to document the patient number also on their patient identification list in the investigator site file. To monitor the recruitment, a site level cap of 25 patients is set for each site, this site cap could be removed upon discussion and agreement from DSE.

All initiated sites are provided with eCRF Completion Guidelines outlining the expected documentation flow and detailing the specifics of Merge eCOS functionality in how to navigate in Merge eCOS, how to add new patients, complete specific forms, handle queries, etc. To access the study database all site staff need to undergo EDC training. Once the training is completed, sites are able to access the study database and can start entering data for patients. Each user account is associated with a defined user role.

For quality purposes, automatic queries are programmed and fired when the eCRF page is saved. In addition, manual queries could also be generated to request specific information and solve data issues (see Section 8.10).

For capturing of the Educational Material Evaluation Survey data Key Survey is used.

The data snapshot of the database was performed on the 29 June 2017 on uncleaned data, efforts have been made prior to the snapshot to ensure high level of data completeness and accuracy. During a month period a higher frequency of cleaning and raising queries, as well as running manual checks were enforced before the snapshot. The presented data have not been through a complete data cleaning process.

8.9. Statistical Methods

The current Interim Study Report is based on a snapshot analysis of unclean data collected for the first wave of participating countries (Switzerland, Germany, UK), on a data snapshot from 29 June 2017.

Data derivations and definitions for the snapshot analysis are based on those required for the final analysis, they are stated in the SAP. The programming was adapted to allow the data derivations taking into account missing data. For all detailed information and references, the last version of the SAP is appended (Section 13.413.4).

8.9.1. Main summary measures

The analyses are purely descriptive and no statistical testing was carried out.

Categorical data are presented using counts and percentages. Counts are presented as whole numbers, while percentages are carried out to one decimal place. When CIs around the percentages are calculated, these are rounded to one decimal place.

For continuous data, n are presented as a whole number. The minimum and maximum are carried out to the same number of decimal places to which the data was reported (x). The mean, median, first quartile, and third quartile are rounded to one decimal place beyond the number to which the data was reported (x+1). Standard deviations are carried out to x+2. Exceptions to these rules might have been applied for very small numbers which would otherwise round up to zero.

8.9.2. Statistical methods

The interim report aims to be descriptive.

CIs were calculated around the proportion of on/off-label users (n). CIs for proportions were computed as exact 95% CIs based on the binomial distribution, using the Clopper and Pearson method (Clopper C. and Pearson S., 1934).

8.9.3. Methods to examine subgroups

This interim report is not considering subgroup analysis.

Subgroup analyses by country will be performed for the final study report. In addition, a particular consideration will be given to patient subgroups for which there is missing information according to the RMP, if numbers permit (for a minimum of 20 subjects):

- Pregnant and/or breastfeeding women;
- Paediatric patients (<18 years old);
- Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk;
- Patients with severe renal impairment (defined as having CrCl < 30 ml/min) or end-stage renal disease (CrCl < 15 ml/min or on dialysis);
- Patients with mechanical heart valves.

8.9.4. How missing data were addressed

For categorical variables, the number and percent of patients with missing data (European Medicines Agency, 2010) are reported for each outcome.

For continuous variables, the number of patients with missing data (European Medicines Agency, 2010) are reported for each outcome as counts.

Missing medication dates are imputed as specified below:

- Start dates:

- If day is missing, this is imputed to the 1st of the month:
  - For edoxaban, if day is missing, this is imputed to the 1st of the month or to the launch date, whichever comes first.
- If month and/or year is missing, no imputation is done.

- Stop dates:
  - If day is missing, this is imputed to the last day of the month, or to the index date, whichever comes first;
  - If month and/or year is missing, no imputation is done.

No other dates are imputed.

8.10. Quality Control/Monitoring

This study is being conducted according to the rules of 'Good Pharmacoepidemiology Practice' and the 'GVP – Module VIII (Rev 1)' EMA/813938/2011 Rev 1. Related quality control mechanisms (e.g. data plausibility checks, monitoring of data) have been implemented accordingly. The physicians comply with the confidentiality policy as described in the site contract. The physicians comply with the observational plan and the requirements described in the contract. The physician is ultimately responsible for the conduct of all aspects of the study at the site and verifies by signature the integrity of all data transmitted to the sponsor.

A data management plan was created that describes all functions, processes, and specifications for data collection, cleaning and validation for the DUS.

High data quality standards are maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality has been enhanced through a range of data quality checks that automatically detect out-of-range or anomalous data. These checks were programmed within the EDC system and system queries are automatically raised and followed up by the sponsor/CRO. The data is also reviewed on an ongoing basis by the sponsor/CRO and manual queries are raised as necessary. The purpose is to ensure that the rights of the patients are protected, that the reported data are accurate and complete, and that the conduct of the study is in compliance with the observational plan and applicable regulatory requirements.

Data Entry/Electronic Data Capture

Mixed data capture applies. The pseudonymised data is entered into electronic eCRFs by the site staff via a secure web-based EDC system. In sites that do not have the capabilities to access the internet to enter data, a provision has been made to collect pseudonymised data recorded on paper CRFs. Sites are instructed to maintain completed paper CRFs in a secure environment prior to dispatch to the CRO.

The EDC system is a secure web-based system using specific encryption mechanisms for exchanging data between the web browser of the user and the data server. All users of the EDC

system (investigators and site personnel as well as sponsor/CRO staff) are able to access their account with a unique personalized username and password. Users have been assigned certain standardized user roles that allow/restrict them to perform specific actions within the EDC application. An audit trail records any actions within the eCRF such as session times, user who accessed the data, initial entry or changes made to the data (including reason for change or correction).

In case of eCRF data capture the sites directly enter the data from their patients' medical records into the standardized English eCRFs. Each participating site has access to its enrolled patient data only. All sites are being fully trained on using the online data capture system, and on the eCRF completion guidelines and other help files. All eCRFs should be completed by designated, trained personnel as appropriate. The eCRF is to be reviewed, electronically signed, and dated by the investigator.

The eCRFs include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous. Edit checks within the eCRF may be checks tied to a certain field or edit checks across multiple fields.

Field checks may include the following:

- Checks on non-conformance (e.g., a non-existing date or a numeric field including text);
- Range checks on numeric fields (e.g., a field that has to be greater than x but lower than y);
- Checks on missing values (e.g., a predetermined required field);
- Checks on future dates.

Edit checks across multiple fields may be any check firing on the condition of another field (or multiple fields) containing a certain value (or a range of values). These may be, for example, a relationship between a parent record and a sub-record or a comparison of different dates.

All edit checks were listed in a Data Management document separate from the Observational Plan with a description of the check firing logic (including pseudo-code as necessary and any ranges defined, if applicable), the type of check and the query message text with reference to the applicable forms and items. To ensure a high quality of data, the Sponsor took one data snapshot and reviewed the data for any potential data errors or discrepancies.

Ad hoc queries are generated within the EDC system and followed up for resolution.

Monitoring

In order to ensure the integrity of the data, sites are monitored by a qualified monitor. During the site initiation visit, the monitor provides training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. A monthly call is planned with each site, for the monitor to discuss all issues.

Risk-based monitoring is being conducted during the study to examine compliance with the protocol and adherence to the data collection procedures, to assess the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained

for the duration of the study. Considering the observational nature of the study, for-cause on-site monitoring visits are planned to be performed in 20% of the sites. In such cases, a minimum of three to four of the participants' eCRF data at each visited site are verified against source documents. In case the site has more than four patients enrolled, the patients to be monitored are randomly selected from the overall list of patients enrolled by the site. During on-site monitoring, the monitor verifies 100% of informed consent documentation, and performs source data verification against the patients' medical records. As no drug or device is under investigation in this study, only the primary variables under statistical consideration are reviewed.

The monitor closes out each site after the last patient data entry and verification of data have been completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures are described in the Clinical Operations Plan. Monitor contact details for each participating site are maintained in the investigator site file.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities are permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9. RESULTS

9.1. Study Population

9.1.1. Site selection

As of 25 August 2017, 47 sites are participating in the ETNA-DUS, 28 (59.6%) sites in Germany, 14 (29.8%) in the UK and five (10.6%) in Switzerland.

The site selection took into consideration the results from the sampling strategy for each country; it was shown to be operationally challenging to follow the exact distribution provided by the sampling strategy. The acceptance of the sites and the potential for patient recruitment at each site are limiting factors to consider for site enrolment strategy. These are outlined in more detail below.

In Germany, the market share of hospital vs. office based edoxaban units was 3.3% vs. 96.7%, 12 months after edoxaban launch in the country. The site selection targeted 30 sites globally in Germany. It was decided to achieve three hospital sites, with at least one in the south and one in the north, and with at least one with the ability to capture patients with a history of PE mainly treated during an hospitalisation. The targeted recruitment of office based physicians is presented in Table 6 below.

Table 6. A priori analysis results in Germany: Edoxaban patients breakdown and projection for site recruitment according to the region & specialty of office based physicians

	Edoxaban patients breakdown (LRx data)		Estimated projections of site recruitment target		Actual sites as of 25 August 2017	
	Northern Germany (%)	Southern Germany (%)	Northern Germany (n)	Southern Germany (n)	Northern Germany (n)	Southern Germany (n)
GPs	29.9%	25.6%	8.1	6.9	7	7
Cardiologists	5.7%	6.8%	1.5	1.8	3	3
Internists others	18.1%	12.4%	4.9	3.4	3	2
Rest others	0.9%	0.6%	0.2	0.2	0	1
Total	**54.6%**	**45.4%**	**14.7**	**12.3**	**13**	**13**

Notes: % calculated on 51206 patients ;%: percentage; N: number; GPs: General Practitioners; Northern Germany includes Bremen, Hamburg, Lower Saxony, Schleswig-Holstein, Mecklenburg-Western Pomerania, Saxony-Anhalt, Berlin, Brandenburg, Hesse, North Rhine and Westphalia-Lippe; Southern Germany includes Baden-Wuerttemberg, Bavaria, Rhineland-Palatinate, Saarland, Thuringia and Saxony.

The recruitment of sites in Germany is still open with two sites still to be recruited.

Site selection in Switzerland, is summarised in Table 7 below.

Table 7. A priori analysis results in Switzerland: Edoxaban patients breakdown and projection for site recruitment according to the language region & specialty

	Edoxaban patients breakdown (LRx data)		Estimated projections of site recruitment target		Actual sites as of 25 August 2017	
	DE-CH (%)	FR/IT-CH (%)	DE-CH (n)	FR/IT-CH (n)	DE-CH (n)	FR/IT-CH (n)
GPs	49.7%	9.4%	2	1	0	0
Cardiologists	5.1%	4.6%	1	0	1	1
Hospital (Accounts)	24.3%	2.5%	1	0	2	0
Others	3.8%	0.6%	0	0	1	0
Total	**82.9%**	**17.1%**	**4**	**1**	**4**	**1**

Notes: % calculated on 1,285 Patients equivalents; DE-CH: German speaking Swiss area includes Espace Mittelland (Bern and Solothurn), Nordwestschweiz, Zürich, Ostschweiz and Zentralschweiz; FR/IT-CH: French and Italian speaking Swiss area includes Espace Mittelland (Freiburg, Neuchâtel and Jura), Région Lémanique and Ticino; GPs: General Practitioners.

No GP site was selected because the interested GPs reported a very low number of eligible patients - from one to two eligible patients per site; any description would have not been possible.

From July 2015 until September 2016, 79.6% of Edoxaban units have been dispensed in the UK in primary care, vs 20.4% dispensed in secondary care. The site selection in the UK is summarised in the Table 8 below.

Table 8. A priori analysis results in the UK: Edoxaban patients breakdown and projection for site recruitment according to the geographical region & type of settings

	Edoxaban patients breakdown (LRx/HPA data)		Estimated projections of site recruitment target		Actual sites as of 25 August 2017	
	Secondary care (%)	Primary care (%)	Secondary care (n)	Primary care (n)	Secondary care (n)	Primary care (n)
London	3.1%	8.8%	1	2	2	0
Midlands & East England	2.6%	17.4%	0	3	1	0
South of England	3.4%	14.3%	1	2	0	1
North of England	8.3%	29.0%	1	5	5	4
Northern Ireland	2.7%	8.9%	0	2	0	1
Scotland	0.1%	0.4%	0	0	0	0
Wales	0.2%	1.0%	0	0	0	0
Total	**20.4%**	**79.6%**	**3**	**14**	**8**	**6**

Notes: HPA: Hospital Pharmavy Audit; Channel Island and Isle of Man reported no dispensed unit of Edoxaban; % calculated on 7,096 Prescriptions in Primarry care (LRx) and 1294 edoxaban units in HPA in secondary care taking into consideration that 79.6% of Edoxaban units in the UK have been dispensed in primary care vs 20.4% dispensed in secondary care.

Each identified and interested GP reported a very low number of patients, so to follow the distribution from the sampling strategy results we should have doubled the global number of sites in the UK. For operational reasons it was decided not to follow the sampling strategy and to allow a naturalistic recruitment of sites, up to 17 selected sites. The geographical distribution of the 14 sites selected in the UK is shown in Table 8 above.

Particular attention will be given to the *a posteriori* analysis (which is only planned for the final report; detailed information can be found in the SAP specifically developed for this purpose Section 13.4), as well as to the screening log description (presented in Table 10 below) to ensure proper data interpretation across all countries.

9.1.2. Site and physician characteristics

Based on the data snapshot on 29 June 2017 used for this snapshot analysis, 25 (53.2%) sites answered the site characteristics form (Table 1. Appended), 20 (80.0%) in Germany, two (8.0%) in Switzerland and three (12.0%) in the UK. Among these sites, 20 (80.0%) were private practices, two (8.0%) were university hospitals, one (4.0%) was a general hospital and one (4.0%) was a general practice site. These sites included 27 physicians participating in the ETNA-DUS, with 23 (85.2%) being principal investigators and 4 (14.8%) sub-investigators.

The physicians reported the following areas of primary practice: 11 (40.7%) general medicine, six (22.2%) cardiology, five (18.5%) internal medicine, two (7.4%) neurology, one (3.7%) anticoagulation specialty and 2 (7.4%) other specialties. Twenty-six (96.3%) physicians reported

previous experience with edoxaban during an average time of 19 months and median time of 17 months (Table 1 in section 12.3).

9.1.3. Patient recruitment

The patient recruitment started on 09 December 2016, in the first wave countries (Switzerland, Germany and the UK).

The patient recruitment status is displayed in Table 9 below.

Table 9. Patient recruitment status

	Number of eligible patients identified by the sites	Number of patients recruited until 29 June 2017 (and included* in the snapshot data analysis)	Number of patients consented until 25 August 2017	Targeted number of patients (12 patients/site)
Switzerland	35	6	14	60
Germany	447	179	246	360
UK	198	15	22	204
Total	**680**	**200**	**282**	**624**

*A total of 33 patients have been excluded from the analysis due to reported start of treatment after the index date.
Note: UK: United Kingdom.

Up to 29 June 2017, 250 patients were recorded within the ETNA-DUS EDC system, among them 33 (13.2%) patients were completely excluded from the data snapshot analysis due to reported start of treatment after the index date, further investigations are on-going at the sites to confirm the ineligibility of these patients, and 217 (86.8%) eligible patients were screened by the participating sites. Among the 217 eligible patients, 17 (7.8%) were not included and added to the screening log and 200 (92.2%) were recruited and consented.

9.2. Descriptive Data

Among the 200 eligible patients included in the study and in the snapshot data analysis, it was reported that 140 (70.0%) patients were initially prescribed edoxaban for NVAF indication[1], 42 (21.0%) patients were initially prescribed edoxaban for VTE indication[2], nine (4.5%) patients were

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

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

prescribed edoxaban for another indication, and in nine (4.5%) patients the indication was unknown (Table 10 below).

Among the 17 eligible patients that were not included in the study, 13 (76.5%) did not sign the ICF and four were not included upon investigator's choice, which appears to be mainly due to edoxaban start of treatment after the index date. The reported indications for initiation of edoxaban treatment in patients non-included into the study were: nine (52.9%) patients prescribed edoxaban for NVAF indication, seven (41.2%) patients prescribed edoxaban for VTE indication, and one patient prescribed edoxaban for other indication (Table 10 below).

Table 10. Disposition of the study population and screening information

	Screen Failures[3] (N=17)	Subjects Included in the Study Full analysis set(FAS) (N=200)	All Screened Subjects[3] All Subjects screened set(SCR) (N=217)
Country, n(%)			
Germany	17 (100.0)	179 (89.5)	196 (90.3)
Switzerland	0 (0.0)	6 (3.0)	6 (2.8)
United Kingdom	0 (0.0)	15 (7.5)	15 (6.9)
Reason for non-inclusion in the study, n(%)			
Informed consent form not signed	13 (76.5)		
Investigator's choice	4 (23.5)		
Missing	0		
Indication for initial prescription of Edoxaban, n (%)			
Prevention of stroke and systemic embolism[1]	9 (52.9)	140 (70.0)	149 (68.7)
Treatment of DVT and PE, and prevention of recurrences[2]	7 (41.2)	42 (21.0)	49 (22.6)
Other	1 (5.9)	9 (4.5)	10 (4.6)
Unknown	0 (0.0)	9 (4.5)	9 (4.1)
Missing	0	0	0
Indication for follow-up prescription of Edoxaban, n(%)			
Prevention of stroke and systemic embolism[1]		102 (51.0)	
Treatment of DVT and PE, and prevention of recurrences[2]		26 (13.0)	
Other		1 (0.5)	
Atrial Fibrillation		1 (0.5)	
Unknown		17 (8.5)	
Missing		54*	

Notes: Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified. (1) Percentage for each region are calculated with the total number of subjects for that particular country in the denominator; (2) SD = Standard Deviation; (3) Percentage calculation can sum to > 100% because subjects can fall in more than one category; *include patients with no follow-up prescription or missing information. Reference Table 2 in section 12.3.

Demographics

Among the patients using edoxaban, with a reported birth year, the mean age was 72.6 years, with a minimum of 26 years and a maximum of 97 years. None of the recruited patients were younger than 18 years and 90 (45.0%) were aged 75 years or older at initial edoxaban prescription. Ninety-six patients (48.0%) were females. Among them four (4.2%) were reported as women of child bearing potential and aged 50 years or younger (Table 11 below, description per initial indication for edoxaban is also available).

Table 11. Demographic characteristics for initial prescription by indication

Indication for Initial Edoxaban Prescription	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Age at initial prescription (years)					
n	121	38	9	9	177
Mean (SD[1])	75.7 (9.87)	65.2 (13.90)	63.4 (16.79)	71.1 (11.52)	72.6 (12.20)
Median	77.0	62.5	66.0	73.0	75.0
Q1, Q3	69, 82	56, 80	60, 72	66, 78	66, 81
Min, Max	38, 97	28, 91	26, 82	48, 85	26, 97
Missing	19	4	0	0	23
Age at initial prescription, n (%)					
< 18 years old	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>= 18 years old and < 65 years old	18 (12.9)	21 (50.0)	3 (33.3)	2 (22.2)	44 (22.0)
>= 65 years old and < 75 years old	30 (21.4)	6 (14.3)	4 (44.4)	3 (33.3)	43 (21.5)
>= 75 years old	73 (52.1)	11 (26.2)	2 (22.2)	4 (44.4)	90 (45.0)
Missing	19	4	0	0	23
Gender, n (%)					
Male	72 (51.4)	20 (47.6)	5 (55.6)	7 (77.8)	104 (52.0)
Female	68 (48.6)	22 (52.4)	4 (44.4)	2 (22.2)	96 (48.0)
Missing	0	0	0	0	0
If female, child bearing potential[2]					
Yes	0 (0.0)	3 (13.6)	1 (25.0)	0 (0.0)	4 (4.2)
No	68 (100.0)	19 (86.4)	3 (75.0)	2 (100.0)	92 (95.8)
Missing	0	0	0	0	0

Notes: (1) SD = Standard Deviation; (2) Percentages are calculated with the total number of females in the denominator. Reference Table 3 in section 12.3.

Behavioural history

Globally, 110 (55.0%) patients never smoked, 13 (6.5%) were current smokers and 28 (14.0%) were former smokers; the smoking status was unknown or missing for 49 (24.5%) patients. Five (2.5%) patients had a reported alcohol consumption of at least three alcohol drinks per day, while 69 (34.5%) patients did not drink any alcohol at all. (Table 12 below, description per initial indication for edoxaban is also available).

Table 12. Behavioural history for initial prescription by indication

Indication for Initial Edoxaban Prescription	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Smoker, n (%)					
Never	75 (53.6)	20 (47.6)	6 (66.7)	9 (100.0)	110 (55.0)
Currently	5 (3.6)	6 (14.3)	2 (22.2)	0 (0.0)	13 (6.5)
Formerly	27 (19.3)	1 (2.4)	0 (0.0)	0 (0.0)	28 (14.0)
Unknown	32 (22.9)	15 (35.7)	1 (11.1)	0 (0.0)	48 (24.0)
Missing	1	0	0	0	1
Alcohol average daily intake*, n(%)					
None	58 (41.4)	8 (19.0)	3 (33.3)	0 (0.0)	69 (34.5)
< 1 drink	27 (19.3)	11 (26.2)	5 (55.6)	0 (0.0)	43 (21.5)
1-2 drinks	20 (14.3)	6 (14.3)	0 (0.0)	0 (0.0)	26 (13.0)
3-4 drinks	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)
> 4 drinks	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)
Unknown	29 (20.7)	17 (40.5)	1 (11.1)	9 (100.0)	56 (28.0)
Missing	1	0	0	0	1

Note: *One drink - e.g.: 0.25L wine, 0.5L beer. Reference Table 3 in section 12.3.

Vital signs

Height and weight were not reported consistently as this information was missing for 158 and 157 patients, respectively. Among the 43 patients with documented weight, six (3.0%) weighted 60 kilograms or less. Among the 42 patients with documented height and weight, the mean Body Mass Index (BMI) was 27.7 kg/m^2 and ranged from 18 to 39 kg/m^2 (Table 13 below, description per initial indication for edoxaban is also available).

Table 13. Vital signs for initial prescription by indication

Indication for Initial Edoxaban Prescription	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Height (cm)					
n	36	4	0	2	42
Mean (SD[1])	168.6 (8.63)	169.3 (13.62)		169.5 (4.95)	168.7 (8.82)
Median	168.0	171.5		169.5	168.0
Q1, Q3	162, 176	158, 181		166, 173	162, 177
Min, Max	150, 184	153, 181		166, 173	150, 184
Missing	104	38	9	7	158
Body Weight (kg)					
n	37	4	0	2	43
Mean (SD[1])	77.6 (15.02)	85.1 (4.33)		81.5 (9.19)	78.5 (14.21)
Median	75.0	85.3		81.5	80.0
Q1, Q3	66, 88	82, 89		75, 88	67, 88
Min, Max	50, 118	80, 90		75, 88	50, 118
Missing	103	38	9	7	157
Body Weight categorized					
<= 60 kg	6 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.0)
> 60 kg	31 (22.1)	4 (9.5)	0 (0.0)	2 (22.2)	37 (18.5)
Missing	103	38	9	7	157
Body Mass Index (kg/m^2)					
n	36	4	0	2	42
Mean (SD[1])	27.4 (4.53)	30.2 (5.39)		28.3 (1.54)	27.7 (4.52)
Median	27.5	30.2		28.3	27.5
Q1, Q3	25, 30	26, 35		27, 29	25, 30
Min, Max	18, 39	25, 36		27, 29	18, 39
Missing	104	38	9	7	158

Note: (1) SD = Standard Deviation. Reference Table 3 in section 12.3.

Patients with initial edoxaban prescription for NVAF

Among the 140 patients with NVAF as an initial indication, the type of NVAF was reported for 138 patients. Fifty-four (39.1%) patients had permanent NVAF, 50 (36.2%) patients had a paroxysmal NVAF, 28 (20.3%) patients had a persistent NVAF and six (4.3%) had a long-standing NVAF. Among the 138 documented NVAF patients, 16 (11.6%) have undergone at least one intervention to treat NVAF. Among these 16 patients, three (18.8%) had a pharmacological cardioversion, five (31.3%) had an electrical cardioversion, three (18.8%) had a catheter ablation therapy, two (12.5%) had a percutaneous coronary intervention, one (6.3%) had a surgical therapy for NVAF and none underwent a left atrial appendage occlusion or a transcatherter aortic valve implantation (Table 14 below, description per type of NVAF).

Table 14. Atrial fibrillation treatment by indication for initial prescription

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
Undergone any interventions for NVAF? n(%)					
Yes	6 (12.0)	2 (7.1)	0 (0.0)	8 (14.8)	16 (11.6)
No	39 (78.0)	22 (78.6)	6 (100.0)	45 (83.3)	112 (81.2)
Unknown	5 (10.0)	4 (14.3)	0 (0.0)	1 (1.9)	10 (7.2)
Missing	0	0	0	0	0
Pharmacological cardioversion[1], n(%)	1 (16.7)	2 (100.0)	0 (0.0)	0 (0.0)	3 (18.8)
Electrical cardioversion[1], n(%)	1 (16.7)	1 (50.0)	0 (0.0)	3 (37.5)	5 (31.3)
Ablation[1], n(%)	1 (16.7)	0 (0.0)	0 (0.0)	2 (25.0)	3 (18.8)
Pacemaker/Defibrillator (ICD)[1], n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Left atrial appendage occlusion[1], n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Surgical therapy for NVAF[1], n(%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	1 (6.3)
Transcatherter Aortic Valve Implantation[1], n(%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Percutaneous Coronary Intervention[1], n(%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (25.0)	2 (12.5)

Notes: (1) Percentages are calculated using the number of subjects with that particular intervention in the denominator; *Type of NVAF is missing for two patients. Reference Table 6 in section 12.3.

Patients with initial edoxaban prescription for venous thromboembolism (VTE)

Among the 42 patients with VTE as the initial indication, the type of VTE was reported for 40 patients. Twenty-nine (72.5%) patients had DVT, five (12.5%) had PE and six (15.0%) had PE with DVT. Twenty-three (57.5%) presented no risk factors prior to the occurrence of the VTE (Table 15 below, description per type of VTE, and details on the risk factors reported). Ten (25.0%) patients had a non-invasive treatment of their VTE, no patient underwent an invasive treatment for VTE.

Table 15. VTE risk factors and therapy by indication for initial prescription

Type of VTE (if indication for prescription is VTE)	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Type of VTE, n(%)			
DVT only	29 (100.0)	0 (0.0)	29 (72.5)
PE with DVT	0 (0.0)	6 (54.5)	6 (15.0)
PE only	0 (0.0)	5 (45.5)	5 (12.5)
Missing	0	0	0
Presence of VTE risk factors, n(%)			
No risk factors	18 (62.1)	5 (45.5)	23 (57.5)
One risk factor	2 (6.9)	0 (0.0)	2 (5.0)
More than one risk factor	9 (31.0)	6 (54.5)	15 (37.5)
Missing	0	0	0
Puerperium, n(%)	1 (3.4)	0 (0.0)	1 (2.5)
Prolonged immobilization, n(%)	3 (10.3)	1 (9.1)	4 (10.0)
> 5 days in bed, n(%)	2 (6.9)	1 (9.1)	3 (7.5)
History of major surgery or trauma, n(%)	1 (3.4)	1 (9.1)	2 (5.0)
Known thrombophillic conditions, n(%)	7 (24.1)	5 (45.5)	12 (30.0)
Other risk factors[1], n(%)			
Antithrombin deficiency	0 (0.0)	0 (0.0)	0 (0.0)
Factor V Leiden	2 (6.9)	1 (9.1)	3 (7.5)
Hyperhomocysteinaemia	0 (0.0)	0 (0.0)	0 (0.0)
Antiphospholipid antibodies	0 (0.0)	1 (9.1)	1 (2.5)
Protein C deficiency	0 (0.0)	1 (9.1)	1 (2.5)
Protein S deficiency	0 (0.0)	0 (0.0)	0 (0.0)
Prothrombin gene mutation	0 (0.0)	0 (0.0)	0 (0.0)
Other	5 (17.2)	2 (18.2)	7 (17.5)
Acute invasive and/or non-invasive VTE therapy, n(%)	9 (31.0)	1 (9.1)	10 (25.0)

Type of VTE (if indication for prescription is VTE)	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Invasive therapy (Open embolectomy, Catheter procedures, Insertion of vena cava filter or others) [3]	0 (0.0)	0 (0.0)	0 (0.0)
Non invasive therapy (Compression stockings or others) [3]	9 (100.0)	1 (100.0)	10 (100.0)

Notes: *Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients; (1) Percentage calculation can sum to > 100% because subjects can fall in more than one category; (2) SD = Standard Deviation. (3) Percentages are calculated using the number of subjects with that particular intervention in the denominator. Reference Table 5 in section 12.3.

Medical history

The reported medical history at the time of initial prescription for all patients is presented in Table 16 below (Table 9 in Section 12.3, description per initial indication for edoxaban is also available).

Table 16. Medical history at the time of initial prescription for all patients

Medical History, n(%)	Non-valvular Atrial Fibrillation (NVAF) (N=140)	Venous Thromboembolic Event (VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Atrial fibrillation	139 (99.3)	2 (4.8)	4 (44.4)	0 (0.0)	145 (72.5)
Hypertension*	100 (71.4)	17 (40.5)	8 (88.9)	1 (11.1)	126 (63.0)
Dyslipidaemia	48 (34.3)	7 (16.7)	7 (77.8)	0 (0.0)	62 (31.0)
Coronary heart disease	39 (27.9)	5 (11.9)	3 (33.3)	1 (11.1)	48 (24.0)
Diabetes mellitus*	36 (25.7)	6 (14.3)	4 (44.4)	0 (0.0)	46 (23.0)
Venous thromboembolic event	4 (2.9)	40 (95.2)	1 (11.1)	0 (0.0)	45 (22.5)
Valvular heart disease	29 (20.7)	3 (7.1)	0 (0.0)	0 (0.0)	32 (16.0)
Stroke*	21 (15.0)	3 (7.1)	1 (11.1)	0 (0.0)	25 (12.5)
Renal disease	22 (15.7)	1 (2.4)	2 (22.2)	0 (0.0)	25 (12.5)
Arthritis	18 (12.9)	3 (7.1)	1 (11.1)	0 (0.0)	22 (11.0)
Malignancy	15 (10.7)	6 (14.3)	1 (11.1)	0 (0.0)	22 (11.0)
Hyper/Hypothyroidism	15 (10.7)	5 (11.9)	0 (0.0)	0 (0.0)	20 (10.0)
Past surgery	17 (12.1)	2 (4.8)	0 (0.0)	0 (0.0)	19 (9.5)
Fracture/Trauma	12 (8.6)	5 (11.9)	2 (22.2)	0 (0.0)	19 (9.5)
Digestive tract disease	11 (7.9)	5 (11.9)	3 (33.3)	0 (0.0)	19 (9.5)
Chronic obstructive pulmonary disease (COPD)	8 (5.7)	3 (7.1)	1 (11.1)	0 (0.0)	12 (6.0)
Ischaemic cardiomyopathy	8 (5.7)	0 (0.0)	1 (11.1)	1 (11.1)	10 (5.0)

Medical History, n(%)	Non-valvular Atrial Fibrillation (NVAF) (N=140)	Venous Thromboembolic Event (VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Peripheral vascular disease	5 (3.6)	1 (2.4)	2 (22.2)	0 (0.0)	8 (4.0)
Sleep apnoea	6 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (3.0)
Major bleeding events that led to a visit to health care professionals	4 (2.9)	1 (2.4)	0 (0.0)	0 (0.0)	5 (2.5)
Lower extremity paralysis	4 (2.9)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.0)
Hepatic disorders	1 (0.7)	2 (4.8)	0 (0.0)	0 (0.0)	3 (1.5)
Chronic thromboembolic pulmonary insufficiency,	1 (0.7)	1 (2.4)	0 (0.0)	0 (0.0)	2 (1.0)
Thrombocytopenia (i.e.: <100000/µL)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Infectious disease (necessitating immobilization)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Listed as part of risk factors related to indication of edoxaban in prevention of stroke and systemic embolism in patients with NVAF. Reference Table 9 in section 12.3.

Pattern of initial edoxaban prescription

In large majority (78.5%) the first prescription of edoxaban was made by the study investigators. The reported major reason for prescribing edoxaban was an expected better safety for 65 (32.5%) patients, an expected better patient compliance for 29 (14.5%) patients, and an expected better efficacy for 20 (10.0%) patients. The reason was unknown for 37 (18.5%) patients (Table 17 below, description per initial indication for edoxaban is also available).

Table 17. Initial prescription of edoxaban by indication

Indication for Initial Edoxaban Prescription⇨	Non-valvular Atrial Fibrillation (NVAF) (N=140)	Venous Thromboembolic Event (VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Was the patient's initial Edoxaban prescription by the investigator? n(%)					
Yes	109 (77.9)	30 (71.4)	9 (100.0)	9 (100.0)	157 (78.5)
No	30 (21.4)	12 (28.6)	0 (0.0)	0 (0.0)	42 (21.0)
Missing	1	0	0	0	1
Type of prescriber[1], n(%)					
Office based physician	15 (50.0)	8 (66.7)	0 (0.0)	0 (0.0)	23 (54.8)
Hospital based physician	14 (46.7)	1 (8.3)	0 (0.0)	0 (0.0)	15 (35.7)
Unknown	1 (3.3)	3 (25.0)	0 (0.0)	0 (0.0)	4 (9.5)
Missing	0	0	0	0	0
Specialty of prescriber[1], n(%)					
General medicine	1 (3.3)	6 (50.0)	0 (0.0)	0 (0.0)	7 (16.7)
Cardiology	21 (70.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (50.0)
Internal medicine	1 (3.3)	1 (8.3)	0 (0.0)	0 (0.0)	2 (4.8)
Neurology	4 (13.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (9.5)
Anticoagulation specialist	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)
Unknown	2 (6.7)	4 (33.3)	0 (0.0)	0 (0.0)	6 (14.3)
Other	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.4)
Surgery	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	1 (2.4)
Missing	0	0	0	0	0
Major reason for initial prescription, n(%)					

Indication for Initial Edoxaban Prescription⇨	Non-valvular Atrial Fibrillation (NVAF) (N=140)	Venous Thromboembolic Event (VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Drug-drug interaction by former treatment	1 (0.7)	2 (4.8)	0 (0.0)	0 (0.0)	3 (1.5)
High variability of former OAC treatment response	5 (3.6)	1 (2.4)	0 (0.0)	1 (11.1)	7 (3.5)
Lack of efficacy of former OAC treatment	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)
Expected better safety	54 (38.6)	9 (21.4)	2 (22.2)	0 (0.0)	65 (32.5)
Expected better efficacy	5 (3.6)	10 (23.8)	5 (55.6)	0 (0.0)	20 (10.0)
Patient's request	3 (2.1)	2 (4.8)	0 (0.0)	0 (0.0)	5 (2.5)
Patient's former non-compliance	6 (4.3)	0 (0.0)	1 (11.1)	0 (0.0)	7 (3.5)
Expected better patient compliance	23 (16.4)	6 (14.3)	0 (0.0)	0 (0.0)	29 (14.5)
Unknown	19 (13.6)	10 (23.8)	0 (0.0)	8 (88.9)	37 (18.5)
Other	20 (14.3)	2 (4.8)	1 (11.1)	0 (0.0)	23 (11.5)
Missing	1	0	0	0	1

Notes: OAC = Oral Anti-Coagulant; (1) Percentages are calculated using the number of subjects which initial edoxaban prescription was not prescribed by the principal investigator as denominator and it can sum to > 100% because subjects can fall in more than one category. Reference Table 19 in section 12.3.

Pattern of edoxaban use

The mean reported duration of edoxaban use during the study was approximately 22 weeks, with the mean duration of treatment being 21.5 weeks for patients prescribed for the NVAF indication and 24.4 weeks for patients prescribed for the VTE indication. One hundred and thirty-seven (68.5%) patients were still using edoxaban at the time of data abstraction. Among the 40 patients that interrupted or discontinued edoxaban before the index date, 18 (9.0%) patients had it suspended, one (0.5%) patient missed a dose and in 21 (10.5%) patients edoxaban was permanently discontinued. The main reported reasons for the interruption or discontinuation of treatment were the following: edoxaban treatment was no longer considered to be necessary for 16 (8.0%) patients, and there were 'other' reasons for 13 (6.5%) patients, details can be found in Table 21 in Section 12.3. One hundred and sixty-nine (84.5%) patients used one intake per day and five (2.5%) used two intakes per day. One hundred and seventeen (58.5%) patients used a total daily dose of 60 mg and 57 (28.5%) patients used a total daily dose of 30 mg (Table 18 below, description per initial indication for edoxaban is also available).

Table 18. Edoxaban utilization pattern for initial prescription by indication

Indication for Initial Edoxaban Prescription	Non-valvular Atrial Fibrillation (NVAF) (N=140)	Venous Thromboembolic Event (VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Duration of Edoxaban prescription (weeks)					
N	121	38	9	9	177
Mean (SD[1])	21.51 (16.993)	24.36 (15.251)	14.30 (11.440)	25.41 (11.626)	21.95 (16.213)
Median	15.29	21.57	11.00	24.00	18.86
Q1, Q3	7.29, 36.86	11.14, 36.14	6.43, 18.14	18.86, 38.14	8.43, 36.86
Min, Max	0.1, 54.7	3.4, 53.3	2.4, 37.9	9.0, 39.3	0.1, 54.7
Missing	19	4	0	0	23
Edoxaban ongoing, n(%)					
Yes	98 (70.0)	25 (59.5)	5 (55.6)	9 (100.0)	137 (68.5)
No	23 (16.4)	13 (31.0)	4 (44.4)	0 (0.0)	40 (20.0)
Missing	19	4	0	0	23
Frequency, n(%)					
Once daily	118 (84.3)	33 (78.6)	9 (100.0)	9 (100.0)	169 (84.5)
Twice daily	2 (1.4)	3 (7.1)	0 (0.0)	0 (0.0)	5 (2.5)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Missing	20	6	0	0	26
Total daily dose (mg), n(%)					
30 mg	48 (34.3)	7 (16.7)	0 (0.0)	2 (22.2)	57 (28.5)
60 mg	72 (51.4)	29 (69.0)	9 (100.0)	7 (77.8)	117 (58.5)
Other	1 (0.7)	2 (4.8)	0 (0.0)	0 (0.0)	3 (1.5)
Missing	19	4	0	0	23
If Edoxaban intake interrupted or discontinued, type, n(%)					
Suspension	11 (7.9)	7 (16.7)	0 (0.0)	0 (0.0)	18 (9.0)
Missed dose	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Permanent discontinuation	11 (7.9)	6 (14.3)	4 (44.4)	0 (0.0)	21 (10.5)

Indication for Initial Edoxaban Prescription	Non-valvular Atrial Fibrillation (NVAF) (N=140)	Venous Thromboembolic Event (VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
If Edoxaban intake interrupted or discontinued, reason, n(%)					
VTE intervention	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (0.5)
ADR/clinical event	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Drug-drug interaction	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Lack of efficacy	1 (0.7)	1 (2.4)	0 (0.0)	0 (0.0)	2 (1.0)
Health care system related prescription/formulary limitations	2 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.0)
Patient's request	3 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)
Treatment no longer considered to be necessary	5 (3.6)	8 (19.0)	3 (33.3)	0 (0.0)	16 (8.0)
Other	10 (7.1)	2 (4.8)	1 (11.1)	0 (0.0)	13 (6.5)

Note: (1) SD = Standard Deviation. Reference Table 21 in section 12.3.

Among the 96 female patients, two (2.1%) were lactating at the time of prescription and none were pregnant. The two lactating women were over 70 years old, the data were queried and correction from the site was still pending at the time of the analysis.

