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Apixaban (new therapeutic indication) –
Benefit assessment according to §35a Social Code Book V[1]

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[3] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BMI	body mass index
DVT	deep vein thrombosis
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
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
PE	pulmonary embolism
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VKA	vitamin K antagonist
VTE	venous thromboembolism

2 Benefit assessment

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 apixaban (new therapeutic indication). 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 25 August 2014.

Research question

The aim of the present report is to assess the added benefit of apixaban compared with the 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 ACT specified by the G-BA for the initial treatment of DVT or PE consists of low molecular weight heparins (LMWHs), and for the secondary prevention (to be started in parallel) of recurrent DVT or PE of a vitamin K antagonist (VKA). It should be noted for the ACT that LMWHs are to be approved for these therapeutic indications and that the drugs are to be administered at the dosages approved for the respective therapeutic indication and optimized for the individual patient.

2 research questions result for the assessment, which are derived from the subindication and the ACT. Table 2 shows an overview of the research questions.

Table 2: ACT for the benefit assessment of apixaban (new therapeutic indication)

Research question	Subindication	Apixaban dosage	ACT[a]
1	Initial treatment of DVT and PE and prevention to be started in parallel in adults	10 mg twice daily for 7 days, then 5 mg twice daily	LMWH (**enoxaparin**) with VKA (**warfarin**) to be started in parallel
2	Long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE)	2.5 mg twice daily	VKA
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.			
ACT: appropriate comparator therapy; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; LMWH: low molecular weight heparin; PE: pulmonary embolism; VKA: vitamin K antagonist			

The assessment was conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs) with a minimum duration of 3 months.

Results

Research question 1: initial treatment of DVT and PE and prevention to be started in parallel

The AMPLIFY study (CV185056) was included in the assessment.

The AMPLIFY study was a randomized, double-blind, active-controlled and multicentre study with a treatment phase of 6 months and a follow-up phase of 30 days.

A total of 5395 patients were randomized to apixaban (N = 2691) or enoxaparin/warfarin (N = 2704). Randomization was stratified according to the index event (symptomatic proximal DVT or symptomatic PE [with or without DVT]).

Patients with a low risk of recurrence due to transient risk factors who are therefore, according to the Summary of Product Characteristics (SPC), treated with apixaban for at least 3 months and for less than 6 months, were not considered in the study.

Apixaban was administered in accordance with the German approval at a dose of 10 mg twice daily for 7 days, followed by a dose of 5 mg twice daily for up to 6 months. The LMWH used in the study was enoxaparin (1 mg/kg every 12 hours up to international normalized ratio (INR) ≥ 2) over a period of ≥ 5 days. The VKA used was warfarin (dosage adjusted to target INR range between 2.0 and 3.0) for 6 months.

The risk of bias at study and outcome level for the AMPLIFY study was rated as low.

Mortality

All-cause mortality

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "all-cause mortality". An added benefit of apixaban in comparison with enoxaparin/warfarin is not proven for this outcome.

Morbidity

Composite outcome: symptomatic recurrent venous thromboembolism (VTE; nonfatal DVT or nonfatal PE) or all-cause mortality

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the composite outcome "symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality.

The composite outcome is not considered further for the overall conclusion because there were relevant effect modifications in the individual components "nonfatal DVT" and "nonfatal PE".

Symptomatic nonfatal DVT

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "symptomatic nonfatal DVT".

However, there was an indication of an effect modification by the characteristic "body mass index (BMI)" for symptomatic nonfatal DVT (interaction test p = 0.164). The results were therefore considered separately by BMI. A hint of an added benefit of apixaban in comparison with enoxaparin/warfarin in patients with a BMI of $> 28 \, kg/m^2$ for the outcome "symptomatic nonfatal DVT" results from the subgroup analyses. No added benefit of apixaban compared with enoxaparin/warfarin is proven in patients with a BMI of $\leq 28 \, kg/m^2$ for this outcome.

Symptomatic nonfatal PE

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "symptomatic nonfatal PE".

However, there was proof of an effect modification by the characteristic "BMI" for symptomatic nonfatal PE (interaction test p = 0.005). The results were therefore considered separately by BMI. An indication of lesser benefit of apixaban compared with enoxaparin/warfarin in patients with a BMI of $\leq 28 \, kg/m^2$ for the outcome "symptomatic nonfatal PE" results from the subgroup analyses. There is no proof of added benefit of apixaban in comparison with enoxaparin/warfarin for patients with a BMI of $> 28 \, kg/m^2$.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the AMPLIFY study. This results in no proof of added benefit of apixaban in comparison with enoxaparin/warfarin for the outcome "health-related quality of life".

Adverse events

Composite outcome: major bleeding or clinically relevant nonmajor bleeding

There was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin for the composite outcome "major bleeding or clinically relevant nonmajor bleeding".

The composite outcome includes serious and non-serious adverse events (AEs). The proportion of non-serious events is considerably greater than the proportion of serious events. The conclusion on the added benefit for the composite outcome would therefore be drawn according to the outcome category of non-serious events. However, the composite outcome would provide no additional information on the extent of added benefit in comparison with the individual component "clinically relevant nonmajor bleeding" (extent "considerable" in both cases). The composite outcome is therefore not considered further for the overall conclusion.

Major bleeding

There was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin for the outcome "major bleeding".

There is an indication of lesser harm from apixaban than from enoxaparin/warfarin for the outcome "major bleeding".

Clinically relevant nonmajor bleeding

There was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin for the outcome "clinically relevant nonmajor bleeding".

There is proof of lesser harm from apixaban than from enoxaparin/warfarin for the outcome "clinically relevant nonmajor bleeding", although only results from one study were available. This is justified by the fulfilment of the criteria additionally required for this: Besides the particular quality of the study, the corresponding p-value is very small ($p < 0.001$), and the results were consistent across the geographical regions (no relevant interaction: $p = 0.364$).

Serious adverse events

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "serious adverse events (SAEs)".

However, there was an indication of an effect modification by the characteristic "index event" for the outcome "SAEs" (interaction test $p = 0.140$). The results were therefore considered separately by index event. A hint of greater harm from apixaban than from enoxaparin/warfarin in patients with index DVT only for the outcome "SAEs" results from the subgroup analyses.

Treatment discontinuation due to AEs

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "treatment discontinuation due to AEs". Greater or lesser harm from apixaban in comparison with enoxaparin/warfarin is not proven for this outcome.

Research question 2: long-term prevention of recurrent DVT and PE after completion of a 6-month treatment of DVT or PE

Since the company submitted no data for the long-term prevention of recurrent DVT and PE after completion of a 6-month anticoagulant treatment of DVT or PE, an added benefit of apixaban in comparison with the ACT is not proven for this research question.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug apixaban compared with the ACT is assessed.

Research question 1: initial treatment of DVT and PE and prevention to be started in parallel with a minimum treatment duration of 6 months

Overall, positive and negative effects remain, which partly depend on the effect modifiers "BMI" and "index event". 2 effect modifiers were considered for the BMI, which is why below the balancing of positive and negative effects is conducted separately for patients with a BMI of ≤ 28 kg/m^2 and for patients with a BMI of > 28 kg/m^2.

Patients with a BMI of ≤ 28 kg/m^2

There is an indication of lesser benefit of apixaban with the extent "considerable" for the outcome "symptomatic nonfatal PE" in patients with a BMI of ≤ 28 kg/m^2. The treatment goal of apixaban in the new therapeutic indication is treatment of DVT and PE and prevention of recurrent DVT and PE in adults. Hence the lesser harm from apixaban observed in the bleeding outcomes does not result in an added benefit of apixaban in the overall assessment. Overall, there is no proof of an added benefit of apixaban in comparison with the ACT for patients with a BMI of ≤ 28 kg/m^2.

