Report Synopsis of Study

"Safety and Efficacy of Low Molecular Weight Heparin for 72 Hours Followed by Dabigatran for the Treatment of Acute Intermediate-Risk Pulmonary Embolism – PEITHO-2"

EudraCT-Nr.: 2015-001830-12

Vorlage-Nr.: 4040790

1) **Name of Sponsor/Company:** University Medical Center of the Johannes Gutenberg-University Mainz represented by the Executive Board of the University, represented by the scientific member of the Executive Board, Univ.-Prof. Dr. U. Förstermann	4) **Individual Study Table Referring to Part of the Dossier:** na[1] Volume: na Page: na	*(For National Authority Use only)*
2) **Name of Finished Product:** **Pradaxa®**		
3) **Name of Active Substance:** **Dabigatran**		

5) **Title of Study[2]:**

"Safety and Efficacy of Low Molecular Weight Heparin for 72 Hours Followed by Dabigatran for the Treatment of Acute Intermediate-Risk Pulmonary Embolism – PEITHO-2"

„Sicherheit und Wirksamkeit von niedermolekularem Heparin über mindestens 72 Stunden, gefolgt von Dabigatran zur Behandlung der akuten Lungenembolie mit intermediärem Risiko – PEITHO-2"

Protocol history:

A) GLOBAL PROTOCOL, latest version: **V3.0 incl. Amendment 2.0, 15.01.2018**

→ Amendments/changes from previous versions:

Protocol version, date	Amendments/changes from previous version
1.1, 16.09.2015	n.a.
2.1 incl **Amendment 1.1** 15.06.2016	Pg 4/5 <u>Synopsis updated</u> Reason: To align wording with the protocol text Pg 9 Examples for adverse events were deleted from the schedule and are illustrated now as footnote 2 Reason: The additional listing of examples of adverse events was confusing. Pg 15 **3** Study Design, 2nd Paragraph: Adapted to a two-step identification of the eligible population: first diagnosis of acute PE and then confirmation of intermediate risk Reason: Adaptation to guidelines and clinical practice, also allowing more time for eligibility checks **3** Study Design, 3rd Paragraph: a time window of +12 hours was added Reason: See pg 19 Pg 16 **3.1** Study duration and schedule updated Reason: Duration of study is 7 months per patient and recruitment time is approximately 2.5 years. Pg 17 **4.2** Inclusion criterion no. 4: Deletion of the sPESI (score ≥ 1) as part of the assessment of risk classification Reason: The "hard criteria", imaging and/or biomarker findings, are considered reliable tools for identification of intermediate risk independently from the sPESI score; in fact, it was recently reported that a number of patients with intermediate risk based on their imaging or biomarker parameters might have been misclassified to low-risk PE because of a sPESI of 0. Thus, the inclusion criteria of the present study are now exclusively based on the "hard" imaging and/or biochemical parameters. Pg 18 **4.3** Exclusion criterion no. 2: Period of contraception corrected Reason: The period of contraception is from trial start until one month after the last application

[1] This information is only required in connection with filing of a dossier for marketing authorization.

[2] The latest protocol version must be clearly stated, this means including all amendments – the amendments are to be declared and identified.

