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**.

Name of company: Boehringer Ingelheim		**Tabulated Non InterventionalStudy Report**	Boehringer Ingelheim
Name of finished product: Not applicable			
Name of active ingredient: Not applicable		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 03 JUN 2014	**Trial No. / Doc No. / Leg Doc:** 1160.170 / c02155743-03 U13-2860-01	**Date of trial:** 01 NOV 2012 – 30 JUN 2013	**Date of revision:** Not applicable

Title of study:	Use of Pradaxa® (dabigatran etexilate) for stroke prevention in patients with non valvular atrial fibrillation and mild to moderate renal impairment
Coordinating Investigator:	Not applicable
Study site(s):	Multicenter study (1072 sites in Germany)
Publication (reference):	Data of this study have not yet been published.
Clinical phase:	IV
Objectives:	The general aim of this clinical study was to gain knowledge of the risk profile of patients with mild to moderate renal impairment who are intended to be treated with Pradaxa® and to analyse the prescribing patterns of doctors in reference to this patient subpopulation.
Methodology:	This prospective, non-interventional, cross-sectional, multicenter study documented findings and the decision for a specific dose of Pradaxa® before taking the first dose of Pradaxa®. The data documented in the case report form (CRF) (demographic factors, medical history and other medicines) constitute the basis for the analysis of the characteristics of the patients.
No. of patients:	
planned:	6000
actual:	entered: 4340 treated: n.a. analysed: 4340 (All Patient Set), 2120 (Per Protocol Set)
Diagnosis and main criteria for inclusion:	Adult male and female patients with mild or moderate renal impairment and non valvular atrial fibrillation and for whom, according to the evaluation performed by the treating physician, the initiation of an anticoagulation therapy for the prevention of stroke and systemic embolism with Pradaxa® was planned in compliance with the German Summary of Product Characteristics (SPC).
Test product(s):	Not applicable
dose:	
mode of admin.:	

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Name of finished product: Not applicable			
Name of active ingredient: Not applicable		**Page:** 2 of 5	**Synopsis No.:**
Module:		**Volume:**	
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Comparator product(s):	Not applicable
dose:	
mode of admin.:	
Duration of treatment:	There was one observation time point upon inclusion of the patient in the study and the selection of the dose of Pradaxa®. The observation was performed directly after the consent of the patient had been obtained and before the first intake of Pradaxa®.
Criteria for evaluation:	
Efficacy:	Not applicable
Safety:	Not applicable
Other:	The primary endpoint was the creatinine clearance at the prescription time point according to the Cockcroft-Gault formula (recalculated using age, gender, body weight, and serum creatinine as documented in the CRF). Further endpoints included physicians' dose selection of dabigatran etexilate.
Statistical methods:	All analyses in connection with this observational study were descriptive; the results were exploratory. There were no pre-specified confirmatory hypotheses and no measures have been taken to adhere to a study-wide 5% significance level or simultaneous confidence intervals. Data were presented as medians with quartiles Q1 and Q3 or as percentages. Significance of differences between treatments, specialty or location of physicians was not formally calculated. Differences were arbitrarily considered as major when medians laid outside of comparable inter-quartile limits or percentages differed by at least 10 percentage points.

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Module:		**Volume:**	
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SUMMARY – CONCLUSIONS:

Efficacy results: Not applicable

Safety results: Not applicable

Other results: Overall, 4340 patients were observed at the prescription time point of Pradaxa®, i.e. before start of treatment. More than half of the patients (N=2220; 51.2%) of this non-interventional study (NIS) was excluded from the per protocol analysis since they did not meet the pre-defined inclusion criteria in this study of non valvular atrial fibrillation with mild or moderate renal impairment as assessed by the clinical judgment of the physician,.

In the Per Protocol Set (PPS), 2120 patients were observed by 551 physicians of whom most were general practitioners (39.9%) and most worked in an urban location (61.0%). The median age of the patients was 76 (inter quartile range 70.0; 81.0) years. The mean age of the patients was 75.2 (± 8.8) years. 51.9% of the patients were male.

The median CHA_2DS_2-VASc score of the patients was 4 (4; 5). Overall, 14 (0.7%) patients belonged to the risk category 0-1, 87 (4.1%) patients to the risk category 2, and 1924 (90.8%) patients to the risk category ≥3. A total of 414 (19.5%) patients had an increased risk of bleeding and 1573 (74.2%) patients had no increased risk of bleeding.

The most patients were treated with one of the two doses of Pradaxa® registered for atrial fibrillation (AF) treatment in Germany, i.e. 150 mg bid (30.4%) or 110 mg bid (64.9%). 3.7% patients received a different dose of Pradaxa®, mainly 75 mg bid.

