Boehringer Ingelheim

Protocol for observational studies based on existing data

Document Number:	**c03412460-01**
BI Study Number:	1160-0235
BI Investigational Product(s):	Dabigatran etexilate (Pradaxa®)
Title:	Pradaxa Initiation Post-Stroke Study: SITS-Pradaxa 1. A retrospective analysis from the SITS-AF Registry on treatment initiation of dabigatran etexilate in non-valvular atrial fibrillation patients hospitalized with acute ischemic stroke
Lay Title	This study uses the SITS Registry to find out when patients with a heart rhythm disorder (atrial fibrillation) start treatment with dabigatran after they had a stroke
Protocol version identifier:	1.0
Date of last version of protocol:	05 July 2017
PASS:	No
EU PAS register number:	EUPAS17165
Active substance:	B01AE07 - dabigatran etexilate (Pradaxa®)
Medicinal product:	Dabigatran etexilate
Product reference:	EU/1/08/442/001-019
Procedure number:	EMEA/H/C/000829
Joint PASS:	No
Research question and objectives:	**Primary Objective:** • To evaluate the timing of dabigatran treatment initiation in patients with non-valvular atrial fibrillation (NVAF) after hospitalization for first ever ischaemic stroke (the index event) in order to prevent secondary stroke. **Secondary Objectives:** • To describe baseline characteristics for patients

	treated with dabigatran according to time of dabigatran initiation. • To describe self-reported factors important for the physician's decision as to the time of dabigatran initiation in the post-ischemic stroke setting. • To describe self-reported factors important for physician's decision as to which dabigatran dose was used in the post-ischemic stroke setting.
Countries of study:	Data from all patients in European countries* actively registered in the SITS Registry until 31 July 2018, will be considered for analysis. (*countries such as, Italy, United Kingdom, Czech Republic, Sweden, Germany, Poland, Spain, Finland, Portugal, Slovakia, Denmark, Estonia, Norway Belgium, Hungary, Slovenia, Croatia, Austria, Lithuania, France, Greece, Netherlands, Ireland, Ukraine and Iceland)
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Date:	05 July 2017

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2. LIST OF ABBREVIATIONS

AE	Adverse Event
AF	Atrial Fibrillation
$CHAD_2$ score	Stroke Risk score based on a point system, which includes history of Congestive heart failure, Hypertension, Age (≥ 75), Diabetes mellitus, Stroke/TIA.
CHA_2DS_2-VASc score	Stroke Risk score based on a point system, which includes history of Congestive heart failure, Hypertension, Age (≥ 75), Diabetes mellitus, Stroke/TIA, Vascular disease, Age 65-74, Sex category
CI	Confidence Interval
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EUPAS	The European Union electronic Register of Post-Authorisation Studies (EU PAS Register)
GVP	Good Pharmacovigilance Practices
HAS-BLED	Bleeding Risk score based on a point system, which includes Hypertension, Abnormal renal and liver function, Stroke (1 point), Bleeding history or predisposition, Labile INR, Elderly (>65 years), Drugs and Alcohol
ICO	International Coordinating Office (at SITS International)
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
LV EF	Left Ventricular Ejection Fraction
MAH	Marketing authorisation holder
MI	Myocardial Infarction
mRS	modified Rankin Scale
N.A.	Not applicable
NIHSS	National Institute of Health Stroke Scale
NOAC	Non-vitamin K Oral Anticoagulation
NVAF	Non-valvular Atrial Fibrillation
OAC	Oral Anticoagulant
p.o.	per os (oral)
PASS	Post-Authorisation Safety Study
q.d.	quaque die (once a day)
SITS	Safe Implementation of Treatment in Stroke (Registry)
SITS-MOST	Safe Implementation of Thrombolysis in Stroke-Monitoring Study
SmPC	Summary of Product Characteristics
TCM	Trial Clinical Monitor
TIA	Transient Ischaemic Attack
t.i.d.	ter in die (3 times a day)
TMF	Trial Master File
TMM	Team Member Medicine
VKA	Vitamin K Antagonist

3. RESPONSIBLE PARTIES

SITS International

Study coordinator:

Study advisor:

Study administrative operator:

SITS Executive Assistant:

Database

SITS User Service and IT

Network and Research Executive:

Boehringer Ingelheim

Team Member Medicine (TMM):

Trial Clinical Monitor (TCM):

