Report Synopsis of Study

„Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban: Prospective Management Trial – HoT-PE“

EudraCT-Nr.: 2013-001657-28

Vorlage-Nr.: 01

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:** **Xarelto®**		
3) **Name of Active Substance:** **Rivaroxaban**		

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

„Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban: Prospective Management Trial – HoT-PE“

„Ambulante Behandlung von Patienten mit risikoarmer Lungenembolie mit dem oralen Faktor Xa-Inhibitor Rivaroxaban: Prospektive Management-Studie“

Protocol history:

A) GLOBAL PROTOCOL, latest version: **V3.0 incl. Amendment 2.0, 09.11.2015**

→ Amendments/changes from previous versions:

Protocol version, date	Amendments/changes from previous version
1.0, 20.09.2013	na
1.1, 12.12.2013	Pg 3 Synopsis updated Reason: To align wording with the protocol text Pg 17 Inclusion Criteria - Additional Criterion no. 6: Absence of right ventricular (RV) enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle, detected by echocardiography or on computed tomography. [with definitions] Exclusion Criteria – Removal of Criterion no. 6: Right ventricular (RV) enlargement or dysfunction, or free floating thrombi in the right atrium or right ventricle, detected by echocardiography or on computed tomography. *Reason: To emphasize that right ventricular function must be properly assessed by either CT or echocardiography* Pg 39 9.2 Data collection: … patient administered questionnaires ……. Data from these latter questionnaires are entered into the clinical data base by authorized staff at the ~~study sites~~ **Center for Thrombosis and Hemostasis in Mainz**. *Reason: A more safe and streamlined process has been agreed upon to assure that this data is being collected.*

[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.

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„Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban: Prospective Management Trial – HoT-PE“

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1.2, 07.01.2014	Pg 3	Synopsis updated *Reason: To align wording with the protocol text*
	Pg 17	Inclusion Criterion no. 4: Acceptable method of contraception for fertile women updated to not recommend the use of hormone-based contraceptives and to request the performance of a pregnancy test in case menstruation is delayed during therapy. *Reason: hormonal contraception is not suitable for women with a history of DVT / PE*
	Pg 18	Exclusion Criterion no. 14: specified that GFR should be calculated by the MDRD formula *Reason: To assure that the calculation of GFR is done in the same manner across all study sites*
	Pg 20	4.1.4. Dosage schedule: specified that GFR should be calculated by the MDRD formula
	Pg 22	5. TRIAL SCHEDULE, Visit 1: added that female subjects of childbearing potential must perform a pregnancy test in case of delayed menstruation in the treatment period
	Pg 50	Appendix 3: New, displaying the MDRD formula
2.0 incl. **Amendment 1**, 24.06.2014	Pg 3	Synopsis updated *Reason: To align wording with the protocol text.*
	Pg 7	Trial Schedule, Visit 2: Time window re-specified to say Day 7-11 *Reason: To allow for scheduling of telephone interviews around weekends and bank holidays*
	Pg 18	3.6.2 Exclusion criterion no. 6: Rewording of text on limits for pre-treatment of index episode with anticoagulants 3.6.2 Exclusion criterion no. 7: Rewording of text on concurrent anticoagulation treatment for previous indications *Reason: Previous text was confusing, partly incorrect and difficult to interpret at study sites.*
	Pg 20	4.1.4 Dosage Schedule, 1st Para.: Rewording of text to align with the changes in Excl. Criteria 6 and 7
3.0 incl. **Amendment 2**, 09.11.2015	Pg 4	Synopsis updated *Reason: To align wording with the revised inclusion criteria in the protocol text as specified below.* Number of sites has been changed to 40-50 not only in Germany but in Europe. *Reason: The recruitment rate in Germany remain very stable, indicating that an increase in recruitment rate is not possible among German sites.*
	Pg 8	Trial Schedule: - The Computer Assisted Telephone Interview (CATI) is done with patients recruited at German sites only. In other countries, a structured telephone call to the patients will be made by the respective study group. *Reason: An operational computerized system is not available in the foreseen non-German countries. The contact with patients will be ensured by phone calls by the site's study team* - Utilization of health care resources will be assesed in German patients only. *Reason: There is no good model available to compare or co-analyze health costs across national health care systems.*
	Pg 16	Duration of the trial has been changed from 28 to 60 months. *Reason: A lower than anticipated recruitment rate.*
	Pg 18	Inclusion Criterion 6: Absence of right ventricular (RV) enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle on echocardiography or computed tomography. In the amendment, RV dysfunction is absent on echocardiography when both criteria listed below are met: - Right/left ventricular end-diastolic diameter ratio < 0.9 (apical or subcostal 4-chamber view) - No paradoxical motion of the interventricular septum. The remaining echocardiographic criteria have been deleted. *Reason: The previous echocardiographic criteria of RV dysfunction were based on those of a randomized trial on intermediate-risk pulmonary embolism (36). That study had been designed back in 2005. Very recently, The American Society of Echocardiography and the European Society of Cardiovascular Imaging published the updated Recommendations for Cardiac Chamber Quantification in Adults (37). In this recent paper, it is emphasized that "RV linear dimensions and areas may vary widely in the same patient with relatively minor rotations in transducer position." Importantly, the echocardiographic criterion of "RV dysfunction" ´based on RV end diastolic diameter ≤30 mm and/or hypokinesis of the RV free wall no longer appears in the 2015 recommendations. Also, the criterion of tricuspid regurgitant jet velocity ≤2.6 m/s, provides an estimate of pulmonary artery pressure (which may be chronically elevated, and not necessarily due to the acute event), and not of RV function per se; therefore, it is also no longer recommended for this purpose. On the basis of these updated recommendations, all outdated or controversial criteria of RV dysfunction have been deleted and only the "simple" criterion, which has been validated in the most*

