Boehringer Ingelheim

Statistical and Epidemiological Analysis Plan (GLORIA-AF Phase III)

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ADR	Adverse drug reaction
AE	Adverse event
AF	Atrial fibrillation
ASA	Acetylsalicylic acid
BI	Boehringer Ingelheim
$CHADS_2$	Congestive heart failure, hypertension, age ≥ 75, diabetes, prior stroke/transient ischemic attack
CHA_2DS_2-VAS_C	Risk factor for stroke and thrombo-embolism in non-valvular AF expressed as a point based scoring system
CI	Confidence interval
CrCl	Creatinine clearance
CRF	Case Report Form
CT	Clinical trial
CTR	Clinical Trial Report
DE	Dabigatran
EEA	European Economic Area
ECG	Electrocardiogram
EDC	Electronic Data Capture
EU	European Union
GFR	Glomerular Filtration Rate
HAS-BLED	Risk score for bleeding: Hypertension, abnormal renal function, prior stroke, prior bleeding, labile INR, age>65, drugs or alcohol
IA	Interim analysis
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
ISPE	International Society for Pharmacoepidemiology
ITT	Intention to treat
KM	Kaplan Meier
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Drug Regulatory Activities
MI	Myocardial Infarction
MDRD	Modification of diet in renal disease
NOAC	New oral coagulant/Non-VKA oral coagulant

Term	Definition / description
NSAID	Non-steroidal anti-inflammatory drugs
OAC	Oral Coagulant
OC	Operations Committee
PAD	Peripheral Artery Disease
PGP	P-glycoprotein
PS	Propensity Score
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
QD	Once a day /lat. quaque die
SAE	Serious Adverse Event
SEE	Systemic Embolism
SD	Standard deviation
SEAP	Statistical and epidemiological analysis plan
SPAF	Stroke Prevention in Atrial Fibrillation
CTL	Clinical Trial Leader
TIA	Transient ischemic attack
US	United States (of America)
VKA	Vitamin K antagonist
WHO	World Health Organization

3. INTRODUCTION

As per ICH E9 [1] and the ISPE Guidelines of Good Pharmacoepidemiology Practice [2], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analyses described in the protocol, and to include procedures for executing the statistical analyses of the data. This document describes the interim and final analyses of Phase III for the global study 1160.129 as well as for the study 1160.136 (EU/EEA incl. Switzerland). The interim and final analyses of phase II are described in a separate document. In addition, the propensity score analyses to assess comparability that are performed during the course of the study are also described in a separate analysis plan.

If not specified differently, all of the described analyses in this document are to be done for 1160.129 as well as for 1160.136.

This SEAP assumes familiarity with the registry protocols including Protocol Amendments. In particular, the SEAP is based on the planned analysis specification as written in the registry protocol Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, SEAP readers may consult the registry protocols for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

SAS® Version 9.4 or later will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Patients that did not take the initially prescribed medication (defined as: not taken one single dose of prescribed medication) do not provide any information on safety and effectiveness of the antithrombotic therapies and will therefore be excluded from all main outcome analyses.

The 1160.129 protocol specifies that 6,000 patients are required in the VKA and DE groups for the comparative analysis. However due to the lower than expected uptake of DE, this number cannot be reached. Acknowledging the smaller precision expected as a consequence of the reduced sample size and the potential limitations, the comparative analysis will still be conducted.

The sensitivity analysis, “a weighted, multivariate regression analysis based on the incomplete failure time data for the individual components of” the composite outcome that was specified in the 1160.129 protocol as an optional analysis will not be implemented.

5. OUTCOMES

5.1 MAIN OUTCOMES

The objectives of the study are

a) To investigate the patient characteristics influencing the choice of antithrombotic treatment for the prevention of stroke in non-valvular atrial fibrillation (AF) patients.

In order to address objective a), the same variables (demographic and lifestyle factors, disease characteristics, antithrombotic treatment characteristics and other chronic concomitant medication) will be defined and classified as for the Phase II interim study report for 1160.129 (c02207362-02) [3]. Antithrombotic treatment groups are defined in Section 6.1.

b) To collect real world data on important outcome events of antithrombotic treatments for the prevention of stroke.

The following events were considered in the 1160.129 protocol as “important outcome events”:

- Stroke (hemorrhagic and ischemic, uncertain classification)
- Transient ischemic attack (TIA)
- Systemic embolism (SEE)
- Pulmonary embolism
- Myocardial infarction (MI)
- Major bleeding events (including life-threatening bleeding events; see definition in study protocol) (MBE)
- Life-threatening bleeding events (see definition in study protocol; derived from bleeding page except for fatal bleeds which are derived as all MBEs which are linked to an SAE with “outcome= fatal” and/or “seriousness code=fatal”.
- All cause death
- Vascular death

In addition, the following two composite outcomes, also defined in the 1160.129 protocol, will be analyzed:

- Stroke, systemic embolism, myocardial infarction, life-threatening bleeding events and vascular death

- Stroke, systemic embolism, myocardial infarction and vascular death (vascular composite outcome)

The outcome event analysis will primarily be based on the data collected on the outcome CRFs (event (yes/no) and date of occurrence). The only exceptions will be made for patients who died, i.e. patients with:

- fatal AEs and without the death being documented on the outcome CRF; the death will be considered in the outcome analysis with "date of death= end date of AE".