4. ABSTRACT

Name of company: **Boehringer Ingelheim**			
Name of finished medicinal product: Pradaxa			
Name of active ingredient: Dabigatran etexilate			
Protocol date: 05 July 2017	**Study number:** 1160-0235	**Version/Revision:** 1.0	**Version/Revision date:** N.A.
Title of study:	Pradaxa Initiation Post-Stroke Study: SITS-Pradaxa 1. A retrospective analysis of existing data from the SITS-AF Registry on treatment initiation of dabigatran etexilate in non-valvular atrial fibrillation patients hospitalized with acute ischemic stroke		
Rationale and background:	Dabigatran etexilate (Pradaxa) is the first non-VKA oral anticoagulant (NOAC) for stroke prevention in non-valvular atrial fibrillation (NVAF) patients. Compared with warfarin, dabigatran 150 mg twice daily exhibited lower rates of stroke and systemic embolism, but similar rates of major haemorrhage; whereas treatment with dabigatran 110 mg twice daily showed similar rates of stroke and systemic embolism, but lower rates of major haemorrhage. Both dosages of dabigatran etexilate were associated with lower rates of intracranial haemorrhage. Dabigatran has been approved in most countries worldwide including Europe and US to reduce the risk of stroke and systemic embolism in patients with NVAF. In addition, the results from the RE-LY study concerning the use and outcome of anticoagulant therapy with dabigatran in NVAF patients have been confirmed in routine clinical practice data. In RE-LY, severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days was excluded and therefore, data in the acute setting on secondary stroke prevention is sparse. The initiation of warfarin for the secondary prevention of ischemic stroke in NVAF has been established over the years of its use and is based on the severity of the index event. It ranges between 2-3 days for TIA up to 3-4 weeks for large ischemic		

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Name of finished medicinal product: Pradaxa			
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	insults. For dabigatran the time ranges of initiation after the index event have not yet been established. Therefore, the aim of this study is to explore the current use of dabigatran etexilate for stroke prevention in NVAF patients in the post-stroke setting in routine clinical practice. In this study, the SITS Registry the entered data of approximately 1000 eligible patients, that initiated dabigatran after the index event, will be extracted for retrospective analysis.
Research question and objectives:	**Primary Objective:** • To evaluate the timing of dabigatran treatment initiation in patients with non-valvular atrial fibrillation (NVAF) the after hospitalization for first ever ischaemic stroke, in order to prevent secondary stroke. **Secondary Objectives:** • To describe baseline characteristics for patients treated with dabigatran according to time of dabigatran initiation. • To describe self- reported factors important for the physician's decision as to the time of dabigatran initiation in the post-ischemic stroke setting. • To describe self- reported factors important for physician's decision as to which dabigatran dose was used in the post-ischemic stroke setting.

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Study design:	This is a retrospective observational study using existing data from the SITS registry
Population:	NVAF patients presenting with their first ever ischemic acute stroke.
Variables:	• Patient characteristics such as age, stroke severity based on NIHSS, selected comorbidities, $CHADS_2$, CHA_2DS_2-VAS_c and bleeding (HAS-BLED) risk scores, prior oral anticoagulation treatment (dabigatran, Factor Xa Inhibitors, VKA) at index stroke date, the timing of dabigatran treatment initiation for secondary prevention of stroke when initiated within 3 months. • Physicians' self-reported factors important for their decisions when to initiate dabigatran in the post-ischemic stroke setting and factors important for physician's decision which dabigatran dose is used in the post-ischemic stroke setting for prevention of stroke in NVAF. •
Data sources:	SITS-AF Registry data of approximately 1000 dabigatran treated patients in European countries registered in the SITS-AF Registry (expected by 31st July 2018).
Study size:	Approximately 1000 NVAF patients who are treated with dabigatran etexilate within 3 months of their first ischemic

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	stroke (index event) constitute the main analysis population.		
Data analysis:	Descriptive statistics (absolute numbers and relative frequencies, means, standard deviations, medians, inter quartile ranges, minimum and maximum values, 95% confidence intervals and proportions, as appropriate) for baseline and demographic characteristics for all included patients will be provided as appropriate for the variable of interest. The main analysis will focus on NVAF patients presenting with first ischemic acute stroke and treated with dabigatran within 3 months of index event. We will describe the timing of dabigatran treatment initiation for secondary prevention of stroke when treatment is initiated within 3 months in the post-stroke setting. We will summarize the self- reported factors (i.e. as collected in the Registry using a dedicated question) important for the physician's decision for the timing when to initiate dabigatran and the self-reported factors important for which dabigatran dose is used in the post-ischemic stroke setting for prevention of stroke. Descriptions will also be stratified according to time of dabigatran initiation if sample size allows. Dabigatran patients will be described stratified by timing of dabigatran treatment initiation, newly diagnosed NVAF or prevalent NVAF, prior treatment with anticoagulation including type of anticoagulation therapy, stroke severity measured by		

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	NIHSS score, dose of dabigatran, if the sample size allows. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable.		
Milestones:	Individual patient data are collected in the SITS-AF Registry since the presentation of 'Extended data entry option for atrial fibrillation and oral anticoagulant', 1st July 2014. After approximately 1000 dabigatran treated patients from European Centres are registered in SITS-AF (expected by July 2018), the data will be extracted and a retrospective final analysis will be performed.		

