OBSERVATIONAL PLAN

ETNA-VTE-EUROPE

Non-Interventional Study on Edoxaban Treatment in Routine Clinical Practice in Patients with Venous Thromboembolism in Europe

DSE-EDO-05-14-EU

Sponsor/MAH:

Daiichi Sankyo Europe GmbH

Zielstattstrasse 48

81379 Munich, Germany

PPD

Version Number: 4.0

Date of Version: 12 August 2016

(EU- PAS register number –EUPAS15504)

PASS INFORMATION

Title	Non-interventional study on **E**doxaban **T**reatment in routi**N**e clinical pr**A**ctice in patients with **V**enous **T**hrombo**E**mbolism in **Europe (ETNA-VTE-Europe)**
Protocol version identifier	DSE-EDO-05-14-EU; Version 4.0
Date of last version of protocol	12 August 2016
EU PAS register number	EUPAS15504
Active substance	Edoxaban tosilate (Proposed ATC: B01AF03)
Medicinal product	Lixiana®
Product reference	EMEA/H/C/002629
Procedure number	EMEA/H/C/002629/MEA/007
Marketing authorisation holder(s)	Daiichi Sankyo Europe GmbH
Joint PASS	No
Research Question and Objectives	Primary objective is the analysis of the overall symptomatic VTE recurrence rate during an overall observational period of 18 months in unselected patients with acute VTE. The co-primary objective of this study is to collect and evaluate real-world safety data on bleeding events, drug related adverse events such as liver adverse events, and mortality (VTE-related, CV mortality, and all-cause mortality) in patients treated with edoxaban. The results relating to safety and effectiveness of this study will be compared with the respective results of other anticoagulants obtained from the PREFER in VTE registry. This registry uses highly harmonised endpoint definitions and will provide comparative data for patients treated with Vitamin K Antagonists (VKAs) and NOACs. In addition, the data obtained in the randomized Hokusai-VTE trial will be used as external comparator for the interpretation of the data collected in the unselected population of this study. The secondary objective is to assess the effect of edoxaban on the symptomatic VTE recurrence rate for patients on edoxaban, the symptomatic VTE recurrence rate for patients who discontinued edoxaban, patient relevant outcomes such as strokes (ischaemic and haemorrhagic), systemic embolic events (SEE), hospitalisations related to CV condition (including VTE related hospitalisation), post-thrombotic syndrome (PTS), extent of exposure and compliance to

Title	Non-interventional study on **E**doxaban **T**reatment in routi**N**e clinical pr**A**ctice in patients with **V**enous **T**hrombo**E**mbolism in **Europe (ETNA-VTE-Europe)**
	edoxaban therapy (judged by the investigator), rate and reasons of permanent discontinuation of edoxaban. The results related to the secondary objective will be compared with external databases (PREFER in VTE and Hokusai-VTE) in the same way as the data related to primary and co-primary objectives. Subgroup analyses will be performed in predefined patient populations for primary and secondary objectives.
Country (-ies) of study	Austria, Belgium, France, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland, United Kingdom
Authors	PPD
Marketing authorisation holder(s)	Daiichi Sankyo Europe GmbH Zielstattstr. 48 81379 Munich, Germany PPD
MAH contact person	PPD

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1. SIGNATURES

PPD

12-08-2016

Clinical Operations and Real World Evidence and International Project Leader
Daiichi Sankyo Europe GmbH — Date

PPD

12.08.16

for Pharmacovigilance
Daiichi Sankyo Europe GmbH — Date

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Physician
Daiichi Sankyo Europe GmbH — Date

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16-08-2016

Daiichi Sankyo Europe GmbH — Date

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AF	Atrial Fibrillation
ALT	Alanine Transaminase
AST	Aspartate Transaminase
BMI	Body Mass Index
BL	Baseline
CA	Competent Authority
CDISC	Clinical Data Interchange Standards Consortium
CHADS2	Risk factor score [derived from cardiac failure, hypertension, age, diabetes, stroke (doubled)]
CHA2DS2-VASc	Risk factor score [derived from cardiac failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled)-vascular disease, age 65–74 and sex category (female)]
CHD	Coronary Heart Disease
CI	Confidence Interval
COP	Clinical Operations Plan
CrCl	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organisation
CSPV	Clinical Safety and Pharmacovigilance
CV	Cardiovascular
DACH	Acronym for the region consisting of Germany, Austria and Switzerland
DB	Database
DM	Data Management
DS	Daiichi Sankyo
DSE	Daiichi Sankyo Europe GmbH
DVT	Deep Vein Thrombosis
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture

EMA	European Medicines Agency
FPI	First Patient In
FU	Follow Up
FXa	Factor Xa
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HAS-BLED	Score for assessment of bleeding risk [hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomitantly]
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
ID	Identification Number
IEC	Independent Ethics Committee
INR	International Normalised Ratio
IPL	International Project Leader
LPI	Last Patient In
LPO	Last Patient Out
LSO	Local safety officer
MAH	Marketing Authorisation Holder
MI	Myocardial Infarction
MedDRA	Medical Dictionary for Regulatory Activities
NOAC	Non-Vitamin K Oral Anticoagulant
NC	National Coordinator
NIS	Non-interventional Study
NVAF	Non-Valvular AF
OAC	Oral Anticoagulant
PASS	Post-Authorisation Safety Study
PE	Pulmonary Embolism
PRAC	Pharmacovigilance Risk Assessment Committee
PREFER in VTE	Prevention of Thromboembolic Events – European Registry in Venous Thromboembolism

pSOC	Primary System Organ Class (MedDRA)
PT	Preferred Term (MedDRA)
PTS	Post-thrombotic syndrome
SADR	Serious Adverse Drug Reaction
SAP	Statistical Analysis Plan
SC	Steering Committee
SAS®	Statistical Analysis Software
SDTM	Study Data Tabulation Model (CDISC)
SEE	Systemic Embolic Event
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist
VTE	Venous Thromboembolism

3. RESPONSIBLE PARTIES

Senior International Project Leader
Daiichi Sankyo Europe GmbH

PPD

Chair of Steering Committee

PPD

European Qualified Person for Pharmacovigilance
Daiichi Sankyo Europe GmbH

PPD

Safety Physician
Daiichi Sankyo Europe GmbH

PPD

Head of Antithrombotics & Cardiovascular
Daiichi Sankyo Europe GmbH

PPD

Study Data Manager Daiichi Sankyo Europe GmbH	PPD
Study Statistician Daiichi Sankyo Europe GmbH	PPD
Contract Research Organisation **Project Leader** Responsible for the conduct of the study in the Switzerland, Austria, Belgium, Ireland, The Netherlands and the United Kingdom and for overall Data Management, Biostatistics and Medical Writing	**Quintiles Switzerland Sàrl** **Real-World Late Phase Research** PPD
Contract Research Organization **Project Leader** Responsible for the conduct of the study in Germany	**SSS International Clinical Research GmbH** PPD
Contract Research Organisation **Project Leader** Responsible for the conduct of the study in France	**ITEC Services** PPD

Contract Research Organisation **Project Leader** Responsible for the conduct of the study in Italy	**Hippocrates Research S.r.l**. PPD
Contract Research Organisation **Project Leader** Responsible for the conduct of the study in Spain and Portugal	IMS Health PPD
Contract Research Organisation **Adjudication Coordinator** Responsible for Coordinating the Event Adjudication	**IPPMed GmbH** PPD

3.1. Steering Committee

The Steering Committee (SC) is the primary group with supervisory responsibility for all aspects of the conduct of this non-interventional PASS in venous thromboembolism (DSE-EDO-05-14-EU). It is contributing to the design of the study, ensuring the maintenance of the scientific quality and integrity of conduct and will support the team in all study related aspects during the run of the study. The SC will evaluate the results together with the Daiichi Sankyo Project Team and will review the study report as well as publications based on the results of the PASS.

The SC consists of external renowned members of the scientific community with a strong medical background in the treatment of VTE and specialists in health economics, biostatistics and epidemiology. Each country will contribute at least one member to the SC. The responsibilities of the SC are:

- Participation in Steering Committee meetings
- Scientific and medical advice prior, during and after the study, including evaluation and interpretation of the results of the study
- Advice in observational plan and electronic case report form (eCRF) development
- Support the performance of the study as a contact person for sites and other personnel involved in the study (act as National Coordinating site for the country)
- Chair and lead local meetings in local language in the corresponding country, if deemed necessary
- Provide scientific and medical advice regarding the PASS results
- Reconciliation of safety and efficacy outcomes
- Support and advice on publication, abstracts, posters, journals and congresses in connection with the study.

To facilitate and drive decisions there will be an executive board that will meet more frequently.

In addition, four selected persons of the Daiichi Sankyo Project Team have been assigned as Steering Committee members from the following functions: Medical Affairs, Late Phase Clinical Operations and Real World Evidence, Clinical Safety and Pharmacovigilance, Biostatistics. These members will participate in the meetings as non-voting members. Members are displayed in Table 1 and Table 2.

Table 1: Voting members of the Steering Committee and National Coordinators (members of the executive board are marked with an asterisk)

Chair	PPD	Guy's and St Thomas' NHS Foundation Trust, King's College London, United Kingdom	SC*, NC
Italy	PPD	University of Perugia, Santa Maria della Misericordia Hospital	SC*, NC
Austria	PPD	Medical University of Vienna	SC, NC
Belgium	PPD	Cliniques Universitaires Saint-Luc, Bruxelles	SC, NC
France	PPD	Centre Hospitalier Universitaire de Saint-Etienne	SC*, NC
Germany	PPD	Hospital of the Ludwig-Maximilians-University (LMU) Munich	SC*, NC
Ireland	PPD	Mater Hospital, Dublin	SC, NC
The Netherlands	PPD	Academisch Medisch Centrum, Amsterdam	SC, NC
Portugal	PPD	Hospital Santa Marta, Lisbon	SC, NC
Spain	PPD	Ramón y Cajal Hospital, Madrid	SC*, NC
Switzerland	PPD	University Hospital Zurich	SC, NC
Health Economy	PPD	Boston Healthcare Associates International GmbH, Steinbeis-University, Berlin, Germany	SC*
Health Economy	PPD	LEDa – LEGOS, Université Paris – Dauphine, France	SC
Health Economy	PPD	Universidad Castilla-La Mancha, Toledo, Spain	SC
Statistics	PPD	Hôpital Fernand Widal, Paris, France	SC*

Table 2: Non-voting members of the Steering Committee

Late Phase Clinical Operations and Real World Evidence	PPD
Biometrics	PPD
Medical Affairs	PPD
Clinical Safety and Pharmacovigilance	PPD

3.2. Clinical Event Adjudication Committee

Events of special importance (recurrent VTE, major bleedings, and deaths) will be adjudicated by an independent clinical event adjudication committee. Assessment will be made by consensus. The scope and process will be described in a separate Event Adjudication Committee Charter.