Patients with a BMI of > 28 kg/m^2

For patients with a BMI of > 28 kg/m^2 overall, there are positive effects both with regard to benefit (symptomatic nonfatal DVT: hint of considerable added benefit), and with regard to AEs (major bleeding: indication of lesser harm [extent "considerable"]; clinically relevant nonmajor bleeding: proof of lesser harm [extent "considerable"]). This is offset by only a hint of greater harm (extent "minor") for patients with index DVT due to more frequent SAEs. In the overall assessment, this did not raise doubts about the positive effects. Overall, there is proof of an added benefit of apixaban in comparison with the ACT with the extent "considerable" for patients with a BMI of > 28 kg/m^2.

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[4] 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), see [1]. 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), see [2].

Research question 2: long-term prevention of recurrent DVT and PE after completion of a 6-month treatment of DVT or PE

There were no data on long-term prevention of recurrent DVT and PE after completion of a 6-month treatment of DVT or PE. An added benefit of apixaban is not proven for this research question

Summary

Table 3 presents a summary of the extent and probability of the added benefit of apixaban.

Table 3: Apixaban – extent and probability of added benefit

Subindication	Apixaban dosage	ACT[a]	Population	Extent and probability of added benefit
Initial treatment of DVT and PE and prevention to be started in parallel in adults	10 mg twice daily for 7 days, then 5 mg twice daily	LMWH (**enoxaparin**) with VKA (**warfarin**) to be started in parallel	Patients with BMI ≤ 28 kg/m^2	Added benefit not proven
			Patients with BMI > 28 kg/m^2	Proof of added benefit, extent "considerable"
Long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE)	2.5 mg twice daily	VKA	Patients after completion of a 6-month anticoagulant treatment	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.				
ACT: appropriate comparator therapy; BMI: body mass index; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; LMWH: low molecular weight heparin; PE: pulmonary embolism; 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.

2.2 Research question

The aim of the present report is to assess the added benefit of apixaban compared with the 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 [3,4].

The ACT specified by the G-BA for the initial treatment of DVT or PE consists of LMWHs, and for the secondary prevention (to be started in parallel) of recurrent DVT or PE of a VKA.

It should be noted for the ACT that LMWHs are to be approved for these therapeutic indications and that the drugs are to be administered at the dosages approved for the respective therapeutic indication and optimized for the individual patient.

2 research questions result for the assessment, which are derived from the subindication and the ACT. Table 4 shows an overview of the research questions.

Table 4: ACT for the benefit assessment of apixaban (new therapeutic indication)

Research question	Subindication	Apixaban dosage	ACT[a]
1	Initial treatment of DVT and PE and prevention to be started in parallel in adults	10 mg twice daily for 7 days, then 5 mg twice daily	LMWH (**enoxaparin**) with VKA (**warfarin**) to be started in parallel
2	Long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE)	2.5 mg twice daily	VKA
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. ACT: appropriate comparator therapy; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; LMWH: low molecular weight heparin; PE: pulmonary embolism; VKA: vitamin K antagonist			

The assessment was conducted based on patient-relevant outcomes and on RCTs with a minimum duration of 3 months.

The company deviated from the research questions because it did not divide the therapeutic indication into the 2 research questions mentioned above (see Section 2.6.2.1 of the full dossier assessment).

2.3 Research question 1: initial treatment of DVT and PE and prevention to be started in parallel

2.3.1 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 apixaban (studies completed up to 30 July 2014)

- bibliographical literature search on apixaban (last search on 8 July 2014)

- search in trial registries for studies on apixaban (last search on 8 July 2014)

To check the completeness of the study pool:

- bibliographical literature search on apixaban (last search on 5 September 2014)

- search in trial registries for studies on apixaban (last search on 5 September 2014)

No additional relevant study was identified from the check.

2.3.1.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: apixaban vs. enoxaparin/warfarin

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored studya (yes/no)	Third-party study (yes/no)
AMPLIFY (CV185056)	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 study pool concurred with the study pool of the company, but the AMPLIFY study was only relevant for research question 1. However, the company used the study for the assessment of the total therapeutic indication, although the AMPLIFY study was unsuitable for research question 2 both because of its duration (6 months) and because of the apixaban dosage (5 mg twice daily).

Section 2.3.4 contains a reference list for the study included.

2.3.1.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AMPLIFY (CV185056)	RCT, double-blind, parallel, active-controlled	Adults (18 years or older) with acute symptomatic proximal DVT or acute symptomatic PE	Apixaban (N = 2691) enoxaparin/warfarin (N = 2704)	Screening: ≤ 48h before randomization Treatment phase: 6 months Follow-up phase: 30 days	Argentina, Australia, Austria, Brazil, Canada, China, Czech Republic, Denmark, France, Germany, Hong Kong, Hungary, India, Israel, Italy, Korea, Malaysia, Mexico, Norway, Poland, Portugal, Romania, Russia, Singapore, South Africa, Spain, Ukraine, United States 8/2008 – 3/2013	Primary: ▪ composite outcome of symptomatic recurrent VTE (including nonfatal DVT or nonfatal PE) or VTE-related death during 6-month treatment Secondary: ▪ composite outcome of symptomatic recurrent VTE (including nonfatal DVT or nonfatal PE) or all-cause mortality and its individual components ▪ composite outcome of major bleeding or clinically relevant nonmajor bleeding and its individual components ▪ adverse events

a: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.

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

Table 7: Characteristics of the interventions – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study	Intervention	Comparison	Concomitant medication
AMPLIFY (CV185056)	Apixaban, orally 10 mg twice daily for 7 days, followed by 5 mg twice daily until the end of 6 months + enoxaparin placebo solution SC every 12 hours until sham INR ≥ 2, for ≥ 5 days + warfarin placebo orally, after sham INR of 2-3, for 6 months	apixaban placebo, orally, twice daily for 6 months + enoxaparin solution 1 mg/kg SC every 12 hours until INR ≥ 2, for ≥ 5 days + warfarin orally, after target INR of 2-3, for 6 months	Prohibited treatment[a]: ■ potent inhibitors of CYP3A4 (e.g. azole antimycotics [itraconazole and ketoconazole], macrolide antibiotics [clarithromycin and telithromycin], protease inhibitors [ritonavir, indinavir, nelfinavir, atazanavir and saquinavir] and nefazodone) ■ aspirin > 165 mg/day ■ dual thrombocyte aggregation inhibition such as simultaneous use of aspirin and a thienopyridine (e.g. clopidogrel, ticlopidine) ■ other antithrombotic agents (e.g. UFH, LMWH, direct thrombin inhibitors, fondaparinux) ■ glycoprotein IIb/IIIa inhibitors (e.g. abciximab, eptifibatide, tirofiban) Restricted treatments[b]: ■ chronic (> 3 months) daily administration of NSAIDs NSAIDs were not administered in dosages that were outside the approval according to the CSR. ■ cytotoxic/myelosuppressive treatment ■ If a patient received a potent CYP3A4 inducer (e.g. rifampicin), the risk of thromboembolism was assessed by the investigator because in this case the apixaban plasma concentration might be lower.
a: In case of necessary treatment with a prohibited agent, study medication was temporarily discontinued and restarted as soon as possible after stopping the prohibited medication or treatment. b: The following medications were administered with caution in view of an increased risk of bleeding. In such cases possible discontinuation of the study medication was to be considered. This decision was made after careful assessment of the risks and potential advantages. CSR: clinical study report; CYP3A4: cytochrome P450 3A4; INR: international normalized ratio; LMWH: low molecular weight heparin; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; UFH: unfractionated heparin; vs.: versus			

The AMPLIFY study (CV185056) was a randomized, double-blind, active-controlled and multicentre study with a treatment phase of 6 months and a follow-up phase of 30 days.