5. AMENDMENTS AND UPDATES

Not applicable

6. MILESTONES

Milestone	Planned Date
Start of study/data collection	17 July 2017
End of data collection	31 July 2018 (The time-point when approximately 1000 dabigatran treated patients with completed observation time are expected to be registered in the database and data extraction will be done for the analysis)
Registration in the EU PAS register	13 July 2017 (registration no. EUPAS 17165)
Final report of study results:	31 December 2018 (Considering that the observation time for 1000 dabigatran treated patients is completed by 31 July 2018.)

7. RATIONALE AND BACKGROUND

Stroke is the third most common cause of death in industrialised countries after myocardial infarcts and tumour diseases. [P90-55974] Stroke is also the most common cause of permanent disability. About 85% of all strokes are ischaemic, the remaining part haemorrhagic. One year after a total anterior circulation infarct, 60% of the patients have died and 35% have so severe neurological deficits that independent activities of daily living are restricted. With milder strokes, about 40% die or remain dependent. [R96-0250] Since the incidence of stroke is strongly age-related, the number of stroke victims is expected to increase substantially over the next decades when the proportion of the population over the age of 70 is estimated to grow from about 13% to 20%. Even within the next decade, the number of stroke victims is expected to increase by about 15%. [R17-1269]
The burden of stroke is heavy for the victims and for society. The yearly direct and indirect costs for stroke in Europe can be estimated to about 25 billion Euros. Since the stroke incidence is expected to be about 750.000 in ten years, these costs might increase by about 10-15% if we do not succeed to prevent more strokes and improve the effect of acute stroke intervention.

Atrial fibrillation (AF) and stroke

Atrial fibrillation (AF) is the most common arrhythmia and the prevalence of AF is about 0.4 to 1% in the general population, rising to 8% in those subjects over 80 years.[R03-1233, R12-2675, P10-00760] The number of patients with AF is likely to increase 2.5-fold during the next 50 years. [R03-1233] Patients with AF have a 5 fold increased risk of ischemic stroke compared to persons without AF.[R96-0252] AF related strokes are more severe, are more likely to cause disability or to recur, and carry a higher mortality risk than strokes in patients without AF.[R09-4892, R10-0658, R10-0340] Clinical practice guidelines developed by the American College of Cardiology, American Heart Association, European Society of Cardiology, and American College of Chest Physicians recommend that all patients with AF and a $CHADS_2$ or CHA_2DS_2-VASc score ≥2 should receive long-term oral anticoagulation.[P10-10141, P11-03902, P12-01676] In the American College of Chest Physicians and European Society of Cardiology guidelines, oral anticoagulation also is recommended in patients with a $CHADS_2$ or CHA_2DS_2-VASc score of 1.[P10-10141] Vitamin K antagonists (e.g. warfarin) were the only oral anticoagulants available until 2010 and updated guidelines include the newer oral anticoagulants as alternatives to vitamin K antagonists for stroke prevention. [P11-03902, P12-01676, P11-03903, P17-04650]

Anticoagulation treatment in patients with AF for stroke preventions
Long-term anticoagulation treatment reduces the incidence of ischemic stroke in patients with AF. In a meta-analysis, adjusted-dose warfarin reduced the risk of stroke by 64% compared to placebo and by approximately 40% compared to antiplatelet therapy.[P07-07953] Warfarin treatment is underused, particularly in elderly population and maintaining appropriate anticoagulation levels with warfarin is often difficult because of variable dose responses, multiple drug-drug and drug-food interactions, a slow onset and offset of action. Warfarin-treated patients require routine coagulation monitoring, dose adjustments, and dietary precautions to ensure a balance between therapeutic anticoagulation and bleeding risk.