		of the trial drug, that is, until the "end of trial visit" and not one month after the end of the trial.
		4.3 Exclusion criterion no. 7: Deleted Reason: This criterion unintentionally excluded patients who, based on clinical suspicion and according to guideline recommendations in case of intermediate or high pre-test clinical probability of PE, were put on anticoagulation before the definitive diagnosis of acute PE. Chronic anticoagulation remains an exclusion criterion, but this is covered by Exclusion criterion 8.
		4.3 Exclusion criterion no. 8: Replacement of index PE episode with VTE Reason: Replaced to include not only PE but also deep vein thrombosis as an indication for chronic therapeutic anticoagulation.
	Pg 19	**5.1.4** Dosage schedule: It is now clearly stated that the switch from LMWH to dabigatran must be attempted 72 hours after confirmation of the PE diagnosis. A time window of +12 hours was added. Reason: Since a sequential approach to the diagnosis of, first acute PE and then intermediate risk is specified, it must be made clear that the 72 hours count from PE diagnosis (and not from the confirmation of intermediate risk). In addition, for administrative, "practical" reasons, that is, if the 72-hour time point is reached, for example, in the middle of the night when switch to an oral drug is impractical and undesirable, a time window of up to 12 hours has been added.
	Pg 21	**6.1** Study flow updated Reason: To align the schedule with the amended sections
	Pg 22	**6.2.2** Switch to oral anticoagulation (dabigatran) therapy (Visit 2): A time window of +12 hours was added. Reason: See pg 19
	Pg 23	**6.2.5** Follow-up after 6 months (Visit 5) Added: Hand-out of pregnancy test for home testing prior to Visit 6 Reason: Visit 6 may be a telephone contact
	Pg 23	**6.2.6** End of study visit (Visit 6) updated Reason: Completed with detailed information of the time of the visit; it must be assured that women of child bearing age has had a pregnancy test after completion of test drug treatment
	Pg 28	**6.4.9** Safety evaluation and reporting by Sponsor, 5th Paragraph updated Reason: To align the timeline for CEC adjudication with the updated study duration
	Pg 31	**7.2.3** Analysis of safety outcomes updated Reason: To align the time of safety outcomes with the foreseen visits VTE-BLEED score was added. Reason: To use data that are gathered as part of this study for validation of the VTE-BLEED score in a specified population
	Pg 31	**7.2.4** Analysis of subgroups: sPESI score at baseline was added as a subgroup definition. Reason: To test if an increased sPESI score in this population predicts the treatment outcome
3.0, incl **Amendment 2.0** 15.01.2018	Title pg	Change of representative of "Operating Institutions of Sponsor" incl. adjustment of contact details Change of head of Interdisciplinary Center for Clinical Trials (IZKS) incl. adjustment of contact details Change of contact details of study statistician and insertion of additional statistician Irene Schmidtmann incl. contact details Reason: Editorial amendments incl. rearrangements
	Pg 6	Synopsis updated Reason: To align wording with the protocol text
	Pg 15	**1.3** Risk-benefit assessment, 4th paragraph Change of follow-up period from 30 days to 6 months Reason: Correction of typographical errors Correction of p for the rejection of H_0 from >6.1 to >0.061. Reason: Correction of typographical errors Inclusion of additional possible DSMB recommendations after completion of first interim analysis Reason: Interim results may suggest that a reduced sample size is sufficient for rejection of H_0.
	Pg 17	**2.5** Safety outcomes 7 months added Reason: To align the time for safety outcomes with the foreseen visits and analysis of safety outcomes
	Pg 17	**3.0** Study design, 2nd paragraph Precision of procedure of enrolment Reason: Adaption to guidelines and clinical practice

Pg 19	**4.3** Exclusion criteria No. 4 corrected for interventional clinical trials Reason: This criterion unintentionally also excluded patients participating in non-interventional clinical trials (e.g. registries).
Pg 22	**5.1.8** Packaging and labelling Correction of the name of the university where the trial medication is packed. Reason: Editorial amendment
Pg 22	**5.1.9** Drug storage, supplies and accountability, 2nd paragraph Linguistic improvements and deletion of storage of the trial medication at room temperature. Reason: There is no storage temperature limit according to the manufacturer´s manual or SmPC.
Pg 23	**6.1** Study flow updated Reason: To align the schedule with the amended sections
Pg 24	**6.2.1** Enrolment (Visit 1) sPESI score: Exchange of reference No. 31 versus 34 Reason: To align reference with the updated reference list
Pg 31	**7.1** Sample size calculation Recalculation of sample size including rationale. The sample size was confirmed by the addition of further data. Reason: Consideration of recently published data allowing for more solid justification of the calculated sample size
Pg 34	**7.2.4** Analysis of subgroups 6th indent: Addition of reference No. 32 Reason: To align with amended reference list
Pg 34	**7.2.5** Interim analysis Change of follow-up period from 30 days to 6 months Reason: Correction of typographical errors Correction of p for the rejection of H_0 from >6.1 to >0.061 Reason: Correction of typographical errors Inclusion of additional possible DSMB recommendations after completion of first interim analysis Reason: Interim results may suggest that a reduced sample size is sufficient for rejection of H_0.
Pg 39	**12** Signatures Change of contact details of study statistician and insertion of additional statistician Irene Schmidtmann Deletion of head of Interdisciplinary Center for Clinical Trials (IZKS) from signature page Reason: Editorial amendments
Pg 42	**14** References Addition of recent references

B) NATIONAL AMENDMENTS and COUNTRY-SPECIFIC VERSIONS for **ROMANIA, FRANCE, and GERMANY** as follows:

- **ROMANIA**, country-specific addendum integrated into global protocol version 2.1 incl. amendment 1.1:

1. Addendum to paragraph 4.3 of protocol: "<u>Exclusion criteria</u>"

In addition to the exclusion criteria 1) – 14) in the protocol, the <u>contraindications</u> and <u>special warnings and precautions for use</u> listed in the Pradaxa® SmPC must be respected:

<u>4.3 Contraindications</u>

- Hypersensitivity to the active substance or to any of the excipients
- Patients with severe renal impairment (CrCL < 30 mL/min)
- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulants e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin, rivaroxaban, apixaban etc) except under specific circumstances of switching anticoagulant therapy or when UFH is given at doses necessary to maintain an open central venous or arterial catheter
- Hepatic impairment or liver disease expected to have any impact on survival
- Concomitant treatment with systemic ketoconazole, cyclosporine, itraconazole and dronedarone
- Prosthetic heart valves requiring anticoagulant treatment.

4.4 Special warnings and precautions for use

Pharmacodynamic and kinetic factors
Age ≥ 75 years

Factors increasing plasma levels
Moderate renal impairment (30-50 mL/min CrCL
P-gp inhibitor co-medication (some P-gp inhibitors are contraindicated
Low body weight (< 50 kg)

Pharmacodynamic interactions
ASA,NSAID, Clopidogrel, SSRIs or SNRIs
Other drugs which may impair haemostasis

Disease & procedures with special haemorrhagic risks
Congenital or acquired coagulation disorders
Thrombocytopenia or functional platelet defects
Recent biopsy, major trauma
Bacterial endocarditis
Esophagitis, gastritis or gastroesophageal reflux

2. Addendum to paragraph 4.4 of protocol: "Withdrawal of subjects":

Examples of bullet 4: "Significant adverse events ….." that require withdrawal of a patient are severe bleeding, acute renal failure,.pregnancy

3. Addendum to paragraph 4. of protocol: New Section "Medicines not allowed during the trial":

Investigational products other than dabigatran during and 3 months prior to study;

Any fibrinolytic agent for the treatment of the index episode of PE;

Long term use of heparin, incl. LMWH (UFH is given at doses necessary to maintain an open central venous or arterial catheter is allowed);

VKA or a NOAC for other indication than VTE;

Antiplatelet agents or ASA > 100mg/day;

Strong inhibitors of P-glycoprotein like ketoconazole, cyclosporin, itraconazole or dronedarone;

Precautions should be taken if the following medicines are prescribed concomitantly: NSAIDs, Clopidogrel, SSRIs or SNRIs, other drugs which may impair haemostasis

4. Addendum to paragraph 6.2 of protocol: "Visit schedule"

Erythrocyte count should be performed at visit 1, 3, 5 and whenever laboratory tests not scheduled per protocol are performed. This is a local safety measure and the results will not be entered into the eCRF

- **ROMANIA**, country-specific amendments based on global versions:

Protocol version, date	Amendments/Changes from global version	
RO1.0, 12.07.2017 (based on global version 2.1 incl. amendment 1.1)	Pg 4-6	Synopsis updated Reason: To align wording with the protocol text
	Pg 17	Inclusion criteria 1) added age < 76 years
	Pg 18	Exclusion criteria 7) reworded to mirror the current SmPC
	Pg 19	Exclusion criteria 11) reworded to align with SmPC Exclusion criteria 13) new: Congenital or acquired coagulation disorders; thrombocytopenia or functional platelet defects; recent biopsy or major trauma, bacterial endocarditis; esophagitis, gastritis or gastroesophageal reflux Section 4.4 Withdrawal of subjects: 4th bullet "Significant adverse events related to therapy" has been completed with ", e.g., severe bleeding, acute renal failure"
	Pg 21	added new section: "5.2. Medicines not allowed during participation in the study" to reiterate the prohibited medication - also listed under exclusion criteria
	Pg 22	added new section: "5.3. Medicines to be taken with caution during participation in the study" to alert the investigator to be careful with such medicines listed under "Precautions" in the SmPC
	Pg 23	6.2 Visit schedule: at every visit with lab. exams, erythrocytes have been added to the list of parameters to be assessed

RO2.0 15.01.2018	This amendment was issued for global reasons. No specific changes for Romania; see global version 3.0 incl. amendment no. 2.0.