- "vital status=dead" and without the death being documented on the outcome CRF or on an AE form; the date of death from the vital status page will be used.

During the data cleaning process, adverse events potentially indicating an outcome event with no matching entry on the outcome CRFs will be queried.

5.3 OTHER VARIABLES

Further variable definitions could be considered for exploratory analyses.

6. GENERAL ANALYSIS DEFINITIONS

6.1 EXPOSURE

Similar treatment regimens (e.g. OAC monotherapy, or in combination with other antithrombotics) will be pooled for analysis by antithrombotic treatment choice at baseline, as specified in Table 6.1:1. The following treatment groups will be used for summary of data (including adverse event data):

Table 6.1: 1 Treatment groups

Treatment group (short name; displayed in column headers)	**Treatment group (long name)**	**Description of treatment regimens included**
Dabigatran	(Combinations with) DE -excluding other NOACs, VKA	Patients with DE +/- other antithrombotics excluding patients with DE + {NOAC, VKA}
VKA	(Combinations with) VKA -excluding NOACs:	Patients with VKA +/- other antithrombotics excluding patients with VKA + {NOAC}
Rivaroxaban	(Combinations with) Rivaroxaban -excluding other NOACs, VKA	Patients with Rivaroxaban +/- other antithrombotics excluding patients with Rivaroxaban + {N OAC, VKA}
Apixaban	(Combinations with) Apixaban -excluding other NOACs, VKA	Patients with Apixaban +/- other antithrombotics excluding patients with Apixaban + {NOAC, VKA}
Edoxaban	(Combinations with) Edoxaban -excluding other NOACs, VKA	Patients with Edoxaban +/- other antithrombotics excluding patients with Edoxaban + {NOAC, VKA}
ASA	(Combinations with) ASA - excluding VKA, NOACs:	Patients with ASA +/- other antithrombotics excluding patients with ASA + {NOAC, VKA}
None	None	no treatment
Total*	Total	All patients irrespective of treatment

NOAC := Dabigatran, Rivaroxaban, Apixaban, Edoxaban
OAC := VKA, NOAC
*The total group includes all possible treatments (including those in Table 6.1:2)

Analysis of baseline data will include all treatment groups defined in the table above, analysis of longitudinal outcome event data (incidence rates and cumulative risks only) will be as well performed for these treatment groups for all groups with at least 500 patients at baseline. For further analyses, baseline data on the dabigatran cohort will be analysed stratified by dabigatran mono vs combi- therapy (DE only, DE + other antithrombotics excluding patients with DE + { NOAC, VKA}) and by dabigatran dose group (DE 110mg bid, DE 150mg bid, DE 75mg bid, DE other dose (incl. 220mg QD, 150mg QD, 110mg QD, 75mg QD, other, unknown)) for the categories with at least 100 patients at baseline. Longitudinal data on the dabigatran cohort will be analysed stratified by dabigatran mono vs combi- therapy and by dabigatran dose group (e.g. DE 110mg bid, DE 150mg bid, DE 75mg bid) for the categories with at least 500 patients at baseline.

Administration of 'combinations of oral anticoagulants' (see table below for definition) are not recommended for long-term use. If after querying, 'combinations of oral anticoagulants' are still confirmed for some patients, they will only be counted for the "Total column" (according to the definitions provided in the table above) for analysis of baseline data. The following additional treatment groups will be defined but will not be part of the main tables on baseline data.

Table 6.1: 2 Additional treatment groups

Treatment group (short name)	**Treatment group (long name)**	**Description of treatment regimens included**
Combinations of oral anticoagulants	Combinations of oral anticoagulants	multiple treatments in{Dabigatran, VKA, Rivaroxaban, Apixaban, Edoxaban} +/- other antithrombotics
Antiplts other than ASA	(Combinations of) Antiplatelets other than ASA	Patients with one or multiple treatments in{Clopidogrel, Ticlopidine, Prasugrel, Dipyridamole, Ticagrelor}

AE data will be tabulated for all treatment groups shown in Table 6.1:1 except the no treatment group.

6.1.1 Treatment regimens / study intervals

In general, if bridging is documented in the CRF, all chronic antithrombotic treatments are stopped, therefore set "antithrombotic treatment stop date = bridging start date - 1" and "Antithrombotic treatment start date = bridging stop date + 1" prior to derivation of treatment interval. Bridging documented up until two weeks after baseline visit, will however be ignored.