Primary endpoint

With regard to the primary endpoint of the NIS, the creatinine clearance according to the Cockcroft-Gault formula (recalculated using age, gender, body weight, and serum creatinine), the median creatinine clearance of the patients was 55.2 (43.6; 68.3) ml/min. 226 (10.7%) patients had no renal impairment, 1003 (47.3%) patients had a mild degree of renal impairment, in 653 (30.8%) patients the renal impairment was moderate, and in 93 (4.4%) patients the renal impairment was documented as severe.

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Name of finished product: Not applicable			
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Module:		**Volume:**	
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Differences between patients with 150 mg bid and 110 mg bid dosing

The study identified some major differences between the patients in the 150 mg bid and 110 mg bid treatment groups. Most importantly, regarding the primary endpoint of the NIS, patients in the 150 mg bid treatment group had a higher median creatinine clearance (66.1 (55.4; 77.8) ml/min) than patients in the 110 mg bid treatment group (51.5 (40.6; 62.2) ml/min). Accordingly, more patients in the 150 mg bid treatment group had a lower degree of renal impairment (19.6% patients with no renal impairment and 57.0% patients with mild renal impairment) compared to the 110 mg bid treatment group (6.9% and 43.9% of patients, respectively).

Furthermore, patients in the 150 mg bid treatment group were younger (median age 71.0 (65.0; 75.0) years) than the patients in the 110 mg bid treatment group (median age 78.0 (73.0; 83.0) years), in the 150 mg bid treatment group relatively more patients were male (60.1%) than in the 110 mg bid treatment group (48.1%), more patients in the 150 mg bid treatment group than in the 110 mg bid treatment group had a paroxysmal atrial fibrillation (38.4% vs. 28.7%), and fewer patients in the 150 mg bid treatment group (9.2%) than in the 110 mg bid treatment group (23.4%) had an increased risk of bleeding.

Differences between patients with regard to the specialty of the physicians

Regarding the specialties of the physicians, there were no major differences in the prescription of Pradaxa® between internists and general practitioners. However, cardiologists treated less patients of the ≥80-age group (23.3%) than internists (35.6%) and general practitioners (37.8%), fewer patients with diabetes mellitus (28.7%) than internists (39.2%) and general practitioners (40.1%), fewer patients with hyperlipidaemia (54.4%) than internists (65.5%) and general practitioners (64.3%) and fewer patients with gastritis, oesophagitis or gastroesophageal reflux (9.5%) than internists (20.9%) and general practitioners (22.1%). Cardiologists also treated fewer patients who had taken vitamin-K-antagonists (VKA) as previous antithrombotic therapy (43.8%) than internists (61.9%) and general practitioners (60.9%).

Differences between patients with regard to the location of the physicians

There were no major differences between patients treated by physicians in urban or rural locations with regard to any of the investigated parameters.

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Conclusions:

In the Per Protocol Set of this non-interventional study, patients with non valvular atrial fibrillation and mild to moderate renal impairment were observed by cardiologists, internists, and general practitioners in urban and rural locations. Patients were documented on the day when Pradaxa® was prescribed for stroke prevention. No further observations and no adverse events were documented in this study. In this population, most patients were treated with one of the two doses registered for stroke prevention in patients with non valvular atrial fibrillation in Germany, i.e. 150 mg and 110 mg bid of Pradaxa®. With regard to the primary endpoint, physicians predominantly prescribed Pradaxa® to patients with mild renal impairment as assessed by creatinine clearance according to the Cockcroft-Gault formula (recalculated using age, gender, body weight, and serum creatinine). There were some major differences between patients to whom 150 mg and 110 mg bid Pradaxa® was prescribed. The 150 mg bid treatment group had higher recalculated median creatinine clearance, and a higher degree of no or mild renal impairment according to the recalculated creatinine clearance. Furthermore, patients in the 150 mg bid treatment group were younger, more frequently male, had more frequently paroxysmal atrial fibrillation and less frequently an increased risk of bleeding. Regarding the specialties of the physicians, there were no major differences in the prescription of Pradaxa® between internists and general practitioners. However, cardiologists treated fewer patients of the ≥80-age group, fewer patients with diabetes mellitus, hyperlipidaemia and gastritis, oesophagitis or gastroesophageal reflux, and fewer patients who had taken vitamin-K-antagonists as previous antithrombotic therapy compared to internists and general practitioners. There were no major differences between patients treated by physicians in urban or rural locations with regard to any of the investigated parameters. In this study, the majority of patients had at least two risk factors indicating that Pradaxa® was predominantly prescribed to mildly or moderately renally impaired atrial fibrillation patients with additional cardiovascular risks. With regard to the possibility of tailored dosing with Pradaxa®, physicians adapted their prescription practice according to the bleeding risk profile of the patients.