- **FRANCE**, country-specific amendments based on global versions:

Protocol version, date	**Amendments/Changes from global version**
FR1.0, 10.10.2017 (based on global version 2.1 incl. amendment 1.1)	Pg 4-7 **Synopsis** updated *Reason: To align wording with the protocol text* Pg 17 **2.5** Safety outcomes: Assessment at month 7 added as per "Schedule of Assessment" *Reason: the text was incomplete compared to study schedule* Pg 20 **4.4** Withdrawal of subjects: 4th bullet: Added that management of patients withdrawn due to (S)AEs must follow local protocols and current guidelines *Reason: Clarification to the management of patients with (serious) adverse events in addition to recommendations given in the SmPC* Pg 22 **5.** TREATMENTS: Added 5.2: Treatment of (serious) adverse events. *Reason: See the entry above to Pg. 20* Pg 30 **6.4.9** Safety evaluation and reporting by Sponsor: Clarification to the rules for reporting of SUSARs to ANSM and CPP Pg 36 **9.9** Early termination of the study: This paragraph has been added. *Reason: Complementary to the stopping rules for safety or futility reasons given in "7.2.5 Interim analysis" a set administrative and GCP-related rules have been added herein*
FR2.0 15.01.2018 (based on global version 3.0 incl. amendment 2.0)	This amendment was issued for global reasons. Specific changes only applicable for France are as follows: Pg. 7: Synopsis: Study duration and dates Reason: Clarification of treatment vs. study duration Pg. 34/35: **6.4.9** Safety evaluation and reporting by Sponsor Reason: To conform with the new regulation in force in France for reporting of SUSARs and other safety-related information.

- **GERMANY**, country-specific amendment based on global version 3.0 incl. amendment 2.0 as required by German competent authority:

Protocol version, date	**Amendments/Changes from global version**
DE3.0, 05.06.2018 (based on global version 3.0 incl. amendment 2.0)	Title pg Indication of country-specific versioning *Reason: Editorial amendments due to protocol amendment* Pg 18 **3.0** Study design, 2nd paragraph Precision of enrolment procedure with regard to the choice of parenteral anticoagulants for the initial treatment. Reference to SmPC links in appendix I. *Reason: Adaption to guidelines and clinical practice* Pg 41 **12** Signatures Deletion of French Principal Investigator Prof. G. Meyer, MD, from signature page *Reason: Editorial amendments due to German-specific amendment* Deletion of Trial Statistician Prof. H. Binder, PhD, from signature page *Reason: Prof. Binder is no longer involved in the trial. Dr. I. Schmidtmann, PhD is the responsible Trial Statistician.* Pg 45 Introduction of additional section: **15** APPENDICES 15.1 Appendix I: Summaries of Product Characteristics (GER: Fachinformationen) for parenteral anticoagulants approved for the initial therapy of acute PE *Reason: Adaption to guidelines and clinical practice*

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8) **Publication (reference):** EURHEARTJ-D-21-00191 (in review)

9) **Studied period (years)[3]:**	10) **Phase of development:** IV
Date of first enrolment: 29.01.2016 Date of last completed: 12.02.2020	

11) **Objectives:**

The primary objective is to determine whether treatment of acute intermediate-risk PE (as defined by the inclusion and exclusion criteria) with parenteral anticoagulation for at least 72 hours after diagnosis, followed by dabigatran over 6 months, is effective and safe.

The secondary objectives are to assess 1) the safety of the studied treatment regimen and 2), the recovery of right ventricular function at 6±1 days after PE-diagnosis or upon discharge, assessed by serial echocardiograms, and to evaluate its importance for the 6-month prognosis of patients with intermediate-risk PE.

12) **Methodology:**

Clinical phase IV, prospective, multicenter, multinational, interventional, single-arm (management) trial

Patients with intermediate-risk PE confirmed within 24 hours of diagnosis of acute PE and fulfilling all of the inclusion and none of the exclusion criteria were enrolled in the study within 24 hours of confirmation of intermediate risk after providing written informed consent.

Enrolled patients continued to receive low-molecular weight heparin (LMWH) at therapeutic dosage. Patients initially treated with unfractionated heparin or fondaparinux were switched to LMWH after enrollment. After completing 72 hours of therapeutic anticoagulation and following a clinical assessment of the patient's condition, LMWH was discontinued and the first dose of dabigatran was administered two hours or less before the time that the next subcutaneous dosage of LMWH would have been due.