		recent pulmonary embolism trials (e.g., 38), i.e. right/left ventricular end-diastolic diameter ratio < 0.9, is kept. This parameter offers the advantage of being easy and fast to obtain and thus “user friendly”; moreover, and, importantly, it corresponds directly to the criterion of RV enlargement/dysfunction on CT angiography.
	Pg 24 ff	The Computer Assisted Telephone Interview (CATI) is done in Germany by a specialized team in Mainz, in other countries, a structured telephone contact is made by the respective study teams at the sites. *Reason: A useful computerized system is not available in the foreseen non-German countries. The contact with patients will be ensured by phone calls by the site’s study team Generally, all references to German regulations have been deleted and replaced by, e.g., “current laws and regulations”.*

B) NATIONAL AMENDMENTS based on global protocol version 3.0 incl. Amendment 2 for **FINLAND, GREECE, and THE NETHERLANDS** containing country-specific addenda as follows:

- **FINLAND**, country-specific addendum:

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
CA	Competent Authority
Fimea	Finnish Medicines Agency
EU	European Union
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organization or performance of the research, for example a pharmaceutical company, academic hospital, scientific organization or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidizing party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
DSMB	Data Safety Monitoring Board

1. Patient Questionnaires

The use of the disease-specific questionnaire Anti-Clot Treatment Scale (ACTS) and Quality of Life Questionnaires (PEmb-QoL) will not be applicable for Finland, only EQ-5D-5L Quality of Life Questionnaires will be used in Finland.

The results from patients’ questionnaires on quality of life belong to the secondary study outcomes. The fact that not all foreseen questionnaires can be applied in all countries due to non-availability does therefore not jeopardize the main outcomes of the study.

2. Addendum to paragraph 6.2.1.7 of protocol

2.1 Registration and notification of SAE and SUSARS

2.1.1 Reporting of SAEs

The sponsor will inform Finnish Medicines Agency (Fimea) and other investigators of SAE as appropriate, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

2.1.1 Reporting Suspected, unexpected and serious adverse reactions (SUSARs)

The sponsor will report expedited the following SUSARs through the European Medicines Agency EudraVigilance network.

