Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country..

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1. ABSTRACT

Name of company: Boehringer Ingelheim			
Name of finished medicinal product: Pradaxa® (Dabigatran etexilate), or Vitamin K Antagonist (VKA)			
Name of active ingredient: Dabigatran, or VKA			
Report date: 08 AUG 2018	**Study number:** 1160.249	**Version/Revision:** 1.0	**Version/Revision date:** NA
Title of study:	Non-interventional study describing patients´ perception on anticoagulant treatment and treatment convenience when treated with Pradaxa® or Vitamin K Antagonist (VKA) for Stroke Prophylaxis in Atrial Fibrillation.		
Keywords:	Dabigatran, fibrillation, anticoagulant, VKA, treatment perception		
Rationale and background:	Pradaxa® (Dabigatran etexilate) is a direct Thrombin inhibitor approved in Europe, USA and many other countries worldwide for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors. Data on how patients perceive Pradaxa® treatment in the context of non-valvular atrial fibrillation and anticoagulation management do only exist to a limited degree in Europe. The decision in clinical practice to use Pradaxa® as the first novel anticoagulant or established vitamin K antagonists depends on many factors related to the patient and prescribing physician. The aim of this non-interventional study is to describe patients' perception of anticoagulant treatment when using Pradaxa® to prevent stroke and systemic embolism while suffering from non-valvular atrial fibrillation (according to its approved indication in the approved dosages of 110 mg or 150 mg twice daily) in comparison to using Vitamin K Antagonist (VKA).		
Research question and objectives:	• Research question 1: How do patients perceive anticoagulation treatment with Pradaxa® for stroke prevention in non-valvular atrial fibrillation (NVAF) in comparison with VKA? o With further exploratory objectives: • Is there a variation of treatment convenience and treatment satisfaction among different age groups? Is there a difference in treatment convenience and treatment satisfaction between switched patients and newly initiated patients? • What is treatment expectation of newly diagnosed NVAF patients before they start treatment with VKA or		

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	Pradaxa® • Is there any geographical variation in treatment perception? • Research question 2: What are the characteristics of patients receiving anticoagulation treatment for stroke prevention regarding demographics, physician rated scores, kidney function, treatment (choice of treatment, dosing)? • Primary objective: Describe the non-valvular atrial fibrillation patient´s treatment perception by using the PACT-Q© (Perception on Anticoagulant Treatment Questionnaire). • Secondary objective: Characterization of patient population (including dosing of Pradaxa®)		
Study design:	Non-interventional study of NVAF patients in Europe with a current VKA therapy and subsequent initiation of Pradaxa® OR patients being newly diagnosed with NVAF and initiated on Pradaxa® or VKA.		
Setting:	Data from approximately 9 000 patients were planned to be collected from approximately 800 sites from 12 Central & Eastern European countries (Russia, Poland, Romania, Hungary, Austria, Czech Republic, Latvia, Estonia, Slovenia, Bulgaria, Serbia, Croatia) and Israel.		
Subjects and study size, including dropouts:	The following inclusion criteria were defined for patients: • Both Cohorts: Written informed consent prior to participation • Cohort A: Female and male patients ≥ 18 years of age with a diagnosis of non-valvular atrial fibrillation. • Cohort A: At least 3 months of continuous VKA treatment for stroke prevention prior to baseline assessment. • Cohort A: Patients switched to Pradaxa® according Summary of Product Characteristics and physician`s discretion. • Cohort B: Female and male patients ≥ 18 years of age newly diagnosed with non-valvular atrial fibrillation and no previous treatment for stroke prevention (no use of any OAC within one year prior to enrolment). • Cohort B: Stroke prevention treatment initiated with Pradaxa® or VKA according to Summary of Product Characteristics and		

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physician`s discretion.