Following the switch from LMWH to oral anticoagulation, the day of hospital discharge was decided on by the treating investigator based on his/her clinical judgment of the patient's condition and local practice. Oral anticoagulation with dabigatran was continued for 6 months. The duration and pharmacological substance of anticoagulation treatment after the 6-month period was at the discretion of the treating investigator and in accordance with current guidelines and the patient's preference.

[3] Here also study suspensions and premature terminations of a trial/premature conclusion of a trial should be listed, including the reasons for that.

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13) **Number of patients (planned and analyzed):**

In total, n = 700 patients were planned to be enrolled in the study

In total, 402 patients were enrolled and analysed.

Reasoning for early recruitment stop: As specified by the study protocol, an interim analysis (IA) was performed after treatment end of the first 140 study patients (20% of the aimed patient number). The incidence rate of the primary endpoint as well as those of important secondary and safety endpoints remained below assumed rates and did not raise concerns about the efficacy or safety of the investigated anticoagulation strategy as compared to "standard" anticoagulation of intermediate-risk pulmonary embolism, respectively. Thus, based on the results of the IA and in consultation with the Data Safety Monitoring Board of the study (DSMB), enrolment was prematurely terminated for the following reasons:

1. Recruitment issues, which would have resulted in a both ethically and financially unacceptably long entire study duration.
2. In addition, the contract termination and the associated cessation of further financial support of the study by the marketing authorization holder of the investigational medicinal product, Boehringer Ingelheim, did not allow for continuation of the study as initially planned.

14) **Diagnosis and main criteria for inclusion:**

Diagnosis: Acute intermediate-risk pulmonary embolism (PE)

Inclusion criteria:

1) Age ≥18 years;
2) Objectively confirmed diagnosis of acute PE by multidetector CT angiography, ventilation/perfusion lung scan, or selective invasive pulmonary angiography, according to established diagnostic criteria, with or without symptomatic deep vein thrombosis (3);
3) Absence of hemodynamic collapse, or decompensation, at presentation;
   Hemodynamic collapse or decompensation is defined as (23):
   - need for cardiopulmonary resuscitation; or
   - systolic BP <90 mm Hg for ≥15 min or drop by ≥40 mm Hg for at least 15 min with end organ hypoperfusion (cold extremities, urinary output <30 ml/h, mental confusion); or
   - need for catecholamines to maintain adequate organ perfusion and a systolic BP of >90 mmHg);
4) Intermediate-risk category of PE severity indicated by the presence of *at least one* of the following a, b, or c criteria:
   a) At least one sign of RV pressure overload/dysfunction on CT angiography or echocardiography (8,23):

      a1) on CT angiography, RV pressure overload/dysfunction is defined as RV/LV end-diastolic diameter ratio >1.0; *or*

      a2) on echocardiography, RV pressure overload/dysfunction is defined by the presence of at least one of the following findings:
      - RV/LV end-diastolic diameter ratio >1.0 (apical or subcostal 4-chamber view);
      - RV end-diastolic diameter >30 mm (parasternal long-axis or short-axis view);
      - RV free wall hypokinesis (any view);
      - Tricuspid regurgitant velocity >2.6 m/s from the apical or subcostal 4-chamber view, or the parasternal short-axis view;
      - Absence of inspiratory collapse of the inferior vena cava.

   b) Signs of myocardial injury as indicated by elevated troponin levels:
      - *Troponin elevation* is defined as an abnormal result of any validated troponin test based on the reference values determined by the local Department of Clinical Chemistry at each participating site;
   c) Signs of (RV) failure as indicated by NT-proBNP levels >600 pg/ml at baseline.
5) Ability of the subject to understand the character and individual consequences of the clinical trial; signed and dated informed consent of the subject available before the start of any specific trial procedures.

