IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A15-29

Edoxaban – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Assessment module I, Sections I 2.1 to I 2.6, and Assessment module II, Sections II 2.1 to II 2.5, of the dossier assessment *Edoxaban – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 October 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Edoxaban – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
20 July 2015

Internal Commission No.:
A15-29

Address of publisher:
Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Edoxaban

Assessment module I

Prevention of stroke and SEE in patients with NVAF

Medical and scientific advice:

- Birgit Linnemann, Praxis am Grüneburgweg, Frankfurt am Main, Germany

IQWiG thanks the medical and scientific advisor for her contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

IQWiG employees involved in the assessment[1]:

- Michael Köhler
- Katharina Biester
- Gertrud Egger
- Andreas Gerber-Grote
- Ulrich Grouven
- Astrid Seidl
- Volker Vervölgyi
- Siw Waffenschmidt

Keywords: edoxaban, atrial fibrillation, benefit assessment

[1] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
ARR	absolute risk reduction
$CHADS_2$	sum score for categorizing stroke risk in atrial fibrillation
EQ-5D-3L	European Quality of Life-5 Dimension 3-Level Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
INR	international normalized ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NVAF	non-valvular atrial fibrillation
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SEE	systemic embolic event
SGB	Sozialgesetzbuch (Social Code Book)
TIA	transient ischaemic attack
VKA	vitamin K antagonists

I 2 Benefit assessment

I 2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug edoxaban. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 20 July 2015.

Research question

The aim of this report was to assess the added benefit of edoxaban in comparison with vitamin K antagonists (VKAs) as appropriate comparator therapy (ACT) in the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).

The G-BA specified VKAs as ACT. The company chose warfarin from the VKAs. The present assessment was conducted in comparison with the ACT specified by the G-BA. The choice was followed for the present benefit assessment. The assessment was conducted based on patient-relevant outcomes on the basis of data presented by the company in the dossier based on randomized controlled trials (RCTs) with a minimum study duration of 6 months.

Results

Study pool and characteristics of the study and of the interventions

The study ENGAGE AF-TIMI 48 was included in the benefit assessment. This was a completed, double-blind RCT with 3 treatment arms. The multicentre study was conducted in countries in North and Latin America, Western and Eastern Europe as well as in Asia and in South Africa.

Adult patients who had atrial fibrillation within the last 12 months were enrolled. The patient population of the study concurred with the target population of the approval. However, patients with a $CHADS_2$ score < 2, who are also comprised by the approval of edoxaban, were excluded from the study.

Patient inclusion and treatment duration were event-driven. The study was intended to last until 448 events of the primary outcome "stroke" or "systemic embolic event (SEE)" had occurred.

The patients were randomly assigned to 2 edoxaban arms, only one of which was relevant for the benefit assessment (60 mg: N = 7035), and to one warfarin arm (N = 7036). Randomization was stratified by $CHADS_2$ score, and within the $CHADS_2$ strata by necessity of dose reduction. According to the approval, the edoxaban dosage of 60 mg/day is halved if

certain conditions are met regarding body weight, creatinine clearance and concomitant medication. Overall, the data on 14071 patients from the study were relevant for the present benefit assessment.

In the control arm, warfarin was administered at an individual dosage to maintain an international normalized ratio (INR) value between 2.0 and 3.0 in the patients. This concurs with the approval.

The study investigated patient-relevant outcomes.

Risk of bias at study level and outcome level

The risk of bias was rated as low both at study level and for all outcomes for which data were available. The study was suitable for deriving indications of an added benefit.

Results

Mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "all-cause mortality" is therefore not proven.

Morbidity – stroke (ischaemic, haemorrhagic or unknown cause)

There was no statistically significant difference between the treatment arms for the outcome "stroke (ischaemic, haemorrhagic or unknown cause)". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "stroke (ischaemic, haemorrhagic or unknown cause)" is therefore not proven.

Morbidity – stroke (ischaemic)

There was no statistically significant difference between the treatment arms for the outcome "stroke (ischaemic)". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "stroke (ischaemic)" is therefore not proven.

Morbidity – stroke (haemorrhagic)

A statistically significant difference in favour of edoxaban was shown for the outcome "stroke (haemorrhagic)". Moreover, there was proof of an effect modification by the characteristic "sex". This resulted in an indication of an added benefit of edoxaban in comparison with warfarin for women. For men, there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit of edoxaban for the outcome "stroke (haemorrhagic)" for men is therefore not proven.

Morbidity – stroke (unknown cause)

There were no evaluable data for the outcome "stroke (unknown cause)". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "stroke (unknown cause)" is therefore not proven.

Morbidity – stroke (disabling)

There was no statistically significant difference between the treatment arms for the outcome "stroke (disabling)". Moreover, there was proof of an effect modification by the characteristic "stroke and SEE risk expressed with the $CHADS_2$ score". This resulted in an indication of an added benefit of edoxaban in comparison with warfarin for patients with a score > 3. For patients with a score ≤ 3, there was no hint of an added benefit of edoxaban in comparison with warfarin. Hence an added benefit of edoxaban for the outcome "stroke (disabling)" is not proven for patients with a $CHADS_2$ score ≤ 3.

Morbidity – SEE

There was no statistically significant difference between the treatment arms for the outcome "SEE". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "SEE" is therefore not proven.

Morbidity – myocardial infarction

There was no statistically significant difference between the treatment arms for the outcome "myocardial infarction". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "myocardial infarction" is therefore not proven.

Morbidity – TIA

There was no statistically significant difference between the treatment arms for the outcome "TIA". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "TIA" is therefore not proven.

Health-related quality of life

The company submitted no evaluable data on health-related quality of life. Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "health-related quality of life" is therefore not proven.

Adverse events – major bleeding or clinically relevant nonmajor bleeding

There was a statistically significant difference in favour of edoxaban for the composite outcome "major bleeding or clinically relevant nonmajor bleeding". Moreover, there was proof of an effect modification by the characteristics "sex" and "renal function (expressed with creatinine clearance)" as well as an indication of an effect modification by the characteristic "region". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes was only shown for the characteristic "sex". Hence only the subgroup results for the characteristic "sex" were considered.

There was an indication of lesser harm from edoxaban than from warfarin for the outcome "major bleeding or clinically relevant nonmajor bleeding" in women. For men, there was no

hint of greater or lesser harm of edoxaban in comparison with warfarin. Hence greater or lesser harm of edoxaban for the outcome "major bleeding or clinically relevant nonmajor bleeding" is not proven for men.

Adverse events – major bleeding

A statistically significant difference in favour of edoxaban was shown for the outcome "major bleeding". This resulted in an indication of lesser harm from edoxaban in comparison with warfarin for this outcome.

Adverse events – clinically relevant nonmajor bleeding

A statistically significant difference in favour of edoxaban was shown for the outcome "clinically relevant nonmajor bleeding". Moreover, there was an indication of an effect modification by the characteristic "age" and proof of an effect modification by the characteristic "sex". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes was only shown for the characteristic "sex". Hence only the subgroup results for the characteristic "sex" were considered.

This resulted in an indication of lesser harm of edoxaban in comparison with warfarin for women. For men, there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Hence greater or lesser harm of edoxaban for the outcome "clinically relevant nonmajor bleeding" is not proven for men.

Adverse events – overall rate of serious adverse events

A statistically significant difference in favour of edoxaban was shown for the overall rate of serious adverse events (SAEs).

Moreover, there was proof of an effect modification by the characteristic "sex". This resulted in an indication of lesser harm of edoxaban in comparison with warfarin for women. For men, there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Hence greater or lesser harm of edoxaban for the outcome "SAEs" is not proven for men.

Adverse events – discontinuation due to adverse events

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to adverse events (AEs)". Hence greater or lesser harm of edoxaban in comparison with warfarin for the outcome "discontinuation due to AEs" is not proven.

Mortality, morbidity and adverse events – stroke, SEE, major bleeding or all-cause mortality

A statistically significant difference in favour of edoxaban was shown for the composite outcome "stroke, SEE, major bleeding or all-cause mortality". This resulted in an indication of an added benefit or lesser harm of edoxaban in comparison with warfarin.

The result is consistent with the results observed for the individual outcomes because an advantage in favour of edoxaban was also shown for major bleeding.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[2]

Based on the results presented, the extent and probability of the added benefit of the drug edoxaban in comparison with the ACT for the therapeutic indication of 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 TIA, is assessed as follows:

In the overall consideration, only positive effects remain, namely in the outcome categories "morbidity", "AEs" and in the composite outcome "mortality, morbidity and AEs". In each case, the probability of an added benefit or lesser harm for all outcomes was indication. The extent of the added benefit was considerable in each of the outcomes "stroke (haemorrhagic)" and "major bleeding". The extent was minor in each of the outcomes "stroke (disabling)", "clinically relevant nonmajor bleeding", "SAEs", and in the composite outcome of stroke, SEE, major bleeding or all-cause mortality.

Consistent interaction across several outcomes was shown for the characteristic "sex". The corresponding results of the subgroup analyses do not raise doubts about the added benefit for the total population, however.

Table 1 presents a summary of the extent and probability of the added benefit of edoxaban in the therapeutic indication of 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 TIA.

[2] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit). For further details see [1,2].

Table 1: Edoxaban – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
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 TIA	VKA **(warfarin)**	Indication of considerable added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NVAF: non-valvular atrial fibrillation; TIA: transient ischaemic attack; VKA: vitamin K antagonist		

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2.2 Research question

The aim of this report was to assess the added benefit of edoxaban in comparison with VKAs as ACT in the 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 TIA.

The G-BA specified VKAs as ACT. The company chose warfarin from the VKAs. The present assessment was conducted in comparison with the ACT specified by the G-BA. The choice was followed for the present benefit assessment. The assessment was conducted based on patient-relevant outcomes on the basis of data presented by the company in the dossier based on RCTs with a minimum study duration of 6 months.

I 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on edoxaban (status: 5 June 2015)
- bibliographical literature search on edoxaban (last search on 16 June 2015)
- search in trial registries for studies on edoxaban (last search on 5 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on edoxaban (last search on 1 July 2015)

No additional relevant study was identified from the check.

I 2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 2: Study pool – RCT, direct comparison: edoxaban vs. warfarin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
ENGAGE AF-TIMI 48	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

Section I 2.6 contains a reference list for the study included.

I 2.3.2 Study characteristics

Table 3 and Table 4 describe the study used for the benefit assessment.

Table 3: Characteristics of the study included – RCT, direct comparison: edoxaban vs. warfarin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
ENGAGE AF-TIMI 48	RCT, double-blind, parallel	Adult patients with documented atrial fibrillation within the preceding 12 months and in whom anticoagulation therapy was indicated and planned for; all study participants were required to have a $CHADS_2$ score ≥ 2	Edoxaban 30 mg (N = 7034)[b] edoxaban 60 mg (N = 7035) warfarin (N = 7036)	Screening: up to 60 days Event-driven study duration: end of study for all patients after 448 events in the primary outcome	1393 centres in 46 countries in North America, Latin America, Western Europe[c], Eastern Europe, Asia and South Africa 11/2008–5/2013	Primary: stroke or SEE Secondary: ▪ stroke[d] ▪ stroke (disabling) ▪ myocardial infarction ▪ TIA ▪ major or clinically relevant nonmajor bleeding and the individual components ▪ stroke, SEE, major bleeding or all-cause mortality and the individual components ▪ AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The edoxaban 30 mg arm is not relevant for the assessment and is therefore no longer considered hereinafter.
c: Including Israel and Turkey.
d: Ischaemic, haemorrhagic or unknown cause.

AE: adverse events; $CHADS_2$: sum score for categorizing stroke risk in atrial fibrillation; N: number of randomized patients; n: relevant subpopulation; RCT: randomized controlled trial; SEE: systemic embolic event; TIA: transient ischaemic attack; vs.: versus

Table 4: Characteristics of the interventions – RCT, direct comparison: edoxaban vs. warfarin

Study	Intervention	Comparison	Prior and concomitant medication
ENGAGE AF-TIMI 48	Edoxaban, orally, 60 mg once daily + placebo Dose reduction to 30 mg once daily when at least one factor was present: ▪ permanent dose reduction when 30 ≤ CrCl ≤ 50mL/min or body weight ≤ 60 kg ▪ temporary dose reduction when concomitant treatment with verapamil, quinidine or dronedarone	Warfarin, orally, individual dosing to maintain INR of 2.0 to 3.0 + placebo	Non-permitted concomitant medication: ▪ other anticoagulants ▪ fibrinolytic agents ▪ dual antithrombotic therapies ▪ long-term use (≥ 4 days) of oral or parenteral NSAIDs except aspirin ▪ P-gp inhibitors ritonavir, nelfinavir, indinavir, saquinavir and ciclosporin Temporary discontinuation of the study medication in case of systemic administration of: ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin (topical use allowed) for ≤ 3 weeks Administration of aspirin was limited to < 100 mg/day except for emergencies
CrCl: creatinine clearance; INR: international normalized ratio; NSAID: nonsteroidal anti-inflammatory drug; P-gp: P-glycoprotein; RCT: randomized controlled trial; vs.: versus			

The ENGAGE AF-TIMI 48 study was a completed double-blind RCT with 3 treatment arms. Edoxaban at different dosages was administered in 2 of these arms, and warfarin was administered in the third arm. The multicentre study was conducted in countries in North and Latin America, Western and Eastern Europe as well as in Asia and in South Africa.