Adverse events

Five (2.5%) patients had at least one documented adverse event (AE) related to edoxaban treatment in their medical data during the observational period; these patients had no reported renal or hepatic impairment within their medical histories.

9.3. Main results

The reported use of edoxaban was summarised to reflect requirements or recommendations of the SmPC (Table 19 below). Among the 200 patients recruited in the ETNA-DUS, 182 patients (91.0%) were initially prescribed edoxaban for at least one of the two labelled indications and 18 (9.0%) were initially prescribed either for other or unknown reasons. The reported other indications for initial prescription of edoxaban were as follows: three (1.5%) patients had an atrial fibrillation, one (0.5%) patient had a dilated cardiomyopathy, one (0.5%) patient had a Lymphangitis, one (0.5%) patient had an peripheral artery occlusive disease, one (0.5%) patient had a peripheral arterial disease, one (0.5%) patient had a stroke, one (0.5%) patient had a stroke without NVAF and one (0.5%) patient had a tarsal arthrosis.

Among the 140 (70.0%) patients prescribed edoxaban for NVAF, 70 (50.0%) patients were taking 60 mg of edoxaban once daily and eight (5.7%) patients were taking 30 mg once daily with an associated reason for daily dose reduction as mentioned in the SmPC. Sixty-two (44.3%) patients were prescribed edoxaban for NVAF outside of the labelled dosing regimen, including patients who could not be identified on a labelled dosing regimen due to missing data. Among these 62 patients, 21 had a daily dose missing, 39 patients were taking 30 mg of edoxaban once daily without an associated reason for daily dose reduction as mentioned in the SmPC, one patient was taking 30 mg twice daily and one patient was taking 60 mg twice daily.

Among the 42 patients prescribed edoxaban for VTE, five (11.9%) patients were prescribed 60 mg of edoxaban once daily following an initial dose of parenteral anticoagulant for at least five days, and no patient was taking 30 mg once daily following an initial dose of parenteral anticoagulant for at least five days with an associated reason for daily dose reduction as mentioned in the SmPC. Thirty-seven (88.1%) patients were prescribed edoxaban for VTE outside of the labelled dosing regimen, including patients who could not be identified on a labelled dosing regimen due to missing data. Among these 37 patients, six patients had a daily dose missing, six patients were taking 30 mg of edoxaban once daily without an associated reason for daily dose reduction as mentioned in the SmPC, 22 patients were taking 60 mg once daily, but no prior history of parenteral anticoagulant for at least five days was reported and three patients were taking 60 mg twice daily.

Table 19. Distribution of patients by edoxaban summary of product characteristics (1/2)

Characteristics n(%)	Overall (N=200)
Indication for initial Edoxaban prescription	
NVAF or VTE	182(91.0)
Other indication or indication unknown	18(9.0)
Indication for initial Edoxaban prescription: NVAF	140(70.0)
60 mg – once daily[1]	70(50.0)
30 mg – once daily and moderate-severe renal impairment[2], or body weight <= 60kg, or concomitant use of P-gp inhibitors[1,4]	8(5.7)
Other[1]	62(44.3)
Indication for initial Edoxaban prescription: VTE	42(21.0)
60 mg – once daily, following initial use of parenteral anticoagulant for at least 5 days, and no simultaneously administration of parenteral anticoagulants[3]	5(11.9)
30 mg – once daily and moderate-severe renal impairment[2], or body weight <= 60kg, or concomitant use of P-gp inhibitors[3,4] , following initial use of parenteral anticoagulant for at least 5 days, and no simultaneously administration of parenteral anticoagulant[4]	0(0.0)
Other[3]	37(88.1)

Notes: VTE=Venous Thromboembolic Event; NVAF=Non-Valvular Atrial Fibrillation; VKA=Vitamin K Antagonist; (1) Percentages are calculated using the number of subjects with NVAF as denominator; (2) Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min; (3) Percentages are calculated using the number of subjects with VTE as denominator; (4) P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole). Reference Table 25 in section 12.3.

Among the 200 patients, one (0.5%) patient reported at least one missed dose. Eleven (5.5%) patients presented at least one lesion or one condition considered to be a significant risk for major bleeding (Table 20 below, for detailed lesion and conditions). Twenty-nine (14.5%) patients concomitantly used edoxaban and another anticoagulant.

Table 20. Distribution of patients by edoxaban summary of product characteristics (2/2)

Characteristics n(%)	Overall (N=200)
Patients with at least one missed dose	1 (0.5)
1 missed dose (single dose/ interruption of one day)[1]	1 (0.5)
>1 missed dose (multiple doses/ interruption longer than one day)[1]	0 (0.0)
Patients with contraindications and special warnings	
ESRD[2] or on dialysis	0 (0.0)
Clinically significant active bleeding	1 (0.5)
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	2 (1.0)
Lesion or condition considered to be a significant risk for major bleeding[3]	11 (5.5)
Current or recent gastrointestinal ulceration	3 (1.5)
Presence of malignant neoplasms at high risk of bleeding	2 (1.0)
Recent brain or spinal injury	5 (2.5)
Recent brain, spinal or ophthalmic surgery	2 (1.0)
Recent intracranial haemorrhage	0 (0.0)
Known or suspected oesophageal varices	0 (0.0)
Arteriovenous malformations	3 (1.5)
Vascular aneurysms	1 (0.5)
Major intraspinal or intracerebral vascular abnormalities	0 (0.0)
Uncontrolled severe hypertension	3 (1.5)
Concomitant treatment of Edoxaban and any other anticoagulant	29 (14.5)
Pregnant or breast-feeding	2 (1.0)
15 mg – once daily, when previous dose was 30 mg – once daily, and following dose is 0 mg (interruption/suspension) and VKA is started (concomitant to 0 mg of edoxaban)	0 (0.0)
Severe bleeding and edoxaban is interrupted/suspended within five days after severe bleeding	0 (0.0)
Patients >= 65 years old and concomitant acetylsalicylic acid drugs	1 (0.5)
Surgical patients and no interruption of edoxaban	3 (1.5)
Patients with mechanical heart valves	0 (0.0)

Notes: VTE=Venous Thromboembolic Event; NVAF=Non-Valvular Atrial Fibrillation; VKA=Vitamin K Antagonist; (1) Percentages are calculated using the number of subjects with at least one missed dose as denominator; (2) ESRD: end stage of renal disease (CrCL<15mL/min); (3) A subject that has multiple conditions is counted once for that condition, and once in Lesion or condition considered to be a significant risk for major bleeding. Reference Table 25 in section 12.3.

Table 21 below summarises the patients showing deviations from the requirements or recommendations of the SmPC.

Table 21. Distribution of patients categorized as inappropriate drug users

Characteristics	Overall (N=200)
Patients in which the product is contraindicated, n (%) 95%CI	46 (23.0) (17.4,29.5)
Hypersensitivity to Edoxaban or any excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC)	1 (0.5)
Clinically significant active bleeding	5 (2.5)
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	2 (1.0)
Lesion or condition considered to be a significant risk for major bleeding	11 (5.5)
Uncontrolled severe hypertension	3 (1.5)
Concomitant treatment of Edoxaban and any other anticoagulant	29 (14.5)
Pregnant or breast-feeding	2 (1.0)
Patients who are not under the indication label per SmPC, n (%) 95%CI	26* (13.0) (8.7,18.5)
Other indication or indication unknown	18 (9.0)
Patient < 18 years old	0 (0.0)
Patients that use a different dose[1], dosing regimen or route of administration, n (%) 95%CI	104 (52.0) (44.8,59.1)
No dose reduction for the patient with moderate-severe renal impairment, or body weight <= 60kg, or concomitant use of P-gp inhibitors	5 (2.5)
Dose reduction without reason	46 (23.0)
Different dosing regimen[1]	104 (52.0)
Different route of administration	0 (0.0)
Patients that demonstrate non-adherence to guidance in the label, n (%) 95%CI	1 (0.5) (0.0,2.8)
Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs.	1 (0.5)

Notes: numbers and percentage could include patients with missing data as part of the defined derivations of variables; CI: calculated Confidence Interval using Clopper-Pearson methods, NVAF: Non-Valvular Atrial Fibrillation, VTE: Venous Thromboembolic Event; Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole); *18 patients had reported other or unknown for the initial prescription, and 8 more patients had reported other or unknown for the follow-up prescription; (1) numbers include missing daily dose as different dose. Reference Table 26 in section 12.3.

9.4. Other analyses – Physician's survey

Up to 29 June 2017, the Physician's survey was completed by ten physicians at initiation. All answers are summarised in Table 27 and 29 in Section 12.3. No physician completed the survey six months after initiation. Due to very low number of completed surveys, the descriptive data are not displayed in this interim report.

10. DISCUSSION

10.1. Key Results

- Most of the patients (91.0%) were initially prescribed edoxaban for at least one of the two labelled indications.
- Eighteen patients (9.0%) were initially prescribed edoxaban for an indication other than NVAF or VTE indication or for an unknown indication.
- No patient aged less than 18 years-old was reported as being prescribed edoxaban. On average, the edoxaban users were elderly, with a mean age of 72.6 years.
- Approximately a fourth of the patients (23.0%, 95% CI: 17.4%, 29.5%) had a contraindicated use of edoxaban.
- Twenty six patients (13.0%, 95% CI: 8.7%, 18.5%) were using edoxaban outside of the labelled indications or for an unknown indication, for either an initial or a follow-up prescription.
- One hundred and four patients (52.0%, 95% CI: 44.8%, 59.1%) were using a different dose or dosing regimen as the ones recommended by the SmPC, including patients who could not be identified as such due to missing data.
- One patient (0.5%, 95% CI: 0.0%, 2.8%) used edoxaban concomitantly with a drug increasing the risk of bleeding.
- Dosing regimen and previous use of a parenteral anticoagulant therapy were incompletely reported and need further investigation to allow for reliable interpretation of data. Additional emphasis will be put on data review and cleaning to ensure data quality and accuracy for the final report.

10.2. Limitations

The data snapshot of the database was performed on 29 June 2017 on uncleaned data, meaning that efforts have been made prior to the snapshot to ensure high level of data completeness and accuracy. During a month period a higher frequency of cleaning and raising queries, as well as running manual checks were enforced before the snapshot. The presented data have not been through a complete data cleaning process. The interpretation is difficult due to missing data or incomplete data entry.

Considering the results from the sampling strategy for each country has shown to be operationally challenging during the site selection process. The acceptance of the site and the potential for patient recruitment at each site is bringing additional challenges.

The independence and confidentiality of the physicians' survey has created challenges for the monitoring of surveys completion. Regular reminders are sent to all physicians to complete the survey. However keeping the answers anonymous without any possibility to identify responders and non responders prevent from a targeted monitoring, The low rate of survey completion might be related to this operational issue.

The interim report aims to be descriptive and technical. The interpretation is made difficult by the low number of patients in sub-categories of interest. The low rate of survey completion also makes the interpretation of the results difficult.

10.3. Interpretation

The physicians prescribing edoxaban as per the report from the QuintilesIMS data assets and the physicians participating in the DUS appeared to be mainly practicing in private offices, and were represented by a variety of specialties, such as general practice, cardiology, neurology, angiology, internal medicine and others. The physicians had a specific geographical distribution in Switzerland, with a higher proportion of prescribers in the German speaking area, as well as in the UK, where edoxaban prescribers were mostly located in England and Northern Ireland (country reports are appended in Section 12.3).

In the first wave countries, the edoxaban users were 70% to be initially prescribed edoxaban for the NVAF indication, 21% for VTE indication, and in 9% of the patients the indication for an initial prescription of edoxaban was either outside the recommendations from SmPC or unknown (listed in Section 9.3). The study population appeared to be elderly, which is consistent with the NVAF indication, and no particular trend was found for gender distribution.

The patients prescribed edoxaban for NVAF had a similar profile to general European atrial fibrillation population with a majority of patients diagnosed with permanent atrial fibrillation (Zoni-Berisso M et al, 2014). Atrial fibrillation is frequently associated with cardiac disease and comorbidities. The most common comorbidities are hypertension, diabetes, heart failure, chronic obstructive pulmonary disease, renal failure, stroke, and cognitive disturbance. The medical history seemed typical for an elderly population with NVAF, with a numerous medical condition reported. In patient using edoxaban for VTE, the low number of patient limit the possibility of data interpretation.

The use as per the recommendations from the SmPC shows a relatively high number of deviations, such as a contraindicated use of edoxaban in 23% of patients, use outside of the labelled indications in 13% of patients, and use with a different dose or dosing regimen as the ones recommended by the SmPC in 52% of patients. However, due to missing and inaccurate data, no specific conclusion can currently be drawn. The high number may be caused by unclean data, which should look into details at the final analysis. Additional effort will be enforced to ensure data completeness and accuracy, to allow for full description of the edoxaban user

population in the targeted European countries.

10.4. Generalisability

Not applicable to the interim report

11. REFERENCES

1. Giugliano RP, Ruff TC, Braunwald E, et.al. Edoxaban versus Warfarin in Patients with Atrial Fibrillation: N Engl J Med 2013; 369:2093-2104.
2. Büller HR, Grosso MA, Mercuri M, et al. Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism: N Engl J Med 2013; 369:1406-15.
3. Almutairi AR, Zhou L, Gellad WF, et al. Effectiveness and Safety of Non-vitamin K Antagonist Oral Anticoagulants for Atrial Fibrillation and Venous Thromboembolism: A Systematic Review and Meta-analyses. Clin Ther. 2017 Jul;39(7):1456-1478.e36.
4. Guideline on good pharmacovigilance practices (GVP) - Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1), 8 September 2014, consulted on August 28, 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/09/WC500172402.pdf
5. Guideline on good pharmacovigilance practices (GVP) - Module VIII – Post-authorisation safety studies (Rev 2), 4 August 2016, consulted on August 28, 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129137.pdf
6. Hatcher L, A step –by Step Approach to Using the SAS System for Factor Analysis and Structural Equation Modeling. Cary; NC: SAS Institute, INC, 1994.
7. Center for Drug Evaluation and Research. Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. United States Food and Drug Administration: Department of Health and Human Services. Docket No: FDA–2012–N–0408, 2012.
8. Clopper C, Pearson S. The use of confidence or fiducial limits illustrated in the case of the Binomial. Biometrika 26: 404-413, 1934.
9. European Medicines Agency. Guideline on Missing Data in Confirmatory Clinical Trials (Rev 1), 2 July 2010, consulted on August 29, 2017, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf)
10. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. Clin Epidemiol. 2014; 6: 213–220.

12. OTHER INFORMATION

12.1. Figures – Contents

12.2. Tables – Contents

12.3. Statistical outputs: Tables

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13. APPENDICES

13.1. Names and addresses of participating investigators

Table 22. List of participating investigators

Site #	PI Name	PI Title	PI Degree	Site Name	Address	City	State/Province	Site Country	Postal Code
0002	Hotz, Michael	Dr.	MD	Christliches Krankenhaus Quakenbrück	Danziger Str.2	Quakenbrueck	Niedersachsen	Germany	49610
0005	Dietrich, Dirk	Dr.	MD	Praxis D. Dietrich	Hauptstr. 65	Heidenau	Sachsen	Germany	01809
0006	Lazaridis, Wasilios	Dr.	MD	Praxis Dr. Laser	Am Stadtpark 2	Nuernberg	Bayern	Germany	90409
0007	Fissan, Herbert	Dr.	MD	Praxis an der Lippe	Wilhelm-Huecker-Str. 13	Bad Lippspringe	Nordrhein Westfalen	Germany	33175
0009	Schmitz, Gregor	Dr.	MD	Schmitz, Gregor	Hauptstrasse 20	Balve	Nordrhein Westfalen	Germany	58802
0010	Ulmer, Achim	Dr.	MD	Ulmer, Hans Joachim	Friesenstrasse 27	Ludwigsburg	Baden Wuerttemberg	Germany	71640
0011	Lukannek, Stefan	Dr.	MD	Kardiologische Praxis Dr. Lukannek	Franziskusstr. 4	Lohne	Niedersachsen	Germany	49393
0012	Schiffer, Clemens	Dr.	MD	Gem. Praxis Drs. Schiffer und Woitge-Kleve-Germany-C	Hagsche Str. 77	Kleve	Nordrhein Westfalen	Germany	47533
0014	Weberling, Focko	Dr.	MD	Dr. Weberling	Beim Eberacker 10	Lahnau	Hessen	Germany	35633
0015	Marziniak, Martin	Prof.	PhD	Klinik für Neurologie kbo-Isar-Amper-Klinikum München-Ost	Ringstraße 56a	Haar	Bayern	Germany	85540
0017	Daunderer, Kamilla	Dr.	MD	Paxis Dr med Kamilla Daunderer	Franziskanerstr.30	München	Bayern	Germany	81669
0019	Bauch, Birgit	Dr.	MD	Gemeinschaftspraxis Dr. Hund und Bauch	Rheinlandstr. 89	Geislingen	Baden Wuerttemberg	Germany	73312
0024	Klein, Harald	Dr.	MD	Praxis Dr. Harald Klein	Reuterallee 27	Darmstadt	Hessen	Germany	64297
0026	Schwittay, Andreas	Dr.	MD	Dr. med. Andreas Schwittay	Leipziger Str. 2	Boehlen	Sachsen	Germany	04564
0027	Hergdt, Gunter	Dr.	MD	Praxis Dr. Hergdt	Pfefferloh 1a	Obermichelbach	Bayern	Germany	90587
0029	Zöller, Thomas	Dr.	MD	Klinische Forschung Berlin	Ansbacher Strasse 17-19	Berlin	Berlin	Germany	10787
0030	Engelhard, Ralf	Dr.	MD	Internistische Gemeinschaftspraxis	Stapenhorststr. 7	Frankenberg	Hessen	Germany	35066
0032	Bönigk, Hagen	Dr.	MD	Praxis für Blutgerinnungsstörungen	Halberstaedter Str. 49	Magdeburg	Sachsen Anhalt	Germany	39112

Site #	PI Name	PI Title	PI Degree	Site Name	Address	City	State/Province	Site Country	Postal Code
0034	Kellner, Bernd-Thomas	Dr.	MD	Gemeinschaftspraxis	Naumburger Strasse 31	Camburg	Thueringen	Germany	07774
0037	Oettler, Wolfram	Dr.	MD	Praxis für Gefäßmedizin	Carolusstraße 214	Goerlitz	Sachsen	Germany	02827
0039	Abdel-Qader, Muwafeg	Dr.	MD	Praxis Dr. med. Abdel-Qader	In den Twieten 6	Winsen	Niedersachsen	Germany	21423
0041	Taggeselle, Jens	Dr.	MD	Taggeselle, Jens	Rathausstrasse 63A	Markkleeberg	Sachsen	Germany	04416
0042	Gerbaulet, Uwe	Dr.	MD	Gemeinschaftspraxis	Goethestrasse 1	Loehne	Nordrhein Westfalen	Germany	32584
0043	Böhme, Mirko	Dr.	MD	Praxis Dr. Mirko Boehme	Pfarrweg 4	Sulzberg	Bayern	Germany	87477
0044	Stolzenburg, Heiko	Dr.	MD	Praxis Dr. Juergen Blume	Isinger Tor 4	Essen	Nordrhein Westfalen	Germany	45276
0045	Hansen, Sabine	Dr.	MD	Praxis Dr. Hansen	Alte Dorfstrasse 11	Unterwellenborn	Thueringen	Germany	07333
0046	Zimny, Hans-Hermann	Dr.	MD	Praxis Dr. med. Zimny	Lortzingstrasse 15	Bad Pyrmont	Niedersachsen	Germany	31812
0047	Schmidt-Reinwald, Astrid	Dr.	MD	Praxis Dr. Schmidt-Reinwald	Brotstr. 30-31	Trier	Rheinland Pfalz	Germany	54290
NCI	Lyrer, Philippe	Prof.	PhD	Universitaetsspital Basel	Petersgraben 4	Basel		Switzerland	4031
6001	Pieper, Michael	Dr.	MD	Kardiologie am Bodensee	Loewenstrasse 16	Kreuzlingen		Switzerland	8280
6002	Lyrer, Philippe	Dr.	PhD	Universitaetsspital Basel	Petersgraben 4	Basel		Switzerland	4031
6004	Morales Lopez, Cleopatra Guadalupe	Dr.	MD	Praxis Dr. med. Cleopatra Morales	Zollikerstrasse 37	Zürich		Switzerland	8008
6005	Acquistapace, Flavio	Dr.	MD	Studio Cardiologico Acquistapace	Via Cantonale 35/d	Manno		Switzerland	6928
6006	Schindewolf, Marc	Dr.	MD	Inselspital - Universitaetsspital Bern	Effingerstrasse 102	Bern		Switzerland	3010
NCI	Bakhai, Ameet	Dr.	MBBS	Royal Free London NHS Foundation Trust	Wellhouse Lane	Barnet	Hertfordshire	United Kingdom	EN5 3DJ
7001	Davis, Gershan	Dr.	MD	Aintree University Hospital	Aintree University Hosp	Liverpool	Merseyside	United Kingdom	L9 7AL
7003	Lip, Gregory	Prof.	MD	City Hospital	Dudley Road	Birmingham	West Midlands	United Kingdom	B18 7QH
7004	Kanumilli, Naresh	Dr.	MBBS	Northenden Group Practice	489 Palatine Road	Northenden	Greater Manchester	United Kingdom	M22 4DH

Site #	PI Name	PI Title	PI Degree	Site Name	Address	City	State/Province	Site Country	Postal Code
7005	Conn, Paul Gilbert	Dr.	MB BCh	Ballygomartin Group Practice	17 Ballygomartin Road	Belfast	County Antrim	United Kingdom	BT13 3BW
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7011	Andersen, Ulla	Dr.	MD	St Johns Medical Centre	Hermitage Road	Woking	Surrey	United Kingdom	GU21 1TD
7012	Saxena, Manish	Dr.	MSc	Barts Hospital	West Smithfield	London	Greater London	United Kingdom	EC1A 7BE
7014	Dutt, Tina	Dr.	PhD	Royal Liverpool University Hospital	Prescot Street	Liverpool	Merseyside	United Kingdom	L7 8XP
7016	Sultan, Ayyaz	Dr.	MBBS	Wrightington Wigan And Leigh	Hall Lane	Wigan	Lancashire	United Kingdom	WN6 9EP
7018	Fairhead, Susan	Dr.	MSc	Cleveleys Group Practice	Kelso Avenue	Thornton-Cleveleys	Lancashire	United Kingdom	FY5 3LF
7019	Kadr, Honer	Dr.	MSc	Queen's Hospital	Rom Valley Way	Romford	Essex	United Kingdom	RM7 0AG
7020	Garg, Scot	Dr.	PhD	Royal Blackburn Hospital	Haslingden Road	Blackburn	Lancashire	United Kingdom	BB2 3HH
7021	McCormack, Terry	Dr.	MBBS	Whitby Group Practice	Spring Vale Medical Centre	Whitby	North Yorkshire	United Kingdom	Y021 1SD
7022	Katira, Ravish	Dr.	MD	Harrogate District Hospital	Lancaster Park Road	Harrogate	North Yorkshire	United Kingdom	HG2 7SX

13.2. Observational Plan

Please see the complete document at the end of the report.

13.3. Sample CRF

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13.4. Statistical Analysis Plans

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12.3. Statistical outputs: Tables

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TABLE 1. SITES AND PHYSICIANS CHARACTERISTICS - PARTICIPATING INVESTIGATORS SET (PIS)

Variable	Sites (N=25)	Physicians (N=27)	Physicians who responded to the LIXIANA survey only at study initiation (N=10)	Physicians who responded to the LIXIANA survey only 6 months after study initiation (N=0)	Physicians who responded to the LIXIANA survey at initiation and 6 months after study initiation (N=0)	Physicians who did not take part to the LIXIANA survey (N=0)
Country and Region[1], n(%)						
Germany	20 (80.0)	22 (81.5)	8 (80.0)	0	0	0
Baden-Wuerttemberg	2 (10.0)	3 (13.6)	1 (12.5)			
Bavaria	3 (15.0)	3 (13.6)	1 (12.5)			
Berlin	1 (5.0)	1 (4.5)	1 (12.5)			
Hesse	3 (15.0)	3 (13.6)	0 (0.0)			
Lower Saxony	3 (15.0)	3 (13.6)	1 (12.5)			
North Rhine	2 (10.0)	3 (13.6)	1 (12.5)			
Saxony	3 (15.0)	3 (13.6)	2 (25.0)			
Saxony-Anhalt	1 (5.0)	1 (4.5)	0 (0.0)			
Thuringia	1 (5.0)	1 (4.5)	1 (12.5)			
Westphalia-Lippe	1 (5.0)	1 (4.5)	0 (0.0)			
Switzerland	2 (8.0)	2 (7.4)	2 (20.0)			
Nordwestschweiz	1 (50.0)	1 (50.0)	0 (0.0)			
Ostschweiz	0 (0.0)	0 (0.0)	2 (100.0)			
Ticino	1 (50.0)	1 (50.0)	0 (0.0)			
United Kingdom (UK)	3 (12.0)	3 (11.1)	0 (0.0)			
Durham	1 (33.3)	1 (33.3)	0 (0.0)			
Lancashire	2 (66.7)	2 (66.7)	0 (0.0)			

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[2] SD = Standard Deviation
[3] Percentage calculation can sum to > 100% because subjects can fall in more than one category

TABLE 1. SITES AND PHYSICIANS CHARACTERISTICS - PARTICIPATING INVESTIGATORS SET (PIS)

Variable	Sites (N=25)	Physicians (N=27)	Physicians who responded to the LIXIANA survey only at study initiation (N=10)	Physicians who responded to the LIXIANA survey only 6 months after study initiation (N=0)	Physicians who responded to the LIXIANA survey at initiation and 6 months after study initiation (N=0)	Physicians who did not take part to the LIXIANA survey (N=0)
Type of Setting, n(%)						
Private Practice	20 (80.0)	22 (81.5)	10 (100.0)	0	0	0
University Hospital	2 (8.0)	2 (7.4)	0 (0.0)			
General Hospital	1 (4.0)	1 (3.7)	0 (0.0)			
General Practice	1 (4.0)	1 (3.7)	0 (0.0)			
Other	0 (0.0)	0 (0.0)	0 (0.0)			
Missing	1	1	0			
Patient Volume						
Volume of Patients of the Setting/unit per year						
n	22			0	0	0
Mean (SD[2])	4643.7 (2917.27)					
Median	4500.0					
Q1, Q3	2600.0, 6000.0					
Min, Max	10, 9951					
Missing	3					
Type of Physician, n(%)						
Principal Investigator		23 (85.2)		0	0	0
Sub-investigator		4 (14.8)				

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Medical Specialty[3], n(%)						
General Medicine		11 (40.7)	4 (40.0)	0	0	0
Cardiology		9 (33.3)	5 (50.0)			
Internal Medicine		11 (40.7)	4 (40.0)			
Neurology		2 (7.4)	0 (0.0)			
Anticoagulation Specialist		2 (7.4)	1 (10.0)			
Other		2 (7.4)	0 (0.0)			
Angiology		1 (3.7)	0 (0.0)			
Pneumology		1 (3.7)	0 (0.0)			
Profession or Area of Primary Practice, n(%)						
General Medicine		11 (40.7)	4 (40.0)	0	0	0
Cardiology		6 (22.2)	4 (40.0)			
Internal Medicine		5 (18.5)	1 (10.0)			
Neurology		2 (7.4)	0 (0.0)			
Anticoagulation Specialist		1 (3.7)	1 (10.0)			
Other		2 (7.4)	0 (0.0)			
Angiology And Haemostaseology		1 (3.7)	0 (0.0)			
Pneumology		1 (3.7)	0 (0.0)			
Missing		0	0			

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TABLE 1. SITES AND PHYSICIANS CHARACTERISTICS - PARTICIPATING INVESTIGATORS SET (PIS)

Variable	Sites (N=25)	Physicians (N=27)	Physicians who responded to the LIXIANA survey only at study initiation (N=10)	Physicians who responded to the LIXIANA survey only 6 months after study initiation (N=0)	Physicians who responded to the LIXIANA survey at initiation and 6 months after study initiation (N=0)	Physicians who did not take part to the LIXIANA survey (N=0)
Experience with Edoxaban, n(%)						
Yes		26 (96.3)	10 (100.0)	0	0	0
No		1 (3.7)	0 (0.0)			
Months of Experience with Edoxaban						
n		24	9	0	0	0
Mean (SD[2])		19.0 (13.20)	23.7 (18.34)			
Median		17.0	18.0			
Q1, Q3		13.5, 20.0	15.0, 18.0			
Min, Max		5, 75	15, 72			
Missing		3	1			
Volume of Patients Treated with Edoxaban/LIXIANA						
n		23	8	0	0	0
Mean (SD[2])		51.6 (59.70)	43.3 (20.92)			
Median		30.0	40.0			
Q1, Q3		20.0, 50.0	29.0, 50.0			
Min, Max		7, 250	20, 88			
Missing		4	2			

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TABLE 2. DISPOSITION OF THE STUDY POPULATION AND SCREENING INFORMATION - SCREENED AND FULL ANALYSIS SETS

	Screen Failures[3] (N=17)	Subjects Included in the Study Full analysis set(FAS) (N=200)	All Screened Subjects[3] All Subjects screened set(SCR) (N=217)
Country, n(%)			
Germany	17(100.0)	179(89.5)	196(90.3)
Belgium	0(0.0)	0(0.0)	0(0.0)
Italy	0(0.0)	0(0.0)	0(0.0)
Spain	0(0.0)	0(0.0)	0(0.0)
Switzerland	0(0.0)	6(3.0)	6(2.8)
United Kingdom	0(0.0)	15(7.5)	15(6.9)
Portugal	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Reason for non-inclusion in the study, n(%)			
Informed consent form not signed	13(76.5)		
No evidence of edoxaban prescription in patient's chart	0(0.0)		
Initiation of edoxaban prescription linked to a clinical trial participation prior to launch date	0(0.0)		
Investigator's choice	4(23.5)		
First Intake Of Lixiana In October 2016	1(5.9)		
First Lixiana Prescription In Nov 2016	1(5.9)		
First Lixiana Therapy On 10sep2016	1(5.9)		
The Initial Regulation Took Place Outsid	1(5.9)		
Missing	0		
Indication for initial prescription of Edoxaban, n(%)			
Prevention of stroke and systemic embolism[1]	9(52.9)	140(70.0)	149(68.7)
Treatment of DVT and PE, and prevention of recurrences[2]	7(41.2)	42(21.0)	49(22.6)
Other	1(5.9)	9(4.5)	10(4.6)
Atrial Fibrillation	0(0.0)	3(1.5)	3(1.4)
Dilated Cardiomyopathy	0(0.0)	1(0.5)	1(0.5)
Lymphangitis	0(0.0)	1(0.5)	1(0.5)
PAVK	1(5.9)	0(0.0)	1(0.5)
Peripheral Arterial Disease	0(0.0)	1(0.5)	1(0.5)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
[1]Prevention of stroke and systemic embolism in adult subjects with NVAF with one or more risk factors
[2]Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
[3]A total of 33 patients have been excluded from the analysis due to reported start of treatment after index date.

TABLE 2. DISPOSITION OF THE STUDY POPULATION AND SCREENING INFORMATION - SCREENED AND FULL ANALYSIS SETS

	Screen Failures[3] (N=17)	Subjects Included in the Study Full analysis set(FAS) (N=200)	All Screened Subjects[3] All Subjects screened set(SCR) (N=217)
Stroke	0(0.0)	1(0.5)	1(0.5)
Stroke Without NVAF	0(0.0)	1(0.5)	1(0.5)
Tarsal Arthrosis	0(0.0)	1(0.5)	1(0.5)
Unknown	0(0.0)	9(4.5)	9(4.1)
Missing	0	0	0
Indication for follow-up prescription of Edoxaban, n(%)			
Prevention of stroke and systemic embolism[1]		102(51.0)	
Treatment of DVT and PE, and prevention of recurrences[2]		26(13.0)	
Other		1(0.5)	
Atrial Fibrillation		1(0.5)	
Unknown		17(8.5)	
Missing		54	

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DVT=Deep Vein Thrombosis
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[1]Prevention of stroke and systemic embolism in adult subjects with NVAF with one or more risk factors
[2]Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults
[3]A total of 33 patients have been excluded from the analysis due to reported start of treatment after index date.

TABLE 3. DEMOGRAPHIC CHARACTERISTICS, BEHAVIORAL HISTORY AND VITAL SIGNS FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
DEMOGRAPHICS					
Age at initial prescription (years)					
n	121	38	9	9	177
Mean (SD[1])	75.7 (9.87)	65.2 (13.90)	63.4 (16.79)	71.1 (11.52)	72.6 (12.20)
Median	77.0	62.5	66.0	73.0	75.0
Q1, Q3	69, 82	56, 80	60, 72	66, 78	66, 81
Min, Max	38, 97	28, 91	26, 82	48, 85	26, 97
Missing	19	4	0	0	23
Age at initial prescription, n (%)					
< 18 years old	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>= 18 years old and < 65 years old	18(12.9)	21(50.0)	3(33.3)	2(22.2)	44(22.0)
>= 65 years old and < 75 years old	30(21.4)	6(14.3)	4(44.4)	3(33.3)	43(21.5)
>= 75 years old	73(52.1)	11(26.2)	2(22.2)	4(44.4)	90(45.0)
Missing	19	4	0	0	23
Gender, n (%)					
Male	72(51.4)	20(47.6)	5(55.6)	7(77.8)	104(52.0)
Female	68(48.6)	22(52.4)	4(44.4)	2(22.2)	96(48.0)
Missing	0	0	0	0	0
If female, child bearing potential[2]					
Yes	0(0.0)	3(13.6)	1(25.0)	0(0.0)	4(4.2)
No	68(100.0)	19(86.4)	3(75.0)	2(100.0)	92(95.8)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
[1]SD = Standard Deviation
[2]Percentages are calculated with the total number of females in the denominator.
[3]One drink - e.g.: 0.25L wine, 0.5L beer

TABLE 3. DEMOGRAPHIC CHARACTERISTICS, BEHAVIORAL HISTORY AND VITAL SIGNS FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
BEHAVIORAL HISTORY					
Smoker, n (%)					
Never	75(53.6)	20(47.6)	6(66.7)	9(100.0)	110(55.0)
Currently	5(3.6)	6(14.3)	2(22.2)	0(0.0)	13(6.5)
Formerly	27(19.3)	1(2.4)	0(0.0)	0(0.0)	28(14.0)
Unknown	32(22.9)	15(35.7)	1(11.1)	0(0.0)	48(24.0)
Missing	1	0	0	0	1
Alcohol average daily intake[3], n(%)					
None	58(41.4)	8(19.0)	3(33.3)	0(0.0)	69(34.5)
< 1 drink	27(19.3)	11(26.2)	5(55.6)	0(0.0)	43(21.5)
1-2 drinks	20(14.3)	6(14.3)	0(0.0)	0(0.0)	26(13.0)
3-4 drinks	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(1.5)
> 4 drinks	2(1.4)	0(0.0)	0(0.0)	0(0.0)	2(1.0)
Unknown	29(20.7)	17(40.5)	1(11.1)	9(100.0)	56(28.0)
Missing	1	0	0	0	1
VITAL SIGNS					
Height (cm)					
n	36	4	0	2	42
Mean (SD[1])	168.6 (8.63)	169.3 (13.62)		169.5 (4.95)	168.7 (8.82)
Median	168.0	171.5		169.5	168.0
Q1, Q3	162, 176	158, 181		166, 173	162, 177
Min, Max	150, 184	153, 181		166, 173	150, 184
Missing	104	38	9	7	158

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
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[3]One drink - e.g.: 0.25L wine, 0.5L beer

TABLE 3. DEMOGRAPHIC CHARACTERISTICS, BEHAVIORAL HISTORY AND VITAL SIGNS FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Body Weight (kg)					
n	37	4	0	2	43
Mean (SD[1])	77.6 (15.02)	85.1 (4.33)		81.5 (9.19)	78.5 (14.21)
Median	75.0	85.3		81.5	80.0
Q1, Q3	66, 88	82, 89		75, 88	67, 88
Min, Max	50, 118	80, 90		75, 88	50, 118
Missing	103	38	9	7	157
Body Weight categorized					
<= 60 kg	6(4.3)	0(0.0)	0(0.0)	0(0.0)	6(3.0)
> 60 kg	31(22.1)	4(9.5)	0(0.0)	2(22.2)	37(18.5)
Missing	103	38	9	7	157
Body Mass Index (kg/m^2)					
n	36	4	0	2	42
Mean (SD[1])	27.4 (4.53)	30.2 (5.39)		28.3 (1.54)	27.7 (4.52)
Median	27.5	30.2		28.3	27.5
Q1, Q3	25, 30	26, 35		27, 29	25, 30
Min, Max	18, 39	25, 36		27, 29	18, 39
Missing	104	38	9	7	158
Body Mass Index categorized					
Underweight (<18.5 kg/m^2)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Healthy weight (18.5-24.9 kg/m^2)	9(6.4)	1(2.4)	0(0.0)	0(0.0)	10(5.0)
Overweight (25-29.9 kg/m^2)	17(12.1)	1(2.4)	0(0.0)	2(22.2)	20(10.0)
Obese (>=30 kg/m^2)	9(6.4)	2(4.8)	0(0.0)	0(0.0)	11(5.5)
Missing	104	38	9	7	158

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
[1]SD = Standard Deviation
[2]Percentages are calculated with the total number of females in the denominator.
[3]One drink - e.g.: 0.25L wine, 0.5L beer

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Type of VTE, n(%)			
DVT only	29(100.0)	0(0.0)	29(72.5)
PE with DVT	0(0.0)	6(54.5)	6(15.0)
PE only	0(0.0)	5(45.5)	5(12.5)
Missing	0	0	0
VENOUS THROMBOEMBOLIC EVENTS RISK FACTORS			
Presence of VTE risk factors, n(%)			
One risk factor	2(6.9)	0(0.0)	2(5.0)
More than one risk factor	9(31.0)	6(54.5)	15(37.5)
No risk factors	18(62.1)	5(45.5)	23(57.5)
Missing	0	0	0
Puerperium, n(%)			
Yes	1(3.4)	0(0.0)	1(2.5)
No	1(3.4)	1(9.1)	2(5.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	27	10	37
Prolonged immobilization, n(%)			
Yes	3(10.3)	1(9.1)	4(10.0)
No	20(69.0)	8(72.7)	28(70.0)
Unknown	6(20.7)	2(18.2)	8(20.0)
Missing	0	0	0
> 5 days in bed, n(%)			
Yes	2(6.9)	1(9.1)	3(7.5)
No	21(72.4)	8(72.7)	29(72.5)
Unknown	6(20.7)	2(18.2)	8(20.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
History of major surgery or trauma, n(%)			
Yes	1(3.4)	1(9.1)	2(5.0)
No	22(75.9)	8(72.7)	30(75.0)
Unknown	6(20.7)	2(18.2)	8(20.0)
Missing	0	0	0
Known thrombophillic conditions, n(%)			
Yes	7(24.1)	5(45.5)	12(30.0)
No	16(55.2)	5(45.5)	21(52.5)
Unknown	6(20.7)	1(9.1)	7(17.5)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Other risk factors[1], n(%)			
Antithrombin deficiency	0(0.0)	0(0.0)	0(0.0)
Factor V Leiden	2(6.9)	1(9.1)	3(7.5)
Hyperhomocysteinaemia	0(0.0)	0(0.0)	0(0.0)
Antiphospholipid antibodies	0(0.0)	1(9.1)	1(2.5)
Protein C deficiency	0(0.0)	1(9.1)	1(2.5)
Protein S deficiency	0(0.0)	0(0.0)	0(0.0)
Prothrombin gene mutation	0(0.0)	0(0.0)	0(0.0)
Other	5(17.2)	2(18.2)	7(17.5)
As A Result Of F. Viii Multiplication	1(3.4)	0(0.0)	1(2.5)
Homozygous Homocysteine Mutation Defect	1(3.4)	1(9.1)	2(5.0)
In Compound-Heterozygous Homocysteine Mutation Defect	1(3.4)	0(0.0)	1(2.5)
In Heterozygous Apc And Homozygous Homocysteine Mutation Defect	0(0.0)	1(9.1)	1(2.5)
In Lupus Anticoagulant And Heterozygous Homocysteine Mutation Defect	1(3.4)	0(0.0)	1(2.5)
Thrombophilia Due To Fviii Multiplication And Heterozygous Homocysteine Mutation Defect Due To Mthfr Polymorphism Without Relevant Hyperhomocysteinemia	1(3.4)	0(0.0)	1(2.5)
Missing	22	6	28

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
VENOUS THROMBOEMBOLIC EVENTS THERAPY			
Acute invasive and/or non-invasive VTE therapy, n(%)			
Yes	9(31.0)	1(9.1)	10(25.0)
No	15(51.7)	8(72.7)	23(57.5)
Unknown	5(17.2)	2(18.2)	7(17.5)
Missing	0	0	0
Invasive therapy			
Open embolectomy[3], n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	9(100.0)	1(100.0)	10(100.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was open embolectomy successful[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was Edoxaban interrupted for open embolectomy[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
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[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Catheter procedures (e.g. catheter fragmentation or embolectomy)[3], n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	9(100.0)	1(100.0)	10(100.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Catheter procedures with local thrombolytic treatment[3], n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was catheter procedures successful[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was Edoxaban interrupted for catheter procedures[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Insertion of vena cava filter[3], n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	9(100.0)	1(100.0)	10(100.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Was insertion of vena cava filter successful[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was Edoxaban interrupted for insertion of vena cava filter[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Other invasive therapies[3], n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	9(100.0)	1(100.0)	10(100.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Were other invasive therapies successful[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was Edoxaban interrupted for other invasive therapies[3]?, n(%)			
Yes	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Non-invasion therapy			
Compression stockings[3], n(%)			
Yes	9(100.0)	1(100.0)	10(100.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Number of stockings			
n	9	1	10
Mean (SD[2])	1.9 (0.33)	2.0 (NA)	1.9 (0.32)
Median	2.0	2.0	2.0
Q1, Q3	2, 2	2, 2	2, 2
Min, Max	1, 2	2, 2	1, 2
Missing	0	0	0
Was compression stockings successful[3]?, n(%)			
Yes	9(100.0)	1(100.0)	10(100.0)
No	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was Edoxaban interrupted for compression stockings[3]?, n(%)			
Yes	1(11.1)	0(0.0)	1(10.0)
No	8(88.9)	1(100.0)	9(90.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 5. VENOUS THROMBOEMBOLIC EVENTS (VTE) RISK FACTORS AND VTE THERAPY BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH VTE

Type of VTE (if indication for prescription is VTE) ⇨	Deep Vein Thrombosis (DVT) (N=29)	Pulmonary Embolism (PE) with or without DVT (N=11)	Overall* (N=40)
Other non-invasive therapies[3], n(%)			
Yes	1(11.1)	0(0.0)	1(10.0)
No	8(88.9)	1(100.0)	9(90.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Were other non-invasive therapies successful[3]?, n(%)			
Yes	1(100.0)	0(0.0)	1(100.0)
No	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
Was Edoxaban interrupted for other non-invasive therapies[3]?, n(%)			
Yes	1(100.0)	0(0.0)	1(100.0)
No	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified.
DVT=Deep Vein Thrombosis
PE=Pulmonary Embolism
VTE=Venous Thromboembolic Event
*Type of VTE is missing for two patients. All data for VTE risk factors are missing in these patients.
[1]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
[2]SD = Standard Deviation
[3]Percentages are calculated using the number of subjects with that particular intervention in the denominator.