Dabigatran, the first new Oral Anticoagulants

Dabigatran etexilate (Pradaxa) is the first non-Vitamin K Antagonist oral anticoagulant (NOAC) for stroke prevention in non-valvular atrial fibrillation (NVAF) patients. Dabigatran, a direct thrombin inhibitor, was evaluated in the phase III Randomized Evaluation of Long-term Anticoagulation Therapy (RE-LY) study. [P09-11669] Compared with warfarin, dabigatran 150 mg twice daily exhibited lower rates of stroke and systemic embolism, but similar rates of major haemorrhage; whereas treatment with dabigatran 110 mg twice daily showed similar rates of stroke and systemic embolism, but lower rates of major haemorrhage. Dabigatran has been approved more than 100 countries world-wide including Europe and US to reduce the risk of stroke and systemic embolism in patients with NVAF.

The European approved current version of Pradaxa® Summary of Product Characteristics (SmPC) can be found on the EMA Webpage:

- http://ec.europa.eu/health/documents/community-register/html/h442.htm.

The US approved version of the SmPC can be found on the FDA webpage:

- https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=022512

Data from clinical studies such as RE-LY and RELY-ABLE [P09-11669, P13-08115] where the safety of dabigatran in stroke prevention has been demonstrated for up to 5 years were confirmed by studies in real world clinical practices in different patient populations. [P14-15648, P15-10687] However, it remains important to continue to address further real world clinical questions, which were so far not assessed in studies.
In RE-LY, severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days was excluded and therefore, data on the initiation of dabigatran treatment post-ischemic stroke for secondary stroke prevention in NVAF patients is sparse.
The initiation of warfarin for the secondary prevention of ischemic stroke in NVAF has been established over the years of its use and is based on the severity of the index event. It ranges between 2-3 days for TIA to 3-4 weeks for large ischemic insults. For dabigatran these initiation ranges after the index event have not yet been established. Therefore, the aim of this study is to explore the current real world use of dabigatran for stroke prevention in NVAF patients in the post-stroke setting. Therefore data on the timing of dabigatran treatment initiation will be described by analysing data on NVAF patients after hospitalization for acute ischemic stroke in this study.

8. RESEARCH QUESTION AND OBJECTIVES

Primary objective:

- To evaluate the timing of dabigatran treatment initiation in patients with non-valvular atrial fibrillation (NVAF) after hospitalization for first ever ischaemic stroke (the index event), in order to prevent secondary stroke.

Secondary objectives:

- To describe baseline characteristics for patients treated with dabigatran according to time of dabigatran initiation.
- To describe self-reported factors important for the physician's decision as to the time of dabigatran initiation in the post-ischemic stroke setting.
- To describe self-reported factors important for physician's decision as to which dabigatran dose was used in the post-ischemic stroke setting.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational, multinational, multicentre, study in patients with NVAF presenting to a hospital with a first acute ischemic stroke. The study is based on existing data recorded in the SITS International Registry by physicians in European countries, such as Italy, United Kingdom, Czech Republic, Sweden, Germany, Poland, Spain, Finland, Portugal, Slovakia, Denmark, Estonia, Norway Belgium, Hungary, Slovenia, Croatia, Austria, Lithuania, France, Greece, Netherlands, Ireland, Ukraine and Iceland. All patients with NVAF will be included that present with the first ever ischemic stroke. For these patients baseline and demographics variables are available such as medical history including comorbidities and concomitant medications. Characteristics will further be used to estimate common stroke ($CHADS_2$, CHA_2DS_2-VAS_c) and bleeding (HAS-BLED) risk scores. Details on NVAF and secondary stroke prevention: time since first diagnosis, prior anticoagulation treatment, dose, and stroke severity of index event measured by National Institute of Health Stroke Scale (NIHSS) score, are recorded in the registry.

For patients that receive dabigatran within 3 months of the index event, details on post-stroke treatment (time from hospital admission – start and dose of dabigatran treatment for stroke prevention in NVAF, concomitant medication) will be analysed. Variables for physician's decision when to initiate oral anticoagulation with dabigatran post-ischemic stroke and the dose selected will be analysed.

In addition any start/stop of dabigatran treatment and doses prescribed will also be assessed at discharge and at 3 months after the index event.

9.2 SETTING

Patients with NVAF presenting with their first ever acute ischemic stroke who are registered in the SITS International Registry from 1 July 2014 until approximately 31 July 2018 will be included in the study.