Table 6.1.1: 1 Treatment regimens

Regimen label	Regimen decode	Derivation for start date
Pre-treatment	Pre-treatment	minimum of date of ICF sign off, date of baseline visit and date of any AE
Treatment	VKA VKA+ASA VKA+Clopi ..... DE 110mg bid DE110mg bid +ASA ..... DE150mg bid DE150mg bid +ASA …… ASA Clopi Clopi+ASA …<all other mono-therapies and actual observed combination therapies> ..... None	For each day from minimum of date of ICF sign off, date of baseline visit and date of any AE, determine treatment status of patient. Combine consecutive days with same regimen decode to treatment interval.
Washout	Washout	Drug stop date +1 day, if the previous treatment was a single treatment or if all drugs administered as combined therapy are stopped simultaneously (i.e. same stop date); duration of washout is 3 days for treatments other than VKA and 6 days for VKA.
Post-study	Post-study	date of study completion/discontinuation +1 day

6.1.2 Specification of treatments for analyses

Reference time periods for the analysis of outcome events, exposure time, AEs are specified in the study protocol:
A patient is considered to have permanently stopped initial antithrombotic treatment according to the definition of antithrombotic treatment start and stop date provided in Table 6.1.2:1.

For the main analysis (as treated analysis) of outcome events, patients will be grouped according to the therapy prescribed for long term treatment at baseline visit, excluding patients who never took the prescribed medication. This will be derived based on the CRF question on planned long-term AF treatment documented at baseline. The number and percentage of patients who never took the prescribed medication (defined as not taken one single dose of prescribed medication) will explicitly be shown in the disposition table (see Table 6.4: 1); they will be excluded from all main outcome analyses if they did not take the treatment group defining medication (e.g. a patient prescribed to VKA+Clopidogrel which took only VKA will be grouped as a VKA patient; a patient prescribed to VKA+Clopidogrel and took only Clopidogrel will be excluded from all main outcome analyses). For potential outcome analyses patients will be included under the treatment (mono/combi) and dose they

were prescribed and actually took. Start and end of initial treatment regimen episode which will be used as analysis period for the main analysis of outcome events are defined as follows:

Table 6.1.2: 1 Treatment regimen episode start and stop

Treatment group	**initial treatment regimen episode start**	**initial treatment regimen episode stop**
(Combinations with) NOAC_X* - excluding combinations with other (N)OACS:	The NOAC treatment start date starts active medication; • if NOAC treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if NOAC start date is missing then use date of ICF sign-off.	minimum{ • permanent stop$ date of NOAC+3days, • start date of other chronic anticoagulant treatment (i.e. VKA, new oral anticoagulants other than original NOAC) -1day • date of study completion/discontinuation }
Combinations of NOAC_X* and oral anticoagulant(s)	• The FIRST NOAC treatment start date starts active medication; • if NOAC treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if NOAC start date is missing then use date of ICF sign-off.	minimum{ • permanent stop$ date of NOAC+3days, • last permanent stop date of oral anticoagulant (other than NOAC) + 6 days (for VKA), + 3 days (for oral anticoagulant other than VKA) • date of study completion/discontinuation }
(Combinations with) VKA - excluding NOACs:	• The VKA treatment start date starts active medication; • if VKA treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if VKA start date is missing then use date of ICF sign-off.	minimum{ • permanent stop$ of VKA+6days), • start date of other chronic anticoagulant treatment (i.e. dabigatran, other new oral anticoagulants) -1day • date of study completion/discontinuation }
(Combinations with) ASA - excluding VKA, NOACs:	• The ASA treatment start date starts active medication; • if ASA treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if ASA start date is missing then use date of ICF sign-off.	minimum{ • permanent stop$ of ASA+3days, • start date of other chronic antithrombotic treatment (i.e. VKA, new oral anticoagulants)-1day, • date of study completion/discontinuation }
(Combinations of) Antiplatelets other than ASA	• The first antiplatelets treatment start date starts active medication; • if first antiplatelets treatment start date(treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if first antiplatelets treatment start date(start date is missing then use date of ICF sign-off .	minimum{ • permanent stop$ of all {Antiplatelets other than ASA}+3days, • start date of other chronic antithrombotic treatment (i.e. ASA, VKA, new oral anticoagulants)-1day, • date of study completion/discontinuation}
None	• Baseline visit date is start date	minimum of { • start date of chronic antithrombotic treatment)-1day, • date of study completion/discontinuation }

$Treatment interruptions (due to bridging or for any other reasons) of more than 30 days are considered permanent stop of medication. Shorter treatment interruptions will be disregarded for the analysis of outcome events (i.e. patient is considered to be on continuous treatment).