TABLE 6. ATRIAL FIBRILLATION (AF) TREATMENT BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH AF

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
ATRIAL FIBRILLATION TREATMENT					
Undergone any interventions for NVAF? n(%)					
Yes	6(12.0)	2(7.1)	0(0.0)	8(14.8)	16(11.6)
No	39(78.0)	22(78.6)	6(100.0)	45(83.3)	112(81.2)
Unknown	5(10.0)	4(14.3)	0(0.0)	1(1.9)	10(7.2)
Missing	0	0	0	0	0
Pharmacological cardioversion[1], n(%)					
Yes	1(16.7)	2(100.0)	0(0.0)	0(0.0)	3(18.8)
No	5(83.3)	0(0.0)	0(0.0)	8(100.0)	13(81.3)
Missing	0	0	0	0	0
Number of interventions[1], n(%)					
1	0(0.0)	2(100.0)	0(0.0)	0(0.0)	2(66.7)
>=2	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(33.3)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]? n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	1(100.0)	2(100.0)	0(0.0)	0(0.0)	3(100.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Electrical cardioversion[1], n(%)					
Yes	1(16.7)	1(50.0)	0(0.0)	3(37.5)	5(31.3)
No	5(83.3)	1(50.0)	0(0.0)	5(62.5)	11(68.8)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
NVAF=Non-Valvular Atrial Fibrillation
[1]Percentages are calculated using the number of subjects with that particular intervention in the denominator.
[2]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
*Type of NVAF is missing for two patients.

TABLE 6. ATRIAL FIBRILLATION (AF) TREATMENT BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH AF

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
Number of interventions[1], n(%)					
1	1(100.0)	1(100.0)	0(0.0)	3(100.0)	5(100.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]? n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	1(33.3)	1(20.0)
No	0(0.0)	1(100.0)	0(0.0)	2(66.7)	3(60.0)
Unknown	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(20.0)
Missing	0	0	0	0	0
Ablation[1], n(%)					
Yes	1(16.7)	0(0.0)	0(0.0)	2(25.0)	3(18.8)
No	5(83.3)	2(100.0)	0(0.0)	6(75.0)	13(81.3)
Missing	0	0	0	0	0
Number of interventions[1], n(%)					
1	1(100.0)	0(0.0)	0(0.0)	2(100.0)	3(100.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]?, n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(33.3)
No	1(100.0)	0(0.0)	0(0.0)	0(0.0)	1(33.3)
Unknown	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(33.3)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
NVAF=Non-Valvular Atrial Fibrillation
[1]Percentages are calculated using the number of subjects with that particular intervention in the denominator.
[2]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
*Type of NVAF is missing for two patients.

TABLE 6. ATRIAL FIBRILLATION (AF) TREATMENT BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH AF

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
Ablation location[1,2], n(%)					
AV node	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(33.3)
Atrial fibrillation	1(100.0)	0(0.0)	0(0.0)	1(50.0)	2(66.7)
Stroke	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Supraventricular tachycardia	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Atrial flutter	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Pacemaker/Defibrillator (ICD)[1], n(%)					
Pacemaker	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Defibrillator	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Neither	3(50.0)	2(100.0)	0(0.0)	8(100.0)	13(81.3)
Missing	3	0	0	0	3
Number of interventions[1], n(%)					
1	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]?, n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Left atrial appendage occlusion[1], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	6(100.0)	2(100.0)	0(0.0)	8(100.0)	16(100.0)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
NVAF=Non-Valvular Atrial Fibrillation
[1]Percentages are calculated using the number of subjects with that particular intervention in the denominator.
[2]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
*Type of NVAF is missing for two patients.

TABLE 6. ATRIAL FIBRILLATION (AF) TREATMENT BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH AF

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
Number of interventions[1], n(%)					
1	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]?, n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Surgical therapy for NVAF[1], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	1(12.5)	1(6.3)
No	6(100.0)	2(100.0)	0(0.0)	7(87.5)	15(93.8)
Missing	0	0	0	0	0
Number of interventions[1], n(%)					
1	0(0.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]?, n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	1(100.0)	1(100.0)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
NVAF=Non-Valvular Atrial Fibrillation
[1]Percentages are calculated using the number of subjects with that particular intervention in the denominator.
[2]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
*Type of NVAF is missing for two patients.

TABLE 6. ATRIAL FIBRILLATION (AF) TREATMENT BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH AF

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
Transcatherter Aortic Valve Implantation (TAVI)[1], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	6(100.0)	2(100.0)	0(0.0)	8(100.0)	16(100.0)
Missing	0	0	0	0	0
Number of interventions[1], n(%)					
1	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban interrupted for interventions[1]?, n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Percutaneous Coronary Intervention (PCI)[1], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	2(25.0)	2(12.5)
No	6(100.0)	2(100.0)	0(0.0)	6(75.0)	14(87.5)
Missing	0	0	0	0	0
Number of interventions[1], n(%)					
1	0(0.0)	0(0.0)	0(0.0)	2(100.0)	2(100.0)
>=2	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
NVAF=Non-Valvular Atrial Fibrillation
[1]Percentages are calculated using the number of subjects with that particular intervention in the denominator.
[2]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
*Type of NVAF is missing for two patients.

TABLE 6. ATRIAL FIBRILLATION (AF) TREATMENT BY INDICATION FOR INITIAL PRESCRIPTION – FULL ANALYSIS SETS (FAS): SUBSET OF PATIENTS WITH AF

Type of Non-valvular Atrial Fibrillation (NVAF) (if indication for prescription is NVAF)⇨	Paroxysmal Non-valvular Atrial Fibrillation (N=50)	Persistent Non-valvular Atrial Fibrillation (N=28)	Long-Standing Non-valvular Atrial Fibrillation (N=6)	Permanent Non-valvular Atrial Fibrillation (N=54)	Overall* (N=138)
Was Edoxaban interrupted for interventions[1]?, n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(50.0)
No	0(0.0)	0(0.0)	0(0.0)	1(50.0)	1(50.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
NVAF=Non-Valvular Atrial Fibrillation
[1]Percentages are calculated using the number of subjects with that particular intervention in the denominator.
[2]Percentage calculation can sum to > 100% because subjects can fall in more than one category.
*Type of NVAF is missing for two patients.

TABLE 9. MEDICAL HISTORY FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Past surgery, n(%)					
Yes	17(12.1)	2(4.8)	0(0.0)	0(0.0)	19(9.5)
No	123(87.9)	40(95.2)	9(100.0)	9(100.0)	181(90.5)
Missing	0	0	0	0	0
Atrial Fibrillation (AF), n(%)					
Yes	139(99.3)	2(4.8)	4(44.4)	0(0.0)	145(72.5)
No	0(0.0)	37(88.1)	5(55.6)	0(0.0)	42(21.0)
Unknown	0(0.0)	3(7.1)	0(0.0)	9(100.0)	12(6.0)
Missing	1	0	0	0	1
Venous Thromboembolic Event, n(%)					
Yes	4(2.9)	40(95.2)	1(11.1)	0(0.0)	45(22.5)
No	121(86.4)	2(4.8)	8(88.9)	0(0.0)	131(65.5)
Unknown	14(10.0)	0(0.0)	0(0.0)	9(100.0)	23(11.5)
Missing	1	0	0	0	1
Valvular heart disease, n(%)					
Yes	29(20.7)	3(7.1)	0(0.0)	0(0.0)	32(16.0)
No	102(72.9)	37(88.1)	9(100.0)	0(0.0)	148(74.0)
Unknown	7(5.0)	2(4.8)	0(0.0)	9(100.0)	18(9.0)
Missing	2	0	0	0	2
Renal disease, n(%)					
Yes	22(15.7)	1(2.4)	2(22.2)	0(0.0)	25(12.5)
No	110(78.6)	36(85.7)	7(77.8)	1(11.1)	154(77.0)
Unknown	6(4.3)	5(11.9)	0(0.0)	8(88.9)	19(9.5)
Missing	2	0	0	0	2

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
Medical history = any disease with date of diagnosis before the date of initial prescription of Edoxaban

TABLE 9. MEDICAL HISTORY FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Hepatic disorders, n(%)					
Yes	1(0.7)	2(4.8)	0(0.0)	0(0.0)	3(1.5)
No	132(94.3)	35(83.3)	9(100.0)	0(0.0)	176(88.0)
Unknown	5(3.6)	5(11.9)	0(0.0)	9(100.0)	19(9.5)
Missing	2	0	0	0	2
Malignancy, n(%)					
Yes	15(10.7)	6(14.3)	1(11.1)	0(0.0)	22(11.0)
No	119(85.0)	31(73.8)	8(88.9)	0(0.0)	158(79.0)
Unknown	4(2.9)	5(11.9)	0(0.0)	9(100.0)	18(9.0)
Missing	2	0	0	0	2
Fracture/Trauma, n(%)					
Yes	12(8.6)	5(11.9)	2(22.2)	0(0.0)	19(9.5)
No	108(77.1)	29(69.0)	7(77.8)	0(0.0)	144(72.0)
Unknown	18(12.9)	8(19.0)	0(0.0)	9(100.0)	35(17.5)
Missing	2	0	0	0	2
Stroke, n(%)					
Yes	21(15.0)	3(7.1)	1(11.1)	0(0.0)	25(12.5)
No	116(82.9)	34(81.0)	8(88.9)	0(0.0)	158(79.0)
Unknown	1(0.7)	5(11.9)	0(0.0)	9(100.0)	15(7.5)
Missing	2	0	0	0	2
Major bleeding events that led to a visit to health care professionals, n(%)					
Yes	4(2.9)	1(2.4)	0(0.0)	0(0.0)	5(2.5)
No	126(90.0)	37(88.1)	9(100.0)	0(0.0)	172(86.0)
Unknown	8(5.7)	4(9.5)	0(0.0)	9(100.0)	21(10.5)
Missing	2	0	0	0	2

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
Medical history = any disease with date of diagnosis before the date of initial prescription of Edoxaban

TABLE 9. MEDICAL HISTORY FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Digestive tract disease, n(%)					
Yes	11(7.9)	5(11.9)	3(33.3)	0(0.0)	19(9.5)
No	118(84.3)	33(78.6)	6(66.7)	0(0.0)	157(78.5)
Unknown	9(6.4)	4(9.5)	0(0.0)	9(100.0)	22(11.0)
Missing	2	0	0	0	2
Hypertension, n(%)					
Yes	100(71.4)	17(40.5)	8(88.9)	1(11.1)	126(63.0)
No	37(26.4)	21(50.0)	1(11.1)	0(0.0)	59(29.5)
Unknown	1(0.7)	4(9.5)	0(0.0)	8(88.9)	13(6.5)
Missing	2	0	0	0	2
Peripheral vascular disease, n(%)					
Yes	5(3.6)	1(2.4)	2(22.2)	0(0.0)	8(4.0)
No	126(90.0)	36(85.7)	7(77.8)	1(11.1)	170(85.0)
Unknown	7(5.0)	5(11.9)	0(0.0)	8(88.9)	20(10.0)
Missing	2	0	0	0	2
Diabetes Mellitus, n(%)					
Yes	36(25.7)	6(14.3)	4(44.4)	0(0.0)	46(23.0)
No	103(73.6)	32(76.2)	5(55.6)	1(11.1)	141(70.5)
Unknown	0(0.0)	4(9.5)	0(0.0)	8(88.9)	12(6.0)
Missing	1	0	0	0	1
Chronic Obstructive Pulmonary Disease (COPD), n(%)					
Yes	8(5.7)	3(7.1)	1(11.1)	0(0.0)	12(6.0)
No	126(90.0)	34(81.0)	8(88.9)	1(11.1)	169(84.5)
Unknown	5(3.6)	5(11.9)	0(0.0)	8(88.9)	18(9.0)
Missing	1	0	0	0	1

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
Medical history = any disease with date of diagnosis before the date of initial prescription of Edoxaban

TABLE 9. MEDICAL HISTORY FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Sleep apnea, n(%)					
Yes	6(4.3)	0(0.0)	0(0.0)	0(0.0)	6(3.0)
No	114(81.4)	36(85.7)	9(100.0)	1(11.1)	160(80.0)
Unknown	19(13.6)	6(14.3)	0(0.0)	8(88.9)	33(16.5)
Missing	1	0	0	0	1
Dyslipidemia, n(%)					
Yes	48(34.3)	7(16.7)	7(77.8)	0(0.0)	62(31.0)
No	88(62.9)	30(71.4)	2(22.2)	0(0.0)	120(60.0)
Unknown	3(2.1)	5(11.9)	0(0.0)	9(100.0)	17(8.5)
Missing	1	0	0	0	1
Hyper/Hypothyroidism, n(%)					
Yes	15(10.7)	5(11.9)	0(0.0)	0(0.0)	20(10.0)
No	119(85.0)	32(76.2)	9(100.0)	1(11.1)	161(80.5)
Unknown	5(3.6)	5(11.9)	0(0.0)	8(88.9)	18(9.0)
Missing	1	0	0	0	1
Thrombocytopenia (i.e.: <100000/µL), n(%)					
Yes	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
No	127(90.7)	35(83.3)	9(100.0)	1(11.1)	172(86.0)
Unknown	11(7.9)	7(16.7)	0(0.0)	8(88.9)	26(13.0)
Missing	1	0	0	0	1
Chronic thromboembolic pulmonary insufficiency, n(%)					
Yes	1(0.7)	1(2.4)	0(0.0)	0(0.0)	2(1.0)
No	129(92.1)	35(83.3)	9(100.0)	1(11.1)	174(87.0)
Unknown	9(6.4)	6(14.3)	0(0.0)	8(88.9)	23(11.5)
Missing	1	0	0	0	1

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
Medical history = any disease with date of diagnosis before the date of initial prescription of Edoxaban

TABLE 9. MEDICAL HISTORY FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Arthritis, n(%)					
Yes	18(12.9)	3(7.1)	1(11.1)	0(0.0)	22(11.0)
No	113(80.7)	35(83.3)	8(88.9)	1(11.1)	157(78.5)
Unknown	8(5.7)	4(9.5)	0(0.0)	8(88.9)	20(10.0)
Missing	1	0	0	0	1
Lower extremity paralysis, n(%)					
Yes	4(2.9)	0(0.0)	0(0.0)	0(0.0)	4(2.0)
No	126(90.0)	39(92.9)	9(100.0)	1(11.1)	175(87.5)
Unknown	9(6.4)	3(7.1)	0(0.0)	8(88.9)	20(10.0)
Missing	1	0	0	0	1
Infectious disease (necessitating immobilization), n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	131(93.6)	39(92.9)	9(100.0)	1(11.1)	180(90.0)
Unknown	8(5.7)	3(7.1)	0(0.0)	8(88.9)	19(9.5)
Missing	1	0	0	0	1
Coronary heart disease, n(%)					
Yes	39(27.9)	5(11.9)	3(33.3)	1(11.1)	48(24.0)
No	95(67.9)	34(81.0)	6(66.7)	0(0.0)	135(67.5)
Unknown	5(3.6)	3(7.1)	0(0.0)	8(88.9)	16(8.0)
Missing	1	0	0	0	1
Ischemic cardiomyopathy, n(%)					
Yes	8(5.7)	0(0.0)	1(11.1)	1(11.1)	10(5.0)
No	127(90.7)	39(92.9)	8(88.9)	0(0.0)	174(87.0)
Unknown	4(2.9)	3(7.1)	0(0.0)	8(88.9)	15(7.5)
Missing	1	0	0	0	1

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
Medical history = any disease with date of diagnosis before the date of initial prescription of Edoxaban

TABLE 16. PREGNANCY LACTATION STATUS – FULL ANALYSIS SETS: SUBSET OF FEMALE PATIENTS (FAS)

Indication for Initial Edoxaban Prescription⇨	Non-valvular Atrial Fibrillation(NVAF) (N=68)	Venous Thromboembolic Event(VTE) (N=22)	Other (N=4)	Unknown (N=2)	Overall (N=96)
Lactating at time of prescription[1], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	2(100.0)	2(2.1)
No	67(98.5)	21(95.5)	4(100.0)	0(0.0)	92(95.8)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	1	1	0	0	2
Pregnant at time of prescription[1], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	67(98.5)	21(95.5)	4(100.0)	2(100.0)	94(97.9)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	1	1	0	0	2
How was the pregnancy confirmed?[2], n(%)					
HCG test positive	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Positive ultrasound scan	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Pregnancy status recorded in the medical notes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Was Edoxaban intake stopped during pregnancy?[2], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
[1]Subset of female subjects.
[2]Percentages are calculated with the total number of females in the denominator.
[3]SD=Standard Deviation
[4]Percentages are calculated with the total number of live births in the denominator.
[5]Percentages are calculated with the total number of still births or terminations in the denominator.

TABLE 16. PREGNANCY LACTATION STATUS – FULL ANALYSIS SETS: SUBSET OF FEMALE PATIENTS (FAS)

Indication for Initial Edoxaban Prescription⇨	Non-valvular Atrial Fibrillation(NVAF) (N=68)	Venous Thromboembolic Event(VTE) (N=22)	Other (N=4)	Unknown (N=2)	Overall (N=96)
Duration of Edoxaban exposure while pregnant (days)					
n	0	0	0	0	0
Mean (SD[3])					
Median					
Q1, Q3					
Min, Max					
Missing	68	22	4	2	96
Pregnancy outcome[2]					
Live birth	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Still birth	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Termination	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Live Birth Were any birth defects detected?[4], n(%)					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0
Still Birth or Termination Was teratogenicity reported[5]?					
Yes	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
No	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Unknown	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
[1]Subset of female subjects.
[2]Percentages are calculated with the total number of females in the denominator.
[3]SD=Standard Deviation
[4]Percentages are calculated with the total number of live births in the denominator.
[5]Percentages are calculated with the total number of still births or terminations in the denominator.

TABLE 19. INITIAL PRESCRIPTION OF EDOXABAN BY INDICATION– FULL ANALYSIS SET (FAS)

Indication for Initial Edoxaban Prescription⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Was the patient's initial Edoxaban prescription by the investigator? n(%)					
Yes	109(77.9)	30(71.4)	9(100.0)	9(100.0)	157(78.5)
No	30(21.4)	12(28.6)	0(0.0)	0(0.0)	42(21.0)
Missing	1	0	0	0	1
Type of prescriber[1], n(%)					
Office based physician	15(50.0)	8(66.7)	0(0.0)	0(0.0)	23(54.8)
Hospital based physician	14(46.7)	1(8.3)	0(0.0)	0(0.0)	15(35.7)
Unknown	1(3.3)	3(25.0)	0(0.0)	0(0.0)	4(9.5)
Missing	0	0	0	0	0
Specialty of prescriber[1], n(%)					
General medicine	1(3.3)	6(50.0)	0(0.0)	0(0.0)	7(16.7)
Cardiology	21(70.0)	0(0.0)	0(0.0)	0(0.0)	21(50.0)
Internal medicine	1(3.3)	1(8.3)	0(0.0)	0(0.0)	2(4.8)
Neurology	4(13.3)	0(0.0)	0(0.0)	0(0.0)	4(9.5)
Anticoagulation specialist	1(3.3)	0(0.0)	0(0.0)	0(0.0)	1(2.4)
Unknown	2(6.7)	4(33.3)	0(0.0)	0(0.0)	6(14.3)
Other	0(0.0)	1(8.3)	0(0.0)	0(0.0)	1(2.4)
Surgery	0(0.0)	1(8.3)	0(0.0)	0(0.0)	1(2.4)
Missing	0	0	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
OAC = Oral Anti-Coagulant
[1] Percentages are calculated using the number of subjects which initial edoxaban prescription was not prescribed by the principal investigator as denominator

TABLE 19. INITIAL PRESCRIPTION OF EDOXABAN BY INDICATION– FULL ANALYSIS SET (FAS)

Indication for Initial Edoxaban Prescription⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Major reason for initial prescription, n(%)					
Drug-drug interaction by former treatment	1(0.7)	2(4.8)	0(0.0)	0(0.0)	3(1.5)
High variability of former OAC treatment response	5(3.6)	1(2.4)	0(0.0)	1(11.1)	7(3.5)
Lack of efficacy of former OAC treatment	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(1.5)
Expected better safety	54(38.6)	9(21.4)	2(22.2)	0(0.0)	65(32.5)
Expected better efficacy	5(3.6)	10(23.8)	5(55.6)	0(0.0)	20(10.0)
Patient’s request	3(2.1)	2(4.8)	0(0.0)	0(0.0)	5(2.5)
Patient’s former non-compliance	6(4.3)	0(0.0)	1(11.1)	0(0.0)	7(3.5)
Expected better patient compliance	23(16.4)	6(14.3)	0(0.0)	0(0.0)	29(14.5)
Unknown	19(13.6)	10(23.8)	0(0.0)	8(88.9)	37(18.5)
Other	20(14.3)	2(4.8)	1(11.1)	0(0.0)	23(11.5)
Atrial Fibrillation	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
DVT Right Leg	0(0.0)	1(2.4)	0(0.0)	0(0.0)	1(0.5)
Decision Made With Patient After Discussion Of Options	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Drug Reaction Of Former Anticoagulant	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
First Line Treatment	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
First Order With Thrombosis	0(0.0)	1(2.4)	0(0.0)	0(0.0)	1(0.5)
Intolerance Of Eliquis	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Local Site Guidelines NOAC As First-Line Therapy	12(8.6)	0(0.0)	0(0.0)	0(0.0)	12(6.0)
Low Price	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Reducing Of Number Of Tablets (Previous Intake Of Pradaxa Bid)	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Renal Impairment	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Suspected Thrombosis	0(0.0)	0(0.0)	1(11.1)	0(0.0)	1(0.5)
Missing	1	0	0	0	1

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
OAC = Oral Anti-Coagulant
[1] Percentages are calculated using the number of subjects which initial edoxaban prescription was not prescribed by the principal investigator as denominator

TABLE 21. EDOXABAN UTILIZATION PATTERN FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Duration of Edoxaban prescription (weeks)					
n	121	38	9	9	177
Mean (SD[1])	21.51 (16.993)	24.36 (15.251)	14.30 (11.440)	25.41 (11.626)	21.95 (16.213)
Median	15.29	21.57	11.00	24.00	18.86
Q1, Q3	7.29, 36.86	11.14, 36.14	6.43, 18.14	18.86, 38.14	8.43, 36.86
Min, Max	0.1, 54.7	3.4, 53.3	2.4, 37.9	9.0, 39.3	0.1, 54.7
Missing	19	4	0	0	23
Edoxaban ongoing, n(%)					
Yes	98(70.0)	25(59.5)	5(55.6)	9(100.0)	137(68.5)
No	23(16.4)	13(31.0)	4(44.4)	0(0.0)	40(20.0)
Missing	19	4	0	0	23
Frequency, n(%)					
Once daily	118(84.3)	33(78.6)	9(100.0)	9(100.0)	169(84.5)
Twice daily	2(1.4)	3(7.1)	0(0.0)	0(0.0)	5(2.5)
Three times daily	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Not documented	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Missing	20	6	0	0	26
Total daily dose (mg), n(%)					
30 mg	48(34.3)	7(16.7)	0(0.0)	2(22.2)	57(28.5)
60 mg	72(51.4)	29(69.0)	9(100.0)	7(77.8)	117(58.5)
Other	1(0.7)	2(4.8)	0(0.0)	0(0.0)	3(1.5)
Missing	19	4	0	0	23

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
ADR=Adverse Drug Reaction
HCP=Health Care Provider
[1]SD=Standard Deviation

TABLE 21. EDOXABAN UTILIZATION PATTERN FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
If Edoxaban intake interrupted or discontinued, type, n(%)					
Suspension	11(7.9)	7(16.7)	0(0.0)	0(0.0)	18(9.0)
Missed dose	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Permanent discontinuation	11(7.9)	6(14.3)	4(44.4)	0(0.0)	21(10.5)
If Edoxaban intake interrupted or discontinued, reason, n(%)					
AF intervention	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
VTE intervention	0(0.0)	1(2.4)	0(0.0)	0(0.0)	1(0.5)
ADR/clinical event	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Invasive procedure	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Drug-drug interaction	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Renal function changed	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Hepatic function changed	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Weight increased/decreased	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
High variability of response	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Lack of efficacy	1(0.7)	1(2.4)	0(0.0)	0(0.0)	2(1.0)
Health care system related prescription/formulary limitations	2(1.4)	0(0.0)	0(0.0)	0(0.0)	2(1.0)
Patient’s transfer to another HCP	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Patient’s lack of compliance	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Patient’s request	3(2.1)	0(0.0)	0(0.0)	0(0.0)	3(1.5)
Treatment no longer considered to be necessary	5(3.6)	8(19.0)	3(33.3)	0(0.0)	16(8.0)
Other	10(7.1)	2(4.8)	1(11.1)	0(0.0)	13(6.5)
Cholecystolithiasis - Surgery - Abdominal Operation	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Exitus Letalis	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Invasive Procedure (Incl. Minor Surgery)	1(0.7)	2(4.8)	0(0.0)	0(0.0)	3(1.5)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
ADR=Adverse Drug Reaction
HCP=Health Care Provider
[1]SD=Standard Deviation

TABLE 21. EDOXABAN UTILIZATION PATTERN FOR INITIAL PRESCRIPTION BY INDICATION– FULL ANALYSIS SETS (FAS)

Indication for Initial Edoxaban Prescription ⇨	Non-valvular Atrial Fibrillation(NVAF) (N=140)	Venous Thromboembolic Event(VTE) (N=42)	Other (N=9)	Unknown (N=9)	Overall (N=200)
Patient's Lack Of Compliance	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Pre Final Status Of Patient	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Proceeding With A Lower Dose	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Pt Has Aortic Stenosis Requiring Valve Replacement	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Skin Irritation	0(0.0)	0(0.0)	1(11.1)	0(0.0)	1(0.5)
Strong Headache	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Tepimplantationan Death At 7-Feb-2016	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)
Unknown At This Time Will Investigate	1(0.7)	0(0.0)	0(0.0)	0(0.0)	1(0.5)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
AF=Atrial Fibrillation
ADR=Adverse Drug Reaction
HCP=Health Care Provider
[1]SD=Standard Deviation

TABLE 24. OCCURRENCE OF ADVERSE DRUG REACTIONS – FULL ANALYSIS SETS (FAS)

History of renal / hepatic impairment ⇨	Renal Impairment (N=24)	No Renal Impairment (N=176)	Hepatic Impairment (N=1)	No Hepatic Impairment (N=199)	Overall (N=200)
Adverse events related to Edoxaban treatment during observational period, Full Analysis Set, n(%)					
n	24	173	1	196	197
Yes	0(0.0)	5(2.8)	0(0.0)	5(2.5)	5(2.5)
No	24(100.0)	168(95.5)	1(100.0)	191(96.0)	192(96.0)
Missing	0	3	0	3	3

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 25. DISTRIBUTION OF PATIENTS BY EDOXABAN SUMMARY OF PRODUCT CHARACTERISTICS – FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Therapeutic indication	
Indication for initial Edoxaban prescription	
NVAF or VTE	182(91.0)
Other indication or indication unknown	18(9.0)
Indication for initial Edoxaban prescription: NVAF	140(70.0)
60 mg – once daily[1]	70(50.0)
30 mg – once daily and moderate-severe renal impairment[2], or body weight <= 60kg, or concomitant use of P-gp inhibitors[1,4]	8(5.7)
Other[1]	62(44.3)
Indication for initial Edoxaban prescription: VTE	42(21.0)
60 mg – once daily, following initial use of parenteral anticoagulant for at least 5 days,and no simultaneously administration of parenteral anticoagulants[3]	5(11.9)
30 mg – once daily and moderate-severe renal impairment[2], or body weight <= 60kg, or concomitant use of P-gp inhibitors[3,4] , following initial use of parenteral anticoagulant for at least 5 days, and no simultaneously administration of parenteral anticoagulant[4]	0(0.0)
Other[3]	37(88.1)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
VKA=Vitamin K Antagonist
[1] Percentages are calculated using the number of subjects with NVAF as denominator
[2] Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min
[3] Percentages are calculated using the number of subjects with VTE as denominator
[4] P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
[5] Percentages are calculated using the number of subjects with at least one missed dose as denominator
[6] ESRD: end stage of renal disease (CrCL<15mL/min)
[7] A subject that has multile conditions is counted once for that condtion, and once in *Lesion or condition considered to be a significant risk for major bleeding*

TABLE 25. DISTRIBUTION OF PATIENTS BY EDOXABAN SUMMARY OF PRODUCT CHARACTERISTICS – FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Patients with at least one missed dose	1(0.5)
1 missed dose (single dose/ interruption of one day)[5]	1(0.5)
>1 missed dose (multiple doses/ interruption longer than one day)[5]	0(0.0)
Patients with contraindications and special warnings	
ESRD[6] or on dialysis	0(0.0)
Clinically significant active bleeding	1(0.5)
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	2(1.0)
Lesion or condition considered to be a significant risk for major bleeding[7]	11(5.5)
Current or recent gastrointestinal ulceration	3(1.5)
Presence of malignant neoplasms at high risk of bleeding	2(1.0)
Recent brain or spinal injury	5(2.5)
Recent brain, spinal or ophthalmic surgery	2(1.0)
Recent intracranial haemorrhage	0(0.0)
Known or suspected oesophageal varices	0(0.0)
Arteriovenous malformations	3(1.5)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
VKA=Vitamin K Antagonist
[1] Percentages are calculated using the number of subjects with NVAF as denominator
[2] Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min
[3] Percentages are calculated using the number of subjects with VTE as denominator
[4] P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
[5] Percentages are calculated using the number of subjects with at least one missed dose as denominator
[6] ESRD: end stage of renal disease (CrCL<15mL/min)
[7] A subject that has multile conditions is counted once for that condtion, and once in *Lesion or condition considered to be a significant risk for major bleeding*

TABLE 25. DISTRIBUTION OF PATIENTS BY EDOXABAN SUMMARY OF PRODUCT CHARACTERISTICS – FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Vascular aneurysms	1(0.5)
Major intraspinal or intracerebral vascular abnormalities	0(0.0)
Uncontrolled severe hypertension	3(1.5)
Concomitant treatment of Edoxaban and any other anticoagulant	29(14.5)
Pregnant or breast-feeding	2(1.0)
15 mg – once daily, when previous dose was 30 mg – once daily, and following dose is 0 mg (interruption/suspension) and VKA is started (concomitant to 0 mg of edoxaban)	0(0.0)
Severe bleeding and edoxaban is interrupted/suspended within five days after severe bleeding	0(0.0)
Patients >= 65 years old and concomitant acetylsalicylic acid drugs	1(0.5)
Surgical patients and no interruption of edoxaban	3(1.5)
Patients with mechanical heart valves	0(0.0)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
VKA=Vitamin K Antagonist
[1] Percentages are calculated using the number of subjects with NVAF as denominator
[2] Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min
[3] Percentages are calculated using the number of subjects with VTE as denominator
[4] P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
[5] Percentages are calculated using the number of subjects with at least one missed dose as denominator
[6] ESRD: end stage of renal disease (CrCL<15mL/min)
[7] A subject that has multile conditions is counted once for that condtion, and once in *Lesion or condition considered to be a significant risk for major bleeding*

TABLE 25. DISTRIBUTION OF PATIENTS BY EDOXABAN SUMMARY OF PRODUCT CHARACTERISTICS – FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Hypersensitivity to Edoxaban or any excipients listed in section 6.1 of the Summary of Product Characteristics	1(0.5)
Edoxaban/Excipient to which the patient is hypersensitive	0(0.0)
Edoxaban	0(0.0)
Mannitol (E421)	0(0.0)
Pregelatinised starch	0(0.0)
Crospovidone	0(0.0)
Hydroxypropylcellulos	0(0.0)
Magnesium Stearate (E470b)	0(0.0)
Hypromellose (E464)	0(0.0)
Macrogol 8000	0(0.0)
Titanium Dioxide (E171)	0(0.0)
Talc	0(0.0)
Carnauba wax	0(0.0)
Iron oxide yellow (E172)	0(0.0)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
VKA=Vitamin K Antagonist
[1] Percentages are calculated using the number of subjects with NVAF as denominator
[2] Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min
[3] Percentages are calculated using the number of subjects with VTE as denominator
[4] P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
[5] Percentages are calculated using the number of subjects with at least one missed dose as denominator
[6] ESRD: end stage of renal disease (CrCL<15mL/min)
[7] A subject that has multile conditions is counted once for that condtion, and once in *Lesion or condition considered to be a significant risk for major bleeding*

TABLE 25. DISTRIBUTION OF PATIENTS BY EDOXABAN SUMMARY OF PRODUCT CHARACTERISTICS – FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Iron oxide red (E172)	0(0.0)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
VTE=Venous Thromboembolic Event
NVAF=Non-Valvular Atrial Fibrillation
VKA=Vitamin K Antagonist
[1] Percentages are calculated using the number of subjects with NVAF as denominator
[2] Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min
[3] Percentages are calculated using the number of subjects with VTE as denominator
[4] P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
[5] Percentages are calculated using the number of subjects with at least one missed dose as denominator
[6] ESRD: end stage of renal disease (CrCL<15mL/min)
[7] A subject that has multile conditions is counted once for that condtion, and once in *Lesion or condition considered to be a significant risk for major bleeding*

TABLE 26. DISTRIBUTION OF PATIENTS CATEGORIZED AS INAPPROPRIATE DRUG USERS– FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Patients in which the product is contraindicated, n (%) 95%CI	46 (23.0) (17.4,29.5)
Hypersensitivity to Edoxaban or any excipients listed in section 6.1 of the Summary of Product Characteristics (SmPC)	1 (0.5)
Clinically significant active bleeding	5 (2.5)
Hepatic disease associated with coagulopathy and clinically relevant bleeding risk	2 (1.0)
Lesion or condition considered to be a significant risk for major bleeding	11 (5.5)
Uncontrolled severe hypertension	3 (1.5)
Concomitant treatment of Edoxaban and any other anticoagulant	29 (14.5)
Pregnant or breast-feeding	2 (1.0)
Patients who are not under the indication label per SmPC, n (%) 95%CI	26 (13.0) (8.7,18.5)
Other indication or indication unknown	18 (9.0)
Patient < 18 years old	0 (0.0)
Patients that use a different dose, dosing regimen or route of administration, n (%) 95%CI	104 (52.0) (44.8,59.1)
No dose reduction for the patient with moderate-severe renal impairment, or body weight <= 60kg, or concomitant use of P-gp inhibitors	5 (2.5)
Dose reduction without reason	46 (23.0)
Different dosing regimen	104 (52.0)
Different route of administration	0 (0.0)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
NA=Not applicable

TABLE 26. DISTRIBUTION OF PATIENTS CATEGORIZED AS INAPPROPRIATE DRUG USERS– FULL ANALYSIS SETS (FAS)

Characteristics	Overall (N=200)
Patients that demonstrate non-adherence to guidance in the label, n (%) 95%CI	1 (0.5) (0.0,2.8)
Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs.	1 (0.5)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
Moderate-severe renal impairment: creatinine clearance (CrCL) in range 15-50 mL/min P-gp inhibitors: P-glycoprotein inhibitors (ciclosporin, dronedarone, erythromycin, ketoconazole)
NA=Not applicable