Inclusion criteria

- Patients with non-valvular Atrial Fibrillation (NVAF)
- Patients presenting with their first acute ischemic stroke
- ≥ 18 years of age

Exclusion criteria

- Documentation that the patient was enrolled or is planned to be enrolled in an investigational clinical trial at the time of the onset of the index event and for the duration of the data collection

9.3 VARIABLES

9.3.1 Exposures

Patient disposition will be provided according to post-stroke treatment (i.e. dabigatran, VKA, factor Xa inhibitors and no OAC therapy). Index event is defined as the acute ischemic stroke that led to hospital admission for eligible patients (baseline visit).
Dabigatran treated patients will be further stratified by newly diagnosed NVAF or prevalent NVAF, prior treatment with anticoagulation including type of anticoagulation therapy (dabigatran, VKA, Factor Xa Inhibitors, no anticoagulation) stroke severity measured by NIHSS score, dose of dabigatran, and timing of dabigatran treatment initiation.
We will describe the timing of dabigatran treatment initiation for secondary prevention of stroke within 3 months after index event in the post-stroke setting. Timing of dabigatran treatment initiation will be summarized as a continuous variable as well as a categorical variable (see section 9.3.2.1). For patients with dabigatran treatment initiated 28 days or more after index event, further analysis maybe carried out to determine their characteristics. These analyses will be detailed in a separate statistical analysis plan (see Appendix 4).

9.3.2 Outcomes

9.3.2.1 Primary outcomes

- The time lapsed from the index event to the initiation of the dabigatran treatment. This will be further categorized in specified time periods.

  The following time periods will be considered, but could be revised (e.g. merging categories) depending on sample size 0-24h, >24-72h, >3-7d >7-14d, >14-28d, >28d-3m.

9.3.2.2 Secondary outcomes

- Description of baseline characteristics for patients treated with dabigatran according to time of dabigatran initiation.

- Description of self-reported factors important for physician's decision when to initiate dabigatran in the post-ischemic stroke setting for prevention of stroke and safety in NVAF.

- Description of self-reported factors important for physician's decision which dabigatran dose is used in the post-ischemic stroke setting for secondary prevention of stroke and safety in NVAF.

Definitions

Ischemic stroke is defined as an event characterised by sudden onset of acute focal neurological deficit (e.g. resulting in an impairment of speech, motor function, cognition, gazes, vision, and/or neglect) presumed to be caused by cerebral ischemia/infarction after exclusion of haemorrhage by imaging scans.

The index event is the date of first ever ischemic stroke.

The 3 month follow-up data point for patients is 90 (+/- 10) days after the index event.

Major intracranial haemorrhage is defined as symptomatic intracranial bleeding at any time after start of dabigatran treatment and within 3 months from index event.

The evaluation of intracranial haemorrhage will be done using the available CT/MRI scan after start of dabigatran treatment and within 3 months from index event.

Major extracranial haemorrhage is derived from safety documentation in the SITS registry.

Death is defined as all cause death.

9.3.3 Covariates

Patient characteristics such as age, stroke severity,(according to NIHSS) comorbidities, $CHADS_2$, CHA_2DS_2-VAS_c) and bleeding (HAS-BLED) risk scores (see appendices 1-3), prior oral anticoagulation treatment (dabigatran, Factor Xa Inhibitors, VKA, no OAC therapy), are regarded as potential covariates.
Patient characteristics will be assessed at index stroke date.

9.4 DATA SOURCES

SITS – International Stroke Treatment Registry (ISTR)

Data from the SITS-International AF registry will be extracted for the purpose of analysis. The SITS-International registry is an ongoing, prospective, internet-based, academic-driven, multinational, stroke register. All centres registering patients in the SITS registry are required to accept the basic rules of participating in registry: consecutive registration of all patients with stroke symptoms receiving alteplase (if the centre registers only patients treated with intravenous thrombolysis), irrespective of whether treatment was on- or off-label. If the centre registers all stroke patients in the registry, consecutive registration of all patients with

stroke symptoms is obligatory. Death is collected separately in the SITS registry; however it is linked to the other outcomes at the 3 month time point from the index event. Register data has some inherent limitations. One of the most important limitations is we do not have any regular monitoring for source data verification, although monitoring was done during the period when the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) was done [P07-00880]. In 2011-12, Karolinska Trial Alliance performed an independent monitoring of some selected Swedish centres and verified that data entered in the registry from these centres are accurate. Moreover, it is important to note that all results published based on SITS data with regard to baseline and demographic characteristics and outcome are comparable to other published data from randomised trials, registry data and centre data. SITS registry has a logical automatic validation system, which prevents the entry of erroneous or impossible data in the registry, to some extent. Regular checking of online report and prompt action by contacting centre is also a part of the work for SITS International Coordination members. Moreover, data are downloaded and cleaned regularly for scientific publications.
The SITS registry has implemented extended data entry for AF and oral anticoagulation since June 2014.

Specification of data collection from the index stroke event

At baseline: Demographic data, NIHSS and pre-stroke mRS, blood pressure, laboratory values (plasma glucose, cholesterol, coagulation status, liver function, kidney function,) medical history including comorbidities and concomitant medication, results of imaging scans, $CHADS_2$, CHA_2DS_2-VASc and bleeding risk by HAS-BLED scores.
At 24 hours: NIHSS score, blood pressure, laboratory and imaging scans if performed.
During hospital stay: details of concomitant medications, additional imaging scans prior to start of dabigatran treatment, any start/stop/change dabigatran treatment any results of the imaging scans
At 7 day or discharge if occurred earlier than 7 days: Date/time discharge, NIHSS scores, blood pressure, type of stroke and AF, medications

SITS is an academic-driven, non-profit, international collaboration. It is an initiative by the medical profession aimed at driving excellence in acute and secondary stroke treatment, and to develop new knowledge and leading research.

9.5 STUDY SIZE

Approximately 1000 NVAF patients who are treated with dabigatran etexilate within 3 months of index event constitute the main analysis population.

In order to address the further objective on characterisation of NVAF, the analysis population will be broadened to include all European patients with NVAF aged ≥18 presenting with their first acute ischemic stroke, regardless of subsequent oral anticoagulation use within the time period until approximately 1000 dabigatran patients are registered in SITS-AF.

Data will be extracted from the SITS-AF registry from the European dataset for retrospective analysis. The number of patients included in the study is not driven by a formal sample size calculation but rather by available patient numbers, only descriptive or exploratory analyses will be performed for this study.

9.6 DATA MANAGEMENT

Data in the SITS registry are entered on-line through the SITS website.

Each investigator/study nurse has a personal access code which must be kept secret and used only by the owner. All data entry from a centre can be made by each member of the local team, but once the data entry is confirmed (i.e., cannot be changed), the person who made the confirmation will be identified on the data entry form.

For the purpose of analysis, a download will be made in Excel/ CSV format which will then be transferred in the appropriate advance data analysis software such as STATISTICA/ SAS.

9.7 DATA ANALYSIS

Descriptive statistics (absolute and relative frequencies, means, standard deviations, medians, inter quartile ranges, minimum and maximum values, 95% confidence intervals and proportions, as appropriate) for baseline and demographic characteristics for all included patients will be provided.

For the baseline characteristics we will calculate percentage proportions by dividing the number of events by the total number of patients, excluding missing or unknown cases as we generally did for all previous SITS-MOST and/or SITS-ISTR publications [P07-00880, P08-11746].

In the separate statistical analysis plan further sensitivity analyses may be added (see Appendix 4).

9.7.1 Main analysis

The main analysis will focus on NVAF patients presenting with first ischemic acute stroke and treated with dabigatran within 3 months of index event:

For patients initiated on dabigatran within 3 months of index event, the time to dabigatran treatment initiation will be summarized as a continuous variable as well as categorical; the following time periods will be considered, but could be revised (e.g. merging categories) depending on sample size 0-24h, >24-72h, >3-7d >7-14d, >14-28d, >28d-3m.

There will be a descriptive analysis of self-reported factors important for physicians decision when to initiate dabigatran and which dose in the post-ischemic stroke setting for prevention of stroke and safety in NVAF. This analysis will be done overall as well as by timing and by dose of dabigatran, respectively.

In addition, baseline and demographic characteristics will be presented stratified by timing and dose of dabigatran as well as by newly diagnosed NVAF or prevalent NVAF, prior treatment with anticoagulation including type of anticoagulation therapy, stroke severity measured by NIHSS score, if the sample size allows. Timing and dose of dabigatran treatment initiation will additionally the summarized for relevant baseline subgroups, e.g. based on stroke severity, if the sample size allows.

9.7.3 Interim analysis

Not applicable.

9.8 QUALITY CONTROL

The automatic quality control of data is included in the SITS-Registry. This includes immediate feedback if data are missing, out of range data, illogical or potentially erroneous data. In addition to automatic quality control, regular online data monitoring is performed by SITS International Coordinating Office (ICO) members. All changes in the registry are automatically logged in the database

In addition to online data monitoring, raw data are downloaded every 6 months to check for inconsistency, completeness. Normally investigators are informed by newsletter regarding the completeness of data entry for overall registry and asked to complete the missing data. In case of major inconsistency or high rate of missing data investigators are contacted personally by e-mail.

9.9 LIMITATIONS OF THE RESEARCH METHODS

Non-interventional study based on existing data

The quality of a study based on existing data relies on accuracy of recorded data. Important data may not be available. In the absence of randomisation and blinding, it can be difficult to control for bias and confounders.

Selection bias

There is a risk of selection bias at the patient level. Sites might preferentially include "interesting" cases to the SITS study. To minimize selection bias at the patient level, centres were reminded by e-mail every 3 months that all consecutive patients from each site who meet entry criteria must be included in the SITS-Registry.

Lost to follow up

As with all observational studies a loss to follow up can occur. In this study this will affect the patients with a pre-planned follow up (patients initiating dabigatran within the 3 months after the index event). However, considering the short time period of the follow up and the lost to follow up at 3 months in the general SITS Registry being 20%, a similar percentage of lost to follow up is expected in this study as well.

Channeling bias

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest: e.g., if dabigatran would be more often prescribed to higher risk patients compared to other treatments,

In order to assess potential channeling bias patients not receiving dabigatran within 3 months of the index event will be assessed. For example, patients initiating VKAs, other NOACs or no oral anticoagulation therapy will be assessed according to important patient baseline characteristics (e.g. age, sex, comorbidities, stroke and bleeding risk scores, concomitant medications).

Confounding

As in any observational study, confounding may affect the estimation of association between variables and clinical outcome events of interest and statistical techniques such as adjustment for covariates, stratified analyses, matching, etc. can be used to correct for these. But as only major confounders for selected research questions can be captured, unmeasured confounding may remain.

Exploratory analyses

No formal power calculation has been done for this descriptive study and up to 1,000 patients with an index stroke are planned to be included. Follow-up is limited to three months after index stroke. Subgroup analyses, in particular those restricted to dabigatran patients, are only exploratory in nature. Exploratory analyses are usually not the definitive answer to the question at hand, but can be useful to define hypotheses to be tested in subsequent confirmatory studies.

9.10 OTHER ASPECTS

9.10.1 Ethical approval and informed consent

The Institutional Review Board (IRB) or Independent Ethics Committee (IEC) of the Regional Ethical Review Board in Stockholm, Sweden (see website www.epn.se/en) has given approval for the SITS-Monitoring Study II (SITS-MOST II) protocol.
SITS-MOST II is an ‘over-arching’ protocol that describes all research and analyses that SITS international is performing with the collected data in the SITS Registry, including this study 1160.235 (a part of the SITS-AF protocol in the SITS Registry).

The appendices in the SITS-MOST II protocol also include a patient information and informed consent form, describing the purpose of the SITS Registry and the reason why the patient is asked to collect their medical data in the SITS registry (see also Section 10).

The SITS-MOST II protocol and the EC approval document will be archived in the electronic Trial Master File (TMF), see Appendix 4.

9.11 SUBJECTS

Patients with non-valvular Atrial Fibrillation (NVAF) presenting with their first acute ischemic stroke and 18 years or older are study subject (see Section 9.2).

9.12 BIAS

To assess potential channeling bias baseline characteristics of all patients fulfilling the in/exclusion criteria and were included in SITS-AF registry in the defined time period will be described based on the treatment they receive for stroke prevention in NVAF within 3 months of the index event.
Differences in the patients that are initiated with dabigatran versus patients initiating with VKA, Factor Xa Inhibitors or no oral anticoagulation therapy will be described and set in context to the observed results in the dabigatran treated patient set (see also Section 9.9).

10. PROTECTION OF HUMAN SUBJECTS

All data entered into the SITS International AF registry are encrypted in order to maintain patient data privacy. The individual patient and its research data is identified by a unique registry identification number. Access to data is strictly controlled by permitting each user a unique username and password. Additionally, each user has restrictions in viewing data sets, depending on their activity role in the database. Each data entry is centrally monitored by internal quality checks, such as automatic range checks and a full audit trail is maintained.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP), Adverse Event (AE) reporting is not required for Non-Interventional Study (NIS) which is based on secondary data use.

As an observational study, based on existing data, all patient data is de-identified and will be analysed in aggregate. Individual patient safety related information will not be captured during this study. Thus, individual safety reporting is not applicable. Safety reporting will be done cumulatively in aggregate in the study report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

After finalisation of the final report, manuscripts based on the results of the study are planned to be submitted to peer-reviewed medical journals. The steering committee will appoint a writing committee who will publish the manuscripts in the name of all investigators. A list of all investigators will be included in the original manuscript.

13. REFERENCES

13.1 PUBLISHED REFERENCES

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Chest 137 (2), 263 - 272 (2010)

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14. APPENDICES

APPENDIX 1: $CHADS_2$ STROKE RISK SCORE

$CHADS_2$ components	**Points**
Congestive heart failure	1
Hypertension	1
Age 75 years or older	1
Diabetes mellitus	1
Prior cerebral ischemia (i.e., stroke, TIA)	2
Maximum score	6

$CHADS_2$ score is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack and 1 point each is assigned for age 75 years or older, hypertension, diabetes, or clinical heart failure or impaired left ventricular systolic function (generally interpreted as an ejection fraction $\leq 40\%$). A $CHADS_2$ score of 0 identifies patients at low stroke risk, a score of 1 to 2 identifies patients at moderate stroke risk, and a score greater than 2 identifies patients at high stroke risk [P06-10925].

APPENDIX 2: CHA_2DS_2-VAS_C STROKE RISK SCORE

$CHA_2DS_2VAS_c$ score	
Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	**Clinically relevant non-major risk factors**
Previous stroke, TIA, or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV EF ≤40 %) Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease
Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VAS_c (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

* Myocardial infarction, complex aortic plaque and PAD

The CHA_2DS_2-VASc risk score is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a hypertension, diabetes, cardiac failure, vascular disease and female sex. On the basis of the risk strata defined in previous guidelines, a CHA_2DS_2-VASc score of 0 corresponds to "low risk", a score of 1 corresponds to "intermediate risk", and a score of 2 or more corresponds to "high risk" [R10-5332].

APPENDIX 3: HAS-BLED BLEEDING RISK SCORE

Clinical characteristics comprising the HAS-BLED bleeding risk score		
Letter	**Clinical characteristic**	**Points awarded**
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
Maximum score		**9**

Hypertension is defined as history of hypertension and current uncontrolled systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 µmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. If a patient is not on VKA the value for 'labile INRs' will be set to 0. Further details will be given in the separate statistical analysis plan (see Appendix 4).

A HAS-BLED score of ≥3 indicates 'high risk' for AF patients to develop a bleed and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin [R10-6394].

APPENDIX 4: LIST OF STAND-ALONE DOCUMENTS

The final version of the following stand-alone documents will be archived in the Trial Master File (TMF)

- Statistical analysis plan (and revisions, if applicable)
- SITS-MOST II protocol (and amendments, if applicable)
- Ethics Committee approval(s) for the SITS-MOST II protocol (and amendments, if applicable)

APPENDIX 5: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Pradaxa Initiation Post-Stroke Study: SITS-Pradaxa 1. An analysis from the SITS-AF Registry on treatment initiation of dabigatran etexilate in non-valvular atrial fibrillation patients hospitalized with acute ischemic stroke

Study reference number: 1160-0235

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	-
1.1.4 Interim progress report(s)	☐	☐	☒	9.7.3
1.1.5 Registration in the EU PAS register	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	See comment
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	9.9

Comments:

2.1.4. Descriptive statistical analysis only

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.9, 11
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	9.3.2.3, 9.7.2
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

3.5 Individual safety reporting (AE collection) will not be done in this observational study, but will be done in aggregated fashion.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2, 9.4, 9.5
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	6
4.2.2 Age and sex?	☒	☐	☐	9.2

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin?	☒	☐	☐	9.1
4.2.4 Disease/indication?	☒	☐	☐	9.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1, 9.7.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.4, 9.8 +see comment
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.7.2
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

5.2: sections 9.4 (Data sources) and 9.8 (Quality control) indirectly addresses the measurement of exposure.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8,
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8, 9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.4, 9.8 +see comment
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

6.3: sections 9.4 (Data Sources) and 9.8 (Quality Control) indirectly addresses the outcome measurements

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.9
	7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	See comment
7.2	Does the protocol address:				
	7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9
	7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☐	☒	☐	See comment
7.3	Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.3

Comments:

7.1.1: No comparisons of clinical outcome events according to treatment received are planned in this study

7.2.2: Selection bias, lost to follow up and channeling bias are described

Section 8: Effect modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

This descriptive study does not assess treatment effects.

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.1,
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8, 9.4
	9.1.3 Covariates?	☒	☐	☐	9.3.3, 9.9
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.1, 9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.1, 9.3.2, 9.4
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3, 9.4
9.3	Is a coding system described for:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	
9.3.3 Covariates?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	10

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.6
10.2 Are descriptive analyses included?	☒	☐	☐	9.3.2.2, 9.5, 9.7
10.3 Are stratified analyses included?	☒	☐	☐	9.3.2, 9,7
10.4 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7, 9.8
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5 +see comment

Comments:
10.6: Statistical power is not assessed as no comparisons are planned.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6, 10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.4, 9.8, 10
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☐	☒	☐	
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	9.2, 9.3.1, 9.5, 9.9

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.10.1
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: _____

Date: 30 - 06 -2017

Signature: _____

ENCePP Checklist for Study Protocols (Revision 3)