This supplement contains the following items:

1. Original protocol (the version of the protocol is unique because it has not been changed).
2. Original statistical analysis plan, final statistical analysis plan, summary of changes

Research project

Efficacy of RIvaroxaban for prevention of venous thromboembolism after Knee Arthroscopy: a randomized double-blind trial (ERIKA Study)

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Study Phase II

Version 1, 18.11.10

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1. Background

Knee arthroscopy (KA) is almost certainly the commonest among orthopaedic procedures performed on a day-care setting, in Italy as well as in the other countries of the Western civilization (more than 3.5 million procedures per year).[1,2]

As observed for other "minor" surgical interventions (i.e. gynaecologic and laparoscopic non-oncologic surgery), KA is believed at "low" risk for developing venous thromboembolic complications even if some papers of the literature report a broad venous thromboembolism (VTE) rate interval, ranging from 0.6% up to 18% without thromboprophylaxis (objectively diagnosed by both venography or ultrasonography). [2-9]

Three studies evaluated the efficacy of low-molecular weight heparins (Dalteparin 2500 or 5000 IU od; or Reviparin 1.750 aXa U od, administered from 4 to 30 days) for prevention of VTE in this setting, but did not reach definite conclusions.[10-12] A recent published study randomized about 2000 patients to receive Nadroparin 3.800 UI od or graduated compression stockings for 7 or 14 days, as prophylaxis against thrombotic events after KA, and showed noteworthy results characterized by a relative reduction of thrombotic events of about 70% in the actively treated group.[13]

Nevertheless, the most recent international ACCP guidelines do not currently recommend group-specific routine prophylaxis after KA (strength of evidence: grade 2B); and, instead, prophylaxis is only suggested for those patients with a higher than normal risk profile, such as those with recognized risk factors for venous thromboembolism, or with complicated procedures needing a short

hospital admission, or with a tourniquet time longer than 60 minutes (strength of evidence: grade 1B).[1]

The efficacy of the new oral Factor Xa inhibitor rivaroxaban for prevention of venous thromboembolism in major orthopaedic surgery is already well demonstrated,[14-17]but no report in literature is available showing its effect in preventing venous thromboembolic events in patients undergoing to knee arthroscopy.

It is the purpose of this study to evaluate the efficacy and safety of Rivaroxaban for prevention of venous thromboembolism after KA, in comparison to placebo.

Xarelto® (rivaroxaban; Bayer Schering Pharma, Berlin, Germany) is an oral once-daily dosing direct specific and highly selective inhibitor of Factor Xa with a predictable pharmacokinetic profile.

Data from the four RECORD trials[14-17] have demonstrated that Xarelto® is more effective than enoxaparin at preventing venous thromboembolic events in adult patients undergoing elective hip or knee replacement surgery, showing a comparable safety profile. Oral once-daily dosing offers an opportunity to improve patient care and save nursing time compared with existing protocols that require subcutaneous administration or dose tailoring.

2. Purpose of the study

2.1 Efficacy variables

The purpose of this study is to assess the value of rivaroxaban for prevention of venous thromboembolism after KA, taking the placebo as the standard of reference.

To reach the primary efficacy objective, the investigators will assess the occurrence in the 3-month period after the randomization of at least one of the following events, objectively proven (by means of CCDU; multi-slice chest TC-angio; autopsy, if necessary, or clinical ground):

- all-cause mortality
- symptomatic venous thromboembolism (including symptomatic distal deep-vein thrombosis, proximal symptomatic deep-vein thrombosis, symptomatic venous thromboembolism)
- asymptomatic proximal deep-vein thrombosis.

The secondary efficacy objectives of the study are:

- to assess the combined incidence of all DVT (including asymptomatic distal deep-vein thrombosis) plus symptomatic PE
- to evaluate the net clinical benefit (primary efficacy outcome plus major bleeding)

The thromboprophylaxis with rivaroxaban or placebo will be performed on patients undergoing therapeutic KA irrespective of the type and duration of the procedure.

