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**.

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Title of study:	**GLORIA - AF: G**lobal Registry on **L**ong-Term **O**ral Anti-thrombotic T**R**eatment **I**n P**A**tients with **A**trial **F**ibrillation (Phase I)
Principal/Coordinating Investigator:	Not applicable
Study site(s):	64 centers in China, The Netherlands, Spain, Germany, Croatia, Egypt, Lebanon, Turkey, and the United Arab Emirates
Publication (reference):	Data from this study have not been published.
Clinical phase:	N/A
Objectives:	For Phase I of this Registry Program: To characterize the newly diagnosed non-valvular atrial fibrillation (AF) patient population at risk for stroke and the selection of antithrombotic treatment for stroke prevention in a real-world setting before dabigatran etexilate is approved for the prevention of strokes and systemic emboli in different regions of the world.
Methodology:	The cross sectional design of the study will include collection of data on patient demographics, AF disease characteristics, antithrombotic treatment, medical history and concomitant medication. Additional collection of data on the types of sites and prescribing physicians.
No. of patients:	
planned:	Up to 10,000 patients were planned
actual:	Enrolled: N=1100 Eligible: N=1063
Diagnosis and main criteria for inclusion:	Patients newly diagnosed with non-valvular AF (diagnosed <3 months before patient's baseline visit) and at risk for stroke (CHA_2DS_2-VAS_c score of at least 1), aged 18 years or older.
Test product(s): **dose:** **mode of admin.:**	Not applicable
Comparator product(s): **dose:** **mode of admin.:**	Not applicable
Duration of treatment:	Not applicable

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Criteria for evaluation:	
Efficacy:	No efficacy or clinical pharmacology evaluations were performed under this protocol.
Safety:	No safety evaluations were performed under this protocol. Reports of AEs and SAEs related to a BI drug, if any, were collected. However, no AEs or SAEs were reported during Phase I of the Registry Program.
Statistical methods:	Descriptive analyses of patient characteristics and antithrombotic treatment strategy selected at baseline and regression models to explore the impact of baseline characteristics on treatment selection.
SUMMARY – CONCLUSIONS:	
Efficacy results:	A total of 1100 patients from 64 centers were enrolled in Phase I of the Registry. Of the enrolled patients, 1063 were eligible for inclusion in the analysis of the Phase I data, from the following regions: Asia (67.1 %; N=713), Europe (27.4%; N=291), and the Middle East (5.6%; N=59). With 67.1% the majority of the eligible patients were from the Asian region (China), which needs to be considered for the following descriptive analyses including all eligible patients. The antithrombotic treatment being received at baseline showed that among the 1063 patients, treatment with ASA was the most common (41.7%; N=443), followed by VKA (32.8%; N=349), and antiplatelets other than ASA (3.4%; N=36). A subset of patients were not on any antithrombotic therapy (20.2%; N=215). Approximately half of the 1063 (54.3%; N=577) and of the patients in each of the treatment groups were male (VKA, 51.0%; ASA, 55.3%; antiplatelets other than ASA, 63.9%; or no antithrombotic, 57.7%). The median age of the eligible patients was 70.0 years (interquartile range 61.0-77.0) and the majority were under 80 years of age (83.9%; N=892). The median age across the patient groups on treatment with VKA, ASA, or no antithrombotic was similar (70.0 [62.0-76.0], 70.0 [61.0-77.0], and 67.0 [54.0-76.0] years, respectively). Mean systolic and diastolic blood pressure were generally similar across treatment groups; 8.3% (N=88) had uncontrolled hypertension; and 64.5% (N=686) had controlled hypertension. The majority of patients had a high CHA_2DS_2-VAS_c score (median score = 3) with 78.7% (N=837) having a score $\geq$2. Most patients (80.9%; N=860) had low bleeding risk defined as HAS BLED score <3. The proportion of patients with low, moderate and high $CHADS_2$ scores differed between the groups. Patients with high stroke risk (score $\geq$2), comprised the majority of patients in groups that received treatment: 61.3% (N=214) on VKA treatment; 56.7% (N=251) on ASA treatment; and 75.0% (N=27) on antiplatelets other than ASA. Patients

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with moderate risk (score of 1; 50.7%; N=109) and low risk (score=0; 16.3%; N=35) combined, comprised the majority of patients who were not on antithrombotic treatment. By CHA_2DS_2-VAS_c score, patients with high stroke risk comprised the majority of patients in all groups: 86.5% (N=302) on VKA treatment; 77.9% (N=345) on ASA treatment; 88.9% (N=32) on antiplatelets other than ASA; and 64.7% (N=139) on no antithrombotic treatment. Patients with moderate risk comprised 35.3% (N=76) who were not on antithrombotic treatment.

Overall, the majority of patients had low bleeding risk (HAS-BLED score <3: 80.9% (N=860), with a missing score for 7.7% (N=82). Patients with high bleeding risk were more prevalent in the group of ASA-treated patients (19.6%/443) than in the group of VKA-treated patients (4.6%/349) and in patients not prescribed any antithrombotic therapy (0.0%). The median HAS-BLED score for VKA, ASA, no antithrombotic treatment was 1.0, 2.0, and 1.0, respectively.

In total, 25.9% of patients in Asia had no antithrombotic therapy compared with 8.6% and 8.5% in the EU and the Middle East, respectively.

Regarding medical history, among the 1063 eligible patients, a history of stroke or TIA was reported for 13.0% (N=138) of patients. The proportion of patients who had a history of stroke or TIA was 15.5%, 11.7%, and 7.4% in patients on VKA, ASA, and no antithrombotic, respectively. For patients on antiplatelets other than ASA, 30.6% had a history of stroke or TIA, but this result is based on only 36 patients in this group.

Regarding concomitant medications, most (69.5%) eligible patients received antihypertensive/heart failure and antiarrhythmic medications, with similar use in patients on VKA and ASA, and lowest use in patients not on antithrombotic treatment. Beta blockers were the most frequent antihypertensive treatment at baseline (59.1% of eligible patients), with similar use in patients on VKA and ASA. Metabolic and anti-inflammatory medications were used by 37.2% of patients, with statin and oral hypoglycemic medications being the most frequent.

Patients eligible for this study were most likely to be enrolled by cardiologists (95.2% of patients) at university hospitals (68.8%) or specialists' offices.

Logistic regression analyses showed the following findings to the research questions.

VKA initiation depends on patients' characteristics and risk profiles.
The most relevant predictors for VKA use were: AF ablation, region, any drugs to treat bleeding (i.e., antiplatelets and/ or NSAIDs), non-CNS arterial embolism, and hepatic disease. Patients with prior ablation or prior non-CNS arterial embolism or from Europe were more likely to be prescribed VKA. Patients

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taking antiplatelets and/or NSAIDs, and patients with hepatic disease were less likely to be prescribed VKA. AF ablation, non-CNS arterial embolism, and hepatic disease are rare conditions, with a prevalence <4% in the study cohort; thus, they have a limited predictive value for VKA use in general.

Although the stroke ($CHADS_2$, CHA_2DS_2-VAS_c) and bleeding risk (HAS-BLED) scores were not included in the multivariable modelling, all 3 risk scores were associated with p-values <0.0001 in univariable logistic regression analyses, confirming that higher stroke risk was associated with an increased use of VKA.

VKA initiation differs by type of site and regions.
Patients enrolled at specialists' offices or university hospitals were more likely to be prescribed VKA than patients enrolled at GP/primary care centers. Patients enrolled in Europe were more likely to be prescribed VKA than patients enrolled in Asia. Only 40 patients were enrolled in the Middle East, but VKA use was intermediate between that in Asia and the EU for these patients.

VKA initiation does not depend on categorisation and type of AF (symptomatic vs. asymptomatic; paroxysmal vs. persistent, paroxysmal vs. permanent AF).
Categorization of AF is not a predictor of VKA use, based on the full multivariable model, after adjusting for other baseline characteristics. Type of AF is an important predictor of VKA, based on all multivariable models. Patients with persistent AF were more likely to be prescribed VKA than patients with paroxysmal AF.

The decision NOT to treat with VKA depends more on the perceived (expected) bleeding risk than on the $CHADS_2$ score. Only 12.6% of patients with $CHADS_2 \geq 2$ triggered the decision not to treat the patients with VKA. For the majority of patients with high stroke risk, the reason for not being treated with VKA was NOT the perceived bleeding risk.

AF patients with TIA or stroke will more frequently be treated with VKA than patients without TIA or stroke.
Previous stroke is not a strong predictor for VKA use, based on the full multivariable model, after adjusting for other patient characteristics. Previous TIA is not a predictor for VKA use, based on the univariable analysis, however, only 25 patients with previous TIA were included in the analysis.

AF patients with history of bleeding event will less frequently be treated with VKA than patients without bleeding event.
A history of bleeding before AF diagnosis is not a predictor for VKA use, based on the univariable analysis, however, only 30 patients with a history of bleeding before AF diagnosis were included in the analysis.

Patients aged ≥80 years will less frequently be treated with VKA than patients

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	<80 years. Age ≥80 years is not a predictor for VKA use. Univariable logistic regression analysis assessing the association between age (<80 vs. ≥80 years) and VKA use resulted p = 0.1382. ***Combination of VKA and antiplatelet medication will be used in patients with coronary artery disease (CAD).*** Combination treatment with VKA and antiplatelets was numerically more frequent in patients with CAD (11.7% for single antiplatelets and 3.5% for multiple antiplatelets) than in patients without CAD (6.4% for single antiplatelets and 0.1% for multiple antiplatelets).
Safety results:	No AEs or SAEs were collected during Phase I of the Registry Program.
Conclusions:	In this first Phase of the GLORIA-AF Registry, the most relevant predictors for VKA use were: prior AF ablation, region, use of any drugs to treat bleeding (i.e., antiplatelets and/ or NSAIDs), prior non-CNS arterial embolism, and hepatic disease. Patients with prior ablation or prior non-CNS arterial embolism as well as patients from Europe (versus Asia or the Middle East) were more likely to be prescribed VKA. Patients taking antiplatelets and/or NSAIDs and patients with hepatic disease were less likely to be prescribed VKA. Further, previous stroke or a risk of bleeding was not a strong predictor of VKA use. Overall, despite the fact that the majority of patients were classified as having high stroke risk and low bleeding risk, approximately 1 in 5 patients remained untreated for their atrial fibrillation. The results should however be interpreted in light of the relatively small sample size per region. In addition, the strong contribution of Chinese patients to the analyses of the overall results limits the generalizability of these findings. The introduction of novel anticoagulants will be explored in Phase II of GLORIA-AF, to determine whether treatment patterns of patients is impacted by the availability of these new agents.