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
1. Concerning the indications for which Lixiana is approved in the European Union, please indicate if the following sentences are true (T) or false (F)			
1a. Lixiana is indicated in the prevention of stroke in adult patients with non-valvular atrial fibrillation with or without risks factors, n(%)			
True (Incorrect answer)	8(80.0)	0(0.0)	0(0.0)
False (Correct answer)	2(20.0)	0(0.0)	0(0.0)
Missing	0	0	0
1b. Lixiana is indicated in the prevention of systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, n(%)			
True (Correct answer)	10(100.0)	0(0.0)	0(0.0)
False (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
1c. Lixiana is indicated in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults, n(%)			
True (Correct answer)	10(100.0)	0(0.0)	0(0.0)
False (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	0	0	0
1d. Lixiana is not indicated in the prevention of recurrent DVT and PE in adults, n(%)			
True (Incorrect answer)	4(40.0)	0(0.0)	0(0.0)
False (Correct answer)	6(60.0)	0(0.0)	0(0.0)
Missing	0	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
1e. Lixiana is indicated in the prevention of VTE in subjects undergoing orthopaedic surgery, n(%)			
True (Incorrect answer)	3(30.0)	0(0.0)	0(0.0)
False (Correct answer)	6(60.0)	0(0.0)	0(0.0)
Missing	1	0	0
1f. Lixiana is indicated in the prevention of atherothrombotic events after acute coronary syndrome, n(%)			
True (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
False (Correct answer)	7(70.0)	0(0.0)	0(0.0)
Missing	1	0	0
2. Concerning the recommended dosing of Lixiana, please indicate if the following sentences are true (T) or false (F)			
2a. In patients with mild to moderate hepatic impairment, the recommended daily dose is of 30mg, n(%)			
True (Incorrect answer)	4(40.0)	0(0.0)	0(0.0)
False (Correct answer)	5(50.0)	0(0.0)	0(0.0)
Missing	1	0	0
2b. In patients with normal renal and hepatic function, the recommended daily dose is of 60mg, n(%)			
True (Correct answer)	9(90.0)	0(0.0)	0(0.0)
False (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	1	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
2c. In patients with moderate to severe renal impairment as defined by a creatinine clearance between 15 and 50 mL/min, the recommended daily dose is of 30mg, n(%)			
True (Correct answer)	9(90.0)	0(0.0)	0(0.0)
False (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	1	0	0
2d. Lixiana has to be taken outside of meals, n(%)			
True (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
False (Correct answer)	9(90.0)	0(0.0)	0(0.0)
Missing	1	0	0
2e. The duration of treatment with Lixiana is well defined and independent of transient or permanent risk factors, n(%)			
True (Incorrect answer)	6(60.0)	0(0.0)	0(0.0)
False (Correct answer)	3(30.0)	0(0.0)	0(0.0)
Missing	1	0	0
2f. Co-administration with cyclosporine does not require any adjustment in the dose of Lixiana, n(%)			
True (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
False (Correct answer)	7(70.0)	0(0.0)	0(0.0)
Missing	1	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
3. Lixiana is contraindicated or not recommended in the following special patient populations (please select all that apply), n(%)			
3a. Severe hepatic impairment (Correct answer)	8(80.0)	0(0.0)	0(0.0)
3b. Elevated liver enzymes ALT/AST 2x ULN (Incorrect answer)	4(40.0)	0(0.0)	0(0.0)
3c. Hepatic disease associated with coagulopathy and clinically relevant bleeding (Correct answer)	8(80.0)	0(0.0)	0(0.0)
3d. In co-administration with low dose ASA (<= 100mg/day) (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
3e. Uncontrolled severe hypertension (Correct answer)	7(70.0)	0(0.0)	0(0.0)
3f. Patients with a body weight <= 60 Kg (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
Missing	0	0	0
4. When initiating treatment with Lixiana, an initial course of heparin for at least 5 days prior to treatment with Lixiana must be observed (please select the correct answer), n(%)			
4a. In the treatment of patients with DVT and PE (Correct answer)	6(60.0)	0(0.0)	0(0.0)
4b. In the prevention of stroke and systemic embolism in patients with NVAF (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
4c. In both the treatment of DVT and PE patients, and prevention of stroke and systemic embolism in patients with NVAF (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
Missing	2	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
5. In the occurrence of a missed dose, the patient should be instructed to take it immediately even if it means to double the prescribed dose on the same day. Please indicate if the sentence is, n(%)			
5a. True (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
5b. False (Correct answer)	7(70.0)	0(0.0)	0(0.0)
5c. I don"t know (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
Missing	2	0	0
6. When switching patients to Lixiana from non-Vitamin K antagonist oral anticoagulants, the non-VKA must be discontinued and Lixiana initiated at the time of the non-VKA next dose. Please indicate if the sentence is, n(%)			
6a. True (Correct answer)	6(60.0)	0(0.0)	0(0.0)
6b. False (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
6c. I don"t know (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	2	0	0
7. When switching patients to Lixiana from Vitamin K antagonist anticoagulants, the INR must be <=2.5 after discontinuing the VKA and before initiating Lixiana. Please indicate if the sentence is, n(%)			
7a. True (Correct answer)	8(80.0)	0(0.0)	0(0.0)
7b. False (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
7c. I don"t know (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	2	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
8. When switching patients from Lixiana to warfarin, the initial dose of Lixiana remains the same during concomitant use. Please indicate if the sentence is, n(%)			
8a. True (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
8b. False (Correct answer)	5(50.0)	0(0.0)	0(0.0)
8c. I don"t know (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
Missing	2	0	0
9. When switching patients from Lixiana to warfarin, the INR should be measured 3 times (please selected the correct answer), n(%)			
9a. Just after taking the daily dose of Lixiana (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
9b. Just prior to taking the daily dose of Lixiana (Correct answer)	5(50.0)	0(0.0)	0(0.0)
9c. One time just before the daily dose of Lixiana, a second time 1h after the daily dose of Lixiana and a third time 2 hours after the daily dose of Lixiana (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
Missing	2	0	0
10. When switching patients to Lixiana from parenteral anticoagulant therapy, or from parenteral anticoagulant therapy to Lixiana, the initial therapy must be always discontinued before initiating the second. Please indicate if the sentence is, n(%)			
10a. True (Correct answer)	5(50.0)	0(0.0)	0(0.0)
10b. False (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
10c. I don"t know (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
Missing	2	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
11. Lixiana must be initiated immediately after discontinuing the continuously administered parenteral anticoagulant therapy. Please indicate if the sentence is, n(%)			
11a. True (Incorrect answer)	2(20.0)	0(0.0)	0(0.0)
11b. False (Correct answer)	6(60.0)	0(0.0)	0(0.0)
11c. I don"t know (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	2	0	0
12. Concerning the perioperative management of patients under treatment with Lixiana (please select the correct answer), n(%)			
12a. Lixiana does not need to be stopped before a surgical intervention or other invasive procedure (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
12b. Lixiana should be stopped at least 12 hours before a surgical intervention or other invasive procedure (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
12c. Lixiana should be stopped at least 24 hours before a surgical intervention or other invasive procedure (Correct answer)	8(80.0)	0(0.0)	0(0.0)
12d. I don"t know (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	2	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 27. KNOWLEDGE ON EDOXABAN UTILIZATION - PARTICIPATING INVESTIGATORS SET (FAS)

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)	Change in no. of correct answers between study initiation and 6 months after (N=0)
13. In case of overdose with Lixiana (please select the correct answer), n(%)			
13a. The patient must be given an antidote during the first 2 hours (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
13b. There is no antidote available, early administration of activated charcoal may be considered to reduce absorption (Correct answer)	7(70.0)	0(0.0)	0(0.0)
13c. Haemodialysis must be considered (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
13d. I don"t know (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	2	0	0
14. In the management of bleeding complications treatment with Lixiana must be delayed or discontinued, n(%)			
14a. True (Correct answer)	8(80.0)	0(0.0)	0(0.0)
14b. False (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
14c. I don"t know (Incorrect answer)	0(0.0)	0(0.0)	0(0.0)
Missing	2	0	0
15. When taking Lixiana, routine coagulation tests include: INR, PT and aPTT. Please indicate if the sentence is, n(%)			
15a. True (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
15b. False (Correct answer)	6(60.0)	0(0.0)	0(0.0)
15c. I don"t know (Incorrect answer)	1(10.0)	0(0.0)	0(0.0)
Missing	2	0	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified

TABLE 29. USE OF INFORMATIVE MATERIAL ON EDOXABAN – PARTICIPATING INVESTIGATORS SETS

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)
16. Are you aware of the Prescriber's Guide for Lixiana?, n(%)		
Yes	6(60.0)	0(0.0)
No	3(30.0)	0(0.0)
Missing	1	0
17. Have you received of the Prescriber's Guide for Lixiana?, n(%)		
Yes	6(60.0)	0(0.0)
No	3(30.0)	0(0.0)
Missing	1	0
18. You received the Prescriber's Guide, n(%)		
Before prescribing Lixiana for the first time	4(40.0)	0(0.0)
After prescribing Lixiana for the first time	5(50.0)	0(0.0)
Missing	1	0
19. Have you read the Prescriber's Guide?, n(%)		
Yes, completely	5(50.0)	0(0.0)
Yes, partially	1(10.0)	0(0.0)
No	3(30.0)	0(0.0)
Missing	1	0
If not,		
20. You have not read the Prescriber's Guide, please select the most relevant reason that applies[1], n(%)		
You prefer other sources of information, such as the Summary of Product Information	0(0.0)	0(0.0)
The Guide was too time consuming	0(0.0)	0(0.0)
It is not the first time you prescribed an anticoagulant factor Xa inhibitor, so you did not think the Guide would add to your knowledge	0(0.0)	0(0.0)
Other	3(100.0)	0(0.0)
Missing	0	0
If yes,		
21. How often have you consulted the Prescriber's Guide thereafter?[2], n(%)		

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
[1]Percentages are calculated with the total of physicians who have not read the Prescriber's Guide
[2]Percentages are calculated with the total of physicians who have read the Prescriber's Guide

TABLE 29. USE OF INFORMATIVE MATERIAL ON EDOXABAN – PARTICIPATING INVESTIGATORS SETS

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)
Never	0(0.0)	0(0.0)
Once	2(33.3)	0(0.0)
2-3 times	1(16.7)	0(0.0)
More than 3 times	2(33.3)	0(0.0)
Missing	1	0
22. You find the information in the Prescriber's Guide, n(%)		
Not useful	1(10.0)	0(0.0)
Useful	4(40.0)	0(0.0)
Missing	5	0
23. Have you referred to other sources of information to aid you in prescribing and managing Lixiana?, n(%)		
No	3(30.0)	0(0.0)
Yes	5(50.0)	0(0.0)
Missing	2	0
24. Are you aware of the Patient Alert Card for Lixiana?, n(%)		
Yes	7(70.0)	0(0.0)
No	1(10.0)	0(0.0)
Missing	2	0
25. Have you referred all your patients to the Patient Alert Card when you first prescribed them Lixiana?, n(%)		
Yes, always	6(60.0)	0(0.0)
Yes, most of the time	1(10.0)	0(0.0)
No, not always	1(10.0)	0(0.0)
No, I often forgot	0(0.0)	0(0.0)
Missing	2	0
26. During follow-up consultation, do you confirm if the patient carries the Patient Alert Card with them?, n(%)		
Yes	4(40.0)	0(0.0)

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
[1]Percentages are calculated with the total of physicians who have not read the Prescriber's Guide
[2]Percentages are calculated with the total of physicians who have read the Prescriber's Guide

TABLE 29. USE OF INFORMATIVE MATERIAL ON EDOXABAN – PARTICIPATING INVESTIGATORS SETS

Question	Responders at study initiation (N=10)	Responders at 6 months after study initiation (N=0)
No	4(40.0)	0(0.0)
Missing	2	0
27. How regularly do you check your patient’s knowledge on the content of the Patient Alert Card?, n(%)		
Never	3(30.0)	0(0.0)
In every consultation	4(40.0)	0(0.0)
At specific occasions	1(10.0)	0(0.0)
Missing	2	0

Percentages are calculated using number of subjects in the column heading as denominator, unless otherwise specified
[1]Percentages are calculated with the total of physicians who have not read the Prescriber’s Guide
[2]Percentages are calculated with the total of physicians who have read the Prescriber’s Guide

OBSERVATIONAL PLAN

DRUG UTILISATION OF EDOXABAN
DSE-EDO-01-14-EU

VERSION NUMBER: FINAL VERSION 6.0
DATE OF VERSION: 08 JUN 2017

SPONSOR/MARKETING AUTHORISATION HOLDER:

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STUDY INFORMATION

Protocol Number	DSE-EDO-01-14-EU, Version 6.0
Medicinal Product	Lixiana®
Product Reference	EMEA/H/C/002629
Procedure Number	EMA/H/C/002629/MEA/005
PASS Register Number	The study has not yet been registered
Active Ingredient	Edoxaban tosilate (Proposed ATC: B01AF03)
Study Title	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study
Date of Last Version of Protocol	08 JUN 2017
Research Question and Objectives	The aim of this Drug Utilisation Study (DUS) is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows: • To characterize users of edoxaban; • To evaluate the pattern of use of edoxaban; • To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization.
Countries of Study	Germany, Italy, Belgium, Switzerland, the United Kingdom (UK), Spain, Portugal
Author	Dr. Petra Laeis Daiichi Sankyo Europe GmbH Zielstattstr. 48 81379 Munich Germany Tel.: +49-89-7808-614
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1. SIGNATURES

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Date (DD MMM YYYY)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
BMI	Body Mass Index
CA	Competent Authority
CDISC	Clinical Data Interchange Standard Consortium
CHF	Congestive Heart Failure
CI	Confidence Interval
CrCl	Creatinine Clearance
CRO	Contract Research Organisation
CSPV	Clinical Safety and Pharmacovigilance
DM	Data Management
DUS	Drug Utilisation Study
DS	Daiichi Sankyo
DSE	Daiichi Sankyo Europe GmbH
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EDC	Electronical Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FPI	First Patient In
GFR	Glomerular Filtration Rate
GP	General Practitioners
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices (GVP) (See section 10)
HCP	Health Care Professionals
ICF	Informed Consent Form
ICSR	Individual Case Safety Report
ID	Identification Number
IEC	Independent Ethics Committee
INR	International Normalised Ratio
ISPE	International Society for Pharmacoepidemiology
LPO	Last Patient Out

MAH	Marketing Authorisation Holder
NC	National Coordinator
NSAID	Nonsteroidal Anti-Inflammatory Drugs
NVAF	Non-valvular Arial Fibrillation
PE	Pulmonary Embolism
PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis System (software)
SDTM	Study Data Tabulation Model
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TIA	Transient Ischemic Attack
UK	United Kingdom
VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

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3.1. List of Participating Centers and Countries

The following countries are planned to participate in the study: Germany, Italy, Switzerland, Belgium, the United Kingdom, Spain and Portugal.

A list of the principal investigators and all collaborating institutions and investigators is kept in a stand-alone document and can be made available upon request.

Table 1 - National Coordinators (Not applicable)

4. SUMMARY

Registry Title	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study
Protocol version identifier	DSE-EDO-01-14-EU, Version 6.0
Date of protocol version	08 Jun 2017
Marketing Authorisation Holder	Daiichi Sankyo Europe GmbH (DSE)
Main Authors	Dr Thomas Malzer, Clinical Safety and Pharmacovigilance (CSPV) Dr Petra Laeis, Head of Late Phase Clinical Operation and Real World Evidence & International Project Lead
Rationale and Background	Edoxaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It is currently approved for use in adult patients with Non-Valvular Atrial Fibrillation (NVAF) with one or more risk factors, such as Congestive Heart Failure (CHF), hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or Transient Ischemic Attack (TIA) for prevention of stroke and systemic embolism. In addition, edoxaban is approved for the treatment of Venous Thromboembolism (VTE) including Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE), and prevention of recurrent VTE in adults. Clinical development programs have been undertaken to support marketing authorization submissions for edoxaban in those indications. However, as it is the case with any medicinal product, real-life use of edoxaban may differ from or extend beyond the patient population that has been studied in the phase 3 program or is included under the approved indication. One of the concerns in real-world use of medicinal practices is the off-label use. Daiichi Sankyo (DS) addressed this concern in the Risk Management Plan (RMP) in order to anticipate necessary risk minimization activities. The potential off-label use of edoxaban in unapproved indications was considered low, because of the availability of approved, indicated and well-established treatment alternatives. However, as it is the case with all other new anticoagulants a residual risk for off-label use might be considered in conditions (for which Edoxaban is not approved) that usually also require mid- or long-term anticoagulant treatment or in cases of poor compliance or contraindications for the patient. Standard routine risk minimisation activities include the communication of the information in the Summary of Product Characteristics (SmPC). In order to further optimise the correct use of the medicinal product by the physician, DSE is implementing additional risk minimisation activities, namely: • Prescriber guide as part of the educational programs to make prescribers fully aware of the approved indications and eligible patients for edoxaban, the dosing recommendations and management of safety concerns;

	• Patient alert card. Furthermore, the Drug Utilisation Study (DUS), described in this document aims to gain insight on how this new European medicinal product is going to be used in real practice. The DUS will help identify prescription patterns, the effectiveness of the educational programs and promptly detect potential safety concerns, so that pharmacovigilance planning and risk management for edoxaban could be effectively refined if necessary on an ongoing basis.

Research Question and Objectives	The aim of this DUS is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows:
	• To characterize sites and physicians:
	  • Geographic location
	  • Profession or area of primary practice
	  • Patient volume
	• To characterize users of edoxaban
	  • According to demographic factors (e.g. age, gender, other);
	  • Patient comorbidity
	  • Patient subgroups for which there is missing information according to the RMP:
	  o Pregnant and/or breastfeeding women
	  o Paediatric patients
	  o Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk
	  o Patients with severe renal impairment (defined as having Creatinine Clearance [CrCl] < 30 ml/min or end-stage renal disease (CrCl < 15 ml/min or on dialysis)
	  o Patients with mechanical heart valves
	  • Patients being treated with dual antiplatelet therapy
	• To evaluate the pattern of use of edoxaban:
	  • Dose (including starting dose) and duration of treatment, including identification of long-term and chronic use, and dosing changes
	  • Use of concurrent/concomitant medications with special focus on medications potentially interacting with edoxaban or contraindicated especially those known to increase the risk of bleeding e.g., aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
	  • Detect the improbable event of use outside the labelled instructions, including use outside the indication[1]

1 According to SmPC, edoxaban is indicated in the prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive

	(particularly indications for which alternative anticoagulants are indicated) and use in contraindicated situations. • History of past use of other anticoagulants • To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization. The specific objectives are: • To evaluate whether the Educational Material reached the target population (physicians prescribing edoxaban) as part of physician packet provided prior to drug supply • To assess clinical knowledge: awareness of the target population and the level of knowledge achieved by the educational intervention
Study Design	This is a multinational, multicentre study involving the retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians will be 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 program. Being retrospective, this study involves no intervention, and will not impact the usual medical care or affect the treatment of patients. Thus, the study will reflect real-world medical practice without the potential for prescriber response bias which may occur in prospective studies. The inception cohort is defined as patients initiating edoxaban during a 12-month period following the launch of the product in each country. An Electronical Data Capture System (EDC) will be used to collect study data. Data collection will be initiated following a study-defined index date, approximately 12 months after product launch. All study prescribers within a country will be assigned the same index date and will not be contacted prior to the index date. Initiation of prescriber-specific activities for selection of patient records meeting study selection criteria will commence on or following the index date. Data on drug utilisation will be censored on the index date. This approach will ensure that study procedures do not influence prescribing practices.
Setting	The study aims to include approximately 1200 medical records of patients who were treated at least once with one or more dose(s) of edoxaban. Country selection will take into account prescription volumes, the number of prescribers per capita, and favorable regulatory and ethical environment to conduct observational studies. It is foreseen that at least the following countries will be included: Germany, Italy, Switzerland, Belgium, the United Kingdom, Spain and Portugal. The sponsor may include additional European countries based on the actual use of edoxaban in initially-

heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA). Edoxaban is also indicated in the treatment of venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent VTE in adults.

	selected countries and to ensure selection reflects geographic representation among European countries. Following the identification of the countries, an independent prescription data source will be used to identify a representative sample of the prescribers in each country. Based on these sources it is possible to retrieve general information on edoxaban number of prescribers per specialty and geographic region. Physicians participating in any interventional currently ongoing/planned study with edoxaban will not be eligible to participate in the DUS and the Educational Material Survey. **Countries and Sites:** At least 100 hospital- and office-based physicians (General Practitioners [GPs], internal medicine physicians and other specialists) in at least 7 Western European countries (Germany, Italy, Switzerland, Belgium, the United Kingdom, Spain and Portugal) are foreseen to participate in the study.
Inclusion/exclusion criteria	Inclusion criteria: All patients with at least one edoxaban prescription record in his/her medical record irrespective of their underlying health conditions or indication for edoxaban prescription and with a written informed consent form. Exclusion criteria: None
Variables	<u>Site/ Physicians' characteristics</u> To evaluate the diversity of sites the following information will be collected for each participating site using the site feasibility questionnaire: • Geographic location of physician site • Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists) • Patient volume (i.e., number of patients and estimated number of patients using edoxaban). <u>Edoxaban treated patient data</u> The following data will be collected from manual chart review: • Demographics and medical history: o Birth (year/month) or age o Race/ethnicity (where permitted) o Height o Body weight o Smoking status o Alcohol consumption o Diagnosis o Risk factors and treatment (pharmacological or non-pharmacological) history pertaining to edoxaban treatment o Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities

	○ Relevant familial medical history; ○ History of haemodialysis ○ History of past use of other anticoagulants ○ Pregnancy and lactation status at the time of prescription ○ Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban ○ Presence of mechanical heart valves ○ Pertinent lab tests upon availability including liver function test, CrCl test and/or Glomerular Filtration Rate (GFR) pertaining to possible hepatic or renal impairment. • Drug utilisation: ○ Edoxaban prescription: ▪ start and end date/ongoing treatment (including repeated prescriptions if any) ▪ daily dose (30 mg, 60mg, other) at the beginning of the treatment and afterwards ▪ reason for use ▪ reason of discontinuation (if applicable) ○ Concomitant medications (including if patient is using dual antiplatelet therapy). <u>Health Care Professional (HCP) Educational Material knowledge assessments</u> • Survey administration variables • Description of survey participants • Assessment of knowledge of the key messages of the educational program.
Data Sources	<u>DUS</u> This study is a retrospective chart review. The identified local site staff will review the medical charts of all patients that have been prescribed edoxaban, over the given time period and extract the desired data elements. The data will be entered pseudonymised into electronic Case Report Forms (eCRFs) via a secure web-based EDC system. In sites that do not have the capabilities to access the internet to enter data, a provision will be made to collect pseudonymised data recorded on paper CRFs and entered into the study database by the Sponsor or designee (e.g. Contract Research Organization, (CRO)) on behalf of the site staff. To assess the representativeness of the sampled patient population, a screening log of all patients prescribed with edoxaban will be maintained by the site staff, including patient's age and gender, and whether the patient's chart data was included in the DUS or not. For patient charts that

were not captured in the DUS, the reasons for non-inclusion will be documented on the screening log.

Educational Material Evaluation Survey

At the prescribers' primary contact (index date), the physicians will be requested to express their preferences for a means of direct-to-physician contact (email or telephone) in order to complete the survey.

The identity and contact details of the participants will only be used for scheduling and carrying out the survey. The survey will assess the physician's level of awareness and understanding of the content of the educational material/SmPC. All information collected during the course of the survey will be kept strictly confidential.

Study Size

The medical records of at least 100-200 patients will be studied per country (sample would be representative dependent on country-specific volumes of edoxaban prescriptions) for 600 to 1,200 treated patients in total across the 7 targeted European countries.

For characterization of users including potential off-label use, we present the level of precision in different scenarios of available number of users of edoxaban for different prevalence of diseases and conditions. In general, the 95% level of confidence is adequate for a prevalence as low as 1% and 1,200 users of edoxaban.

The sample size has been estimated based on the distance from the assumed proportion of patients with off-label use to the limits of the corresponding 95% confidence Interval (CI). Table 2 presents the precision in the estimate of the proportion of the off label use of edoxaban out of the labelled indication for tentative proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) and different sample sizes.

Table 2 - Precision of estimation for proportions of 0.02, 0.03. 0.04, 0.05 (2%3%, 4% 5%) of off label use and increasing sample size

Sample Size Scenario

	proportion = 0.02			proportion = 0.03			proportion = 0.04			proportion = 0.05		
sample size	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.030	0.020	0.080
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067
800	0.010	0.010	0.030	0.012	0.018	0.042	0.014	0.026	0.054	0.015	0.035	0.065
1000	0.009	0.011	0.029	0.011	0.019	0.041	0.012	0.028	0.052	0.014	0.036	0.064
1200	0.008	0.012	0.028	0.010	0.020	0.040	0.011	0.029	0.051	0.012	0.038	0.062

Note: CI: 2-sided 95% Confidence Interval (CI); ½ CI: distance from proportion to lower/upper limit of the two-sided 95% CI (equals half of the width of the CI); L95%: lower limit of the 95% CI; U95%: upper limit of the 95% CI.

Table 2 shows that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients shows additional (though

	small) effects on the width of the 95% CI. Therefore, the current aim of recruiting 1,200 patients will assure to receive reliable results. In addition, it is estimated that approximately 100 physicians will have to complete the survey to allow reasonable precision around estimates of the physician's awareness and understanding levels. No target thresholds for physicians reported awareness and understanding have been established in advance. However if it is assumed that 85% of physicians will demonstrate appropriate awareness and understanding of the survey. Given this, the lower bound of the 95% CI will be above 78% for a sample size of N=100.
Data Analysis	Details of the data analysis strategy will be fully described in a Statistical Analysis Plan (SAP). Briefly, descriptive statistics will be used to characterize prescriber and patient information. Summary statistics for continuous variables will include the number of observations, along with measures of location (means, medians) and variation (e.g., standard deviation, range). Categorical data will include counts and percentages. The 95% CIs will be reported where appropriate. Per country analyses will be performed where reasonable, as some subgroups might be too small to be looked at per country. The data may also be evaluated and presented for other meaningful subgroups of patients (e.g., by patients for which there is missing information). Among edoxaban users retrieved from the charts, the number and percentage of the following categories will be described: • All users (100%) • Patients categorized as inappropriate drug users as defined (but not restricted to) : (a) use in patients in which the product is contraindicated, (b) use in patients who are not under the indication label per SmPC (c) use involving a different dose (e.g. no dose reduction or dose reduction without reason), dosing regimen or route of administration or (d) use that demonstrates non-adherence to guidance in the label. • Body weight • Patients <18 years • Patients > 65 years • Pregnant women • Patients in any other disease groups, by specific disease type (renal, hepatic impairment) • Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs. The number of patients who have been prescribed edoxaban inappropriately will be identified and characterized separately per country. Concerning the survey data, it will be reported as descriptive statistics for all the variables (survey administration variables, description of

	survey population, and assessment of knowledge of the key messages of the educational program). Data will be presented overall, by country and by key characteristics (e.g. specialty of physician, geographic location, etc.). The safety results will be described according to physicians' knowledge and awareness of the material.
Quality Control	This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII (Rev 1)' EMA/813938/2011 Rev 1. Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.
Milestones	Final protocol including questionnaires: within 3 months after marketing authorization in the European Union. Start of data collection (in waves depending on the launch): expected to start at 12 months after product launch or protocol approval whichever occurs the last, (mainly driven by regulatory approvals and edoxaban market uptake to have sufficient numbers of patients treated). End of data collection: approximately 12 months after start of abstraction in the respective countries. Final study report: 6 months after entire database lock. Final Report Planned for Q2 2019 (latest 6 months after data base lock)

5. AMENDMENTS AND UPDATES

This is the revised protocol according to the questions and comments received after review of the PRAC (see Table 3). In case of essential changes of the observational plan the investigators will be informed as well as the respective competent authorities and Independent Ethics Committees as required by local laws or regulations.

Table 3 - Amendments and updates of the observational plan

No	Date	Section of study protocol	Amendment or update	Reason
1	24. Nov 2015	Full protocol	Amendment to V 1.0; new version 2.0	PRAC request
2	09 May 2016	Full protocol	Amendment to V 2.0; new version 3.0	PRAC request
3	05 August 2016	Full protocol	Amendment to V 3.0; new version 4.0	PRAC request
4	17 May 2017	Full protocol	Amendment to V 4.0; new version 5.0	Changes of - the participating countries list: France and the Netherlands excluded and Belgium, Spain and Portugal added; - the study milestones; - wording of section 11.2, Reporting of suspected ADRs by the Investigators
5	08 June 2017	Full protocol	Amendment to V 5.0; new version 6.0	Changes of - End of Data Collection per country: from “6 to 9 months” to “approximately 12 months”; - LPI milestone for all countries.

6. MILESTONES

The main milestones for the Drug Utilisation Study (DUS) will be:

Table 4 - Main study milestones

Start of data collection	Q3 2016
Interim report (planned)	Q3 2017
Planned end of data collection	Q4 2018
Final study report	Q2 2019 (latest 6 months after data base lock)

Recruitment will be performed in waves, as described in Table 5 (current planning dates – may be subject to change).

Table 5 - Milestones per country

Country	First Patient In (FPI)	Last Patient In (LPI)	Wave
Switzerland	Q3 2016	Q3 2017	I
Germany	Q3 2016	Q3 2017	I
United Kingdom	Q3 2016	Q3 2017	I
Belgium	Q3 2017	Q3 2018	II
Italy	Q3 2017	Q3 2018	II
Spain	Q3 2017	Q3 2018	II
Portugal	Q1 2018	Q4 2018	II

7. RATIONALE AND BACKGROUND

Edoxaban has been approved by the U.S. Food and Drug Administration FDA, the Swissmedic and by the European Medical Agency (EMA). In the EU it is approved for the following indications:

- Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischemic attack (TIA).
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.

The approval is based on the following pivotal studies:

The **ENGAGE AF-TIMI 48** study (N=21105; mean $CHADS_2$ score = 2.8) compared edoxaban 60 mg once daily (high-dose regimen) and edoxaban 30 mg once daily (low dose regimen) with dose-adjusted warfarin (International Normalised Ratio [INR] 2.0–3.0) and found that both edoxaban regimens were non-inferior to warfarin in the prevention of stroke and systemic embolism in patients with NVAF. Both edoxaban regimens also provided significant reductions in the risk of haemorrhagic stroke, cardiovascular mortality, major bleeding and intracranial bleeding.[2]

The **Hokusai-VTE** study (N=8292) in patients with symptomatic VTE had a flexible treatment duration of 3–12 months and found that following initial heparin, edoxaban 60 mg once daily was non-inferior to dose-adjusted warfarin (INR 2.0–3.0) for the prevention of recurrent VTE, and also had a significantly lower risk for the composite of major or non-major clinically relevant bleedings (primary safety outcome).[3.]

Those clinical development programs have been undertaken to support marketing authorisation submissions for edoxaban in those indications. However, as is the case with any medicinal product, real-life use of edoxaban may differ from or extend beyond the patient population that has been studied in the phase 3 program or is included under the approved indication. One of the concerns in real-world use of medicinal practices is the off-label use. Daiichi Sankyo (DS) addressed this concern in the Risk Management Plan (RMP) in order to anticipate necessary risk minimization activities. The potential off-label use of edoxaban in unapproved indications was considered low, because of the availability of approved, indicated and well-established treatment alternatives. However, as it is the case with all other new anticoagulants a residual risk for off-label use might be considered in conditions (for which edoxaban is not approved) that usually also require mid- or long-term anticoagulant treatment or in cases of poor compliance or contraindications of the patient.

Standard routine risk minimisation activities include the communication of the information in the Summary of Product Characteristics (SmPC). In order to further optimise the correct use of the medicinal product by the physician, Daiichi Sankyo Europe GmbH (DSE) is implementing additional risk minimisation activities, namely, prescriber guide as part of the educational programs to make prescribers fully aware of

the approved indications and eligible patients for edoxaban, the dosing recommendations and management of safety concerns. In addition, Patient Alert Cards will be distributed.

The patient alert card is included in every edoxaban package in the European Union (EU).

Furthermore, the DUS, described in this document aims to gain insight on how this new European medicinal product is going to be used in real practice in order to identify prescription patterns, the effectiveness of the educational programs and promptly detect any safety concern, so that pharmacovigilance planning and risk management for edoxaban could be effectively refined, if necessary, on an ongoing basis.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Primary Objectives

The aim of this DUS is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows:

To characterize sites and physicians:

- Geographic location of physician site
- Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists
- Patient volume (i.e., number of patients and estimated number of patients using edoxaban).

To characterize users of edoxaban according to:

- Demographic factors (e.g. age, gender, other)
- Patient comorbidity
- Patient subgroups for which there is missing information according to the RMP:
  - Pregnant and/or breastfeeding women
  - Paediatric patients
  - Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk
  - Patients with severe renal impairment (defined as having Creatinine Clearance [CrCl] < 30 ml/min) or end stage renal disease (CrCl < 15 ml/min or on dialysis)
  - Patients with mechanical heart valves
- Patients being treated with dual antiplatelet therapy

To evaluate the pattern of use of edoxaban:

- Dose (including starting dose) and duration of treatment, including identification of long-term and chronic use, and changes
- Use of concurrent/concomitant medications with special focus on medications potentially interacting with edoxaban or contraindicated especially those known to increase the risk of bleeding e.g., aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- Detect the improbable event of use outside the labelled instructions, including use outside the indication[1] (particularly indications for which alternative anticoagulants are indicated) and use in contraindicated situations.
- History of past use of other anticoagulants

To evaluate the effectiveness of the edoxaban Educational Material as a tool for risk minimization. The specific objectives are:

- To evaluate whether the Educational Material reached the target population (physicians prescribing edoxaban) as part of physician packet provided prior to drug supply
- To assess clinical knowledge: awareness of the target population and the level of knowledge achieved by the educational intervention

9. RESEARCH METHODS

9.1. Study Design

Multinational, multicentre study involving the retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians will be 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 program.

Being retrospective, this study involves no intervention, and will not impact the usual medical care or affect the treatment of patients. Thus, the study will reflect real-world medical practice without the potential for prescriber response bias which may occur in prospective studies. The inception cohort is defined as patients initiating edoxaban during a 12 month period following the launch of the product in each country.

The study design will allow the evaluation of the effectiveness of the risk minimisation activities targeting the minimisation of any potential off-label use as follows:

On the one hand, the surveys will assess physician' knowledge of the educational materials. But a survey methodology might not be the most appropriate approach for the evaluation of behavior, since surveys collect and analyse self-reported data from healthcare professionals and patients.

Therefore, real-world prescribers' behavior will be assessed by the collection of data from the patients' medical records.

9.2. Setting

The study aims to include approximately 1,200 medical records of consecutive patients who were treated at least once with one or more dose(s) of edoxaban.

9.2.1. Participating Sites

About 100 hospital- and office-based physicians (General Practitioners [GPs], internal medicine physicians and other specialists) in at least 7 Western European countries (Germany, Italy, Switzerland, the United Kingdom, Belgium, Spain and Portugal) are foreseen to participate in the study.

Country selection will take into account prescription volumes, the number of prescribers per capita, and favorable regulatory and ethical environment to conduct observational studies as well as the launch sequence of edoxaban in the different European countries. The sponsor may include additional European country(ies) based upon the actual use of edoxaban in initially-selected countries and to ensure selection reflects geographic representation among European countries.

Following the identification of the countries, an independent prescription data source (IMS Lifelink^{TM}) will be used to identify a representative sample of the prescribers in each country. Based on these sources it is possible to retrieve general information on edoxaban number of prescribers per specialty and geographic region.

At least 100 prescribers of edoxaban will be recruited in 7 European countries following each country-specific product launch and the distribution of the health care professional (HCP) Educational Material. These could include GPs, cardiologists, internal medicine specialists (and other specialists) from a variety of settings (e.g., office-based vs. hospital-based, urban vs. rural).

Physicians participating in interventional programs for edoxaban will not be eligible to participate in the study. By applying this approach both representativeness and comprehensiveness of the sample in terms of types of prescribers are ensured.

In the selected countries, available national prescription databases will be screened to identify geographic and edoxaban prescriber characteristics. Data from IMS LifeLink™ database for dispensing data in the community care setting, or another appropriate data source, will identify prescribers of edoxaban. This data source will be complementary to the full study and will be obtained prospectively on a quarterly basis, during the study period. On a national level for the targeted countries, the distribution of regional location of the sites as well as the distribution of the prescribers' specialty will be provided. Therefore, IMS LifeLink™ will be used to refine the a priori sampling strategy for the full study (using regional and specialty distribution of prescribers), and a posteriori to assess the representativeness of prescribers and patients included in the full study. This approach will contribute significantly to the enrolment of a more balanced population of edoxaban and alternative drugs prescribers at both the country and study level to cover broad indications. Potential sites for this DUS must meet the following criteria:

- Willing to provide a list of patients receiving edoxaban
- To allow/have access to patients' source data that are treated with edoxaban
- To be able to complete the study in the EDC system (only in exceptional cases paper CRFs are possible if no access to internet is provided)
- To be able to conduct the study adequately with respect to staff and time capacities.

9.2.2. Source Population

The current study aims to draw conclusions on the pattern of use of edoxaban. Therefore it aims to generalise its conclusions to all users that have been prescribed edoxaban since its launch in Europe.

Sites will be required to maintain a patient enrolment log of eligible patients at their treatment sites. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. The overall number of patients and sites may be adjusted during the study to meet enrolment goals, if needed. To the extent possible, consecutive patients meeting inclusion/exclusion criteria will be enrolled.

9.2.2.1. Inclusion criteria

Patients can be enrolled when they had at least one edoxaban prescription record in his/her medical record irrespective of the underlying health condition and with a written informed consent form.

9.2.2.2. Exclusion criteria

No exclusion criteria are defined.

9.2.3. Patient Groups

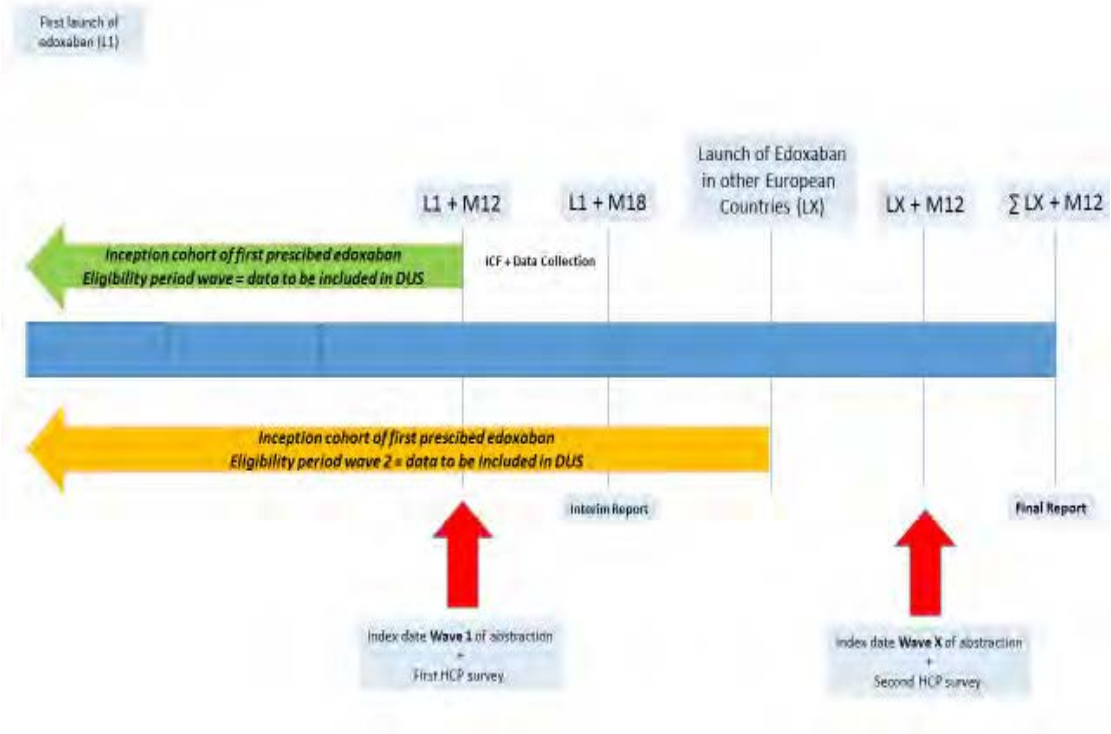
Not applicable

9.2.4. Schedule

The inception cohort is defined as patients initiating edoxaban during a 12-month period following the launch of the product in each country.