A total of 5395 patients were randomized to apixaban (N = 2691) or enoxaparin/warfarin (N = 2704). Randomization was stratified according to the index event (symptomatic proximal DVT or symptomatic PE [with or without DVT]).

Adults with acute symptomatic proximal DVT or acute symptomatic PE were included. Another inclusion criterion was that patients with unprovoked or provoked index event had to have known or acquired risk factors for recurrence (e.g. permanent immobility). Patients for whom anticoagulant treatment of < 6 months was planned after their DVT or PE (index event) were excluded from the study. Hence patients with a low risk of recurrence due to transient risk factors who are therefore, according to the SPC [3,4], treated with apixaban for at least 3 months and for less than 6 months, were not considered in the study.

Apixaban was administered in accordance with the German approval at a dose of 10 mg twice daily for 7 days, followed by a dose of 5 mg twice daily for up to 6 months. The LMWH used in the study was enoxaparin (1 mg/kg every 12 hours up to INR ≥ 2) over a period of ≥ 5 days. The VKA used was warfarin (dosage adjusted to target INR range between 2.0 and 3.0) for 6 months. Both drugs were used in compliance with their approval. Warfarin/enoxaparin placebo was administered in addition to apixaban; and apixaban placebo was administered in addition to warfarin and enoxaparin.

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. The drugs prohibited were to be stopped as soon as possible to continue with the study medication. The use of other drugs was also restricted in view of an increased risk of bleeding.

Primary outcome of the study was the composite outcome of symptomatic recurrent VTE (including nonfatal DVT or nonfatal PE) or VTE-related death.

Table 8 to Table 10 show the characteristics of the patients in the AMPLIFY study included.

Table 8: Characteristics of the study populations – demography and baseline data – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study group	N	Age [years] mean (SD)	Sex [F/M] %	Index event[a] proximal DVT/PE %	Anatomical extent of index event		BMI [kg/m²] mean (SD)	Ethnicity [white/black/ Asian/other/ not reported] %	Treatment discontin- uations n (%)
					DVT [low/moderate/high risk/not reported][b] %[c]	PE [limited/ intermediate/ extensive/not reported][d] %[c]			
AMPLIFY (CV185056)									
Apixaban	2691	57 (16)	42/58	66/34	24.4/32.6/43.1/0	8.5/42.2/38.4/11.0	29 (6)	82.4/3.9/8.4/3.5[e]/1.7	377 (14.0)
Enoxaparin/ warfarin	2704	57 (16)	41/59	67/33	24.7/32.8/42.3/0.2	9.8/43.6/36.0/10.6	29 (6)	83.0/3.6/8.4/3.2[e]/1.8	413 (15.3)

a: In case a patient had both DVT and PE, the patient was recorded with index PE. The events are not adjudicated.
b: Low risk: blood clot only in popliteal vein, intermediate risk: neither low nor high risk, high risk: blood clot in iliac vein or femoral vein.
c: The percentage refers to the number of patients with index DVT or PE.
d: Limited: not more than one lobe with a perfusion deficit of 25% or less, intermediate: neither limited nor extensive, extensive: ≥ 2 lobes with a perfusion deficit of ≥ 50%.
e: Institute's calculation. The data on "other" ethnicities also include American Indians and native Alaskans.

BMI: body mass index; DVT: deep vein thrombosis; F: female; M: male; N: number of randomized patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 9: Characteristics of the study populations – initial anticoagulant treatment of index VTE before randomization – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study group	N	UFH infusion [hours] n (%)	Total LMWH and UFH [hours] n (%)	Warfarin/VKA [Number of dosages] n (%)	Heparin n (%)	LMWH once daily [number of dosages] n (%)	LMWH twice daily [number of dosages] n (%)
AMPLIFY (CV185056)							
Apixaban	2691	0: 1593 (59.2) up to 12: 59 (2.2) 12 to 24: 110 (4.1) 24 to 36: 120 (4.5) >36: 3 (0.1) ND: 800 (29.7)	0: 358 (13.3) up to 12: 371 (13.8) > 12 to 24: 1116 (41.5) > 24 to 36: 587 (21.8) > 36 to 48: 231 (8.6) > 48: 22 (0.8)	0: 2038 (75.7) 1: 289 (10.7) 2: 79 (2.9) > 2: 2 (< 0.1) ND: 277 (10.3)	2327 (86.5)	0: 1762 (65.5) 1: 380 (14.1) 2: 195 (7.2) > 2: 1 (< 0.1) ND: 347 (12.9)	0: 906 (33.7) 1: 384 (14.3) 2: 734 (27.3) 3: 435 (16.2) > 3: 14 (0.5) ND: 212 (7.9)
Enoxaparin/ warfarin	2704	0: 1590 (58.8) up to 12: 52 (1.9) 12 to 24: 133 (4.9) 24 to 36: 132 (4.9) > 36: 4 (0.1) ND: 787 (29.1)	0: 381 (14.1) up to 12: 341 (12.6) > 12 to 24: 1126 (41.6) > 24 to 36: 613 (22.7) > 36 to 48: 211 (7.8) > 48: 26 (1.0)	0: 2043 (75.6) 1: 311 (11.5) 2: 58 (2.1) > 2: 0 ND: 286 (10.6)	2317 (85.7)	0: 1779 (65.8) 1: 368 (13.6) 2: 180 (6.7) > 2: 3 (0.1) ND: 368 (13.6)	0: 954 (35.3) 1: 378 (14.0) 2: 714 (26.4) 3: 460 (17.0) > 3: 8 (0.3) ND: 184 (6.8)

LMWH: low molecular weight heparin; N: number of randomized patients; n: number of patients with event; ND: no data; RCT: randomized controlled trial; UFH: unfractionated heparin; VKA: vitamin K antagonist; vs.: versus; VTE: venous thromboembolism

Table 10: Characteristics of the study populations – concomitant anticoagulant treatment during the treatment phase without day 1 and the last 2 days of treatment – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study group	N	Heparins n (%)	VKAs n (%)	Other n (%)
AMPLIFY (CV185056)				
Apixaban	2676	167 (6.2)	90 (3.4)	1 (< 0.1)
Enoxaparin/ warfarin	2689	179 (6.7)	100 (3.7)	1 (< 0.1)
N: number of randomized patients who received at least one dose of study medication; n: number of patients with event; RCT: randomized controlled trial; VKA: vitamin K antagonist; vs.: versus				

The mean age of the patients included in the AMPLIFY study was 57 years; and most of the patients were white. Somewhat more men than women were enrolled in the study. Approximately 2 thirds of the study population had proximal DVT as index event, and approximately one third PE (with/without DVT). The severity grade (based on anatomical extent) of most patients with proximal DVT was intermediate or high, and for patients with PE intermediate or extensive.

After their index event, patients were treated with anticoagulants before administration of the first study medication (see Table 9). Overlaps between this initial treatment and the study medication were possible. Approximately 3 quarters of the patients received no warfarin/VKA as part of their initial treatment. Approximately 86% of the patients were pretreated with heparin. Anticoagulant treatment could be started in both treatment groups before the end of the study. Hence overlaps of the study medication and the anticoagulant were possible again. As a result, primarily approximately 52% of the patients in the study were treated with concomitant medication prohibited in the study, such as antithrombotics (see Table 7), for at least a short period of time. An analysis, in which initial anticoagulant treatment in the beginning and in the end of the 6-month treatment phase of the study was excluded (see Table 10) showed, however, that only approximately 10% of the patients received concomitant treatment with anticoagulants in the treatment phase of the study. Only for these patients was the treatment not compliant with the approval of apixaban. Furthermore, if treatment with an agent that was prohibited in the study and according to the approval became necessary, the study medication was temporarily discontinued in these patient, and restarted as soon as possible after stopping the prohibited medication or treatment. Hence overall, no doubts were raised about the approval-compliant use of apixaban during the treatment phase in the AMPLIFY.

