

## RE-LY: Randomized Evaluation of Long-Term Anticoagulant Therapy, Warfarin, Compared with Dabigatran

### Trial Design Background

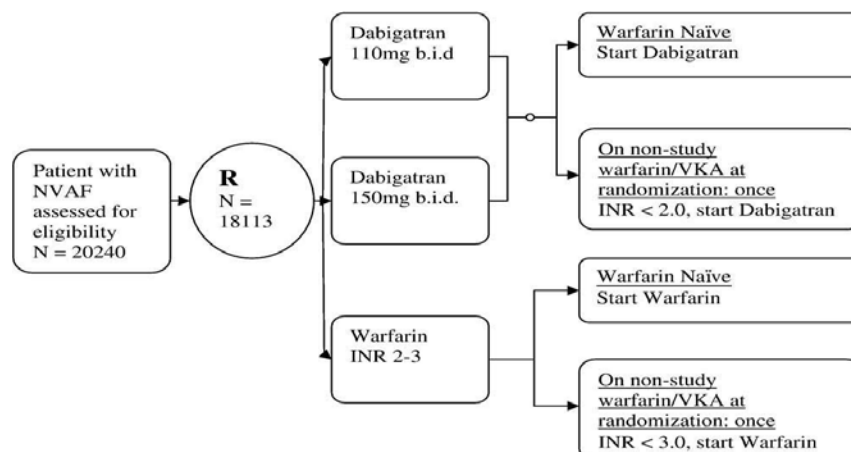
#### Study Overview

- The Phase III RE-LY® (Randomized Evaluation of Long term anticoagulant therapy) trial was designed as a non-inferiority trial to compare the long-term efficacy and safety of the oral direct thrombin inhibitor dabigatran etexilate with warfarin (titrated to international normalized ratio, INR, 2.0-3.0), for the prevention of stroke and non-CNS systemic embolism in patients with non-valvular atrial fibrillation (AF)<sup>1</sup>
- The trial enrolled 18,113 patients,<sup>1</sup> making it the largest outcomes trial in atrial fibrillation to date<sup>1</sup>
  - Patients in the RE-LY trial were enrolled from 967 centers in 44 countries<sup>1</sup> and all had at least one risk factor for stroke<sup>1</sup>
- The trial included almost equal numbers of anticoagulant naïve (defined as patients who previously had received a total of  $\leq 2$  months of vitamin K antagonist therapy) and vitamin K antagonist (VKA) experienced patients<sup>1</sup> to determine if these two groups of patients differ in their response to treatment (either efficacy or safety)<sup>1</sup>
  - RE-LY enrolled more anticoagulant naïve patients than any previous stroke prevention trial in patients with non-valvular atrial fibrillation<sup>1</sup>

#### Study Design

- RE-LY is a multicenter, prospective, randomized, open-label trial with blinded evaluation of all outcomes (PROBE design)<sup>1</sup> over a minimum follow-up period of one year<sup>1</sup>
  - All investigators, members of the coordinating center, the operations committee, the steering committee, the event adjudication committee and the sponsor were blinded to treatment level analyses of efficacy and safety throughout the study<sup>1</sup>
- Eligible patients were randomized to receive either warfarin or one of two doses of dabigatran (110mg BID or 150mg BID)<sup>1</sup>

#### RE-LY Trial Design<sup>1</sup>



### **Primary Outcome Measure**

- The primary outcome was incidence of stroke (including hemorrhagic) and systemic embolism<sup>2</sup>

### **Secondary Outcome Measures**

- Secondary outcomes included a composite of:<sup>2</sup>
  - Incidence of stroke (including hemorrhagic), systemic embolism and all death
  - Incidence of stroke (including hemorrhagic), systemic embolism, pulmonary embolism, acute myocardial infarction, and vascular death (including death from bleeding)

### **Safety Endpoints**

- Safety endpoints included:<sup>1</sup>
  - Bleeding events (major and minor)
  - Intracerebral hemorrhage
  - Other intracranial hemorrhage
  - Elevations in liver transaminases, bilirubin and hepatic dysfunction
  - Other adverse events