Adult patients who had atrial fibrillation within the last 12 months were enrolled. The patient population of the study concurred with the target population of the approval. However, patients with a $CHADS_2$ score < 2, who are also comprised by the approval of edoxaban, were excluded from the study.

Patient inclusion and treatment duration were event-driven. The study was intended to last until 448 events of the primary outcome "stroke" or "SEE" had occurred.

The patients were randomly assigned to 2 edoxaban arm (30 mg: N = 7034; 60 mg: N = 7035) and one warfarin arm (N = 7036). Randomization was stratified by $CHADS_2$ score, and within the $CHADS_2$ strata by necessity of dose reduction. Approval-compliant dosage of edoxaban was used only in the 60 mg arm. Hereinafter, only this edoxaban arm is therefore considered. Hence overall, the data on 14071 patients from the study were relevant for the present benefit assessment.

Dosage was halved if certain conditions were met, such as creatinine clearance of 30 mL/min to 50 mL/min and body weight of 60 kg or less. According to the approval, the dose is also reduced to 30 mg in case of concomitant use of ciclosporin, dronedarone, erythromycin, or ketoconazole [3]. Deviating from the approval, the edoxaban dose was temporarily halved in case of concomitant treatment with verapamil, quinidine and dronedarone. The number of patients receiving verapamil and quinidine, who therefore received edoxaban at a dose that was too low, was below 5%, however. Only about 1% of the patients received erythromycin or ketoconazole without their edoxaban dose being halved. The deviations from the approval-compliant use were therefore considered to be irrelevant for the benefit assessment.

In the control arm, warfarin was administered at an individual dosage to maintain an INR value between 2.0 and 3.0 in the patients. This concurs with the approval.

Concomitant medication with certain drugs, including other anticoagulants, was prohibited in both relevant study arms. These could only be used if the study medication was temporarily discontinued.

Primary outcome of the study was the composite outcome of stroke or SEE. Secondary outcomes included stroke (ischaemic, haemorrhagic or unknown cause), myocardial infarction, TIA, health-related quality of life as well as bleeding events of different severities and further AEs.

Table 5 shows the characteristics of the patients in the studies included.

Table 5: Characteristics of the study populations – RCT, direct comparison: edoxaban vs. warfarin

Study **Characteristics** **Category**	**Edoxaban** **N = 7035**[a]	**Warfarin** **N = 7036**[a]
ENGAGE AF-TIMI 48		
Age [years], mean (SD)	71 (10)	71 (9)
Sex [F/M], %	38/62	38/62
$CHADS_2$ score, median (upper quartile; lower quartile)	3.0 (2.0; 3.0)	3.0 (2.0; 3.0)
HAS-BLED score, median (upper quartile; lower quartile)	1.0 (1.0; 2.0)	1.0 (1.0; 2.0)
Prior stroke, n (%)	1299 (18.5)	1326 (18.8)
Prior TIA, n (%)	837 (11.9)	797 (11.3)
Prior VKA treatment[b], n (%)	4140 (58.8)	4138 (58.8)
Body weight (kg), mean (SD)	84.1 (20.40)	83.7 (20.10)
Creatinine clearance [mL/min], mean (SD)	76.5 (31.42)	76.1 (31.18)
Region, n (%)		
North America	1559 (22.2)	1562 (22.2)
Latin America	886 (12.6)	888 (12.6)
Western Europe	1079 (15.3)	1078 (15.3)
Eastern Europe	2383 (33.9)	2381 (33.8)
Asia/Pacific (without Japan) and South Africa	792 (11.3)	790 (11.2)
Japan	336 (4.8)	337 (4.8)
Ethnicity, n (%)		
White	5693 (80.9)	5697 (81.0)
Black	96 (1.4)	88 (1.3)
Asian	964 (13.7)	967 (13.7)
American Indian/native Alaskan	13 (0.2)	16 (0.2)
Native Hawaiian/pacific islander	3 (< 0.1)	1 (< 0.1)
Other	266 (3.8)	267 (3.8)
Study discontinuations, n (%)	807 (11.5)	879 (12.5)
Treatment discontinuations, n (%)	2415 (34.4)[c]	2417 (34.5)[c]

a: Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: The number of patients who had received other anticoagulants was below 1%.
c: Safety population, in both treatment groups N = 7012.
$CHADS_2$: sum score for categorizing stroke risk in atrial fibrillation; F: female; HAS-BLED: sum score for categorizing bleeding risk in atrial fibrillation; M: male; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; TIA: transient ischaemic attack; VKA: vitamin K antagonist; vs.: versus

The characteristics of the patients included in the ENGAGE AF-TIMI 48 study were comparable between the treatment groups. The mean age of the patients was 71 years. About one third of the patients were women.

In all patients, the risk of stroke and SEE was initially investigated using the $CHADS_2$ score and the risk of bleeding using the HAS-BLED score. The $CHADS_2$ score is a scale from 1 to 6 points to assess the risk of stroke and SEE using the presence of the following factors: chronic cardiac failure (1 point), hypertension (1 point), age ≥ 75 years (1 point), diabetes mellitus (1 point) and prior stroke/TIA/thromboembolism (2 points) [4]. The median $CHADS_2$ score was 3 points in both treatment arms.

The HAS-BLED score is a scale from 1 to a maximum of 9 points to assess the risk of bleeding using the following factors: arterial hypertension (1 point), abnormal liver function/abnormal renal function requiring dialysis (1 to 2 points), stroke (1 point), bleeding (1 point), labile INR value (1 point), older age (1 point) and drug or alcohol abuse (1 to 2 points). The median HAS-BLED score of the patients was 1 point.

About 59% of the patients had already received VKA pretreatment at the start of the study. About 19% and 12% had already had a stroke or TIA.

The mean body weight was about 84 kg, the mean creatinine clearance was about 76 mL/min.

The vast majority of patients (81%) were white with most patients being from North America (22%) or Eastern Europe (34%).

The rate of study discontinuations was about 12%, the rate of treatment discontinuations was a little above 34%.

Table 6 shows the mean and median treatment duration of the patients, the mean and median study duration and the percentage of the time during which the patients were treated with edoxaban or warfarin during the study duration.

Table 6: Information on the course of the study – RCT, direct comparison: edoxaban vs. warfarin

Study **Duration of the study phase** **Outcome category**	**Edoxaban** **N = 7035**	**Warfarin** **N = 7036**
ENGAGE AF-TIMI 48		
Treatment duration [days]		
Median [min; max]	904 [1; 1530]	904 [1; 1540]
Mean (SD)	805.9 (309.82)	811.0 (383.14)
Study duration [days]		
Median [min; max]	1023 [2; 1547]	1021 [1; 1540]
Mean (SD)	999.6 (249.94)	993.9 (254.15)
Exposure days [%]		
Median [min; max]	99.0 [0.1; 100]	98.9 [0.1; 100]
Mean (SD)	80.3 (32.51)	81.4 (31.27)
Patients who temporarily discontinued treatment at least once, n (%)[a]	4386 (62.5)[b]	4590 (65.5)[b]

a: Temporary discontinuation of treatment was considered to be a non-administration of the study medication for ≥ 3 days that was continued afterwards.
b: Safety population, in both treatment groups N = 7012.
max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

There were no important differences in treatment duration with edoxaban or warfarin between the treatment groups. Hence there were no notable differences in temporary treatment discontinuations.

During participation in the study, it was possible to discontinue treatment with the study medication and restart again later. This applied to 63% and 66% of the patients in the edoxaban and warfarin arm.

Table 7 shows the risk of bias at study level.

Table 7: Risk of bias at study level – RCT, direct comparison: edoxaban vs. warfarin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
ENGAGE AF-TIMI 48	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low. This concurs with the company's assessment.

I 2.4 Results on added benefit

I 2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section I 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - stroke (ischaemic, haemorrhagic or unknown cause)
    - stroke (ischaemic)
    - stroke (haemorrhagic)
    - stroke (unknown cause)
  - stroke (disabling)
  - SEE
  - myocardial infarction
  - TIA
- Health-related quality of life

- Adverse events
  - major or clinically relevant nonmajor bleeding
  - major bleeding (including presentation of intra- and extracranial location)
  - clinically relevant nonmajor bleeding
  - overall rate of SAEs
  - discontinuation due to AEs
- Mortality, morbidity and adverse events
  - stroke, SEE, major bleeding or all-cause mortality

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section I 2.7.2.4.3 of the full dossier assessment). These were partly composite outcomes (stroke or SEE; stroke, SEE or all-cause mortality; stroke, SEE or cardiovascular mortality; serious adverse cardiovascular event) represented more comprehensively with the included composite outcome "stroke, SEE, major bleeding or all-cause mortality". Moreover, cardiovascular mortality was not considered to be relevant because it was sufficiently represented with all-cause mortality. No evaluable patient-relevant analyses were available for the instrument European Quality of Life-5 Dimension 3-Level Scale (EQ-5D-3L), which the company used to record health-related quality of life.

The outcomes on gastrointestinal bleeding and treatment discontinuation due to AEs were also not included in the present assessment. In contrast to the company's approach, no specific AEs beyond bleeding were included in the present assessment.

The company used the hazard ratio (HR) as effect measure for most outcomes included by the company. The company used the effect measures relative risk (RR), odds ratio (OR) and absolute risk reduction (ARR) as effect estimates for AEs except bleeding events. Since there was hardly any difference between the treatment groups in mean and median treatment duration, the RR could be used for the outcomes on AEs.

Table 8 shows for which outcomes data were available in the studies included.

Table 8: Matrix of outcomes – RCT, direct comparison: edoxaban vs. warfarin

Study	Outcomes																
	All-cause mortality	Stroke (ischaemic, haemorrhagic or unknown cause)	Stroke (ischaemic)	Stroke (haemorrhagic)	Stroke (unknown cause)	Stroke (disabling)	SEE	Myocardial infarction	TIA	Health-related quality of life	Major or clinically relevant nonmajor bleeding	Major bleeding[c]	Clinically relevant nonmajor bleeding	SAEs	Discontinuation due to AEs	Stroke, SEE, major bleeding or all-cause mortality
ENGAGE AF-TIMI 48	Y	Y	Y	Y	No[a]	Y	Y	Y	Y	No[b]	Y	Y	Y	Y	Y	Y

a: The company stated only descriptively that no stroke of unknown cause occurred; this information is not comprehensible (see Section I 2.7.2.4.3 of the full dossier assessment).
b: The company did not record health-related quality of life with a suitable instrument.
c: Including presentation of intra- and extracranial location.

AE: adverse event; RCT: randomized controlled trial; SAE: serious adverse event; SEE: systemic embolic event; TIA: transient ischaemic attack; vs.: versus; Y: yes

I 2.4.2 Risk of bias

Table 9 shows the risk of bias for the relevant outcomes.

Table 9: Risk of bias at study and outcome level – RCT, direct comparison: edoxaban vs. warfarin

Study	Outcomes																
	Study level	All-cause mortality	Stroke (ischaemic, haemorrhagic or unknown cause)	Stroke (ischaemic)	Stroke (haemorrhagic)	Stroke (unknown cause)	Stroke (disabling)	SEE	Myocardial infarction	TIA	Health-related quality of life	Major or clinically relevant nonmajor bleeding	Major bleeding[b]	Clinically relevant nonmajor bleeding	SAEs	Discontinuation due to AEs	Stroke, SEE, major bleeding or all-cause mortality
ENGAGE AF-TIMI 48	L	L	L	L	L	–[a]	L	L	L	L	–[a]	L	L	L	L	L	L

a: No evaluable data available.
b: Including presentation of intra- and extracranial location.
AE: adverse event; L: low; RCT: randomized controlled trial; SAE: serious adverse event; SEE: systemic embolic event; TIA: transient ischaemic attack; vs.: versus

The outcome-specific risk of bias was rated as low for all outcomes for which data were available. This concurs with the company's assessment. The study was suitable for deriving indications of an added benefit.