Exclusion criteria

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1) Pregnancy (a negative serum or urine pregnancy test should be available for women of child-bearing potential before study inclusion) or lactation;
2) Women of childbearing potential who do not practice a medically accepted highly effective contraception during the trial. Highly effective contraception methods are:
   a. combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
      - oral
      - intravaginal
      - transdermal
   b. progestogen-only hormonal contraception associated with inhibition of ovulation:
      - oral
      - injectable
      - implantable
   c. intrauterine device (IUD)
   d. intrauterine hormone-releasing system (IUS)
   e. bilateral tubal occlusion
   f. vasectomized partner
   g. sexual abstinence
3) History of hypersensitivity to the investigational medicinal product or to any drug with similar chemical structure or to any excipient present in the pharmaceutical form of the investigational medicinal product;
4) Participation in another interventional clinical trial during the present clinical trial or within the last three months;
5) Medical or psychological condition that would not permit completion of the trial or signing of informed consent;
6) Use of a fibrinolytic agent, surgical thrombectomy, interventional (catheter-directed) thrombus aspiration or lysis, or use of a cava filter to treat the index episode of PE;
7) Need for long-term treatment with a low molecular weight heparin, vitamin K antagonists or NOAC, for an indication other than VTE, or for antiplatelet agents except acetylsalicylic acid at a dosage ≤100 mg/day;
8) Active bleeding or known significant bleeding risk (e.g., gastrointestinal ulcer, malignant neoplasms, injuries or recent surgeries of the brain, spinal cord or eyes, recent intracranial bleedings, known or suspected esophagus varices, aneurysms or intraspinal or intracranial vascular abnormalities);
9) Artificial heart valves requiring treatment with an anticoagulant
10) Renal insufficiency with estimated creatinine clearance <30 ml/min/1.73m^2;
11) Chronic liver disease with aminotransferase levels two times or more above the local upper limit of normal range;
12) Concomitant administration of strong inhibitors of P-glycoprotein like ketoconazole, cyclosporin, itraconazole or dronedarone;
13) Unwillingness or inability to adhere to treatment or to the follow-up visits;
14) Life expectancy less than 6 months.

15) **Test product, dose and mode of administration, batch number:**

- Pradaxa® (Dabigatran), 150 mg, hard capsules

  Manufacturer's batch numbers: 503376, 607042, 801223, 804018, 804747

or

- Pradaxa® (Dabigatran), 110 mg, hard capsules

  Manufacturer's batch numbers: 502928, 606259, 708189, 806421

16) **Duration of treatment:** Once daily for 6 months

17) **Reference therapy, dose and mode of administration, batch number:** na

18) **Criteria for evaluation[4]:**

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH

Report Synopsis of Study

"Safety and Efficacy of Low Molecular Weight Heparin for 72 Hours Followed by Dabigatran for the Treatment of Acute Intermediate-Risk Pulmonary Embolism – PEITHO-2"

EudraCT-Nr.: 2015-001830-12

Vorlage-Nr.: 4040790

Efficacy:

The primary efficacy outcome was symptomatic VTE or PE-related death within the first 6 months of anticoagulation therapy.

The secondary efficacy outcomes were as follows:

1) Recovery of RV function at 6±1 days or upon discharge (whichever comes first) and at 6-month follow-up, as assessed by echocardiography; RV recovery is defined as:
   (i) complete recovery: normalization of all echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria;
   (ii) partial recovery: normalization of some echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria, but at least one sign remaining;
   (iii) no recovery: all echocardiographic signs of RV pressure overload/dysfunction as defined by the inclusion criteria established at baseline, are still present;
   (iv) deterioration: appearance of additional signs of RV pressure overload/dysfunction during follow-up as defined by the inclusion criteria to those established at baseline;
2) Temporal pattern of changes in NT-proBNP levels during follow-up (measurement at baseline, 6±1 days or at discharge, and at 6 months)
   (i) normalization: NT-proBNP levels below the age and gender dependent normal threshold at follow-up;
   (ii) improvement: NT-proBNP levels >600 pg/ml at baseline that have decreased to ≤600 pg/ml but are still above the age and gender dependent normal threshold at follow-up;
   (iii) no improvement: NT-proBNP levels ≤600 pg/ml but still above the age and gender dependent normal threshold at all three measurements; or NT-proBNP levels >600 pg/ml at follow-up;
   (iv) deterioration: normal NT-proBNP levels at baseline but abnormal during follow-up; or baseline NT-proBNP levels ≤600 pg/ml, but above the age and gender dependent normal threshold, that increase to >600 pg/ml during follow-up;
3) Death from any cause, or hemodynamic collapse or decompensation, within the first 30 days;
4) PE-related death, or PE-related or hemodynamic collapse or decompensation, within the first 30 days;
   Hemodynamic collapse or decompensation is defined as:
   (i) need for cardiopulmonary resuscitation; or
   (ii) systolic BP <90 mm Hg for ≥15 min or drop by ≥40 mm Hg for at least 15 min with end organ hypoperfusion (cold extremities, urinary output <30 ml/h, mental confusion); or
   (iii) need for catecholamines to maintain adequate organ perfusion and a systolic BP of >90 mm Hg;
4) Overall duration of hospital stay (index event and repeated hospitalizations due to PE [index or recurrent event] or to a bleeding event) within 6 months;
5) Death from any cause within 6 months.