SUSARs occurring in Finland must be reported to the Finnish Medicines Agency, Fimea database and to the European Medicines Agency.

SUSARs occurring abroad are reported to the European Medicines Agency

The expedited reporting of SUSARs through the web portal Eudravigilance is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

3. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the Fimea and the appropriate ethics committee once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

4. Addendum to paragraph 10.8 Independent data safety monitoring board (DSMB)

The advice(s) of the DSMB will only be sent to the Steering Committee of the study. Should the Steering Committee decide not to fully implement the advice of the DSMB, the Steering Committee will send the advice to the reviewing ethics committee, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

5. Addendum to paragraph 10.10.2 End of study report

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study to Fimea.

- **GREECE**, country-specific addendum:

1. Patient Questionnaires

The use of the disease-specific questionnaires PEmb-QoL and Anti-Clot Treatment Scale (ACTS) will not be applicable for Greece.

The results from patients' questionnaires on quality of life belong to the secondary study outcomes. The fact that not all foreseen questionnaires can be applied in all countries due to non-availability does therefore not jeopardize the main outcomes of the study.

- **THE NETHERLANDS**, country-specific addendum:

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
EU	European Union
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study, but does not commission is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medischwetenschappelijk Onderzoek met Mensen

1. Addendum to 1.2 Trial rationale

The Dutch guideline on PE treatment advises home treatment for patients with low-risk PE. This advice is based on clinical study findings of patients treated with low-molecularweight-heparin injections and an oral vitamin K-antagonist such as acenocoumarol, which was the previous 'standard therapy' until recently. Now, treatment with a direct oral anticoagulant such as rivaroxaban (brandname: Xarelto) is defined as the novel 'standard therapy' according to the latest guidelines.

2. Patient Questionnaires

The use of the disease-specific questionnaire Anti-Clot Treatment Scale (ACTS) will not be applicable for the Netherlands.
The results from patients' questionnaires on quality of life belong to the secondary studyoutcomes. The fact that not all foreseen questionnaires can be applied in all countries due to non-availability does therefore not jeopardize the main outcomes of the study

3. Addendum to paragraph 6.2.1.7 of protocol

3.1 Registration and notification of SAE and SUSARS

3.1.1 Reporting of SAEs

The sponsor will report the SAEs through the web portal *ToetsingOnline* to theaccredited METC that approved the protocol, within 7 days of first knowledge for SAEs
that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

3.1.2 Reporting Suspected unexpected serious adverse reactions (SUSARs)

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The expedited reporting of SUSARs through the web portal Eudravigilance or ToetsingOnline is sufficient as

notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

4. Addendum to paragraph 10.9 Insurance

Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

5. Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

5. Addendum to paragraph 10.8 Independent data safety monitoring board (DSMB)

The advice(s) of the DSMB will only be sent to the Steering Committee of the study. Should the Steering Committee decide not to fully implement the advice of the DSMB, the Steering Committee will send the advice to the reviewing METC, including a note to substantiate why (part of) the advice of the DSMB will not be followed.

6. Addendum to paragraph 10.10.2 End of study report

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

6) **Principal Investigator(s):**

Prof. Dr. med. Stavros Konstantinides

Prof. Dr. med. Rupert Bauersachs
Prof. Dr. med. Sebastian Schellong
Prof. Dr. med. Daniel Dürschmied
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Prof. Dr. med. Joachim Ficker
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Prof. Dr. med. Johannes Brachmann
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Prof. Walter Ageno, MD
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Dr. Francesca Cortellaro, MD
Prof. Athanasios Manginas, MD