2.2 Safety variables

The primary safety variable of the study is to evaluate the incidence of major bleedings. Major bleeding include: clinically overt haemorrhage associated with haemoglobin drop of at least 2 g/L or requiring the transfusion of two or more units of packed red-blood cells; retroperitoneal or intracranial events; bleeding requiring re-intervention; and hemarthrosis with a joint drainage of more than 450 millilitres of blood.

The secondary safety variable comprises the overall incidence of bleeding, including minor episodes.

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

3. Materials and Methods

The study will be multicentre and coordinated by the Unit of Angiology of the University of Padua, Italy.

The study will be approved by the Local Ethical Committee and all patients will sign an informed consent form after explanation of protocol and purpose of the study.

The patients will be selected according to the protocol's inclusion and exclusion criteria.

3.1 Study population

A total of 500 patients undergoing therapeutic KA will be enrolled.

Patients will be randomized on a 1:1 basis to receive either rivaroxaban or placebo.

Patients will be included in the study only after being screened for inclusion and exclusion criteria (see below) and if accepting (signed informed consent form) to participate. Patients will be encouraged to ask any questions regarding the study aims and procedures, to be answered straightforwardly by one of the investigators.

Inclusion Criteria

1. Adult patient (18 years and older)
2. Knee arthroscopy not combined with open surgery
3. Patients eligible for surgical treatment.
4. Patients are willing and able to continue study participation to ensure completion of all procedures and observations required by the study
5. Fully informed and signed consent must be obtained from each patient.

Exclusion Criteria

1. Diagnostic arthroscopy
2. Patients concomitantly treated systemically with strong concurrent CYP3A4- and P-gp-inhibitors, i.e. azole-antimycotics or HIV protease inhibitors
3. Hypersensitivity to the active substance or to any of the excipients of study drug
4. Pregnant women or breast-feeding

5. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk

6. Known thrombophilia (hereditary or acquired)

7. Mandatory anticoagulation

8. Known severe bleeding tendency

9. Clinically significant active bleeding

10. Severe renal failure (GFR<30mL/min/1.73m^2)

11. Patients participating in another clinical trial

12. Recent mayor surgery (6 to 12 weeks).

Every patient has the right to refuse further participation in the study at any time and without providing any reasons. Patients may be withdrawn from the study at any time at the discretion of the Investigator; the reason should be fully documented. Should the patient, during the course of the study, develop conditions which would have prevented his/her entry into the study according to the exclusion criteria, he/she must be withdrawn immediately. The termination of an individual's participation should be considered in case of a SAE or considerable worsening of the patient's clinical symptoms.

All patients who did not complete the study will be replaced.

3.2 Investigational plan

In actual medical knowledge the risk of VTE after KA is maximum in early phase of postoperative period.

This will be a multicenter, randomized, double blind, double dummy superiority trial comparing two arms:

•(R-7d) Rivaroxaban (10 mg od os) for 7 days

•(PL-7d) Placebo for 7 days.

No specific safety or laboratory tests planned.

Enrolled patients will be randomized to receive one tablet of study drug at the dosage of 10 mg/die or one tablet of placebo starting 8-10 hours after the end of KA procedure and every 24 hours for the following 6 days.

3.3 Visits schedule and follow-up

The study consists of 3 visits.

Randomization, performed after enrollment, will be computer-based and centralized, having arthroscopy tourniquet time (<=60 minutes vs. >60 minutes), meniscectomy (yes vs. no) and experimental Centre as stratification variables.

A visit and a bilateral whole-leg colour-coded Doppler ultrasonography (CCDU) is scheduled for all patients at 7 (+1) days of follow-up; additionally, CCDU will be performed if the patients develop symptoms or signs suggestive of venous thromboembolism earlier. A follow-up visit is planned 3-month period after the randomization.

3.4 Observations and measurements

The Investigator or a delegate will complete a Case Report Form (CRF) to document the study data.

