Extended Anticoagulant Treatment with Full- or Reduced-Dose Apixaban in Patients with Cancer-Associated Venous Thromboembolism: The API-CAT Study

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Supplementary Table S1 Eligibility criteria

Inclusion criteria	
Patients who have any cancer diagnosed histologically (other than basal-cell or squamous-cell carcinoma of the skin, primary brain tumor, or intracerebral metastasis) Active cancer is defined as the presence of measurable disease or ongoing (or planned) chemotherapy, radiotherapy, hormonotherapy, or targeted therapy at inclusion	
Patients who have: An objectively documented index event of: symptomatic or incidental proximal lower-limb, iliac, inferior vena cava deep-vein thrombosis, or symptomatic or incidental pulmonary embolism in a segmental or larger pulmonary artery. Completed at least 6 months of anticoagulant therapy at therapeutic dosage (whatever the drug and the dosing), or completed assigned clinical trial study treatment, for the treatment of the index event; and patient still receiving anticoagulant treatment 6 months after occurrence or the VTE index event. No objectively documented symptomatic recurrence of VTE between the index event and randomization.	
• Anticipated duration of anticoagulant treatment of at least 12 months at the time of randomization	
• Signed written informed consent	
• *Exclusion criteria*	
1. Sex and reproductive status	a) Women of child-bearing potential who are unwilling or unable to use an acceptable method of birth control (such as oral contraceptives, other hormonal contraceptives [vaginal products, skin patches, or implanted or injectable products], or mechanical products such as an intrauterine device or barrier methods [condoms]) to avoid pregnancy for the entire study
	b) Women who are pregnant or breastfeeding
	c) Women with a positive pregnancy test on enrolment or prior to investigational product administration
2. Index VTE related	a) Isolated subsegmental (incidental or symptomatic) PE without associated DVT
	b) Isolated distal DVT of the legs
	c) Isolated upper-extremity DVT or superior vena cava thrombosis
	d) Isolated visceral thrombosis
	e) Isolated catheter thrombosis
	f) Objectively documented symptomatic recurrence of VTE after the index event under anticoagulant treatment
	g) VTE during anticoagulant treatment given at therapeutic dosage
3. Medical history and concurrent diseases	a) Subjects with indications for long-term treatment with a VKA, such as mechanical heart valve or antiphospholipid syndrome
	b) Subjects with indication for long-term anticoagulation with a VKA or a DOAC at therapeutic dosage
	c) Conditions increasing the risk of serious bleeding: intracranial or intraocular bleeding within 6 months, major surgery within 2 weeks prior to randomization, overt major bleeding at time of randomization
	d) Life expectancy <12 months
	e) ECOG level 3 or 4
	f) Bacterial endocarditis
	g) Uncontrolled hypertension: systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg
4. Physical and laboratory test findings	a) Platelet count $<75{,}000/mm^3$
	b) Hemoglobin <8 g/dL
	c) Creatinine clearance <30 mL/min based on the Cockcroft–Gault equation
	d) Acute hepatitis, chronic active hepatitis, liver cirrhosis; or an alanine aminotransferase level 3 times or more and/or bilirubin level 2 times or more higher the upper limit of the normal range
5. Prohibited treatments and/or therapies	a) Subjects requiring ASA >165 mg/day at randomization or thienopyridine therapy (clopidogrel, prasugrel, or ticagrelor)

(*Continued*)

Supplementary Table S1 (*Continued*)

	b) Subjects requiring dual antiplatelet therapy (such as ASA plus clopidogrel or ASA plus ticlopidine) at randomization. Subjects who transition from dual antiplatelet therapy to monotherapy prior to randomization will be eligible for the trial
	c) Concomitant use of strong inhibitors of both cytochrome P450 3A4 and P glycoprotein (e.g., human immunodeficiency virus protease inhibitors or systemic ketoconazole) or strong inducers of both cytochrome P450 3A4 and P glycoprotein (e.g., rifampicin, carbamazepine, or phenytoin)
6. Other exclusion criteria	a) Prisoners or subjects who are involuntarily incarcerated
	b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness
	c) Hypersensitivity to apixaban
	d) Patients participating in another pharmacotherapeutic program with an experimental therapy that is known to affect the coagulation system
	e) Patients under 18 years old
	f) Patients under legal protection (guardianship)

Abbreviations: ASA, acetylsalicylic acid; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; ECOG, Eastern Cooperative Oncology Group; PE, pulmonary embolism; VKA, vitamin K antagonist; VTE, venous thromboembolism.