7) **Study centre(s):**

Universitätsmedizin der Johannes Gutenberg-Universität Mainz
Klinikum Darmstadt GmbH
Städtisches Klinikum Dresden - Standort Friedrichstadt
Universitätsherzzentrum Freiburg
Universitätsklinikum Carl Gustav Carus, Dresden
Klinikum Nürnberg
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Klinikum der Ludwig-Maximilians-Universität München
Klinikum Augsburg
Universitätsklinikum Tübingen
Universitätsmedizin der Georg-August-Universität Göttingen
Universitätsklinikum Heidelberg
Praxis für Interventionelle Angiologie Kaiserslautern
Kliniken Maria Hilf GmbH
Katholisches Klinikum Mainz
Universitätsmedizin Mannheim
Keski-Suomi Central Hospital, Jyväskylä, FI
Helsinki University Hospital, FI
University General Hospital of Patras, Rio Achaia, GR
General Hospital Asklepeion Voulas, Athen, GR
A.Ol Ospedale di Circolo e Fondazione Macchi, Varese, IT
A.O.U. Santa Maria della Misericordia di Udine, Udine, IT
A.O. di Perugia - Ospedale Santa Maria della Misericordia, Perugia, IT
ULSS2 Distretto socio sanitario Sede di Conegliano, Conegliano, IT
A.S.S.T. Grande Ospedale Metropolitano Niguarda, Mailand, IT
ASST Papa Giovanni XXIII, Bergamo, IT
IRCCS AOU San Martino IST, Genova, IT
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Hospital da Luz, Lissabon, PT
Hospital Garcia d'Orta, Almada, ES
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EudraCT-Nr.: 2013-001657-28

Vorlage-Nr.: 01

Albert Schweitzer Hospital, Dordrecht, NL
General University Hospital of Larissa, Larissa, GR
A.O. Santa Maria di Terni, Terni, IT
A.O. Spedali Civili di Brescia, Brescia, IT
ASST Santi Paolo e Carlo
Mediterraneo Hospital, Athen, GR

8) **Publication (reference):**

Manuscript ID: ERJ-02368-2020

9) **Studied period (years)[3]:**	10) **Phase of development:** IV
Date of first enrolment: 27.05.2014 Date of last completed: 26.11.2019	

11) **Objectives:**

Primary objective: To determine whether early discharge and out-of-hospital treatment of patients with low-risk acute PE (as defined by the inclusion and exclusion criteria) with the new oral factor Xa inhibitor rivaroxaban is feasible, effective, and safe.

Secondary objectives:

- To determine whether early discharge and out-of-hospital treatment of low-risk acute PE with the new oral factor Xa inhibitor rivaroxaban can result in good quality of life and patient satisfaction; and
- to obtain valid health economic variables as a basis for description of resource utilization, including validation of a disease-specific quality of life questionnaire, and of existing Markov models.

12) **Methodology:**

Prospective, multicenter, single-arm, phase 4 management (cohort) study.

In patients clinically suspected of having acute pulmonary embolism (PE), confirmation of the diagnosis was to be completed within 24 hours of admission. Treatment with an approved parenteral anticoagulant (unfractionated heparin administered intravenously, or low-molecular-weight heparin [LMWH] or fondaparinux administered subcutaneously) could have started before screening and enrolment. Anticoagulant treatment was to be started upon clinical suspicion of PE and no later than 3 hours after confirmation of PE.

Patients fulfilling all the inclusion criteria and none of the exclusion criteria were enrolled in the study after providing written informed consent. The first dose of rivaroxaban was given in-hospital. In case anticoagulant therapy was initiated before enrolment, the first dose of rivaroxaban was administered 2 hours or less before the time that the next dosage of low molecular weight heparin (LMWH) or an oral anticoagulant would have been due, or at the time of discontinuation of intravenous unfractionated heparin. Rivaroxaban was to be taken at a dosage of 15 mg twice daily for the first 21 days, followed by 20 mg once daily.

Patients were tob e discharged from the hospital within 48 hours of presentation to the clinic. A 24-hour emergency number was to be provided by the site.