The eCRF will be used to collect study data. Data collection will be initiated following a study-defined index date, approximately 12 months after product launch (see study milestones; section 6). All study prescribers within a country will be assigned the same index date and will not be contacted prior to the index date. Initiation of prescriber-specific activities for selection of patient records meeting study selection criteria will commence on or following the index date. Data on drug utilisation will be censored on the index date. This approach will ensure that study procedures do not influence prescribing practices.

Figure 1 - Study flow chart per patient



Notes: DUS: Drug Utilisation Study. HCP: Health Care Professionals. ICF: Informed Consent Form. L1: Launch date in the first European country participating in the study; LX: Launch date in other European countries participating in the study. ΣLX: All medicinal products launched. M12: 12 months later. Final report planned latest 6 months after data base lock.
The launch of edoxaban in other European countries (LX) may also occur before the end of data collection for the first country.

9.2.5. Permanent discontinuation of Study Drug

Not applicable

9.2.6. Withdrawal of Consent from Registry Participation

Not applicable as data will be retrospectively retrieved from patients source data.

9.3. Variables

The following information will be entered in the CRF

I. **Site/ Physicians' characteristics**

To evaluate the diversity of sites the following information will be collected for each participating site from the site feasibility questionnaire:

- Geographic location of physician site;
- Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists;
- Patient volume (i.e., number of patients and estimated number of patients using edoxaban).

II. **Edoxaban treated patient data**

1. **Demographics and medical history:**
   - Birth (year/month) or age
   - Race/ethnicity (where permitted)
   - Height
   - Body weight
   - Smoking status
   - Alcohol consumption
   - Diagnosis
   - Risk factors and treatment (pharmacological or non-pharmacological) history pertaining to edoxaban treatment
   - Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities
   - History of haemodialysis

- Relevant familial medical history
- History of past use of other anticoagulants
- Pregnancy and lactation status at the time of prescription
- Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban
- Presence of mechanical heart valves
- Pertinent lab tests upon availability including liver function test, CrCl and/or Glomerular Filtration Rate (GFR) pertaining to possible hepatic or renal impairment.

2. Drug utilisation:

- Edoxaban prescription
  - start and end date/ongoing treatment (including repeated prescriptions if any)
  - daily dose (30 mg, 60mg, other) at the beginning of the treatment and afterwards
  - reason for use
  - reason of discontinuation (if applicable)
- Concomitant medications (including if patient is using dual antiplatelet therapy)

III. **HCP Educational Material knowledge assessments**

1. Survey administration variables:

- Number of physicians in sample, in total and by key characteristic;
- Number of physicians attempted to contact
- Number of physicians effectively contacted
- Number of contacted physicians who agreed to participate
- Of those agreed to participate, number who completed survey.

2. Description of survey participants

- Medical specialty
- Country
- Setting (type, geography)
- Experience with edoxaban (yes/no and if yes number of months)
- Receipt of educational material (yes/no) and time elapsed since its return.

3. **Assessment of knowledge of the key messages of the educational program:**
    - Frequency and distribution of response to each survey question
    - Percentage of respondents indicating correct and incorrect responses to each question
    - The success/failure rate of the survey (proportion of correct and incorrect answers) overall and by each section (group of related items)
    - Assessment of HCPs' opinion/satisfaction on the utility of educational material.

9.4. Data Sources

DUS

This study is a retrospective chart review. The participating site staff will review the medical charts of the specified number of patients that have been prescribed edoxaban, over the given time period and extract the desired data elements. The data will be entered pseudonymised into electronic Case Report Forms (eCRFs) by the prescribers via a secure web-based electronic data capture (EDC) system. In sites that do not have the capabilities to access the internet to enter data, a provision will be made to collect pseudonymised data recorded on paper CRFs and entered into the study database by the the Sponsor or designee (e.g., Contract Research Organization, CRO) on behalf of the site staff. Data quality will be enhanced through a range of data quality checks that automatically detect out-of-range or anomalous data. These checks will be programmed within the EDC system and system queries will be automatically raised and followed-up by the sponsor/CRO. The data will also be reviewed on an ongoing basis by the sponsor/CRO and manual queries raised as necessary. Further details on validity checks can be found in section 9.6 (Data Management).

Some limitations with regard to data completeness may occur in this study, mainly related to the type and completeness of the information captured in the patients' medical records. Measures to ensure the completion of the eCRF in a systematic, professional, and unbiased manner include:

- eCRF completion guidelines will provide consistent instructions on completion of the eCRF.
- All individuals performing data abstraction from medical records will be trained on appropriate data abstraction techniques in order to minimize possible discrepancies between interpretation of the information recorded by the prescriber in the medical records and the individual performing the review and abstraction of the data.
- Missing data will be followed up during remote monitoring contacts.

To assess the representativeness of the sampled patient population, a screening log of all patients prescribed with edoxaban will be maintained by the site staff, including patient's

age and gender, and whether the patient's chart data was included in the DUS or not. For patient charts that were not captured in the DUS, the reasons for non-inclusion will be documented on the screening log.

Educational Material Evaluation Survey

The survey will be administered either by phone or on line through a secure unique web link concomitantly at the time of the site initiation visit, thus minimizing the impact of any previous reading of the Educational Material by the physician. Six months later, the same Survey will be administered de novo.

The afore-described strategy, together with a comparative analysis of respondents and non-respondents' characteristics, is expected to minimize and detect any response bias or trend among the survey population.

The Educational Material will be distributed to all physicians prior to edoxaban availability and irrespectively from the participation in the DUS. However, investigators participating in the DUS may take part in the survey to assess the physicians' level of awareness and understanding of the content of the educational material/SmPC, including:

- Indications
- Dosing recommendations and dose reduction
- Populations at higher risk of bleeding
- Information on switching patients to or from edoxaban
- Perioperative management
- Temporary discontinuation
- Overdose
- Bleeding complications
- Coagulation testing

Physicians will not be individually assessed. Results will be reported in aggregate form only and not linked to any personal identifier. All information collected during the course of the survey will be kept strictly confidential.

9.5. Study Size

The medical records of approximately 200 patients will be studied per country (sample would be representative dependent on country-specific volumes of edoxaban prescriptions) to approximately 1,200 treated patients in total across the 6 targeted European countries.

For characterization of users including potential off-label use, we present the level of precision in different scenarios of available number of users of edoxaban for different prevalence of diseases/conditions. In general, the 95% level of confidence is adequate for a prevalence as low as 1% and 1,200 users of edoxaban.

The sample size has been estimated based on the precision of a percentage, that is, the width of the 95% confidence Interval (CI). Table 2 (see summary page 17) presents the precision in the estimate of the proportion of use of edoxaban out of the labelled indication for tentative proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) and different sample sizes.

Table 6 - Precision of estimation for proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) of off-label use and increasing sample size

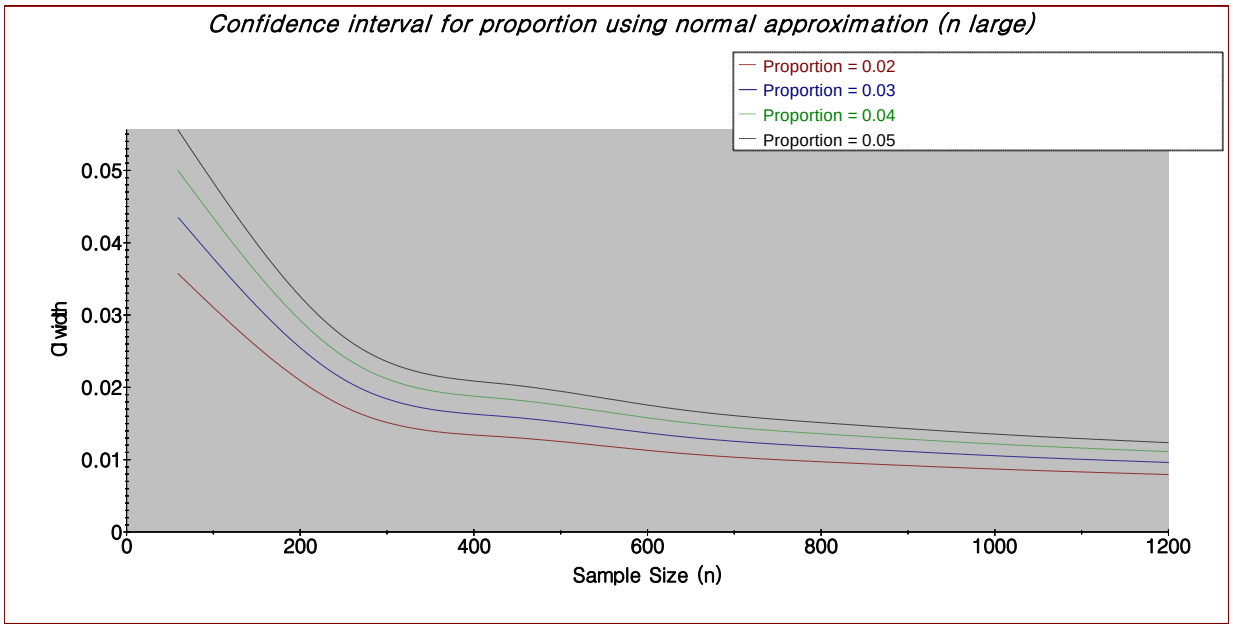
	Proportion											
	0.02			0.03			0.04			0.05		
Sample Size	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.030	0.020	0.080
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067
800	0.010	0.010	0.030	0.012	0.018	0.042	0.014	0.026	0.054	0.015	0.035	0.065
1000	0.009	0.011	0.029	0.011	0.019	0.041	0.012	0.028	0.052	0.014	0.036	0.064
1200	0.008	0.012	0.028	0.010	0.020	0.040	0.011	0.029	0.051	0.012	0.038	0.062

Note: CI: 95% of Confidence Interval (CI); ½ CI: distance from proportion to lower/upper limit of the two-sided 95% CI (equals half of the width of the CI); L95%; L95%: lower limit of the 95% CI; U95%: upper limit of the 95% CI.

Table 2 shows that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients shows additional (though small) effects on the width of the 95% CI. Therefore, the current aim of recruiting 1,200 patients will assure to receive reliable results.

A sample size of 600 patients for instance will allow the detection of a rate of 5% of off-label with a precision of 1.7%, that is, the estimated proportion will be comprised between 3.3% and 6.7%. A sample size of 1,200 patients will allow for an even higher precision, as a rate of 5% of off-label is detected with a precision of 1.2%, that is, the estimated proportion will be comprised between 3.8% and 6.2%.

Figure 2 - Confidence Interval (CI) for half of CI width



In addition, it is estimated that approximately 100 physicians will have to complete the survey to allow reasonable precision around estimates of the physician's awareness and understanding levels.

In order to achieve robust results from the various statistical validation methods, it is recommended to have at least 10 physicians per questionnaire item/observation. This rule has been adopted as the standard for psychometric (fit for purpose) validation with its origin within the classical test theory of principal component analysis.[4]

No target thresholds for physicians reported awareness and understanding have been established in advance. However if it is assumed that 85% of physicians will demonstrate appropriate awareness and understanding of the survey. Given this, the lower bound of the 95% CI will be above 78% for a sample size of N=100.[5]

9.6. Data Management (DM)

A data management plan (DMP) will be created that will describe all functions, processes, and specifications for data collection, cleaning and validation for the DUS.

High data quality standards will be maintained and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

9.6.1. Data Entry/Electronic Data Capture

Mixed data capture will apply: The pseudonymized data will be entered into electronic Case Report Forms (eCRFs) by the site staff via a secure web-based electronic data capture (EDC) system. In sites that do not have the capabilities to access the internet to enter data, a provision will be made to collect pseudonymised data recorded on paper

CRFs. Sites will be instructed to maintain completed paper CRFs in a secure environment prior to dispatch to the CRO.

The EDC system will be a secure web-based system using specific encryption mechanisms for exchanging data between the web browser of the user and the data server. All users of the EDC system (Investigators and site personnel as well as sponsor/CRO staff) will be able to access their account with a unique personalized username and password. Users will be assigned certain standardized user roles that will allow/restrict them to perform specific actions within the EDC application. An audit trail will record any actions within the eCRF such as session times, user who accessed the data, initial entry or changes made to the data (including reason for change or correction).

In case of eCRF data capture the sites will directly enter the data from their patients' medical records into the standardized English eCRFs. Each participating site will have access to its enrolled patient data only. All sites will be fully trained on using the online data capture system, and on the eCRF completion guidelines and other help files. All eCRFs should be completed by designated, trained personnel as appropriate. The eCRF is to be reviewed, electronically signed, and dated by the investigator.

The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous.

Edit checks within the eCRF may be checks tied to a certain field or edit checks across multiple fields.

Field checks may include the following:

- Checks on non-conformance (e.g., a non-existing date or a numeric field including text)
- Range checks on numeric fields (e.g., a field that has to be greater than x but lower than y)
- Checks on missing values (e.g., a predetermined required field)
- Checks on future dates

Edit checks across multiple fields may be any check firing on the condition of another field (or multiple fields) containing a certain value (or a range of values). These may be e.g. a relationship between a parent record and a sub-record or a comparison of different dates.

All edit checks will be listed in a Data Management document separate from the Observational Plan with a description of the check firing logic (including pseudo-code as necessary and any ranges defined, if applicable), the type of check and the query message text with reference to the applicable forms and items.

To ensure a high quality of data the Sponsor will take data snapshots at pre-defined time points and review the data for any potential data errors or discrepancies.

Ad hoc queries will be generated within the EDC system and followed up for resolution.

Paper CRFs completed by the sites will be collected by CRO staff and entered by trained CRO personnel into the EDC system. Queries will be posted on paper forms and sent to the sites for clarification.

The data from the project specific database will be exported into SAS data sets as per Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) definition for further validation and analysis.

9.6.2. Source Documents

The source documents are contained in the patient's medical record and data collected on the eCRFs must be traceable to these source documents. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the Sponsor before any destruction of medical records of study participants.

9.7. Data Analysis

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

Assessing prescription patterns

Details of the data analysis strategy will be fully described in a Statistical Analysis Plan (SAP). Briefly, descriptive statistics will be used to characterize prescriber and patient information. Summary statistics for continuous variables will include the number of observations, along with measures of location (means, medians) and variation (e.g., standard deviation, range). Categorical data will include counts and percentages. The 95% CIs will be reported where appropriate. Per country analyses will be performed where reasonable, as some subgroups might be too small to be looked at per country. The data may also be evaluated and presented for other meaningful subgroups of patients (e.g., by patients for which there is missing information).

Among edoxaban users retrieved from the charts, the number and percentage of the following categories will be described:

- All users (100%)
- Patients categorized as inappropriate drug users as defined (but not restricted to) :

  (a) use in patients in which the product is contraindicated,

  (b) use in patients who are not under the indication label per SmPC

  (c) use involving a different dose (e.g. no dose reduction or dose reduction without reason), dosing regimen or route of administration or

  (d) use that demonstrates non-adherence to guidance in the label.
- Body weight
- Patients <18 years
- Patients > 65 years

- Pregnant women
- Patients in any other disease groups, by specific disease type (renal, hepatic impairment)
- Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs.

The number of patients who have been prescribed edoxaban in a way that differs from what is described in the SmPC will be enrolled and characterized overall and by country.

The distribution of time on edoxaban for the categories outlined above will be calculated. Information on dose and discontinuations will be examined. Number of prescriptions of edoxaban per patient per year or number of prescription fills and refills since first prescription to index date will be characterised.

The history of use of other anticoagulants will be described for all edoxaban users and by patient's categories defined above.

Assessing clinical knowledge

The data will be reported as descriptive statistics for the variables already presented in section 9.3 (survey administration variables, description of survey population, and assessment of knowledge of the key messages of the educational program). Data will be presented overall, by country and by key characteristics (e.g. specialty of physician, geographic location, etc.).

Physicians who do not respond to the survey will be categorized into non-responders. Moreover, the responders and non-responders characteristics will be compared.

A comparison of responders and overall target population characteristics will also be performed.

9.8. Quality Control

This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on Good Pharmacovigilance Practices (GVP) – Module VIII (Rev 1)' EMA/813938/2011 Rev 1. Related quality control mechanisms (e.g. data plausibility checks, monitoring of data) will be performed accordingly.

The physician will comply with the confidentiality policy as described in the site contract. The physician will comply with the observational plan and the requirements described in the contract. The physician is ultimately responsible for the conduct of all aspects of the study at the site and verifies by signature the integrity of all data transmitted to the sponsor.

During the site initiation visit, the monitor will provide training on the conduct of the study to the investigator, co-investigator(s), and all site staff involved in the study. In order to ensure the integrity of the data, sites will be monitored by a qualified monitor. A risk based monitoring approach will be conducted during the study to examine compliance with the protocol and adherence to the data collection procedures, to assess

the accuracy and completeness of submitted clinical data, and to verify that records and documents are being properly maintained for the duration of the study. This will include regular remote data monitoring and on site monitoring will be performed in 20% of the sites. During on-site monitoring, the monitor will verify 100% of informed consent documentation and perform source data verification against the patient's medical records in randomly selected patients (3 per site).

Data quality checks will be performed on an ongoing regular basis. Queries will be raised by the responsible CRO and shall be answered by the site in due course. The purpose is to ensure that the rights of the patients are protected, that the reported data are accurate and complete, and that the conduct of the study is in compliance with the observational plan and applicable regulatory requirements.

The monitor will close out each site after the last patient's final follow-up assessment is completed, all data have been entered and all outstanding monitoring issues have been resolved or addressed. All monitoring procedures will be described in a Clinical Operations Plan (COP). Monitor contact details for each participating site will be maintained in the Investigator Site File.

Representatives of the Sponsor's quality assurance unit/monitoring team and competent regulatory authorities must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs and the patients' original medical records. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.9. Limitations of the Research Methods

As this study aims at collecting real-world evidence, some limitations common to non-interventional studies apply. In addition to this, the following aspects need to be considered:

Although sites will be selected to promote representativeness for the respective country or region as much as possible, sites also need to have sufficient interest and capacities to participate in the registry.

Although eligible patients should be consecutively enrolled at a site, it needs to be considered, that patients need to give their informed consent for their medical records to be extracted. This might hamper consecutive enrolment at a site.

To allow for demonstrating representativeness of edoxaban patients included into the trial, an enrolment log will have to be filled by the sites, where all patients treated with edoxaban at the site at discretion of the physician need to be listed and the reason to participate or not to participate needs to be documented.

No explicit non-eligibility criteria are defined to avoid selection of patients and thus violation of the "real-life" principle.

However, as data collected in the study is part of routine medical practice and not collected for the purpose of the study, the extent of available information and the classification/description of medical data and procedures could vary.

Concerning the evaluation of effectiveness of the educational program, it could be noted that participation in a survey may not be representative of the target users given that participation is more likely amongst engaged healthcare professionals and/or more motivated or educated individuals.

10. PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the Guidelines for Good Pharmacovigilance Practices (GVPs) and Good Pharmacoepidemiology Practices (GPPs) issued by the International Society for Pharmacoepidemiology (ISPE), the Declaration of Helsinki and its amendments, and any applicable national guidelines.

10.1. Review by Ethics Committees/Competent Authorities (CAs)

Notification to or approval by IECs and CAs or other organizations will be performed as required by national regulations in the participating countries before commencement of enrolment at a study site.

10.2. Insurance and Liability

All treatments of patients included in this DUS are local standard of care and occur as part of the daily routine practice. The registry is non-interventional and does not foresee any change from treatment nor additional examinations apart from the standard of care. Insurance coverage will only be provided with regards to the product liability. A specific patient's insurance for DUS is not necessary (if not in contradiction with specific legal requirements in the country of conduct).

10.3. Patient Information, Informed Consent

Written Informed Consent will be obtained from all patients in informed consent forms (ICFs) in order to agree his/her patient source data are being transferred into an eCRF and are evaluated and analysed for scientific purposes.

10.4. Data Protection

The patients' privacy will be kept according to the requirements of Directive 95/46 EC and national legislation for data protection. Data will be collected in a pseudonymous way. A patient identification number (ID) assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting any study-related data.

Only authorised personnel as hospital/site staff, representatives of the sponsor and CRO, and CAs should have access to personalised patient data e.g. in original source documents (medical records). The patient will agree to this by signing a respective statement on the ICF.

10.5. Numbering and Identification of Patients

A patient ID will be assigned to each patient when reporting data in the eCRF or on the paper CRF. The patient ID will consist of the country code, followed by a three digit site number and the consecutive patient number (e.g. UK-001-001). Medical record number or other local reference identifiers are not collected.

At each site a patient ID list will be kept linking the ID to the patient's identity.

10.6. Assessments

The investigators or the data retriever will be instructed regarding the correct documentation of the required information to be captured for each patient in the eCRF. These data are available as part of the routine treatment.

11. MANAGEMENT AND REPORTING OF ADVERSE DRUG REACTIONS (ADR)

All adverse drug reactions that are judged by the investigator as related to edoxaban need to be reported according to the national requirements and local laws. The documentation and reporting follows the Guideline on Good Pharmacovigilance Practices (GVP Module VI).

11.1. Definitions

Adverse Drug Reaction (ADR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

Serious Adverse Drug Reaction

Serious adverse reaction means an adverse reaction which results in:

- Death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalisation or development of dependency or abuse.

11.2. Reporting of suspected ADRs by the Investigator

All Edoxaban related adverse drug reactions need to be reported by the site to the pharmacovigilance department of the sponsor as spontaneous ADR reports. The study specific ADR reporting form has to be sent to the respective Daiichi Sankyo affiliate in the country where the site is located and will then be forwarded to the sponsor (Daiichi Sankyo Europe GmbH, Clinical Safety & Pharmacovigilance Department, Zielstattstrasse 48, 81379 Munich, Germany). The sponsor will process all the ADR details in line with the requirements for spontaneous ADR reporting and in accordance with the Guideline on Good Pharmacovigilance Practices (GVP).

In addition, the investigator has to confirm in the eCRF whether or not an ADR has been reported.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1. Progress Reports

As already mentioned in section 11 Daiichi Sankyo will summarise relevant safety information or information with potential impact in the benefit-risk assessment (if any) in Periodic Safety Update Reports.

12.2. Annual/Interim Analyses and Reporting

The interim report will be prepared after the completion of data collection in the first wave countries. The interim report will be provided in the third Quarter 2017.

13. DOCUMENTATION AND ARCHIVING

The Sponsor is responsible for archiving study specific documentation (Observational plan, potential amendments, Final Report and Database) for at least ten years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required.

The investigator is responsible for archiving the patient ID list, all signed ICFs and his/her contract for at least ten years and in accordance with local legislation.

Physicians are obliged to keep patient files according to national requirements.

14. LEGAL REQUIREMENTS

This DUS fulfils the requirements of the Directive 2001/83 EC, Module VIII of GVP, Directive 95/46 EC, the Declaration of Helsinki and will be conducted in accordance with the respective Standard Operating Procedures (SOP) of DSE.

14.1. Reimbursement

Compensation according to local regulations and to the time spent to inform patients and to document patient data will be paid two times a year if not specified otherwise in the site contract.

Investigator fees per patient:
will account for the time spent related to the study and is estimated to 7.5hours per patient. The fees are split to different study personals (investigators, study coordinators, study nurses) involved in the DUS. The number of hours was calculated taking into account:

- Repeated time by patient (information and consent discussion, extraction of patients data, data completed within the secured eCRF, edit checks and quality of data and regular monitoring
- Set up of the study (site initiation Visits, eCRF training, initial screening of potential eligible patients, Lixiana ® Survey questionnaires (2)).

The investigator fees will be calculated taking the Fair Market Value benchmarking priced within the industry in considerations.

14.2. Registration

In accordance with the 2010 EU pharmacovigilance legislation, information about this DUS will be entered into the publically available European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) E-Register of Studies. The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

15. FINAL REPORT

A final report will be presented by end of the second Quarter 2019, latest 6 months after data base lock. . The final report will encompass all planned analyses, including a description of the complete study population (in all countries), as described above and in the SAP.

16. PUBLICATION

In order to protect confidential information and/or the interests of DSE, all publications (manuscripts and congress presentations) or announcements originating from this research are governed the Sponsor.

17. PREMATURE TERMINATION OF THE NIS/REGISTRY

The physician may withdraw his/her participation in this registry at any time. In the case of a premature termination of the entire DUS by the sponsor, the project leader has to inform all participating sites, IECs, and CAs.

18. REFERENCES

[1] SmPCs Edoxaban

[2] Edoxaban versus Warfarin in Patients with Atrial Fibrillation
Giugliano RP, Ruff TC, Braunwald E, et.al. Edoxaban versus Warfarin in patients with Atrial Fibrillation: N Engl J Med 2013; 369:2093-2104

[3] Büller HR, Grosso MA, Mercuri M, et.al ; Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism: N Engl J Med 2013; 369:1406-15

[4] Hatcher, L (1994) A step –by Step Approach to Using the SAS System for Factor Analysis and structural Equation Modeling. Cary; NC: SAS Institute, INC

[5] Center for Drug Evaluation and Research. Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. United States Food and Drug Administration: Department of Health and Human Services. Docket No: FDA–2012–N–0408, 2012.

APPENDIX 1. ENCEPP CHECKLIST

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study

Study reference number:
DSE-EDO-01-14-EU

Section 1:	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	22
1.1.2 End of data collection[3]	☒	☐	☐	22
1.1.3 Study progress report(s)	☐	☒	☐	
1.1.4 Interim progress report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	22

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Page Number(s)**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	25
2.1.2 The objective(s) of the study?	☒	☐	☐	25-26
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	28
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Not applicable.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	27-28

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Page Number(s)**
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☐	☐	☒	
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	

Comments:

Descriptive analysis will be performed.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	28
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	29
4.2.2 Age and sex?	☐	☐	☒	
4.2.3 Country of origin?	☒	☐	☐	30
4.2.4 Disease/indication?	☒	☐	☐	30
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	33

Comments:

Not Applicable.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	31
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	31

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

Eligible patients are those prescribed edoxaban since its launch.

Section 6: Endpoint definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
6.1 Does the protocol describe how the endpoints are defined and measured?	☐	☐	☒	
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☐	☒	

Comments:

Not applicable.

Section 7: Confounders and effect modifiers	**Yes**	**No**	**N/A**	**Page Number(s)**
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☐	☐	☒	
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Not applicable.

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	30-32

Section 8: Data sources	**Yes**	**No**	**N/A**	**Page Number(s)**
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☐	☐	☒	
8.1.3 Covariates?	☒	☐	☐	33-36
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☐	☒	☐	
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

It is not know yet what information will effectively be available on the medical records.

Section 9: Study size and power	**Yes**	**No**	**N/A**	**Page Number(s)**
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	33-36

Comments:

Not applicable.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Page Number(s)**
10.2 Is the choice of statistical techniques described?	☒	☐	☐	33-36
10.3 Are descriptive analyses included?	☒	☐	☐	33-36
10.4 Are stratified analyses included?	☒	☐	☐	33-36
10.5 Does the plan describe methods for adjusting for confounding?	☐	☒	☐	
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

The Analysis Plan will be further developed in a specific Statistical Analysis Plan.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Page Number(s)**
11.1 Is information provided on the management of missing data?	☒	☐	☐	33-36
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.3 Are methods of quality assurance described?	☒	☐	☐	38-39
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	39
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	38

Comments:

Not Applicable.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	39
12.1.2 Information biases?(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	39
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☒	☐	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Page Number(s)**
12.3 Does the protocol address other limitations?	☒	☐	☐	38

Comments:

Not Applicable.

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Page Number(s)**
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	41
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	41

Comments:

Not Applicable.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Page Number(s)**
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	12

Comments:

Not Applicable.

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Page Number(s)**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	45
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	49

Comments:

Not Applicable.

Name of the main author of the protocol: _____

Date: 18/05/2016

Signature: _____  _____

APPENDIX 2. LIXIANA® - SURVEY QUESTIONNAIRE

Thank you for participating in this voluntary survey to monitor the use of edoxaban in Europe. Please answer each question/statement as honestly as possible. You will not be individually assessed as results will be reported in aggregate form only and not linked to any personal identifier. All information collected during the course of the survey will be kept strictly confidential.

Part I – Edoxaban utilisation

1. Concerning the indications for which Lixiana is approved in the European Union, please indicate if the following sentences are true (T) or false (F):
    a. Lixiana is indicated in the prevention of stroke in adult patients with nonvavular atrial fibrillation with or without risks factors ___
    b. Lixiana is indicated in the prevention of systemic embolism in adult patients with nonvalvular atrial fibrillation with one or more risk factors ___
    c. Lixiana is indicated in the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) in adults ___
    d. Lixiana is not indicated in the prevention of recurrent DVT and PE in adults ___
    e. Lixiana is indicated in the prevention of VTE in subjects undergoing orthopaedic surgery___
    f. Lixiana is indicated in the prevention of atherothrombotic events after acute coronary syndrome

2. Concerning the recommended dosing of Lixiana, please indicate if the following sentences are True (T) or false (F):
    a. In patients with mild to moderate hepatic impairment, the recommended daily dose is of 30mg___
    b. In patients with normal renal and hepatic function, the recommended daily dose is of 60mg___
    c. In patients with moderate to severe renal impairment as defined by a creatinine clearance between 15 and 50 mL/min, the recommended daily dose is of 30mg___
    d. Lixiana has to be taken outside of meals___
    e. The duration of treatment with Lixiana is well defined and independent of transient or permanent risk factors___
    f. Co-administration with cyclosporine does not require any adjustment in the dose of Lixiana___

3. Lixiana is contraindicated or not recommended in the following special patient populations (please select all that apply):

    a. Severe hepatic impairment
    b. Elevated liver enzymes ALT/AST 2x ULN
    c. Hepatic disease associated with coagulopathy and clinically relevant bleeding
    d. In co-administration with low dose ASA (≤ 100mg/day)
    e. Uncontrolled severe hypertension
    f. Patients with a body weight ≤ 60 Kg

4. When initiating treatment with Lixiana, an initial course of heparin for at least 5 days prior to treatment with Lixiana must be observed (please select the correct answer):

    a. In the treatment of patients with DVT and PE
    b. In the prevention of stroke and systemic embolism in patients with NVAF
    c. In both the treatment of DVT and PE patients, and prevention of stroke and systemic embolism in patients with NVAF

5. In the occurrence of a missed dose, the patient should be instructed to take it immediately even if it means to double the prescribed dose on the same day. Please indicate if the sentence is:

    a. True
    b. False
    c. I don’t know

6. When switching patients to Lixiana from non-Vitamin K antagonist oral anticoagulants, the non-VKA must be discontinued and Lixiana initiated at the time of the non-VKA next dose. Please indicate if the sentence is:

    a. True
    b. False
    c. I don’t know

7. When switching patients to Lixiana from Vitamin K antagonist anticoagulants, the INR must be ≤2.5 after discontinuing the VKA and before initiating Lixiana. Please indicate if the sentence is:

    a. True
    b. False
    c. I don’t know

8. When switching patients from Lixiana to warfarin, the initial dose of Lixiana remains the same during concomitant use. Please indicate if the sentence is:

    a. True
    b. False
    c. I don't know

9. When switching patients from Lixiana to warfarin, the INR should be measured 3 times (please selected the correct answer):

    a. Just after taking the daily dose of Lixiana
    b. Just prior to taking the daily dose of Lixiana
    c. One time just before the daily dose of Lixiana, a second time 1h after the daily dose of Lixiana and a third time 2 hours after the daily dose of Lixiana

10. When switching patients to Lixiana from parenteral anticoagulant therapy, or from parenteral anticoagulant therapy to Lixiana, the initial therapy must be always discontinued before initiating the second. Please indicate if the sentence is:

    a. True
    b. False
    c. I don't know

11. Lixiana must be initiated immediately after discontinuing the continuously administered parenteral anticoagulant therapy. Please indicate if the sentence is:

    a. True
    b. False
    c. I don't know

12. Concerning the perioperative management of patients under treatment with Lixiana (please select the correct answer):

    a. Lixiana does not need to be stopped before a surgical intervention or other invasive procedure
    b. Lixiana should be stopped at least 12 hours before a surgical intervention or other invasive procedure
    c. Lixiana should be stopped at least 24 hours before a surgical intervention or other invasive procedure
    d. I don't know

13. In case of overdose with Lixiana (please select the correct answer):

    a. The patient must be given an antidote during the first 2 hours

b. There is no antidote available, early administration of activated charcoal may be considered to reduce absorption
c. Haemodialysis must be considered
d. I don't know

14. In the management of bleeding complications treatment with Lixiana must be delayed or discontinued

a. True
b. False
c. I don't know

15. When taking Lixiana, routine coagulation tests include: INR, PT and aPTT. Please indicate if the sentence is:

a. True
b. False
c. I don't know

Part II – General questions

16. Are you aware of the Prescriber's Guide for Lixiana?

- Yes
- No

17. Have you received the Prescriber's Guide for Lixiana?

- Yes
- No

18. You received the Prescriber's Guide:

- Before prescribing Lixiana for the first time
- After prescribing Lixiana for the first time

19. Have you read the Prescriber's Guide?

- Yes, completely
- Yes, partially
- No

If not:

20. You have not read the Prescriber's Guide, please select the most relevant reason that applies.

    - You prefer other sources of information, such as the Summary of Product Information
    - The Guide was too time consuming
    - It is not the first time you prescribed an anticoagulant factor Xa inhibitor, so you did not think the Guide would add to your knowledge
    - Other (please specify)_____

If yes:

21. How often have you consulted the Prescriber's Guide thereafter?

    - Never
    - Once
    - 2-3 times
    - More than 3 times

22. You find the information in the Prescriber's Guide:

    - Not useful
    - Useful

23. Have you referred to other sources of information to aid you in prescribing and managing Lixiana?

    - No
    - Yes, please refer which ones:_____

24. Are you aware of the Patient Alert Card for Lixiana?

    - Yes
    - No

25. Have you referred all your patients to the Patient Alert Card, when you first prescribed them Lixiana?

    a. Yes, always
    b. Yes, most of the time
    c. No, not always
    d. No, I often forget

26. During follow-up consultations, do you confirm if the patient carries the Patient Card with them?

    a. Yes
    b. No

27. How regularly do you check your patients' knowledge on the content of the Patient Alert Card?

    a. Never
    b. In every consultation
    c. At specific occasions (please specify)_____

13.3. Sample CRF

IBM Clinical Development Blank Pages

Study Name:	Daiichi Sankyo ETNA-DUS MSU2
Study Revision	3
Language	English (US)

1. Schedule

Data Abstraction	Page	Notes
Data Entry Instruction		
	Instructions	
Characteristics		
	Site Characteristics	
	Physician Characteristics	(Repeats, Maximum= Unlimited)
Data Abstraction		
	Demographics and Screen Log	
	ICF and Re-consent Trigger	
	ICF Re-Consent	(Repeats, Maximum= Unlimited)
	Vital Signs (Height and Weight)	
	Vital Signs (Height and Weight) Details	(Repeats, Maximum= Unlimited)
	Edoxaban Prescription	
	Edoxaban Treatment	(Repeats, Maximum= Unlimited)
	Behavioural History	
	Medical History and Comorbidities (1)	
	Medical History and Comorbidities (2)	
	Risk Factors and Treatment History	
	Past Surgical History	
	Past Surgical History Details	(Repeats, Maximum= Unlimited)
	Pregnancy lactation status at time of prescription	
	History of Past Use of Other Anticoagulants	
	History of Other Anticoagulants - Vitamin K	(Repeats, Maximum= Unlimited)
	History of Other Anticoagulants - Oral Non-Vit K	(Repeats, Maximum= Unlimited)
	History Other Anticoagulants–Heparin/Fondaparinux	(Repeats, Maximum= Unlimited)
	Concomitant Medication including antiplatelet drug	
	Concomitant Med including antiplatelet drug detail	(Repeats, Maximum= Unlimited)
	Adverse Drug Reaction	
	Conclusion of Data collection	
	PI Sign	

Data Entry Instruction

Instructions

(Visit ID = 20, Page ID = 10)

Unique Identifier page-2919747-2919751-20-10

Data Entry Instructions

Please complete the Site and Physician(s) Characteristics form as the first record for your site (#001).

Then, add Patient Data in the subsequent record numbers (starting from #002 and following).

Please click "Save" to continue.

Characteristics

Site Characteristics

(Visit ID = 30, Page ID = 10)

Unique Identifier page-2919784-2919786-30-10

Geographic location:		
Country	○ Germany ○ Italy ○ Switzerland ○ United Kingdom (UK) ○ Spain ○ Belgium	(select only one)
Individual Country	○ England ○ Northern Ireland	(select only one)

County	○ Bedfordshire ○ Berkshire ○ Buckinghamshire ○ Cambridgeshire ○ Cheshire ○ Cornwall ○ Cumberland ○ Derbyshire ○ Devon ○ Dorset ○ Durham ○ Essex ○ Gloucestershire ○ Hampshire ○ Herefordshire ○ Hertfordshire ○ Huntingdonshire ○ Kent ○ Lancashire ○ Leicestershire ○ Lincolnshire ○ Middlesex ○ Norfolk ○ Northamptonshire ○ Northumberland ○ Nottinghamshire ○ Oxfordshire ○ Rutland ○ Shropshire ○ Somerset ○ Staffordshire ○ Suffolk ○ Surrey ○ Sussex ○ Warwickshire ○ Westmorland ○ Wiltshire ○ Worcestershire ○ Yorkshire	(select only one)

County	○ Antrim ○ Armagh ○ Down ○ Fermanagh ○ Londonderry ○ Tyrone	(select only one)
Region	○ Andalucia ○ Aragon ○ Canarias ○ Cantabria ○ Castilla y Leon ○ Castilla-La Mancha ○ Cataluna ○ Comunidad de Madrid ○ Comunidad Foral de Navarra ○ Comunidad Valenciana ○ Extremadura ○ Galicia ○ Islas Baleares ○ La Rioja ○ Pais Vasco ○ Principado de Asturias ○ Region de Murcia	(select only one)
Region	○ Espace Mittelland ○ Freiburg ○ Neuchâtel ○ Jura ○ Région lémanique ○ Ticino ○ Bern ○ Solothurn ○ Nordwestschweiz ○ Zürich ○ Ostschweiz ○ Zentralschweiz	(select only one)

Region	○ Baden-Wuerttemberg ○ Bavaria ○ Berlin ○ Brandenburg ○ Bremen ○ Hamburg ○ Hesse ○ Mecklenburg-Western Pomerania ○ Lower Saxony ○ North Rhine ○ Rhineland-Palatinate ○ Saarland ○ Saxony ○ Saxony-Anhalt ○ Schleswig-Holstein ○ Thuringia ○ Westphalia-Lippe	(select only one)
Region	○ Abruzzo ○ Valle d'Aosta ○ Puglia ○ Basilicata ○ Calabria ○ Campania ○ Emilia-Romagna ○ Friuli-Venezia Giulia ○ Lazio ○ Liguria ○ Lombardia ○ Marche ○ Molise ○ Piemonte ○ Sardegna ○ Sicilia ○ Trentino-Alto Adige ○ Toscana ○ Umbria ○ Venice	(select only one)

Region	○ Antwerp ○ East Flanders ○ Flemish Brabant ○ Limburg ○ West Flanders ○ Hainaut ○ Liege ○ Luxembourg ○ Namur ○ Walloon Brabant	(select only one)
Type of setting	○ Private practice ○ University hospital ○ Private hospital ○ General hospital ○ Other, specify	(select only one)
Other, specify		
Volume of all patients of the setting/unit per year		(format 9999)

Characteristics

Physician Characteristics

(Visit ID = 30, Page ID = 20)

Unique Identifier page-2919757-2919786-30-20

Physician Seq. #		
Type of Physician	○ Principal Investigator ○ Sub-Investigator	(select only one)
Medical specialty(ies) (tick all that apply)		
General medicine	☐	
Cardiology	☐	
Internal medicine	☐	
Neurology	☐	
Anticoagulation specialist	☐	
Other, specify	☐	
Other, specify		
Profession or area of primary practice:		
If more than one Medical Specialty is selected above, please tick below only the specialty of primary practice)	○ General medicine ○ Cardiology ○ Internal medicine ○ Neurology ○ Anticoagulation specialist ○ Other, specify	(select only one)
Other, specify		
Experience of treating patients taking Edoxaban	○ Yes ○ No	(select only one)
Experience of treating patients taking Edoxaban (number of months)		(format 999)
Volume of all patients treated so far with Edoxaban/LIXIANA		(format 9999)

Data Abstraction

Demographics and Screen Log

(Visit ID = 10, Page ID = 10)

Unique Identifier page-2919733-2921844-10-10

Start date of abstraction		(DD-MMM-YYYY)
Screening log		
Was the patient included in this study?	○ Yes ○ No	Inclusion criteria: All patients with at least one Edoxaban prescription record in his/her medical record irrespective of their underlying health conditions or indication for Edoxaban prescription. Exclusion criteria: None(select only one)
If no, please provide the reason for non-inclusion	○ ICF Not signed ○ No Evidence of Edoxaban prescription in patient's chart ○ Initiation of Edoxaban prescription linked to a clinical trial participation prior to launch date ○ Investigator's choice, specify	(select only one)
Investigator's choice, specify		

Indication for which Edoxaban was initially prescribed prior to index date	○ Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors ○ Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (see section 4.4 of SMPC) ○ Unknown ○ Other, specify	For option 1 Risk Factors for NVAF: Congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA) For option 2 Section 4.4 of SMPC: Haemodynamically unstable PE patients or patient who require thrombolysis or pulmonary embolectomy Lixiana is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Edoxaban have not been established in these clinical situations.(select only one)

Other, specify

Risk Factors for nonvalvular atrial fibrillation (NVAF):
Congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

Section 4.4 of SMPC:
Haemodynamically unstable pulmonary embolism (PE) patients or patient who require thrombolysis or pulmonary embolectomy.
Lixiana is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Edoxaban have not been established in these clinical situations.

