Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

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..

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 products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable
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, anticoagulant treatment, dabigatran, treatment convenience, treatment satisfaction		
Rationale and background:	Pradaxa® (dabigatran etexilate) is a direct thrombin inhibitor approved in Europe, USA, and many other countries worldwide (including many Asian countries) for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors. The decision in clinical practice to use established vitamin K antagonists or Pradaxa®, a new oral anticoagulant not requiring anticoagulation monitoring, depends on many factors that are related to the patient and the prescribing physician. Prior to this study, data on how patients in Asia perceive their anticoagulant treatment with Pradaxa® in the context of anticoagulation management were not available. Therefore, this non-interventional study aimed at describing the NVAF patients' perception of their anticoagulant treatment when using Pradaxa® to prevent stroke and systemic embolism (according to its approved indication at the approved dosages of 150 or 110 mg twice daily) in comparison to using a vitamin K antagonist (VKA).		
Research questions and objectives:	*Research questions:* • How did patients perceive their anticoagulant treatment with Pradaxa® for stroke prevention in NVAF in comparison with VKA treatment? • 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 started treatment with VKA or Pradaxa®? • Was there any geographical variation in treatment perception? • What were the characteristics of patients receiving anticoagulant		

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable

Research questions and objectives (cont.):	treatment for stroke prevention regarding demographics, physician rated scores, kidney function, and treatment (choice of treatment, dosing)? *Objective 1:* The primary objective was to describe the NVAF patients' treatment perception by using the PACT-Q questionnaire (Perception on Anticoagulant Treatment Questionnaire) at 3 time points: at baseline, during the initiation period (7 to 124 days after baseline), and during the continuation period (125 to 365 days after baseline). *Objective 2:* The secondary objective was to characterise the patient population (including dosing of Pradaxa®) in the participating SEASK countries.
Study design:	This was a multicentre, multinational, non-interventional study in NVAF patients in Asia who had been treated with a VKA and were then switched to Pradaxa® (Cohort A) or patients who were newly diagnosed with NVAF and initiated on either Pradaxa® or VKA (Cohort B).
Setting:	Data of NVAF patients were collected at 49 cardiologist and non-cardiologist sites regularly prescribing Pradaxa® and VKA for stroke prevention in atrial fibrillation in 5 SEASK (South East Asia and South Korea) countries: Indonesia, Malaysia, Singapore, South Korea, and Thailand.
Subjects and study size, including dropouts:	Female and male consented NVAF patients aged ≥18 years with at least 3 months of continuous VKA treatment for stroke prevention prior to the baseline assessment and switched to Pradaxa® according to the approved country label and at the treating physician's discretion were included in Cohort A. Female and male consented patients aged ≥18 years with newly diagnosed NVAF who had no previous treatment for stroke prevention and were initiated on Pradaxa® or VKA according to the approved country label and at the treating physician's discretion were included in Cohort B. Reasons for exclusion were contraindications to the use of Pradaxa® or VKA, prescription of Pradaxa® or VKA for any other condition than stroke prevention in atrial fibrillation, and participation in any other clinical study or in a registry on the use of oral anticoagulants at the same time. Overall 1344 patients (planned number: 1790 patients) were enrolled in this

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable
Subjects and study size, including dropouts (cont.):	study: 1121 patients were enrolled in South Korea, 112 patients in Malaysia, 62 patients in Thailand, 34 patients in Indonesia, and 15 patients in Singapore. Of the enrolled patients, 1313 patients were eligible, that is, they received either Pradaxa® or VKA and did not have any important protocol violations. Of the eligible patients, 379 patients were in Cohort A, 591 patients were in the Cohort B/Pradaxa® group, and 343 patients were in the Cohort B/VKA group. A total of 932 patients (71.0%) were followed up to the last assessment as planned, whereas 367 patients (28.0%) discontinued from the study prematurely (Cohort A: 94 patients, 24.8%; Cohort B/Pradaxa®: 182 patients, 30.8%; Cohort B/VKA: 91 patients, 26.5%). No information on study termination was available for 14 patients (1.1%). Of the eligible patients, 324 patients (24.7%) discontinued from their prescribed treatment (Cohort A: 84 patients, 22.2%; Cohort B/Pradaxa®: 156 patients, 26.4%; Cohort B/VKA: 84 patients, 24.5%). These patients also had to discontinue from the study. No information on treatment termination was available for 17 patients (1.3%). Overall, the most frequently reported reasons for premature study discontinuation were 'lost to follow-up' (131 patients, 10.0%), 'other' (105 patients, 8.0%), and 'other adverse event' (87 patients, 6.6%).		
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 Primary outcome for Cohort B (newly diagnosed NVAF patients initiated on either VKA or Pradaxa®): • Mean PACT-Q2 scores at second and last assessment compared between treatment groups Secondary outcome for Cohort A: • Mean PACT-Q2 scores at last assessment compared to second assessment Secondary outcome for Cohort B: • Description of PACT-Q1 items at baseline		