3.3. List of Participating Sites and Countries

A list of the principal investigators and all collaborating institutions is kept in a stand-alone document and can be made available upon request. For planned sites and patient numbers refer to Section 9.2.1.

It is planned to include 2,700 patients from approximately 660 sites in up to 11 European countries [Austria, Belgium, France, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland and United Kingdom].

4. ABSTRACT

Study Title	Non-interventional study on **E**doxaban **T**reatment in routi**N**e clinical pr**A**ctice in patients with **V**enous **T**hromboEmbolism in **Europe (ETNA-VTE-Europe)**
Protocol Version Identifier	DSE-EDO-05-14-EU Version 4.0
Date of Protocol Version	12 August 2016
Marketing Authorisation Holder (MAH)	Daiichi Sankyo Europe GmbH (DSE) Zielstattstr. 48 81379 Munich, Germany
Main Authors	PPD IPL Daiichi Sankyo Europe GmbH
Rationale and Background	Edoxaban is an orally administered anticoagulant that inhibits coagulation factor Xa. It has been recently approved by the European Medical Agency (EMA) for use in adult patients for the treatment of acute venous thromboembolism (VTE) including deep vein thrombosis (DVT) and/or pulmonary embolism (PE), and prevention of recurrent VTE in adults. According to current guidelines, duration of anticoagulant treatment after a venous thromboembolic event varies from 3 months to indefinite treatment depending on the estimated risks of venous thromboembolism (VTE) recurrence and bleeding. Current data for edoxaban are limited to a maximum treatment duration of 12 months (Hokusai-VTE; N Engl J Med. 2013; 369:1406-15). Therefore, this study aims to gather further insight into efficacy (i.e. symptomatic recurrent VTE) and safety (i.e. bleeding events, liver adverse events, all-cause mortality and other drug related adverse events) of extended treatment with edoxaban up to 18 months in an unselected patient population in routine clinical practice.
Research Question and Objectives	**Primary Objective:** • Primary objective is the analysis of the overall symptomatic VTE recurrence rate during an overall observational period of 18 months in unselected patients with acute VTE. • The co-primary objective of this study is to collect and evaluate real-world safety data on bleeding events, drug related adverse events such as liver adverse events, and mortality (VTE-related, CV mortality, and all-cause mortaility) in patients treated with edoxaban. The results relating to safety and effectiveness of this study will be compared with the respective results of other anticoagulants obtained

	from the PREFER in VTE registry. This registry uses highly harmonised endpoint definitions and will provide comparative data for patients treated with Vitamin K Antagonists (VKAs) and NOACs. In addition, the data obtained in the randomized Hokusai-VTE trial will be used as external comparator for the interpretation of the data collected in the unselected population of this study. **Secondary Objectives:** To assess the effect of edoxaban on the: • symptomatic VTE recurrence rate for patients on edoxaban • symptomatic VTE recurrence rate for patients who permanently discontinued edoxaban • patient relevant outcomes such as strokes (ischaemic and haemorrhagic), systemic embolic events (SEE), • hospitalisations related to CV condition (including VTE related hospitalisation), post-thrombotic syndrome (PTS) • extent of exposure and compliance to edoxaban therapy (judged by the investigator), rate and reasons of permanent discontinuation of edoxaban The results related to the secondary objective will be compared with external databases (PREFER in VTE and Hokusai-VTE) in the same way as the data related to primary and co-primary objectives. Subgroup analyses will be performed in predefined patient populations for primary and secondary objectives.
Study Design	Multinational, multicentre, prospective, non-interventional post-authorisation safety study (PASS). Patients from different countries and care settings will be enrolled and followed up for 18 months.
Population	**Setting** Patients from different countries and care settings (primary care and secondary care, different specialities) to ensure representativeness and extended assessment is planned for collection of VTE recurrences for up to 18 months after last data collection point for patients who entered the PASS early. • Period of patient recruitment: 2 years per country • Documentation of baseline and follow up information at 1, 3, 6, 12, and 18 months (only when available). In addition, recurrence of symptomatic VTE and death will be captured retrospectively at time point of Last Patient Out per country

	• Patients who discontinue permanently edoxaban during the observational period will be followed up according to the same scheme • Electronic data capture (EDC) **Sites and Countries** • About 660 sites including hospitals and office-based sites in up to 11 European countries [Austria, Belgium, France, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland and United Kingdom]. **Study Population** • Approximately 2,700 patients with acute VTE
Inclusion/exclusion criteria	• Established acute initial or recurrent VTE • Patients treated with edoxaban according to Summary of Product Characteristics (SmPC). To ensure that the physician's prescribing behaviour will not be influenced, patients may only be included after the treating physician has made the clinical decision to prescribe edoxaban • Written informed consent for participation in the study (ICF) • Not simultaneously participating in any interventional study
Variables (Observation Criteria)	Parameters recorded during the observational period: **Patient characteristics** (demography, medical history, history/diagnosis and current status of VTE, PTS assessment (will be collected in specific centres only) risk factors, comorbidities, concomitant medication, previous interventions) **Clinical outcome** **Efficacy:** (symptomatic recurrent VTE (i.e. the composite of DVT, non-fatal PE, and fatal PE), strokes (ischaemic and haemorrhagic), systemic embolic events (SEE)), hospitalisations related to CV condition (including VTE related hospitalisation) **Safety:** bleeding (major bleeding events including intracranial haemorrhage, clinically relevant non-major bleeding events, minor bleeding events), suspected edoxaban related adverse events will be collected and coded using the standardized Medical Dictionary for Regulatory Activities (MedDRA)) **Mortality:** VTE related mortality CV mortality, all-cause mortality. **Laboratory values** (as available in medical records* - e.g. aspartate transaminase (AST), alanine transaminase (ALT), bilirubin, creatinine, creatinine clearance (CrCl))

	(*) physicians will not be required to perform any mandatory laboratory assessment **Use pattern** of edoxaban in VTE (documentation of therapy, dosage, prescription intervals, dose adjustments, discontinuations, switches and reasons for these, concomitant medication, additional therapy/interventions, physician judgment on the compliance to edoxaban.
Data Sources	As this is a non-interventional study, only data on clinical routine practice will be documented. To facilitate accurate recording of data, patients can optionally fill in a memory aid to note important details.
Study Size	**Sample size justification with respect to primary objective:** The overall recurrence rate of symptomatic VTE during the 18-month observation period is assumed to be 8.0 % (0.08).* Assuming furthermore a relative precision of 15% (i.e. an absolute precision of 1.2% resp. 0.012), for a two-sided 95%-confidence interval at least 1,964 patients are needed. Given a drop-out-rate of 25%, it will be sufficient to enroll approx. 2,700 patients into the study. *The assumed rate refers to all patients regardless of the fact whether they stopped treatment with edoxaban during the 18 months or not. **Sample size considerations with respect to co-primary objective:** For the co-primary objective, i.e. to collect and evaluate real-world safety data, the intention is to use a data pool as large as possible. Therefore, the safety data of this PASS (ETNA-VTE-Europe, DSE-EDO-05-14-EU) is combined with the safety data of a parallel edoxaban PASS (ETNA-AF-Europe, DSE-EDO-04-14-EU) which allows the total dataset to be in line with the presentation of the safety profile in the European SmPC. ETNA-AF-Europe is conducted in non valvular atrial fibrillation (NVAF) patients and is planned to recruit 13,100 patients. In both studies a combined total of 15,800 patients shall be recruited. Assuming a drop-out rate of 20% within the first 18 months, 12,640 patients should be evaluable for the estimation of the 95% confidence intervals of the incidence rates of interest (e.g. bleeding, mortality, adverse drug reactions) after 18 months. For uncommon adverse drug reactions (i.e. incidence rates between 0.1% and 1%), the 95% CIs will be estimated taking the actual number of patients into account. For the assumed number of 12,640 patients from the combined safety databases, the 95% CI will have a precision ranging from ± 0.06% for an incidence rate of 0.1% to ± 0.17% for an incidence rate of 1%. The power will be sufficient to capture uncommon adverse drug reactions with low incidence rates.
Data Analysis	For the final analysis of the safety data, two analyses are planned: • Final analysis based on the data of the ETNA-VTE-Europe (including the comparison to the corresponding results of the

	PREFER in VTE (disease registry) as well as to the results of the Hokusai-VTE study (clinical trial)) • Combined safety analysis of ETNA-AF-Europe and ETNA-VTE-Europe based on the 18-month safety data of both studies. Data snapshots are planned on a yearly basis. (First data snapshot is planned in Q1 2018). Details of the data analysis strategy will be fully described in the two respective Statistical Analysis Plans (SAPs). Binary, categorical, and ordinal parameters will be summarised by means of absolute and relative (percentage) frequencies within the various categories. Continuous parameters will be summarised by means of standard descriptive summary statistics. In addition, adequate graphs (e.g. bar charts, box-whisker plots) will be presented. Kaplan-Meier plots will be generated where applicable to characterize the risk over time for each outcome. Time-to-event parameters will be analysed by means of Cox proportional hazard regression model to compare the pre-defined sub-populations. The purpose of all analyses will not be confirmatory but purely descriptive/ exploratory.
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.
Milestones	**First Patient In (FPI)/Start of data collection:** Q4 2016 **Last Patient Out (LPO)/End of data collection:** Q4 2020 **Interim reports:** Regular interim status reports, annual data snapshots, pooled safety analysis after 18 months of follow up (combined with ETNA-AF-Europe) **Final report:** Q3 2021

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 (version 1.0, dated 20 Feb 2015)

No	Date	Section of study protocol	Amendment or update	Reason
1	30 Nov 2015	Full protocol	Amendment to V 1.0; New version 2.0	PRAC request
2	11 May 2016	Full protocol	Amendment to V 2.0; New version 3.0	PRAC request
3	12 August 2016	Full protocol	Amendment to V 3.0; New version 4.0	PRAC request

6. MILESTONES

The main milestones for ETNA-VTE-Europe will be as described in Table 4.

