Supplementary Material to van Es et al. “Edoxaban for treatment of venous thromboembolism in patients with cancer. Rationale and design of the Hokusai VTE-cancer study” (Thromb Haemost 2015; 114.6)

Suppl. Table 1: Stratification

1. Bleeding risk (assessed at time of randomization)
   • surgery within 2 weeks prior to randomization
   • use of antiplatelet agents (e.g., aspirin ≤ 100 mg/day) that will continue during the study
   • brain tumour or brain metastases present at the time of randomization
   • metastatic disease present at the time of randomization
   • regionally advanced cancer present at the time of randomization
   • gastrointestinal cancer at randomization or diagnosed within a 6-month period prior to randomization
   • urothelial cancer at randomization or diagnosed within a 6-month period prior to randomization
   • bevacizumab use at randomization or given within the 6-week period prior to randomization

2. Need for dose adjustment
   • body weight ≤ 60 kg, or
   • creatinine clearance between 30 and 50 mL/min inclusive, or
   • concomitant use of P-glycoprotein inhibitors

Suppl. Table 2. Exclusion criteria

1. Thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent to treat the current (index) episode of DVT and/or PE;
2. More than 72 hours pre-treatment with therapeutic dosages of anticoagulant treatment (LMWH, unfractionated heparin, and fondaparinux per local labelling), DOAC, or VKA prior to randomization to treat the current (index) episode;
3. Treatment with therapeutic doses of an anticoagulant other than that used for pre-treatment
of the current (index) VTE episode prior to randomization;

4. Active bleeding or any contraindication for treatment with LMWH/dalteparin or edoxaban;

5. Indication for dalteparin other than DVT and/or PE;

6. An Eastern Cooperative Oncology Group (ECOG) Performance Status of 3 or 4 at the time of randomization;

7. Calculated creatinine clearance < 30 mL/min;

8. History of heparin associated thrombocytopenia;

9. Acute hepatitis, chronic active hepatitis, liver cirrhosis;

10. Hepatocellular injury with concurrent transaminase (alanine transaminase [ALT]/aspartate transaminase [AST] > 3 × upper limit of normal [ULN]) and bilirubin (> 2 × ULN) elevations in the absence of a clinical explanation;

11. Life expectancy < 3 months;

12. Platelet count < 50,000/mL;

13. Uncontrolled hypertension as judged by the Investigator (e.g., systolic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg despite antihypertensive treatment);

14. Women of childbearing potential without proper contraceptive measures, and women who are pregnant or breast feeding;

15. Chronic treatment with non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) including both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) inhibitors for ≥ 4 days/week anticipated to continue during the study;

16. Treatment with aspirin in a dosage of more than 100 mg/per day or dual antiplatelet therapy (any 2 antiplatelet agents including aspirin plus any other oral or intravenous antiplatelet drug) anticipated to continue during the study;

17. Treatment with the P-glycoprotein inhibitors ritonavir, nelfinavir, indinavir, or saquinavir anticipated to continue during the study;

18. Systemic use of the P-glycoprotein inhibitors ketoconazole, itraconazole, erythromycin, azithromycin or clarithromycin at the time of randomization; subsequent use is permitted;

19. Subjects with any condition that as judged by the Investigator would place the subject at increased risk of harm if he/she participated in the study.