I 2.4.3 Results

Table 10 summarizes the results for the comparison of edoxaban with warfarin for the prevention of stroke and SEE in adult patients with NVAF with certain risk factors. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 10: Events – RCT, direct comparison: edoxaban vs. warfarin

Study Outcome category Outcome	Edoxaban N	Edoxaban Patients with event n (%) Event rate (%/year)[a]	Warfarin N	Warfarin Patients with event n (%) Event rate (%/year)[a]	Edoxaban vs. warfarin HR[b] [95% CI]; p-value
ENGAGE AF-TIMI 48					
Mortality					
All-cause mortality	7035	773 (11.0) (4.0)	7036	839 (11.9) (4.4)	0.92 [0.83; 1.01]; 0.082
Morbidity					
Stroke (ischaemic, haemorrhagic or unknown cause)	7035	281 (4.0) (1.5)	7036	317 (4.5) (1.7)	0.88 [0.75; 1.03]; 0.112
Stroke (ischaemic)	7035	236 (3.4) (1.3)	7036	235 (3.3) (1.3)	1.00 [0.83; 1.19]; 0.972
Stroke (haemorrhagic)	7035	49 (0.7) (0.3)	7036	90 (1.3) (0.5)	0.54 [0.38; 0.77]; < 0.001
Stroke (unknown cause)	No evaluable data[c]				
Stroke (disabling)	7035	54 (0.8) (0.3)	7036	57 (0.8) (0.3)	0.94 [0.65; 1.36]; 0.746
SEE	7035	15 (0.2) (0.1)	7036	23 (0.3) (0.1)	0.65 [0.34; 1.24]; 0.191
Myocardial infarction	7035	133 (1.9) (0.7)	7036	141 (2.0) (0.8)	0.94 [0.74; 1.19]; 0.602
TIA	7035	106 (1.5) (0.6)	7036	95 (1.4) (0.5)	1.11 [0.84; 1.47]; 0.450
Health-related quality of life	Not recorded[d]				
Adverse events					
Major or clinically relevant nonmajor bleeding	7012	1722 (24.6) (10.6)	7012	1969 (28.1) (12.4)	0.85 [0.80; 0.91]; < 0.001
Major bleeding	7012	546 (7.8) (3.0)	7012	674 (9.6) (3.7)	0.80 [0.72; 0.90]; < 0.001
Intracranial major bleeding	7012	88 (1.3) (0.5)	7012	166 (2.4) (0.9)	0.52 [0.41; 0.68]; < 0.001
Extracranial major bleeding	7012	464 (6.6) (2.5)	7012	523 (7.5) (2.9)	0.88 [0.78; 1.00]; 0.049
Clinically relevant nonmajor bleeding	7012	1355 (19.3) (8.1)	7012	1526 (21.8) (9.3)	0.87 [0.81; 0.94]; < 0.001
AEs	7012	6092 (86.9) ND	7012	6065 (86.5) ND	-
SAEs	7012	2979 (42.5) ND	7012	3118 (44.5) ND	RR: 0.96 [0.92; 0.99]; 0.018
Discontinuation due to AEs	7012	784 (11.2) ND	7012	768 (11.0) ND	RR: 1.02 [0.93; 1.12]; 0.667

(continued)

Table 10: Events – RCT, direct comparison: edoxaban vs. warfarin (continued)

Study Outcome category Outcome	Edoxaban		Warfarin		Edoxaban vs. warfarin
	N	Patients with event n (%) Event rate (%/year)[a]	N	Patients with event n (%) Event rate (%/year)[a]	HR[b] [95% CI]; p-value
Mortality, morbidity and AEs					
Stroke, SEE, major bleeding or all-cause mortality	7035	1323 (18.8) (7.3)	7036	1462 (20.8) (8.1)	0.89 [0.83; 0.96]; 0.003

a: Calculated from the number of events/yearly exposure time; yearly exposure time is the sum of the number of years until occurrence of the event or censoring.
b: Unless otherwise stated.
c: According to the company, there were no strokes of unknown cause; see Section I 2.7.2.4.3 of the full dossier assessment for more information.
d: No patient-relevant instrument was used to record health-related quality of life (see Section I 2.7.2.4.3 of the full dossier assessment).

AE: adverse event; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SEE: systemic embolic event; TIA: transient ischaemic attack; vs.: versus

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "all-cause mortality" is therefore not proven. This concurs with the company's assessment.

Morbidity

Stroke (ischaemic, haemorrhagic or unknown cause)

There was no statistically significant difference between the treatment arms for the outcome "stroke (ischaemic, haemorrhagic or unknown cause)". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "stroke (ischaemic, haemorrhagic or unknown cause)" is therefore not proven. This concurs with the company's assessment.

Stroke (ischaemic)

There was no statistically significant difference between the treatment arms for the outcome "stroke (ischaemic)". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "stroke (ischaemic)" is therefore not proven. This concurs with the company's assessment.

Stroke (haemorrhagic)

A statistically significant difference in favour of edoxaban was shown for the outcome "stroke (haemorrhagic)". Moreover, there was proof of an effect modification by the characteristic "sex". This resulted in an indication of an added benefit of edoxaban in comparison with warfarin for women. For men, there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit of edoxaban for the outcome "stroke (haemorrhagic)" for men is therefore not proven.

This deviates from the company's assessment, which found an indication of an added benefit for the total population.

Stroke (unknown cause)

There were no evaluable data for the outcome "stroke (unknown cause)". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "stroke (unknown cause)" is therefore not proven.

The assessment of the added benefit does not concur with the company's assessment insofar as the company only described descriptively that there had been no corresponding events (see Section I 2.7.2.4.3 of the full dossier assessment for more information).

Stroke (disabling)

There was no statistically significant difference between the treatment arms for the outcome "stroke (disabling)". Moreover, there was proof of an effect modification by the characteristic "stroke and SEE risk expressed with the $CHADS_2$ score". This resulted in an indication of an added benefit of edoxaban in comparison with warfarin for patients with a score > 3. For patients with a score ≤ 3, there was no hint of an added benefit of edoxaban in comparison with warfarin. Hence an added benefit of edoxaban for the outcome "stroke (disabling)" is not proven for patients with a $CHADS_2$ score ≤ 3.

This deviates from the company's assessment, which found no indication of added benefit for this outcome.

Systemic embolic event

There was no statistically significant difference between the treatment arms for the outcome "SEE". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "SEE" is therefore not proven. This concurs with the company's assessment.

Myocardial infarction

There was no statistically significant difference between the treatment arms for the outcome "myocardial infarction". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "myocardial infarction" is therefore not proven. This concurs with the company's assessment.

Transient ischaemic attack

There was no statistically significant difference between the treatment arms for the outcome "TIA". Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "TIA" is therefore not proven. This concurs with the company's assessment.

Health-related quality of life

The company submitted no evaluable data on health-related quality of life. Hence there was no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit for the outcome "health-related quality of life" is therefore not proven.

The assessment of the overview of the evidence concurred with that of the company; from the company's point of view, however, the company presented data on health-related quality of life, which it considered to be not evaluable because of the low response rates.

Adverse events

Major bleeding or clinically relevant nonmajor bleeding

There was a statistically significant difference in favour of edoxaban for the composite outcome "major bleeding or clinically relevant nonmajor bleeding". Moreover, there was proof of an effect modification by the characteristics "sex" and "renal function (expressed with creatinine clearance)" as well as an indication of an effect modification by the characteristic "region". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes was only shown for the characteristic "sex". Hence only the subgroup results for the characteristic "sex" were considered.

There was an indication of lesser harm from edoxaban than from warfarin for the outcome "major bleeding or clinically relevant nonmajor bleeding" in women.

For men, there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Hence greater or lesser harm of edoxaban for the outcome "major bleeding or clinically relevant nonmajor bleeding" is not proven for men.

The approach for the outcome "major bleeding or clinically relevant nonmajor bleeding" deviates from the company, which derived an indication of lesser harm for this outcome at the level of the total population without considering subgroup results.

Major bleeding

A statistically significant difference in favour of edoxaban was shown for the outcome "major bleeding". This resulted in an indication of lesser harm from edoxaban in comparison with warfarin for this outcome. This concurs with the company's assessment.

Clinically relevant nonmajor bleeding

A statistically significant difference in favour of edoxaban was shown for the outcome "clinically relevant nonmajor bleeding". Moreover, there was an indication of an effect modification by the characteristic "age" and proof of an effect modification by the characteristic "sex". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes was only shown for the characteristic "sex". Hence only the subgroup results for the characteristic "sex" were considered.

This resulted in an indication of lesser harm of edoxaban in comparison with warfarin for women. For men, there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Hence greater or lesser harm of edoxaban for the outcome "clinically relevant nonmajor bleeding" is not proven for men.

This deviates from the company's assessment, which found an indication of lesser harm for the total population.

Overall rate of serious adverse events

A statistically significant difference in favour of edoxaban was shown for the overall rate of SAEs.

Moreover, there was proof of an effect modification by the characteristic "sex". This resulted in an indication of lesser harm of edoxaban in comparison with warfarin for women. For men, there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Hence greater or lesser harm of edoxaban for the outcome "SAEs" is not proven for men.

This deviates from the company's assessment, which found an indication of lesser harm for the total population.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment arms for the outcome "discontinuation due to AEs". Hence greater or lesser harm of edoxaban in comparison with warfarin for the outcome "discontinuation due to AEs" is not proven. This concurs with the company's assessment.

Mortality, morbidity and adverse events

Stroke, systemic embolic event, major bleeding or all-cause mortality

A statistically significant difference in favour of edoxaban was shown for the composite outcome "stroke, SEE, major bleeding or all-cause mortality". This resulted in an indication of an added benefit or lesser harm of edoxaban in comparison with warfarin. This concurs with the company's assessment.

The result is consistent with the results observed for the individual outcomes because an advantage in favour of edoxaban was also shown for major bleeding.

I 2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the benefit assessment:

- age (< 75 years/≥ 75 years)
- sex (male/female)
- $CHADS_2$ score at baseline (≤ 3, > 3)
- creatinine clearance at baseline (< 30 mL/min, ≥ 30 to ≤ 50 mL/min, > 50 to < 80 mL/min, ≥ 80 mL/min)
- ethnicity (white, black, Asian, American Indian/native Alaskan, native Hawaiian/Pacific islander, other)
- region (North America, Latin America, Western Europe, Eastern Europe, Asia/Pacific [without Japan] and South Africa, Japan)

Below, only the results on subgroups and outcomes are presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. In addition, there had to be a statistically significant effect in at least one of the subgroups. In effect modifiers with more than 2 categories, where meaningful with regard to content, the categories of neighbouring effect estimates were summarized if the heterogeneity test provided a p-value of ≥ 0.2.

The prerequisite for proof of an effect modification was a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provided an indication of an effect modification.

Table 11 summarizes the subgroup results for the comparison of edoxaban with warfarin in adult patients with NVAF with certain risk factors. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Table 11: Subgroups – RCT, direct comparison: edoxaban vs. warfarin

Study Outcome Characteristic Subgroup	Edoxaban N	Edoxaban Patients with event n (%) Event rate (%/year)	Warfarin N	Warfarin Patients with event n (%) Event rate (%/year)	Edoxaban vs. warfarin HR[b] [95% CI]	Edoxaban vs. warfarin p-value
ENGAGE AF-TIMI 48						
Stroke (haemorrhagic)						
Sex						
Female	2669	11 (0.4) (0.2)	2641	36 (1.4) (0.5)	0.30 [0.15; 0.59]	0.001
Male	4366	38 (0.9) (0.3)	4395	54 (1.2) (0.5)	0.70 [0.46; 1.06]	0.094
					Interaction:	0.037[a]
Stroke (disabling)						
$CHADS_2$ score						
≤ 3	5422	41 (0.8) (0.3)	5445	30 (0.6) (0.2)	1.36 [0.85; 2.18]	0.198
> 3	1613	13 (0.8) (0.3)	1591	27 (1.7) (0.7)	0.47 [0.24; 0.91]	0.026
					Interaction:	0.011[a]
Major bleeding or clinically relevant nonmajor bleeding						
Sex						
Female	2659	587 (22.1) (9.4)	2629	750 (28.5) (12.7)	0.75 [0.67; 0.83]	< 0.001
Male	4353	1135 (26.1) (11.4)	4383	1219 (27.8) (12.3)	0.93 [0.85; 1.00]	0.06
					Interaction:	0.002[a]
Creatinine clearance [mL/min]						
≤ 50					0.71 [0.62; 0.82][c]	< 0.001[c]
< 30	*70*	*14 (20.0[c]) (9.3)*	*51*	*16 (31.4[c]) (16.2)*	*0.55 [0.27; 1.13]*	*ND*
≥ 30 to ≤ 50	*1302*	*358 (27.5[c]) (12.7)*	*1305*	*467 (35.8[c]) (17.8)*	*0.72 [0.63; 0.83]*	*ND*
> 50					0.90 [0.84; 0.97][c]	0.007[c]
> 50 to < 80	*3007*	*812 (27.0[c]) (11.8)*	*3048*	*890 (29.2[c]) (13.0)*	*0.91 [0.82; 1.002]*	*ND*
≥ 80	*2633*	*538 (20.4[c]) (8.4)*	*2608*	*596 (22.9[c]) (9.5)*	*0.89 [0.79; 0.997]*	*ND*
					Interaction:	0.031[a]