Information to be collect at enrollment includes:

- date of informed consent
- patient demographic data
- patient vital signs (weight, height, smoking and alcohol consume)
- brief medical history and concomitant medications
- baseline haemoglobin value

After surgery:

- type of surgery
- surgery length
- type of anesthesia
- intraoperative complications
- Adverse Events

At first follow-up visit:

- possible study drug interruption
- other mechanism of VTE prophylaxis
- start of complete weight bearing
- CCDU results and possible procedure deviation
- bleeding events (in positive case a bleeding questionnaire has to be completed)

- any other Adverse Events

At second follow-up visit:

- data on possible bleeding or VTE events

- any other Adverse Events

3.5 Data Quality

Monitoring procedures will be followed, in order to comply with Good Clinical Practice (GCP) guidelines. Each center will be visited at regular intervals by a monitor to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the case report forms (CRF) for completeness and clarity, cross-checking with source documents, and clarification of administrative matters.

4. Statistical analysis

Analyses of efficacy and safety will be performed using data from all subjects for whom CRF entries are available and who comply with the study protocol (per protocol population).

Data from patients who terminated the study prematurely will not be assessed.

Additional safety analyses will be performed using data from all subjects for whom CRF entries are available irrespective of protocol deviations (ITT population). Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated for quantitative variables; frequency counts by

category will be given for qualitative variables. Individual listings will be provided for each parameter examined in this clinical study.

Demographic variables and baseline characteristics will be summarized by treatment group for all 2 analysis populations (ie, ITT and PP populations). Medical history findings and adverse events will be coded by Medical Dictionary for Regulatory Activities (MedDRA) codes.

4.1 Criteria for selection of evaluable cases

The full analysis set (FAS) consists of all patients included into this trial.

The intent-to-treat (ITT) set is a subset of the FAS and consists of all patients who fulfill the complete set of in- and exclusion criteria and who have received any amount of rivaroxaban or placebo. The ITT is analyzed for safety.

The per-protocol (PP) set is a subset of the ITT excluding patients with major protocol deviations. The PP set is the analysis set for efficacy (analysis of the primary and secondary efficacy variables).

A dropout is defined as a subject who was enrolled in the study but did not receive any amount of rivaroxaban or placebo. Dropouts will be excluded from any statistical analyses. Missing data will not be replaced during the statistical analysis of efficacy and safety. Patients with missing data will be excluded from the respective analysis.

4.2 Sample size determination

In the absence of prophylaxis the incidence of venous thromboembolism (primary efficacy end-point) after KA, as assessed with CCDU, is about 8.0% (combining weighted results of various paper).[18,19]

Prophylaxis with low-molecular weight heparins assures approximately a 60-70% relative risk reduction in this setting[10-13]. Based on the findings of published trials investigating the efficacy of Rivaroxaban for prevention of venous thromboembolism after elective hip and knee surgery, when using a low-molecular-weight heparin as comparator, we can speculate that Rivaroxaban will further reduce this incidence (at least 1.2%).

The sample size calculation is based on the primary efficacy endpoint, the occurrence of venous thromboembolism in the 3-month period after randomization, assuming that the proportions of patients experiencing an episode of VTE is 8.0% and 1.2% in the groups receiving placebo or rivaroxaban for 7 days, respectively.

A two group continuity corrected chi-square test with a 0.050 two-sided significance level will have 90% power to detect the difference between a placebo group proportion of 0.080 and a rivaroxaban group proportion of 0.012 when the sample size in each group is 226. Anticipating a 10% dropout rate, the total number of patients to be randomized is approximately 500.

4.3 Interim Analysis

After the enrollment of 200 patients, an interim analysis will be conducted in order to get a more precise estimate of the prevalence of the disease in the studied sample. Based on the analysis results, a recalculation of the needed number of subjects will be performed. In principle, neither a formal comparison between treatments nor formal stopping rules will be applied, unless otherwise suggested by the Steering Committee of the study.

5. Serious Adverse Events

Safety assessments are limited to recording of (S)AE's as expressed by the patients upon indirect questioning.

5.1 (Serious) Adverse Event Definition

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product.

A serious adverse event (SAE) is classified as any untoward medical occurrence that at any dose:

- results in death, or

- is life-threatening, or
- requires inpatient hospitalization or prolongation of existing hospitalization, or
- results in persistent or significant disability/ incapacity, or
- is a congenital anomaly/ birth defect.

Appropriate diagnostic and therapeutic measures to minimize the risk to the patient will be taken.

Every subject will be closely observed during the study procedure and immediately after. Every subject will be asked for any kind of adverse events up to 24 hours after the last administration of rivaroxaban or placebo.

5.2 (Serious) Adverse Event Reporting

All the adverse events will be recorded and reported to the Ethics Committee and to Bayer Schering Pharma according to the contract.

(S)AE's will be recorded on the CRF and – if required – reported to the responsible authorities and Bayer Schering Pharma. The Investigator) will be responsible for obtaining all data related to (S)AE's including time of onset, duration, intensity, drug relationship, study drug action, outcome.

6. Insurance

All subjects participating in the study will have insurance coverage by the Sponsor, which is in line with applicable laws and/or regulations.

7. References

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Original
Statistical & Analytical Plan and Methodology

Interim Analysis

After the enrollment of 200 patients, an interim analysis will be conducted in order to get a more precise estimate of the prevalence of the disease in the studied sample. Based on the analysis results, a recalculation of the needed number of subjects will be performed. In principle, neither a formal comparison between treatments nor formal stopping rules will be applied, unless otherwise suggested by the Steering Committee of the study.

Final Analysis

The database will locked and the final analysis will be performed when the study will stop, that is at the first case between a total of 500 subject will be randomized or 3 years from study start.

Final Analysis Set

The full analysis set (FAS) consists of all patients included into this trial.

The intent-to-treat (ITT) set is a subset of the FAS and consists of all patients who fulfill the complete set of in- and exclusion criteria and who have received any amount of rivaroxaban or placebo. The ITT is analyzed for safety.

The per-protocol (PP) set is a subset of the ITT excluding patients with major protocol deviations. The PP set is the analysis set for efficacy (analysis of the primary and secondary efficacy endpoints).

A dropout is defined as a subject who was enrolled in the study but did not receive any amount of rivaroxaban or placebo. Dropouts will be excluded from any statistical analyses. Missing data will not be replaced during the statistical analysis of efficacy and safety. Patients with missing data will be excluded from the respective analysis.

Final Efficacy Analysis Primary Endpoint

The primary efficacy objective is the occurrence in the 3-month period after the randomization of at least one of the following events:
• All-cause mortality.
• Symptomatic venous thromboembolism (including symptomatic distal deep-vein thrombosis, proximal symptomatic deep-vein thrombosis, symptomatic venous thromboembolism).
• Asymptomatic proximal deep-vein thrombosis.

Final Efficacy Analysis Secondary Endpoints

• Combined incidence of all DVT (including asymptomatic distal deep-vein

thrombosis) plus symptomatic PE.
• The net clinical benefit (primary efficacy outcome plus major bleeding).

Final Safety Analysis Primary Endpoint

• Major bleeding (clinically overt haemorrhage associated with haemoglobin drop of at least 2 g/L or requiring the transfusion of two or more units of packed red-blood cells; retroperitoneal or intracranial events; bleeding requiring re-intervention; and hemarthrosis with a joint drainage of more than 450 millilitres of blood).

Final Safety Analysis Secondary Endpoint

• Overall incidence of bleeding, including minor episodes.

Final Efficacy and Safety Endpoints Analysis Methods

A two groups continuity corrected chi-square test will use compare the rate of endpoints into the two groups.

Other factors independently associated with the development of venous thromboembolic events (secondary efficacy endpoint) will be identified by multivariate logistic regression models, adjusting for listed characteristics (age, gender, body-mass-index, diabetes, hormonal treatment, hyperlipemia, hypertension, autoimmune disease, renal impairment, varicose vein, superficial VT, history of previous VTE or TIA/stroke, tourniquet application time, meniscectomy, cartilage shaving, cruciate ligament repair), applying a forward stepwise selection (Wald's method).

Level of Significance

The significance level for analysis is 5% bilateral.

Final
Statistical & Analytical Plan and Methodology

Interim Analysis

No interim analysis was performed because of the difficulties of recruitment, which led to reach the expected 200 subjects only a short time before the planned end.

Final Analysis

The database will locked and the final analysis will be performed when the study will stop, that is at the first case between a total of 500 subject will be randomized or 3 years from study start.

Final Analysis Set

The full analysis set (FAS) consists of all patients included into this trial.

The intent-to-treat (ITT) set is a subset of the FAS and consists of all patients who fulfill the complete set of in- and exclusion criteria and who have received any amount of rivaroxaban or placebo. The ITT is analyzed for safety.

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A dropout is defined as a subject who was enrolled in the study but did not receive any amount of rivaroxaban or placebo. Dropouts will be excluded from any statistical analyses. Missing data will not be replaced during the statistical analysis of efficacy and safety. Patients with missing data will be excluded from the respective analysis.

The intent-to-treat (ITT) set and the per-protocol (PP) set were the same because no major protocol deviations were observed. Then the population of interest will be the ITT.

Final Efficacy Analysis Primary Endpoint

The primary efficacy objective is the occurrence in the 3-month period after the randomization of at least one of the following events:
• All-cause mortality.
• Symptomatic venous thromboembolism (including symptomatic distal deep-vein thrombosis, proximal symptomatic deep-vein thrombosis, symptomatic venous thromboembolism).
• Asymptomatic proximal deep-vein thrombosis.

Final Efficacy Analysis Secondary Endpoints

• Combined incidence of all DVT (including asymptomatic distal deep-vein thrombosis) plus symptomatic PE.
• The net clinical benefit analysis (primary efficacy outcome plus major bleeding) will not be estimated because no major bleeding was observed

Final Safety Analysis Primary Endpoint

• Major bleeding (clinically overt haemorrhage associated with haemoglobin drop of at least 2 g/L or requiring the transfusion of two or more units of packed red-blood cells; retroperitoneal or intracranial events; bleeding requiring re-intervention; and hemarthrosis with a joint drainage of more than 450 millilitres of blood).

No major bleeding was observed, and then no primary endpoint for safety will be analyzed.

Final Safety Analysis Secondary Endpoint

• Overall incidence of bleeding, including minor episodes.

Final Efficacy and Safety Endpoints Analysis Methods

The expected two groups continuity corrected chi-square test will be replaced for more robust Fisher's exact test, in order to compare the rate of endpoints into the two groups of much smaller size than expected.

Other factors independently associated with the development of venous thromboembolic events (secondary efficacy endpoint) will be identified by multivariate logistic regression models, adjusting for listed characteristics (age, gender, body-mass-index, diabetes, hormonal treatment, hyperlipemia, hypertension, autoimmune disease, renal impairment, varicose vein, superficial VT, history of previous VTE or TIA/stroke, tourniquet application time, meniscectomy, cartilage shaving, cruciate ligament repair), applying a forward stepwise selection (Wald's method).

Level of Significance

The significance level for analysis is 5% bilateral.

Summary of changes for
Statistical & Analytical Plan and Methodology

- No interim analysis was performed because of the difficulties of recruitment, which led to reach the expected 200 subjects only a short time before the planned end.

- The intent-to-treat (ITT) set and the per-protocol (PP) set were the same because no major protocol deviations were observed. Then the population of interest will be the ITT.

- The net clinical benefit analysis (primary efficacy outcome plus major bleeding) will not be estimated because no major bleeding was observed.

- No major bleeding was observed, and then no primary endpoint for safety will be analyzed.

- The expected two groups continuity corrected chi-square test will be replaced for more robust Fisher's exact test, in order to compare the rate of endpoints into the two groups of much smaller size than expected.