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at study level – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

| 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			
AMPLIFY (CV185056)	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

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

2.3.2 Results on added benefit

The following patient-relevant outcomes were considered in this assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - All-cause mortality

- Morbidity
  - composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality
  - symptomatic nonfatal DVT
  - symptomatic nonfatal PE

- Health-related quality of life

- Adverse events
  - overall rate of SAEs (excluding outcomes individually analysed by the company)
  - treatment discontinuation due to AEs (excluding outcomes individually analysed by the company)
  - composite outcome: major bleeding or clinically relevant nonmajor bleeding
  - major bleeding
  - clinically relevant nonmajor bleeding

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4). The primary outcome of the study, a composite outcome of symptomatic recurrent VTE or VTE-related death, was not included in the benefit assessment, for example, because the recording of all-cause mortality was relevant for the present assessment (see Section 2.6.2.4.3 of the full dossier assessment). Additionally, the company did not define health-related quality of life as patient-relevant outcome.

Table 12 shows for which outcomes data were available in the studies included.

Table 12: Matrix of outcomes – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study	Outcomes									
	All-cause mortality	Composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality	Symptomatic nonfatal DVT	Symptomatic nonfatal PE	Health-related quality of life	Composite outcome: major bleeding or clinically relevant nonmajor bleeding	Major bleeding	Clinically relevant nonmajor bleeding	SAEs	Treatment discontinuations due to AEs
AMPLIFY (CV185056)	Yes	Yes	Yes	Yes	No[a]	Yes	Yes	Yes	Yes	Yes

a: Outcome not recorded.
AE: adverse event; DVT: deep vein thrombosis; PE: pulmonary embolism; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; VTE: venous thromboembolism

Except for health-related quality of life, which was not recorded in the AMPLIFY study, results were available for all patient-relevant outcomes included in the benefit assessment.

Table 13 shows the risk of bias for the outcomes recorded in the AMPLIFY study.

Table 13: Risk of bias at study and outcome level – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study	Study level	Outcomes									
		All-cause mortality	Composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality	Symptomatic nonfatal DVT	Symptomatic nonfatal PE	Health-related quality of life	Composite outcome: major bleeding or clinically relevant nonmajor bleeding	Major bleeding	Clinically relevant nonmajor bleeding	SAEs	Treatment discontinuations due to AEs
AMPLIFY (CV185056)	L	L	L	L	L	–[a]	L	L	L	L	L
a: No data recorded.											
AE: adverse event; DVT: deep vein thrombosis; L: low; PE: pulmonary embolism; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus; VTE: venous thromboembolism											

The risk of bias for all outcomes was rated as low. The assessment of the risk of bias concurs with that of the company. Hence in principle, indications, e.g. of an added benefit, can be derived from the AMPLIFY study for the individual outcomes.

Certain additional criteria have to be fulfilled for the derivation of proof. Since the AMPLIFY study was a multicentre study (358 centres) of high quality, it was additionally checked for outcomes with a very small corresponding p-value ($p < 0.001$) whether the result was consistent across different contexts. The characteristic "geographical region" (North America/Latin America/Europe, Middle East, Africa/Asia, Pacific region) was used for this because this characteristic is assumed to reflect different contexts. If the results are consistent (no indication of interaction), proof can be derived for the probability of an added benefit (see Section 2.6.2.8.1 of the full dossier assessment).

The approach for deriving proof for the probability of an added benefit deviates from the company's assessment, which generally derived proof from the AMPLIFY study.

2.3.2.1 Results

The results of the total population of the AMPLIFY study on the comparison of apixaban with enoxaparin/warfarin in adult patients for the initial treatment of DVT and PE and prevention to be started in parallel are summarized in Table 14.

Table 14: Results (dichotomous outcomes) – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study outcome category outcome	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI]; p-value[a]
AMPLIFY (CV185056)					
Mortality					
All-cause mortality	2608	41 (1.6[b])	2630	52 (2.0[b])	0.80 [0.53; 1.19]; 0.296[c]
Morbidity					
Composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality	2609	84 (3.2)	2635	104 (3.9[b])	0.82 [0.61; 1.08] 0.155
Symptomatic nonfatal DVT	2608	22 (0.8)	2633	35 (1.3)	0.63 [0.37; 1.08] 0.090
Symptomatic nonfatal PE	2606	27 (1.0)	2632	25 (0.9[b])	1.09 [0.63; 1.89] 0.746
Adverse events					
Composite outcome: major bleeding or clinically relevant nonmajor bleeding	2676	115 (4.3)	2689	261 (9.7)	0.44 [0.36; 0.55] < 0.001
Major bleeding	2676	15 (0.6[b])	2689	49 (1.8)	0.31 [0.17; 0.55] < 0.001
Clinically relevant nonmajor bleeding	2676	103 (3.8[b])	2689	215 (8.0)	0.48 [0.38; 0.60] < 0.001
AEs[d]	2676	1713 (64.0)	2689	1787 (66.5)	
SAEs[d]	2676	343 (12.8)	2689	308 (11.5)	1.11 [0.96; 1.29] 0.141
Treatment discontinuation due to AEs[d]	2676	109 (4.1)	2689	113 (4.2)	0.97 [0.74; 1.25] 0.796

a: Unless stated otherwise, RR, the corresponding 95% CI and the corresponding p-value are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT).
b: Institute's calculation.
c: Institute's calculation of RR, CI and p-value because of deviating information on the number of analysed patients between Module 4 and the CSR (Fisher exact test).
d: Excluding outcomes individually analysed by the company.

AE: adverse event; CI: confidence interval; CSR: clinical study report; DVT: deep vein thrombosis; N: Number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus; VTE: venous thromboembolism

Mortality

All-cause mortality

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "all-cause mortality". An added benefit of apixaban in comparison with enoxaparin/warfarin is not proven for this outcome.

The assessment of added benefit concurs with that of the company.

Morbidity

Composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the composite outcome "symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality.

The composite outcome is not considered further for the overall conclusion because there were relevant effect modifications in the individual components "nonfatal DVT" and "nonfatal PE".

Symptomatic nonfatal DVT

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "symptomatic nonfatal DVT".

However, there was an indication of an effect modification by the characteristic "BMI" for symptomatic nonfatal DVT (interaction test p = 0.164). The results were therefore considered separately by BMI (see Section 2.3.2.2). A hint of an added benefit of apixaban in comparison with enoxaparin/warfarin in patients with a BMI of > 28 kg/m^2 for the outcome "symptomatic nonfatal DVT" results from the subgroup analyses. No added benefit of apixaban compared with enoxaparin/warfarin is proven in patients with a BMI of ≤ 28 kg/m^2 for this outcome.

The results do not concur with the company's assessment, which made no conclusions on added benefit based on subgroup results.

Symptomatic nonfatal PE

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "symptomatic nonfatal PE".

However, there was proof of an effect modification by the characteristic "BMI" for symptomatic nonfatal PE (interaction test p = 0.005). The results were therefore considered separately by BMI (see Section 2.3.2.2). An indication of lesser benefit of apixaban compared with enoxaparin/warfarin in patients with a BMI of ≤ 28 kg/m^2 for the outcome "symptomatic nonfatal PE" results from the subgroup analyses. There is no proof of added benefit of apixaban in comparison with enoxaparin/warfarin for patients with a BMI of > 28 kg/m^2.

The results do not concur with the company's assessment, which made no conclusions on added benefit based on subgroup results.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the AMPLIFY study. This results in no proof of added benefit of apixaban in comparison with enoxaparin/warfarin for the outcome "health-related quality of life".

The company did not address the outcome "health-related quality of life" in its results and justified this by stating that this outcome was not recorded in the AMPLIFY study.

Adverse events

Composite outcome: major bleeding or clinically relevant nonmajor bleeding

There was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin for the composite outcome "major bleeding or clinically relevant nonmajor bleeding".

The composite outcome includes serious and non-serious AEs. The proportion of non-serious events is considerably greater than the proportion of serious events. The conclusion on the added benefit for the composite outcome would therefore be drawn according to the outcome category of non-serious events. However, the composite outcome would provide no additional information on the extent of added benefit in comparison with the individual component "clinically relevant nonmajor bleeding" (extent "considerable" in both cases). The composite outcome is therefore not considered further for the overall conclusion.

Major bleeding

There was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin for the outcome "major bleeding".

There is an indication of lesser harm from apixaban than from enoxaparin/warfarin for the outcome "major bleeding". No proof can be derived in this case, although the criteria additionally required for this were partly fulfilled: Besides the particular quality of the study, the corresponding p-value is very small ($p < 0.001$). However, the examination of consistency between the geographical regions showed an indication of interaction ($p = 0.198$; see Figure 1, Appendix C of the full dossier assessment). Hence inconsistency between the results of the geographical regions is assumed.

This result deviates from the company's assessment, which derived proof of lesser harm from apixaban for the outcome "major bleeding".

Clinically relevant nonmajor bleeding

There was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin for the outcome "clinically relevant nonmajor bleeding".

There is proof of lesser harm from apixaban than from enoxaparin/warfarin for the outcome "clinically relevant nonmajor bleeding", although only results from one study were available. This is justified by the fulfilment of the criteria additionally required for this: Besides the particular quality of the study, the corresponding p-value is very small ($p < 0.001$), and the results were consistent across the geographical regions (no relevant interaction: $p = 0.364$; see Figure 2, Appendix C of the full dossier assessment).

This assessment concurs with that of the company.

Serious adverse events

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "SAEs".

However, there was an indication of an effect modification by the characteristic "index event" for the outcome "SAEs" (interaction test $p = 0.140$). The results were therefore considered separately by index event (see Section 2.3.2.2). A hint of greater harm from apixaban than from enoxaparin/warfarin in patients with index DVT only for the outcome "SAEs" results from the subgroup analyses.

The result does not concur with the company's assessment, which made no conclusions on added benefit based on subgroup results.

Treatment discontinuations due to adverse events

There was no statistically significant difference between apixaban and enoxaparin/warfarin for the outcome "treatment discontinuation due to AEs". Greater or lesser harm from apixaban in comparison with enoxaparin/warfarin is not proven for this outcome.

The assessment concurs with that of the company.

2.3.2.2 Subgroups and other effect modifiers

The following subgroup characteristics were considered to be relevant for the present benefit assessment:

- Age
    - category I (< 65 years/65 - < 75 years/> 75 years)
    - category II (< 75 years/> 75 years)
- Sex
- Index event (PE [with or without DVT]/DVT only)
- Anatomical extent of PE (risk groups: limited/intermediate/extensive)
- Anatomical extent of DVT (risk groups: low/intermediate/high)

- BMI

    □ category I (≤ 28 kg/m²/> 28 kg/m² to ≤ 33 kg/m²/> 33 kg/m²)

    □ category II (≤ 25 kg/m²/> 25 to ≤ 30 kg/m²/> 30 to ≤ 35 kg/m²/> 35 kg/m²)

- Ethnicity (white/black or African American/Asian/other)

All subgroup characteristics and their dimension and thresholds were defined beforehand in the AMPLIFY study.

Below, only the results for subgroups and outcomes are presented in which there were at least indications of an effect modification between treatment effect and subgroup. In addition, there must be a statistically significant effect in at least one of the subgroups. The prerequisite for proof of an effect modification is a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provides an indication of an effect modification.

Morbidity

Composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality as well as individual components "symptomatic nonfatal DVT" or "symptomatic nonfatal PE"

Table 15 to Table 17 show the results of the subgroup analyses for subgroup characteristics for which there was an indication or proof of an effect modification for the composite outcome "symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality" as well as for the individual components "symptomatic nonfatal DVT" and "symptomatic nonfatal PE".

Table 15: Subgroups: composite outcome: symptomatic recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause mortality – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study characteristic subgroup	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
AMPLIFY (CV185056)						
BMI category I					Interaction:	0.072
≤ 28 kg/m^2	1321	54 (4.1)	1328	49 (3.7)	1.11 [0.76; 1.62]	0.616[b]
> 28 kg/m^2	1274	30 (2.4)[c]	1290	54 (4.2)[c]	0.56 [0.36; 0.87][d]	0.010[b]
> 28 – 33 kg/m^2	*767*	*17 (2.2)*	*784*	*32 (4.1)*	*0.54 [0.30; 0.97]*	*0.042[b]*
> 33 kg/m^2	*507*	*13 (2.6)*	*506*	*22 (4.3)*	*0.59 [0.30; 1.16]*	*0.126[b]*
Anatomical extent of PE					Interaction:	0.093
Limited[e]/ intermediate[f]	454	22 (4.8)[c]	473	18 (3.8)[c]	1.27 [0.69; 2.34][d]	0.445[g]
Limited[e]	*72*	*4 (5.6)*	*88*	*3 (3.4)*	*1.58 [0.34; 7.23]*	*0.599[g]*
Intermediate[f]	*382*	*18 (4.7)*	*385*	*15 (3.9)*	*1.19 [0.61; 2.32]*	*0.602[g]*
Extensive[h]	351	7 (2.0)	318	16 (5.0)	0.40 [0.16; 0.97]	0.032[g]

a: Unless stated otherwise, the RR and the corresponding 95% CI are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT) if possible.
b: Institute's calculation, Fisher exact test.
c: Institute's calculation.
d: Calculation of RR and corresponding 95% CI without consideration of stratification.
e: Not more than one lobe with a perfusion deficit of 25% or less.
f: Neither limited nor extensive.
g: Institute's calculation, unconditional exact test (CSZ method according to [5]).
h: ≥ 2 lobes with a perfusion deficit of $\geq 50\%$.

BMI: body mass index; CI: confidence interval; CSZ: convexity, symmetry, z score; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 16: Subgroups: symptomatic nonfatal DVT – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study characteristic subgroup	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
AMPLIFY (CV185056)						
Sex					Interaction:	0.168
Men	1523	17 (1.1)	1555	21 (1.4)	0.83 [0.44; 1.56]	0.626[b]
Women	1085	5 (0.5)	1078	14 (1.3)	0.36 [0.13; 0.99]	0.040[b]
BMI category I					Interaction:	0.164
≤ 28 kg/m^2	1321	13 (1.0)	1328	12 (0.9)	1.09 [0.50; 2.38]	0.844[b]
> 28 kg/m^2	1273	9 (0.7)[c]	1288	22 (1.7)[c]	0.41 [0.19; 0.90][d]	0.029[b]
$> 28 – 33$ kg/m^2	766	5 (0.7)	783	16 (2.0)	0.32 [0.12; 0.87]	0.026[b]
> 33 kg/m^2	507	4 (0.8)	505	6 (1.2)	0.65 [0.19; 2.30]	0.546[b]

a: Unless stated otherwise, the RR and the corresponding 95% CI are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT) if possible.
b: Institute's calculation, Fisher exact test.
c: Institute's calculation.
d: Calculation of RR and corresponding 95% CI without consideration of stratification.
BMI: body mass index; CI: confidence interval; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 17: Subgroups: symptomatic nonfatal PE – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study characteristic subgroup	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
AMPLIFY (CV185056)						
BMI category I					Interaction:	0.005
≤ 28 kg/m^2	1320	18 (1.4)	1327	5 (0.4)	3.62 [1.35; 9.71]	0.006[b]
> 28 kg/m^2	1272	9 (0.7)[c]	1288	20 (1.6)[c]	0.46 [0.21; 1.00][d]	0.060[b]
$> 28 – 33$ kg/m^2	765	7 (0.9)	782	12 (1.5)	0.60 [0.24; 1.51]	0.357[b]
> 33 kg/m^2	507	2 (0.4)	506	8 (1.6)	0.25 [0.05; 1.21]	0.064[b]

a: Unless stated otherwise, the RR and the corresponding 95% CI are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT) if possible.
b: Institute's calculation, Fisher exact test.
c: Institute's calculation.
d: Calculation of RR and corresponding 95% CI without consideration of stratification.
BMI: body mass index; CI: confidence interval; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; vs.: versus

The results showed consistent effect modification by the characteristic "BMI" for the 2 outcomes DVT and PE and for the composite outcome. Such consistency was not observable for the characteristics "sex" and "anatomical extent". Only the effect modifications on the characteristic "BMI" are therefore considered below. The subgroup analyses on the composite outcome are also not considered further because there were relevant effect modifications for the individual components.

Symptomatic nonfatal DVT

There was an indication of an effect modification by the characteristic "BMI category I" for the individual component "symptomatic nonfatal DVT" (interaction test p = 0.164).

For the outcome "symptomatic nonfatal DVT", there was no relevant heterogeneity for the characteristic "BMI category I" for the two neighbouring BMI categories > 28 to 33 kg/m^2 and > 33 kg/m^2 (interaction test p = 0.372). These 2 categories are therefore summarized. Hence for symptomatic nonfatal DVT, there was no statistically significant result in patients with a BMI of ≤ 28 kg/m^2. For patients with a BMI of > 28 kg/m^2, there was a statistically significant result in favour of apixaban in comparison with enoxaparin/warfarin. Since there was only an indication of an effect modification and, in contrast to the result of the total population, the subgroup result was not statistically significant (see Table 14), there is a hint of an added benefit of apixaban in comparison with enoxaparin/warfarin in patients with a BMI of > 28 kg/m^2 for the outcome "symptomatic nonfatal DVT". There is no proof of added benefit of apixaban in comparison with enoxaparin/warfarin for patients with a BMI of ≤ 28 kg/m^2.

Symptomatic nonfatal PE

There was proof of an effect modification by the characteristic "BMI category I" for the individual component "symptomatic nonfatal PE" (interaction test p = 0.005). Furthermore, an indication of an effect modification was identified for the BMI category II (interaction test p = 0.069). The result of the BMI category II is not considered further because of the proof of an effect modification for the BMI category I.

There was no relevant heterogeneity for the characteristic "BMI category I" for the two neighbouring BMI categories > 28 to 33 kg/m^2 and > 33 kg/m^2 (interaction test = 0.341) so that these categories are summarized. Hence there was no statistically significant result in patients with a BMI of > 28 kg/m^2. For patients with a BMI of ≤ 28 kg/m^2, in contrast, there was a statistically significant result to the disadvantage of apixaban in comparison with enoxaparin/warfarin. Because there is proof of an effect modification, there is an indication of lesser benefit of apixaban compared with enoxaparin/warfarin in patients with a BMI of ≤ 28 kg/m^2 for the outcome "symptomatic nonfatal PE". There is no proof of added benefit of apixaban in comparison with enoxaparin/warfarin for patients with a BMI of > 28 kg/m^2.

Adverse events

Major bleeding, clinically relevant nonmajor bleeding

Table 18 and Table 19 show the results of the subgroup analyses for subgroup characteristics for which there was an indication of an effect modification for the outcomes "major bleeding" and "clinically relevant nonmajor bleeding". There was no proof of effect modification.

Table 18: Subgroups: major bleeding – RCT, direct comparison: apixaban vs. enoxaparin/ warfarin (research question 1)

Study characteristic subgroup	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
AMPLIFY (CV185056)						
Index event					Interaction:	0.087
PE (with or without DVT)	928	4 (0.4)	902	25 (2.8)	0.16 [0.05; 0.45]	< 0.001[b]
DVT only	1738	11 (0.6)	1773	24 (1.4)	0.47 [0.23; 0.95]	0.040[b]
Anatomical extent of DVT					Interaction:	0.194
Low[c]/intermediate risk[d]	992	9 (0.9)[e]	1020	13 (1.3)[e]	0.71 [0.31; 1.66][f]	0.522[b]
Low risk[c]	*423*	*3 (0.7)*	*440*	*7 (1.6)*	*0.44 [0.12; 1.71]*	*0.239[g]*
Intermediate risk[d]	*569*	*6 (1.1)*	*580*	*6 (1.0)*	*1.01 [0.32; 3.13]*	*> 0.999[b]*
High risk[h]	746	2 (0.3)	750	11 (1.5)	0.18 [0.04; 0.82]	0.022[b]

a: Unless stated otherwise, the RR and the corresponding 95% CI are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT) if possible.
b: Institute's calculation, Fisher exact test.
c: Blood clot only in popliteal vein.
d: Neither low risk nor high risk.
e: Institute's calculation.
f: Calculation of RR and corresponding 95% CI without consideration of stratification.
g: Institute's calculation, unconditional exact test (CSZ method according to [5]).
h: Blood clot in the iliac vein or in the femoral vein.

CI: confidence interval; CSZ: convexity, symmetry, z score; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Table 19: Subgroups: clinically relevant nonmajor bleeding – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study characteristic subgroup	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
AMPLIFY (CV185056)						
Index event					Interaction:	0.052
PE (with or without DVT)	928	40 (4.3)	902	104 (11.5)	0.37 [0.26; 0.53]	< 0.001[b]
DVT only	1738	63 (3.6)	1773	111 (6.3)	0.58 [0.43; 0.78]	< 0.001[b]
Anatomical extent of PE					Interaction:	0.101
Limited[c]	79	8 (10.1)	88	9 (10.2)	0.96 [0.39; 2.35]	> 0.999[d]
Intermediate[e]/ extensive[f]	747	30 (4.0)[g]	719	86 (12.0)[g]	0.34 [0.22; 0.50][h]	< 0.001[b]
Intermediate[e]	*391*	*18 (4.6)*	*394*	*49 (12.4)*	*0.37 [0.22; 0.62]*	*< 0.001[d]*
Extensive[f]	*356*	*12 (3.4)*	*325*	*37 (11.4)*	*0.30 [0.16; 0.56]*	*< 0.001[d]*

a: Unless stated otherwise, the RR and the corresponding 95% CI are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT) if possible.
b: Institute's calculation, Fisher exact test.
c: Not more than one lobe with a perfusion deficit of 25% or less.
d: Institute's calculation, unconditional exact test (CSZ method according to [5]).
e: Neither limited nor extensive.
f: ≥ 2 lobes with a perfusion deficit of $\geq 50\%$.
g: Institute's calculation.
h: Calculation of RR and corresponding 95% CI without consideration of stratification.
CI: confidence interval; CSZ: convexity, symmetry, z score; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Both for major bleeding and for clinically relevant nonmajor bleeding, there was an indication of effect modification for the characteristic "index event" (interaction test $p = 0.087$ and $p = 0.052$). However, the result was statistically significant both for patients with index PE and for those with index DVT only. These effect modifications are therefore not considered further for the overall conclusion.

There was an additional indication of effect modification for major bleeding within the group of patients with index DVT only, namely for the extent of DVT (interaction test $p = 0.194$). In contrast, there was an indication of effect modification for clinically relevant nonmajor bleeding for the group of patients with index PE, again for the extent of the index event (interaction test $p = 0.101$). Since these effect modifications were not consistent across the bleeding outcomes, they are also not considered further for the overall conclusion.

Serious adverse events

Table 20 shows the results of the subgroup analyses for subgroup characteristics for which there was an indication or proof of an effect modification for the outcome "SAEs".

Table 20: Subgroups: SAEs (excluding outcomes individually analysed by the company) – RCT, direct comparison: apixaban vs. enoxaparin/warfarin (research question 1)

Study characteristic subgroup	Apixaban		Enoxaparin/warfarin		Apixaban vs. enoxaparin/warfarin	
	N	Patients with events n (%)	N	Patients with events n (%)	RR [95% CI][a]	p-value
AMPLIFY (CV185056)						
Index event					Interaction:	0.140
PE (with or without DVT)	928	144 (15.5)	902	143 (15.9)	0.98 [0.79; 1.21]	0.847[b]
DVT only	1738	198 (11.4)	1773	165 (9.3)	1.22 [1.01; 1.49]	0.046[b]
Anatomical extent of DVT					Interaction:	0.047
Low risk[c]	423	39 (9.2)	440	40 (9.1)	1.02 [0.67; 1.54]	0.993[d]
Intermediate risk[e]	569	68 (12.0)	580	38 (6.6)	1.82 [1.24; 2.66]	0.002[b]
High risk[f]	746	91 (12.2)	750	87 (11.6)	1.05 [0.80; 1.39]	0.750[b]

a: RR and the corresponding 95% CI are results determined by the company using the Cochran-Mantel-Haenszel method, taking into account stratification according to index event (DVT only or PE with/without DVT) if possible.
b: Institute's calculation, Fisher exact test.
c: Blood clot only in popliteal vein.
d: Institute's calculation, unconditional exact test (CSZ method according to [5]).
e: Neither low risk nor high risk.
f: Blood clot in the iliac vein or in the femoral vein.
CI: confidence interval; CSZ: convexity, symmetry, z score; DVT: deep vein thrombosis; N: number of analysed patients; n: number of patients with event; PE: pulmonary embolism; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

For the outcome "SAEs", there was an indication of an effect modification by the characteristic "index event" (interaction test p = 0.140), and proof of an effect modification by the characteristic "anatomical extent of DVT" within the patient group with index DVT only (interaction test p = 0.047). There were further indications of an effect modification also by the characteristics "BMI" (interaction test p = 0.167) and "anatomical extent of PE" (interaction test p = 0.196), but since the effect was not statistically significant in any of the subgroups, the corresponding subgroup results are not presented.

There was no statistically significant result for the subgroup with index PE (with or without DVT), whereas there was a statistically significant result to the disadvantage of apixaban in comparison with enoxaparin/warfarin for the subgroup with index DVT. The direction of effect was even reversed. Since there was only an indication of an effect modification and, in contrast to the result of the total population, the result in the subgroup of patients with index

DVT was statistically significant, there is a hint of greater harm from apixaban in comparison with enoxaparin/warfarin for patients with index DVT only for the outcome "SAEs".

There was proof of an effect modification (interaction test $p = 0.047$) for the characteristic "anatomical extent of DVT". However, the results for non-neighbouring (low and high risk) were similar, but not the ones for neighbouring risk groups. This effect modification is therefore not considered further for the overall conclusion.

2.3.3 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.

2.3.3.1 Assessment of added benefit at outcome level

The data presented in Section 2.3.2 resulted in a hint of an added benefit and proof and indication of lesser harm from apixaban versus enoxaparin/warfarin. However, there was also an indication of lesser benefit and a hint of greater harm of apixaban versus enoxaparin/warfarin.

Moreover, there were proof and indications of an effect modification by the subgroup characteristics "BMI" and "index event". The extent of the respective added benefit at outcome level was estimated from these results (see Table 21).

Table 21: Extent of added benefit at outcome level: apixaban vs. enoxaparin/warfarin (research question 1)

Outcome category outcome *effect modifier[a]* subgroup	Apixaban vs. enoxaparin/warfarin proportion of events effect estimate [95% CI] p-value probability[b]	Derivation of extent[c]
Mortality		
All-cause mortality	1.6% vs. 2.0% RR: 0.80 [0.53; 1.19] p = 0.296	Lesser benefit/added benefit not proven
Morbidity		
Symptomatic nonfatal DVT		
BMI *≤ 28 kg/m²*	*1.0% vs. 0.9%* *RR: 1.09 [0.50; 2.38]* *p = 0.844*	Lesser benefit/added benefit not proven
> 28 kg/m²	*0.7% vs. 1.7%* *RR: 0.41 [0.19; 0.895]* *p = 0.029* *probability: "hint"*	Outcome category: serious/severe symptoms/late complications $CI_u < 0.90$ added benefit, extent: "considerable"
Symptomatic nonfatal PE		
BMI *≤ 28 kg/m²*	*1.4% vs. 0.4%* *RR: 3.62 [1.35; 9.71]* *RR[d] 0.28 [0.10; 0.74]* *p = 0.006* *probability: "indication"*	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$, risk < 5% lesser benefit, extent: "considerable"
> 28 kg/m²	*0.7% vs. 1.6%* *RR: 0.46 [0.21; 1.00]* *p = 0.060*	Lesser benefit/added benefit not proven
Health-related quality of life		
	No data available	Lesser benefit/added benefit not proven
Adverse events		
Major bleeding	0.6% vs. 1.8% RR: 0.31 [0.17; 0.55] p < 0.001 probability: indication	Outcome category: serious/severe AEs $CI_u < 0.75$, risk < 5% lesser harm, extent: "considerable"

(continued)

Table 21: Extent of added benefit at outcome level: apixaban vs. enoxaparin/warfarin (research question 1) (continued)

Outcome category outcome *effect modifier[a]* *subgroup*	Apixaban vs. enoxaparin/warfarin proportion of events effect estimate [95% CI] p-value probability[b]	Derivation of extent[c]
Clinically relevant nonmajor bleeding	3.8% vs. 8.0% RR: 0.48 [0.38; 0.60] p < 0.001 probability: "proof"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm, extent: "considerable"
SAEs (excluding outcomes individually analysed by the company)		
Index event *PE (with/ without DVT)*	*15.5% vs. 15.9% RR: 0.98 [0.79; 1.21] p = 0.847*	Greater/lesser harm not proven
DVT only	*11.4% vs. 9.3% RR: 1.22 [1.01; 1.49] RR[d] 0.82 [0.67; 0.99] p = 0.046 probability: "hint"*	Outcome category: serious/severe AEs $CI_u < 1.00$ greater harm, extent: "minor"
Treatment discontinuation due to AEs (excluding outcomes individually analysed by the company)	4.1% vs. 4.2% RR: 0.97 [0.74; 1.25] p = 0.796	Greater/lesser harm not proven
a: Data provided if relevant for the extent of added benefit at outcome level. b: Probability provided if statistically significant differences were present. c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. d: Proportion of events apixaban vs. enoxaparin/warfarin (reversed direction of effect to enable direct use of limits to derive the extent of added benefit). AE: adverse event; BMI: body mass index; CI: confidence interval; CI_u: upper limit of the CI; DVT: deep vein thrombosis; PE: pulmonary embolism; RR: relative risk; SAE: serious adverse event; vs.: versus		

The results show that relevant effect modifications for the characteristic "BMI" occurred in the outcomes "symptomatic nonfatal DVT" and "symptomatic nonfatal PE". For the characteristic "index event", there was a relevant effect modification for the outcome "SAEs". In these cases, consideration of the individual subgroups produced different conclusions on the added benefit at outcome level. Both for patients with a BMI of $> 28 \text{ kg/m}^2$ and of $\leq 28 \text{ kg/m}^2$ as well as for index DVT, separate conclusions on added benefit are therefore necessary.

For all other outcomes, if data were available, the conclusion on the added benefit and lesser/greater harm was based on the total population.

2.3.3.2 Overall conclusion on added benefit

Table 22 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 22: Positive and negative effects from the assessment of apixaban compared with enoxaparin/warfarin (research question 1)

Positive effects	Negative effects

Serious/severe symptoms/late complications
▪ symptomatic nonfatal DVT
  BMI > 28 kg/m^2: hint of added benefit – extent "considerable"
	Serious/severe symptoms/late complications
	▪ symptomatic nonfatal PE
	  BMI ≤ 28 kg/m^2: hint of lesser benefit – extent "considerable"

Serious/severe adverse events
▪ major bleeding
  indication of lesser harm – extent "considerable"
	Serious/severe adverse events
	▪ SAEs (excluding outcomes individually analysed by the company)
	  index DVT only: hint of greater harm – extent "minor"

Non-serious/non-severe adverse events ▪ clinically relevant nonmajor bleeding proof of lesser harm – extent "considerable"	
BMI: body mass index; DVT: deep vein thrombosis; PE: pulmonary embolism; SAE: serious adverse event	

Overall, positive and negative effects remain, which partly depend on the effect modifiers "BMI" and "index event". 2 effect modifiers were considered for the BMI, which is why below the balancing of positive and negative effects is conducted separately for patients with a BMI of ≤ 28 kg/m^2 and for patients with a BMI of > 28 kg/m^2.

Patients with a BMI of ≤ 28 kg/m^2

There is an indication of lesser benefit of apixaban with the extent "considerable" for the outcome "symptomatic nonfatal PE" in patients with a BMI of ≤ 28 kg/m^2. The treatment goal of apixaban in the new therapeutic indication is treatment of DVT and PE and prevention of recurrent DVT and PE in adults [3,4]. Hence the lesser harm from apixaban observed in the bleeding outcomes does not result in an added benefit of apixaban in the overall assessment.

Overall, there is no proof of an added benefit of apixaban in comparison with the ACT for patients with a BMI of ≤ 28 kg/m^2.

Patients with a BMI of > 28 kg/m^2

For patients with a BMI of > 28 kg/m^2 overall, there are positive effects both with regard to benefit (symptomatic nonfatal DVT: hint of considerable added benefit), and with regard to AEs (major bleeding: indication of lesser harm [extent "considerable"]; clinically relevant nonmajor bleeding: proof of lesser harm [extent "considerable"]). This is offset by only a hint of greater harm (extent "minor") for patients with index DVT due to more frequent SAEs. In the overall assessment, this did not raise doubts about the positive effects. Overall, there is

proof of an added benefit of apixaban in comparison with the ACT with the extent "considerable" for patients with a BMI of > 28 kg/m^2.

2.3.4 List of included studies

AMPLIFY CV185056

Agnelli G, Buller HR, Cohen AT, Curto M, Gallus AS, Johnson M et al. Oral apixaban for the treatment of acute venous thromboembolism. N Engl J Med 2013; 369(9): 799-808.

Bristol-Myers Squibb. A safety and efficacy trial evaluating the use of apixaban in the treatment of symptomatic deep vein thrombosis and pulmonary embolism: revised protocol number 02 incorporating amendment(s) 04 and administrative letters 02, 03 and 04+ protocol amendment 01 (version 1.0 dated 21-Apr-08); site-specific-molecular profiling supplement samples for Pfizer's Exploratory Research Biobank [online]. In: Pharmnet.Bund Klinische Prüfungen. [Accessed: 8 July 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Bristol-Myers Squibb. Efficacy and safety study of apixaban for the treatment of deep vein thrombosis or pulmonary embolism: full text view [online]. In: Clinicaltrials.gov. 17 April 2014 [accessed: 4 November 2014]. URL: http://ClinicalTrials.gov/show/NCT00643201.

Pfizer. A study to evaluate safety and eficacy of apixaban in Japanese acute deep vein thrombosis (DVT) and pulmonary embolism (PE) patients: full text view [online]. In: Clinicaltrials.gov. 26 June 2014 [accessed: 7 July 2014]. URL: http://ClinicalTrials.gov/show/NCT01780987.

2.4   Research question 2: long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE)

2.4.1   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 apixaban (studies completed up to 30 July 2014)
- bibliographical literature search on apixaban (last search on 8 July 2014)
- search in trial registries for studies on apixaban (last search on 8 July 2014)

To check the completeness of the study pool:

- bibliographical literature search on apixaban (last search on 5 September 2014)
- search in trial registries for studies on apixaban (last search on 5 September 2014)

No relevant study was identified from the check.

2.4.2   Results on added benefit

The company presented no data on the assessment of the added benefit in the research question of long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE). An added benefit of apixaban versus the ACT is therefore not proven for this research question.

2.4.3   Extent and probability of added benefit

Since the company submitted no data on long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE), an added benefit of apixaban in comparison with the ACT is not proven for this research question.

2.5   Extent and probability of added benefit – summary

The added benefit, which results from the assessment of apixaban versus the ACT, is displayed in Table 23.

Table 23: Apixaban – extent and probability of added benefit

Subindication	Apixaban dosage	ACT[a]	Population	Extent and probability of added benefit
Initial treatment of DVT and PE and prevention to be started in parallel in adults	10 mg twice daily for 7 days, then 5 mg twice daily	LMWH (**enoxaparin**) with VKA (**warfarin**) to be started in parallel	Patients with BMI ≤ 28 kg/m²	Added benefit not proven
			Patients with BMI > 28 kg/m²	Proof of added benefit, extent "considerable"
Long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE)	2.5 mg twice daily	VKA	Patients after completion of a 6-month anticoagulant treatment	Added benefit not proven
ACT: appropriate comparator therapy; BMI: body mass index; DVT: deep vein thrombosis; G-BA: Federal Joint Committee; LMWH: low molecular weight heparin; PE: pulmonary embolism; VKA: vitamin K antagonist				
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.				

In summary, an added benefit is not proven for initial treatment of DVT and PE and prevention to be started in parallel in adults with a BMI of ≤ 28 kg/m² and a treatment duration of at least 6 months. There is proof of added benefit with the extent "considerable" for patients with a BMI of > 28 kg/m². An added benefit is not proven for long-term prevention of recurrent DVT and PE (after completion of a 6-month treatment of DVT or PE).

This deviates from the company's approach, which derived proof of added benefit with the extent "considerable" for the total target population of apixaban in the new therapeutic indication.

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

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Bristol-Myers Squibb, Pfizer. Eliquis 5 mg Filmtabletten: Fachinformation [online]. July 2014 [accessed: 10 September 2014]. URL: http://www.fachinfo.de.

4. Bristol-Myers Squibb, Pfizer. Fachinformation Eliquis 2,5 mg Filmtabletten: Fachinformation [online]. July 2014 [accessed: 28 October 2014]. URL: http://www.fachinfo.de.

5. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-28-apixaban-zulassungsweiterung-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6322.html.