

DRAFT Questions 3/11/09

Rivaroxaban was studied in four phase 3 clinical studies (RECORD studies) that examined its ability to prevent deep vein thrombosis (DVT) and pulmonary embolus (PE) among patients undergoing hip (HR) or knee replacement (KR) surgery. Additional clinical studies are currently ongoing to assess the drug's effects in multiple other settings.

The primary endpoint in the RECORD studies was a comparison of the occurrence of a composite endpoint that consisted of venographic evidence of DVT, non-fatal PE or death. The primary endpoint results in the four RECORD studies are shown below:

RECORD Studies: Primary Endpoint Rates

Study	Rivaroxaban	Enoxaparin	p-value
RECORD 1	18/1595 (1.1%)	58/1558 (3.7%)	< 0.05
RECORD 2	17/864 (2.0%)	81/869 (9.3%)	< 0.05
RECORD 3	79/824 (9.6%)	166/878 (18.9%)	< 0.05
RECORD 4	67/965 (6.9%)	97/959 (10.2%)	< 0.05

The main safety finding in the RECORD studies was increased bleeding among patients who received rivaroxaban, compared to patients who received enoxaparin. Major bleeding occurred at a rate of 0.4% within the rivaroxaban group and 0.2% within the enoxaparin group. The only bleeding-related death occurred among a patient who received rivaroxaban. Safety findings were also notable for a numeric excess in the occurrence of serious alanine aminotransferase (ALT) elevations among patients receiving rivaroxaban (0.3% versus 0.2%) as well as the occurrence of a composite liver marker (ALT > 3X upper limit of normal with total bilirubin > 2X upper limit of normal (0.2% versus 0.1%).

1. (Vote) Do the available data identify a risk for hepatotoxicity that would preclude approval of rivaroxaban for the prophylaxis of DVT and PE among patients undergoing hip or knee replacement surgery?
2. (Vote) Rivaroxaban is proposed for use over a maximum of 14 (knee surgery) or 35 (hip surgery) days. If the drug is approved, physicians may desire to prescribe it for longer periods of time. Are the data from the on-going clinical studies essential to assess rivaroxaban safety prior to its approval for the prophylaxis of DVT and PE among patients undergoing hip or knee replacement surgery?
3. (Vote) Do the current clinical data demonstrate a favorable risk-benefit profile for rivaroxaban in the prophylaxis of DVT and PE in patients undergoing hip or knee replacement surgery?