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable

Variables (cont.):	Further exploratory outcomes are described in the main part of the non-interventional study report. *For Objective 2:* Primary outcome: Characterisation of patients from both cohorts according to age, gender, CHA_2DS_2-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, comorbidities, concomitant therapies, dosing of Pradaxa®, duration of previous VKA treatment (for Cohort A)
Data sources:	This was a study on newly collected data. Data sources for Objective 1 were self-administered PACT-Q questionnaires which were completed by the patients. The PACT-Q questionnaire consists of 2 parts that cover the dimensions 'treatment expectations' (PACT-Q1), and 'convenience' and 'treatment satisfaction' (PACT-Q2). For Objective 2, patients' characteristics were recorded by the treating physicians.
Statistical methods:	In this non-interventional study, cross-sectional data at study baseline and longitudinal follow-up data were collected. Data were collected at 3 time points: at Visit 1 (baseline), at Visit 2 (treatment initiation period), and at Visit 3 (treatment continuation period). Visit 2 data collected between 7 and 124 days after treatment initiation and Visit 3 data collected between 125 and 365 days after treatment initiation were included for analysis. For Cohort A, mean PACT-Q2 scores at Visit 2 and Visit 3 were compared with the scores at baseline using paired t-tests. Likewise, mean PACT-Q2 scores at Visit 3 were compared with the scores at Visit 2. In Cohort B, Pradaxa® and VKA patients were matched based on propensity scores (using a variable ratio, parallel, balanced 2:1, nearest neighbour approach), then mean PACT-Q2 scores were compared between matched Pradaxa® and VKA patients at Visit 2 and Visit 3 using paired t-tests. Furthermore, scores of 7 individual items of PACT-Q1 at baseline were summarised descriptively for all Cohort B patients overall and by treatment. Due to the nature of this non-interventional study, analyses were descriptive in nature and p-values from statistical models were used for explorative purposes.

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable

Statistical methods (cont.):

Patient demographic and disease characteristics at baseline were summarised descriptively for all eligible patients in Cohort A and by treatment in Cohort B.

No interim analysis was conducted for this study.

Results:

Primary and secondary outcomes for Objective 1 (treatment perception)

For Cohort A patients, that is, NVAF patients who had previously been treated with a VKA and were then switched to Pradaxa®, both mean convenience dimension and mean satisfaction dimension scores were significantly improved during the treatment initiation period (Visit 2) and were further improved during the treatment continuation period (Visit 3) in comparison to the baseline assessment (Table 1).

Table 1: Analysis of PACT-Q2 scores for Cohort A using paired t-test

PACT-Q2	N	Mean (SD)	p-value (compared to baseline)	p-value (compared to Visit 2)
Convenience dimension score				
Baseline	377	71.4 (21.8)		
Visit 2	317	79.6 (18.1)	<0.0001	
Visit 3	266	82.0 (16.8)	<0.0001	0.1234
Satisfaction dimension score				
Baseline	377	61.0 (13.3)		
Visit 2	317	63.2 (14.6)	0.0174	
Visit 3	266	64.4 (14.7)	0.0004	0.9740

In Cohort B, that is, patients newly diagnosed with NVAF, patients initiated on Pradaxa® had significantly higher mean convenience dimension and satisfaction dimension scores at the end of the treatment continuation period (Visit 3) than patients initiated on a VKA (Table 2). A significantly higher convenience dimension score for Pradaxa® patients compared to VKA patients was already observed during the treatment initiation period (Visit 2).

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable

Results (cont.):

Table 2: Analysis of PACT-Q2 scores for Cohort B using propensity score matching analysis

PACT-Q2	Number of matched patient sets (N)	Cohort B Pradaxa® Mean (SD)	Cohort B VKA Mean (SD)	p-value (comparison of Pradaxa® and VKA)
Convenience dimension score				
Visit 2	217	78.4 (14.6)	75.1 (19.6)	0.0423
Visit 3	157	80.4 (13.6)	76.0 (18.9)	0.0287
Satisfaction dimension score				
Visit 2	217	61.5 (12.7)	59.9 (13.5)	0.2226
Visit 3	157	63.9 (11.6)	60.9 (12.8)	0.0300

PACT-Q1 scores reflect the Cohort B patients' expectations at baseline, that is, before they started treatment with either Pradaxa® or VKA (Table 3).

Table 3: Mean PACT-Q1 scores at baseline for Cohort B

Treatment expectations PACT-Q1 item (score range 1 to 5)	Cohort B Pradaxa® (N=580[1]) Mean (SD)	Cohort B VKA (N=340[1]) Mean (SD)	Cohort B Total (N=920[1]) Mean (SD)
A1: Confidence in prevention of blood clots	3.4 (1.0)	3.3 (1.0)	3.4 (1.0)
A2: Expectations of symptom relief	3.4 (0.9)	3.3 (1.0)	3.4 (0.9)
A3: Expectations of side effects	2.5 (1.0)	2.6 (1.0)	2.6 (1.0)
A4: Importance of ease of use	3.7 (0.9)	3.5 (1.0)	3.6 (0.9)
A5: Worries about making mistakes	2.5 (1.2)	2.5 (1.2)	2.5 (1.2)
A6: Importance of independency	3.7 (0.9)	3.7 (1.0)	3.7 (1.0)
A7: Worries about cost	2.7 (1.2)	2.6 (1.2)	2.7 (1.2)

[1]Number of patients with valid PACT-Q1 data. PACT−Q1 completed after the first dose or using incorrect procedure were excluded.

In general, the scores for the PACT-Q1 items were very similar for Pradaxa® and VKA patients with differences in mean scores between 0 and 0.2. Most patients rated independency (A6) and ease of use (A4) very high and also expected that their treatment would prevent blood clots (A1) and relieve symptoms (A2), whereas concerns about costs (A7), making mistakes (A5), or side effects (A3) played a minor role.

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable

Results (cont.):

For item A4 (ease of use), a difference in mean score of 0.2 was observed in favour of Pradaxa® (p = 0.0167, two-sample t test), indicating that for patients in the Pradaxa® group the ease of use of their anticoagulant treatment was even more important than it was for patients in the VKA group.

Primary outcome for Objective 2 (patient characteristics)

The patient population consisted of 849 (64.7%) male and 464 (35.3%) female patients. The mean (standard deviation [SD]) age of the patient population was 67.0 (10.2) years. Patients in the Cohort B/VKA group were on average younger with 63.4 (10.9) years compared with patients in Cohort A with 69.7 (9.0) years and the Cohort B/Pradaxa® group with 67.3 (9.8) years.

The mean (SD) CHA_2DS_2-VASc stroke risk score was 3.1 (1.4) in Cohort A, 2.6 (1.4) in the Cohort B/Pradaxa® group, and 2.0 (1.6) in the Cohort B/VKA group. The 2 Pradaxa® treatment groups had the highest percentages of high-risk patients (CHA_2DS_2-VASc score ≥2; Cohort A 87.3%, Cohort B 81.6%), whereas only 54.5% of VKA patients were high-risk patients. The mean (SD) HAS-BLED bleeding risk score was 1.8 (1.1) in Cohort A, 1.3 (0.9) in the Cohort B/Pradaxa® group, and 1.1 (1.1) in the Cohort B/VKA group.

The mean (SD) baseline creatinine clearance was 68.1 (23.1) mL/min in Cohort A, 75.4 (29.0) mL/min in the Cohort B/Pradaxa® group, and 73.0 (29.2) mL/min in the Cohort B/VKA group. A total of 13 patients (1.0%) had a baseline creatinine clearance of <30 mL/min, all of them VKA patients since Pradaxa® patients with a creatinine clearance of <30 mL/min were excluded from the eligible patients. For 31.7% of patients in Cohort A, 29.6% of patients in the Cohort B/Pradaxa® group, and 44.9% of patients in the Cohort B/VKA group, no baseline serum creatinine value was available.

The most frequently reported concomitant diseases were hypertension (Cohort A 43.3%, Cohort B/Pradaxa® 37.9%, Cohort B/VKA 25.9%), hyperlipidaemia (Cohort A 33.8%, Cohort B/Pradaxa® 24.9%, Cohort B/ VKA 19.8%), diabetes mellitus (Cohort A 17.9%, Cohort B/Pradaxa® 15.4%, Cohort B/VKA 9.9%), congestive heart failure (Cohort A 17.2%, Cohort B/Pradaxa® 8.8%, Cohort B/VKA 9.0%), and stroke (Cohort A 9.2%, Cohort B/Pradaxa® 4.2%, Cohort B/VKA 7.3%).

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable

Results (cont.):

The most frequently prescribed concomitant therapies were antihypertensives (Cohort A 67.5%, Cohort B/Pradaxa® 56.0%, Cohort B/VKA 47.8%) and lipid-modifying agents (Cohort A 46.7%, Cohort B/Pradaxa® 33.5%, Cohort B/VKA 28.0%).

In Cohort A, 31.9% of patients were prescribed Pradaxa® 150 mg twice daily and 68.1% of patients were prescribed Pradaxa® 110 mg twice daily. In Cohort B, 42.0% of patients were prescribed Pradaxa® 150 mg twice daily and 58.0% of patients were prescribed Pradaxa® 110 mg twice daily.

For Cohort A, the mean (SD) duration of continuous VKA treatment prior to baseline was 4.28 (3.63) years, ranging from 0.3 to 24.8 years.

Of all patients, 54.1% were treated at a private hospital or practice, 42.6% were treated at a public hospital or practice, and 3.4% of patients were treated at another type of hospital or practice. The vast majority of patients were treated by a cardiologist (95.7%), only 0.3% of patients were treated by a general practitioner, and 4.0% of patients were treated by other specialists.

Safety

Due to the nature of this non-interventional study, a systematic collection and systematic analysis of adverse events (AEs) was neither planned nor performed. Safety reporting focused on serious and non-serious adverse drug reactions (ADRs) to Pradaxa® and VKA and on fatal AEs.

ADRs were reported for 7.7% of all eligible patients (Cohort A 11.6%, Cohort B/Pradaxa® 7.6%, Cohort B/VKA 3.5%). Gastrointestinal disorders were the most frequently reported ADRs (all patients 5.1%, Cohort A 9.0%, Cohort B/Pradaxa® 5.4%, Cohort B/VKA 0.3%). Non-serious ADRs were reported for 6.9% of all patients (Cohort A 10.3%, Cohort B/Pradaxa® 7.4%, Cohort B/VKA 2.0%). Serious ADRs were reported for 0.9% of all patients (Cohort A 1.3%, Cohort B/Pradaxa® 0.2%, Cohort B/VKA 1.7%). Fatal ADRs were reported for 1 patient (0.3%) in Cohort A. Unrelated fatal AEs were reported for 0.6% of all patients (Cohort A 0.5%, Cohort B/ Pradaxa® 0.8%, Cohort B/VKA 0.3%).

Conclusions:

This non-interventional study, which was conducted in 5 SEASK countries, aimed at collecting real world data on how Asian patients with NVAF perceive their anticoagulant treatment with Pradaxa® in comparison to treatment with a VKA.

Name of company: Boehringer Ingelheim			
Name of finished medicinal products: Pradaxa® (dabigatran etexilate) or vitamin K antagonist			
Name of active ingredient: Dabigatran etexilate or vitamin K antagonist			
Report date: 23 Oct 2018	**Study number:** 1160.261	**Version/Revision:** 01	**Version/Revision date:** Not applicable
Conclusions (cont.):	Patients who were switched from VKA to Pradaxa® treatment rated treatment convenience higher and were more satisfied with their new Pradaxa® treatment as compared with their previous VKA treatment. The improvement in treatment convenience dimension and satisfaction dimension scores of the PACT-Q2 questionnaire was observed already during the treatment initiation period, and the scores continued to improve during the treatment continuation period of the study. In the cohort of patients who were newly initiated on Pradaxa® or a VKA, the patients' perception of their anticoagulant treatment was better for Pradaxa® patients than for VKA patients, as evidenced by the Pradaxa® patients' higher treatment convenience dimension score during the treatment initiation period and also during the treatment continuation period and by their higher satisfaction dimension score during the treatment continuation period. At the beginning of the study, the majority of newly diagnosed patients in both treatment groups had high expectations of their anticoagulant treatment, as measured by the scores for the 7 PACT-Q1 items. The patients set a high value on their independency and the ease of use of their anticoagulant treatment, and they expected that the treatment would prevent blood clots and relieve their symptoms, whereas concerns about costs, side effects, or making mistakes played a minor role. Treatment expectations were similar for patients initiated on Pradaxa® and patients initiated on a VKA, however, the ease of use of the anticoagulant treatment seemed to be more important for Pradaxa® patients than for VKA patients. The safety data collected in this study did not give rise to any new safety concerns. Taken together, the results of this study indicate that the treatment perception of Asian patients who are treated for stroke prevention in atrial fibrillation is better on Pradaxa® than on VKA.		
Marketing Authorisation Holder:	Boehringer Ingelheim International GmbH Binger Str. 173 55216 Ingelheim am Rhein, Germany		
Names and affiliations of investigators:	A list of all participating sites and investigators is available in Annex 2 of the non-interventional study report.		