Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

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Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's Policy on Transparency and Publication of Clinical Study Data**.

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: 24 July 2019	**Study number:** 1160.247	**Version/Revision:** 01	**Version/Revision date:** n.a.
Title of study:	Non-interventional study describing patients´ perception on anticoagulant treatment and treatment convenience when treated with Pradaxa® or Vitamin K Antagonist for Stroke Prophylaxis in Atrial Fibrillation.		
Keywords:	Non-valvular atrial fibrillation, dabigatran, 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 atrial fibrillation and anticoagulation management do only exist to a limited degree in Europe. (R15-1312). 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 was 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:	Objective 1: How did patients perceive anticoagulation treatment with Pradaxa® for stroke prevention in non-valvular atrial fibrillation (NVAF) in comparison with VKA, as recorded on the Perception on Anticoagulant Treatment Questionnaire (PACT-Q©)? o With further exploratory objectives: • Was there a variation of treatment convenience and treatment satisfaction among different age groups? • Was there a difference in treatment convenience and treatment satisfaction between switchers and newly initiated patients? • What was the treatment expectation of newly diagnosed NVAF patients before they start treatment with VKA or Pradaxa®? • Was there any geographical variation in treatment perception? Objective 2: What were the characteristics of patients receiving anticoagulation		

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	treatment for stroke prevention in atrial fibrillation (SPAF) regarding demographics, physician rated scores, kidney function, concomitant diseases and concomitant medications, treatment for SPAF (choice of treatment, dosing)?
Study design:	Non-interventional study of NVAF patients in Europe who were using VKA therapy and were switched to Pradaxa® therapy OR patients who were newly diagnosed with NVAF and initiated on Pradaxa® or VKA.
Setting:	Data of approximately 3.000 patients were planned to be collected from approximately 220 sites in 7 European countries (Belgium, Denmark, Greece, Norway, Portugal, Sweden and The Netherlands).
Subjects and study size, including dropouts:	The following inclusion criteria were defined for patients: • Written informed consent prior to participation. • Female and male patients ≥ 18 years of age. • For Cohort A: patients with a diagnosis of non-valvular atrial fibrillation who have had at least 3 months of continuous VKA treatment for stroke prevention prior to baseline assessment. • For Cohort A: patients must have been switched to Pradaxa® according to the Summary of Product Characteristics and physician`s discretion. • For Cohort B: patients newly diagnosed with non-valvular atrial fibrillation, who have had no previous treatment for stroke prevention (must not have used of any anticoagulant within one year prior to enrolment). • For Cohort B: patients must have been initiated to treatment with Pradaxa® or VKA for stroke prevention according to Summary of Product Characteristics and physician`s discretion. Patients fulfilling the following exclusion criteria were excluded from study participation: • Patients with contraindications to the use of Pradaxa® or VKA as described in the Summary of Product Characteristics (SmPC). • All patients who were receiving Pradaxa® or VKA for any other condition than stroke prevention in atrial fibrillation. • Patients who were participating in any clinical trial of a drug or device, or participating in a Registry, e.g. the Gloria registry program, on the use of oral anticoagulation in AF. Overall 1852 patients diagnosed with NVAF were actually enrolled in the study in 133 sites in 7 countries, of which:

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	• 1822 patients were eligible for the study and received Pradaxa® or VKA treatment according to Pradaxa® or respective VKA label. • 101 patients stopped Pradaxa® or VKA treatment prematurely, i.e. before study completion period of approximately 6 months . • 130 patients prematurely stopped the study (with or without stopping the Pradaxa® or VKA treatment).		
Variables	**For objective 1:** **Primary outcome** **For Cohort A (NVAF patients on VKA who were 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 regions (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 - Age		

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	- Gender - Stroke- and/or bleeding related risk factors in medical history and at baseline, i.e.: - CHA_2DS_2-VASc score (R10-5332) - HAS-BLED score (modified HAS-BLED for newly initiated patients) (R10-6394) - Kidney function (creatinine clearance) - Co-morbidities - Co-medication - 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 follow-up data over 6 months were collected. Baseline data were analysed using a descriptive approach. Data from the longitudinal follow-up were summarized descriptively. For Cohort A, mean differences in PACT-Q2 scores between assessments were assessed using paired t-tests. For Cohort B, mean differences in PACT-Q2 scores between Pradaxa® and VKA patients were assessed using propensity score matched analysis. No (confirmatory) hypothesis testing was foreseen 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 conducted for this study.
Results:	Altogether 1852 patients were enrolled, of which 1822 were found eligible for the study. An enrolled patient was not considered eligible for analyses if an important protocol violation took place, or if the patient did not take the Pradaxa® or VKA treatment, or not according to Pradaxa® or respective VKA label. Of the eligible patients, 585 entered the Cohort A/Pradaxa group, 1159 the Cohort

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B/Pradaxa group and 78 the Cohort B/VKA group.