Rivaroxaban was to be taken for a total of at least 3 months. After that period, continuation of anticoagulation and the anticoagulant drug to be used was at the discretion of the patient's physician.

Follow-up was to be performed at 8 days, 3 weeks, 3 months, and 1 year.

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

In total, n = 1,100 patients were planned to be allocated to treatment; of these, n = 1,050 patients were planned to be analysed.

The predefined interim analysis after evaluation of 525 (50%) of the envisaged patient number rendered 3 primary endpoints and thus, allowed for the premature termination of recruitment (s. section 9, statistical methods).

In total, 576 patients were enrolled and analyzed.

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

Diagnosis: Acute low-risk pulmonary embolism (PE)

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

Inclusion criteria:

1) Age ≥18 years;
2) Ability of subject to understand character and individual consequences of clinical trial;
3) Signed and dated informed consent of the subject available before the start of any specific trial procedures;
4) Women of childbearing potential have to practice a medically accepted contraception (non-hormonal intrauterine device, two independent barriers, female or male surgical sterilization, or two years postmenopausal) during the trial, and a negative pregnancy test (serum or urine) should be available before inclusion in the trial;
5) Objectively confirmed diagnosis of acute PE by multidetector computed tomographic (CT) pulmonary angiography, pulmonary angiography, or V/Q lung scan according to established diagnostic criteria, with or without symptomatic deep vein thrombosis;
6) Absence of right ventricular (RV) enlargement or dysfunction, and of free floating thrombi in the right atrium or right ventricle on echocardiography or computed tomography.

   On echocardiography, RV enlargement/dysfunction is absent when *both* criteria listed below are met:
   - Right/left ventricular end-diastolic diameter ratio $\leq$ 0.9 (apical or subcostal 4-chamber view)
   - No paradoxical motion of the interventricular septum

   On CT angiography, RV enlargement/dysfunction is absent when the following criterion is met:
   - Right/left short-axis diameter ratio < 0.9 (transverse plane)

Exclusion criteria:

1) Pregnancy or lactation;
2) 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;
3) Participation in other clinical trials during the present clinical trial or within the last six months;
4) Medical or psychological condition that would not permit completion of the trial or signing of informed consent;
5) Hemodynamic instability at presentation, indicated by at least one of the following: (i) systolic blood pressure (SBP) < 100 mm Hg, or heart rate >100 beats per minute, or SBP drop by > 40 mm Hg, for > 15 min; (ii) need for catecholamines to maintain adequate organ perfusion and a systolic blood pressure of >100 mm Hg; (iii) need for cardiopulmonary resuscitation;
6) Treatment of the acute (index) episode with unfractionated heparin, low-molecular-weight heparin, fondaparinux, or a new oral anticoagulant for more than 48 hours, or with more than a single dose of a vitamin K antagonist prior to inclusion in the study;
7) Chronic treatment with a vitamin K antagonist, rivaroxaban or any other oral or parenteral anticoagulant drug:
8) Use of a fibrinolytic agent, surgical thrombectomy, interventional (transcatheter) thrombus aspiration or lysis, or use of a cava filter to treat the index episode of PE;
9) Need for supplemental oxygen administration to maintain oxygen saturation >90%;
10) Pain requiring parenteral administration of analgesic agents;
11) Other medical conditions/comorbidities requiring hospitalization;
12) Acute PE diagnosed in a patient already hospitalized for another condition;
13) Active bleeding or known significant bleeding risk;
14) Severe renal insufficiency (estimated GFR <15 ml/min/1.73m2 by the MDRD formula) or end-stage renal disease;
15) Severe hepatic failure;
16) Concomitant administration of strong inhibitors of P-gp and CYP3A4 such as azole antimycotic agents or HIV protease inhibitors;
17) Need for long-term treatment vitamin K antagonists, or for antiplatelet agents except acetylsalicylic acid at a dosage ≤100 mg/day;
18) Non-compliance or inability to adhere to treatment or to the follow-up visits; or lack of a family environment or support system for home treatment;
19) Life expectancy less than 3 months.

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

The manufacturer Bayer Health Care provided the test product/investigational medicinal product.

- Xarelto® (Rivaroxaban), 15 mg, film-coated tablets, twice daily from Day 1 to 21

  Manufacturer's batch numbers: KM5009Z, KM6007C;
- Xarelto® (Rivaroxaban), 20 mg, film-coated tablets, once daily from Day 22 to 90

  Manufacturer's batch numbers: KM500A6, KM600B8;

16) **Duration of treatment:** 90 days

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

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

Efficacy:

The primary efficacy outcome was symptomatic recurrent venous thromboembolism, or pulmonary embolism-related death within three months of enrolment.

The secondary efficacy outcomes included all-cause death within three months and one year of enrolment, rehospitalisations due to PE or to a bleeding event within three months as well as the assessment of validated quality of life and treatment satisfaction questionnaires.

Safety:

The safety outcomes included major bleeding (defined by the criteria of the International Society on Thrombosis and Haemostasis) [16], clinically relevant non-major bleeding, and serious adverse events.

19) **Statistical methods[5]:**

The primary and secondary outcome analysis was done in the ITT population, consisting of patients who signed the informed consent. Safety analysis was conducted in the safety population, including all patients who received at least one dose of study drug. Per-protocol analysis was carried out as a sensitivity analysis for the primary outcome, including all patients who received at least one dose of study drug and fulfilled the protocol requirements for early discharge from the hospital.

Differences of the quality of life scores between 3-week and 3-month visits were done using paired t-tests in case of normally distributed data or using the Wilcox-signed-rank test. To check for associations between baseline pre-defined explanatory variables characterized by low multicollinearity and an outcome variable (PEmb-QoL, Visual Analogue Scale), a linear regression model was fitted for the 3-week and 3-month visit as well as for the difference between 3 weeks and 3 months. For each linear regression model, the assumption of normal distributed residuals was confirmed. In case the number of missing values for both explanatory and outcome variable(s) was low (< 5%), an imputation technique was not deemed to be crucial.

20) Summary – Conclusions[5]:

Efficacy results: The primary efficacy outcome, symptomatic recurrent venous thromboembolism or pulmonary embolism-related death occurred in three (0.5%; one-sided upper 95.0% confidence interval [CI] 1.3%; one-sided p-value <0.0001) of the 576 patients of the ITT population within three months of enrolment. All three recurrent events were nonfatal recurrent PE. The primary outcome occurred in two (0.4%; two-sided 95% CI 0.04-1.3%; two-sided p-value <0.0001) of the 547 patients included in the per-protocol population.

Secondary efficacy outcome: Twelve (2.1%) patients were hospitalised for suspected pulmonary embolism recurrence or bleeding within 3 months of enrolment, which was then confirmed in 7 (1.2%). Fourteen patients died after a median of 6.8 (Q1-Q3 4.7-11.4) months, corresponding to a one-year mortality rate of 2.4% (95% CI 1.3-4.0%). Cancer was the most frequent cause of death and was recorded in nine patients. The three-month mortality rate was 0.4% (95% CI 0.04-1.25%),

[4] This section should also contain information about the chosen risk management approach, as outlined by ICH E3, section 9.6 (only if the study was approved after June 14th, 2017).

[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).

and both deaths were due to progressive metastatic cancer.

Analysis of the PEmb-QoL was conducted on a total of 425 patients who completed the questionnaire at both visits. The mean PEmb-QoL score decreased from 28.9% (SD 20.6%) at 3 weeks to 19.9% (SD 18.4%) at 3 months; this corresponds to a mean reduction of -9.1% (SD 15.4%; paired t-test <0.0001), indicating a significant improvement in the patients' self-reported quality of life. The improvement was consistent across all PEmb-QoL dimensions. In a multivariable linear regression model, female sex, higher body-mass index, and the presence of cardiopulmonary disease were associated with a poorer quality of life (indicated by a higher PEmb-QoL score) at both week 3 and month 3 of the follow-up. Of note, older age and the presence of cancer were not associated with worse quality of life at these timepoints, and they were in fact associated with 'faster improvement' of disease-specific quality of life over time. Specifically, we documented a +0.2% increase in the slope (per unit increase) between week 3 and month 3 per year of age (p=0.001), and a +6.4% increase in patients with versus without cancer (p=0.001).

The EQ-5D-5L analysis was conducted in a total of 473 patients who filled the questionnaire at both visits. The EQ-5D-5L index score was 0.89 (SD 0.12) 3 weeks after enrolment and improved to 0.91 (SD 0.12) at 3 months (paired t-test for difference; p<0.0001). The number of patients reporting 'no problems' in any of the five dimensions increased from 61.2% at week 3 to 72.0% at month 3, paralleled by a consistent reduction of the proportion of patients with slight (from 25.7% to 18.4%), modera (from 10.3% to 7.4%), severe (from 1.9% to 1.8%), or extreme (from 0.3% to 0.2%) problems. These positive changes were consistent across all five EQ-5D-5L dimensions.

The Visual Analogue Scale of the EQ-5D-5L increased from 76.2 (SD 16.1) to 80.2 (SD 16.4) points (paired t-test for difference; p<0.0001). In a multivariable linear regression model, female sex and the presence of cardiopulmonary disease were associated with a lower Visual Analogue Scale, indicating a poorer quality of life, at both week 3 and month 3. Older age was associated with faster worsening of generic quality of life according to the Visual Analogue Scale (-0.1% per year of increase between week 3 and month 3; p=0.02).

Anti-Clot Treatment Scale (ACTS): The analysis was conducted on a total of 421 patients who completed the questionnaire at both visits. After 3 weeks, the percentage of patients not reporting none of the ACTS burden items was 56.9%, and increased to 66.0% after 3 months. The ACTS burden score increased from 40.5 (SD 6.6) at week 3 to 42.5 (SD 5.9) points at month 3, indicating an improvement in terms treatment satisfaction (paired t-test; p<0.0001). Three weeks after acute PE, 26.3% of the patients reported to be 'extremely satisfied' based on the ACTS benefit items; this percentage increased to 31.7% at 3 months. The ACTS benefit score was 11.4 (SD 2.9) at week 3, and 11.4 (SD 3.1) at month 3 (paired t-test; p=0.4189).

Safety results: Of the 569 patients included in the safety population, six (1.1%, two-sided 95% CI 0.4-2.3%) had a major bleeding episode during rivaroxaban treatment within 3 months of enrolment. Clinically relevant non-major bleeding was recorded in 30 (5.3%; two-sided 95% CI 3.6-7.4%) patients. The median duration of first rehospitalisation was 6 (Q1-Q3: 3-9) days. Serious adverse events within 3 months of enrolment occurred in 68 (12.0%) patients, of which 64 required rehospitalisation.

Conclusion:

The results of the complete analysis of the HoT-PE trial support the early discharge and ambulatory oral anticoagulation treatment of carefully selected patients with acute low-risk pulmonary embolism. Anticoagulation with rivaroxaban initiated in the hospital and continued over at least three months was effective and safe. All-cause mortality was extremely low over the entire 12-month follow-up period. The patients' quality of life improved early during follow-up in the overall study population, as assessed on the basis of standardised, disease-specific and generic quality of life questionnaires. Future studies should aim to enhance the improvement in the quality of life of individuals with specific baseline characteristics such as female sex, an increased body-mass index, and a history of cardiac or pulmonary disease.

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

21) **Date of the report:** 09 July 2020

Print Name: **Dr. Dorothea Becker (Study Manager)**

Signature:

Print Name: **Prof. Dr. Stavros Konstantinides (Coordinating Investigator)**

Signature: