**Efficacy and Safety of Betrixaban for Extended Duration Thromboprophylaxis among Acutely Ill Medical Patients**

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**Background**
Acutely ill medical patients remain at risk for venous thromboembolism (VTE) well beyond their hospital stay; nevertheless, the adequate duration of thromboprophylaxis for these patients has not been established. The Acute Medically Ill VTE Prevention with Extended Duration Betrixaban (APEX) trial was a multicenter, randomized, double-blind, trial that evaluated the efficacy and safety of extended-duration oral betrixaban compared with standard-duration subcutaneous enoxaparin followed by placebo (NCT01583318).

**Methods**
Patients hospitalized for an acute medical illness who were anticipated to be immobile and had risk factors for VTE were randomized to either subcutaneous enoxaparin 40 mg once daily for 10 days or oral betrixaban 25 mg or 75 mg twice daily for 35 to 42 days with subcutaneous placebo for 10 days. A sequential testing procedure was used to analyze three pre-specified sequential cohorts: Cohort 1—patients with D-dimer at least twice the upper limit of normal, Cohort 2—patients with D-dimer at least twice the upper limit of normal or age 75 years or older, and the overall study population. The primary efficacy endpoint was the composite of asymptomatic proximal deep-vein thrombosis, symptomatic VTE, or VTE-related death. The primary safety endpoint was ISTH major bleeding through 7 days after discontinuation of the study drug.

**Results**
A total of 7,713 patients were randomized. In cohort 1 (D-dimer at least twice the upper limit of normal by local lab), the primary efficacy endpoint occurred in 9.8% of patients randomized to betrixaban compared with 8.5% of patients randomized to enoxaparin (RR = 0.97; 95% CI [0.86, 1.09]; P = 0.554). In cohort 2 (D-dimer at least twice the upper limit of normal or age 75 years or older), the primary endpoint occurred in 5.6% of patients on betrixaban compared with 7.1% of patients on enoxaparin (RR = 0.80; 95% CI [0.65, 0.99]; P = 0.029). A similar reduction was also observed among patients in the overall population (5.3% vs. 7.0%; RR = 0.76; 95% CI [0.63, 0.92]; P = 0.046). Symptomatic events occurred less frequently among patients randomized to betrixaban (4.5%) compared with enoxaparin (1.1%) (RR = 0.6; 95% CI [0.42, 0.82]; P = 0.04). Betrixaban was not associated with a significant increase in ISTH major bleeding (0.67% for betrixaban vs. 1.19% for enoxaparin; RR = 1.16; 95% CI [0.67, 2.12]; P = 0.554).

**Conclusions**
Compared with standard-duration enoxaparin, extended-duration betrixaban demonstrated a reduction in the primary efficacy endpoint of asymptomatic proximal DVT or symptomatic venous thromboembolism among patients in the first analysis cohort (D-dimer at least twice the upper limit of normal by local lab) that was on the margin of statistical significance. In the second analysis cohort (D-dimer at least twice the upper limit of normal or age 75 years or older) and the overall population, betrixaban significantly reduced the primary efficacy endpoint. Extended-duration betrixaban was not associated with an increased risk of ISTH major bleeding.

**Background**
- Approximately 8 million acutely ill medical patients the US and 12 million in the EU are at risk of developing VTE annually.
- Despite standard of care agents available, more than 400,000 VTE events, including an estimated 150,000 VTE related deaths, occur in this patient population.
- Approximately 1 out of 2 DVT and PE events occur within 6 weeks of discharge where no agents are currently approved or guideline recommended for thromboprophylaxis.
- Betrixaban is an oral factor Xa inhibitor with rapid on-set, 1 day half-life (19-23 h), a renal clearance of administered dose of 5%, and no interaction with major CYP450 enzymes.

**Methods**
- **Study Design**
  - **Cohort 1**
    - D-dimer ≥ 2x ULN
  - **Cohort 2**
    - Age ≥ 75 years
  - **Cohort 3**
    - Age ≥ 75 years and D-dimer ≥ 2x ULN
  - **Cohort 4**
    - All patients in the overall population
- **Analysis Cohorts & Closed-Testing Procedure**
  - **Primary Efficacy**
    - Composite of asymptomatic proximal DVT (detected on ultrasound), symptomatic DVT (general criteria), non-fatal PE, and VTE-related death through 7 days after discontinuation of randomized treatment.
  - **Secondary Efficacy**
    - Intracranial Hemorrhage
    - Fatal or Inevitable Outcomes
  - **Safety Endpoints**
    - Composite of asymptomatic proximal DVT, symptomatic proximal DVT, non-fatal PE, and VTE-related death

**Results**
- **Primary Efficacy**
  - **Local D-Dimer to Define Cohorts**
  - **Central D-Dimer to Define Cohorts**
  - **Anticipated Need for Prolonged Anticoagulation**
  - **Race**
  - **Body Mass Index**
  - **Mean Weight**
  - **Male**

**Conclusions**
- In a subgroup of medically Ill D-Dimer positive patients, extended duration betrixaban demonstrated a reduction in VTE events that approached statistical significance (P=0.054), and in pre-specified exploratory analyses of central lab D-dimer values, and progressively larger cohorts, including all patients, the totality of the data demonstrated a consistent and significant reduction in VTE.
- Betrixaban was not associated with a significant increase in major or fatal bleeding (P = 0.55).
- When both the primary safety and primary efficacy endpoints were taken into account, betrixaban was associated with a favorable net clinical benefit in the overall efficacy population (P = 0.011).