

LBA--2 Once-Daily Oral Rivaroxaban Versus Placebo in the Long-Term Prevention of Recurrent Symptomatic Venous Thromboembolism. the Einstein-Extension Study

*Late-breaking Abstracts*

*Session: Late-Breaking Abstract Session*

*Tuesday, December 8, 2009, 7:30 AM-9:00 AM*

*Hall F (Ernest N. Morial Convention Center)*

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## On behalf of the Einstein investigators

**Background** In a large proportion of patients that have completed 6 to 12 months of treatment with a vitamin K antagonist (VKA) for their acute episode of venous thromboembolism (VTE) the question arises whether to stop or continue this treatment. Continuation implies the need for regular laboratory control and subsequent dose adjustments. Furthermore, the risk of bleeding persists. New oral anticoagulants hold the promise of simple fixed-dose regimens without the need for monitoring and could make continuation of therapy more attractive. The Einstein-Extension study was therefore designed to assess the relative efficacy and safety of rivaroxaban, a direct oral factor Xa inhibitor, versus placebo in patients who had completed 6 to 12 months of anticoagulant treatment for their acute episode of VTE. Patients in whom there was a clear indication for continued anticoagulant treatment were not eligible.

**Study Design** This randomized, double-blind, placebo-controlled, superiority study evaluated therapy with rivaroxaban 20 mg once-daily for an additional 6 or 12 months. The primary efficacy outcome was symptomatic recurrent VTE (i.e., the composite of recurrent DVT, non-fatal PE, and fatal PE). The principal safety outcome was major bleeding. Also the occurrence of clinically relevant non-major bleeding (e.g. nose bleeds, large skin hematomas, and macroscopic hematuria) was recorded. The study was event-driven requiring a minimum of 30 confirmed recurrent events. All outcomes were adjudicated by an independent blinded committee.

**Results** A total of 1197 patients were randomized between February 2007 and May 2009 by 280 study sites in 28 countries. The intention-to-treat population consisted of 602 rivaroxaban and 594 placebo patients. Baseline characteristics and risk factors for VTE were comparable between the two groups. The mean duration of study treatment was 190 days in both groups. During the treatment period, symptomatic recurrent VTE events occurred in 42 (7.1%) of the placebo treated patients and in 8 (1.3%) of the rivaroxaban recipients (hazard ratio, 0.18; 95 % CI, 0.09 – 0.39;  $p < 0.0001$ ). After the stop of study medication, 6 symptomatic

recurrent VTE events occurred in each group during the one month observational period. Major bleeding did not occur in placebo patients and was observed in 4 (0.7%) rivaroxaban recipients ( $p=0.106$ ). None of these bleeding events were fatal or in a critical site. Clinically relevant non-major bleeding was noted in 7 (1.2%) and 32 (5.4%) of the placebo and rivaroxaban recipients, respectively. Two (0.3%) patients in the placebo group died versus 1 (0.2%) in the rivaroxaban group. No patients were observed to have an alanine aminotransferase (ALT) rise above 3 times the upper limit of normal (xULN) combined with a total bilirubin above 2 xULN.

**Conclusion** A fixed dose of 20 mg of rivaroxaban once-daily is associated with an 82% relative risk reduction in the recurrence of VTE in patients who had completed a 6 to 12 month course of anticoagulant therapy for their index event. Based on the estimated cumulative incidence rates, approximately, 15 patients need to be treated to prevent one recurrent VTE event. This clinically relevant reduction in recurrence was associated with a low incidence of major bleeding (0.7%). This oral once-daily regimen provides the clinician with a simple option for patients in whom continued anticoagulant treatment is indicated.

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