Demography

Birth year		(format 9999)
Ethnic group	○ Caucasian ○ Black ○ Asian ○ Prefer not to answer or not allowed by local law ○ Other, specify	(select only one)

Other, specify

Sex	○ Male ○ Female	(select only one)
If female, child-bearing potential	○ Yes ○ No	(select only one)

Data Abstraction

ICF and Re-consent Trigger

(Visit ID = 10, Page ID = 20)

Unique Identifier page-2919767-2921844-10-20

	Was Informed Consent provided?	○ Yes ○ No	(select only one)
	Informed consent date		(DD-MMM-YYYY)
	Version of the observational plan under which the subject entered this study.	○ Final Version 4.0 dated 05-AUG-2016	(select only one)
	Date observational plan version was approved for use at this site		(DD-MMM-YYYY)
	Was re-consent provided?	○ Yes ○ No	(select only one)
	If Yes, Please complete the <B>ICF Re-Consent form</B>.		

Data Abstraction

ICF Re-Consent

(Visit ID = 10, Page ID = 30)

Unique Identifier page-2919780-2921844-10-30

Enter the observational plan version the re-consent corresponds to. Do not enter the version of the informed consent form itself.

Line number		
Re-consent (signature date)		(DD-MMM-YYYY)
Observational plan version to which this re-consent corresponds	○ Final Version 4.0 dated 05-AUG-2016	(select only one)
Date observational plan version was approved for use at this site		(DD-MMM-YYYY)
Reason for re-consent consent	○ Protocol Amendment ○ ICF template error correction ○ Other	(select only one)
Other, please specify		

Data Abstraction

Vital Signs (Height and Weight)

(Visit ID = 10, Page ID = 40)

Unique Identifier page-2919726-2921844-10-40

Were Vital Signs performed during the observational period (i.e. from Edoxaban launch date to index date) or before?	○ Yes ○ No	(select only one)

If Yes, please complete the Vital Signs (Height and Weight) Details form.

Data Abstraction

Vital Signs (Height and Weight) Details

(Visit ID = 10, Page ID = 50)

Unique Identifier page-2919777-2921844-10-50

Please complete height and weight starting with the latest value available before start of Edoxaban intake and report any further measurements made during the observational period as available

Date of vital signs		(DD-MMM-YYYY)
Height (cm)		(format 999)
Height not done/not documented	☐	
Weight (kg)		(format 999.9)
Weight not done/not documented	☐	
BMI	(auto calculated)	(format 99.99)

Data Abstraction

Edoxaban Prescription

(Visit ID = 10, Page ID = 60)

Unique Identifier page-2919735-2921844-10-60

Initial Edoxaban Prescription (first time treatment of Edoxaban for the patient)		
Was the patient's initial Edoxaban prescription by the investigator?	○ Yes ○ No	(select only one)
Type of Prescriber	○ Office based physician ○ Hospital based physician ○ Unknown	(select only one)
Specialty of Prescriber	○ General medicine ○ Cardiology ○ Internal medicine ○ Neurology ○ Anticoagulation specialist ○ Unknown ○ Other, specify	(select only one)
Other, specify		
Date of initial prescription		(DD-MMM-YYYY) Complete the treatment for the initial prescription as first record on the Edoxaban treatment form
Indication for initial Edoxaban prescription	(remote value)	
	(remote value)	

Major reason for initial prescription	○ Drug-drug interaction by former treatment ○ High variability of former OAC treatment response ○ Lack of efficacy of former OAC treatment ○ Expected better safety ○ Expected better efficacy ○ Patient's request ○ Patient's former non-compliance ○ Expected better patient compliance ○ Unknown ○ Other, specify	(select only one)

Other, specify

Follow-up Edoxaban Prescriptions		
Were there any follow-up prescriptions during the observational period following the initial prescription?	○ Yes ○ No	(select only one)
Was there any follow-up prescription by the investigator?	○ Yes ○ No	(select only one)
Type of prescriber	○ Office based physician ○ Hospital based physician ○ Unknown	(select only one)
Specialty of prescriber	○ General medicine ○ Cardiology ○ Internal medicine ○ Neurology ○ Anticoagulation specialist ○ Unknown ○ Other, specify	(select only one)

Other, specify

Indication for follow-up Edoxaban prescription	○ Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors ○ Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (see section 4.4 of SMPC) ○ Unknown ○ Other, specify	(select only one)

Risk Factors for nonvalvular atrial fibrillation (NVAF):
Congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

Section 4.4 of SMPC:
Haemodynamically unstable pulmonary embolism (PE) patients or patient who require thrombolysis or pulmonary embolectomy.
Lixiana is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Edoxaban have not been established in these clinical situations.

Other, specify

Major reason for follow-up prescription	○ Drug-drug interaction by former treatment ○ High variability of former OAC treatment response ○ Lack of efficacy of former OAC treatment ○ Expected better safety ○ Expected better efficacy ○ Patient's request ○ Patient's former non-compliance ○ Expected better patient compliance ○ Unknown ○ Other, specify	(select only one)

Other, specify

Hypersensitivity

Is the patient hypersensitive to Edoxaban or any excipients listed in section 6.1 of the Summary of Product Characteristics (SMPC)?	○ Yes ○ No ○ Unknown	(select only one)

Please select Edoxaban/Excipient (tick any that apply)

Edoxaban	☐
Mannitol (E421)	☐
Pregelatinised starch	☐
Crospovidone	☐
Hydroxypropylcellulose	☐
Magnesium stearate (E470b)	☐
Hypromellose (E464)	☐
Macrogol 8000	☐
Titanium dioxide (E171)	☐
Talc	☐
Carnauba wax	☐
Iron oxide yellow (E172)	☐
Iron oxide red (E172)	☐

Data Abstraction

Edoxaban Treatment

(Visit ID = 10, Page ID = 70)

Unique Identifier page-2919768-2921844-10-70

Seq. no.		
Edoxaban intake start date		(DD-MMM-YYYY)
Edoxaban intake stop date		(DD-MMM-YYYY)
Ongoing	☐	
Is Edoxaban currently prescribed for the same indication as initially?	○ Yes ○ No	(select only one)
Indication	○ Prevention of stroke and systemic embolism in adult patients with NVAF with one or more risk factors ○ Treatment of DVT and PE, and prevention of recurrent DVT and PE in adults (see section 4.4 of SMPC) ○ Unknown ○ Other, specify	(select only one)

Risk Factors for nonvalvular atrial fibrillation (NVAF):
Congestive heart failure, hypertension, age >75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

Section 4.4 of SMPC:
Haemodynamically unstable pulmonary embolism (PE) patients or patient who require thrombolysis or pulmonary embolectomy.
Lixiana is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of Edoxaban have not been established in these clinical situations.

Other, specify

Total daily dose(mg)	○ 30 mg ○ 60 mg ○ Other, specify	(select only one)

Other, specify		
Frequency	○ Once daily ○ Twice daily ○ Three times daily ○ Not Documented ○ Other, specify	(select only one)
Other, specify		
Reason for adapted dose	○ Drug-drug interaction ○ Renal function impaired ○ Hepatic function impaired ○ Low weight ○ Patient's request ○ Reason for reduced dose no longer given ○ Other, specify	(select only one)
Other, specify		
If Edoxaban intake interrupted or discontinued, type	○ Suspension ○ Missed dose ○ Permanent discontinuation	(select only one)

If Edoxaban intake interrupted or discontinued, reason	○ AF intervention ○ VTE intervention ○ ADR/clinical event ○ Invasive procedure (incl. minor surgery) ○ Drug-drug interaction ○ Renal function changed (worsening/improvement) ○ Hepatic function changed (worsening/improvement) ○ Weight increased/decreased ○ High variability of response ○ Lack of efficacy ○ Health care system related prescription/formulary limitations ○ Patient's transfer to another HCP ○ Patient's lack of compliance ○ Patient's request ○ Treatment no longer considered to be necessary ○ Other, specify	(select only one)
Other, specify		

Data Abstraction

Behavioural History

(Visit ID = 10, Page ID = 80)

Unique Identifier page-2919769-2921844-10-80

Smoking History		
Has the patient ever smoked?	○ Never ○ Currently ○ Formerly ○ Unknown	(select only one)
Date that patient last smoked		(DD-MMM-YYYY)
Alcohol intake history		
Alcohol consumption (number of drinks, daily average) (one drink, eg: 0.25 L wine, 0.5 L beer)	○ None ○ < 1 ○ 1-2 ○ 3-4 ○ More than 4 ○ Unknown	(select only one)

Data Abstraction

Medical History and Comorbidities (1)

(Visit ID = 10, Page ID = 91)

Unique Identifier page-2919781-2921844-10-91

Please record all medical information before and during treatment with Edoxaban

Please complete the family history information only related to first degree relative e.g. father, mother, brother, sister

Please complete all Edoxaban treatment in the Edoxaban treatment form

Please complete any past surgeries reported during the observational period on the Past Surgical History Details form.

Please record any concomitant medications reported during the observational period in the Concomitant Med including antiplatelet drug detail form

History of Atrial Fibrillation (AF)

History of Atrial Fibrillation (AF)	○ Yes ○ No ○ Unknown	(select only one)

Please document the history of the patient's non-valvular atrial fibrillation (NVAF)

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Type of non-valvular atrial fibrillation (NVAF)	○ Paroxysmal (recurrent episodes that self-terminate within 48 hours up to 7 days) ○ Persistent (>7d) ○ Long-standing persistent (lasted for >1 year when it is decided to adopt a rhythm control strategy) ○ Permanent (accepted by the patient and physician)	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban Prescription	○ Yes ○ No ○ Unknown	(select only one)

Symptomatic / Asymptomatic at first diagnosis	○ Yes ○ No ○ Unknown	(select only one)

History of Venous Thromboembolic Event (VTE)

History of Venous Thromboembolic Event (VTE)	○ Yes ○ No ○ Unknown	(select only one)

Please document the history of the patient's past Venous Thromboembolic Events (VTE)

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)

Type of Venous Thromboembolic Event (VTE)

Deep Vein Thrombosis (DVT)	☐	
Deep Vein Thrombosis (DVT) with Pulmonary embolism (PE)	☐	
Pulmonary embolism (PE)	☐	

Previous Deep Vein Thrombosis (DVT)

Number of events		(format 99)
Start date of last event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	☐	
Stop date of last event		(DD-MMM-YYYY)

Previous Deep Vein Thrombosis (DVT) with Pulmonary embolism (PE)

Number of events		(format 99)
Start date of last event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	☐	
Stop date of last event		(DD-MMM-YYYY)

Previous Pulmonary Embolism (PE)

Number of events		(format 99)
Start date of last event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	☐	
Stop date of last event		(DD-MMM-YYYY)

Medical History

	Medical history condition		Is this medical history present in the family?		Date of diagnosis	Ongoing at the time of Edoxaban prescription?	
Diabetes Mellitus	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Chronic Obstructive Pulmonary Disease (COPD)	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Sleep Apnea	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Dyslipidemia	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Hyper-/Hypothyroidism	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Thrombocytopenia (ie. <100.000/µl)	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Chronic Thromboembolic Pulmonary Hypertension	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Chronic Venous Insufficiency	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Arthritis	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)

Lower extremity paralysis	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Infectious disease (necessitating immobilization)	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Coronary Heart Disease	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)
Ischemic Cardiomyopathy	○Yes ○No ○Unknown	(select only one)	○Yes ○No ○Unknown	(select only one)	(DD-MMM-YYYY)	○Yes ○No ○Unknown	(select only one)

Data Abstraction

Medical History and Comorbidities (2)

(Visit ID = 10, Page ID = 92)

Unique Identifier page-2921510-2921844-10-92

Please record all medical information before and during treatment with Edoxaban

Please complete the family history information only related to first degree relative e.g. father, mother, brother, sister

Please complete all Edoxaban treatment in the Edoxaban treatment form

Please complete any past surgeries reported during the observational period on the Past Surgical History Details form.

Please record any concomitant medications reported during the observational period in the Concomitant Med including antiplatelet drug detail form

History of Valvular Heart Disease

Does the patient have any history of Valvular Heart Disease	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Severity	○ Mild ○ Moderate ○ Moderately severe ○ Severe	(select only one)
Type of valvular heart disease	○ Aortic Stenosis ○ Mitral Stenosis ○ Insufficiency	(select only one)
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Was there a valve replacement / repair?	○ Yes ○ No ○ Unknown	(select only one)
Mechanical Heart Valves	○ Yes ○ No ○ Unknown	(select only one)
Are there any further valvular heart diseases to report?	○ Yes ○ No	(select only one)

Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Severity	○ Mild ○ Moderate ○ Moderately severe ○ Severe	(select only one)
Type of valvular heart disease	○ Aortic Stenosis ○ Mitral Stenosis ○ Insufficiency	(select only one)
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Was there a valve replacement / repair?	○ Yes ○ No ○ Unknown	(select only one)
Mechanical Heart Valves	○ Yes ○ No ○ Unknown	(select only one)
Are there any further valvular heart diseases to report?	○ Yes ○ No	(select only one)

Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Severity	○ Mild ○ Moderate ○ Moderately severe ○ Severe	(select only one)
Type of valvular heart disease	○ Aortic Stenosis ○ Mitral Stenosis ○ Insufficiency	(select only one)
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)

Was there a valve replacement / repair?	○ Yes ○ No ○ Unknown	(select only one)
Mechanical Heart Valves	○ Yes ○ No ○ Unknown	(select only one)
History of Renal Disease		
Does the patient have any history of renal disease?	○ Yes ○ No ○ Unknown	(select only one)
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Please document stage of chronic kidney disease	○ Stage 1 (GFR ≥ 90 ml/min/1.73 m²) ○ Stage 2 (GFR ≥ 60-89 ml/min/1.73 m²) ○ Stage 3 (GFR ≥ 30-59 ml/min/1.73 m²) ○ Stage 4 (GFR ≥ 15-29 ml/min/1.73 m²) ○ Stage 5 (GFR < 15ml/min/1.73m²)	(select only one)
Does the patient have severe renal impairment (defined as having Creatinine Clearance [CrCl]<30ml/min or end-stage renal disease [CrCl] <15 ml/min)?	○ Yes ○ No ○ Unknown	(select only one)
Was a hemodialysis necessary?	○ Yes ○ No ○ Unknown	(select only one)
Date of last hemodialysis prior to first administration of Edoxaban		(DD-MMM-YYYY)
Renal related lab tests		
Serum Creatinine lab value		(format 9999.99)

Serum Creatinine unit	○ mg/dL ○ umol/L	(select only one)
Upper Limit Normal		(format 9999.99)
Lower Limit Normal		(format 9999.99)
Date of lab		(DD-MMM-YYYY)
Date not documented	☐	
Creatinine Clearance (CrCl) (mL/min)		(format 9999.9)
Glomerular Filtration Rate (GFR) (mL/min)		(format 9999.9)
Ethnic group (where allowed by local regulation)	(remote value)	

(Information only required for MDRD and CKD-EPI CrCl assessment)

History of Hepatic Disorders		
Does the patient have any history of liver disease	○ Yes ○ No ○ Unknown	(select only one)
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Oesophageal varices	○ Yes ○ No ○ Unknown	(select only one)
Type of Chronic Hepatic Disease / pre-existing Hepatic Disease	○ Cirrhosis ○ Infectious liver disease (eg. Hep B or C) ○ Toxic liver disease ○ Other, specify	(select only one)
Other, specify		

Corresponding hepatic parameters

Bilirubin > 2xUpper Limit Normal	○ Yes ○ No ○ Unknown	(select only one)

Aspartate aminotransferase (AST) and/or Alanine aminotransferase (ALT) > 3xUpper Limit Normal	○ Yes ○ No ○ Unknown	(select only one)
History of Malignancy		
Does the patient have any history of malignancies?	○ Yes ○ No ○ Unknown	(select only one)
Name of malignancy		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Type of therapy	○ Chemotherapy ○ Radiotherapy ○ Other, specify	(select only one)
Other, specify		
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further malignancies to report?	○ Yes ○ No	(select only one)
Name of malignancy		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Type of therapy	○ Chemotherapy ○ Radiotherapy ○ Other, specify	(select only one)
Other, specify		
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further malignancies to report?	○ Yes ○ No	(select only one)

Name of malignancy		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Type of therapy	○ Chemotherapy ○ Radiotherapy ○ Other, specify	(select only one)
Other, specify		
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)

History of Fracture / Trauma

Does the patient have any history of fracture / trauma?	○ Yes ○ No ○ Unknown	(select only one)
Type of fracture / trauma	○ Bone fracture ○ Soft tissue trauma ○ Brain injury ○ Spinal injury ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of fracture / trauma		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further fractures / traumas to report?	○ Yes ○ No	(select only one)

Type of fracture / trauma	○ Bone fracture ○ Soft tissue trauma ○ Brain injury ○ Spinal injury ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of fracture / trauma		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further fractures / traumas to report?	○ Yes ○ No	(select only one)
Type of fracture / trauma	○ Bone fracture ○ Soft tissue trauma ○ Brain injury ○ Spinal injury ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of fracture / trauma		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further fractures / traumas to report?	○ Yes ○ No	(select only one)
Type of fracture / trauma	○ Bone fracture ○ Soft tissue trauma ○ Brain injury ○ Spinal injury ○ Other, specify	(select only one)

Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of fracture / trauma		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further fractures / traumas to report?	○ Yes ○ No	(select only one)
Type of fracture / trauma	○ Bone fracture ○ Soft tissue trauma ○ Brain injury ○ Spinal injury ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of fracture / trauma		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
History of Stroke		
Does the patient have any history of stroke	○ Yes ○ No ○ Unknown	(select only one)
Type of stroke	○ Ischemic ○ Intracranial Hemorrhage (ICH) ○ Transient Ischemic Attack (TIA) ○ Unknown ○ Other, specify	(select only one)
Other, specify		

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of stroke		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further strokes to report?	○ Yes ○ No	(select only one)
Type of stroke	○ Ischemic ○ Intracranial Hemorrhage (ICH) ○ Transient Ischemic Attack (TIA) ○ Unknown ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of stroke		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further strokes to report?	○ Yes ○ No	(select only one)
Type of stroke	○ Ischemic ○ Intracranial Hemorrhage (ICH) ○ Transient Ischemic Attack (TIA) ○ Unknown ○ Other, specify	(select only one)
Other, specify		

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of stroke		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further strokes to report?	○ Yes ○ No	(select only one)
Type of stroke	○ Ischemic ○ Intracranial Hemorrhage (ICH) ○ Transient Ischemic Attack (TIA) ○ Unknown ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of stroke		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further strokes to report?	○ Yes ○ No	(select only one)
Type of stroke	○ Ischemic ○ Intracranial Hemorrhage (ICH) ○ Transient Ischemic Attack (TIA) ○ Unknown ○ Other, specify	(select only one)
Other, specify		

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of stroke		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
History of Major Bleeding Events		
Did patient suffer a major bleeding event that led to a visit to health care professional?	○ Yes ○ No ○ Unknown	(select only one)
Type of bleeding event	○ Gastro Intestinal ○ Other Organ ○ Epidural or Subdural Hematoma ○ Unknown ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of major bleeding event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further major bleeding events to report?	○ Yes ○ No	(select only one)
Type of bleeding event	○ Gastro Intestinal ○ Other Organ ○ Epidural or Subdural Hematoma ○ Unknown ○ Other, specify	(select only one)
Other, specify		

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of major bleeding event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further major bleeding events to report?	○ Yes ○ No	(select only one)
Type of bleeding event	○ Gastro Intestinal ○ Other Organ ○ Epidural or Subdural Hematoma ○ Unknown ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of major bleeding event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further major bleeding events to report?	○ Yes ○ No	(select only one)
Type of bleeding event	○ Gastro Intestinal ○ Other Organ ○ Epidural or Subdural Hematoma ○ Unknown ○ Other, specify	(select only one)
Other, specify		

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of major bleeding event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further major bleeding events to report?	○ Yes ○ No	(select only one)
Type of bleeding event	○ Gastro Intestinal ○ Other Organ ○ Epidural or Subdural Hematoma ○ Unknown ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of major bleeding event		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
History of Digestive Tract Disease		
Does the patient have any history of digestive tract disease?	○ Yes ○ No ○ Unknown	(select only one)
Digestive tract disease type	○ Gastro Intestinal Ulcer ○ Gastro Intestinal Dysplasia ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)

Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further digestive tract diseases to report?	○ Yes ○ No	(select only one)
Digestive tract disease type	○ Gastro Intestinal Ulcer ○ Gastro Intestinal Dysplasia ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further digestive tract diseases to report?	○ Yes ○ No	(select only one)
Digestive tract disease type	○ Gastro Intestinal Ulcer ○ Gastro Intestinal Dysplasia ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)

History of Hypertension

Does the patient have any history of hypertension?	○ Yes ○ No ○ Unknown	(select only one)
Uncontrolled severe hypertension?	○ Yes ○ No	(select only one)
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
History of Peripheral Vascular Disease		
Does the patient have any history of peripheral vascular disease?	○ Yes ○ No ○ Unknown	(select only one)
Type of peripheral vascular disease	○ Arteriovenous malformations ○ Vascular aneurysms ○ Major intraspinal vascular abnormalities ○ Intracerebral vascular abnormalities ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further peripheral vascular diseases to report?	○ Yes ○ No	(select only one)

Type of peripheral vascular disease	○ Arteriovenous malformations ○ Vascular aneurysms ○ Major intraspinal vascular abnormalities ○ Intracerebral vascular abnormalities ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further peripheral vascular diseases to report?	○ Yes ○ No	(select only one)

Type of peripheral vascular disease	○ Arteriovenous malformations ○ Vascular aneurysms ○ Major intraspinal vascular abnormalities ○ Intracerebral vascular abnormalities ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)

Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further peripheral vascular diseases to report?	○ Yes ○ No	(select only one)
Type of peripheral vascular disease	○ Arteriovenous malformations ○ Vascular aneurysms ○ Major intraspinal vascular abnormalities ○ Intracerebral vascular abnormalities ○ Other, specify	(select only one)
Other, specify		
Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)
Are there any further peripheral vascular diseases to report?	○ Yes ○ No	(select only one)
Type of peripheral vascular disease	○ Arteriovenous malformations ○ Vascular aneurysms ○ Major intraspinal vascular abnormalities ○ Intracerebral vascular abnormalities ○ Other, specify	(select only one)
Other, specify		

Is this medical history present in the family?	○ Yes ○ No ○ Unknown	(select only one)
Date of diagnosis		(DD-MMM-YYYY)
Ongoing at the time of Edoxaban prescription	○ Yes ○ No ○ Unknown	(select only one)

Data Abstraction

Risk Factors and Treatment History

(Visit ID = 10, Page ID = 100)

Unique Identifier page-2919778-2921844-10-100

Primary diagnosis for initial prescription of Edoxaban	○ Deep Vein Thrombosis (DVT) ○ Deep Vein Thrombosis (DVT) with Pulmonary Embolism (PE) ○ Pulmonary Embolism (PE) ○ Non-valvular Atrial Fibrillation (NVAF) ○ Other, specify	(select only one)
Type of non-valvular atrial fibrillation (NVAF)	○ Paroxysmal (recurrent episodes that self-terminate within 48 hours up to 7 days) ○ Persistent (>7d) ○ Long-standing persistent (lasted for >1 year when it is decided to adopt a rhythm control strategy) ○ Permanent (accepted by the patient and physician)	(select only one)

Other, specify

Please record events during observational period (i.e. from Edoxaban launch date to index date)

Please document non-phamacological treatment during observational period (i.e. from Edoxaban launch data to index date).

Venous Thromboembolic Events (VTE) risk factors (within 3 months prior to start of the acute Venous Thromboembolic Events (VTE) event)		
Puerperium	○ Yes ○ No ○ Unknown	(select only one)

Prolonged immobilization	○ Yes ○ No ○ Unknown	(select only one)
> 5 days in bed	○ Yes ○ No ○ Unknown	(select only one)
History of major surgery or trauma	○ Yes ○ No ○ Unknown	(select only one)
Known thrombophillic conditions	○ Yes ○ No ○ Unknown	(select only one)
Antithrombin deficiency	☐	
Factor V Leiden	☐	
Hyperhomocysteinaemia	☐	
Antiphospholipid antibodies	☐	
Protein C deficiency	☐	
Protein S deficiency	☐	
Prothrombin gene mutation	☐	
Other, specify	☐	
Other, specify		

Acute invasive and/or non-invasive VTE Therapy

Please record events during observational period (i.e. from Edoxaban launch date to index date)

Acute invasive and/or non-invasive VTE Therapy	○ Yes ○ No ○ Unknown	(select only one)
Invasive therapy		
- Open embolectomy	○ Yes ○ No ○ Unknown	(select only one)
Date of Therapy		(DD-MMM-YYYY)
Was the therapy successful?	○ Yes ○ No	(select only one)
Was Edoxaban interrupted for Therapy	○ Yes ○ No ○ Unknown	(select only one)

Please enter any Edoxaban interruption on the Edoxaban Treatment form

- Catheter procedures (e.g. catheter fragmentation or embolectomy)	○ Yes ○ No ○ Unknown	(select only one)
Date of Therapy		(DD-MMM-YYYY)
With local thrombolytic treatment?	○ Yes ○ No	(select only one)
Was the therapy successful?	○ Yes ○ No	(select only one)
Was Edoxaban interrupted for Therapy	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Insertion of Vena Cava Filter	○ Yes ○ No ○ Unknown	(select only one)
Date of Therapy		(DD-MMM-YYYY)
Was the therapy successful?	○ Yes ○ No	(select only one)
Was Edoxaban interrupted for Therapy	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Other invasive therapies	○ Yes ○ No	(select only one)
Other invasive therapy details		
Date of therapy		(DD-MMM-YYYY)
Was the therapy successful?	○ Yes ○ No	(select only one)
Was Edoxaban interrupted for Therapy	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
Non-invasive therapy		
- Compression stockings	○ Yes ○ No	(select only one)
Number of stockings		(format 99)

Date of therapy		(DD-MMM-YYYY)
Was the therapy successful?	○ Yes ○ No	(select only one)
Was Edoxaban interrupted for Therapy	○ Yes ○ No ○ Unknown	(select only one)

Please enter any Edoxaban interruption on the Edoxaban Treatment form

- Other non-invasive therapies	○ Yes ○ No	(select only one)
Other non-invasive therapy details		
Date of therapy		(DD-MMM-YYYY)
Was the therapy successful?	○ Yes ○ No	(select only one)
Was Edoxaban interrupted for Therapy	○ Yes ○ No ○ Unknown	(select only one)

Please enter any Edoxaban interruption on the Edoxaban Treatment form

Atrial Fibrillation (AF)- Interventions/Non-pharmacological treatment

Please record events during observational period (i.e. from Edoxaban launch date to index date)

Had the patient undergone any interventions for non-valvular atrial fibrillation (NVAF) (eg. ablation, cardioversion, pacemaker/defibrillator implantation, others)	○ Yes ○ No ○ Unknown	(select only one)

If yes, complete the interventions listed

- Pharmacological Cardioversion	○ Yes ○ No	(select only one)
Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)

Please enter any Edoxaban interruption on the Edoxaban Treatment form

- Electrical Cardioversion	○ Yes ○ No	(select only one)

Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Ablation	○ Yes ○ No	(select only one)
Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Ablation location (tick all that apply)		
AV node	☐	
Atrial fibrillation	☐	
Stroke	☐	
Supraventricular tachycardia	☐	
Atrial flutter	☐	
- Pacemaker / Defibrillator (ICD)	○ Pacemaker ○ Defibrillator (ICD) ○ Neither	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Number of interventions	○ 1 ○ >=2	(select only one)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Left atrial appendage occlusion	○ Yes ○ No	(select only one)
Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)

Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Surgical therapy for non-valvular atrial fibrillation (NVAF)	○ Yes ○ No	(select only one)
Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Transcatheter Aortic Valve Implantation (TAVI)	○ Yes ○ No	(select only one)
Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Percutaneous Coronary Intervention (PCI)	○ Yes ○ No	(select only one)
Number of interventions	○ 1 ○ >=2	(select only one)
Date of last intervention		(DD-MMM-YYYY)
Was Edoxaban interrupted for intervention?	○ Yes ○ No ○ Unknown	(select only one)
Please enter any Edoxaban interruption on the Edoxaban Treatment form		
- Other interventions		
Other interventions	○ Yes ○ No	(select only one)
Other intervention details		

Data Abstraction

Past Surgical History

(Visit ID = 10, Page ID = 110)

Unique Identifier page-2919728-2921844-10-110

Were there any past surgical histories to report during observational period (i.e. from Edoxaban launch date to index date)?	○ Yes ○ No	(select only one)

Data Abstraction

Past Surgical History Details

(Visit ID = 10, Page ID = 120)

Unique Identifier page-2919782-2921844-10-120

Please complete each log line per surgery during the observational period

If Edoxaban intake was interrupted due to surgery, please complete the relevant treatment information in Edoxaban treatment form and report interruption below

Seq. no.

Surgery Type	○ Minimal invasive surgery (specify below) ○ Ophthalmic/Cataract surgery ○ Oral surgery (including tooth extractions) ○ Hip replacement surgery ○ Knee replacement surgery ○ Open abdominal surgery ○ Open chest surgery ○ Vascular surgery ○ Other, specify	(select only one)
Minimal invasive surgery, specify		
Other, specify		
Surgery date		(DD-MMM-YYYY)
Duration of surgery (minutes)		(format 999)

Please enter duration of surgery in minutes e.g if a surgery was 2hr in duration, please enter 120

Duration unknown ☐

Was Edoxaban intake interrupted for this surgery?	○ Yes ○ No ○ Not applicable ○ Unknown	(select only one)

Please enter any Edoxaban interruption on the Edoxaban Treatment form

Data Abstraction

Pregnancy lactation status at time of prescription

(Visit ID = 10, Page ID = 130)

Unique Identifier page-2919647-2921844-10-130

Was the patient lactating at the time of prescription?	○ Yes ○ No ○ Unknown	(select only one)
Was the patient pregnant at the time of prescription?	○ Yes ○ No ○ Unknown	(select only one)
Please ensure this event is reported to Daiichi Sankyo Europe Clinical Safety & Pharmacovigilance department		
How was the pregnancy confirmed?	○ HCG test positive ○ Positive Ultrasound scan ○ Pregnancy status recorded in the medical notes ○ Unknown	(select only one)
Was Edoxaban intake stopped during pregnancy?	○ Yes ○ No	(select only one)
Duration of Edoxaban exposure while pregnant (days)		(format 999)
Pregnancy outcome	○ Live Birth ○ Still Birth ○ Termination ○ Unknown	(select only one)
If live birth		
Were any birth defects detected?	○ Yes ○ No ○ Unknown	(select only one)
If still birth or termination		
Was teratogenicity reported?	○ Yes ○ No ○ Unknown	(select only one)
Please ensure this event is reported to Daiichi Sankyo Europe Clinical Safety & Pharmacovigilance department		

Data Abstraction

History of Past Use of Other Anticoagulants

(Visit ID = 10, Page ID = 140)

Unique Identifier page-2919727-2921844-10-140

Was patient previously treated with other anticoagulants to report during observational period (i.e. from Edoxaban launch date to index date)?	○ Yes ○ No ○ Unknown	(select only one)
Vitamin K Antagonists	○ Yes ○ No ○ Unknown	(select only one)
Please complete the History of Past Use of Other Anticoagulants - Vitamin K form		
Non-Vitamin K Oral Antagonists	○ Yes ○ No ○ Unknown	(select only one)
Please complete the History of Past Use of Other Anticoagulants - Oral Non-Vitamin K form		
Heparin/Fondaparinux	○ Yes ○ No ○ Unknown	(select only one)
Please complete the History of History of Past Use of Other Anticoagulants - Heparin/Fondaparinux form		

Data Abstraction

History of Other Anticoagulants - Vitamin K

(Visit ID = 10, Page ID = 150)

Unique Identifier page-2919783-2921844-10-150

Please document each treatment change separately on this form

Seq. no.

Specific VKA	○ Warfarin ○ Phenprocumon ○ Acenocumarol ○ Fluindione ○ Other	(select only one)
VKA start date		(DD-MMM-YYYY)
VKA start date unknown or not documented	☐	
VKA stop date		(DD-MMM-YYYY)
VKA stop date unknown or not documented	☐	
VKA ongoing at time of index date	☐	
Total daily dose		(format 9999.99)
Dose unit	○ mg ○ mg/mL ○ Other, specify	(select only one)
Other, specify		
VKA dosing frequency	○ Once daily ○ Twice daily ○ Three times daily ○ Not Documented ○ Other, specify	(select only one)
Other, specify		

VKA major reason for discontinuation (if stopped)	○ VTE-intervention ○ AF-intervention ○ Patient's request ○ Patient's non-compliance ○ Lack of efficacy ○ Invasive procedure (incl. minor surgery) ○ High variability of response ○ Drug-drug interaction ○ ADR / Clinical Event ○ Other	(select only one)

Data Abstraction

History of Other Anticoagulants - Oral Non-Vit K

(Visit ID = 10, Page ID = 160)

Unique Identifier page-2919742-2921844-10-160

Please document each treatment change separately on this form

Seq. no.

Specific Oral Non-VKA	○ Apixaban ○ Dabigatran ○ Rivaroxaban ○ Other than Edoxaban (not specified)	(select only one)
Oral Non-VKA start date		(DD-MMM-YYYY)
Oral Non-VKA start date unknown or not documented	☐	
Oral Non-VKA stop date		(DD-MMM-YYYY)
Oral Non-VKA stop date unknown or not documented	☐	
Oral Non-VKA ongoing at time of index date	☐	
Total daily dose (mg)		(format 9999.99)
Oral Non-VKA dosing frequency	○ Once daily ○ Twice daily ○ Three times daily ○ Not Documented ○ Other, specify	(select only one)
Other, specify		

Oral Non-VKA major reason for discontinuation (if stopped)	○ VTE-intervention ○ AF-intervention ○ Patient's request ○ Patient's non-compliance ○ Lack of efficacy ○ Invasive procedure (incl. minor surgery) ○ High variability of response ○ Drug-drug interaction ○ ADR / Clinical Event ○ Other	(select only one)

Data Abstraction

History Other Anticoagulants–Heparin/Fondaparinux

(Visit ID = 10, Page ID = 170)

Unique Identifier page-2919737-2921844-10-170

Please document each treatment change separately on this form

Seq. no.

Specific Heparin/Fondaparinux	○ Unfractionated Heparin ○ LMW (low molecular weight) Heparins ○ Fondaparinux	(select only one)
Heparin/Fondaparinux start date		(DD-MMM-YYYY)
Heparin/Fondaparinux start date unknown or not documented	☐	
Heparin/Fondaparinux stop date		(DD-MMM-YYYY)
Heparin/Fondaparinux stop date unknown or not documented	☐	
Heparin/Fondaparinux ongoing at time of index date	☐	
Total daily dose		(format 9999.99)
Dose unit	○ UI/mL ○ mg/mL	(select only one)
Heparin/Fondaparinux dosing frequency	○ Once daily ○ Twice daily ○ Three times daily ○ Not Documented ○ Other, specify	(select only one)
Other, specify		

Heparin/Fondaparinux major reason for discontinuation (if stopped)	○ VTE-intervention ○ AF-intervention ○ Patient's request ○ Patient's non-compliance ○ Lack of efficacy ○ Invasive procedure (incl. minor surgery) ○ High variability of response ○ Drug-drug interaction ○ ADR / Clinical Event ○ Other	(select only one)

Data Abstraction

Concomitant Medication including antiplatelet drug

(Visit ID = 10, Page ID = 180)

Unique Identifier page-2919697-2921844-10-180

	Was the patient taking any concomitant medications (other than Edoxaban) or non-drug therapies during observational period (i.e. from Edoxaban launch date to index date)?	○ Yes ○ No	(select only one)

Data Abstraction

Concomitant Med including antiplatelet drug detail

(Visit ID = 10, Page ID = 190)

Unique Identifier page-2919738-2921844-10-190

Please document each treatment change separately on this form

Seq. no.

Treatment type	○ Concomitant Medication ○ Non-Drug Therapy/Procedure	(select only one)
Medication name		
Non-drug therapy/procedure name		
Start date		(DD-MMM-YYYY)
Stop date		(DD-MMM-YYYY)
Ongoing at time of index date	☐	
Dose		

Dose unit	○ Capsule ○ Drops ○ Grain ○ Gram(s) ○ Microcurie ○ Microgram ○ Microliter ○ Miligram(s) ○ Mililiter/Cubic centimeter ○ Milicurie ○ Ounce ○ Puff ○ Spray/Squirt ○ Suppository ○ Tablet ○ Teaspoon ○ Tablespoon ○ IU ○ Unknown ○ Other, specify	(select only one)
If other unit, please specify		
Frequency	○ Once ○ Daily ○ Twice a day ○ Three times a day ○ Weekly ○ PRN (as needed) ○ Every 4 hours ○ Every other day ○ Unknown ○ Other	(select only one)
If Other frequency, please specify		

Route	○ Intraarticular ○ Intramuscular ○ Intravenous ○ Nasal ○ Oral ○ Rectal ○ Subcutaneous ○ Transdermal ○ Topical ○ Vaginal ○ Unknown ○ Other	(select only one)
If Other route, please specify		
Indication	○ Medical History ○ Adverse Drug Reaction ○ Other, specify	(select only one)
Medical History		
Other, specify		

Data Abstraction

Adverse Drug Reaction

(Visit ID = 10, Page ID = 200)

Unique Identifier page-2919695-2921844-10-200

Were there any adverse events related to Edoxaban treatment during observational period (i.e. from Edoxaban launch date to index date)?	○ Yes ○ No	(select only one)

If Yes, please ensure that the paper ADR form is completed and this ADR is reported to the department of Clinical Safety & Pharmacovigilance at your national Daiichi Sankyo affiliate.