Patients fulfilling the following exclusion criteria were excluded from study participation:

- Contraindication to the use of Pradaxa® or VKA as described in the respective Summary of Product Characteristics (SmPC)
- Patients receiving Pradaxa® or VKA for any other condition than stroke prevention in non-valvular atrial fibrillation.
- Current participation in any clinical trial of a drug or device
- Current participation in a Registry, e.g. the Gloria registry program, on the use of oral anticoagulation in AF

Overall 9472 patients were enrolled into the study (all patients with valid inclusion/exclusion criteria), 4103 patients in Cohort A and 5369 patients in Cohort B, in 698 sites and 12 countries (Croatia was excluded at the beginning of the study regarding study timeliness), of which:

- 9465 patients (main analysis set) were eligible for the study and received Pradaxa® or VKA treatment according to Pradaxa® or respective VKA label (4100 patients from cohort A and 5365 patients from cohort B; i.e out of enrolled patients 3 patients from Cohort A and 4 patients from Cohort B and were excluded due to no available information on the study treatment status).
- 8888 patients received the treatment until the end of the last visit; 3860 Cohort A patients and 5028 Cohort B patients respectively. In detail, out of eligible patients in Cohort A 157 (3.8%) patients discontinued the treatment during the study and for another 83 (2.0%) patients the treatment status was unknown. In Cohort B 161 (5.1%) patients from the Pradaxa® group and 110 (5.0%) patients from the VKA group discontinued the treatment during the study and for 49 (1.5%) patients from the Pradaxa® group and 17 (0.8%) from the VKA group the treatment status was unknown. 42 (1.9%) patients from the VKA group discontinued the treatment due to switching to Pradaxa®.
- In cohort B 4941 patients (2885 from the Pradaxa® group, 2056 from the VKA group) were successfully matched through the pre-defined procedure and thus were included in the Propensity

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	score matched set (PSMS).		
Variables and data sources:	**VARIABLES** **For objective 1:** **Primary outcome** **For Cohort A (NVAF patients on VKA who are switched to Pradaxa®):** • Mean PACT-Q2 scores at second and last assessment compared to baseline assessment. **For Cohort B (newly diagnosed NVAF patients initiated to either VKA or Pradaxa®):** • Mean PACT-Q2 scores at second and last assessment compared between treatment groups. **Secondary outcome** **For Cohort A (switched to Pradaxa®):** • Mean PACT-Q2 scores at last assessment compared to second assessment. **For Cohort B (newly initiated to VKA or Pradaxa®):** • Description of PACT-Q1 items at baseline. **Further exploratory outcomes:** • Variation of PACT-Q2 scores at baseline, during initiation period and during the continuation period in respective treatment Cohorts between countries (both Cohorts). • Variation of PACT-Q2 scores in different age groups (both Cohorts). • Variation of treatment expectations, measured with PACT-Q1 items at baseline in different age groups (Cohort B). • Geographical variation in treatment perception **For objective 2:** **Primary outcome:** Characterization of patients from both Cohorts according to		

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	• Age • Gender • CHA2DS2-VASc score • HAS-BLED score (modified HAS-BLED for newly initiated • patients) • Kidney function (creatinine clearance) • Stroke- and/or bleeding related risk factors in medical history and at baseline • Co-morbidities • Concomitant therapies • Dosing of Pradaxa® • Duration of previous VKA treatment (for Cohort A) **DATA SOURCES** • New data collection • Questionnaires completed by patients • Patient characteristics completed by physician's judgement and records.		
Statistical methods:	In this non-interventional study, cross-sectional data at study baseline and longitudinal observational data over the course of 6 months was collected. Data collected at the baseline and during longitudinal observational period was summarized descriptively. For Cohort A, mean differences in PACT-Q2 scores between assessments were evaluated using paired t-tests. For Cohort B, mean differences in PACT-Q2 scores between Pradaxa® and VKA patients were assessed using propensity score matching and the random intercept model (RIM) as the primary analysis, and "within-set" method as sensitivity analysis. With respect to Cohort B, it was observed, during the course of the study that the number of patients enrolled in the Pradaxa® group was considerably higher than the number of patients enrolled in the VKA group. In order to account for this imbalance and make the best use of the available data, the final analysis was based on a nearest neighbour propensity score matching with variable ratio 1:n (n-max=3)[8]. The RIM was used due to the variable size of the matched sets. In principle, the		

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	RIM is the generalisation of paired t-test and allows to compare patients paired with one or more 'controls'[15]. In the "within-set" set method[8] treatment effect estimates were obtained by calculating the difference within each matched set between the VKA patients score and the mean score of the matched Pradaxa® patients, the overall treatment effect was then estimated as the mean of those differences and its statistical significance was evaluated by a t-test[8]. No (confirmatory) hypothesis testing was expected in a strict statistical sense. Analyses were descriptive in nature and p-values from statistical models were used for exploratory purposes. Summary statistics for continuous variables included the N, mean, standard deviation, minimum, median, and maximum value; tabulations of categorical variables present all possible categories and display the number of observations per category as well as percentages. No interim analysis was planned for Cohort A. The interim analysis for Cohort B was conducted as planned in the protocol to assess the comparability of patients in the VKA and Pradaxa® groups based on propensity scores. It was performed when approximately half of the target sample size was reached.		
Results:	Out of 9472 patients enrolled in this observational study, 9465 were eligible and therefore included in the main analysis set as the study treatment information was available, 9411 patients had actual follow-up (i.e. had data collected in the actual observational period) and thus were included in the safety set. Of the eligible patients, 4100 entered the Cohort A (Pradaxa® group) and 5365 the Cohort B (3179 newly introduced to Pradaxa® group and 2186 to VKA group). Of the eligible Cohort B patients 4941 patients (2885 from the Pradaxa® group, 2056 from the VKA group) were successfully matched through the pre-defined procedure and thus were included in the Propensity score matched set (PSMS). Out of enrolled patients, 240 Cohort A patients and 337 Cohort B patients (210 from the Pradaxa® group, 127 from the VKA group) discontinued treatment during the observational period or have unknown treatment status at the end of observation. All data collected from a patient before premature discontinuation were included in the analyses. Data was collected at 3 time points: at treatment initiation as baseline -		

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Visit 1 (V1) and two follow-up visits: initiation period - Visit 2 (V2) and continuation period - Visit 3 (V3). In the initial protocol the tighter time windows for data collection at visits V2 and V3 were proposed as recommendations for sites. But in reality, visits were performed outside of those windows by sites. Therefore, for the purpose of the analysis, the time windows were revised and extended as follows: Initiation period (V2): 7 - 124 days after baseline and continuation period (V3): 125 - 365 days after baseline.

Primary outcomes of objective 1:

Patients in Cohort A (patients switched from VKA to Pradaxa®) had statistically significant increase in both treatment convenience and satisfaction PACT-Q2 scores ($p<0.001$) at V2 (78.6±16.5, resp. 68.4±12.9) and V3 (82.2±14.9, resp. 71.8±13.3) from baseline (58.0±22.0, resp. 50.9±16.9).

For Cohort B, mean treatment convenience and satisfaction PACT-Q2 scores were statistically different in favour of Pradaxa® at both V2 and V3 ($p<0.001$). At V2, convenience and satisfaction scores were 60.9 (±20.2) and 52.2 (±14.4), respectively, for VKA and 79.3 (±16.3) and 68.1 (±12.6), respectively, for Pradaxa®; at V3 it was 59.3 (±20.6) and 51.4 (±15.1), respectively, for VKA and 82.7 (±14.9) and 70.4 (±13.0), respectively, for Pradaxa®.

Secondary outcomes of objective 1:

For Cohort A mean change in treatment convenience and satisfaction PACT-Q2 scores between V3 and V2 was 3.62 (±12,977) and 3.33 (±12,863) respectively ($p<0.001$).

Patients in Cohort B were given PACT-Q1 to assess patients` expectation from anticoagulation therapy (AT). Majority of patients had high confidence in AT to prevent stroke or systemic embolism and moderate to high expectation of symptom relief. Dosing complexity, worries about keeping recommended dosage regimen, and reimbursement options were of high importance.

Primary outcomes of objective 2:

Mean age of enrolled patients was 70.5 (±9.57) and 68.6 (±9.89) years in Cohort A and B respectively with gender representation approximately 1:1 ratio in both Cohorts and treatment groups (Cohort

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	A: 48.7% females; Cohort B: in total 50.0% females, Pradaxa 50.4% females, VKA 49.4 % females). Neither race nor ethnicity data was collected. Major specialization of treating physician was cardiology. In Cohort A majority of patients had full reimbursement, in Cohort B majority of patients paid for AT themselves. Majority of enrolled patients in both Cohorts (almost 90%) were in high risk of stroke and systemic embolism (CHA2DS2-VASc score ≥ 2). Risk of bleeding complications (HAS-BLED score ≥ 3) was high in majority of Cohort A patients (59.2%), in Cohort B on the contrary majority of patients were in lower risk (HAS-BLED score of < 3) of bleeding (30.0%). Kidney function was normal in both Cohorts (glomerular filtration rate ≥ 80 mL/min), majority of patients had cardiovascular comorbidities (about 83%), which reflected into concomitant therapy. Dose of Pradaxa® was 150 mg twice daily in 65.1% of patients in Cohort A with previous VKA therapy median duration of 19 months (mean duration 34 months). 69.6% of patients in Pradaxa® subgroup of Cohort B had dose 150 mg twice daily. **Safety:** For this non-interventional study conducted within the conditions of the approved marketing authorisation safety data collection included: - all ADRs (serious and non-serious), - all AEs with fatal outcome (serious adverse events), - all pregnancies Out of eligible patients included in safety set of patients, any ADR (serious and non-serious) was reported for 2.3% – 2.8% of patients in all treatment groups (Cohort A: 94 (2.3%), Cohort B: 140 (2.6%) in total, 80 (2.5%) for Pradaxa, 60 (2.8%) for VKA). At system organ class level the most frequently reported ADR contained cardiac disorders (cardiac failure), gastrointestinal disorders (gastrointestinal haemorrhage) and nervous system disorders (ischaemic stroke). Any Serious Adverse Drug Reaction (SADR) was reported for 0.6% – 0.8% patients in all treatment groups (Cohort A: 26 (0.6 %), Cohort B: 40 (0.7%) in total, 25 (0.8%) for Pradaxa, 15 (0.7%) for VKA). At system organ class level, the most frequently reported ADR contained cardiac disorders (cardiac failure) and nervous system disorders (ischaemic stroke).		

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	Patients experienced an adverse drug reaction leading to drug discontinuation were 43 (1.1%) in Cohort A and in Cohort B, 32 (1.0%) patients in the Pradaxa® group and 4 (0.2%) patients in the VKA group. Patients experienced an adverse drug reaction leading to death were in total 11: 5 in Cohort A and 6 in Cohort B (i.e. 2 Pradaxa® patients and 4 VKA patients).		
Discussion/Conclusion:	The aim of this non-interventional study was to assess patients` perception of anticoagulation therapy while suffering from NVAF. Anticoagulation in stroke and systemic embolism prevention in NVAF patients is long-term, it is indicated in patients with moderate to high risk of thromboembolic complications. However, data on patients` perception of long-term anticoagulation therapy in NVAF are limited. To assess patient perception of AT, PACT-Q questionnaire was used in several time-points (baseline V1, initiation period V2, continuation period V3) in Cohort A (patients switched from long-term VKA to Pradaxa®) and in Cohort B (newly diagnosed patients with NVAF started on either VKA or either Pradaxa®). After switching from VKA to Pradaxa® in Cohort A, mean PACT-Q2 scores statistically significantly increased over time through following visits in both treatment convenience and satisfaction scores in comparison to baseline values. In newly diagnosed patients with NVAF, mean differences in PACT-Q2 scores in both treatment convenience and satisfaction were statistically significantly different in favour of Pradaxa® in comparison to VKA therapy.		
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Names and affiliations of principal investigators:	Total number of participating sites is 698.		