Safety:

1) Major bleeding, based on the International Society of Thrombosis and Haemostasis (ISTH) definition, during initial parenteral heparin anticoagulation, at 6 months and at 7 months; *ISTH major bleeding* is defined as any bleeding resulting in death; symptomatic bleeding in a critical organ including intracranial, intraspinal, intraocular, retroperitoneal, intraarticular and pericardial bleeding and muscle bleeding resulting in compartment syndrome; symptomatic bleeding resulting in a decrease in the hemoglobin concentration of at least 2g/dl or resulting in the transfusion of at least two packs of blood red cells;

2) Clinically relevant bleeding, defined as a composite of major or clinically relevant non-major bleeding, during initial parenteral heparin anticoagulation, at 6 months and at 7 months; *Clinically relevant non-major bleeding* is defined as bleeding fulfilling at least one of the following criteria: spontaneous skin hematoma of at least 25 cm^2; spontaneous nose bleeding of more than 5 minutes duration; macroscopic hematuria, either spontaneous or, if associated with intervention, lasting more than 24 hours; spontaneous rectal bleeding; gingival bleeding for more than 5 minutes; bleeding leading to hospitalization and/or requiring surgical treatment; bleeding leading to transfusion of less than 2 units of whole blood or red cells; any other bleeding event considered clinically relevant by the investigator.

3) Serious adverse events (SAE) within 72 hours, 30 days, 6 months and 7 months.

19) **Statistical methods:**

The primary outcome of this trial was whether symptomatic VTE or PE-related death occurs within the first 6 months of anticoagulation therapy (yes/no). The sample size calculation was based on the expected 6-month incidence of the primary outcome. This was estimated to be at least 3.0%, the incidence observed in the subgroup of patients with acute 'intermediate-risk' PE (right ventricular to left ventricular diameter ratio ≥ 0.9 on imaging, or N-terminal pro-brain natriuretic peptide (NT-proBNP) concentration ≥ 500 pg/mL) treated with the NOAC edoxaban in the Hokusai-VTE study (Brekelmans et al., Lancet

E3, section 9.6 (only if the study was approved after June 14th, 2017).

Haematol 2016;3(9):e437-45). Our more conservative point estimate was set at 3.3% (probability [π1] = 0.033), assuming that a significant proportion of the patients to be enrolled in PEITHO-2 would have intermediate-high-risk PE,1 i.e. both signs of RV dysfunction and biomarker elevation, and might thus be more seriously ill than the reported subgroup of patients in Hokusai-VTE. Available data from prospective cohort studies (summarised in Becattini et al., Eur Respir J 2016; 48(3):780-6) as well as data from the RECOVER and RECOVER II dabigatran trials (Goldhaber et al., Thromb Haemost 2016;116(4):714-21) pointed to 6.1% (π0 = 0.061) as the highest expected probability of the primary outcome in PEITHO-2. Accordingly, we tested the null hypothesis (H0; π ≥ 0.061; 6.1%) against the alternative hypothesis (H1; π < 0.061), using a one-sided exact binomial test in a two stage Pocock group sequential design, with interim analysis after enrolment and completed follow-up of 20% of the patients. The significance level was chosen as α = 5%, leading to a nominal α = 0.003037 at the first stage. It was calculated that 650 patients would provide a power of 90% for rejecting H0 at the final stage, if the true 6-month incidence of the primary outcome were indeed π = π1 = 0.033. Taking into account possible dropouts, we planned to include 700 patients.

A predefined interim analysis was performed after inclusion and completed 6-month follow-up of the first 140 enrolled patients. The observed 6-month incidence of the primary outcome was 2.86% (4 events), and thus, lower than the initially expected incidence of 3.3%; in addition, no safety concerns were raised. Based on (i) the results of the interim analysis, and (ii) the fact that enrolment was slower than anticipated, the independent data and safety monitoring board (DSMB) recommended recalculation of the sample size. Revising the point estimate to a more optimistic 3.0% (π1* = 0.03) based on the interim analysis, and accepting a conditional power (CP) between 80 and 90%, yielded a total sample size of 398 patients and a CP (π1*) of 0.8247. The DSMB reviewed this information and, taking into account that 344 patients had already been enrolled by that date, recommended continuation of the trial until the inclusion of 400 patients.