Data Abstraction

Conclusion of Data collection

(Visit ID = 10, Page ID = 210)

Unique Identifier page-2919671-2921844-10-210

Are all available data captured for this subject?	○ Yes ○ No	(select only one)
Data completion date		(DD-MMM-YYYY)
If no please provide the primary reason for not capturing all available data for this subject	○ Withdrawal of informed consent ○ Investigator's choice ○ Other, specify	(select only one)
Other, specify		
Patient's current status	○ Alive ○ Deceased	(select only one)
Date of death		(DD-MMM-YYYY)
Cause of death		

Data Abstraction

PI Sign

(Visit ID = 10, Page ID = 220)

Unique Identifier page-2919717-2921844-10-220

I certify that I have reviewed all pertinent source documentation and all corresponding data entered in this eCRF. By applying my electronic signature, I confirm that this information is correct to the best of my knowledge.	☐

13.4. Statistical Analysis Plans

Statistical Analysis Plan (SAP)

Non-interventional Study on Edoxaban Treatment in Routine Clinical Practice for Patients with Venous Thromboembolism in Europe.

Drug Name:	Edoxaban tosilate
Study Code:	DSE-EDO-01-14-EU
Accronym:	ETNA-DUS-Europe
Version Number:	2.0
Date of Version:	10 July 2017

Sponsor:
DAIICHI SANKYO EUROPE GmbH
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500 Brook Drive
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Fax: +44 (0)118 450 8300

Confidentiality Statement

SIGNATURE PAGE

We, the undersigned, have read this Statistical Analysis Plan and confirm to the best of our knowledge it accurately describes the analysis of this non-interventional study.

Signature	Date
Valentina Dall'Armi	17 JUL 2017
Prepared & Approved by Valentina Dall'Armi Study Statistician, QuintilesIMS	
A TAJAR	17/07/2017
Reviewed & Approved by Abdelouahid Tajar Associate Director Biostatistics, QuintilesIMS	
	17 JUL 2017
Reviewed & Approved by Elodie Aubrun Study Epidemiologist, QuintilesIMS	
Y Matsushita	10. JUL 2017
Reviewed and Approved by Yasuyuki Matsushita Director Biostatistics & Study Statistician, DAIICHI SANKYO EUROPE GmbH	
i.V.	17 JUL 2017
Reviewed and Approved by Thomas Malzer Safety Physician, DAIICHI SANKYO EUROPE GmbH	
i.V.	11 - JUL - 2017
Reviewed and Approved by Wolfgang Zierhut Head of Antithrombotic & Cardiovascular Therapeutic Area, DAIICHI SANKYO EUROPE GmbH	
i.V.	11-07-2017
Reviewed and Approved by Petra Laeis Head of Late Phase Clinical Operations and Real World Evidence Market Access, DAIICHI SANKYO EUROPE GmbH	

DOCUMENT HISTORY

Version Number	Author	Date	Change
0.1	Valentina Dall'Armi	15 July 2016	First Draft
0.2	Valentina Dall'Armi	14 October 2016	Second Draft: Changes to implement SAP draft 1 comments
0.3	Valentina Dall'Armi	23 November 2016	Third Draft: Changes to implement SAP draft 2 comments
1.0	Valentina Dall'Armi	28 November 2016	Final SAP V1.0: Changes as per DSE comments from previous SAP V0.3 dated 23Nov2016 (sponsor review)
2.0	Yasuyuki Matsushita	10 July 2017	- Update name of QIMS biostatistics reviewer -Portugal added due to observational plan amendment -Exact index date confirmed for wave one countries in Table2 -Subsection added in section 17 -Definition modified for creatinine clearance, renal impairment, and hepatic impairment in section 17.5

ABBREVIATIONS

ADR	Adverse Drug Reactions
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
CI	Confidence Interval
CHA_2DS_2-VASC	Score for vascular disease combining the following factors: Congestive heart failure, Hypertension, Age > 75 years, Diabetes mellitus, Prior stroke or transient ischemic attack.
CrCl	Creatinine Clearance
CRF	Case Report Form
DBL	Database Lock
DSE	Daiichi Sankyo Europe GmbH
DUS	Drug Utilisation Study
DVT	Deep Vein Thrombosis
eCRF	Electronic Case Report Form
EDOX	Edoxaban
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
ETNA-DUS	Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study
FAS	Full analysis set
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
GP	General Practitioner
HCP	Health care provider/professionals
ICF	Informed consent form
L95%	Lower limit of the 95% confidence interval
MED	Medication other than edoxaban
NSAID	Nonsteroidal Anti-Inflammatory Drug
NVAF	Non-valvular atrial fibrillation
PE	Pulmonary Embolism
PIS	All participating investigators set
P-gp	P-glycoprotein

Q1	First quartile
Q3	Third quartile
RMP	Risk Management Plan
SAP	Statistical Analysis Plan
SAS®	Statistical Analysis Software
SCR	All subjects screened
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TLFs	Tables, Listings and Figures
U95%	Upper limit of the 95% confidence interval
UFH	Unfractionated Heparin
UK	United Kingdom
ULN	Upper Normal Limit
VKA	Vitamin-K Antagonist
VTE	Venous Thromboembolism

Contents

1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of edoxaban patterns of use in real practice and the effectiveness of the educational program data for observational plan DSE-EDO-01-14-EU. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.

This statistical analysis plan (SAP) is based on observational plan version 6.0, dated 8th of June 2017.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVE

The aim of this study titled "Edoxaban prescription patterns in Europe: a retrospective drug utilisation chart review study" (ETNA-DUS) is to provide real-world data related to the current prescription patterns of edoxaban. Study objectives are as follows:

To characterize sites and physicians:

- Geographic location of physician site
- Profession or area of primary practice (e.g., general practitioners (GPs), cardiologists, and other specialists)
- Patient volume (i.e., number of patients and estimated number of patients using edoxaban).

To characterize users of edoxaban according to:

- Demographic factors (e.g. age, gender, other)
- Patient comorbidity
- Patient subgroups for which there is missing information according to the risk management plan (RMP):
  - Pregnant and/or breastfeeding women
  - Paediatric patients (< 18 years old)
  - Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk
  - Patients with severe renal impairment (defined as having creatinine clearance [CrCl] < 30 ml/min) or end stage renal disease (ESRD) (CrCl < 15 ml/min or on dialysis)
  - Patients with mechanical heart valves
- Patients being treated with dual antiplatelet therapy

To evaluate the pattern of use of edoxaban:

- Dose (including starting dose) and duration of treatment, including identification of long-term and chronic use (≥ 6 months), and changes

- Use of concurrent/concomitant medications with special focus on medications potentially interacting with edoxaban or contraindicated especially those known to increase the risk of bleeding e.g., aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)
- Detect the improbable event of use outside the labelled instructions, including use outside the indication [Lixiana Summary of Product Characteristics (SmPC)[1], last updated on 23rd September 2016] (particularly indications for which alternative anticoagulants are indicated) and use in contraindicated situations:
  - Use outside the indication
  - Hypersensitivity
  - Clinically significant active bleeding
    - Hepatic disease associated with coagulopathy and clinically relevant bleeding risk
    - Significant risk for major bleeding
    - Current or recent gastrointestinal ulceration
    - Presence of malignant neoplasms at high risk of bleeding
    - Recent brain or spinal injury
    - Recent brain, spinal or ophthalmic surgery
    - Recent intracranial haemorrhage
    - Known or suspected oesophageal varices
    - Arteriovenous malformations
    - Vascular aneurysms
    - Major intraspinal vascular abnormalities
    - Intracerebral vascular abnormalities.
    - Uncontrolled severe hypertension.
    - Concomitant treatment with any other anticoagulants
    - Unfractionated heparin (UFH)
    - Low molecular weight heparins (enoxaparin, dalteparin, etc.)
    - Heparin derivatives (fondaparinux, etc.)
    - Oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.)
    - Pregnancy and breast-feeding
- History of past use of other anticoagulants

To evaluate the effectiveness of the edoxaban educational material as a tool for risk minimization. The specific objectives are:

- To evaluate whether the educational material reached the target population (physicians prescribing edoxaban) as part of physician packet provided prior to drug supply
- To assess clinical knowledge: awareness of the target population and the level of knowledge achieved by the educational intervention

3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

3.1.1. STUDY DESIGN

Multinational, multicenter study involving the retrospective chart review of edoxaban users' medical records. Nested in the study, a cross-sectional survey of all participating prescribing physicians will be 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 program.

3.1.2. SETTING AND PARTICIPATING SITES

The study aims to include approximately 1,200 medical records of consecutive patients who were treated at least once with one or more dose(s) of edoxaban.

About 100 hospital- and office-based physicians (GPs, internal medicine physicians and other specialists) in at least 7 Western European countries (Germany, Italy, Switzerland, United Kingdom [UK], Belgium, Spain, and Portugal) are foreseen to participate in the study. Initially France and The Netherlands were selected to take part into the study, however they have been substituted by Belgium and Spain by taking into account prescription volumes, the number of prescribers per capita, and favorable regulatory and ethical environment to conduct observational studies. Additional European country(ies) may be included based upon the actual use of edoxaban.

Available national prescription databases will be screened to identify edoxaban prescriber characteristics. Data from IMS LifeLink™ database for dispensing data in the community care setting, or another appropriate data source, will identify prescribers of edoxaban.

On a national level for the targeted countries, the distribution of regional location of the sites as well as the distribution of the prescribers' specialty will be provided.

Therefore, IMS LifeLink™ will be used:

- *a-priori* to refine the sampling strategy for the full study (using regional and specialty distribution of prescribers)
- *a-posteriori* to assess the representativeness of prescribers and patients included in the full study.

Details are provided in a separate SAP for sample validation.

Physicians participating in interventional programs for edoxaban will not be eligible to participate in the study. By applying this approach both representativeness and comprehensiveness of the sample in terms of types of prescribers are ensured.

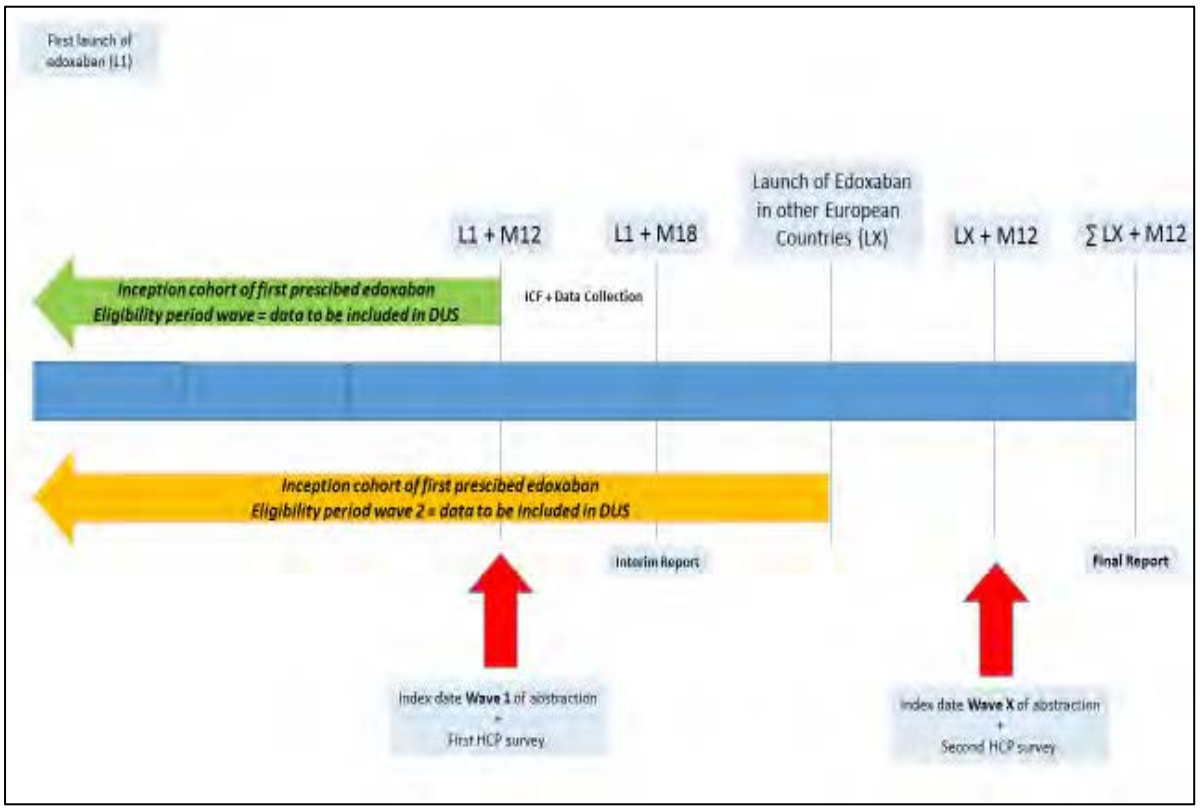
3.1.3. SCHEDULE

The study flow chart per patient is presented in **Figure** 1. The inception cohort is defined as patients initiating edoxaban during a 12 month period following the launch of the product in each country. Individual edoxaban treatment periods for a single patient can vary between 1 day and 12 months and are dependent on when the patient started edoxaban with respect to the index date. For UK this period can extend to 16 months.

The recruitment will occur according to the following plan: first wave countries will be Switzerland, Germany and UK; second wave countries will be Belgium, Italy and Spain.

The electronic case report form (eCRF) will be used to collect study data. Data collection will be initiated following a study-defined index date, approximately 12 months after product launch. All study prescribers within a country will be assigned the same index date and will not be contacted prior to the index date. Initiation of prescriber-specific activities for a selection of patient records who meet study selection criteria will commence on or following the index date. Data on drug utilization will be censored on the index date. This approach will ensure that study procedures do not influence prescribing practices.

Figure 1- Study flow chart per patient



Notes: DUS: Drug Utilisation Study. HCP: Health Care Professionals. ICF: Informed Consent Form. L1: Launch date in the first European country participating in the study; LX: Launch date in other European countries participating in the study (Recruitment wave I: Switzerland: May2015; Germany: Aug2015; UK: Jul2015; Recruitment wave II: Belgium: Oct2016; Italy: Sep2016; Spain: Sep2016; Portugal: Mar2017). ΣLX: All medicinal products launched. M12: 12 months later. M18: 18 months later.
The launch of edoxaban in other European countries (LX) may also occur before the end of data collection for the first country.

3.1.4. STUDY POPULATION

The Study Population consists of patients that have been prescribed edoxaban since its launch in Europe.

Sites will be required to maintain a patient log of eligible patients at their treatment sites. This screening log will be captured within the case report form (CRF) and will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. The overall number of patients and sites may be adjusted during the study to meet enrolment goals, if needed. To the extent possible, consecutive patients meeting inclusion/exclusion criteria will be included in the study.

Inclusion/exclusion criteria: Patients can enter the study when they have at least one edoxaban prescription record in his/her medical record irrespective of the underlying health condition. No exclusion criteria are defined.

3.1.5. SAMPLE SIZE

The medical records of approximately 200 patients will be studied per country (sample would be representative dependent on country-specific volumes of edoxaban prescriptions) to approximately 1,200 treated patients in total across the 6 targeted European countries.

For characterization of users including potential off-label use, we present the level of precision in different scenarios of available number of users of edoxaban for different prevalence of diseases/conditions. In general, the 95% level of confidence is adequate for a prevalence as low as 1% and 1,200 users of edoxaban.

The sample size has been estimated based on the precision of a percentage, that is, the width of the 95% confidence interval (CI). **Table 1** presents the precision in the estimate of the proportion of use of edoxaban out of the labelled indication for tentative proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) and different sample sizes.

Table 1 Precision of estimation for proportions of 0.02, 0.03, 0.04, 0.05 (2%, 3%, 4%, 5%) of off-label use and increasing sample size

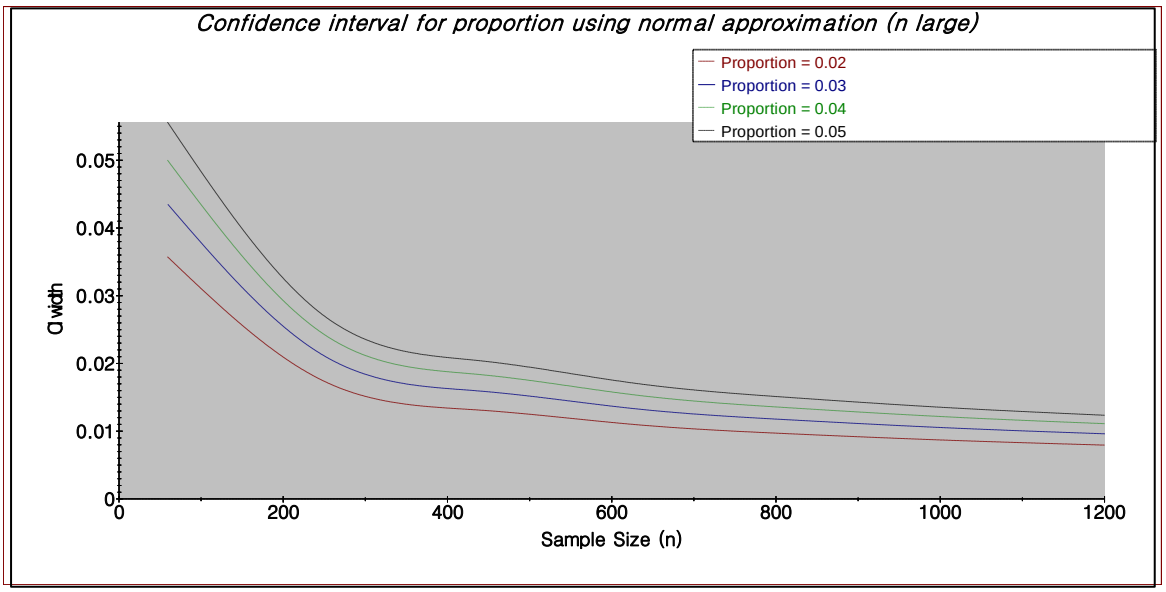
	Proportion											
	0.02			0.03			0.04			0.05		
Sample Size	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%	½ CI	L95%	U95%
200	0.019	0.001	0.039	0.024	0.006	0.054	0.027	0.013	0.067	0.030	0.020	0.080
400	0.014	0.006	0.034	0.017	0.013	0.047	0.019	0.021	0.059	0.021	0.029	0.071
600	0.011	0.009	0.031	0.014	0.016	0.044	0.016	0.024	0.056	0.017	0.033	0.067
800	0.010	0.010	0.030	0.012	0.018	0.042	0.014	0.026	0.054	0.015	0.035	0.065
1000	0.009	0.011	0.029	0.011	0.019	0.041	0.012	0.028	0.052	0.014	0.036	0.064
1200	0.008	0.012	0.028	0.010	0.020	0.040	0.011	0.029	0.051	0.012	0.038	0.062

Note: CI: 95% of Confidence Interval (CI); ½ CI: distance from proportion to lower/upper limit of the two-sided 95% CI (equals half of the width of the CI); L95%: lower limit of the 95% CI; U95%: upper limit of the 95% CI.

Table 1 shows that the width of the 95% CI decreases as sample size increases; samples greater than 500 patients enable the estimation of the proportion of off-label use with an acceptable degree of precision. Increasing the sample size beyond 600 patients shows additional (though small) effects on the width of the 95% CI. Therefore, the current aim of recruiting 1,200 patients will ensure reliable results.

A sample size of 600 patients for instance will allow the detection of a rate of 5% of off-label use with a precision of 1.7%. That is, the estimated proportion will be between 3.3% and 6.7%. A sample size of 1,200 patients will allow for an even higher precision, as a rate of 5% of off-label use is detected with a precision of 1.2%. That is, the estimated proportion will be between 3.8% and 6.2%.

Figure 2- Confidence Interval (CI) for half of CI width



In addition, it is estimated that approximately 100 physicians will have to complete the survey to allow reasonable precision around estimates of the physician's awareness and understanding levels.

In order to achieve robust results from the various statistical validation methods, it is recommended to have at least 10 physicians per questionnaire item/observation. This rule has been adopted as the standard for psychometric (fit for purpose) validation with its origin within the classical test theory of principal component analysis [Hatcher, L (1994)[2]].

No target thresholds for physicians reported awareness and understanding have been established in advance. However if it is assumed that 85% of physicians will demonstrate appropriate awareness and understanding of the survey. Given this, the lower bound of the 95% CI will be above 78% for a sample size of N=100 [Food and Drug Administration (FDA), FDA–2012–N–0408 (2012)[3]].

3.2. CHANGES TO ANALYSIS FROM OBSERVATIONAL PLAN

There are no changes in analysis nor definitions from those planned in the final observational plan.

4. PLANNED ANALYSES

The following analyses will be performed for this study:

- Snapshot analysis for the interim report
- Final analysis

4.1. SNAPSHOT ANALYSIS FOR THE INTERIM REPORT

A snapshot analysis for an interim report will take place at the end of the data collection of the first wave of countries (Switzerland, Germany and UK) on unclean data.

Derivations and definitions for the data snapshot analysis will be based on those required for the final analysis, unless deviations are stated. The list of tables, listings and figures (TLFs) to be provided for the data snapshot analysis will be a subset of the full TLFs shells set planned for the final analysis.

4.2. FINAL ANALYSIS

All final, planned analyses identified in this SAP will be performed by QuintilesIMS Real-World Evidence Solutions Biostatistics department following Daiichi Sankyo Europe GmbH (DSE) authorization of this SAP and after database lock (DBL).

4.3. ANALYSIS OF REPRESENTATIVENESS OF THE STUDY POPULATION

An ancillary study will be carried out with the aim to support and validate externally the ETNA-DUS sampling method of edoxaban in terms of prescribers' profile (*a-priori* and *a-posteriori* analysis) and patients' profile (*a-posteriori* analysis).

The *a-priori* analysis will serve to refine the sampling strategy for the full study (using regional and specialty distribution of prescribers).

The *a-posteriori* analysis will serve to assess the representativeness of prescribers and patients included in the full study.

Details of the analysis methodology is provided in a separate SAP for sample validation.

5. ANALYSIS SETS

5.1. ALL SUBJECTS SCREENED SET [SCR]

The all subjects screened set (SCR) will contain all subjects screened to participate to the study and with at least one edoxaban prescription record in his/her medical record irrespective of the underlying health condition.

5.2. FULL ANALYSIS SET [FAS]

The full analysis set (FAS) will contain all screened subjects who agreed to participate to the study and met inclusion criteria.

Patients who did not sign informed consent form, had no evidence of edoxaban prescription in patient's chart, or initiated edoxaban prescription linked to a clinical trial participation prior to launch date are not included in FAS.

5.3. ALL PARTICIPATING INVESTIGATORS SET [PIS]

The all participating investigators set (PIS) will contain investigators participating in the ETNA-DUS.

The investigators participating to the survey for evaluating the effectiveness of the physician educational program will be referred to as responders (PIS-responders). The investigators not participating to the survey will be referred to as non-responders.

6. GENERAL CONSIDERATIONS

6.1. LAUNCH DATE AND INDEX DATE

The launch date (LX) is the date when edoxaban is launched in the market and varies from country to country.

The index date is set 12 months after the launch date and indicates the date when the retrospective data collection can start in a country. It also indicates the last date of data collection in a country. An exception is made for United Kingdom, which index date is set 16 months after the launch date.

Table 2 below shows the launch and index dates for the different countries that take part to the ETNA-DUS.

Table 2 Launch dates and index dates by country

Country	Launch Date	Index Date	Recruitment Wave
Switzerland	01-May-15	01-Jul-16	I
Germany	01-Aug-15	24-Aug-16	I
United Kingdom	16-Jul-15	10-Nov-16	I
Belgium	01-Oct-16	Oct-17	II
Italy	09-Sep-16	Sep-17	II
Spain	01-Sep-16	Sep-17	II
Portugal	01-Mar-17	Mar-18	II

6.2. Reference Start Date and Study Day

Reference start date is defined as the date of first dose of edoxaban (Day 1 is the day of the first dose of edoxaban). See **Figure 3** below for a pictorial representation.

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

- If the date of the event is on or after the reference date then:

Study Day = (date of event – reference date) + 1.

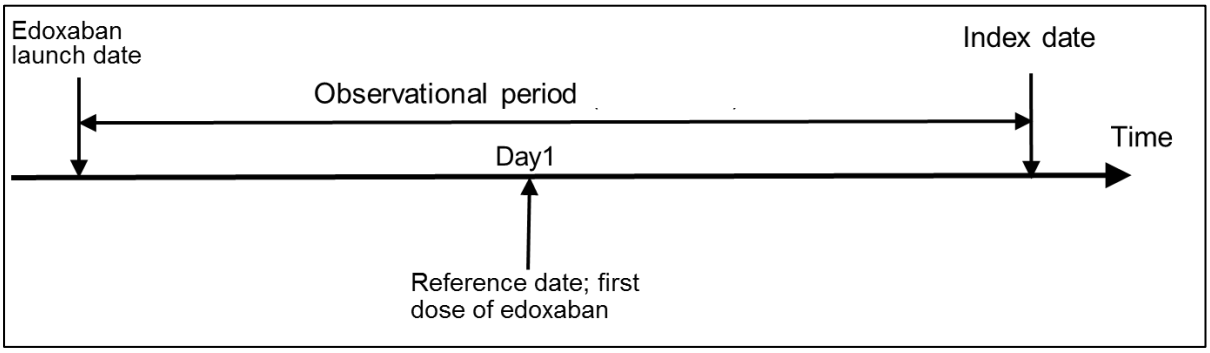
- If the date of the event is prior to the reference date then:

Study Day = (date of event – reference date).

As a results of these formulae, study day will never be equal to zero.

In the situation that the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day, and any corresponding durations, will be presented based on the imputations specified in Section 7.2.

Figure 3 – Reference start date and study day



Observational period is defined as the period from edoxaban launch date to index date. Observational period is 12 months except for UK, and 16 months for UK

6.3. Windowing Conventions

No visit windowing will be performed for this study.

Baseline data refer to data available on or prior to the reference date.

6.4. CONFIDENCE INTERVALS (CIS)

Confidence intervals (CIs) will be calculated around the proportion of on/off-label users (n). CIs for proportions will be computed as exact 95% CIs based on the binomial distribution, using the Clopper and Pearson method [Clopper, C. and Pearson, S. (1934)[4]].

Let p_L and p_U be the exact (Clopper and Pearson)[4] lower and upper confidence limits, respectively. For $n_1 = 1,2, \ldots, n-1$, the following equations are satisfied:

$$\sum_{x=n_1}^{n} \binom{n}{x} p_L^x (1-p_L)^{n-x} = \propto/2$$

$$\sum_{x=0}^{n_1} \binom{n}{x} p_U^x (1-p_U)^{n-x} = \propto/2$$

Thus, $p_L = 0$ when $n_1 = 0$, and $p_U = 1$ when $n_1 = n$.

The confidence limits follow the F distribution, where $F(\propto, b, c)$ is the $\propto$-th percentile of the F distribution, with b and c degrees of freedom. The exact confidence limits can be calculated using the following equations:

$$p_L = \left(1 + \frac{n - n_1 + 1}{n_1 F\left(1 - \propto/2\,, 2n_1, 2(n - n_1 + 1)\right)}\right)^{-1}$$

$$p_U = \left(1 + \frac{n - n_1}{(n_1 + 1) F\left(\propto/2\,, 2(n_1 + 1), 2(n - n_1)\right)}\right)^{-1}$$

6.5. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.2 or higher.

7. STATISTICAL CONSIDERATIONS

7.1. PRESENTATION OF SUMMARY STATISTICS

The analyses will be purely descriptive and no statistical testing will be carried out.

Categorical data will be presented using counts and percentages. Counts will be presented as whole numbers while percentages will be carried out to one decimal place. When CIs around the percentages are calculated, these will be presented to two decimal places.

For continuous data, n will be presented as a whole number. The minimum and maximum will be carried out to the same number of decimal places to which the data was reported (x). The mean, median, first quartile (Q1), and third quartile (Q3) will be carried out to one decimal place beyond the number to which the data was reported (x+1). Standard deviation (SD) will be carried out to x+2. Exceptions to these rules might be needed for very small

numbers which would otherwise round up to zero.

7.2. MISSING DATA

For categorical variables, the number and percent of patients with missing data [European Medicines Agency (EMA), (2011)[5]] will be reported for each outcome.

For continuous variables, the number of patients with missing data [European Medicines Agency (EMA), (2011)[5]] will be reported for each outcome as counts.

Missing medication dates will be imputed as specified below:

- Start dates:
  - If day is missing, this will be imputed to the 1st of the month
    - For edoxaban, if day is missing, this will be imputed to the 1st of the month or to the launch date, whichever comes first
  - If month and/or year is missing, these will not be imputed
- Stop dates:
  - If day is missing, this will be imputed to the last day of the month, or to the index date, whichever comes first
  - If month and/or year is missing, these will not be imputed

No other dates will be imputed.

Imputed dates will NOT be presented in the listings.

Imputed dates will be used for the classification of prior/concomitant/post medications. See section 16 for details on the classification of prior/concomitant/post medications.

7.3. EXAMINATION OF SUBGROUPS

Subgroup analyses by country will be performed for this study.

Additionally, the data will be examined after the interim analysis to determine if any other meaningful subgroups should be examined at the final analysis. Particular consideration will be given to patient subgroups for which there is missing information according to the RMP, if numbers permit (for a minimum of 20 subjects):

- Pregnant and/or breastfeeding women
- Pediatric patients (<18 years old)
- Patients with hepatic impairment with coagulopathy and clinically relevant bleeding risk
- Patients with severe renal impairment (defined as having Creatinine Clearance [CrCl] < 30 ml/min or end-stage renal disease (CrCl < 15 ml/min or on dialysis)
- Patients with mechanical heart valves

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

Templates for TLFs are provided in a separate document (TLFs Shells) and will describe the format and content of the summary TLFs to be provided by QuintilesIMS Biostatistics.

9. DISPOSITION AND WITHDRAWALS

The study population will be characterized by comparing the screened patients (SCR) and those who participate to the study (FAS).

To assess the representativeness of the sampled patient population, subjects disposition and reasons for non-inclusion will be presented for the SCR; reasons for withdrawal from the study will also be presented for the FAS.

10. SITE AND PHYSICIANS' CHARACTERISTICS

One of the primary objectives of this study is to characterize the sites and physicians (PIS) who took part in this ETNA-DUS.

The following site and physicians' characteristics will be reported for this study:

- Geographic location of physician site (i.e.: country, region)
- Type of setting (e.g.: private practice, university hospital)
- Type of physician (principal investigator/sub-investigator)
- Medical specialty of the physician (e.g.: general medicine, cardiology)
- Profession or area of primary practice (e.g., GPs, cardiologists, and other specialists)
- Patient volume and experience in treating patients taking edoxaban (e.g., volume of patients of the setting/unit per year, volume of patients treated with edoxaban/LIXIANA by each physician).

11. HEALTH-CARE PROVIDERS EDUCATIONAL MATERIAL KNOWLEDGE

One of the primary objectives of this study is to evaluate the effectiveness of the edoxaban educational material as a tool for risk minimization.

To assess the representativeness of the physicians who responded to the survey on the clinical knowledge on edoxaban (PIS-responders), the disposition and characteristics of the responders and non-responders will be presented for the PIS.

Furthermore, to assess the clinical knowledge HCP educational material knowledge will be presented for the PIS-responders.

The following information will be summarized in aggregate format:

1. **Survey administration variables:**
    - Number of physicians in the sample, in total and by key characteristic (country, region, type of setting, type of physician, medical specialty, and profession or area of primary practice)
    - Number of physicians attempted to contact
    - Number of physicians effectively contacted (corresponding to those attempted to contact since all physicians participating to the ETNA-DUS will be asked to participate to the survey)
    - Number of contacted physicians who agreed to participate
    - Of those who agreed to participate, number who completed survey (PIS-responders).
2. **Description of survey participants**
    - Medical specialty
    - Country
    - Setting (type, geography)
    - Experience with edoxaban (yes/no and if yes number of months)
    - Receipt of educational material (yes/no).
3. **Assessment of knowledge of the key messages of the educational program:**
    - Frequency and distribution of correct and incorrect responses to each survey question at site initiation and after 6 months
    - Frequency and distribution of changes in response to each survey question from site initiation to 6 months
    - Assessment of HCPs' opinion/satisfaction on the utility of educational material (frequency of answers to the survey questions: "You have not read the Prescriber's Guide, please select the most relevant reason that applies" and "You find the information in the Prescriber's Guide").

12. DEMOGRAPHIC CHARACTERISTICS AND MEDICAL HISTORY DATA

One of the primary objectives of this study is to characterize users of edoxaban.

The following demographic and medical history data will be presented for the FAS:

- Demographics, vital signs and life-style factors
    - Age/age category
    - Gender
    - If female, child-bearing potential
    - Height

- Body weight
- Body Mass Index (BMI)
- Smoking status
- Alcohol consumption

- Diagnosis (i.e., indication for prescription of edoxaban)
- Risk factors and treatment history
- Cardiovascular comorbidities (including valvular disease) and other relevant somatic comorbidities
- History of haemodialysis
- Relevant familial medical history
- History of past use of other anticoagulants
- Pregnancy and lactation status at the time of prescription
- Time and type of any surgery (including orthopaedic surgery) during the treatment with edoxaban
- Presence of mechanical heart valves
- Pertinent lab tests upon availability including liver function test, CrCl and/or Glomerular Filtration Rate (GFR) pertaining to possible hepatic or renal impairment.

13. DRUG UTILIZATION

One of the primary objectives of this study is to evaluate the pattern of use of edoxaban in the FAS.

The following drug utilization data will be reported for this study:

- Edoxaban prescription
  - Duration of treatment/ongoing treatment (including repeated prescriptions if any)
  - Daily dose (30 mg, 60mg, other) at the beginning of the treatment and afterwards
  - Reason for use
  - Type of discontinuation (permanent/suspension)
  - Reason of discontinuation (if applicable)

- Number of prescriptions of edoxaban per patient
- Concomitant medications (including dual antiplatelet therapy)

The number and percentage of patients in the following categories will be described:

- All users (100%)
- Patients categorized as inappropriate drug users which means improbable event of edoxaban use outside the labelled instructions as defined (See also Section 17):

(a) use in patients in which the product is contraindicated

(b) use in patients who are not under the indication label per SmPC (e.g.: patient<18 years old, pregnant/lactating women)

(c) use involving a different dose (e.g.: no dose reduction or dose reduction without reason, body weight), dosing regimen or route of administration

(d) use that demonstrates non-adherence to guidance in the label (see Section 17 for details on derivation)

- Patients in any other disease groups, by specific disease type (renal, hepatic impairment)
- Patients using concomitant drugs known to increase the risk of bleeding e.g., aspirin, NSAIDs.
- Any violation with regards to switching to a vitamin-K antagonist (VKA) (e.g.: Lixiana was taken as 15mg without switching to a VKA)
- Lixiana was not stopped 24h prior to surgery
- Once a day administration

14. ADVERSE DRUG REACTIONS (ADRS)

The occurrence of adverse drug reactions (ADRs) (yes/no) will be reported on the FAS, by country, and by renal and hepatic impairment subgroups.

Line listings with details of ADRs experienced by patients will be appended to the clinical study report and will not be part of the statistical analysis.

15. MEDICATIONS

Medications will be classified as prior, concomitant, post or non-concomitant with respect to edoxaban (**Figure 4**). Section 7.2 provides details on handling of partial dates for medications. Section 16 provides details on the classification of prior/concomitant/post medications. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study medication (date of first dose of edoxaban).

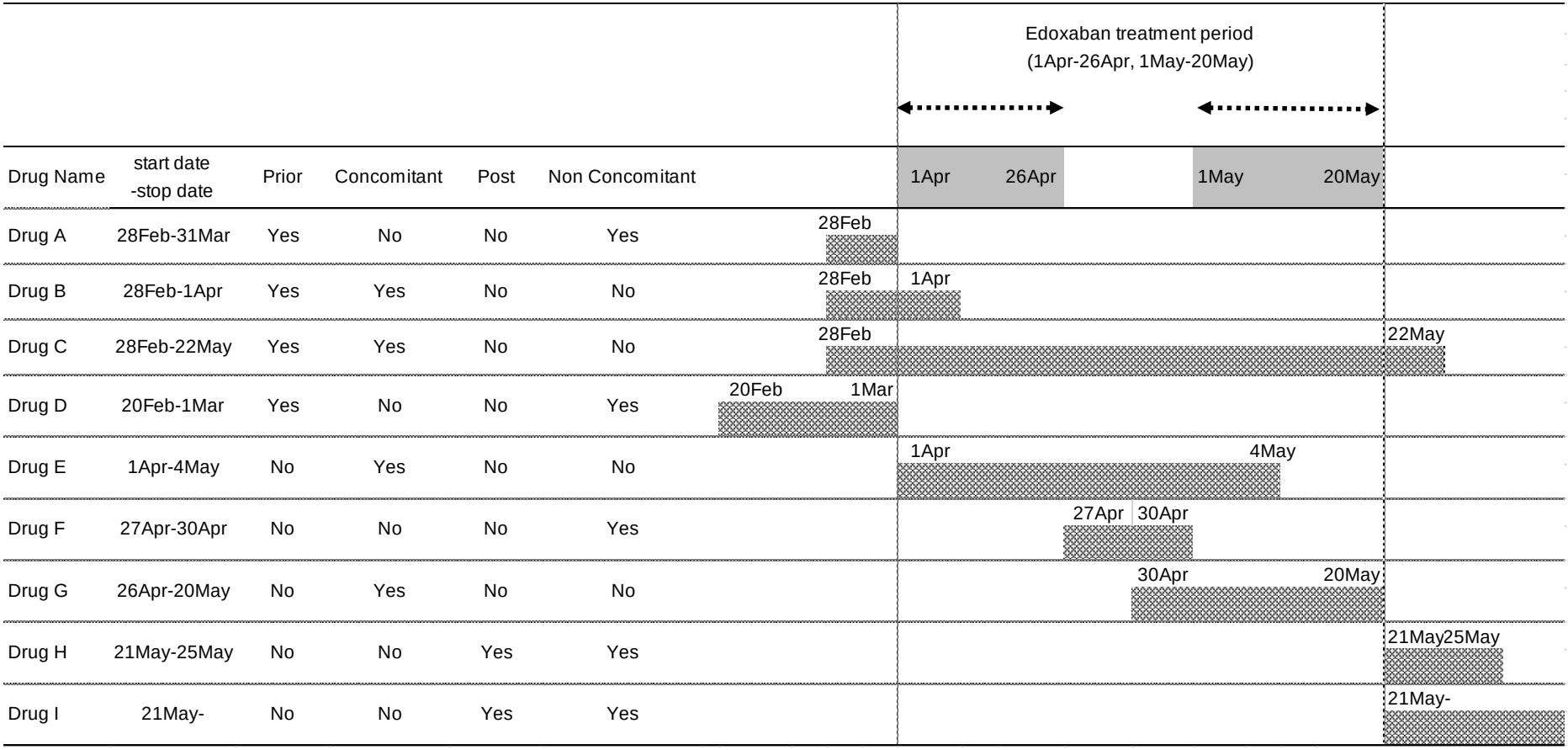
- 'Concomitant' medications are medications taken during a period of edoxaban intake up to and including day of edoxaban suspension or permanent discontinuation, if edoxaban was interrupted.

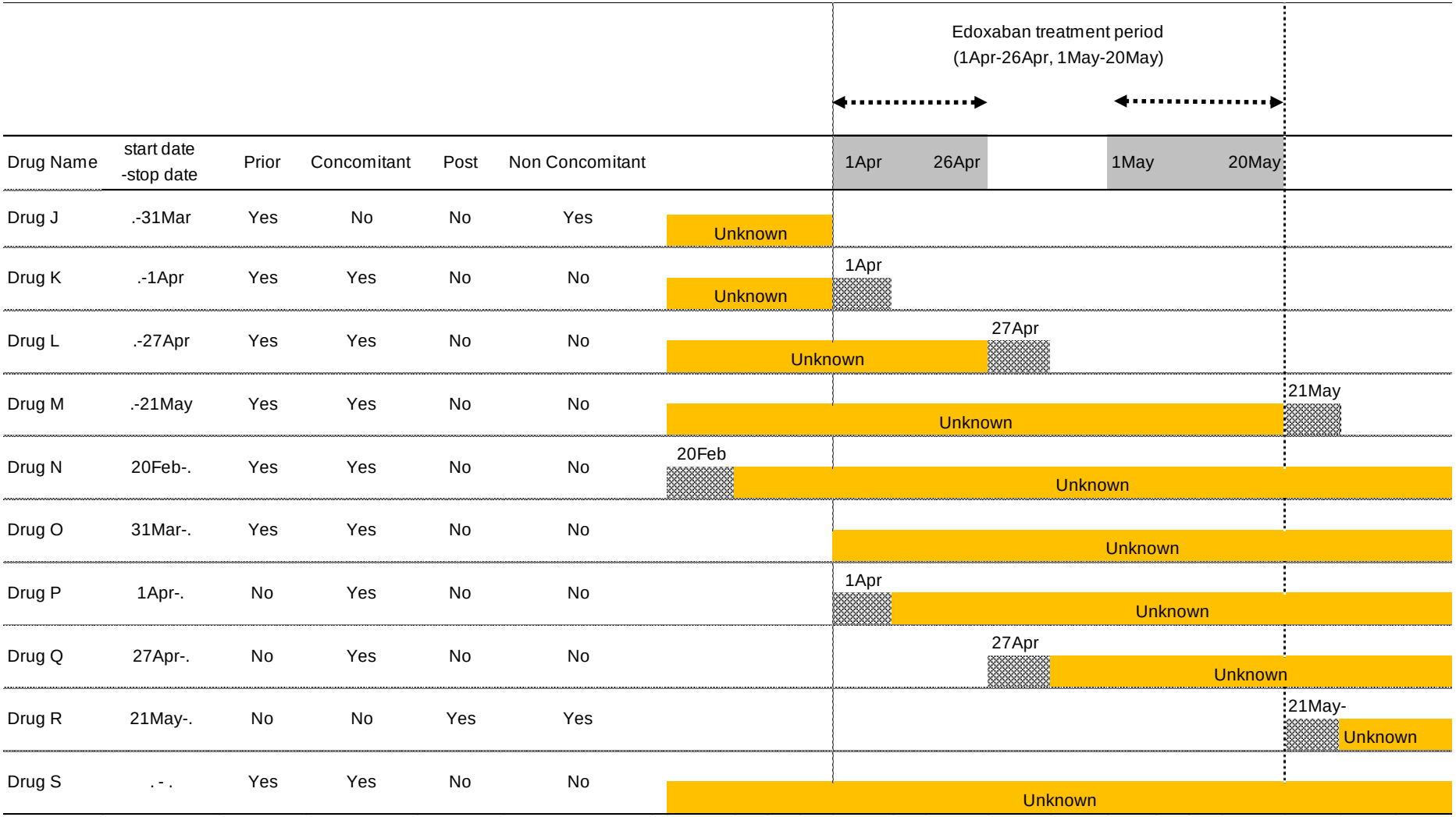
- 'Post' medications are medications which started following the last dose of study medication (permanent discontinuation).

- 'Non Concomitant' medications are medications which:

    - started and stopped prior to the first dose of study medication,
    - OR started following edoxaban suspension and stopped before edoxaban was re-started,
    - OR started following edoxaban permanent discontinuation.

Figure 4 Case Scenarios of Prior / Concomitant / Post Medications:





Drug Name	start date -stop date	Prior	Concomitant	Post	Non Concomitant
Drug J	.-31Mar	Yes	No	No	Yes
Drug K	.-1Apr	Yes	Yes	No	No
Drug L	.-27Apr	Yes	Yes	No	No
Drug M	.-21May	Yes	Yes	No	No
Drug N	20Feb-.	Yes	Yes	No	No
Drug O	31Mar-.	Yes	Yes	No	No
Drug P	1Apr-.	No	Yes	No	No
Drug Q	27Apr-.	No	Yes	No	No
Drug R	21May-.	No	No	Yes	Yes
Drug S	. - .	Yes	Yes	No	No

16. ALGORITHM FOR PRIOR / CONCOMITANT / POST MEDICATIONS

START DATE	STOP DATE	ACTION
Known	Known	If MED stop date < EDOX start date of 1st dose, assign as prior medication *If only one prescription of EDOX was given:* If MED stop date >= EDOX start date and MED start date <= (end of EDOX treatment), assign as concomitant medication *If more than one prescription of study medication was given:* [If MED stop date >= min(EDOX start date for all prescriptions) and MED start date <= (end of EDOX treatment)] and [(MED start date ≥ EDOX stop date for one of the prescriptions) AND (MED stop date < EDOX start date of the following prescription OR no following prescriptions exist)], assign as concomitant medication If MED stop date >= EDOX start date and MED start date > (end of EDOX treatment), assign as post medication
Known	Missing	If MED stop date is missing could never be assumed a prior medication If MED start date <= (end of EDOX treatment), assign as concomitant medication If MED start date > end of EDOX treatment, assign as post medication
Missing	Known	If MED stop date < EDOX start date of 1st dose, assign as prior medication If MED stop date >= EDOX start date, assign as concomitant medication
Missing	Missing	Assign as concomitant medication

MED = medication other than Edoxaban
EDOX = edoxaban

17. DERIVATIONS

17.1. AGE:

Year part of (reference date) – Birth year

Age categories are defined as:

- <18 years old
- ≥18 and <65 years old
- ≥65 and <75 years old
- ≥75 years old

17.2. TOTAL DAILY DOSE FOR CONCOMITANT MEDICATIONS, INCLUDING ANTIPLATELET DRUGS:

DOSE	DOSING FREQUENCY	ACTION
Known	Once	Assign as missing
	Once daily	Assign as dose
	Twice daily	Assign as 2 x dose
	Three time daily	Assign as 3 x dose
	Weekly	Assign as dose/7
	PRN (as needed)	Assign as missing
	Every 4 hours	Assign as 6 x dose
	Every other day	Assign as dose/2
	Other	Assign as missing
	Unknown	Assign as missing
Unknown	Once	Assign as missing
	Once daily	Assign as missing
	Twice daily	Assign as missing
	Three time daily	Assign as missing
	Weekly	Assign as missing
	PRN (as needed)	Assign as missing
	Every 4 hours	Assign as missing
	Every other day	Assign as missing
	Other	Assign as missing
	Unknown	Assign as missing

17.3. CREATININE CLEARANCE CATEGORIZATION:

- If serum creatinine is available, apply the Cockroft-Gault formula to calculate creatinine clearance

  = {[[(140-age) x weight]/(72 x serum creatinine)] x sex}

  with sex=1 in males and sex=0.85 in females
- If serum creatinine is not available, use reported Creatinine Clearance (CrCl) if available
- If < 30 mL/min then creatinine clearance group="<30 mL/min"
- If ≥ 30 mL/min and ≤ 50 mL/min then creatinine clearance group="≥ 30 and ≤ 50 mL/min"
- If > 50 mL/min and ≤ 80 mL/min then creatinine clearance group=" > 50 and ≤ 80 mL/min"
- If > 80 mL/min then creatinine clearance group="> 80 mL/min"

17.4. RENAL IMPAIRMENT:

- If serum creatinine is available, apply the Cockroft-Gault formula

  = {[[(140-age) x weight]/(72 x serum creatinine)] x sex}

  with sex=1 in males and sex=0.85 in females, where
  - renal impairment is not present if value is greater than 80ml/min (Cockroft, 1976)
  - renal impairment is present if value is less or equal to 80 ml/min

  If serum creatinine lab value is expressed in µmol, multiply serum creatinine value by 88.4. (1 µmol/L = 88.4 mg/dL)
- If serum creatinine is not available, use reported Creatinine Clearance (CrCl) if available, where
  - renal impairment is not present if value is greater than 80ml/min
  - renal impairment is present if value is less or equal to 80 ml/min
- If serum creatinine and reported Creatinine Clearance (CrCl) are not available, use the investigators statement on renal disease, where
  - renal impairment is not present, if *"Renal Disease = No"* OR *"Renal Disease = Yes"* and *"stage of chronic kidney disease = Stage 1"*

- renal impairment is present if "*Renal Disease = Yes"* and "*stage of chronic kidney disease ≠ Stage 1*"

17.5. HEPATIC IMPAIRMENT:

- If *bilirubin>2xULN = Yes* AND *Aspartate Transaminase (AST)/* Alanine Transaminase *(ALT) >3xULN = Yes,* then *Hepatic Impairment = Yes*
- If *bilirubin>2xULN = No* OR *AST/ALT >3x upper normal limit (ULN) = No,* then *Hepatic Impairment = No*
- If *bilirubin>2xULN is missing* AND/OR *AST/ALT >3xULN is missing,* use the investigators statement on hepatic disorders, where hepatic impairment is present if *"Liver disease = Yes"* and no present if *"Liver disease = No"*

17.6. PATIENTS WITH HEPATIC IMPAIRMENT WITH COAGULOPATHY AND CLINICALLY RELEVANT BLEEDING RISK:

- This group is defined as *Hepatic impairment = Yes* AND (*Coagulopathy status = Yes* OR *Clinically relevant bleeding risk = Yes)*
- *Coagulopathy = Yes* in venous thromboembolism (VTE) patients with any VTE risk factors, or NVAF patients with one or more risk factor(s) which are components of CHA_2DS_2-VASC score
- *Clinically relevant bleeding risk = Yes* is defined as *History of major bleeding events = Yes*

17.7. DURATION OF EXPOSURE [WEEKS]:

Duration of exposure [weeks] = SUM [(stopdate$_i$ - startdate$_i$)+ 1))/7], where

i=1, 2, …, n,

'startdate$_i$' and 'stopdate$_i$' are start date and stop date for the i-th prescriptions of edoxaban in a given patient

stopdate for the last prescription=index date if no stop date after last start date available and no interruption/permanent discontinuation documented.

17.8. DEFINITION OF IMPROBABLE EVENT OF EDOXABAN USE OUTSIDE THE LABELLED INSTRUCTIONS:

Step 1 – Verification of the use of edoxaban based on the therapeutic indications:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart

failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults.
- other

Step 2 – Verification of the presence of any contraindication at the time of the initial prescription:

- Contraindications
  - Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC.
  - 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. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities. Recent is defined as < 6 months.
  - Uncontrolled severe hypertension.
  - Concomitant treatment with any other anticoagulants e.g. UFH, low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, rivaroxaban, apixaban etc.) except under specific circumstances of switching oral anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.
  - Pregnancy and breast-feeding.

Step 3 – Verification of adherence to the recommended dosing regimen for edoxaban:

- Posology
- Prevention of stroke and systemic embolism
  - The recommended dose is 60 mg edoxaban 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. Edoxaban and initial parenteral anticoagulant should not be administered simultaneously.
  - The duration of therapy for treatment of DVT and PE (VTE), and prevention of recurrent VTE should be individualized after careful assessment of the

treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, and immobilization) and longer durations should be based on permanent risk factors or idiopathic DVT or PE. Recent is defined as < 6 months.

- 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.

Step 4 – Verification of the use of edoxaban in special populations:

Boarder line users regarding what is recommended in the SmPC 4.4 Special warnings and precautions for use.

17.9. SURVEY QUESTIONNAIRE KEYS:

Question	Correct/Incorrect Answers					
	a	b	c	d	e	f
1	False	True	True	False	False	False
2	False	True	True	False	False	False
3	True	False	True	False	True	False
4	True	False	False	N/A	N/A	N/A
5	False	True	False	N/A	N/A	N/A
6	True	False	False	N/A	N/A	N/A
7	True	False	False	N/A	N/A	N/A
8	False	True	False	N/A	N/A	N/A
9	False	True	False	N/A	N/A	N/A
10	True	False	False	N/A	N/A	N/A
11	False	True	False	N/A	N/A	N/A
12	False	False	True	False	N/A	N/A
13	False	True	False	False	N/A	N/A
14	True	False	False	N/A	N/A	N/A
15	False	True	False	N/A	N/A	N/A
16-27	General questions. No correct/incorrect answer					

N/A: Not applicable

18. REFERENCES

[1] European Medicines Agency, 2016. SUMMARY OF PRODUCT CHARACTERISTICS - Lixiana (last update on 23rd September 2016). [Online] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf [Accessed 16 November 2016].

[2] Hatcher, L (1994) A step –by Step Approach to Using the SAS System for Factor Analysis and structural Equation Modeling. Cary; NC: SAS Institute, INC

[3] Center for Drug Evaluation and Research. Risk Evaluation and Mitigation Strategy Assessments: Social Science Methodologies to Assess Goals Related to Knowledge. United States Food and Drug Administration: Department of Health and Human Services. Docket No: FDA–2012–N–0408, 2012.

[4] Clopper, C. and Pearson, S. The use of confidence or fiducial limits illustrated in the case of the Binomial. Biometrika 26: 404-413, 1934.

[5] European Medicines Agency. Guideline on Missing Data in Confirmatory Clinical Trials. Retrieved December 15, 2011, from European Medicines Agency: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf

APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

Dates & Times

Depending on data available, dates will take the form yyyy-mm-dd.

Spelling Format

English US.

Listings

All listings will be ordered by the following (unless otherwise indicated in the template):

- Center-subject ID

Statistical Analysis Plan

EDOXABAN TREATMENT IN ROUTINE CLINICAL PRACTICE – DRUG UTILISATION STUDY (ETNA-DUS)

Prepared for:

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81379 Munich, Germany
Phone: +49 89 7808-0
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Observational Plan version used: Final version 05.08.2016

Case Report Form version used: Version 2.0 28.10.2016

Date Statistical Analysis Plan approved:

Preparation

Name	Responsibility	Signature	Date
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Joelle Asmar	Consultant, QuintilesIMS		28 Nov 2016
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	Petra Laeis	Head of Late Phase Clinical Operations, DAIICHI SANKYO EUROPE GmbH		01-Feb 2017
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	Wolfgang Zierhut	Head of Antithrombotic & Cardiovascular Therapeutic Area, DAIICHI SANKYO EUROPE GmbH	i.V.	01-FEB 2017
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Version No: 1.0

Date: [24/01/2017]

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Version No: 1.0

Date: [24/01/2017]

1. ABBREVIATIONS

Acronym	Definition
ADR	Adverse drug reaction
CHF	Congestive Heart Failure
CI	Confidence Interval
CRO	Contract Research Organisation
CSPV	Clinical Safety and Pharmacovigilance
DM	Data Management
DS	Daiichi Sankyo
DSE	Daiichi Sankyo Europe GmbH
DVT	Deep Vein Thrombosis
EMC	Electronical Data Capture
EMR	Electronical Medical Records
ENCePP®	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETNA-DUS	Edoxaban Treatment in routiNe clinical prActice – Drug Utilisation Study
FPI	First Patient In
GP	General Practitioners
HEOR	Health Economics Outcomes Research
ICH	International Council for Harmonisation
LPI	Last Patient In
MAH	Marketing Authorisation Holder
NC	National Coordinator
NOACs	New Oral Anticoagulants
NVAF	Non-valvular Arial Fibrillation
OACs	Oral Anticoagulants
PE	Pulmonary Embolism
IQR	inter quartile range
SAP	Statistical Analysis Plan
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TIA	Transient Ischaemic Attack
VTE	Venous Thromboembolism

2. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of Edoxaban patterns of use in real practice and the effectiveness of the educational programs data for Observational plan DSE-EDO-01-14-EU. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed.
This statistical analysis plan (SAP) is based on observational plan final version 4.0, dated 05August 2016.

Study Rationale

The ETNA-DUS aims to gain insight on how this new European medicinal product is going to be used in real practice. The ETNA-DUS will help identify prescription patterns, the effectiveness of the educational programs and promptly detect any safety concern, so that pharmacovigilance planning and risk management for Edoxaban could be effectively refined if necessary on an ongoing basis.

To maximize the representativeness of the physician and patient selection and hence the external validity of the study, Daiichi Sankyo Europe GmbH aims physician sites being selected using several tools, including intelligence databases, e.g., IMS LifeLink™, to obtain a representative sample of Edoxaban users (patients).

3. STUDY OBJECTIVES

3.1. Primary Objectives

The objectives are to support and validate externally the DUS sampling method of Edoxaban in terms of prescribers profile (a priori and posteriori analysis) and patients profile (a posteriori analysis).

- a priori analysis: to refine the sampling strategy for the full study (using regional and specialty distribution of prescribers).
- a posteriori analysis: to assess the representativeness of prescribers and patients included in the full study

3.2. Secondary Objectives

Non applicable

4. STUDY DESIGN

4.1. Study Type

This is a multinational, multicentre study using retrospective data from databases. Being retrospective, this study involves no intervention, and will not impact the usual medical care or affect the treatment of patients.

4.2. Study scope and information sources

A single database for all target countries is not available. Therefore, a study approach was chosen which includes multiple data sources to gather information for prescriber and patient treated with Edoxaban in European target countries:

- IMS RWD LRx (Longitudinal prescription database) will be used for the a priori analysis, to identify a representative sample of the prescribers in Switzerland, Germany, UK, Belgium and Italy. MIDAS National Prescription Audit and Medical Audit will be used for Spain. Based on these sources it is possible to retrieve general information on Edoxaban per speciality and geographic region.
- Longitudinal patient database (LPD, LRx, THIN, Patient Analyser) will be used to the a posteriori analysis to describe Edoxaban patients characteristics and to assess the representativeness of patients included in the full study

Data will be extracted from appropriate databases that are representative for the countries of the study.

Table 1 – Data sources by country

Country	wave	A priori analysis – Prescriber level information	A posterior analysis – Patient level information
		Database	**Database**
Switzerland	I	**IMS RWD LRx:** (Gps + Specialists) Approx 480 Pharmacies (around 24% of Swiss pharmacies for Pharmacy Channel and >50% of physicians for Self-dispensing (SD) physicians)	**IMS RWD LRx** (Gps + Specialists)
Germany	I	**IMS RWD LRx**: 12,800 pharmacies (60% national coverage)	**IMS RWD DA** (Gps + Specialists) Anonymized patient records collected from Patient Management software used by GPs and specialists
UK	I	**IMS RWD LRx:** 8,460 pharmacies (60% national coverage) **IMS Hospital Pharmacy Audit (HPA) :** records of products which are dispensed via hospital pharmacy (92 – 100% coverage depending of the Region)	**THIN**: Anonymized patient records collected from Patient Management software used by GPs
Belgium	II	**IMS RWD LRx:** 1,600 pharmacies (35% national coverage)	**IMS RWD LPD (300 Gps)** Anonymized patient records collected from Patient Management software used by GPs
Italy	II	**IMS RWD LRx:** 17.800 pharmacies (90% national coverage)	**IMS RWD LPD (560 Gps practices)** Anonymized patient records collected from Patient Management software used by GPs + Patient Analyser (Specialists)
Spain	II	**MIDAS National Prescription Audit** 92 Wholesalers; 1,200 pharmacies (sell in); 148 Hospitals (coverage: 92% sell in and 29% Hospital consumption) **Medical Audit** 965 doctors, GPs + 18 specialties. All places of practice, except in-patients	**NA**

4.3. Sample Selection

This study will be conducted using secondary data (physician's outpatient data) extracted from IMS Real Word Evidence databases in European countries.

4.3.1. Inclusion criteria

- For the a priori analysis: physician who have prescribed Edoxaban at least once during the A priori observation period.
- For the a posteriori analysis: Patients can be enrolled when they had at least one Edoxaban prescription record in his/her medical record during the A posteriori observation period.

4.3.2. Exclusion criteria

No exclusion criteria are defined

4.4. Observation Period

The overall observation time will cover period from Q2 2015 to Q3 2017. The observation time per country depends on the respective launch date of Edoxaban:

- Switzerland: May 2015
- UK: July 2015
- Germany: August 2015
- Italy and Spain: September 2016
- Belgium: October 2016

Table 2 – Observation period by country

Country	Launch of Edoxaban	Wave	A priori Analysis Observation time	A posteriori Analysis Observation time
Switzerland	01-May 2015	I	From June 2015 to May 2016	From May 2015 to May 2016
UK	07-July 2015	I	From July 2015 to Sept 2016	From July 2015 to Nov 2016
Germany	01 August 2015	I	From August 2015 to July 2016	From August 2015 to August 2016
Belgium	01 October 2016	II	From October 2016 to Sept 2017	From October 2016 to October 2017
Italy	01 Sept 2016	II	From Sept 2016 to Aug 2017	From Sept 2016 to Sept 2017
Spain	01 Sept 2016	II	From Sept 2016 to Aug 2017	From Sept 2016 to Sept 2017

4.5. Sample Size Calculation

All patients available in the data sources who fulfilled the inclusion criteria will be considered for the analysis.

4.6. Study Variables

The following variables will be included in the analysis:

- **Edoxaban information for the sampling strategy:**

To refine the sampling strategy for the full study and to identify a representative sample of the prescribers the following information will be collected for each country from an independent prescription data source:

- Geographic location (region) and /or Language region (DE-CH vs FR/IT-CH – Only for Switzerland)
- Specialty, profession or area of primary practice (eg., GPs, cardiologists, other specialists (hospital vs office based when applicable))

The information will be provided in Patients and/or Prescriptions and/ or Prescribers or Units dispensed level (depending of the country).

- **Edoxaban patients characteristics will be provided (when available in the EMR db)**
  - age(year) / age category(at 1st date of prescription during the period = reference date)
  - Gender
  - Weight

- **Indication (NVAF, VTE, Others): (diagnoses are mapped to ICD-10 classification) :**

A hierarchical approach will be used to assign prescriptions to the indication categories:

- In the first step only diagnoses associated with Edoxaban prescription (linked to the prescription or diagnoses on the same day) will be considered for this analysis.
  These diagnoses will be assigned into 2 categories:
  1/ Indication of interest: NVAF, VTE
  2/ Other diagnoses associated with Edoxaban prescription

- In case multiple diagnoses are recorded on the prescription day, a hierarchy will be used to assign a diagnosis to the prescription (hierarchy to be defined)

- If no diagnoses associated with prescription will be identified, in the second step diagnosis records of relevant conditions (NVAF, VTE) will be assessed within ±1 month around the Edoxaban prescription date. In case of multiple relevant diagnoses they will be prioritised as described above. If no diagnoses of relevant conditions are recorded within ±1 month around the prescription date the indication for prescription will be considered as "unknown".

- **Duration of Edoxaban prescription (days):**

Prescribed duration will be analysed based on duration instruction/recommendation reported by the physician.
In the case the duration recommendation is not recorded, the prescription duration will be estimated based on the quantity prescribed. The calculation will use the number of tablets/pack size and the prescribed daily dose.
The proportion of prescriptions with missing duration will be reported.

- **Dosage, daily dose (30 mg, 60mg, other):**

Prescribed daily dose will be analysed based on strength and dosage instruction/recommendation reported by the physician.
In the case the dosage recommendation is not recorded, prescribed daily dose will not be calculated. The proportion of prescriptions with missing dosage instruction/recommendation will be reported.

- **Concomitant medications:**

Concomitant use of medication will be stated in case of overlapping prescription durations of Edoxaban and the substances of interest (defined at Anatomical Therapeutic Chemical classification (ATC)).
Analysis will be conducted hierarchically. In the first step, all relevant substances of interest prescribed within prescription duration of Edoxaban will be identified and considered as concomitant. For the remaining Edoxaban prescriptions the 60 days period before Edoxaban prescription date will be examined. All relevant substances which were prescribed in this period and had overlapping prescription duration with Edoxaban will be considered as concomitant (to overlap with Edoxaban)

Table 3 – Substances of interest for concomitant medications

ATC Code	Molecule Name	Classification
L04AD01	ciclosporin	P-gp inhibitors
C01BD07	dronedarone	P-gp inhibitors
J01FA01	erythoromycin	P-gp inhibitors
J02AB02	ketoconazole	P-gp inhibitors
C01BA01	quinidine	P-gp inhibitors
C08DA01	verapamil	P-gp inhibitors
C01BD01	amiodarone	P-gp inhibitors
N03AB02	phenytoin	P-gp inducers
N03AF01	carbamazepine	P-gp inducers
N03AA02	phenobarbital	P-gp inducers
B01AC (except Aspirin)	Antiplatelets (except Aspirin)	Antiplatelets (except Aspirin)
A01AD05, B01AC06, B01AC56, C10BX02, N02BA01, N02BA51, N02BA71	Aspirin	- Low dose Aspirin ≤100mg - High dose Aspirin (>100mg)
M01A	NSAIDs	NSAIDs

- **Medical history:**

  Diseases and conditions of interest will be searched in all history period prior to the reference date (reference date = date of first prescription of Edoxaban on the study period). If the Disease or condition of interest has been recorded in the medical history, then the value will be equal to yes, if not then it will be equal to No.

  The ICD-10 diagnosis codification will be used to define the disease and condition of interest. List of ICD-10 will be provided and validated prior to the analysis.

Table 4 – Variables of interest by country

	Wave 1			Wave 2		
	Switzerland	**Germany**	**UK**	**Belgium**	**Italy**	**Spain**
Edoxaban and NOAC prescribers	**A prior analysis – Prescriber level information**					
• Geographic location (region)	✓	✓	✓	✓	✓	✓
• Language region	✓					
• Specialty	✓	✓		✓		✓
Edoxaban patients characteristics	**A posterior analysis – Patient level information**					
• Age(year) / age category	✓	✓	✓	✓	✓	
• Gender	✓	✓	✓	✓	✓	
• Weight		✓	✓	✓	✓	
• Indication		✓	✓	✓	✓	
• Dosage, daily dose	✓	✓	✓	✓	✓	
• Duration of prescription		✓	✓	✓	✓	
• Concomitant medications	✓	✓	✓	✓	✓	
• Medical History		✓	✓	✓	✓	

5. DERIVED VARIABLES

Non applicable.

6. COMMON CALCULATIONS

Age will be calculated as:

- Year part of (reference date) – Birth year

Age categories will be calculated as:

- < 18 years old
- ≥ 18 years old and < 65 years old
- ≥ 65 years old and < 75 years old
- ≥ 75 years old
- missing

Weight categories will be calculated as:

- ≤ 60 kg
- > 60 kg
- missing

7. STATISTICAL METHODOLOGY

7.1. Data Management

The processes for database management differ by country. Generally, data are stored at the database level and analysed locally. Statistical Analysis System (SAS) Software will be utilized for access to the raw data, to manage the analytic datasets and to conduct data analysis. The IMS Health data will be processed according to the standard operation procedures (SOPs) of IMS Health. The datasets extracted from the IMS® databases will be stored in IMS files to allow analysis in the future. If the study is conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures. This study will follow the relevant chapters of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Conference on Harmonisation (ICH) guidelines for data management.

7.2. General Analytical Aspects

All analyses will be conducted separately by country and database. According to the objectives of the study, the analyses will be descriptive and exploratory.
All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

No imputation on missing data will be done. Missing data will be presented in the table.
For categorical variables, the number and percent of patients with missing data will be reported for each outcome.
For continuous variables, the number of patients with missing data will be reported for each outcome as counts.

7.3. Statistical methods

7.3.1. Descriptive analysis

Descriptive statistics will be used to characterize prescribers and patients information.

Categorical data will be presented using counts and percentages. Counts will be presented as whole numbers while percentages will be carried out to one decimal place. When CIs around the percentages are calculated, these will be presented to two decimal places.

For continuous data, n will be presented as a whole number. The minimum and maximum will be carried out to the same number of decimal places to which the data were reported (x). The mean, median, inter quartile range (IQR) (Q1, and Q3) will be carried out to one decimal place beyond the number to which the data was reported (x+1). Standard deviation (SD) will be carried out to x+2.

7.3.2. Tests for comparing proportions and means between EMR sample population and DUS population

To compare variables between groups, we will look at standardized differences. The standardized differences is define as:

$$d = \frac{(\bar{x}_{group1} - \bar{x}_{group2})}{\sqrt{\frac{s^2_{group1} + s^2_{group2}}{2}}}$$, for continuous variables

And,

$$d = \frac{(\hat{p}_{group1} - \hat{p}_{group2})}{\sqrt{\frac{\hat{p}_{group1}(1-\hat{p}_{group1}) + \hat{p}_{group2}(1-\hat{p}_{group2})}{2}}}$$, for qualitative vairables

The groups will be considered as unbalanced if the standardized differences is greater than 0.1[1]. Moreover, standardized differences will only be calculated on the variables of interest, to be defined with the sponsor.

7.4. Statistical analyses

7.4.1. A priori analysis – Information for sampling strategy

Among Edoxaban prescriber's retrieved from databases, the number and percentage of the following categories will be described:

- Speciality of the prescriber (not available for UK and Italy)
  - Identification of main prescribers
  - Number and percentage of prescribers (if available)
  - Number and percentage of patients (if available)
  - Number and percentage of prescriptions (if available)
  - Number and percentage of units dispensed (if available)
- Geographical location of the prescriber
  - Number and percentage of prescribers (if available)
  - Number and percentage of patients (if available)
  - Number and percentage of prescriptions (if available)
  - Number and percentage of units dispensed (if available)
- Geographical location of the prescriber for the main specialities
  - Number and percentage of prescribers (if available)
  - Number and percentage of patients (if available)
  - Number and percentage of prescriptions(if available)
  - Number and percentage of units dispensed (if available)

7.4.2. A posteriori analysis – Information for Edoxaban patient representativeness validation

- Edoxaban patients' demographic characteristics: age, gender,
- Edoxaban prescriptions characteristics: dosage, duration, indication, concomitant medication
- Edoxaban patients' medical history

7.5. Handling bias, missing values and loss of follow-up

The study will be conducted using health information recorded in population-based databases that collect and record data on a regular basis.

However, there are limitations in the conduct of this study

- Edoxaban is a new drug so the number of patients and amount of follow-up for the Edoxaban patients may be limited (in particular for the posteriori analysis).
- Potential for missing/incomplete data: No individual patient identifiers will be available. It is therefore impossible to query the physicians providing the data for any missing information.

[1] Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biometr J* 2009; **51**: 171–184.

- Recording of the indication of each prescribed treatment is mandatory in the physician software, but the physicians are free to enter any diagnosis and can for instance enter the reason of visit (e.g. flu) as indication for all treatments prescribed at the visit.
- For Belgium, Germany and Italy, we will not have information on Hospital data.
- For Spain, the a posteriori analysis will not be performed (no National coverage EMR data available in Spain).

Due to the nature of this database study, non-imputing process will be applied. The analyses will be based on available data.

8. DESCRIPTION OF STATISTICAL TABLES :

The tables will be performed for each country separately. The comparison through standardize differences will be performed only on the variables of interest (to be defined with the sponsor).

8.1. A priori analysis

Table 1. Specialty of Edoxaban prescriber

	Number of prescribers		Number of patients treated with edoxaban		Number of prescriptions/deliveries	
	EMR sample population (N)	DUS population (N)	EMR sample population (N)	DUS population (N)	EMR sample population (N)	DUS population (N)
Specialty						
GP's	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Spe1	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Spe2	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
...	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Spe n	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Hospital	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Total	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Geographic region						
Region 1	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Region 2	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Region 3	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Region 4	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
....	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Region n	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)
Total	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)	XX (X%)

Table 2. Geographic region per specialty of Edoxaban prescriber - unit =Patients / Prescriptions/Prescribers/units dispensed

	GP		Spe1		Spe2		Total	
	EMR sample population (N)	DUS population (N)	EMR sample population (N)	DUS population (N)	EMR sample population (N)	DUS population (N)	EMR sample population (N)	DUS population (N)
Geographic region								
Region 1	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)
Region 2	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)
Region 3	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)
Region 4	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)
....	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)
Region n	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%)
Total	XX (x%)	XX (x%)	XX (x%)	XX (x%)	XX (x%	XX (x%)		

8.2. A posteriori analysis

The tables will be performed for each country separately. The comparison through standardize differences will be performed only on the variables of interest (to be defined with the sponsor).

Table 1. Population demographic characteristics

	EMR sample population (N)	DUS population (N)	Standardized difference
Age at edoxaban initiation (years)			
Mean (SD[1])	xx.x (xx.xx)	xx.x (xx.xx)	x.xxx
Median	xx.x	xx.x	
Q1, Q3	xx.x, xx.x	xx.x, xx.x	
Min, Max	xx, xx	xx, xx	
Missing	xx	xx	
Age at edoxaban initiation by classes			
< 18 years old	xx (xx.x)	xx (xx.x)	
≥ 18 years old and < 65 years old	xx (xx.x)	xx (xx.x)	
≥ 65 years old and < 75 years old	xx (xx.x)	xx (xx.x)	
≥ 75 years old	xx (xx.x)	xx (xx.x)	
Missing	xx	xx	
Gender			
n	xx	xx	
Male	xx (xx.x)	xx (xx.x)	x.xxx
Female	xx (xx.x)	xx (xx.x)	
Missing	xx	xx	
Weight			
n	xx	xx	
<=60 kg	xx (xx.x)	xx (xx.x)	
>60 kg	xx (xx.x)	xx (xx.x)	x.xxx
Missing	xx	xx	

Percentages are calculated with the total of non-missing information 'n' in the denominator unless otherwise indicated.
[1] SD = Standard Deviation

Table 2. Medical history for initial prescription

	EMR sample population (N)	DUS population (N)	Standardized difference
Atrial Fibrillation (AF), n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Venous Thromboembolic Event (VTE) n(%),			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Valvular Heart Disease, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Renal disease, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Hepatic disorder, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Malignancy, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Fracture/Trauma, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Stroke, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Major bleeding event, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Digestive Tract Disease, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	

	EMR sample population (N)	DUS population (N)	Standardized difference
Hypertention, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Peripheral Vascular Disease , n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Diabetes Mellitus, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Chronic Obstructive Pulmonary Disease (COPD) , n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Sleep Apnea, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Dyslipidemia, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Hyper/Hypothyroidism, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Thrombocytopenia (i.e.: <100000/µL) , n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Chronic Thromboembolic Pulmonary Insufficiency, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Arthritis, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	

	EMR sample population (N)	DUS population (N)	Standardized difference
Coronary Heart Disease, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Ischemic Cardiomyopathy, n(%)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	

Table 3. Past Use of Anticoagulants during observational period

	EMR sample population (N)	DUS population (N)	Standardized difference
Other anticoagulants			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
VKA (Vitamin-K Antagonists)			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
VKA type			
Warfarin	xx (xx.x)	xx (xx.x)	
Phenprocumon	xx (xx.x)	xx (xx.x)	
Acenocumarol	xx (xx.x)	xx (xx.x)	
Fluindione	xx (xx.x)	xx (xx.x)	
Other	xx (xx.x)	xx (xx.x)	
Oral Non-VKA			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Non-VKA type			
Apixaban	xx (xx.x)	xx (xx.x)	
Dabigatran	xx (xx.x)	xx (xx.x)	
Rivaroxaban	xx (xx.x)	xx (xx.x)	
Heparin/Fondaparinux			
Yes	xx (xx.x)	xx (xx.x)	x.xxx
No	xx (xx.x)	xx (xx.x)	
Heparin/Fondaparinux type			
Unfractionated Heparin	xx (xx.x)	xx (xx.x)	
LMW (low molecular weight) Heparins	xx (xx.x)	xx (xx.x)	
Fondaparinux	xx (xx.x)	xx (xx.x)	

Table 4. Edoxaban Utilization Pattern

	EMR sample population (N)	DUS population (N)	Standardized difference
Duration of edoxaban prescription (days)			
n	xx	xx	
Mean (SD[1])	xx.x (xx.xx)	xx.x (xx.xx)	x.xxx
Median	xx.x	xx.x	
Q1, Q3	xx.x, xx.x	xx.x, xx.x	
Min, Max	xx, xx	xx, xx	
Missing	xx	xx	
Frequency			
n	xx	xx	
Once daily	xx (xx.x)	xx (xx.x)	x.xxx [1)]
Twice daily	xx (xx.x)	xx (xx.x)	
Three times daily	xx (xx.x)	xx (xx.x)	
Missing	xx (xx.x)	xx (xx.x)	
Other	xx (xx.x)	xx (xx.x)	
Total daily dose (mg)			
n	xx	xx	
30 mg	xx (xx.x)	xx (xx.x)	
60 mg	xx (xx.x)	xx (xx.x)	x.xxx [2)]
Other	xx (xx.x)	xx (xx.x)	
Missing	xx (xx.x)	xx (xx.x)	
Total daily dose (mg) for patient with Renal Impairment			
n	xx	xx	
30 mg	xx (xx.x)	xx (xx.x)	x.xxx [3)]
60 mg	xx (xx.x)	xx (xx.x)	
Other	xx (xx.x)	xx (xx.x)	
Missing	xx (xx.x)	xx (xx.x)	
Indication:			
n	xx	xx	
Non-valvular atrial fibrillation (NVAF)	xx (xx.x)	xx (xx.x)	x.xxx
Venous Thromboembolic (VTE)	xx (xx.x)	xx (xx.x)	x.xxx
Other	xx (xx.x)	xx (xx.x)	

	EMR sample population (N)	DUS population (N)	Standardized difference
Edoxaban ongoing at the end of the observation period			
n	xx	xx	
Yes	xx (xx.x)	xx (xx.x)	
No	xx (xx.x)	xx (xx.x)	

1) Standardized difference for once daily or not
2) Standardized difference for 60mg or not
3) Standardized difference for 30mg or not

Table 5. Use of Medications Other than Edoxaban: concomitant

	EMR sample population (N)	DUS population (N)	Standardized difference
Concomitant medication to Edoxaban			
n	xx	xx	
Treatment type			
P-gp inhibitors (ciclosporin, dronedarone, erythoromycin, or ketoconazole)	xx (xx.x)	xx (xx.x)	x.xxx
ciclosporin	xx (xx.x)	xx (xx.x)	
dronedarone	xx (xx.x)	xx (xx.x)	
erythoromycin	xx (xx.x)	xx (xx.x)	
ketoconazole	xx (xx.x)	xx (xx.x)	
P-gp inhibitors (quinidine, verapamil, amiodarone)	xx (xx.x)	xx (xx.x)	x.xxx
quinidine	xx (xx.x)	xx (xx.x)	
verapamil	xx (xx.x)	xx (xx.x)	
amiodarone	xx (xx.x)	xx (xx.x)	
P-gp inducers (phenytoin, carbamazepine, phenobarbital)	xx (xx.x)	xx (xx.x)	x.xxx
phenytoin	xx (xx.x)	xx (xx.x)	
carbamazepine	xx (xx.x)	xx (xx.x)	
phenobarbital	xx (xx.x)	xx (xx.x)	
Antiplatelets	xx (xx.x)	xx (xx.x)	x.xxx
Treatment 1	xx (xx.x)	xx (xx.x)	
Treatment 2	xx (xx.x)	xx (xx.x)	
Treatment X	xx (xx.x)	xx (xx.x)	
Low dose Aspirin (≤100 mg/day)	xx (xx.x)	xx (xx.x)	x.xxx
High dose Aspirin (>100 mg/day)	xx (xx.x)	xx (xx.x)	x.xxx
NSAIDS	xx (xx.x)	xx (xx.x)	x.xxx
Treatment 1	xx (xx.x)	xx (xx.x)	
Treatment 2	xx (xx.x)	xx (xx.x)	
Treatment X	xx (xx.x)	xx (xx.x)	