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.

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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..

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

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| **Name of company:** Boehringer Ingelheim | | |  |
| **Name of finished medicinal product:** Pradaxa® | | | |
| **Name of active ingredient:** Dabigatran etexilate | | | |
| **Report date:** 17OCT2016 | **Study number:** 1160.200 | **Version/Revision:** 1.0 | **Version/Revision date:** N/A |
| **Title of study:** | A retrospective cohort study with chart review to assess the management of major bleeding events in non-valvular atrial fibrillation (NVAF) patients treated with dabigatran etexilate | | |
| **Keywords:** | Dabigatran etexilate, non-valvular atrial fibrillation, retrospective, real world, bleed management | | |
| **Rationale and background:** | Although there is a substantial body of data available relating to dabigatran-associated bleeding in the clinical trial setting, data regarding the management of acute bleeding events in patients receiving dabigatran in routine care are lacking. Therefore, this study was conducted to collect data on the management of major bleeding events in patients with NVAF who were taking dabigatran as per the US label, and who either presented to an emergency department (ED)/emergency room (ER) or were hospitalized for the management of a major bleeding event (index bleeding event). ICD-9 codes were run for all patients who presented to ED/ER from October 2010 to March 2015. The chart review was conducted between 20th August 2014 and 4th March 2015. Data entry was closed on 23rd April 2015, and database lock occurred on 6th May 2015. | | |
| **Research question and objectives:** | There are scarce data relating to the clinical characteristics and management of dabigatran-associated bleeding events in the real-world setting. The objective of this study was to assess the clinical characteristics of the major bleeding events in patients with NVAF at five U.S. sites who were taking dabigatran and who either presented to an ED/ER or were hospitalized primarily for management of a major bleeding event. Another objective was to collect information describing the diagnostic evaluations and treatments provided to resolve those events, and the clinical outcomes of these events at these sites. | | |
| **Study design:** | Retrospective observational study | | |
| **Setting:** | Multicenter | | |
| **Patients and study size, including dropouts:** | Patients enrolled in the study were those who met the inclusion criteria:<br>• Confirmed diagnosis of NVAF<br>• ≥18 years of age<br>• Presentation to an ED/ER or hospitalized primarily for a major bleeding | | |

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| | event (index event), and<br>• Documentation that the index event occurred in a patient who reportedly had taken at least one dose of dabigatran as per the U.S. label within 5 days prior to the index event<br>During the initial screening, the medical records of 284 patients were captured using the core algorithm, which identified patients with a diagnosis of NVAF in the first instance, then limited the records further to those of patients who, firstly, had a major bleeding event and, secondly, were on dabigatran. These 284 records were then reviewed and assessed against the study's inclusion and exclusion criteria; the medical records of 93 patients were assessed as ineligible for study entry and excluded, while those of the remaining 191 patients' were assessed as eligible and included in the final study cohort. |
| **Variables and data sources:** | Data were collected from eligible patients with NVAF who were identified using hospital electronic databases. The following variables were abstracted from the medical records of patients in the final study cohort using a standardized electronic case report form (eCRF):<br>• Demographic information<br>• Medical history<br>• Information on treatment with dabigatran and concomitant medications, and doses/dosing<br>• Bleeding event characteristics<br>• Laboratory results<br>• Information regarding the evaluation and treatments aimed at managing the bleeding event (including the timing from event onset to its management, and the type and amount of allogeneic blood products, purified and recombinant protein concentrates, and pharmacologic agents)<br>• Clinical outcome (resolved/recovery ongoing / deceased) |
| **Results:** | Most of the index bleeding events (n=165, 86.4%) in the study cohort were resolved. The index events were unresolved in less than 8.0% of the patients at discharge (n=14, 7.3%); 12 (6.3%) patients died, and four (2.1%) deaths were related to the index event.<br><br>The majority (n=118, 61.8%) of the index events were in the gastrointestinal (GI) tract; 43 (22.5%) cases were in the upper GI, 65 (34.0%) were in the lower GI and 10 (5.2%) were of unknown GI location. Brain/intracranial hemorrhage constituted 18.8% (n=36) of the index events; of these, eight (4.2%) were non-traumatic cases and 28 (14.7%) were traumatic cases. Thirty-six (18.8%) of the index events were in "other" locations, where the frequency of bleeding was <1.7% in each individual location recorded. There was one (0.5%) patient for whom the index bleeding location was unknown but found to meet the International Society of Thrombosis and Haemostasis (ISTH) criteria for major bleeding.<br><br>Fluid transfusion, administered in 139 (72.8%) patients, was the most commonly used intervention for the management of index events in the study cohort. Blood transfusion (whole blood or packed red blood cells) |

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| | was the second most common intervention. In particular, transfusion of packed red blood cells (PRBCs) was used to manage the index event in 99 (51.8%) patients (where recorded, a mean of 1,073 mL was administered [SD 661]) while whole red blood cell transfusion was used in 10 (5%) subjects) while whole red blood cell transfusion was utilized in 10 (5.2%) patients. Fresh frozen plasma and platelet transfusion were used less frequently, in 47 (24.6%) and 11 (5.8%) patients, respectively. Cryoprecipitate (n=3, 1.6%) and plasma expanders (n=2, 1.0%) were rarely used. Blood coagulation factor concentrates (n=11, 5.8%) and hemodialysis (n=1, 0.5%) also were infrequently used. |
| **Discussion:** | Overall, outcomes in this study were consistent with those observed in patients on dabigatran with major bleeding events in the RE-LY trial. In RE-LY, major bleeding events in NVAF patients on dabigatran were treated more frequently with blood transfusions (59.2%) than with plasma (19.8%) and hemostatic treatments (e.g., plasma, vitamin K, factor concentrates, cryoprecipitate, or platelets) were used infrequently – a pattern that was similarly observed in this study.(Majeed, et al, 2013)<br><br>The generalizability of these results is limited given that this study was restricted to five sites and had a small sample size. |
| **Marketing Authorisation Holder:** | Boehringer Ingelheim |
| **Names and affiliations of principal investigators:** | [redacted], M.D., [redacted] (Site 1)<br>[redacted], M.D., [redacted] (Site 2)<br>[redacted], M.D., [redacted] (Site 3)<br>[redacted], M.D., [redacted] (Site 5)<br>[redacted] M.D., [redacted] (Site 6)*<br><br>*There was an additional site (Site 4) that was considered for participation in the study but declined to participate. This report is adhering to the site identifying numbers used in the data analysis sets; consequently, there is a jump in the site numbering sequence, with Site 4 intentionally missing and [redacted] identified as Site 6 even though there was a total of only five study sites. |