Analyses were performed in the intention-to-treat (ITT) population. Categorical variables are presented as frequencies and corresponding 95% confidence intervals (95% CI); continuous variables, with medians and the corresponding interquartile range (IQR). Subgroups were analyzed with regard to the primary outcome; death or haemodynamic collapse/decompensation (PE-related, or from any cause) within the first 30 days; overall duration of the hospital stay for the index event; subsequent rehospitalization because of VTE recurrence or bleeding complications within 6 months; death from any cause within 6 months; and serious adverse events within 6 months. In addition, the incidence of major and clinically relevant non-major bleeding during the 6-month follow-up period was calculated. Incidence of efficacy and safety outcomes was calculated separately for patients with intermediate-high- and intermediate-low-risk-PE.

20) **Summary – Conclusions[5]:**

Efficacy results: The primary outcome, symptomatic VTE or death from a PE-related cause during the 6-month follow-up, occurred in 7 of 402 patients included in the ITT analysis (1.7%, upper bound of right-sided 95% CI 3.2%), permitting rejection of the null hypothesis with a P-value of 0.000022. Two patients died of PE 6 and 66 days after the index event, respectively, and five patients suffered non-fatal recurrent VTE. All but one primary efficacy outcome occurred after switching to dabigatran, and all events occurred in patients with intermediate-high-risk PE. Accordingly, the 6-month incidence of the primary outcome in patients with intermediate high-risk PE was 2.5% (upper bound of right-sided 95% CI 4.6%). Two of the patients who suffered a (non-fatal) primary outcome, 9 and 150 days after enrolment respectively, had presented with a sPESI of 0.

Secondary efficacy and safety results: PE-related death or haemodynamic collapse/decompensation occurred within the first 30 days in 0.7%. The 30-day incidence was 1.1% among patients with intermediate-high-risk PE; no patient with intermediate-low-risk PE suffered early PE-related death or haemodynamic collapse. Death from any cause or haemodynamic collapse/decompensation within the first 30 days occurred in 1.2%; the 30 day incidence was 1.4% among patients with intermediate-high-risk PE, whereas, again, no patient with intermediate-low risk PE suffered early death from any cause or haemodynamic collapse.

The 6-month incidence of major bleeding events was 2.7% (95% CI 1.4-4.8%), and that of non-major clinically relevant bleeding 4.0% (95% CI 2.3-6.4%). One patient suffered a fatal bleeding event; this was intracranial haemorrhage, which occurred before switch to dabigatran.

A total of 16 patients were re-admitted to the hospital due to VTE recurrence or bleeding complications during the follow-up period; the median duration of rehospitalization was 8 (IQR 5.5-12) days.

Recovery of RV function: At 6-day echocardiographic follow-up, 40 patients (10%) hat complete recovery of RV function, whereas 171 (14.2%) had incomplete recovery and 135 (33.6%) had no recovery; data were missing in 56 (13.9%) patients. At 6-month echocardiographic follow-up, 57 patients (14.2%) hat complete recovery of RV function, whereas 177 (44%) had incomplete recovery and 113 (28.1%) had no recovery; data were missing in 55 (13.7%) patients. It is planned to repeat these analyses after verification of the source data, i.e. the originally measured parameters of the echocardiographic examinations.

Conclusion: The present prospective multinational trial focusing on patients with intermediate-risk PE found that a management strategy of early switch from heparin to dabigatran upon rigorous clinical assessment of stabilization at 72 hours was both

[5] Results should also summarize important deviations from the predefined quality tolerance limits and remedial actions taken (only if the study was approved after June 14th, 2017).

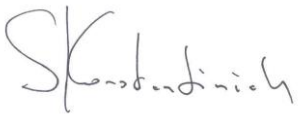
effective and safe.

Our results help to close existing gaps in evidence concerning the initial anticoagulation treatment of patients at elevated risk of early complications. They also support the clinical relevance of identifying patients with intermediate-high-risk PE, presenting both with signs of RV dysfunction and with elevated cardiac troponin levels, as this patient group may need closer early monitoring and long-term follow-up to prevent a complicated course. The knowledge obtained from the present study aids in fine-tuning future recommendations on the risk-adjusted management of acute pulmonary embolism.

I hereby confirm, that the data in the results report were collected properly and are correct.

21) **Date of the report:** 21.01.2021

Print Name: Prof. Dr. med. Stavros Konstantinides

Signature: 

Print Name: Dr. rer. nat. Dorothea Becker

Signature: