EXECUTIVE SUMMARY OF PROTOCOL

Name of company: Boehringer Ingelheim GmbH			
Name of product: **PRADAXA®**			
Name of active ingredient: Dabigatran			
Protocol date 01 APRIL 2015	**Study number**	**Planned study period** Period of study conduct	
Title of study: <u>Non Valvular Atrial Fibrillation (NVAF), Anticoagulant drugs and Stroke</u> **SPA study (Stroke Prevention and Anticoagulants)**			
Team Member Epidemiology			
Project Team:	List all responsible researchers and nominate principal investigator if this is not the Team Member Epidemiology.		
Study data source:	PGRx		

Objectives:

To assess the relative risk of stroke (ischaemic or haemorrhagic stroke) in patients with atrial fibrillation using dabigatran and in those using other new oral anticoagulant therapies (rivaroxaban, apixaban) as compared to the use of any vitamin K antagonist (VKA: fluindione, acenocoumarol or warfarin); For clarity, an odds ratio will be estimated for dabigatran vs. VKA (any), for rivaroxaban vs. VKA (any) and for apixaban vs. VKA. The study is powered for the assessment of dabigatran use vs. VKA (any) use.

Secondary objectives:

- To describe the patterns of use of dabigatran and other anticoagulant therapies in non-valvular atrial fibrillation
- To assess the risk of haemorrhage in patients participating in the study treated with anticoagulants (dabigatran, rivaroxaban, apixaban, VKA)
- To assess what risk factors influence the risk of stroke in patients with and without the different anticoagulant therapies

Methodology/ Study design:	A systematic case-referent design A pool of referents is systematically collected and controls are selected among them to be matched to cases.
Expected number of patients:	17 000 stroke patients recorded, out of which 2650 cases with NVAF and stroke + 5300 controls
Main criteria for inclusion:	<u>General inclusion criteria</u> • Nonvalvular AF NVAF known for at least 24 hours before stroke for cases and recruitment date for referents. • Fibrillation documented by ECG or cardiologist report at hand, • Male or Female gender • Age 18 and over at recruitment • Patient living in France • Patient accepting to participate in the study • Patient or their proxy can read the interview guide or answer a telephone interview questionnaire in French. <u>Inclusion criteria for stroke cases:</u> A stroke not older than three months ('incident stroke') defined as: An ischemic stroke (cerebral infarction) or haemorrhagic stroke (that is an intracranial haemorrhage, i.e. intraparenchymal or intraventricular, subdural and subarachnoid haemorrhage) that is documented by CT scan or MRI, whatever the duration of symptoms (i.e. including transient ischemic attacks with lesion).

Main criteria for exclusion:	Known history of documented stroke or cerebro-vascular incidents prior to the index date (date of current episode of stroke). A history of documented TIA is an exclusion criterion. Atrial fibrillation related to an acute event (e.g. flu, trauma) or hypertrophic cardiomyopathy or hyperthyroidism. Previous valvular disease. Patient unable to consent or participate and without a proxy
Study product:	PRADAXA®
Comparison group:	Cases of incident stroke with non valvular atrial fibrillation (NVAF) will be compared to matched controls with AF and without history of stroke, selected from the pool of referents (or Reference pool). The Reference pool is composed of a representative sample of AF patients in the country. Two controls per case on average who meet the same general inclusion and exclusion criteria as the cases and with an history of NVAF will be randomly selected from the pool of Referents and matched to each case. The matching variables will be: Gender, Age and CHA_2DS_2VASc score.
Expected duration of exposure:	N/A as it is a case-control methodology. Exposure is the variable we will analyse.
Outcomes:	. The outcome is represented by stroke cases.

Data Analysis Methods:	For the main analysis, a multivariate conditional logistic regression will be conducted where patients will be categorised for their recent use of anticoagulant therapy, taking into account all anticoagulant past use and switches: dabigatran, rivaroxaban, apixaban, any VKA (any of: fluindione, acenocoumarol or warfarin), or no use. One model will be used with all exposures to anticoagulants and reference; from this model, a comparison of dabigatran vs VKA and a comparison of other new oral anticoagulant vs VKA will be derived. The model will use the risk factors identified a priori and a posteriori as associated with the risk of stroke. The SAP will determine time windows to be considered; this model will be using one variable with 5 categories (eg: no anticoagulant=0, dabigatran= 1, rivaroxaban=2, apixaban=3, any VKA= 4). The outcome for the above model will be any stroke (IS or HS). Patients who will have used two different drugs recently (recent switchers, polytherapy i.e. use of different anticoagulant in the same time) will be excluded from this analysis (Dates of use of drugs reported currently and recently are sought for). For the first objective listed, a comparative odds ratio between each of the individual new anticoagulant therapy and VKA will be estimated, that is an odds ratio for dabigatran vs. VKA, one for rivaroxaban vs. VKA and one for apixaban vs. VKA. The SAP will determine what method will be used to assess the 95% confidence intervals for these comparative odds ratios, according to the categorisation of exposure used in the main model.