Supplementary Table S2 Criteria required for the diagnosis of efficacy and safety outcomes

Primary efficacy outcome: composite of recurrent symptomatic VTE or incidental VTE or death due to PE	1. *New or recurrent PE (symptomatic or incidental) with one of the following findings*: • A new intraluminal filling defect in segmental or more proximal branches on spiral CT scan; • A new intraluminal filling defect or an extension of an existing defect or a new sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; • A new perfusion defect of at least 75% of a segment with a local normal ventilation result (high probability) on VPLS; or • Inconclusive spiral CT, pulmonary angiography, or VPLS, with demonstration of a new or extended proximal DVT in the lower extremities by compression ultrasound or venography. Or
	2. *New or recurrent DVT (symptomatic or incidental) with one of the following findings*: A recurrent deep vein thrombosis, distal or proximal lower-limb, iliac, inferior or superior vena cava, upper extremity or central venous catheter, must be distinguished from the original thrombus by comparing serial imaging modalities. (a) For a NEW DVT, criteria include: • Abnormal compression ultrasound (CUS), including grey-scale or color-coded Doppler; or • An intraluminal filling defect on venography • A new filling defect on computed tomography or MRI (b) For a RECURRENT DVT, criteria include: • Abnormal CUS where compression had been normal or, if noncompressible previously, a substantial increase (4 mm or more) in diameter of the thrombus during full compression; or • An extension of an intraluminal filling defect, or a new intraluminal filling defect or an extension of nonvisualization of veins in the presence of a sudden cut-off on venography. Or
	3. *Adjudicated VTE-related death including* • PE based on objective diagnostic testing, autopsy, or • Sudden death; i.e., death occurring within 1 hour of the onset of new symptoms which cannot be attributed to a documented cause (unexplained death) and for which PE/DVT cannot be ruled out as the cause.
Principal safety outcome: clinically relevant bleeding	*Composite of*: • *Major bleeding (ISTH definition)* Acute clinically overt bleeding with one or more of the following: - A decrease in hemoglobin of 2 g/dL or more - A transfusion of 2 or more units of packed red blood cells - Symptomatic bleeding that occurs in at least one of the following critical sites: intracranial, intraspinal, intraocular (within the corpus of the eye; thus, a conjunctival bleed is not an intraocular bleed), pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal

Supplementary Table S2 (*Continued*)

	Fatal bleeding: bleeding event that the independent adjudication committee determines is the primary cause of death or contributes directly to death. • *Clinically relevant nonmajor bleeding* - Any bleeding compromising hemodynamics; - Any bleeding leading to hospitalization; - Subcutaneous hematoma larger than 25 cm^2, or 100 cm^2 if there was a traumatic cause; - Intramuscular hematoma documented by ultrasonography; - Epistaxis that lasted for more than 5 minutes, was repetitive (i.e., two or more episodes of bleeding more extensive than spots on a handkerchief within 24 hours), or led to an intervention (e.g., packing or electrocoagulation); - Gingival bleeding occurring spontaneously and leading to medical intervention; - Hematuria that was macroscopic and lasted for more than 24 hours; - Macroscopic gastrointestinal hemorrhage, including at least one episode of melena or hematemesis, if clinically apparent; - Rectal blood loss, if more than a few spots on toilet paper and leading to medical intervention; - Hemoptysis, if more than a few speckles in the sputum and not occurring within the context of pulmonary embolism; or - Any other bleeding type considered to have clinical consequences for a subject such as medical intervention, the need for unscheduled contact (visit or telephone call) with a physician, or temporary cessation of a study drug; or associated with pain or impairment of activities of daily life.

Abbreviations: CT, computed tomography; CUS, compression ultrasound; DVT, deep vein thrombosis; ISTH, International Society on Thrombosis and Haemostasis; MRI, magnetic resonance imaging; PE, pulmonary embolism; VPLS, ventilation/perfusion lung scan; VTE, venous thromboembolism.