(continued)

Table 11: Subgroups – RCT, direct comparison: edoxaban vs. warfarin (continued)

Study Outcome Characteristic Subgroup	Edoxaban N	Edoxaban Patients with event n (%) Event rate (%/year)	Warfarin N	Warfarin Patients with event n (%) Event rate (%/year)	Edoxaban vs. warfarin HR[b] [95% CI]	Edoxaban vs. warfarin p-value
Region						
North America	1559	581 (37.3[c]) (17.0)	1556	612 (39.3[c]) (18.3)	0.93 [0.83; 1.04]	ND
Latin America	884	178 (20.1[c]) (9.2)	885	235 (26.6[c]) (12.8)	0.72 [0.60; 0.88]	ND
Western Europe	1075	256 (23.8[c]) (10.3)	1070	300 (28.0[c]) (12.6)	0.82 [0.70; 0.97]	ND
Eastern Europe	2374	366 (15.4[c]) (6.1)	2378	423 (17.8[c]) (7.2)	0.86 [0.75; 0.99]	ND
Asia/Pacific and South Africa (without Japan)	784	201 (25.6[c]) (11.5)	786	257 (32.7[c]) (15.6)	0.75 [0.62; 0.90]	ND
Japan	336	140 (41.7[c]) (20.1)	337	142 (42.1[c]) (19.8)	1.02 [0.80; 1.29]	ND
					Interaction:	0.097[a]
Clinically relevant nonmajor bleeding						
Age						
< 75	4174	721 (17.3) (7.0)	4207	783 (18.6) (7.6)	0.92 [0.83; 1.01]	0.091
≥ 75	2838	634 (22.3) (9.8)	2805	743 (26.5) (12.1)	0.81 [0.73; 0.91]	< 0.001
					Interaction:	0.114[a]
Sex						
Female	2659	453 (17.0) (7.0)	2629	584 (22.2) (9.5)	0.74 [0.66; 0.84]	< 0.001
Male	4353	902 (20.7) (8.7)	4383	942 (21.5) (9.2)	0.95 [0.87; 1.04]	0.285
					Interaction:	0.001[a]
SAEs						
Sex						
Female	2659	1100 (41.4) ND	2629	1219 (46.4) ND	RR: 0.89 [0.84; 0.95]	< 0.001
Male	4353	1879 (43.2) ND	4383	1899 (43.3) ND	RR: 1.00 [0.95; 1.05]	0.879
					Interaction:	0.005

(continued)

Table 11: Subgroups – RCT, direct comparison: edoxaban vs. warfarin (continued)

a: The p-value for the interaction was based on a Cox proportional hazards model including treatment, the 2 stratification factors $CHADS_2$ score and dose adjustment (in each case dichotomized), subgroup, treatment, and subgroup interaction.
b: Unless otherwise stated.
c: Institute's calculation.
AE: adverse events; $CHADS_2$: sum score for categorizing stroke risk in atrial fibrillation; CI: confidence interval; HR: hazard ratio; N: number of randomized patients; n: number of patients with (at least one) event; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; TIA: transient ischaemic attack; vs.: versus

Morbidity

Stroke (haemorrhagic)

There was proof of an effect modification by the characteristic "sex" for the outcome "stroke (haemorrhagic)". There was a statistically significant difference in favour of edoxaban for women. This resulted in an indication of an added benefit of edoxaban in comparison with warfarin for the outcome "stroke (haemorrhagic)" for women. For men, there was no statistically significant difference between the treatment arms. This resulted in no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit of edoxaban for this outcome for men is therefore not proven.

This deviates from the company's assessment, which derived an indication of an added benefit of edoxaban only at the level of the total population without considering the subgroup results.

Stroke (disabling)

For the outcome "stroke (disabling)", there was proof of an effect modification by the characteristic "stroke and SEE risk expressed with the $CHADS_2$ score". There was no statistically significant difference between the treatment arms for patients with a $CHADS_2$ score ≤ 3. For these patients, there was therefore no hint of an added benefit of edoxaban in comparison with warfarin. An added benefit of edoxaban for the outcome "stroke (disabling)" is therefore not proven for patients with a $CHADS_2$ score ≤ 3. A statistically significant difference in favour of edoxaban was shown for patients with a $CHADS_2$ score > 3. This resulted in an indication of an added benefit of edoxaban in comparison with warfarin for the outcome "stroke (disabling)" for these patients.

This deviates from the company's assessment, which derived no added benefit of edoxaban at the level of the total population without considering the subgroup results.

Adverse events

Major bleeding or clinically relevant nonmajor bleeding

For the composite outcome "major bleeding or clinically relevant nonmajor bleeding", there was in each case proof of an effect modification by the characteristics "sex" and "renal

function (expressed with creatinine clearance)" as well as an indication of an effect modification by the characteristic "region". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes was only shown for the characteristic "sex" so that only the corresponding subgroup results on this characteristic were considered for the benefit assessment.

A statistically significant difference in favour of edoxaban was shown for the outcome "major bleeding or clinically relevant nonmajor bleeding" for women. This resulted in an indication of lesser harm from edoxaban in comparison with warfarin for this outcome for women.

For men, there was no statistically significant difference between the treatment arms. Hence there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Greater or lesser harm of edoxaban for this outcome for men is therefore not proven.

The approach for the outcome "major bleeding or clinically relevant nonmajor bleeding" deviates from that of the company, which derived lesser harm of edoxaban at the level of the total population without considering subgroup results.

Clinically relevant nonmajor bleeding

For the outcome "clinically relevant nonmajor bleeding", there was an indication of an effect modification by the characteristic "age" and proof of an effect modification by the characteristic "sex". Not all the subgroup results could be interpreted because data for the investigation of possible dependencies between the subgroup characteristics were missing. Consistent interaction across several outcomes was only shown for the characteristic "sex" so that only the corresponding subgroup results on this characteristic were considered for the benefit assessment.

There was a statistically significant difference in favour of edoxaban for women. This resulted in an indication of lesser harm from edoxaban in comparison with warfarin for the outcome "clinically relevant nonmajor bleeding" for women.

For men, there was no statistically significant difference between the treatment arms. Hence there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Greater or lesser harm of edoxaban for the outcome "clinically relevant nonmajor bleeding" for men is therefore not proven.

The approach for the outcome "clinically relevant nonmajor bleeding" deviates from that of the company, which derived lesser harm of edoxaban at the level of the total population without considering subgroup results.

Overall rate of serious adverse events

There was proof of an effect modification by the characteristic "sex" for the outcome "SAEs". There was a statistically significant difference in favour of edoxaban for women. This resulted

in an indication of lesser harm from edoxaban in comparison with warfarin for the outcome "SAEs" for women.

For men, there was no statistically significant difference between the treatment arms. Hence there was no hint of greater or lesser harm of edoxaban in comparison with warfarin. Greater or lesser harm of edoxaban for the outcome "SAEs" for men is therefore not proven.

This deviates from the company's assessment, which derived lesser harm of edoxaban at the level of the total population without considering the subgroup results.

I 2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2.5.1 Assessment of added benefit at outcome level

The data presented in Section I 2.4 resulted in indications of an added benefit for the following outcomes: stroke (haemorrhagic), stroke (disabling), major bleeding, clinically relevant nonmajor bleeding, SAEs, and the composite outcome of stroke, SEE, major bleeding or all-cause mortality. In addition, there was proof of an effect modification for the subgroup characteristics "sex" and "risk of stroke and SEE (expressed with the $CHADS_2$ score)". The extent of the respective added benefit at outcome level was estimated from these results (see Table 12).

Table 12: Extent of added benefit at outcome level: edoxaban versus warfarin

Outcome category **Outcome** **Effect modifier** **Subgroup**		**Edoxaban vs. warfarin** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality			
All-cause mortality		11.0% vs. 11.9% HR 0.92 [0.83; 1.01] p = 0.082	Lesser benefit/added benefit not proven
Morbidity			
Stroke (ischaemic, haemorrhagic or unknown cause)		4.0% vs. 4.5% HR 0.88 [0.75; 1.03] p = 0.112	Lesser benefit/added benefit not proven
Stroke (ischaemic)		3.4% vs. 3.3% HR 1.00 [0.83; 1.19] p = 0.972	Lesser benefit/added benefit not proven
Stroke (haemorrhagic)			
Sex	Female	0.4% vs. 1.4% HR 0.30 [0.15; 0.59] p = 0.001 probability: “indication”	Outcome category severe/serious symptoms/late complications $CI_u < 0.75$, risk < 5% added benefit, extent: “considerable”
	Male	0.9% vs. 1.2% HR 0.70 [0.46; 1.06] p = 0.094	Lesser benefit/added benefit not proven
Stroke (unknown cause)		No evaluable data	
Stroke (disabling)			
$CHADS_2$ score	≤ 3	0.8% vs. 0.6% HR 1.36 [0.85; 2.18] p = 0.198	Lesser benefit/added benefit not proven
	> 3	0.8% vs. 1.7% HR 0.47 [0.24; 0.91] p = 0.026 probability: “indication”	Outcome category severe/serious symptoms/late complications $CI_u < 1.00$ added benefit, extent: “minor”
SEE		0.2% vs. 0.3% HR 0.65 [0.34; 1.24] p = 0.191	Lesser benefit/added benefit not proven
Myocardial infarction		1.9% vs. 2.0% HR 0.94 [0.74; 1.19] p = 0.602	Lesser benefit/added benefit not proven
TIA		1.5% vs. 1.4% HR 1.11 [0.84; 1.47] p = 0.450	Lesser benefit/added benefit not proven

(continued)

Table 12: Extent of added benefit at outcome level: edoxaban versus warfarin (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**		**Edoxaban vs. warfarin** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life			
Not recorded			
Adverse events			
Major bleeding or clinically relevant nonmajor bleeding			
Sex	Female	22.1% vs. 28.5% HR 0.75 [0.67; 0.83] p < 0.001 probability: "indication"	Outcome category: non-severe/non-serious AEs CI_u < 0.90 lesser harm, extent: "minor"
	Male	26.1% vs. 27.8% HR 0.93 [0.85; 1.00] p = 0.06	Greater/lesser harm not proven
Major bleeding		7.8% vs. 9.6% HR 0.80 [0.72; 0.898] p < 0.001 probability: "indication"	Outcome category: severe/serious AEs CI_u < 0.90 lesser harm, extent: "considerable"
Clinically relevant nonmajor bleeding			
Sex	Female	17.0% vs. 22.2% HR 0.74 [0.66; 0.84] p < 0.001 probability: "indication"	Outcome category: non-severe/non-serious AEs CI_u < 0.90 lesser harm, extent: "minor"
	Male	20.7% vs. 21.5% HR 0.95 [0.87; 1.04] p = 0.285	Greater/lesser harm not proven
SAEs			
Sex	Female	41.4% vs. 46.4% RR: 0.89 [0.84; 0.95] p < 0.001 probability: "indication"	Outcome category: severe/serious AEs CI_u < 1.00 lesser harm, extent: "minor"
	Male	43.2% vs. 43.3% RR: 1.00 [0.95; 1.05] p = 0.879	Greater/lesser harm not proven
Discontinuation due to AEs		11.2% vs. 11.0% RR: 1.02 [0.93; 1.12] p = 0.667	Greater/lesser harm not proven

(continued)

Table 12: Extent of added benefit at outcome level: edoxaban versus warfarin (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Edoxaban vs. warfarin** **Proportion of events** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality, morbidity and adverse events		
Stroke, systemic embolic event, major bleeding or all-cause mortality	18.8% vs. 20.8% 0.89 [0.83; 0.96] p = 0.003 probability: "indication"	Outcome category severe/serious symptoms/late complications $CI_u < 1.00$ Added benefit or lesser harm, extent: "minor"
a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; HR: hazard ratio; RR: relative risk; SAE: serious adverse event; SEE: systemic embolic event; TIA: transient ischaemic attack; vs.: versus		

Deviating from the company, the outcome "clinically relevant nonmajor bleeding" was allocated to the outcome category "non-severe and non-serious late complications". It was inferred from the operationalization of this outcome in the dossier that events are included here that meet the criteria of an SAE (in this case mainly hospitalization or prolongation of hospitalization). However, the operationalization also comprised events that do not necessarily require hospitalization, such as nasal cavity packing, compression, discontinuation of study medication or change of concomitant treatment. There was no information that the majority of clinically relevant nonmajor bleeding led to hospitalization. It was therefore assumed for the benefit assessment that this was a non-serious event.