Table 4: Main study milestones

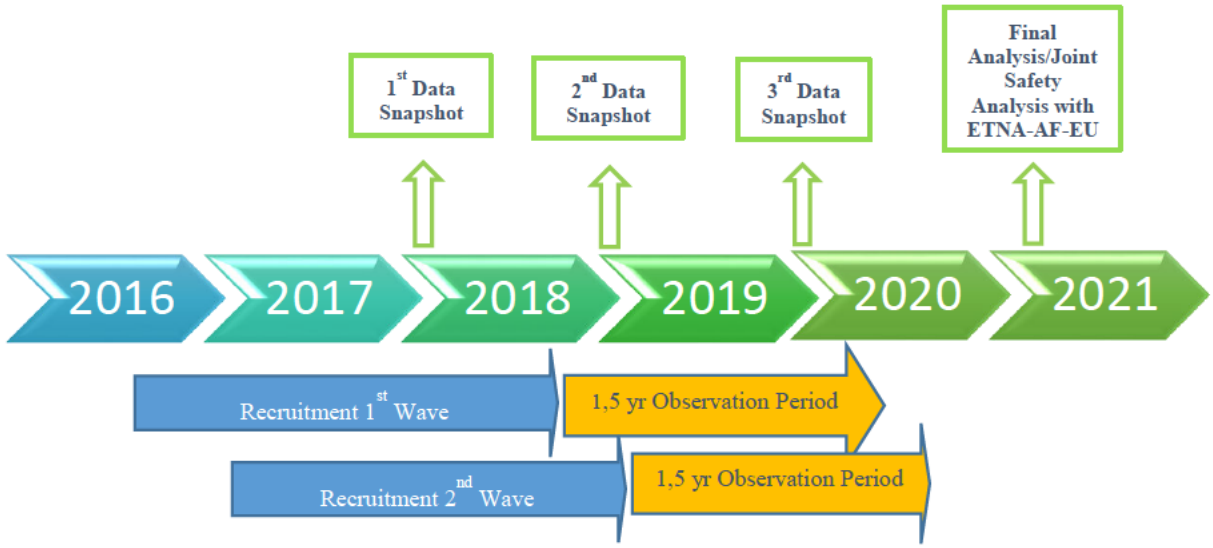
Start of data collection[1]	Q4 2016
Planned end of data collection	Q4 2020
Planned data snapshots (n=3)	Starting in Q1 2018, annually
18-month combined safety analysis	Q1 2021[2]
Final study report (planned)	Q3 2021

1 enrolment was started in Aug 2015 and set on hold in agreement with PRAC until protocol approval by PRAC and Ethics Committee positive opinion to restart patient enrolment
[2] time of analysis

Data snapshots will be performed to allow an overview of the study progress, however no reports will be generated.

Recruitment of patients is planned to be performed in waves as described in Figure 1. Each country will have a patient recruitment period of two years. Each patient will be followed up for 18 months. In addition, recurrence of symptomatic VTE and death will be captured retrospectively at time point of Last Patient Out (LPO) per country.

Figure 1: Overview study flow



7. RATIONALE AND BACKGROUND

Venous Thromboembolism (VTE)

VTE is the third most common cardiovascular disease after myocardial infarction (MI) and stroke.[1] Often occurrence of VTE can be attributed to various risk factors such as immobilisation, trauma, cancer, obesity and hereditary or acquired thrombophilia. The incidence of VTE is approximately 1-2 per 1,000 of the population with incidence increasing with age. It is estimated that 1 in 20 people will have a VTE at some point in their life and approximately half the cases are associated with prior hospitalisation for medical illness or surgery. VTE can be categorized as idiopathic (primary, unprovoked) and as provoked (secondary). Patients with idiopathic VTE are much more likely to suffer a recurrent event than those with secondary VTE after discontinuation of anticoagulation.

Detailed estimates of the annual number of VTE events are hard to obtain since VTE is often asymptomatic and difficult to diagnose, resulting in a marked underestimation of VTE incidence. The VTE Impact Assessment Group in Europe designed an incidence-based model to estimate the total annual number of non-fatal incident and recurrent VTE events as well as the VTE-related deaths in France, Germany, Italy, Spain, Sweden and UK.[2] For the year 2004, a total of 761,697 non-fatal VTE events and 370,012 VTE-related deaths were estimated to have occurred across these six EU countries. This highlights the importance of implementing appropriate strategies for prevention and treatment of VTE.

Edoxaban

Edoxaban has been approved by the U.S. Food and Drug Administration FDA, 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 trial** was a multinational, randomised, double-blind, double-dummy, non-inferiority study comparing the efficacy and safety of two dosing regimens of once-daily edoxaban to dose-adjusted warfarin (target international normalised ratio [INR] 2.0 to 3.0) in adult patients (N=21,105) with non-valvular AF at moderate-to-high risk of stroke.[3,4] Patients randomised to the edoxaban once-daily group received high dose 60 mg or low dose 30 mg (with 50% dose reduction in each dose group for patients with moderate renal impairment, low body weight, or concomitant P-gp inhibitor use). Among the exclusion criteria was the presence of conditions associated with high risk of bleeding such as overt gastrointestinal bleeding or active

ulcer within the previous year or if patients were receiving medications that increased the risk of bleeding.

The primary efficacy endpoint was the time to the first adjudicated stroke (ischaemic or haemorrhagic) or systemic embolic event. The median duration of treatment exposure was approximately 2.4 years and the median follow-up was 2.8 years. The median time in the therapeutic range (TTR) in the warfarin group was 68.4%.[3,4]

Both high-dose edoxaban (60 mg or dose-reduced 30 mg [60/30 mg]) and low-dose edoxaban (30 mg or dose-reduced 15 mg [30/15 mg]) once-daily were non-inferior to well-controlled warfarin for the prevention of stroke or systemic embolism in patients with AF, with a 21% reduction in risk in the high-dose edoxaban (60/30 mg) arm ($p<0.001$ for non-inferiority).

An analysis of ischaemic stroke found a similar event rate between the high-dose edoxaban (60/30 mg) and warfarin arms but a significantly higher rate in the low-dose edoxaban (30/15 mg) arm than in the warfarin arm (absolute rate increase 41%; $p<0.001$ vs. warfarin). This unfavourable outcome for ischaemic stroke for the 30/15 mg dose led to the selection of the 60/30 mg dose for the regulatory submissions to FDA and EMA.

The **Hokusai-VTE study** (N=8,292) 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).[5, 6]

According to current guidelines, duration of anticoagulant treatment after a venous thromboembolic event varies from 3 months to indefinite treatment depending on the estimated risks of venous thromboembolism (VTE) recurrence and bleeding. Current data for edoxaban are limited to a maximum treatment duration of 12 months.[5]

Rationale

In order to understand the risks and benefits of edoxaban use in a real-world clinical setting, Daiichi-Sankyo introduced this PASS (ETNA-VTE-Europe) as part of the Risk Management Plan of edoxaban to gain insight into efficacy (i.e. symptomatic recurrent VTE) and safety (i.e. bleeding events including intracranial haemorrhage, drug related adverse events such as liver adverse events, hospitalisation related to cardiovascular (CV) condition (including VTE related hospitalisations), CV and all-cause mortality of VTE patients) of treatment with edoxaban up to 18 months in an unselected patient population in routine clinical practice.

Real-world evidence data in routine clinical practice use of edoxaban up to 18 months will be collected in 2,700 patients, treated by specialized as well as non-specialized physicians in hospitals and office based centres.

For designing ETNA-VTE-Europe, the PREFER in VTE as well as the RIETE registry were taken into consideration.

The **PREFER in VTE** disease registry (Prevention of Thromboembolic Events –European Registry in Venous Thromboembolism)[7] was a prospective, observational, multicentre disease registry conducted in seven European countries to assess the characteristics and the management of patients with VTE, by investigating the safety and efficacy. In addition, the use of health care resources, as well as the costs for 12 months treatment following a first-time and/or recurrent VTE diagnosed in hospitals or specialized or primary care centres was part of the assessment. Three hundred and eighty one centres participated, which enrolled 3,464 patients with an acute event at the time of enrolment. Patients were eligible to be enrolled into the registry if they were at least 18 years old, had a symptomatic, objectively confirmed first time or recurrent acute VTE defined as either distal or proximal deep vein thrombosis, pulmonary embolism or both. After the baseline data collection point at the time of the acute VTE event, further follow-up documentations occurred at 1, 3, 6 and 12 months.

The **RIETE** registry, an ongoing, international, multicentre, prospective cohort of consecutive patients presenting with symptomatic venous thromboembolism (deep-vein thrombosis, PE, or both) was explored by the MAH.8 RIETE is the largest ongoing registry, using a similar design (non-interventional, non-randomized single arm trial) with a large sample size (n~ 43,000) and investigating the same objective, namely the safety and efficacy of patients with acute VTE treated with an anticoagulant.[7,8]

Thus, real-world evidence data in routine clinical practice use of edoxaban up to 18 months will be collected in 2,700 patients, treated by specialized as well as non-specialized physicians in hospitals and office based centres. The single-arm approach without a comparator group was chosen as patient profiles between treatment arms differ in a non-randomized, non-interventional setting. As a comparator group is nevertheless useful to understand the results obtained and in order to put the results into the right perspective, the results gained in ETNA-VTE-Europe will be compared to data from the PREFER in VTE disease registry. The PREFER registry, was selected as it is similar in bleeding definition, comparable in data collection point schedules, with a robust number of patients (~3,500 patients) enrolled.

As the PREFER in VTE enrolled patients treated with different oral anticoagulants, analysis on different treatments can be conducted (e.g. NOACs, VKA, and heparin alone or on combinations for Europe and per country). In addition, several subgroup analyses (renal impaired, hepatic impaired patients) can be performed based on the data from the PREFER in VTE.

The PREFER database will allow a meaningful comparison of the data collected in ETNA-VTE-Europe. Furthermore, the results obtained in the ETNA-VTE-Europe will be put in relation to the results of the Hokusai VTE study.

8. RESEARCH QUESTION AND OBJECTIVES

In order to understand the risks and benefits of edoxaban use in a clinical setting close to 'real-world', Daiichi-Sankyo introduced this non-interventional post-authorization safety study (PASS) as part of the Risk Management Plan of edoxaban to gain insight into the efficacy (overall symptomatic VTE recurrence rate) and safety (bleeding events including intracranial haemorrhage, drug related adverse events such as liver adverse events, hospitalisation related to cardiovascular (CV) conditions including VTE related hospitalization, VTE related, CV mortality and all-cause mortality in VTE patients) in non-preselected patients with VTE treated with Edoxaban.

8.1. Primary Objective

Primary objective is the analysis of the overall symptomatic VTE recurrence rate during an overall observational period of 18 months in unselected patients with acute VTE.

The co-primary objective of this study is to collect and evaluate real-world safety data on bleeding events, drug related adverse events such as liver adverse events, and mortality (VTE-related, CV mortality, and all-cause mortality) in patients treated with edoxaban.

The results relating to safety and effectiveness of this study will be compared with the respective results of other anticoagulants obtained from the PREFER in VTE registry. This registry uses highly harmonised endpoint definitions and will provide comparative data for patients treated with Vitamin K Antagonists (VKAs) and NOACs. In addition, the data obtained in the randomized Hokusai-VTE trial will be used as external comparator for the interpretation of the data collected in the unselected population of this study.

8.2. Secondary Objectives

Secondary objectives are to assess the effect of edoxaban on the

- symptomatic recurrence rate of VTE for patients on edoxaban and
- symptomatic recurrence rate of VTE for patients who permanently discontinued edoxaban
- patient relevant outcomes such as strokes (ischaemic and haemorrhagic), systemic embolic events (SEE), post-thrombotic syndrome (PTS)
- Hospitalisations related to CV conditions (including VTE related hospitalisation)
- extent of exposure and compliance to edoxaban therapy, rate and reasons of permanent discontinuation of edoxaban

The results related to the secondary objective will be compared with external databases (PREFER in VTE and Hokusai-VTE) in the same way as the data related to primary and co-primary objectives.

In addition, subgroup analyses will be performed in the predefined patient populations (see Section 9.7.3). Furthermore, primary and secondary objectives will be presented for all patients that permanently discontinue edoxaban.

9. RESEARCH METHODS

9.1. Study Design

This study is an European, multicentre, prospective, non-interventional post-authorisation safety study. This PASS is conducted to evaluate the effectiveness and safety in patients with acute VTE treated with edoxaban in up to 11 European countries (Austria, Belgium, France, Germany, Ireland, Italy, Portugal, Spain, Switzerland, The Netherlands, United Kingdom). Patients from different countries and care settings (primary care and secondary care, different specialities) will be enrolled to ensure representativeness. An extended follow up is planned for collection of VTE recurrences for up to 18 months. In addition, recurrence of symptomatic VTE and death will be captured retrospectively at time point of Last Patient Out (LPO) per country.

9.2. Setting

Edoxaban is currently approved for use in adult patients for the treatment of acute first time (initial) or recurrent VTE including DVT and/or PE, and prevention of recurrent VTE in adults.

Treatment pattern, treatment initiation, continuation or changes to edoxaban are solely at the discretion and responsibility of the physician and the patient. In order to ensure that the prescribing patterns of any individual treating physician is not influenced, patients may only be included in the study after the treating physician has made the clinical decision to prescribe edoxaban. All medication will be prescribed according to the usual standard of care and will not be provided by the study sponsor. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study. No study specific data collection points are to be performed.

Patients from different countries and care settings will be enrolled and followed up for 18 months. A two-year patient recruitment period per country is planned.

The overall number of patients per site and the number of sites per country 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. In order to make sure that a sufficient number of sites and patients will be involved in the study, a comprehensive contingency plan is put in place as part of the Recruitment Strategy Plan.

Patients should be included in the study within two weeks after start of the acute VTE event. All efficacy and safety related events will be retrospectively documented beginning with the first heparin administration. At baseline, the relevant patient history will be recorded including VTE-related events. Furthermore, the current status of the patient will be recorded.

After baseline assessment, data will be documented approximately at 1, 3, 6, 12 and 18 months at the site. The proposed follow up visits are data collection points only that are in line with the clinical routine in all participating countries. Patients will not be invited for any study specific reasons and are not obliged to return according to the planned schedule for data documentation. The proposed data collection points are voluntarily and do not interfere with the daily practice. Patient visits to the treating physician will only occur in line with clinical routine in the participating countries and not for study purposes.

If possible, patients who permanently discontinue treatment with edoxaban will be followed up according to the same scheme. In case investigators are not able to see the patient again at the follow up data collection point, investigators can follow up the patients via phone if this procedure is in line with their clinical routine.

Patient memory aids will be distributed to the patients. The patient can note in this memory aid all information important to recall when he/she is asked by his/her physician. The memory aid is to be used on a voluntary basis and will not be collected by the site.

Table 5 (Section 9.4) outlines the data to be collected with associated timings. The data sources used in this study are clinical records, and data from telephone interviews.

9.2.1. Participating Sites

About 660 hospital- and office-based physicians [general practitioners, internal medicine physicians and other specialists] in 11 European countries [Austria, Belgium, France, Germany, Ireland, Italy, The Netherlands, Portugal, Spain, Switzerland and United Kingdom] are planned to participate in the study. For regional comparisons, the following regions are pre-specified:

DACH	Austria, Switzerland and Germany (around 250 sites)
UK/IE	United Kingdom and Ireland (around 75 sites)
FR	France (around 100 sites)
BE/NL	Belgium, The Netherlands (around 70 sites)
ES/PT	Iberia with Spain and Portugal (around 90 sites)
IT	Italy (around 75 sites).

For site selection, a stepwise process will be performed to allow for representative regional distribution of sites, site specialities and health care settings of the acute VTE treatment with edoxaban. First, different databases are used to put a site list of potential sites together (Daiichi Sankyo internal database, CRO Investigator CTMS database, external databases as available).

To take different site characteristics into consideration the sites will be asked to specify site details (e.g. size of site or location) in a site qualification questionnaire before being chosen for study participation. At least 5 times the targeted number of active sites are contacted. If a site fulfils the requirements to participate in the study, the corresponding CRO will inform the site. These contacted sites are free to accept or refuse to participate within the ETNA-VTE-Europe.

The site must meet the following criteria in order to be selected for participation in this study:

- To have access to patients with acute VTE who are expected to be treated with edoxaban during the 2 years recruitment period.
- To be able to document the data in English language.

- To be able to access the EDC system, reliable internet connection [broadband] and computer.
- To be able to conduct the study adequately, with enough time and staff to identify eligible patients, conduct the patient consent process, participate in required trainings, enter study data, and follow-up with study related activities.
- To agree, to follow up the patients according to the clinical practice.
- To ensure patient representativeness every site is ask to fill in a screening log to ensure consecutive enrolment of patients. The enrolment per site is initially capped with a maximum of 10 patients. Based on the development of the enrolment, the cap may be adjusted throughout the study.

Sites who have not recruited any patient in the first 12 months after site initiation can be excluded from further participation.

9.2.2. Eligibility Criteria

Patients can be enrolled when they fulfil the following inclusion criteria:

- Established acute initial or recurrent VTE
- Patients treated with edoxaban according to Summary of Product Characteristics. Patients will only be included in the study after the treating physician has made the clinical decision to prescribe edoxaban ensuring that the prescribing behavior of the physician is not influenced.
- Written informed consent for participation in the study
- Not simultaneously participating in any interventional study

As this is a non-interventional study, no additional selection criteria apply.

A simultaneous participation in any other non-interventional study/registry is allowed. No other explicit exclusion criteria exist to avoid selection bias and to allow for documentation of routine clinical practice.

Sites will be asked to complete a patient screening log of eligible patients for ETNA-VTE- Europe at their treatment centres. This log will document patients treated with edoxaban who have not been included into the study, in order to assess the representativeness of the study population. Minimal, non-identifiable information will be recorded for these patients, but no patient-identifiable information should be recorded.

9.2.3. Patient Groups

There are no formal patient groups planned. However, in case a patient permanently discontinues edoxaban treatment in the course of the observation period, he/she will be followed up in a separate group as scheduled at baseline or until the end of the 18 months observational period per patient is reached.

For this group, safety reporting for drugs other than edoxaban will be covered outside the scope of this study through the local processes of spontaneous reporting by the treating physician(s). The eCRF will be customized to allow for documentation of other therapies. During the follow up period for both the edoxaban and discontinued groups, the data documentation schedule will be applied in the same manner.

9.2.4. Schedule

The total study period from FPI to LPO is 59 months. The individual start per country depends on market availability of edoxaban and will range approximately from Q4 2016 to Q1 2017. Thus, it is currently anticipated that the last patient will complete the ETNA-VTE-Europe in Q4 2020.

The study started patient enrolment already in August 2015 in Germany, however, patient enrolment was set on hold until PRAC approval of the protocol is received and the positive opinions of the ECs in charge are received.

As the observational plan for the ETNA-VTE-Europe has already been approved by the Swissmedic in its original version (V1.0, from 20 Feb 2015), and also the positive vote of the central Ethics Committee in Switzerland has been received, the Swiss sites are able to enrol patients. However, once PRAC approved the revised ETNA-VTE-Europe protocol, the Swiss regulatory bodies will be informed about the protocol changes and their approval will be sought as well. Once this is received, the revised protocol will also be implemented in Switzerland.

Per country, the patient recruitment period consists of 24 months, followed by an 18 months follow up period per patient, summing up to 42 months per country.

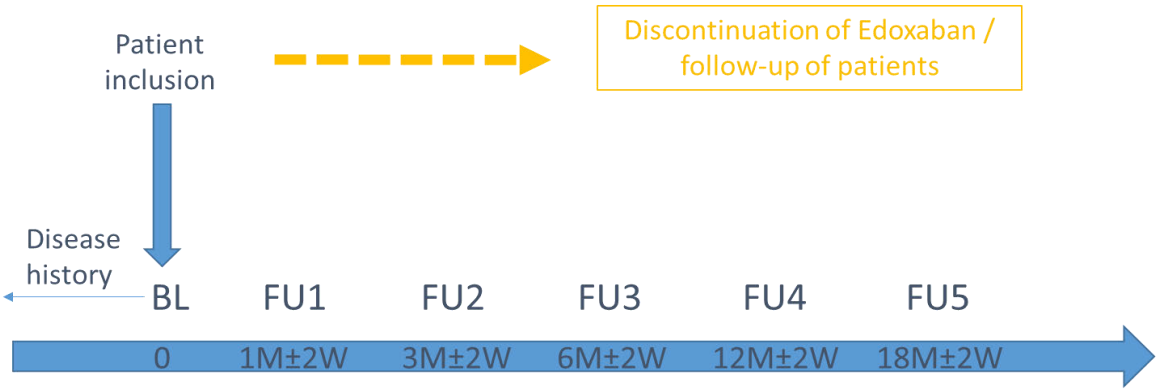
Documentation of patient data will be offered at 6 points in time (for reference see Figure 2):

- Baseline (BL) at enrolment (beginning with the first heparin administration)
- FU1 approximately 1 month after baseline
- FU2 approximately 3 months after baseline
- FU3 approximately 6 months after baseline
- FU4 approximately 12 months after baseline
- FU5 approximately 18 months after baseline
- In addition, recurrence of symptomatic VTE and death will be captured retrospectively at time point of LPO per country

For variables to be documented at the different data collection time points refer to Section 9.3 and Section 9.4. Follow up data collection points will be planned and conducted according to the clinical practice on the discretion of the treating physician. Those patients who will not see routinely the treating physician again, might be followed up by phone using standardized telephone interview. The patient is asked within the ICF, whether he/she is willing to get contacted by the treating physician for standardized telephone interviews and needs to agree to provide contact details as long this procedure is in line with the clinical practice

If possible, the follow up data collection points of patients, who permanently discontinued edoxaban treatment, will be at the same intervals as for all patients (see Section 9.2.5).

Figure 2: Study schedule



(S)ADR reporting on an ongoing basis according to spontaneous reporting timelines

BL – Baseline, FU – Follow Up, M – Month, W – Week,
(S)ADR – (serious) adverse drug reactions

9.2.5. Permanent Discontinuation of Edoxaban

If a patient's treatment on edoxaban is permanently discontinued or temporarily interrupted due to any reason at any time after the baseline visit, this information needs to be documented in the eCRF during the respective next follow up data collection point.

9.2.6. Early Study Termination

In case a patient terminates the study early, reason for early study termination (lost to follow-up, investigator's decision, adverse events, withdrawal of consent etc.) will be recorded.

The treating physician should at least get awareness of the patient's vtial status at the time of the early termination of participation in the study.

Withdrawal of Consent from PASS Participation

In accordance with the Declaration of Helsinki and other applicable regulations, a patient has the right to withdraw consent for participation in the study at any time and for any reason without prejudice to his or her future medical care by the physician or at the institution.

If a patient withdraws consent to participate in the study, the investigator will complete and report the observations as thoroughly as possible up to the date of consent withdrawal and including the date of the final dose of anticoagulation therapy. The investigator will clearly document the reason (if given) for consent withdrawal in the medical record and will complete the associated electronic case report form (eCRF) section.

9.3. Variables

To allow for comparability with the outcomes of the PREFER in VTE registry as well as the Hokusai-VTE interventional study, the variables and approaches are defined as close as possible to the ones used in PREFER in VTE/Hokusai-VTE and as feasible in a non-interventional trial.

9.3.1. Exposure Definition

This is a non-interventional study of real-world use patterns of patients taking edoxaban. The protocol does therefore not recommend the use of any specific treatments. No study medication is provided to the sites or patients by the sponsor.

As a long-term, non-interventional study to evaluate safety and clinical outcome in patients treated with edoxaban in the post-authorization setting, no restrictions on concomitant treatments are associated with the study. Relevant concomitant treatments will be recorded as described further in Section 9.4.1 Baseline/Enrolment (beginning with the first heparin administration) and Section 9.4.2 Follow-up in order to evaluate their potential influence on the outcomes of interest.

Exposure to edoxaban will be based on the data obtained from the prescribing health care providers. Treatment with edoxaban will be characterized according to the VTE relevant concomitant medication used at that time. Persistence to therapy will be assessed by looking at the rate and reasons of permanent discontinuation of edoxaban and the duration of time on therapy. In addition, physicians will be asked how they estimate the compliance to edoxaban therapy.

All time under observation for enrolled subjects will be classified in the following categories of exposure for use of edoxaban:

- Current use: Beginning the day of medication start through date of last use
- Recent use: Beginning after the last date of current use continuing for 3 days
- Past use: Beginning after 3 days of the last date of current use and continuing through end of study follow-up

The recent use exposure period is recommended to define a brief period during which increased biologic effects may be expected to persist after edoxaban use is terminated and to set apart from other non-use.

Furthermore, a sensitivity analysis will be performed based on a fourth exposure category:

- Extended-recent use: Beginning after the last date of current use continuing for 30 days

Patients switching to another antithrombotic therapy or no therapy at all will be evaluated depending on the proportions documented. Details will be described in the SAP.

9.3.2. Safety Measures

The co-primary objective of this study is to collect and evaluate real-world safety data on bleeding events, drug related adverse events such as liver adverse events, and mortality (VTE-related, CV mortality, and all-cause mortality) in patients treated with edoxaban.

Safety measures therefore include:

- Major bleeding (for definition please see below)
- Clinically relevant non-major bleedings (for definition please see below)
- Minor bleeding
- Adverse drug reactions (for definition please see Section 11.1)

In addition, mortality (VTE-related, CV mortality, and all-cause mortality) will be assessed.

Special focus will be given to safety in certain patient subgroups as renal or hepatic impaired patients.

Definition for bleeding events:

Major bleeding event:

A clinically overt bleeding event (i.e. bleeding that is visualized by examination or radiologic imaging) that meets at least one of the following:

a) Fatal bleeding

b) Symptomatic bleeding in a critical area or organ such as:

- Retroperitoneal

- Intracranial
- Intraocular
- Intraspinal
- Intra-articular
- Pericardial
- Intramuscular with compartment syndrome

c) A clinically overt bleeding event that causes a fall in haemoglobin level of 2.0 g/dL (> 1.24 mMol/L) or more, adjusted for transfusions. Each unit of packed red blood cells or whole blood is counted as a 1.0 g/dL decrease in haemoglobin. In the case of surgical procedural related bleeding, the bleeding must be in excess of that normally associated with the surgery/procedure. In the absence of haemoglobin data, a fall of haematocrit of 6.0% or more, adjusted for transfusion, will satisfy the criteria for a major bleeding event.

Major bleeding events will also be further subclassified as life-threatening or non-life threatening. A life-threatening major bleed is defined as a bleeding event that is either intracranial or is associated with haemodynamic compromise requiring intervention.

Clinically relevant non-major bleeding events:

A clinically overt bleeding event that requires medical attention that do not fulfil the criteria for major bleeding event. Examples of bleeding requiring medical attention include, but are not limited to, bleeding events that result in the following diagnostic or therapeutic measures:

- Requires or prolongs hospitalization
- Laboratory evaluation
- Imaging studies
- Endoscopy, colonoscopy, cystoscopy, or bronchoscopy
- Nasal packing
- Compression
- Ultrasound guided closure of an aneurysm
- Coil embolization
- Inotropic support
- Surgery
- Interruption or stopping anticoagulation at the advice of a physician
- Changing concomitant therapies (eg. reducing the dose of or discontinuing aspirin) at the advice of a physician

Note: an outpatient data collection point without any of the above or similar diagnostic/therapeutic measures does not satisfy the criteria for 'requiring medical attention'.

Other overt bleeding events that do not fulfil the criteria of a major bleeding event or a clinically relevant non-major bleeding event (eg. epistaxis that does not require medical attention) will be classified as a minor bleeding event.

NOTE: All other events (eg. decline in haemoglobin with no overt bleeding event) will be classified as 'no bleeding event'.

9.3.3. Effectiveness Measures

Effectiveness will be assessed by the following outcomes:

- Symptomatic recurrence rate of VTE for patients on edoxaban and
- Symptomatic recurrence rate of VTE for patients who permanently discontinued edoxaban
- Strokes (ischaemic and haemorrhagic)
- SEE (systemic embolic events)
- Hospitalisations related to CV condition (including VTE related hospitalisation)
- Post thrombotic syndrome

9.4. Data Sources

Scheduled documentation time-points for the study are presented in the Data Collection Flow Chart provided below (Table 5). All data elements will be collected from information routinely recorded in the patient files/medical records or during telephone follow-up interviews. No data collection points or examinations, laboratory tests or procedures are mandated as part of this non-interventional study.

9.4.1. Baseline/Enrolment

The following data will be collected at baseline for all enrolled patients:

- Demographics i.e.
  - Age
  - Gender
- Vital Signs i.e.

  - Blood pressure
  - Heart rate
  - Height
  - Weight
- Medical History (past and current status) i.e.
  - Relevant comorbidities present at baseline (e.g. diabetes, COPD, dyslipidemia)
- VTE-History, Diagnosis and Interventions (past and current status) i.e.
  - Type of VTE (DVT or/and PE, first or recurrent), date of first diagnosis, symptoms at first diagnosis and current, etc.
  - Type of interventions, date and number of interventions
- VTE-related clinical events (past and current status) i.e.
  - Stroke (ischemic and hemorrhagic), bleeding events, systemic embolism, non-valvular atrial fibrillation, malignancies, others
- Hospitalisations related to CV condition (including VTE related hospitalisation)
- VTE-related treatment (past and current)
- Heparin treatment (dose, duration)
- Edoxaban treatment (past and current)
- Other VTE-relevant patient information e.g.
  - Bleeding disposition
  - Thrombocytopenia
  - Alcohol consumption
  - Smoking status
  - Frailty
- Hospitalisations related to CV condition (including VTE related hospitalisation)
  - Start/Stop date
  - Emergency Room
  - Intense Care Unit
  - Clinical Event

The necessary data to calculate BMI and risk scores (e.g. HASBLED) will be documented by the site. BMI and risk scores will be calculated automatically by the EDC system.

Table 5: Data Collection Flow Chart

CRF-Forms	**BL**	**FU1**	**FU2**	**FU3**	**FU4**	**FU5**	**(FU 6)****
Time point [months]	0	1*	3*	6*	12*	18*	**LPO** **
Date	x	x	x	x	x	x	
Eligibility	x						
Demographics	x						
Physical examination							
Vital signs	x	x	x	x	x	x	
VTE and other related diseases							
VTE history & current status: Diagnosis and interventions	x						
VTE recurrence: Diagnosis and interventions		x	x	x	x	x	
Medical History	x						
Concomitant Medication	x	x	x	x	x	x	
Lab parameters (as available)	x	x	x	x	x	x	
Other VTE-related clinical events	x	x	x	x	x	x	
Other disease history	x						
Assessment of post-thrombotic syndrome (as available)			x		x	x	
Hospitalizations		x	x	x	x	x	
VTE related therapy							
VTE-related therapy	x						
Edoxaban therapy (history/current/since last data collection point)	x	x	x	x	x	x	
VTE therapy compliance (physician judgment only) (optional)	x	x	x	x	x	x	
ADR reporting for edoxaban	Continuously						-
Permanent discontinuation of edoxaban (reasons, subsequent therapy)	if applicable						-
Final assessment	at premature study termination or final FU data collection point						x**

*based on the regular clinical care this data collection point may be conducted in person or by phone (depending on the availability of the patient and according to the clinical routine practice)
** at time point of last patient out per country; retrospective data collection on recurrent VTE only (YES/NO) since FU5

9.4.2. Follow-up

The following data are planned to be collected at the FU data collection points:

- Date of documentation
- Current vital signs and weight

Additionally any change in the current status needs to be recorded regarding:

- VTE recurrence
- VTE symptoms and diagnostics

Any change since the last data collection point needs to be recorded for:

- Edoxaban exposure
- Diagnosis
- Medication changes
- Other anticoagulant treatment
- Interventions
- Clinical Events
- Hospitalisations related to CV condition (including VTE related hospitalisation)
- Other VTE relevant patient information

To facilitate data entry in the eCRF, the following forms (so called common folders) can be accessed at any time and allow an ongoing documentation:

- VTE recurrence form
- Edoxaban treatment form
- VTE-related treatment form (heparin/fondaparinux, systemic thrombolysis, NOACs, VKA, antiplatelets, other relevant treatments)
- VTE relevant clinical events (stroke (ischemic and hemorrhagic), bleeding events, SEE, non-valvular atrial fibrillation, malignancies, other VTE relevant clinical events)
- Hospitalisations related to CV condition (including VTE related hospitalisation)
- Adverse drug reactions

Reporting of patients' compliance by investigator judgement to edoxaban therapy is asked to be recorded at each data collection point (optional)

Data from routine patient data collection points or telephone interviews at the respective site should be documented directly in the Medical Records and entered shortly thereafter into the eCRF.

9.4.3. Adverse Drug Reaction Reporting

In case a patient experiences an adverse event that the investigator judges to be related to edoxaban, this ADR needs to be documented immediately and data collection point independent in the respective eCRF section (refer to Section 11).

The ADR documentation, processing and reporting follows the Guideline on Good Pharmacovigilance Practices (GVP) Module VI (Management and reporting of adverse reactions to medicinal products).

9.4.4. Edoxaban Treatment Discontinuation

In case a patient permanently discontinues treatment with edoxaban the treatment discontinuation needs to be documented as part of the subsequent follow up data collection point.

The following data should be captured:

- Date of treatment discontinuation
- Details and reason for discontinuation (in case of an event or hospitalization this needs to be captured as well)
- Future anticoagulation therapy intended (to be documented in the form VTE-related treatment or edoxaban treatment respectively).

It is recommended that the site documents this information as soon as it becomes aware of the permanent discontinuation of edoxaban.

9.4.5. Final Assessment

At the end of the follow up period (i.e. 18 months after enrolment) or at early study termination the final assessment needs to be documented.

The final assessment includes:

- Date of final assessment
- Reason for final assessment (e.g. end of observational period reached, withdrawal of consent, death, transfer to another institution, lost to follow up)
- Intended further treatment for VTE

9.5. Study Size

Sample size justification with respect to primary objective:

The overall recurrence rate of symptomatic VTE during the 18 months observation period is assumed to be 8.0 % (0.08). The assumed rate refers to all patients regardless from the fact whether they stopped treatment with edoxaban during the 18 months or not. Assuming furthermore a relative precision of 15% (i.e. an absolute precision of 1.2% resp. 0.012), for a two-sided 95%-confidence interval at least 1,964 patients are needed. Given a drop-out-rate of 25%, approx. 2,700 patients should be included into the study.

Sample size considerations with respect to co-primary objective:

For the co-primary objective, i.e. to collect more real-world safety data the intention is to use a data pool as large as possible. Therefore, the safety data of this PASS (ETNA-VTE-Europe, DSE-EDO-05-14-EU) will be combined with the safety data of a parallel edoxaban PASS (ETNA-AF-Europe, DSE-EDO-04-14-EU), which allows the total dataset to be in line with the presentation of the safety profile in the European SmPC. ETNA-AF-Europe is conducted in non valvular atrial fibrillation (NVAF) patients and is going to recruit 13,100 patients. In both studies 15,800 patients shall be recruited. Assuming a common drop-out rate of 20% within the first 18 months, 12,640 patients should be evaluable for the estimation of the 95% confidence intervals of the incidence rates of interest (i.e. major bleeding and mortality) after 18 months of follow-up. For uncommon adverse drug reactions (i.e. incidence rates between 0.1% and 1%), the 95% CIs will be estimated taking the actual number of patients into account. For the assumed number of 12,640 patients from the combined safety data bases, the 95% CI will have a precision ranging from ±0.06% for an incidence rate of 0.1% to ±0.17% for an incidence rate of 1%.The power will be sufficient to capture uncommon adverse drug reactions with low incidence rates.

9.6. Data Management (DM)

The Medidata Rave EDC system will be used for data capture. Data will be collected in standardised English eCRFs.

A data management plan will be created in the study start phase and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include automated plausibility checks (e.g. range checks, conditional checks, etc.) at data entry to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous and allow for correction or confirmation by the site. Concurrent manual data review will be performed based on parameters defined in the data management plan. If necessary, queries will be manually generated within the EDC system and followed up for resolution.

Critical fields will be defined that need to be filled in by the site prior to signing the eCRF.

Data from the project specific Rave database will be exported into SAS and converted into CDISC SDTM standardized datasets for further validation and analysis.

For (S)ADRs a reconciliation will be performed as described in the (S)ADR Reconciliation Plan.

9.6.1. Data Entry/Electronic Data Capture

Data will be collected and entered directly into the Medidata Rave EDC system. Each participating site will have access to the data of its own enrolled patients. All sites will be fully trained on using the on line data capture system, including eCRF completion guidelines and other help files. Sites will be responsible for entering patient data into the secure internet-based EDC database via the eCRF. Investigators and other site personnel will access their account with a unique username and password. All eCRFs should be completed by designated and trained personnel, as appropriate. Each eCRF has to be reviewed and electronically signed and dated by the investigator. All changes or corrections to eCRFs are documented in the audit trail and an adequate explanation is required.

9.6.2. Source Documents

In most cases, the source documents are contained in the patient's medical record and data collected on the eCRFs must be traceable to these source documents in the patient's medical records. In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the investigator's site clearly identifying those data that will be recorded directly in the eCRF, and for which the eCRF will stand as the source document. 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.

9.6.3. File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms, and source documents. The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study that is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 10 years or according to local legislation respectively after completing the participation in the study. Documents to be archived include the patient identification list, screening log, copy of eCRF burned on a CD, and the signed informed consent form (ICF) and the site contract.

9.7. Data Analysis

9.7.1. Overview on planned analyses

The following two analyses are planned:

1. Final analysis on the data of the ETNA-VTE-Europe study (including comparison of the results with the respective results of the PREFER in VTE (disease registry) as well as with the results of the Hokusai-VTE study (clinical trial))

2. Combined safety analysis of ETNA-AF-Europe and ETNA-VTE-Europe based on the 18-months safety data of both studies, which will refer to the co-primary endpoint of this study (will be reported separately).

For these analyses two separate Statistical Analysis Plans will be written.

Three data snapshots of the ETNA-VTE-Europe are planned and will be analysed before the final analysis will take place after data base lock:

1. Snapshot:	Q1 2018
2. Snapshot:	Q1 2019
3. Snapshot:	Q1 2020
Combined Analysis	Approx. Q1 2021

All analyses will contain a summary of all data plus a summary of data per country/region.

The writing of the SAP for the ETNA-VTE-Europe will start right after the finalisation of the observational plan and a version 1.0 of the SAP will be available before the (re-)start of the study after final PRAC approval. If the SAP needs to be revised for a snapshot or the final analysis, the adaptation will always be finalised and signed before the extraction of data for the respective snapshot or the final data base lock, respectively.

The time point of the combined safety analysis is triggered by the 18-months data collection point of the last patient from the ETNA-VTE-Europe and will be based on the data base lock for the ETNA-VTE-Europe (which will come before the 2 years data collection point of the ETNA-AF-Europe, presumably Q2 2021. All events during edoxaban treatment with an onset date of $\leq$ 18 months relative to the baseline data collection point will be included in this 1.5-year safety analysis.

The final European analysis and report will be performed after the planned end of the data collection (Q4 2020) and data lock and will cover all data from all countries to allow for comparability.

The report will include - but is not limited to - descriptive statistics of all documented parameters overall, per region and per country. Details will be given in the SAP and in the statistical section of the report. Interpretation of all results will be purely descriptive/explorative.

9.7.2. Overview on the statistical methodology

All computations and generation of tables, listings and data for figures will be performed using SAS® version 9.3 or higher (SAS Institute, Cary, NC, USA).

The statistical analyses will be performed in a purely explorative descriptive way based on the non-interventional character of this study. While the principal conduct of the statistical analysis will follow DSE SOP R-440 (which is understood as an umbrella SOP), concrete statistical procedures will be performed in accordance to the more specific SOPs of Quintiles.

All ADR verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities (MedDRA).

All statistical methodology will be described in detail in the Statistical Analysis Plan (SAP) for which a version 1.0 of the SAP will be available before the start of the study after final PRAC approval.

All variables collected in the CRFs as well as all derived parameters will be used in the statistical analysis. Any derivation of parameters, corrections of inconsistencies and imputations of values will be described in the respective SAP section.

Each table will be presented in general for VTE as well as by the diagnoses PE (i.e. PE ± DVT) and DVT (i.e. DVT only).

Categorical variables will be summarized by the number and percentage (%) of patients in each category. Continuous variables will be summarized using number of non-missing observations, number of missing observations, mean, SD, median, first quartile and third quartile, minimum and maximum values. The 95% CIs will also be provided for selected variables.

In addition, adequate graphs (e.g. bar charts, box-whisker plots) may be presented.

Kaplan-Meier plots will be generated where applicable to characterize the risk over time for each outcome.

Time-to-event variables will be analysed via a Cox proportional hazard regression model presenting hazard ratios and corresponding 95% confidence intervals and p-values for comparisons of the pre-defined subgroups. All Cox models will include diagnosis as an additional covariate.

9.7.3. Analysis of primary endpoint

The primary endpoint refers to the overall study period of 18 months.

Analysis of primary endpoint within the data of ETNA-VTE study

For the primary endpoint, the overall symptomatic VTE recurrence rate during an overall observational period of 18 months, absolute and relative frequencies (including the 95% confidence interval) will be presented.

Furthermore, for the primary endpoint, the following subgroups will be descriptively compared:

- renal impairment (yes, no)
- hepatic impairment (yes, no)
- diagnosis (PE with/without DVT, DVT only)
- age (< 75 years, ≥ 75 years)
- gender (male, female)
- initial edoxaban dose (30mg, 60mg) at study start
- active cancer at randomization (yes, no)

Further comparisons of the above subgroups will be done via Cox proportional hazard regression models presenting hazard ratios and corresponding 95% confidence intervals. Again, the interpretation of the results will be purely descriptive/explorative. All Cox models will include diagnosis as an additional covariate. Based on the results of the HOKUSAI-VTE and the PREFER in VTE, there are no further confounders that need to be considered upfront. Nevertheless, if relevant differences in Baseline characteristics are detected, these variables will be added to the model as additional covariates.

In addition, Kaplan-Meier estimates will be calculated for the first re-occurrence of VTE.

Setting into perspective with results from the other studies (PREFER in VTE and the Hokusai-VTE)

The obtained result for the primary endpoint are compared with results from other studies, namely the PREFER in VTE and the Hokusai-VTE. Both of these studies had only an observation period of one year. Therefore, also for the ETNA-VTE-Europe the observed recurrence rate for VTE after one year is calculated. It will be set into perspective with the recurrence rate after 1 year from the Hokusai-VTE and the PREFER in VTE registry for:

- o patients treated with NOACs (PREFER in VTE registry)
- o patients treated with a VKA (PREFER in VTE registry)
- o patients treated with edoxaban in a clinical setting (Hokusai-VTE)

- o patients treated with warfarin in a clinical setting (Hokusai-VTE)

The comparisons will be purely descriptive/explorative, i.e. the obtained rates from the ETNA-VTE-Europe will just be contrasted with the respective rates obtained in the PREFER in VTE registry and the Hokusai-VTE, respectively. There will be no joint model that compares the different treatments directly.

Analysis of the co-primary endpoint (based on combined 18-month safety data)

One focus of the analysis of the combined 18-month-safety data will be the estimation of the incidences of ADRs and especially the detection of rare ADRs. Therefore, the analysis will include at least but is not limited to the presentation of:

- absolute and relative frequencies of all ADRs, listed separately by primary System Organ Class (pSOC in internationally agreed order) and Preferred Term (with order of PT in descending order of incidence). 95%-CIs for the proportion will be presented in addition.
- absolute and relative frequencies of all ADRs (listed as described above) for all subgroups of patients that are specified for the ETNA-AF-Europe (please see Section 9.7.3 of the observational plan of the ETNA-AF-Europe) as well as for the ETNA-VTE-Europe (please see above)

Furthermore, it will be looked at

- major bleedings *(for definition, see 9.3.2)*
- clinically relevant non-major bleedings *(for definition, see 9.3.2)*
- minor bleeding
- hospitalisations related to CV condition including VTE related hospitalisations
- mortality (VTE-related, CV-related and all cause)

Data will be summarized descriptively and presented for all exposure categories (see 9.3.1 for details).

These analyses will be repeated for all the subgroups of patients that are specified for the ETNA-AF-Europe (please see Section 9.7.3 of the observational plan of the ETNA-AF-Europe) as well as for the ETNA-VTE-Europe (please see above).

All the above outlined analyses of the combined 18 month safety data will be repeated for the data of the ETNA-VTE-Europe only, if they are not already covered by the secondary objectives.

9.7.4. Analysis of secondary endpoints

Analysis of secondary endpoints within the data of ETNA-VTE study

While the primary endpoint only refers to all patients during the whole observation period and does not consider whether patients are still treated with edoxaban or not, within the secondary endpoints it is additionally looked at the

- recurrence rate of VTE in the single exposure categories (i.e. current use, recent use and past use, and - as a sensitivity analysis – extended recent use).

The analyses will follow the above outlined analysis of the primary endpoint. Absolute and relative frequencies (including the 95% confidence interval) will be presented.

Further secondary objectives of the study that mainly refer to the effectiveness of Edoxaban are:

- Stroke (ischaemic and haemorrhagic)
- SEE
- Hospitalisations related to CV condition including VTE related hospitalisation
- Post-thrombotic syndrome (PTS)

Other secondary objectives not related to the effectiveness do cover

- Extent of exposure and compliance by investigator judgment to edoxaban therapy, rate and reasons of permanent discontinuation of edoxaban
- Malignancy

For all secondary endpoints, summary statistics, frequencies and rates (including the 95% confidence interval) will be presented overall and within the different exposure categories (see 9.3.1 for details). Kaplan-Meier estimates will be calculated for the first occurrence of re-occurrence of stroke (ischaemic and haemorrhagic), SEE, and malignancy. Again, for the Kaplan-Meier estimates only the overall observational period will be looked at.

In analogy to the primary endpoint, comparisons of patients will be performed for the following subgroups

- renal impairment (yes, no)
- hepatic impairment (yes, no)
- diagnosis (PE with/without DVT, DVT only)
- age (< 75 years, ≥ 75 years)
- gender (male, female)

- initial dose (low, high)
- active cancer at randomization (yes, no)

These comparisons will be performed purely descriptively presenting summary statistics, frequencies or rates. For all secondary endpoints (except for hospitalizations related to CV conditions, permanent discontinuations from edoxaban therapy, reasons for permanent discontinuation, duration on therapy as well as compliance rating and post thrombotic symptom) results of the Cox proportional hazard regression models are presented as well (hazard ratios and corresponding 95% confidence intervals). All Cox models will include diagnosis as an additional covariate. Based on the results of the PREFER in VTE and the HOKUSAI-VTE, there are no further confounders are considered upfront. Nevertheless, if relevant differences in Baseline characteristics are detected, these variables will be added to the model as additional covariates.

Comparison for hospitalizations related to CV conditions, permanent discontinuations from edoxaban therapy, reasons for permanent discontinuation, duration on therapy as well as compliance rating and post thrombotic symptom will only be performed by means of absolute numbers and percentages or by means of standard statistics.

<u>Setting the results for the secondary endpoints into perspective with results from the other studies (Hokusai-VTE and the PREFER in VTE)</u>

Results of the ETNA-VTE-Europe will be put in perspective to the results from the Hokusai-VTE and the PREFER in VTE registry for:

- patients treated with NOACs (PREFER in VTE registry)
- patients treated with a VKA (PREFER in VTE registry)
- patients treated with edoxaban in a clinical setting (Hokusai-VTE)
- patients treated with warfarin in a clinical setting (Hokusai-VTE)

As both, the Hokusai-VTE as well as the PREFER in VTE registry, had an observation period of one year, for all secondary endpoints of the ETNA-VTE study the corresponding summary statistics, frequencies and rates, respectively, after one year will be calculated. The 95% confidence intervals will also be provided. These results will be contrasted with the corresponding results from the Hokusai-VTE and the PREFER in VTE registry.

It is important to understand that these comparisons will be purely descriptive/explorative and that there will be no joint model that compares the different treatments directly. Furthermore, although every effort was made to align the endpoint definitions of the ETNA-VTE as much as possible to the endpoint definitions of the Hokusai-VTE and the PREFER in VTE, respectively, the compared

endpoints are highly harmonised but not necessarily identical. The SAP will explicitly outline this for each endpoint.

The results will be presented overall by countries and regions as well as for the above-specified subgroups, namely

- renal impairment (yes, no)
- hepatic impairment (yes, no)
- diagnosis (PE with/without DVT, DVT only)
- age (< 75 years, ≥ 75 years)
- gender (male, female)
- initial dose (low, high)
- active cancer at randomization (yes, no).

Further data like patient characteristics or laboratory data will be summarized as appropriate, i.e. by means of absolute numbers and percentages or by means of standard statistics.

Additional exploratory analyses may be performed and will be outlined in the SAP prior to analysis.

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 PASS at the study site and verifies by signature the integrity of all data transmitted to the sponsor.

All monitoring details will be described in a separate Clinical Operations Plan (COP).

On-site monitoring will be performed in approx. 30% randomly selected 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 (approx. 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 is accurate and complete, and that the

conduct of the study is in compliance with the Observational Plan and applicable regulatory requirements.

Particular attention will be paid during monitoring activities to the completeness and correctness of safety 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, the following aspects need to be considered:

- Although sites will be selected to guarantee representativeness for the respective country or region as much as possible, sites also need to have sufficient capabilities, interest and capacities to participate in the PASS and they need to be able to follow up a patient for 18 months at the site. This may influence the sites' representativeness in some smaller regions.
- Eligible patients not giving their informed consent to participate in the PASS cannot be enrolled. Therefore this may impact the consecutive enrolment at a site. To be able to assess the consecutiveness of enrolment, eligible patients will be listed in the patient screening log. Patients participating in competing interventional trials are not eligible and will not be entered in the screening list.
- To allow for demonstrating patients included into the study are representative of patients prescribed edoxaban, a screening log will have to be completed by the sites, where all VTE patients with an acure VTE event or a VTE recurrence treated with edoxaban at the site need to be listed as well as the reason not to participate, age and gender.
- At the documentation time point all relevant changes/events since the last documentation time point need to be entered. Due to the longer time between two data collection points an underreporting of data might occur that are not considered essential or that are difficult to remember. The patient memory aid and the patients' medical records at the site shall support the precise documentation of the time between two data documentation time points. The utility of both records is however influenced by the precision and accuracy with which the memory aid and the medical records have been completed in the meantime. It is expected that possible underreporting will not appear in case of severe events and hospitalizations and that this data is considered to be representative for the whole study population.
- In addition to the above mentioned underreporting of events, the time between two documentation points might cause a wrong documentation of treatment changes. This could lead to a misclassification with respect to the exposure. However, this risk is considered to be low as relevant treatment changes (i.e. those that are VTE-related) are usually documented in the medical records and can furthermore be entered into the eCRF at any time (log-file approach). In addition, the patient memory aid again supports a precise documentation.

- In addition to confirm the robustness of the safety data from the ETNA-VTE study, the reported events from the study will be compared with the spontaneously reported events in the global safety database and external Electronic Medical Records data will be used to put the reported events into perspective to available local medical records collecting relevant outcomes from daily clinical practice.

  The Electronic Medical Records data will be evaluated for the information on the study's primary objective which is symptomatic VTE recurrence rate and on the co-primary objective of real-world safety data on bleeding events, drug related adverse events such as liver adverse events, and mortality in patients treated with edoxaban. Data will be summarized descriptively. If possible, Electronic Medical Records data will also be descriptively compared for certain subgroups, such as renal impairment, hepatic impairment, age, gender, edoxaban dose, and chronic concomitant antiplatelet use.

  Details of this descriptive comparison will be included in the SAP.

  Electronic Medical Records data is provided by PHARMO Database Network in the Netherlands. The PHARMO Institute can provide Electronic Medical Records data from the Netherlands and, through collaborations, other European countries where the use of edoxaban and relevant outcomes are captured in Electronic Medical Records from daily clinical practice. The data collected in the PHARMO Database Network is retrieved from electronic records at the source (i.e. the respective healthcare providers) and linked within the Network by a Trusted Third Party between the data source and the PHARMO Institute. Relevant data sources for this study include general practitioner, pharmacy, hospitalisation and laboratory databases. The PHARMO Institute works with several other databases in Europe which also include general practitioner (-based) databases, national registers, claims databases and pharmacy (-based) databases. The main event of interest is bleeding. This can be identified in hospital and/or primary records depending on the severity of the event. Other events of interest are rash, liver and renal abnormalities and nausea. Those can also be identified in hospital and/or primary records as well as in laboratory records, again depending on the severity of the event. Edoxaban users can be followed over time to monitor the occurrence of events of interest. These rates can be used to provide context for the rates found in the PASS.

- For rating compliance, there might be differences due to different type of sites, namely hospital and office based sites. The respective tables will be stratified by type of site to detect these discrepancies (if any) and to allow for a careful and appropriate interpretation of the results.

- Also differences between the countries/regions might occur, especially when rating compliance. Therefore, especially for the compliance the analysis by country/region will careful looked at. In case that there will be mentionable differences the interpretation has to be very careful and should consider regional differences.

- As the study is non-interventional, only data from the clinical routine treatment can be obtained. Therefore some information may be missing or unavailable. This needs to be taken into account when data are analysed and reported.

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

9.10. Other aspects

Not applicable

10. PROTECTION OF HUMAN SUBJECTS

10.1. Review by Ethics Committees/Competent Authorities

Notification to or approval by institutional ethics committees (IECs) and competent authorities (CAs) or other organizations will be performed as required by national regulations in the participating countries before commencement of enrolment at a study centre.

10.2. Insurance and Liability

All treatments of patients included in this PASS are local standard of care and occur as part of the routine clinical practice. The study is non-interventional and does not foresee any change of treatment nor additional examinations apart from the standard of care. Claims of the patient upon his physician resulting from an inappropriate use of the edoxaban will not be covered by Daiichi Sankyo. Insurance coverage will only be provided with regards to the product liability. A specific patient insurance for PASS 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 (ICF) will be obtained from all patients before or on baseline data collection point and not thereafter.

It is the responsibility of the investigator to inform the patient about his/her disease, possibilities for diagnostic and therapeutic measures, independent of a possible participation in any survey and therefore this information will not be part of the ICF.

The written ICF will be provided to the sites in the local language(s) of the planned patient population. The ICF and any revision(s) should be approved by the Independent Ethics Committee (IEC) prior to being provided to potential patients.

The patient's written informed consent will be documented in the patient's medical records of the investigator. Two ICF forms should be signed and personally dated both by the patient and by the investigator who conducted the informed consent discussion. One original signed ICF should be retained at the study centre (preferably in the patient's medical records). The second original of the signed consent form should be provided to the patient. The date informed consent was given will also be recorded in the Case Report Forms (eCRF).

In addition, the patient has to agree with his/her signature to provide his/her contact details (address, phone number, email) to a separate data base in case the investigator contacts the patient for follow up. The patients must declare with a signature to agree to the follow-up by calls or email.

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. An identification

number assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting adverse drug reactions and/or other study-related data.

All patient contact information required for follow-up calls will be kept strictly confidential and will only be accessible by the site. This personalized data will be stored separately from the project specific database on a server located in the EU and the data will be destroyed after database lock.

Only authorised personnel at the site has access to the identification list or original source documents (medical records). Representatives of the sponsor, the contract research organisation (CRO), and authorities are allowed access in case of audit or inspection or for monitoring purposes. The patient will agree to this by signing a respective statement on the ICF.

The database will be maintained under the global Daiichi Sankyo domain by the service provider with all safety instalments for a physically and logically secure computer system. The system is fully validated and in line with industry and regulatory standards. The system also meets the standards of the International Council on Harmonisation of Technical Requirements for Pharmaceutical for Human Use (ICH) guideline E6 R1 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

10.5. Numbering and Identification of Patients

A unique identification number (patient ID) will be assigned to each patient when reporting data in the eCRF or on the paper patient questionnaires.

At each study centre a patient identification list will be kept linking the identification number to the patient's identity.

10.6. Assessments

The investigators will be instructed about the correct documentation of the required variables for each patient in the eCRF. These data are available as part of the routine treatment. All examinations performed depend on the discretion and clinical routine of the physician. No diagnostic or monitoring procedures are applied to the patients in the study others than those performed as standard of care.

11. MANAGEMENT AND REPORTING OF ADVERSE DRUG REACTIONS

All adverse drug reactions (ADRs) that are judged by the investigator as related to edoxaban need to be documented in the eCRF and will be reported according to the national requirements and local laws. The documentation and reporting follows the Guideline on Good Pharmacovigilance Practices (GVP Module IV). All ADRs have to be entered in the respective section of the eCRF as soon as the physician becomes aware of it.

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 (SADR)

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 severe allergic reactions, blood abnormalities or convulsions that do not result in hospitalisation or development of dependency or abuse.

11.2. Reporting of Suspected ADRs by the Investigator

All occurring edoxaban related adverse reactions need to be documented in the eCRF by the site. The pharmacovigilance department of the sponsor (Daiichi Sankyo Europe GmbH, Clinical Safety & Pharmacovigilance Department, Zielstattstrasse 48,-81379 Munich, Germany) and the local safety officers (LSO) at the Daiichi Sankyo affiliate will receive an automated notification email if the ADR is entered into the eCRF. All ADR details will be obtained from the eCRF and will be processed further in line with the requirements for spontaneous reporting and in accordance with the Guideline on Good Pharmacovigilance Practices (GVP).

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

For publishing the study results a separate publication plan will be set up by the scientific Steering Committee. The final study report will be made publicly available within 6 months after LPO. Full manuscripts are planned to be submitted for the baseline data and for final data. Single country reports may be published as soon as they are available. The joint-safety analysis after 18 months (i.e. the combined analysis with safety data from the ETNA-AF PASS; see also Section 9.7) will be submitted to the PRAC. In addition, PRAC will receive a summary of the progress of the study as part of the PSURs.

13. DOCUMENTATION AND ARCHIVING

The sponsor is responsible for archiving study specific documentation (Observational Plan, amendments, copy of eCRF burned on CD, 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 identification list, all signed ICFs, copy of his eCRF burned on a CD, and his 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 PASS 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 and the Declaration of Helsinki and will be conducted in accordance with the respective standard operating procedures (SOPs) 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. This compensation also includes the honorarium for responding to queries, the ongoing reporting of edoxaban related ADRs and for onsite monitoring data collection points.

14.2. Registration

This study will be listed in in the EU-PAS register and a public study database which meets International Committee of Medical Journal Editors requirements.

15. FINAL REPORT

A final report will be presented at the latest 6 months after LPO, if not required earlier by local legislation. It will be prepared according to the specific guidelines for PASS reports provided by the EMA.

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 jointly by the SC and the sponsor.

Aside from the main publication, participating investigators in the study can propose subgroup analysis and related second level publications to the SC and the sponsor. Such publications may be produced by a dedicated team of authors other than the SC in common agreement with and governed jointly by the SC and the sponsor.

17. PREMATURE TERMINATION OF THE PASS

In the case of a premature termination of the entire PASS by the sponsor, the project leader has to inform all participating sites, Ethics Committees, and authorities including PRAC. In case the PASS is terminated by the authorities, the project leader informs all participating sites and Ethics Committees.

18. REFERENCES

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APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Informed Consent Form (ICF) – English master template
Site Qualification Questionnaire – English master template
Site list (to be added after site selection process is finished)
SmPC for edoxaban
eCRF and corresponding manual in local language
Patient Memory Aid – English master
Steering Committee Charter (draft)
Event Adjudication Committee Charter (draft)
Statistical Analysis Plans(SAP)
Data Management Plan (DMP)
(S)ADR Reconciliation Plan
Clinical Operations Plan (COP)

APPENDIX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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:
Non-Interventional Study on Edoxaban Tretment in Routine Clinical Practice in Patients with Venous Thromboembolism in Europe

Study reference number:
DSE-EDO-05-14-EU

Section 1: Milestones	**Yes**	**No**	**N/A**	**Page Number(s)**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	23,24,25
1.1.2 End of data collection[2]	☒	☐	☐	23,24,25
1.1.3 Study progress report(s)	☒	☐	☐	23,24,45,
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☒	☐	☐	58
1.1.6 Final report of study results.	☒	☐	☐	23,24,58

Comments:
Study progress reports will be part of the PSURs, no interim reports are planned

[1] 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.
[2] Date from which the analytical dataset is completely available.

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)	☒	☐	☐	18,28,29
2.1.2 The objective(s) of the study?	☒	☐	☐	18,28,29
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	20,30,
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:

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)	☒	☐	☐	19, 29
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	18, 28,29
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)	☒	☐	☐	46

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Page Number(s)**
4.1 Is the source population described?	☒	☐	☐	30,31
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	23,24,33
4.2.2 Age and sex?	☒	☐	☐	38
4.2.3 Country of origin?	☐	☐	☒	
4.2.4 Disease/indication?	☒	☐	☐	20,38
4.2.5 Co-morbidity?	☒	☐	☐	38
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:

No limitations on age and sex or country origin that differ from the SmPC

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)	☒	☐	☐	35,36
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective				

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Page Number(s)**
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)	☒	☐	☐	35,36
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	35,36
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

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?	☒	☐	☐	36-39
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:

Both 6.1 and 6.2 will additionally be addressed in the Clinical Event Adjudication Charter and the Statistical Analysis Plan.

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)	☒	☐	☐	46-53
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☒	☐	☐	46-53

Comments:

Both 7.1 and 7.2 will be addressed in the Statistical Analysis Plan.

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.)	☒	☐	☐	35
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.)	☒	☐	☐	36-39
8.1.3 Covariates?	☐	☐	☒	
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)	☒	☐	☐	35
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	36-39
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	50

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☒	46
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☒	☐	☐	46
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:
8.4.: no linkage with data sources applicable

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	21,42

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☐	☒	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	46-53
10.3 Are descriptive analyses included?	☒	☐	☐	46-53
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:
10.4, 10.5 and 10.6 will be addressed in the 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?	☒	☐	☐	46,
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	57
11.3 Are methods of quality assurance described?	☒	☐	☐	51
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	52
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	15-17

Comments:
to 11.5: Clinical Event Adjudication Committee as well as Scientific Steering Committee.

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	30,31,52
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)	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	30,31,52
12.3 Does the protocol address other limitations?	☒	☐	☐	52

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	53
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	55

Comments:
EC review has been done for protocol version 1.0 (positive opinion was received in Germany, Switzerland, UK so far, however, needs to be resubmitted with new version 2.0)

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?	☒	☐	☐	24

Comments:

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)?	☒	☐	☐	57
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	57

Comments:

Name of the main author of the protocol: PPD

Date: 18/5/2016

Signature: PPD