A possible reason for the relatively low number of VKA patients as compared to Pradaxa patients in Cohort B, might have been the changed healthcare environment since the initial design of the study, resulting in a decreased prescription of VKA as compared to non-Vitamin K oral anticoagulants (NOACs) like Pradaxa.

Patients who prematurely and permanently discontinued their anticoagulant treatment (Pradaxa or VKA) were also regarded as discontinued prematurely from the study, and if PACT-Q data were collected after stop or switch of anticoagulant treatment during the continuation period of the study then these scores were discarded from the analysis. All data collected from a patient before premature discontinuation were included in the analyses.

Overall, 54.9% was male and 45.1% was female and the mean age was 73.0 (±9.1) years. Race and ethnicity were not collected as per study protocol.

Mean CHA_2DS_2-VASc stroke risk score was 3.4 (±1.5) for Cohort A/Pradaxa patients, 3.2 (±1.4) for Cohort B/Pradaxa and 3.8 (±1.3) Cohort B/VKA patients. Cohort B/VKA had the highest percentage (96.2%) of the patients with a high stroke risk (score of ≥ 2), followed by Cohort A/Pradaxa (91.8%) and Cohort B/Pradaxa (89.1%). The mean HAS-BLED bleeding risk score was 2.1 (±0.9) for Cohort A/Pradaxa patients, 1.7 (±0.8) for Cohort B/Pradaxa and 2.0 (±1.0) Cohort B/VKA patients, of which 66.3%, of the Pradaxa patients in Cohort A, 89.0% and 75.6% of the Pradaxa and VKA patients in Cohort B, were classified with low bleeding risk (score <3). The mean number of years since first diagnosis of NVAF was 4.87 (ranging from min. 0.2 years to max. 26.9 years) for Cohort A/Pradaxa patients, 0.56 years (ranging from min. 0.0 years to max. 33 years) for Cohort B/Pradaxa patients and 0.27 years (ranging from min. 0.0 years to max. 12.3 years) for Cohort B/VKA patients. The mean duration of VKA treatment in Cohort A patients was 4.44 years (ranging from 0.3 to 24.3 years). The mean creatinine clearance at baseline was 74.4 (±27.1) mL/min in Cohort A/Pradaxa, 75.9 (±26.6) mL/min in Cohort B/Pradaxa and 63.8 (±37.6) mL/min in Cohort B/VKA.

Primary outcomes of objective 1:

- Analysis of the PACT-Q2 scores for eligible patients in Cohort A switched to Pradaxa, using paired t-test showed that the mean convenience dimension scores of 77.3 (19.4) at Visit 2 and 79.2 (±17.9) at Visit 3, were significantly higher as compared to the mean convenience dimension score of 63.4 (±25.2) at baseline Visit 1 ($p < .0001$). The mean satisfaction dimension score of 67.7 (±13.9) at Visit 2 and 70.0 (±13.0) at Visit 3, were also significantly higher as

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compared to the mean satisfaction score of 53.8 (±16.8) at baseline (p< .0001). Thus, both the convenience score and the satisfaction dimension score significantly improved for Cohort A patients after one month of treatment with Pradaxa and these scores were further improving significantly after 6 months when compared to baseline.

- Analysis of the PACT-Q2 scores of eligible newly treated patients in Cohort B, using a propensity score matching method on VKA patients and their matched Pradaxa patients (number of matched sets: N = 63 at Visit 2 and N = 62 at Visit 3), showed the following. Mean convenience dimension scores of 78.3 (±13.4) were reported by Cohort B/Pradaxa patients, and 69.1 (±22.6) by Cohort B/VKA patients at Visit 2 (after approximately 1 month use), which is a statistically significant difference (p = 0.0005) in favour of Pradaxa. At Visit 3, after approximately 6 months use, the difference in mean convenience score is also significant (p= 0.0002), i.e. 80.3 (±10.5) for Pradaxa patients and 69.5 (±22.3) for VKA patients . The mean satisfaction dimensions scores, 65.9 (±7.8) for Pradaxa patients and 58.0 (±13.3) for VKA patients at Visit 2 also showed a statistically significant difference (p = 0.0002) in favour of Pradaxa. Significant differences in satisfaction dimension scores are also observed at Visit 3, 68.4 (±8.8) for Pradaxa patients and 58.8 (±15.9) for VKA patients, with (p = 0.0004.

Secondary outcomes of objective 1:

- Analysis of the PACT-Q2 scores for eligible patients in Cohort A switched to Pradaxa, using paired t-test showed that the mean convenience and mean satisfaction dimension scores at Visit 3 (79.2 ±17.9 and 70.0±13.0, respectively), after 6 months of treatment, were significantly higher than those at Visit 2 (77.3±19.4 and 67.7±13.9, respectively), after 1 month of treatment (p < 0.0001). This means that the patients' perception about the new treatment with Pradaxa continued to improve significantly even after 6 months.
- Descriptive summary analysis with regard to the treatment expectations of newly diagnosed NVAF eligible patients in Cohort B, as measured with the PACT-Q1 at baseline Visit 1, was extended with a Fisher's exact test and two sample t-test to compare the two treatment groups in Cohort B by treating the scores as categorical or as continuous variables, respectively. This comparative analysis showed that patients who were to be treated with Pradaxa had significantly higher expectations with regard to relief of symptoms (item A2) and importance on ease of use (item A4). The mean A2 score of 3.1 (±1.2) for Pradaxa patients was significantly higher than the mean

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score of 2.8 (±1.2) for VKA patients, as shown by the p-value of 0.0411 (with two sample t-test) and the mean A4 scores of 4.2 (±0.8) for Pradaxa and 3.8 (±1.0) for VKA were significantly different, using two sample t-test and Fisher's exact test (p- values 0.0220 and 0.0098, respectively). A comparison of the other PACT-Q1 items (A1, A3, A5, A6, and A7) did not show any significant differences in mean scores between Pradaxa or VKA patients . See the following Summary Table for all mean (SD) PACT-Q1 scores:

Summary Table of mean PACT-Q1 scores at baseline for Cohort B patients

	Cohort B Pradaxa (N = 1148)		Cohort B VKA (N = 77)	
	mean	(SD)	mean	(SD)
A1 (confidence in prevention of blood clots)	3.8	(0.8)	3.7	(0.8)
A2 (expectations of symptom relief)	3.1	(1.2)	2.8	(1.2)
A3 (expectations of side effects)	2.7	(0.9)	2.8	(1.0)
A4 (importance of ease of use)	4.2	(0.8)	3.8	(1.0)
A5 (worries about making intake mistakes)	2.8	(1.4)	2.9	(1.4)
A6 (importance of independence [self-taking care of treatment])	4.1	(0.9)	3.9	(1.0)
A7 (worries about costs of treatment)	2.9	(1.4)	2.8	(1.5)

Primary outcomes of objective 2:

The patient characterization at baseline ,included age, gender, Stroke- and/or bleeding related risk factors in medical history and at baseline, co-morbidities, concomitant therapies, dosing of Pradaxa®, and duration of previous VKA treatment (for Cohort A). The most relevant are summarized in the following table:

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	Cohort A Pradaxa		Cohort B Pradaxa		Cohort B VKA	
Eligible patients (N, %)	585	100.0	1159	100.0	78	100.0
Female (N, %)	258	44.1	520	44.9	43	55.1
Male (N, %)	327	55.9	639	55.1	35	44.9
Age in years (mean, SD)	73.3	8.9	72.7	9.1	74.9	10.1
Years since 1st NVAF diagnosis (mean, SD)	4.87	4.33	0.56	2.40	0.27	1.48
Duration previous VKA treatment (mean, SD)	4.44	3.65	-	-	-	-
Pradaxa dose (N, %):						
110 mg twice daily	327	55.9	664	57.3	-	-
150 mg twice daily	258	44.1	495	42.7	-	-
Co-Morbidities (N, %):						
o Thromboembolisms	34	5.8	46	4.0	7	9.0
o Cardiovascular conditions	466	79.7	920	79.4	64	82.1
o Bleedings	21	3.6	30	2.6	6	7.7
Concomitant Medications (N, %):						
o Antihypertensives	496	84.8	940	81.1	66	84.6
o Lipid modifying agents	265	45.3	494	42.6	40	51.3
o Antiarrhythmic agents	172	29.4	294	25.4	15	19.2
o Proton Pump inhibitors	110	18.8	184	15.9	21	26.9
o Antithrombotic agents	43	7.4	117	10.1	17	21.8

Additional patient characterization at baseline, using continuous parameters, included CHA_2DS_2-VASc stroke risk score, HAS-BLED bleeding risk score, and Kidney function (creatinine clearance) are summarized in the table below:

	Cohort A Pradaxa		Cohort B Pradaxa		Cohort B VKA	
CHA_2DS_2-VASc stroke risk score (mean, SD)	3.4	1.5	3.2	1.4	3.8	1.3
HAS-BLED bleeding risk score (mean, SD)	2.1	0.9	1.7	0.8	2.0	1.0
Baseline creatinine clearance [mL/min] (mean, SD)	74.4	27.1	75.9	26.6	63.8	37.6

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	Safety: The analysis of Adverse Events (AE) was based on collected serious or non-serious Adverse Drug Reactions (ADR) and fatal Adverse Events for eligible patients only. Of 1822 eligible patients, AEs were reported for 82 (4.5%) patients in total. As a result of the specific safety reporting requirements for NIS, and consequent reporting bias, most reported AEs were drug related: ADRs were reported for 76 (4.2%) patients in total, with a numerically higher percentage of ADRs in the Cohort A/Pradaxa group (5.8%; 34 of 585 patients) as compared to Cohort B/Pradaxa (3.4%; 39 out of 1159 patients) or Cohort B/VKA (3.8%; 3 out of 78 patients). AEs of severe intensity were reported for 9 (0.5%) patients in total. AEs leading to discontinuation of anticoagulant treatment were reported for 54 (3.0%) patients in total: 3.6% (21 out of 585 patients) in Cohort A/Pradaxa and 2.8% (33 out of 1159 patients) in Cohort B/Pradaxa. None of the VKA patients (total N = 78) terminated treatment because of AE. Serious AEs were reported for 14 (0.8%) patients in total, four of them in the Cohort A/Pradaxa group (0.7%), eight in the Cohort B/Pradaxa group (0.7%) and two in Cohort B/VKA group (2.6%). These included deaths (7 patients, 0.4%), events that required hospitalisation (6 patients, 0.3%), an event that prolonged hospitalisation (1 patient, 0.1%) and an event in the category other (1 patient, 0.1%).		
Conclusions:	To date, only limited data exist on how patients perceive Pradaxa treatment in the context of atrial fibrillation disease management. With this non-interventional study we aimed to show, in real world practice in (selected) European countries, if and how a switch to another type of anticoagulant (from VKA to Pradaxa), or new/first initiation of an anticoagulant (VKA or Pradaxa) for the prevention of stroke in NVAF patients, have an impact on the patients' perception on anticoagulant treatment after approximately 1 and 6 months. The characteristics of the eligible study patients from 7 European countries, receiving anticoagulation treatment (Pradaxa or VKA) for stroke prevention in atrial fibrillation, were also described. The study results have shown that • The treatment perception (calculated by the mean convenience and satisfaction dimension scores using PACT-Q2) of patients , who were switched from VKA to Pradaxa treatment (Cohort A), significantly improved after approximately 1 month of Pradaxa treatment and continued to significantly improve after approximately 6 months of Pradaxa treatment, as compared to their perception about their previous VKA treatment recorded at baseline. • The treatment perception of patients, who were newly initiated to Pradaxa, was significantly better as compared to the treatment perception of patients		

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	who were newly treated with VKA (in Cohort B), after approximately 1 month and 6 months of treatment. • The treatment expectations, as measured by individual scores for the seven PACT-Q1 items at baseline, by patients newly treated with anticoagulant (Cohort B) showed that Pradaxa patients had significantly higher treatment expectations with regard to symptom relief and the ease of use as compared to VKA patients. Some of the Cohort B results must be interpreted with caution due to the low number VKA patients (78) as compared to Pradaxa patients (1159) participating in the study Cohort B. This was not a safety study and the study was also not designed to capture specific outcomes (e.g. bleedings or stroke). The reported serious and non-serious adverse drug reactions in this study (for both Cohorts) are consistent with known / listed side-effects of Pradaxa. The reported fatal events were all considered non-related to the anticoagulant treatment. Overall, no changes were observed in the safety profile for Pradaxa.
Marketing Authorisation Holder(s):	Boehringer Ingelheim International GmbH Binger Str. 173 D-55216 Ingelheim am Rhein, Germany
Names and affiliations of principal investigators:	Coordinating Investigator : [redacted] The Netherlands Annex 2 of the full report contains a complete list of all participating sites