It was deviated from the company's approach also regarding the composite outcome "major or clinically relevant nonmajor bleeding". This outcome was composed of severe or serious events (major bleeding) and non-severe or non-serious events (clinically relevant nonmajor bleeding). The proportion of non-severe and non-serious events is considerably greater than the proportion of severe and serious events (see Table 10 and Table 12). The conclusion on lesser or greater harm for the composite outcome would therefore be drawn according to the outcome category of non-severe and non-serious events. However, the composite outcome would provide no additional information on the extent of harm in comparison with the assessment of the individual component "clinically relevant nonmajor bleeding" (due to the proof of interaction regarding the characteristic "sex", the conclusions on harm were drawn on the basis of the subgroup results in both cases; in each case extent "minor" for women and no proof for men). The composite outcome is therefore not considered further for the overall conclusion.

I 2.5.2 Overall conclusion on added benefit

Table 13 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 13: Positive and negative effects from the assessment of edoxaban in comparison with warfarin

Positive effects	Negative effects
Sex: female Indication of an added benefit – extent: "considerable" (outcome category severe/serious symptoms/late complications: stroke [haemorrhagic])	-
$CHADS_2$ score: > 3 Indication of an added benefit – extent: "minor" (outcome category severe/serious symptoms/late complications: stroke [disabling])	
Indication of lesser harm – extent: "considerable" (outcome category severe/serious AEs: major bleeding)	
Sex: female Indication of lesser harm – extent: "minor" (outcome category non-severe/non-serious AEs: clinically relevant nonmajor bleeding)	
Sex: female Indication of lesser harm – extent: "minor" (outcome category severe/serious AEs: SAEs)	
Indication of an added benefit – extent: "minor" (outcome category severe/serious symptoms/late complication and severe/serious AEs: stroke, SEE, major bleeding or all-cause mortality)	
AE: adverse event; $CHADS_{2:}$ sum score for categorizing stroke risk in atrial fibrillation on the basis of chronic cardiac failure (1 point), hypertension (1 point), age ≥ 75 years (1 point), diabetes mellitus (1 point) and prior stroke/TIA/thromboembolism (2 points); SAE: serious adverse event; SEE: systemic embolic event; TIA: transient ischaemic attack	

In the overall consideration, only positive effects remain, namely in the outcome categories "morbidity", "AEs" and in the composite outcome "mortality, morbidity and AEs". In each case, the probability of an added benefit or lesser harm for all outcomes was indication.

The extent of the added benefit was considerable in each of the outcomes "stroke (haemorrhagic)" and "major bleeding". The extent was minor in each of the outcomes "stroke (disabling)", "clinically relevant nonmajor bleeding", "SAEs", and in the composite outcome of stroke, SEE, major bleeding or all-cause mortality.

For the outcomes "stroke (haemorrhagic)", "clinically relevant nonmajor bleeding" and "SAEs", added benefit or lesser harm was determined only for women. For the outcome

"stroke (disabling)", the added benefit was only determined for patients with a $CHADS_2$ score > 3.

The results of the subgroup analyses do not raise doubts about an added benefit for the total population because there was an indication of considerable added benefit for all patients at least for one outcome of the category "severe or serious AEs (major bleeding)".

In summary, there is an indication of considerable added benefit of edoxaban in comparison with the ACT for the 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 TIA.

The result of the assessment of the added benefit of edoxaban in comparison with the ACT is summarized in Table 14.

Table 14: Edoxaban – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
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 TIA.	VKA **(warfarin)**	Indication of considerable added benefit
a: Presentation of the appropriate comparator therapy specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NVAF: non-valvular atrial fibrillation; TIA: transient ischaemic attack; VKA: vitamin K antagonist		

The extent and probability of added benefit concur with the company's assessment.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

I 2.6 List of included studies

ENGAGE AF-TIMI 48

Daiichi Sankyo. Global study to assess the safety and effectiveness of edoxaban (DU-176b) vs standard practice of dosing with warfarin in patients with atrial fibrillation (EngageAFTIMI48): full text view [online]. In: ClinicalTrials.gov. 12 March 2015 [accessed: 6 October 2015]. URL: https://clinicaltrials.gov/show/NCT00781391.

Daiichi Sankyo. Global study to assess the safety and effectiveness of edoxaban (DU-176b) vs standard practice of dosing with warfarin in patients with atrial fibrillation (EngageAFTIMI48): study results [online]. In: ClinicalTrials.gov. 12 March 2015 [accessed: 6 October 2015]. URL: https://clinicaltrials.gov/ct2/show/results/NCT00781391.

Daiichi Sankyo. A phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for evaluation of efficacy and safety of DU-176b (edoxaban) versus warfarin in subjects with atrial fibrillation: Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE AF-TIMI 48); version 2.0; study DU176B-C-U301; clinical study report [unpublished]. 2013.

Daiichi Sankyo Pharma Development. A phase 3, randomized, double-blind, double-dummy, parallel group, multi-center, multi-national study for evaluation of efficacy and safety of du-176b versus warfarin in subjects with atrial fibrillation: Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation (ENGAGE-AF) [online]. In: EU Clinical Trials Register. [Accessed: 6 October 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2008-004522-16.

Daiichisankyo. A phase 3, randomized, double-blind, double-dummy, parallel group, multi-center, multi-national study for evaluation of efficacy and safety of DU-176b versus warfarin in subjects with atrial fibrillation [online]. In: Clinical Trials Information/JapicCTI. 31 July 2014 [accessed: 6 October 2015].
URL: http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-090775.

Di Pasquale G, Riva L. Edoxaban nella fibrillazione atriale: lo studio ENGAGE AF-TIMI 48. G Ital Cardiol (Rome) 2014; 15(12 Suppl 1): 22S-26S.

Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL et al. Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2013; 369(22): 2093-2104.

Giugliano RP, Ruff CT, Rost NS, Silverman S, Wiviott SD, Lowe C et al. Cerebrovascular events in 21 105 patients with atrial fibrillation randomized to edoxaban versus warfarin: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48. Stroke 2014; 45(8): 2372-2378.

Gupta DK, Shah AM, Giugliano RP, Ruff CT, Antman EM, Grip LT et al. Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48. Eur Heart J 2013; 35(22): 1457-1465.

Kaba RA, Ahmed O, Cannie D. ENGAGE AF: effective anticoagulation with factor Xa in next generation treatment of atrial fibrillation. Glob Cardiol Sci Pract 2013; 2013(4): 354-356.

Mega JL, Walker JR, Ruff CT, Vandell AG, Nordio F, Deenadayalu N et al. Genetics and the clinical response to warfarin and edoxaban: findings from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015; 385(9984): 2280–2287.

O'Donoghue ML, Ruff CT, Giugliano RP, Murphy SA, Grip LT, Mercuri MF et al. Edoxaban vs. warfarin in vitamin K antagonist experienced and naive patients with atrial fibrillation. Eur Heart J 2015; 36(23): 1470-1477.

Ruff CT, Giugliano RP, Braunwald E, Mercuri M, Curt V, Betcher J et al. Transition of patients from blinded study drug to open-label anticoagulation: the ENGAGE AF-TIMI 48 trial. J Am Coll Cardiol 2014; 64(6): 576-584.

Ruff CT, Giugliano RP, Braunwald E, Morrow DA, Murphy SA, Kuder JF et al. Association between edoxaban dose, concentration, anti-Factor Xa activity, and outcomes: an analysis of data from the randomised, double-blind ENGAGE AF-TIMI 48 trial. Lancet 2015; 385(9984): 2288–2295.

Steffel J, Giugliano RP, Braunwald E, Murphy SA, Atar D, Heidbuchel H et al. Edoxaban vs. warfarin in patients with atrial fibrillation on amiodarone: a subgroup analysis of the ENGAGE AF-TIMI 48 trial. Eur Heart J 2015; 36(33): 2239-2245.

References for English extract

Please see full assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.2 [online]. 22 April 2015 [accessed: 20 October 2015]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-2.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2 July 2015 [Epub ahead of print].

3. European Medicines Agency. Lixiana: European public assessment report; product information [online]. 3 July 2015 [accessed: 6 October 2015]. URL: http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf.

4. Kirchhof P, Goette A, Gulba D, Hindricks G, Hohnloser SH. Kommentar zu den Leitlinien der ESC zum Vorhofflimmern. Der Kardiologe 2012; 6(1): 12-27.

Edoxaban

Assessment module II

Treatment and prevention of (recurrent) DVT and PE

Medical and scientific advice:

- Birgit Linnemann, Praxis am Grüneburgweg, Frankfurt am Main, Germany

IQWiG thanks the medical and scientific advisor for her contribution to the assessment. However, the advisor was not involved in the actual preparation of the assessment. The responsibility for the contents of the assessment lies solely with IQWiG.

IQWiG employees involved in the assessment[1]:

- Peter Kiencke
- Katharina Biester
- Andreas Gerber-Grote
- Ulrich Grouven
- Michaela Florina Kerekes
- Astrid Seidl
- Volker Vervölgyi
- Siw Waffenschmid

Keywords: edoxaban, venous thromboembolism, pulmonary embolism, benefit assessment

[1] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

Page

List of abbreviations

Abbreviation	Meaning
ACCP	American College of Chest Physicians
ACT	appropriate comparator therapy
ARR	absolute risk reduction
DVT	deep vein thrombosis
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HR	hazard ratio
INR	international normalized ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LMWH	low molecular weight heparin
OR	odds ratio
PE	pulmonary embolism
RCT	randomized controlled trial
RR	relative risk
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VKA	vitamin K antagonist
VTE	venous thromboembolism

II 2 Benefit assessment

II 2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug edoxaban. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 20 July 2015.

Research question

The aim of the present report is to assess the added benefit of edoxaban compared with vitamin K antagonists (VKAs) as appropriate comparator therapy (ACT) for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. In accordance with the approval, the treatment of haemodynamically unstable PE patients is not part of the assessment.

The G-BA named VKAs as ACT for the treatment of DVT and PE, and prevention of recurrent DVT and PE (venous thromboembolism [VTE]) following initial parenteral anticoagulation.

In the present therapeutic indication it should be differentiated between a patient population for whom limited treatment and prevention of 3 to 6 months is indicated and a patient population for whom continuous prevention for longer than 3 to 6 months (referred to as "long-term prevention" in the present report) is indicated. The company did not differentiate between these patient populations in its research question. Such a differentiated consideration of the patient groups is considered necessary for the present benefit assessment, however. This is supported by guidelines as well as by the approval. Table 1 shows an overview of the 2 research questions resulting from this.

Table 1: Appropriate comparator therapy for the benefit assessment of edoxaban

Research question	Subindication	ACT[a]
1	After completion of initial treatment[b] of DVT and PE: treatment of DVT and PE and prevention of recurrent DVT and PE in adults[c]	VKA **(warfarin)**
2	Long-term prevention of recurrent DVT and PE in adults[d]	VKA **(warfarin)**

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Edoxaban is approved following initial use of parenteral anticoagulant for at least 5 days.
c: Limited treatment and prevention (3 to 6 months).
d: Continuous prevention (longer than 3 to 6 months).
ACT: appropriate comparator therapy; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; PE: pulmonary embolism; VKA: vitamin K antagonist

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. The derivation of the added benefit was to be conducted based on randomized controlled trials (RCTs). A minimum study duration of 3 months was defined for research question 1, and a minimum study duration of 12 months for research question 2.

Results

Study pool of the company, characteristics of the study and of the interventions

The company included the RCT Hokusai-VTE. This study was a randomized, double-blind, active-controlled and multinational study on the comparison of edoxaban with warfarin. Adult patients diagnosed with acute symptomatic proximal DVT and/or symptomatic PE who required anticoagulant treatment were included. No patients with distal DVT and no patients with asymptomatic VTE were included.

In the study, a total of 8292 patients were randomly assigned to low molecular weight heparin (LMWH) followed by edoxaban 60 mg/day (N = 4143), and to LMWH with concurrent administration of warfarin (N = 4149) followed by warfarin alone. According to the approval, the edoxaban dosage of 60 mg/day is halved if certain conditions are met regarding body weight, creatinine clearance and concomitant medication. Warfarin was administered at an individual dosage (dosage to target international normalized ratio [INR] range 2.0 to 3.0). Treatment was to be continued for at least 3 months and for a maximum of 12 months. The planned treatment duration of 3, 6 or 12 months was documented by the treating physician before randomization. Irrespective of the treatment duration, the primary outcome was recorded after 12 months.

Patient inclusion and treatment duration were event-driven. The study was intended to last until 220 events of the primary outcome had occurred. Randomization was stopped at this time point. Treatment ended for all the patients in the study after up to 6 months after the last patient had been randomized so that completion of a 6-month treatment was possible also for the last patient randomized. A final study visit was conducted one month after the end of treatment.

The study investigated patient-relevant outcomes.

The study was principally relevant for the benefit assessment because patients were included who can be allocated to one of the two research questions mentioned above. From the information presented by the company in the dossier, however, no analyses could be identified that sufficiently represent the 2 research questions. No suitable analyses of the Hokusai-VTE study were available for the present benefit assessment because of this.

No available data for research questions 1 and 2

Before randomization, the treating physicians were to document the planned treatment duration for each patient on the basis of an American clinical practice guideline. Due to the individual clinical status of each patient, it was possible that actual treatment durations

differed from the planned treatment durations. It can be assumed that the Hokusai-VTE study comprised both patients for whom limited treatment and prevention was indicated (research question 1) and patients for whom long-term prevention (research question 2) was indicated. Hence corresponding analyses of those patients in the study who can be allocated to the individual research questions are required. It was checked whether factors existed on the basis of which an adequate approximation of this differentiation is possible.

Analyses for the present research questions

Separate analysis of patients according to planned treatment duration

Since the research questions differed according to whether patients required long-term prevention or not, analyses according to planned treatment durations seemed to be a suitable approximation of adequate analyses for the present assessment, even though actual treatment durations could deviate from them. The planned treatment durations were based on guideline-based assessments of the physicians, and therefore reflected the subindication for the treatment duration within the present therapeutic indication. Results analysed separately by actual treatment durations are unsuitable because these treatment durations may already be influenced by the study medication.

Hence analyses relevant for the benefit assessment should be based on separate analyses for planned treatment durations of 3, 6 and 12 months and on a meaningful summary corresponding to research questions 1 and 2.

Potentially suitable analyses not directly based on planned treatment durations

Patients with transient risk factors are more likely to receive limited treatment duration than patients with other risk factors. Hence separate analyses on patients with transient risk factors and patients with other risk factors also might have been suitable for the benefit assessment. Such analyses are contained in the dossier also in the form of subgroup analyses. However, it became clear on the basis of the baseline characteristics separated according to planned treatment available for the edoxaban group that a differentiation of the risk factors in transient and other represents no good approximation of a division of the patients into research questions 1 and 2. The proportions of patients in the planned treatment durations of 3, 6 and 12 months for patients with transient risk factors was 11%, 47% und 42%; whereas for patients with other risk factors, the proportions were 3%, 34% und 62%. This did not show that shorter or longer treatment duration was clearly planned for patients with certain risk factors, particularly transient risk factors. Such estimation was not possible for the warfarin group because of missing data.

Supplementary presentation of the results on the total population of the Hokusai-VTE study

Since the Hokusai-VTE study only included patients who can be allocated to one of both research questions – or at least there were no signs that this was not the case – the results for the total population were presented as additional information.

A statistically significant difference between the treatment groups was shown for the total population for the outcome "major bleeding or clinically relevant nonmajor bleeding". Most results of this outcome consisted of events of the outcome "clinically relevant nonmajor bleeding", for which a statistically significant difference between the treatment groups was also found. The outcome "clinically relevant nonmajor bleeding" can be allocated to the outcome category "non-serious and non-severe symptoms and adverse events (AEs)". The effect size was only marginal for both outcomes. Hence an added benefit of edoxaban would not be proven even if the total population was used for the benefit assessment.

Extent and probability of the added benefit, patient groups with therapeutically important added benefit

The result of the assessment of the added benefit of edoxaban in comparison with the ACT is summarized in Table 2.

Table 2: Edoxaban – extent and probability of added benefit

Subindication	**ACT**[a]	**Extent and probability of added benefit**
After completion of initial treatment[b] of DVT and PE: treatment of DVT and PE and prevention of recurrent DVT and PE in adults[c]	VKA **(warfarin)**	Added benefit not proven
Long-term prevention of recurrent DVT and PE in adults[d]	VKA **(warfarin)**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Edoxaban is recommended following initial use of parenteral anticoagulant for at least 5 days. c: Limited treatment and prevention (3 to 6 months). d: Continuous prevention (longer than 3 to 6 months). ACT: appropriate comparator therapy; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; PE: pulmonary embolism; VKA: vitamin K antagonist		

The G-BA decides on the added benefit.

II 2.2 Research question

The aim of the present report is to assess the added benefit of edoxaban compared with VKAs as ACT for the treatment of DVT and PE, and prevention of recurrent DVT and PE in adults.

In accordance with the approval, the treatment of haemodynamically unstable PE patients is not part of the assessment [1].

The G-BA named VKAs as ACT for the treatment of DVT and PE, and prevention of recurrent DVT and PE (VTE) following initial parenteral anticoagulation.

In the present therapeutic indication it should be differentiated between a patient population for whom limited treatment and prevention of 3 to 6 months is indicated and a patient population for whom continuous prevention for longer than 3 to 6 months (referred to as "long-term prevention" in the present report) is indicated (see Section II 2.3.3). Table 3 shows an overview of the 2 research questions resulting from this.

Table 3: Appropriate comparator therapy for the benefit assessment of edoxaban

Research question	Subindication	ACT[a]
1	After completion of initial treatment[b] of DVT and PE: treatment of DVT and PE and prevention of recurrent DVT and PE in adults[c]	VKA **(warfarin)**
2	Long-term prevention of recurrent DVT and PE in adults[d]	VKA **(warfarin)**

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b: Edoxaban is approved following initial use of parenteral anticoagulant for at least 5 days [1].
c: Limited treatment and prevention (3 to 6 months).
d: Continuous prevention (longer than 3 to 6 months).
ACT: appropriate comparator therapy; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; PE: pulmonary embolism; VKA: vitamin K antagonist

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. The derivation of the added benefit was to be conducted based on RCTs. A minimum study duration of 3 months was defined for research question 1, and a minimum study duration of 12 months for research question 2.

The research questions deviated from the research question of the company, which did not differentiate between the 2 subindications in the therapeutic indication. Hence the minimum study duration for research question 2 also deviated from the company's specification, which specified 3 months for the total population. The specification of a minimum study duration of 12 months did not affect the relevance of the study presented, however, because the total study duration was 12 months.

II 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on edoxaban (status: 5 June 2015)
- bibliographical literature search on edoxaban (last search on 16 June 2015)
- search in trial registries for studies on edoxaban (last search on 5 June 2015)

To check the completeness of the study pool:

- search in trial registries for studies on edoxaban (last search on 1 July 2015)

No additional relevant study was identified from the check.

II 2.3.1 Company's study included

The study listed in the following table was included in the company's benefit assessment.

Table 4: Study pool of the company – RCT, direct comparison: edoxaban vs. warfarin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Hokusai-VTE	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The company used the Hokusai-VTE study [2,3] for the assessment of the total approved therapeutic indication. The study is principally relevant, but in its assessment the company did not differentiate between the 2 subindications in the therapeutic indication, which are mentioned in Section II 2.2. Such differentiated consideration is necessary, however (see Section II 2.3.3). From the information presented by the company in the dossier, however, no analyses could be identified that sufficiently represent the 2 research questions. No suitable analyses of the Hokusai-VTE study were available for the present benefit assessment because of this. This is justified in the following sections.

Firstly, the Hokusai-VTE study and the interventions are described in the following Section II 2.3.2. In Sections II 2.3.3 and II 2.3.4, it is then explained why no suitable data for the research questions relevant in the present benefit assessment are available. In Section II 2.3.5, the results of the total population of the Hokusai-VTE study are presented as additional information.

II 2.3.2 Characteristics of the Hokusai-VTE study

Table 5 and Table 6 describe the study used for the benefit assessment.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: edoxaban vs. warfarin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Hokusai-VTE	RCT, double-blind, parallel	Adult patients diagnosed with acute symptomatic proximal DVT and/or symptomatic PE who require anticoagulant treatment	Edoxaban (N = 4143) warfarin (N = 4149)	Screening: 3 days Initial treatment: at least 5 days heparin in both arms (+ placebo or warfarin); then treatment with edoxaban or warfarin up to a maximum of 12 months[b] Event-driven study duration: end of treatment for all patients after 220 events in the primary outcome, assessment of outcomes after 12 months Follow-up for AEs: 1 month	439 centres in 37 countries: Australia, New Zealand, South Africa, and countries in Asia, Europe, North America, South America 1/2010–6/2013	Primary: ▪ symptomatic recurrent VTE (composite outcome of DVT, nonfatal PE and fatal PE) and individual components Secondary: ▪ composite outcome of DVT, nonfatal PE, major bleeding, all-cause mortality and individual components ▪ composite outcome of major bleeding and clinically relevant nonmajor bleeding and individual components ▪ AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: The study was planned in such a way that completion of a 6-month treatment was possible also for the last patient enrolled. The minimum treatment duration was 3 months.

AE: adverse event; DVT: deep vein thrombosis; N: number of randomized patients; PE: pulmonary embolism; RCT: randomized controlled trial; VTE: venous thromboembolism; vs.: versus

Table 6: Characteristics of the interventions – RCT, direct comparison: edoxaban vs. warfarin

Study	Intervention	Comparison	Prior and concomitant medication
Hokusai-VTE	**Initial treatment (at least 5 days):**		**Pretreatment:**
	LMWH[a] + placebo	LMWH[a] + warfarin + placebo	▪ anticoagulant treatment, including a single dose of a VKA, allowed until no later than 48 hours before randomization
	Treatment and prevention:		**Concomitant medication:**
	Edoxaban 60 mg orally once daily + placebo	Warfarin orally, flexible[b] dose + placebo	▪ aspirin ≤ 100 mg/day (higher dose allowed in clinical emergencies, e.g. MI) ▪ verapamil, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole ▪ temporary discontinuation of the study medication during concomitant treatment with fibrinolytic agents
	Dose reduction to 30 mg once daily when ≥ 1 of the following criteria is present: ▪ permanent when 30 ≤ CrCl ≤ 50mL/min or body weight ≤ 60 kg ▪ temporary when concomitant treatment with erythromycin, ketoconazole, verapamil, quinidine, azithromycin, clarithromycin or itraconazole		**Non-permitted concomitant medication:** ▪ dronedarone ▪ other oral anticoagulants ▪ dual antithrombotic therapies ▪ long-term use (≥ 4 days/week) of oral or parenteral NSAIDs except aspirin ▪ P-gp inhibitors: ritonavir, nelfinavir, indinavir, saquinavir and ciclosporin

a: Enoxaparin 1 mg/kg, twice daily subcutaneously, enoxaparin 1.5 mg/kg once daily, or UFH intravenously, individually for each study centre according to local standards.
b: Adjustment to maintain a stable level of INR between 2.0 and 3.0.

CrCl: creatinine clearance; INR: international normalized ratio; LMWH: low molecular weight heparin; MI: myocardial infarction; NSAID: nonsteroidal anti-inflammatory drug; P-gp: P-glycoprotein; RCT: randomized controlled trial; UFH: unfractionated heparin; VKA: vitamin K antagonist; vs.: versus

The Hokusai-VTE study was a randomized, double-blind, active-controlled and multicentre study with a maximum treatment phase of 12 months. The study was conducted in centres in Australia, New Zealand, South Africa and in countries in Asia, Europe, North America and South America.

Adult patients diagnosed with acute symptomatic proximal DVT and/or symptomatic PE who required anticoagulant treatment were included. No patients with distal DVT and no patients with asymptomatic VTE were included.

Patient inclusion and treatment duration were event-driven. The study was intended to last until 220 events of the primary outcome had occurred. Randomization was stopped at this time point. Treatment ended for all the patients in the study after up to 6 months after the last patient had been randomized so that completion of a 6-month treatment was possible also for the last patient randomized. A final study visit was conducted one month after the end of treatment. Treatment was to be continued for at least 3 months and for a maximum of

12 months. The planned treatment duration of 3, 6 or 12 months was documented by the treating physician before randomization on the basis of an American guideline [4]. It was assumed that 25% of the patients would end treatment after 3 months, another 40% would be treated after 6 months, and that 35% would be treated for 12 months. Irrespective of the treatment duration, the primary outcome was recorded after 12 months.

In the study, a total of 8292 patients were randomly assigned to LMWH followed by edoxaban 60 mg/day (N = 4143), and to LMWH with concurrent administration of warfarin (N = 4149) followed by warfarin alone. Warfarin was administered at an individual dosage (dosage to target INR range 2.0 to 3.0). The use was in compliance with the approval. The patients received the respective placebo to maintain blinding of edoxaban and warfarin.

Randomization was stratified by index event, risk factors at baseline, and by necessity to reduce the dose to 30 mg. The dose was permanently reduced in case of a body weight of 60 kg or less, creatinine clearance between 30 mL/min and 50 mL/min. The dose was temporarily reduced in case of concomitant medication with the P-gp inhibitors verapamil, quinidine, erythromycin, azithromycin, clarithromycin, ketoconazole or itraconazole. The dosage of edoxaban and the dose reduction to 30 mg in the weight mentioned above, the creatinine clearance mentioned above and, in principle, in the concomitant use of P-gp inhibitors concurred with the approval. However, the P-gp inhibitors defined in the study only partially concurred with the ones defined in the Summary of Product Characteristics (SPC). The SPC named ciclosporin, dronedarone, erythromycin or ketoconazole. A total of 11% had taken P-gp inhibitors that did not concur in the 2 lists so that a missing dose reduction as well as a dose reduction contrary to the approval was uncritical for the total population (see Section II 2.6.2.4.1 of the full dossier assessment).

Concomitant medication with certain drugs, including other anticoagulants, was prohibited in both study arms. These could only be used if the study medication was temporarily discontinued. Primary outcome was symptomatic recurrent VTE, which constituted a combination of symptomatic DVT, nonfatal PE and fatal PE. Furthermore, morbidity and AEs were investigated in the study. Health-related quality of life was not recorded in the study.

II 2.3.3 Differentiation between patient populations

The company did not differentiate between a patient population for whom limited treatment and prevention of DVT and PE is indicated and a patient population for whom continuous prevention of recurrent DVT and PE is indicated.

Such a differentiated consideration of the patient groups is considered necessary for the present benefit assessment, however. On the one hand, this is supported by guidelines, and on the other, by the approval.

The European Society of Cardiology (ESC) guideline differentiates between patients with provoked (transient or reversible) risk factors such as surgery, trauma or pregnancy, and

patients with unprovoked (permanent) risk factors in the absence of the risk factors mentioned above. This differentiation may result in different treatment durations [5]. A treatment duration of at least 3 months is recommended for patients with transient or reversible risk factors. However, treatment for longer than this period of time is not recommended, provided that the underlying risk factor no longer exists. The balance between the individual risk of recurrence of VTE and that of bleeding is necessary for the decision whether treatment is continued beyond 3 months or whether even an indefinite treatment duration, such as long-term prevention, is required. An indefinite treatment duration should be considered for patients with a low risk of bleeding [5]. Several individual criteria influence the decision on the treatment duration, including origin of the DVT, number of prior thrombotic events, possibly also persistence of risk factors and patient's preference [6]. The therapeutic indication for long-term prevention, which is "determined for more than 3 to 6 months" is to be evaluated on an individual basis [6]. This also concurs with the more recent European guideline [5]. Also in the Hokusai-VTE study, the patients included were divided according to planned treatment duration on the basis of the American College of Chest Physicians (ACCP) guideline [4].

The approval also differentiated between the 2 patient groups, which is also eventually reflected in different treatment durations. It is also clear from the SPC that the duration of therapy for treatment of DVT and PE, and prevention of recurrent VTE should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Nonetheless, the SPC differentiates between patients with transient risk factors and resulting short treatment duration (at least 3 months) and patients with permanent risk factors or idiopathic DVT or PE, for whom longer treatment duration is required [1].

Overall it is clear that different patient groups are generally differentiated in the present therapeutic indication of edoxaban, and that this differentiation is based on criteria that are already known at the start of the treatment (e.g. origin of the DVT or number of prior thrombotic events). This results in different planned treatment durations. It is also true that, beyond that, the actual treatment duration has to be determined using factors that occur in the course of the treatment, such as adverse events, in this case individual risk of bleeding. This is not decisive for the general differentiation of the patients at the start of treatment and applies to a large number of treatments in different diseases.

Hence in the present therapeutic indication it should be differentiated between a patient population for whom limited treatment and prevention of 3 to 6 months is planned and a patient population for whom continuous prevention for longer than 3 to 6 months is planned at the start of treatment. Two research questions resulted from this differentiation in 2 subindications, which differed in the following aspects:

1) after completion of initial treatment of DVT and PE: treatment of DVT and PE and prevention of recurrent DVT and PE (= limited treatment duration [3 to 6 months])

2) long-term prevention of recurrent DVT and PE (= continuous prevention [beyond 3 to 6 months])

II 2.3.4 No available data for research questions 1 and 2

It was described above that the patients in the Hokusai-VTE study were treated for at least 3 to a maximum of 12 months. Before randomization, the treating physicians were to document the planned treatment duration for each patient on the basis of an American guideline [4]. Due to the individual clinical status of each patient, it was possible that actual treatment durations differed from the planned treatment durations.

Based on the treatment durations pre-estimated by the physicians, it can be assumed that the Hokusai-VTE study comprised both patients for whom limited treatment and prevention was indicated and patients for whom long-term prevention was indicated. Hence regarding the research questions for the present benefit assessment defined in Sections II 2.2 and II 2.3.3, both patients relevant for research question 1 and patients relevant for research question 2 were included in the study. The total population of the Hokusai-VTE study was unsuitable to answer both research questions separately, however. Instead, this requires corresponding analyses of those patients in the study who can be allocated to the individual research questions. The dossier did not contain such analyses, however. No factor that allows such differentiation of the patients according to the 2 research questions could be inferred from the study documents either. It was therefore checked for the present benefit assessment whether factors exist on the basis of which an adequate approximation of this differentiation is possible.

Analyses for the present research questions

Separate analysis of patients according to planned treatment duration

The study documents contained information on the planned treatment durations for both study arms. It could then be inferred from the approval documents [7] for how long the patients with a certain planned treatment duration were actually treated; however this information was only available for the edoxaban group. There was no such information for the warfarin group, which would be required for a comparative consideration, however.

Table 7 firstly shows the planned treatment durations of the patients.

Table 7: Information on the planned treatment duration – RCT, direct comparison: edoxaban vs. warfarin

Study	**Edoxaban N = 4118 n (%)**	**Warfarin N = 4122 n (%)**
Hokusai-VTE		
Planned treatment duration		
3 months	221 (5.4)	245 (5.9)
6 months	1555 (37.8)	1502 (36.4)
12 months	2339 (56.8)	2371 (57.5)
N: number of analysed patients; n: number of patients in the category; RCT: randomized controlled trial; vs.: versus		

A treatment duration of 12 months was planned for somewhat more than half of the patients in both groups. A 3-month treatment duration was planned for only few patients, and a 6-month treatment duration for somewhat more than one third.

Table 8 shows for how many patients in the edoxaban group treatment duration was equal to, longer or shorter than the planned treatment duration.

Table 8: Information on the actual treatment duration in relation to the planned treatment duration – RCT, direct comparison: edoxaban vs. warfarin (edoxaban group)

Study **Actual treatment duration**	**Planned treatment duration 3 months N = 221**	**Planned treatment duration 6 months N = 1555**	**Planned treatment duration 12 months N = 339**
Hokusai-VTE			
Mean (SD) [days]	136.0 (98.97)	207.5 (91.37)	292.7 (106.35)
Median [days]	93.0	182.0	357.0
	n (%)	**n (%)**	**n (%)**
≤ 3 months	123 (55.7)	145 (9.3)	214 (9.1)
> 3 to ≤ 6 months	54 (24.4)	816 (52.5)	206 (8.8)
> 6 months	44 (19.9)	594 (38.2)	1919 (81.2)
≥ 12 months	22 (10.0)	280 (18.0)	1359 (58.1)
N: number of analysed patients; n: number of patients in the category; RCT: randomized controlled trial; SD: standard deviation; vs.: versus			

Overall it was shown that there were deviations of different extent between the planned treatment durations and the actual treatment durations. Information was insufficient to estimate how large the deviations actually were. It remained unclear, for example, how many patients in the period of 3 to ≤ 6 months were treated rather for 3 or rather for 6 months.

As described above, it would have been necessary for the present benefit assessment to analyse patients in such a way that they could have been allocated to the individual research questions. Since the research questions differed according to whether patients required long-term prevention or not, analyses according to planned treatment durations seemed to be a suitable approximation of adequate analyses for the present benefit assessment, despite the deviations described above. The planned treatment durations were based on guideline-based assessments of the physicians, and therefore reflected the subindication for the treatment duration within the present therapeutic indication. Results analysed separately by actual treatment durations are unsuitable because these treatment durations were unknown at the start of the study and may already be influenced by the study medication.

Hence analyses relevant for the benefit assessment should be based on separate analyses for planned treatment durations of 3, 6 and 12 months and on a meaningful summary corresponding to research questions 1 and 2.

The dossier contained no analyses separated by planned treatment. Information on the characteristics of the population in the edoxaban group separated by planned treatment can be inferred from the approval documents (see II Appendix A of the full dossier assessment). However, there are no such data for the warfarin group, which would also be required.

Potentially suitable analyses not directly based on planned treatment durations

Patients with transient risk factors are more likely to receive limited treatment duration than patients with other risk factors [6,8]. Hence separate analyses on patients with transient risk factors and patients with other risk factors also might have been suitable for the benefit assessment. Such analyses are contained in the dossier also in the form of subgroup analyses. However, it became clear on the basis of the baseline characteristics separated according to planned treatment available for the edoxaban group that a differentiation of the risk factors in transient and other represents no good approximation of a division of the patients into research questions 1 and 2. The proportions of patients (Institute's calculation based on Table 17 in II Appendix A of the full dossier assessment) in the planned treatment durations of 3, 6 and 12 months for patients with transient risk factors was 11%, 47% und 42%; whereas for patients with other risk factors, the proportions were 3%, 34% und 62%. This did not show that shorter or longer treatment duration was clearly planned for patients with certain risk factors, particularly transient risk factors. Such estimation was not possible for the warfarin group because of missing data.

The company's analyses by risk factors at the start of the study in the framework of its subgroup analyses were therefore considered unsuitable for the benefit assessment.

Overall, there were no suitable analyses for the relevant research questions of the benefit assessment.

Further approach for the benefit assessment

As described above, the dossier contained no suitable analyses of the Hokusai-VTE study for the separate investigation of research questions 1 and 2 of the present benefit assessment. It should be noted, however, that only patients who can be allocated to one of both research questions – or at least there were no signs that this was not the case – were included in the study. For this reason, the results of the total population of the Hokusai-VTE study are presented as additional information.

II 2.3.5 Supplementary presentation of the results on the total population of the Hokusai-VTE study

Characteristics of the total population in the Hokusai-VTE study

Table 9 shows the characteristics of the total population of the Hokusai-VTE study.

Table 9: Characteristics of the study populations – RCT, direct comparison: edoxaban vs. warfarin (total population; supplementary presentation)

Study **Characteristics** **Category**	**Edoxaban** **N = 4118**	**Warfarin** **N = 4122**
Hokusai-VTE		
Age [years], mean (SD)	56 (16)	56 (16)
Sex [F/M], %	43/57	43/57
Index event[a], n (%)		
PE	1671 (40.6)	1679 (40.7)
With DVT	611 (14.8)	560 (13.6)
Without DVT	1060 (25.7)	1119 (27.1)
DVT only	2447 (59.4)	2443 (59.3)
Anatomical extent of index event, n (%)		
PE	1550 (37.6[b])	1583 (38.4[b])
Limited	128 (8.3)	123 (7.8)
Intermediate	679 (43.8)	682 (43.1)
Extensive	743 (47.9)	778 (49.1)
DVT	2433 (59.1[b])	2418 (58.7[b])
Limited	603 (24.8)	596 (24.6)
Intermediate	795 (32.7)	773 (32.0)
Extensive	1035 (42.5)	1049 (43.4)
Risk factors		
Transient	1132 (27.5)	1140 (27.7)
All others	2986 (72.5)	2982 (72.3)
Prior VKA treatment, n (%)		
Yes	334 (8.1)	385 (9.3)
No	3784 (91.9)	3737 (90.7)
Creatinine clearance [mL/min], mean (SD)	105.2 (40.4)[c]	104.9 (40.2)[c]
Body weight (kg), mean (SD)	81.8 (19.5)	82.2 (20.1)
Region, n (%)		
Western Europe	680 (16.5)	679 (16.5)
Southern Europe[d]	586 (14.2)	590 (14.3)
Central Europe	468 (11.4)	464 (11.3)
Eastern Europe	483 (11.7)	485 (11.8)
Northern countries	174 (4.2)	180 (4.4)
China/Japan	349 (8.5)	344 (8.3)
Other Asian countries	501 (12.2)	503 (12.2)
Australia/New Zealand	145 (3.5)	145 (3.5)
South Africa/South America	316 (7.7)	312 (7.6)
USA/Canada	416 (10.1)	420 (10.2)

(continued)

Table 9: Characteristics of the study populations – RCT, direct comparison: edoxaban vs. warfarin (total population; supplementary presentation) (continued)

Study Characteristics Category	Edoxaban N = 4118	Warfarin N = 4122
Hokusai-VTE		
Ethnicity, n (%)		
White	2867 (69.6)	2895 (70.2)
Black	156 (3.8)	144 (3.5)
Asian	866 (21.0)	861 (20.9)
Other	220 (5.3)	211 (5.1)
No data	9 (0.2)[b]	7 (0.2)[b]
Study discontinuations, n (%)[e]	181 (4.4)	167 (4.1)
Treatment discontinuations, n (%)	695 (16.9)	718 (17.4)

a: Contradictory data on the number of patients with index event PE or DVT at different places in the CSR, which cannot be explained by the presentation for different populations (ITT for number of patients with index event PE or DVT and mITT for the separation by PE with/without DVT and the categories on the anatomical extent of the index event).
b: Institute's calculation.
c: Missing data for 237 patients in the edoxaban arm and 251 patients in the warfarin arm.
d: Including France, Israel, Turkey.
e: Patients who did not complete their individually planned study duration (3, 6 or 12 months).
CSR: clinical study report; DVT: deep vein thrombosis; F: female; ITT: intention to treat; M: male; mITT: modified intention to treat (all randomized and treated patients); N: number of analysed patients; n: number of patients in the category; PE: pulmonary embolism; RCT: randomized controlled trial; SD: standard deviation; VKA: vitamin K antagonist; vs.: versus

The characteristics of the patients included in the Hokusai-VTE study were comparable between the treatment groups. The mean age of the patients was 56 years. Somewhat more men than women were enrolled in the study. About 60% of the study population had only DVT, and about 40% had PE (with or without DVT) as index event. The severity grade (measured with the respective anatomical extent) of most patients with DVT was intermediate or extensive (about 75%). Most patients with PE also had a mainly intermediate or extensive severity grade, but their proportion was higher (about 90%). About 28% of the study population at the start of the study consisted of patients with only transient risk factors such as trauma, surgery, immobilization, oestrogen therapy, etc. Only about 9% of the patients had received VKA therapy before the study. The mean body weight was about 82 kg, the mean creatinine clearance was 105 mL/min. Most patients were white (70%). Most patients originated from Western Europe (17%), Southern Europe (14%) and other Asian countries (12%) (without China and Japan).

The rate of study discontinuations was about 4% in both study arms, the rate of treatment discontinuations was 17%.

Table 10 shows the mean and median treatment duration of the patients, the study duration and the time during which the patients were treated with edoxaban or warfarin during the study duration.

Table 10: Information on the course of the study – RCT, direct comparison: edoxaban vs. warfarin (total population; supplementary presentation)

Study **Duration of the study phase**	**Edoxaban** **N = 4118**	**Warfarin** **N = 4122**
Hokusai-VTE		
Treatment duration [days][a]		
Median [min; max]	267.0 [ND]	266.0 [ND]
Mean (SD)	251.9 (112.04)	250.3 (113.01)
Patients with different treatment duration, n (%)		
≤ 3 months	485 (11.8)	528 (12.8)
< 3 months	353 (8.6)	360 (8.7)
3 months	132 (3.2)	168 (4.1)
3–6 months	1076 (26.1)	1084 (26.3)
> 3 to < 6 months	228 (5.5)	237 (5.7)
6 months	848 (20.6)	847 (20.5)
> 6 months	2557 (62.1)	2510 (60.9)
> 6 to < 12 months	896 (21.8)	851 (20.6)
≥ 12 months	1661 (40.3)	1659 (40.2)
Duration of exposure to study treatment [days][b]		
Median [min; max]	265.0 [ND]	261.0 [ND]
Mean (SD)	250.3 (111.75)	248.4 (112.61)
Study duration [days]		
Median [min; max]	374.0 [2; 780]	373.0 [2; 841]
Mean (SD)	354.0 (73.10)	354.2 (72.45)
Patients who temporarily discontinued treatment at least once[c], n (%)	373 (9.1)	443 (10.7)

a: Total treatment duration including temporary discontinuation of the study medication.
b: Actual treatment duration excluding temporary discontinuations.
c: Temporary discontinuation of treatment was considered to be a non-administration of the study medication for ≥ 3 days.
N: number of analysed patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The treatment duration and the number of exposure to edoxaban or warfarin did not differ considerably between the treatment groups. During participation in the study, it was possible to discontinue treatment with the study medication and restart again later. This applied to about 9% of the patients in the edoxaban group and to about 11% in the warfarin group. No

relevant differences between the treatment groups were shown regarding the median observation period either.

Results for the total population in the Hokusai-VTE study

Table 11 summarizes the results for the total population on the comparison of edoxaban and warfarin for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

Reasons for the choice of outcomes are given in Section II 2.6.2.4.3 of the full dossier assessment. The company used the hazard ratio (HR) as effect measure for most outcomes included by the company. The company used the effect measures relative risk (RR), odds ratio (OR) and absolute risk reduction (ARR) as effect estimates for AEs except bleeding events. The Kaplan-Meier curves on outcomes for which the HR was used can be found in II Appendix B of the full dossier assessment.

Table 11: Results – RCT, direct comparison: edoxaban vs. warfarin (total population; supplementary presentation)

Study Outcome category Outcome	Edoxaban		Warfarin		Edoxaban vs. warfarin
	N	Patients with event n (%)	N	Patients with event n (%)	HR[a] [95% CI]; p-value
Hokusai-VTE					
Mortality					
All-cause mortality	4143	138 (3.3)	4149	130 (3.1)	1.06 [0.84; 1.35]; 0.629
Morbidity					
Recurrent VTE (symptomatic DVT, fatal or nonfatal PE)	4143	132 (3.2)	4149	146 (3.5)	0.90 [0.72; 1.14]; 0.402
PE ± symptomatic DVT	4143	78 (1.9)	4149	85 (2.1)	0.92 [0.68; 1.25]; 0.584
Symptomatic DVT[b]	4143	62 (1.5)	4149	71 (1.7)	0.87 [0.62; 1.23]; 0.439
Health-related quality of life	Not recorded				
Adverse events					
Major bleeding or clinically relevant nonmajor bleeding	4118	405 (9.8)	4122	461 (11.2)	0.87 [0.76; 0.99]; 0.039
Major bleeding	4118	75 (1.8)	4122	79 (1.9)	0.95 [0.69; 1.31]; 0.755
Clinically relevant nonmajor bleeding	4118	344 (8.4)	4122	400 (9.7)	0.85 [0.74; 0.98]; 0.026
AEs	4118	2951 (71.7)	4122	3041 (73.8)	-
SAEs	4118	654 (15.9)	4122	678 (16.5)	RR: 0.97 [0.88; 1.07]; 0.485
Discontinuation due to AEs	4118	195 (4.7)	4122	185 (4.5)	RR: 1.06 [0.87; 1.28]; 0.593
Mortality, morbidity and AEs					
Symptomatic recurrent VTE, major bleeding, all-cause mortality	4143	284 (6.9)	4149	283 (6.8)	1.00 [0.85; 1.18]; 0.969

a: Unless otherwise stated.
b: The company stated that no fatal DVT occurred.
AE: adverse event; CI: confidence interval; DVT: deep vein thrombosis; HR: hazard ratio; N: Number of analysed patients; n: number of patients with (at least one) event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus; VTE: venous thromboembolism

Mortality

All-cause mortality

No statistically significant difference between edoxaban and warfarin was shown for the outcome "all-cause mortality" for the total population of the Hokusai-VTE study.

Morbidity

Recurrent VTE (symptomatic DVT, fatal or nonfatal PE) and individual components

No statistically significant difference between edoxaban and warfarin was shown for the composite outcome "recurrent VTE" or for its individual components for the total population of the Hokusai-VTE study.

Health-related quality of life

Health-related quality of life was not investigated in the Hokusai-VTE study.

Adverse events

Major bleeding or clinically relevant nonmajor bleeding

A statistically significant difference in favour of edoxaban in comparison with warfarin was shown for the outcome "major bleeding or clinically relevant nonmajor bleeding" for the total population in the Hokusai-VTE study.

Major bleeding

No statistically significant difference between edoxaban and warfarin was shown for the outcome "major bleeding" for the total population of the Hokusai-VTE study.

Clinically relevant nonmajor bleeding

A statistically significant difference in favour of edoxaban in comparison with warfarin was shown for the outcome "clinically relevant nonmajor bleeding" for the total population in the Hokusai-VTE study.

Serious adverse events and discontinuation due to adverse events

No statistically significant difference between edoxaban and warfarin was shown both for the outcome "SAEs" and for the outcome "discontinuation due to AEs" for the total population of the Hokusai-VTE study.

Mortality, morbidity and AEs

Symptomatic recurrent VTE, major bleeding, all-cause mortality

For the composite outcome of recurrent VTE, major bleeding and all-cause mortality or for the individual components of symptomatic recurrent VTE described above, no statistically significant difference between edoxaban and warfarin was shown for the total population of the Hokusai-VTE study.

Summary

A statistically significant difference between the treatment groups was shown for the total population for the outcome "major bleeding or clinically relevant nonmajor bleeding". Most results of this outcome consisted of events of the outcome "clinically relevant nonmajor bleeding", for which a statistically significant difference between the treatment groups was also found. The outcome "clinically relevant nonmajor bleeding" can be allocated to the

outcome category "non-serious and non-severe symptoms and AEs". The effect size was only marginal for both outcomes because of the upper limits of the confidence interval of 0.99 and 0.98. Hence an added benefit of edoxaban would not be proven even if the total population was used for the benefit assessment.

II 2.4 Results on added benefit

Module 4 A contained no suitable data for the derivation of the added benefit of edoxaban for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults for research question 1 or for research question 2; in each case an added benefit is therefore not proven.

II 2.5 Extent and probability of added benefit

No suitable analyses of the patients in the Hokusai-VTE study were available for the benefit assessment for research question 1 or for research question 2.

The added benefit of edoxaban in comparison with the ACT for the treatment of DVT and PE and prevention of recurrent DVT and PE in adults is therefore not proven for any of the relevant populations. Hence there are also no patient groups for whom a therapeutic added benefit can be derived.

The result of the assessment of the added benefit of edoxaban in comparison with the ACT is summarized in Table 12.

Table 12: Edoxaban – extent and probability of added benefit

Subindication	**ACT**[a]	**Extent and probability of added benefit**
After completion of initial treatment[b] of DVT and PE: treatment of DVT and PE and prevention of recurrent DVT and PE in adults[c]	VKA **(warfarin)**	Added benefit not proven
Long-term prevention of recurrent DVT and PE in adults[d]	VKA **(warfarin)**	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. b: Edoxaban is recommended following initial use of parenteral anticoagulant for at least 5 days [1]. c: Limited treatment and prevention (3 to 6 months). d: Continuous prevention (longer than 3 to 6 months). ACT: appropriate comparator therapy; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; PE: pulmonary embolism; VKA: vitamin K antagonist		

This deviates from the company’s approach, which derived an indication of minor added benefit for the total population.

The G-BA decides on the added benefit.

References for English extract

Please see full assessment for full reference list.

1. European Medicines Agency. Lixiana: European public assessment report; product information [Deutsch] [online]. 3 July 2015 [accessed: 15 July 2015]. URL: http://www.ema.europa.eu/docs/de_DE/document_library/EPAR_-_Product_Information/human/002629/WC500189045.pdf.

2. Daiichi Sankyo Pharma Development. A phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center, multi-national study for the evaluation of efficacy and safety of (LMW) heparin/edoxaban versus (LMW) heparin/warfarin in subjects with symptomatic deep-vein thrombosis and/or pulmonary embolism: study DU176B-D-U305; clinical study report [unpublished]. 2014.

3. Buller HR, Decousus H, Grosso MA, Mercuri M, Middeldorp S, Prins MH et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. N Engl J Med 2013; 369(15): 1406-1415.

4. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians evidence-based clinical practice guidelines (8th Edition). Chest 2008; 133(6 Suppl): 454S-545S.

5. Konstantinides SV, Torbicki A, Agnelli G, Danchin N, Fitzmaurice D, Galiè N et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J 2014; 35(43): 3033-3069.

6. Blättler W, Gerlach H, Hach-Wunderle V, Konstantinides SV, Noppeney T, Pillny M et al. Interdisziplinäre S2-Leitlinie Diagnostik und Therapie der Venenthrombose und der Lungenembolie. Vasa 2010; 39(Suppl 78): 1-39.

7. European Medicines Agency. Lixiana: rapporteurs' day 150 joint response assessment report; clinical-assessment of the responses to the CHMP list of questions [unpublished]. 2014.

8. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. Lancet 2012; 379(9828): 1835-1846.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-29-edoxaban-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6904.html.