

AMPLIFY-EXT

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Sponsor:

Pfizer Global Research & Development

Study Purpose:

Protocol CV185057: A safety and efficacy trial evaluating the use of apixaban for the extended treatment of deep vein thrombosis and pulmonary embolism.

(Apixaban after the initial Management of PuLmonary embolism and deep vein thrombosis with First-line therapY- EXTended treatment. The **AMPLIFY-EXT** study)

Objective:

To determine if at least one of the apixaban dose regimens is superior to placebo in the combined endpoint of symptomatic, recurrent VTE (nonfatal DVT or nonfatal PE) or all-cause death in subjects who have an objectively documented index event of symptomatic proximal DVT or symptomatic PE, have completed approximately 6 to 12 months of anticoagulant therapy for the treatment of the index event, and have no objectively documented symptomatic recurrence of VTE after the index event.

Inclusion Criteria:**1) Signed Written Informed Consent**

- a) Subjects must be willing and able to give written informed consent.

2) Target Population

- a) Subjects who have:

- an objectively documented index event of symptomatic proximal DVT or symptomatic PE;

(1) Symptomatic proximal DVT is defined as symptomatic DVT with evidence of proximal thrombosis that involves at least the popliteal vein or a more proximal vein, demonstrated by imaging with compression ultrasound (CUS), including grey-scale or color-coded Doppler, or ascending contrast venography.

(2) Symptomatic PE with evidence of thrombosis demonstrated by imaging as follows:

- an intraluminal filling defect in segmental or more proximal branches

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on spiral CT scan; or

– an intraluminal filling defect or a sudden cutoff of vessels more than 2.5 mm in diameter on the pulmonary angiogram; or

– a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan (VPLS)

- completed approximately 6 to 12 months of standard anticoagulant therapy, or completed assigned CV185056 (AMPLIFY) study treatment, for the treatment of the index event; and

- no objectively documented symptomatic recurrence of VTE after the index event.

b) Subjects should be randomized within approximately 7 days of the last dose of their initial 6-to 12-month treatment or

- when their INR is 2 or less, if a VKA was used as standard anticoagulant therapy, or

- when their blinded INR is 2 or less if the subject received CV185056 (AMPLIFY) study treatment.

c) Every attempt should be made to randomize subjects as soon as possible after discontinuation of their initial treatment.

d) The index DVT and/or PE will be adjudicated by the ICAC according to the adjudication manual. Investigators are encouraged to assemble and to submit imaging dossiers to the ICAC as soon as possible during the period that extends from the beginning of the screening period up to 2 weeks after randomization. Please refer to the diagnostic test manual for details regarding the assembly and submission of dossiers to the ICAC.

3) Age and Sex

a) Men and women, ages 18 years or greater.

b) Women of childbearing potential (WOCBP) must be using an adequate method of contraception to avoid pregnancy throughout the study in such a manner that the risk of pregnancy is minimized. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy [HRT] with documented serum follicle stimulating hormone [FSH] level >35 mIU/mL). Even women who are using 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 (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence or where their partner is sterile (eg, vasectomy) should be considered to be of childbearing potential. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start. Women are considered surgically sterile only if they have undergone a hysterectomy, bilateral tubal

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ligation, or bilateral oophorectomy. Women are considered postmenopausal only if they have had amenorrhea for ≥ 12 consecutive months, or for women on hormone replacement therapy (HRT), if they have a documented serum follicle stimulating hormone (FSH) level >35 mIU/mL of investigational product.

Exclusion Criteria:

1) Sex and Reproductive Status

a) WOCBP 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 (diaphragm, condoms, spermicides)] to avoid pregnancy for the entire study

b) Women who are pregnant or breastfeeding

c) Women with a positive pregnancy test on enrollment or prior to investigational product administration

2) Medical History and Concurrent Diseases

a) Subjects whose index and past DVT(s) and/or PE(s) have all been due solely to a transient (reversible) risk factor (ie, provoked event, eg, secondary to surgery), and who are not expected to have, for 12 months or longer after randomization, persistence of a risk factor (e.g., wheelchair-bound) for DVT and/or PE recurrence.

b) More than 12 months of anticoagulation planned for the most recent DVT or PE (index event).

c) Subjects with the following indications for long-term treatment with a VKA, such as:

- Mechanical valve
- Atrial fibrillation or atrial flutter with moderate to high risk of systemic thromboembolism
- Multiple episodes of unprovoked DVT or PE
- Documented anti-phospholipid antibodies, anti-thrombin III deficiency, protein C deficiency, protein S deficiency, homozygous factor V Leiden, or homozygous prothrombin gene mutation.

d) Subjects with cancer who will be treated indefinitely with anticoagulation therapy;

e) Active and clinically significant liver disease (eg, hepatorenal syndrome);

f) Life expectancy < 12 months;

g) Bacterial endocarditis;

h) Uncontrolled hypertension: systolic blood pressure >180 mm Hg or diastolic blood pressure >100 mm Hg.

3) Physical and Laboratory Test Findings

a) Platelet count $<100,000/\text{mm}^3$ or hemoglobin <9 g/dL

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b) Serum creatinine >2.5 mg/dL [221 umol/L] or a calculated creatinine clearance <25 ml/min.

c) ALT or AST >2 times upper limit of normal, or a total bilirubin >1.5 times upper limit of normal (unless the latter has an alternative causative factor identified [eg, Gilbert's syndrome]).

4) Prohibited Treatments and/or Therapies

a) Subjects requiring ASA >165 mg/day at randomization.

b) Subjects requiring dual anti-platelet 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.

5) 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 (eg, infectious disease) illness

c) Receiving concurrent investigational agents or has received an investigational agent within the past 30 days prior to the first dose of study treatment (with the exception of approved medications being used for an approved indication, eg, investigating a new dosing regimen for an approved indication). Subjects who participated in the CV185056 (AMPLIFY) study may participate in this study and are exempt from this exclusion (see Section 5.7)

d) Any condition, which in the opinion of the investigator, would put the subject at an unacceptable risk from participating in the study; or

e) Any other medical, social, logistical, or psychological reason, which in the opinion of the investigator, would preclude compliance with, or successful completion of, the study protocol

Status:

Active enrollment

If you have any questions, please feel free to contact the coordinators, and they will be happy to answer any questions you have regarding this study.