### **About Dabigatran Etexilate**

- Dabigatran etexilate is a direct thrombin inhibitor (DTI)<sup>3</sup> in a class of oral anticoagulants being studied for the prevention and treatment of acute and chronic thromboembolic diseases, including:
  - Stroke prevention in patients with non-valvular atrial fibrillation<sup>1</sup>
  - Prevention of atherothrombotic events in patients with acute coronary syndrome (ACS)<sup>4</sup>
  - Primary prevention of venous thromboembolism (VTE) in patients undergoing elective total hip and knee replacement surgeries<sup>5,6,7</sup>
  - Secondary prevention of VTE<sup>8</sup>
  - Treatment of acute VTE<sup>9</sup>
- Dabigatran etexilate is not approved by the FDA for use in the United States. Dabigatran etexilate is approved as Pradaxa<sup>®</sup> in 40 countries for the primary prevention of venous thromboembolic events (blood clots) in patients who have undergone elective surgery for total hip or total knee replacement

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1 Ezekowitz M D, et al. “Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulation therapy, warfarin, compared with dabigatran.” *American Heart Journal*. 2009; 157: 805-810.

2 ClinicalTrials.gov. “Randomized Evaluation of Long Term Anticoagulant Therapy (RE-LY) With Dabigatran Etxilate.” <http://clinicaltrials.gov/ct2/show/NCT00262600?term=dabigatran&rank=11>. Accessed: March 11, 2009.

3 Di Nisio, et al. “Direct Thrombin Inhibitors.” *New England Journal of Medicine*. 2005; 353: 1028-40.

4 ClinicalTrials.gov. “RandomizEd Dabigatran Etxilate Dose Finding Study in Patients With Acute Coronary Syndromes Post Index Event With Additional Risk Factors for Cardiovascular Complications Also Receiving Aspirin and Clopidogrel: Multi-Centre, Prospective, Placebo Controlled, Cohort Dose Escalation Study (RE-DEEM).” <http://www.clinicaltrials.gov/ct2/show/NCT00621855?term=dabigatran&rank=11>. Accessed on: January 28, 2009.

5 Eriksson, et al. “Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomized, double-blind, non-inferiority trial.” *The Lancet*. 2007; 370:949-956.

6 The RE-MOBILIZE Writing Committee. Oral Thrombin Inhibitor Dabigatran Etxilate vs North American Enoxaprin Regiment for Prevention of Venous Thromboembolism After Knee Arthroplasty Surgery. *The Journal of Arthroplasty*. 2009; 24: 1-9

7 ClinicalTrials.gov. “A Phase III Randomised, Parallel Group, Double-Blind, Active Controlled Study to Investigate the Efficacy and Safety of Orally Administered 220 mg Dabigatran Etxilate Capsules (110 mg Administered on the Day of Surgery Followed by 220 mg Once Daily) Compared to Subcutaneous 40 mg Enoxaparin OnceDaily for 28-35 Days, in Prevention of Venous Thromboembolism in Patients With Primary Elective Total Hip Arthroplasty Surgery. (RE-NOVATE II).”

8 ClinicalTrials.gov. “A Randomised, Multicenter, Double-Blind, Active Controlled Study to Investigate the Efficacy and Safety of Dabigatran Etxilate, 150 mg b.i.d Administered Orally (Capsules) for 18 Months, Compared to Warfarin Tablets p.r.n. (Target INR) for the Secondary Prevention of Venous Thromboembolism.” <http://www.clinicaltrials.gov/ct2/show/NCT00329238?term=dabigatran&rank=12>. Accessed on: January 28, 2009.

9 ClinicalTrials.gov. “A Phase III, Randomised, Double Blind, Parallel-Group Study of the Efficacy and Safety of Oral Dabigatran Etxilate (150 mg Bid) Compared to Warfarin (INR 2.0-3.0) for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism, Following Initial Treatment (5-10 Days) With a Parenteral Anticoagulant Approved for This Indication.” <http://www.clinicaltrials.gov/ct2/show/NCT00680186?term=dabigatran&rank=5>. Accessed on: January 28, 2009.