*for new oral coagulants/non-VKA oral coagulants (NOACs) in general separate treatment groups for Dabigatran, Rivaroxaban, Apixaban and Edoxaban will be presented. NOAC_X stands for one specific NOAC out of the following: Dabigatran, Rivaroxaban, Apixaban, or Edoxaban

For the sensitivity analysis of outcome events according to the intention-to-treat approach (analysis by carrying forward antithrombotic treatment at baseline), patients will not be censored after index treatment discontinuation (for additional details, see Section 6.8; in particular, an exception is the event death, i.e. death captured via the vital status page will still be considered after the patient`s discontinuation). This analysis is based on the same patient set as the main analysis (i.e. the “restricted” and “matched” patient sets, only including those who took at least once the treatment, see Section 6.3). Study period refers to the time from start of initial treatment regimen (see table above) to start of the post-study phase (see Table 6.1.1:1 in Section 6.1.1).

Furthermore (1160.129 only), regarding baseline data and incidence rate analyses, the cohort of patients initiating (Combinations with) DE – excluding combinations with other (N)OACs (this group is part of first definition shown in Table 6.1.2:1), at baseline will be further stratified by Dabigatran mono vs combi-therapy and by dose. Additionally, the outputs by dose will be broken down by US and Non-US patients (as the 75mg dose is only approved for SPAF in US). The analyses regarding baseline data will be performed for the categories with at least 100 patients at baseline. The analyses regarding incidence rates will be performed at least for the main composite outcome for the categories with at least 500 patients at baseline. Analysis periods for analyses of outcome events are defined as follows:

Table 6.1.2: 2 Treatment regimen episode start and stop (mono/combi therapy and by dose)

Treatment group	**initial treatment regimen episode start**	**initial treatment regimen episode stop**
Mono/Combi Therapy		
DE mono-therapy	The DE treatment start date starts active medication; • if DE treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if DE start date is missing then use date of ICF sign-off.	minimum{ • permanent stop^{+} date of DE+3days, • start date of other chronic anticoagulant treatment or antiplatelet treatment - 1day • date of study completion/discontinuation }
DE combi-therapy	The DE treatment start date starts active medication; • if DE treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead • if DE start date is missing then use date of ICF sign-off.	minimum{ • permanent stop^{+} date of DE+3days , • permanent stop^{+} date of any of the combi antithromb. therapies administered +3days , • start date of other chronic anticoagulant treatment -1day • date of study completion/discontinuation }
Analysis by dose		
DE 110mg bid	The DE treatment start date starts active medication; • if DE treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead if DE start date is missing then use date of ICF sign-off.	minimum{ • permanent stop^{+} date of DE+3days, • change in DE dose – 1 day • start of other chronic anticoagulant treatment -1day • date of study completion/discontinuation }
DE 150mg bid	The DE treatment start date starts active medication; • if DE treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead if DE start date is missing then use date of ICF sign-off.	minimum{ • permanent stop^{+} date of DE+3days, • change in DE dose – 1 day • start of other chronic anticoagulant treatment -1day • date of study completion/discontinuation }
DE 75mg BID	The DE treatment start date starts active medication; • if DE treatment start date<min(date of ICF sign off, date of baseline visit) then use min(date of ICF sign off, date of baseline visit) instead if DE start date is missing then use date of ICF sign-off.	minimum{ • permanent stop^{+} date of DE+3days , • change in DE dose – 1 day • start of other chronic anticoagulant treatment -1day • date of study completion/discontinuation }

For the analysis of adverse events, the concept of treatment emergent AEs will be used, i.e. an AE is assigned to the treatment group under which it occurred whereas AEs with onset time during the washout period are to be assigned to the previous active treatment.
Note: not all active treatment intervals are followed by a washout period ("switcher"; as defined in Section 7.7, patients are considered switchers if they initiate another OAC within 30 days after stop of index treatment); the term "treatment period" refers to the time period of active treatment interval including the consecutive washout period (if applicable). The length of washout, 3 days for NOACs and 6 days for VKA, is defined based on pharmacologic

properties of the treatments (half-life of the drug). Further sensitivity analyses with a different washout period length or a different definition of "permanent stop of medication" might be considered.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 Important Protocol (eligibility criteria) violations

Category / Code		Description	Definition	Excluded from	To be checked manually?
A		Entrance criteria not met			
	A1	Inclusion criteria not met			
	A1.1	Age < 18 years Age <20 years for Japan only		All eligible	no
	A1.2	Informed consent not given	Date of written informed consent missing/ Privacy form missing	All enrolled	No yes
	A1.3	Informed consent given too late	Date of written informed consent after date of baseline visit	None	no
	A1.4	No new AF diagnosis	≥ 3 months between date of diagnosis and date of baseline visit ≥ 4.5 months between date of diagnosis and date of baseline visit for Latin American region only	All eligible	no
	A1.5	No additional risk factor	CHA_2DS_2-VAS_c score of 0	All eligible	no
	A1.6	Other deviations in terms of informed consent process	Includes cases where HIPAA section not signed and other major deviations from regular ICF procedure	None	yes
	A2	Exclusion criteria violated			
	A2.1	Presence of any mechanical heart valve, or valve disease that is expected to require valve replacement intervention (surgical or non-surgical) during the course of the assigned registry phase.		All eligible	no
	A2.2	Warfarin prevalent	More than 60 days of oral anticoagulant treatment (VKA) in patient`s lifetime prior to baseline visit	All eligible	no
	A2.3	AF with a generally reversible cause	AF secondary to cardiac surgery, pulmonary embolism, untreated hypothyroidism, etc.	All eligible	no
	A2.4	Life expectancy < 1 year		All eligible	no
	A2.5	Patient with medical condition other than AF for which chronic use of an oral anticoagulant (VKA) is indicated		All eligible	no
	A2.6	Participating in any clinical trial of a drug or device		All eligible	no
	A2.7	Current participation in an international registry on the use of oral anticoagulation in AF		All eligible	no

Table 6.2: 1 Important Protocol (eligibility criteria) violations (Continued)

Category / Code		Description	Definition	Excluded from	To be checked manually?
	A2.8	Patient was enrolled in any other phase of the GLORIA-AF Program		All eligible	no
	A2.9	Patient with no further follow-up possible with enrolling investigator during planned study period (such as anticipated relocation)		All eligible	no

According to the study protocol, patients who are erroneously enrolled, should be discontinued from study (i.e. documentation in EDC should be terminated) as soon as the violation of in-/exclusion criteria is identified. The violation of in-/exclusion criteria should be reported on the end of study form. Patients who develop a violation of in-/exclusion criteria during the course of the study but who did not violate any in-/exclusion criteria at baseline will NOT be discontinued automatically but can be withdrawn if they participate in another international drug study or registry on the use of oral anticoagulation in AF, or in a clinical trial with a drug or device. The exception is with clinical studies of idarucizumab (Praxbind) where explicit provision for collection of this data has now been included.

The important protocol violations (PVs) which result in exclusion from any analysis population (“all enrolled” or “all eligible”) correspond to those in/exclusion criteria for which violation will result in discontinuation of patient from study.

The important protocol (eligibility criteria) violations will be described in the study report. A summary table of protocol violations will be created based on "all enrolled" (see Section 6.3) patients.

Based on the CRF, all important protocol violations given in Table 6.2: 1 will be identified programmatically in SAS (based on the End-of-Study CRF page and for ICF based on the baseline forms) except for A1.6 which is handled as manual IPV and occurrences need to be reported to the study team by the Co-CTLs for each region during e.g. Medical and quality review meetings. Additional important PVs might be defined during the course of the study and will be assessed during the Medical and quality review meetings; if the list of important protocol violations needs to be enlarged, this will be documented in the report planning meeting minutes before database lock.

In case of important site level protocol violations additional sensitivity analyses excluding patients from those sites might be performed.

6.3 PATIENT SETS ANALYSED

Four patient sets are defined: "all enrolled", "all eligible" and “restricted” and “matched”; the following rules are used to assess if a patient is included in an analysis set:

ENROLLED: if patient is entered in EDC system and Informed Consent is signed.

ELIGIBLE: if patient is ENROLLED and is eligible (see Table 6.2: 1). For all sites, all attempts to obtain approval for all visit forms up to final database lock or to site closure for closed sites are made. In addition, for the final database lock, patients not fulfilling the below additional criteria (previously used for Phase II outcome analyses) will be excluded from the final analyses:

For patients from open sites

- Medications form is approved (i.e. signature is available)
- All other available forms are marked as complete (unless there are forms that contain no data i.e. 'blanked forms' due to entry errors)

For patients from closed sites

- Medications form is marked as complete
- All other available forms are marked as complete (unless there are forms that contain no data i.e. 'blanked forms' due to entry errors)

Excluding patients not fulfilling the additional criteria above may generate selection bias if the excluded eligible patients differ in terms of exposure to index antithrombotic treatment or in terms of outcomes. In addition, it may make the results less generalizable if the excluded patients differ in their baseline characteristics from the other eligible patients. To assess these risks, the following analyses will be performed:

- The proportion of patients with any outcome of interest will be compared between eligible patients not fulfilling the additional criteria and the ones fulfilling them
- The index antithrombotic treatment prescribed will be compared between those groups
- If the eligible patients not fulfilling the data cleaning criterion are >= 100, a description of their baseline characteristics will be done

Depending on the results of these assessments, sensitivity analyses with different definitions of the additional eligibility criteria may be performed. The outputs for these sensitivity analyses may be reported along with the main analysis results.

Sensitivity analyses using alternative criteria definitions may include:

1) First sensitivity analysis (more restrictive eligibility criteria)

   - For patients from open sites, all available forms should be approved where applicable (i.e. signature is available) (unless there are forms that contain no data i.e. 'blanked forms' due to entry errors)

   - For patients from closed sites, the criteria remain unchanged.

   The purpose of this definition is to focus on the data with the higher quality level.

2) Second sensitivity analysis (no additional eligibility criteria)

   No additional eligibility criteria on top of those specified in Table 6.2: 1 would be considered in this sensitivity analysis. All patients who fulfil the criteria in Table 6.2:1 would be included for analyses.

RESTRICTED: The restricted population is composed of all eligible (defined by Table 6.2: 1 and above additional criteria) patients within the trimmed patient set which lie within the region of propensity score overlap (for definition see Section 7). As the propensity score analysis will be based on eligible patients who at least once took the prescribed treatment, the restricted population excludes patients prescribed the treatment but who did not take it.

The restricted patient set is defined for Dabi and VKA patients only. Only Dabi and VKA patients are shown to be comparable in Phase II and their comparison is the main focus in Phase III. If later on BI considers performing other treatment group comparisons a similar approach and a similar patient set definition might be used for other treatment groups.

MATCHED: The patient set used for PS matched pair analysis (for a detailed definition see Section 7.6 sensitivity analyses).

For the 1160.129 study report, patient sets are derived based on all patients enrolled globally whereas for the 1160.136 study report, patient sets are restricted to patients enrolled in the EU/EEA member states and Switzerland.

6.5 POOLING OF CENTRES

Not applicable.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general missing data will be handled by imputation. If cause of death is missing (neither provided on the patient vital status page nor on the outcome events page) the death will be considered as "death of unknown cause" during the data collection. If a reason of death is not

entered on the outcome CRF page but only in the free text field on the vital status page (vital status page is only to be filled for patients who discontinued the study early but allowed for vital status follow up), a medical review will be done to classify the death into vascular/non-vascular/unknown death. The classification will be documented prior to final database lock in the report planning meeting/database lock meeting minutes. For the outcome analyses regarding vascular death, as the primary approach, multiple imputation will be used to impute the unknown cause of death using the data of patients who died. The following further two alternative approaches will be considered as sensitivity analyses: (1) Unknown cause of death will be imputed as a vascular cause; (2) Unknown cause of death will be imputed as a non-vascular cause. As an additional optional sensitivity analysis for the composite outcomes, all cause death would replace vascular death (Section 7.6).

Incomplete/Missing information on outcome event occurrence / medication due to changes in visit schedule

Missed visits and visits outside visit schedule (see protocol): The CRF is set up in such a way that investigators have to enter all outcome event information and changes in medication since the last study visit; therefore complete information on outcome events is ensured even if intermittent visits are missed by using all available information from the completed study visits.

Missing outcome event date information:

The handling of missing outcome event date will be handled on a patient by patient basis. If the outcome event date for a patient is missing, all collected data for this patient will be reviewed to recover the missing outcome event date. If no information is available, the date of the outcome event will be imputed with the start of the initial treatment regimen episode+1day, if the event was documented in the first follow up visit; and with the visit date of the previous follow up visit, elsewise. The proportion of patients with partial dates will be evaluated.

The decision for each missing date will be documented in the report planning meeting minutes.

Other missing dates:

Missing or incomplete AE dates are imputed according to BI standards (see DM&SM "Handling of missing data and incomplete AE dates" [4]). Other special handling for missing dates will be documented in the report planning meeting.

Missing baseline data in context of multivariable modelling

See Section 7.6.

Patients discontinued prematurely from study

In order to assess the effects of lost to follow-up patients, percentages of dropouts and reason for loss to follow-up will be summarized in patients with a pre-planned follow up (all patients in Phase III). In addition, baseline characteristics of patients (including treatment) will be compared over all treatment groups (full cohort, eligible patient set) between:

- Patients who were lost to follow-up
- patients with a complete follow-up
- patients who discontinue early for other reasons,

Only categories with at least 100 patients will be considered for the comparison. If the number of patients lost to follow-up is below 100, this group will not be characterized separately but pooled with patients discontinued early for other reasons.

Outliers

No specific analysis regarding to outliers is planned.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline visit is defined as the physical visit where the patient is enrolled in the registry program. See Section 6.1.2 for definition of antithrombotic treatment status at baseline.

For other medications, medication status at day of Baseline visit is used to derive medication variables for analysis (i.e. for medication which is documented via start/stop dates: if "treatment start date ≤ baseline visit ≤ stop date", patient will be flagged as being on the co-medication; for medication which is documented via tick-boxes: the same rule will be applied after imputing treatment start/ stop date with the date of visit where treatment is documented to be started/ stopped).

6.8 CALCULATION OF TIME TO EVENTS OR CENSORING

The derivations of time to event and time to censoring for the time to event analyses are specified in this section. The information from the outcome event pages will be used to collect events. Deaths reported via the vital status or serious adverse event page will also be included.

Events to be counted in the study period are all events with onset date ≤ patient`s study termination date. Events occurring after the patient`s study termination date will NOT be included in the analysis (irrespective of whether they occur during the washout period or later) as treatment information will in general not be documented in the CRF for this time period. The event death is an exception. Death captured via the vital status page will still be considered after the patient`s discontinuation.

For composite outcome events, the onset date of the first occurring component event will be used.

The following rules will be used for the main analysis of outcome events:

The analysis will be based on the antithrombotic treatment choice selected at baseline (long-term treatment information, as collected in the following CRF question: "Please report any antithrombotic treatments that you prescribed for long term use at the time of the baseline visit, or any antithrombotic treatments that the patient was already on at the time of the baseline visit that the patient will remain on for long term use") and the initial treatment regimen episode (as specified in Section 6.1.2). An event will be counted for the main analysis if it occurs during the initial treatment regimen episode of the antithrombotic therapy selected at baseline.

The time to event will be calculated as: event date - initial treatment regimen episode start date + 1.

The time to censoring will be calculated as initial treatment regimen episode stop date - initial treatment regimen episode start date + 1 (as described in Table 6.1.2:1).

Patients participating in a clinical trial with a drug or device or in another international drug study or registry on the use of oral anticoagulation in AF will be censored when they enter the trial/study. The exception is with clinical studies of idarucizumab (Praxbind) where explicit provision for collection of this data has now been included.

The following rules will be used for the intention-to-treat analysis of outcome events :

The analysis will be based on the antithrombotic treatment choice selected at baseline and the study period. An event will be counted for the intention-to-treat analysis if it occurs during the study period (see exception for inclusion of death events after patient´s discontinuation, cf. Section 6.8 above).

The time to event will be calculated as: event date - study period start date (=initial treatment regimen episode start date) + 1.

The time to censoring will be calculated as study period stop date - study period start date (=initial treatment regimen episode start date) + 1.

Patients participating in a clinical trial with a drug or device or in another international drug study or registry on the use of oral anticoagulation in AF will be censored when they enter the trial/study. The exception is with clinical studies of idarucizumab (Praxbind) where explicit provision for collection of this data has now been included.

For the ITT analyses, follow-up therefore begins at initial regimen episode start date and continues until occurrence of a study outcome or end of the study period, whichever occurs first (with the exception of death). Study period refers to the time from start of initial treatment regimen (see Table 6.1.2:1) to start of the post-study phase (date of study completion/discontinuation +1 day, see Table 6.1.1:1 in Section 6.1.1).

Rules to be used for the analysis of adverse events (based on enrolled patients) are specified in Section 7.9.

7. PLANNED ANALYSIS

At the end of phase III, propensity scores will be derived on the Phase III data set on a regional level once the data is cleaned. This propensity score analysis will be based on patients who took the prescribed treatment at least once. The propensity score model and approach with regards to missing data will be the same as the one used in the phase II and III interim analysis model for propensity score assessment (see SEAP interim analysis - propensity scores [5]). As described in the propensity score SEAP the same logistic regression model will be used to model the probability of receiving Dabigatran in comparison to Warfarin, i.e. high propensity scores, close to 1, indicate a higher probability of Dabigatran use.

For the main analysis based on a regional level, to reduce the potential channeling bias, asymmetric propensity score trimming will be used on the patient set with a cut-point at the 1.5th percentiles of the propensity score distribution in the Dabigatran-exposed group, i.e. Dabigatran patients with a propensity score <=1.5th percentile will be excluded, and the upper 98.5th percentiles of the propensity score distribution in the Warfarin-exposed group, such that Warfarin patients with a propensity score >= 98.5th percentile will be excluded (Stürmer 2010 [6]). In a second step for each geographical region only those patients are regarded as comparable that lie in the region of overlap based on the asymmetrically trimmed population. This patient set is denoted as the **restricted patient set in the SEAP**.

Patients excluded from the main outcome analysis will be included in the descriptive baseline data analyses and safety analyses on ADRs and AE.

Patient disposition (enrolled patients, eligible patients, restricted patient set and matched cohort) will be summarized by antithrombotic treatment choice at baseline and by region and country (all countries but countries with n<200 will only be presented in the Appendix 16.1.9.2). The disposition table will additionally show the number of patients prescribed to one specific long-term treatment at baseline who had never taken the drug.

For all patients the descriptive summary will include the proportion of patients who completed study, reasons for premature discontinuation of study (including information on availability of vital status information), proportion of patients who permanently stopped antithrombotic treatment selected at baseline (as described in Table 6.1.2:1), and the reason for permanent stop of medication, if applicable. This analysis will be done per antithrombotic treatment prescribed at baseline using the long-term treatment information.

Summary statistics for continuous variables will include the N, mean, standard deviation, minimum, Q1 (lower quartile), median, Q3 (upper quartile), and maximum value; tabulations of categorical variables will present all possible categories and will display the number of observations per category as well as percentages. The number/percentage of missing values will be present as a separate category.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Details of the analysis of demographic and other baseline characteristics can be found in Section 7.6.

7.2 CONCOMITANT DISEASES AND MEDICATION

Details of the analysis of concomitant diseases, medical history and concomitant medication at the time of baseline visit (including PGP-inhibitor/ PGP-inducer) can be found in Section 7.6.

For antihypertensive, heart failure and antiarrhythmic co- therapies and for intermittent NSAIDs use, proportion of patients with co-medication will be summarized by visit and antithrombotic treatment prescribed at baseline based on all eligible patients and the full observation time (irrespective of treatment change).

Patients with/without intervention including type of intervention for cardioversion, AF-ablation, pacemaker implantation and major surgery and minor surgery) during Dabigatran period will be characterized. The analysis might be considered for other treatment groups.

7.3 TREATMENT ADHERENCE

“Adherence” in the context of this study encompasses treatment compliance and persistence. Analysis of treatment compliance and persistence is defined as further analysis. Details regarding the further analyses can be found in Section 7.7.

7.4 METHODS ADDRESSING BIAS

In order to assess the effects of lost to follow-up patients, percentages of dropouts and reason for loss to follow-up will be summarized in patients with a pre-planned follow up (all patients in Phase III). In addition, baseline characteristics of patients (including treatment) will be compared over all treatment groups (full cohort) between:

- Patients who were lost to follow-up
- patients with a complete follow-up
- patients who discontinue early for other reasons,

Only categories with at least 100 patients will be considered for the comparison. If the number of patients lost to follow-up is below 100, this group will not be characterized separately but pooled with patients discontinued early for other reasons. In addition, see analyses described in Sections 7.6, and 7.7.

7.5 METHODS ADDRESSING CONFOUNDING / EFFECT MEASURE MODIFICATION

See analyses described in Sections 7.6, 7.7.

7.6 MAIN ANALYSES

Analyses for the main outcome events are mainly defined for patients in the restricted patient set and, in some occasions for patients in the eligible patient set who took at least once the treatment and patients in the matched patient set. All those analyses in this section for the main outcome events that are defined on the restricted and eligible patient sets will be repeated as well for the EU 1160.136 study if not stated otherwise.

If not stated otherwise, the main analyses of longitudinal outcomes will be as-treated (only the first treatment period is included), censoring patients after the initial treatment regimen episode stop (see Section 6.8).

Patient characteristics influencing choice of antithrombotic treatment at baseline

Demographics and baseline characteristics (including stroke/bleeding risk scores, and pre-treatment of OAC) will be summarized descriptively for all eligible patients by antithrombotic treatment choice for long-term treatment at the baseline visit. This will be repeated overall and on a regional level for patients included in the restricted patient set, i.e. for Dabigatran and VKA patients only. For the matched cohort, i.e. for Dabigatran and VKA patients a condensed set of baseline variables will be summarized. In case additional restricted and matched patient sets would be derived for other treatment groups, the same analyses could be performed.

Baseline data might be further analyzed in post-hoc tables showing the treatment distributions (with different treatment group categorizations) within specific subgroups.

Important outcome events – Incidence rates

For the main treatment groups including the total group as defined in Table 6.1: 1 and for all important outcome events including the two composite outcomes incidence rates with 95%-CIs, cumulative risks, and KM curves will be calculated on the eligible patient set on the first treatment period only. Only patients from the eligible patient set that took the prescribed treatment at least once are considered. Patients who discontinue initial antithrombotic treatment for stroke prevention permanently will be censored at date of last drug intake + 3 days (for dabigatran and non VKA treatments) and +6 days (for VKA treatment or combinations of VKA with other antithrombotic treatments) or at first intake of other relevant chronic antithrombotic treatment for stroke prevention, whatever comes first (unless the event occurred prior to the time of censoring). A patient is considered to have permanently stopped initial antithrombotic treatment for stroke prevention, if other relevant chronic antithrombotic treatment is initiated for stroke prevention or otherwise dependent on the duration of treatment interruption.

The main analysis of overall incidence rates with 95% confidence intervals, cumulative risks and KM curves will be repeated for at least the following subgroups, acknowledging the limited precision given the sample size: region (1160.129 only), chronic antiplatelet treatment (1160.136 only), antithrombotic treatment, age, gender, CHADS2, CHA2DS2-VASc and HAS-BLED risk scores. A graphical (forest-plot-like) display will additionally be prepared to

summarize the subgroup results per outcome on the eligible patient set for the first treatment period only. Additional subgroup analyses might be conducted as needed.

For all important outcome events (including composite outcomes) for patients initiating VKA at baseline, and patients initiating Dabigatran at baseline, incidence rates, cumulative risks with 95%-confidence intervals will be calculated by treatment, and for a graphical comparison Kaplan Meier curves will be plotted. These statistics will be calculated on the restricted and the matched patient sets and only the first treatment period is taken into account, i.e. patients who never took the prescribed treatment will not be included.
For the matched and the restricted patient sets as a sensitivity analysis, the calculation of incidence rates and cumulative risks will be performed without censoring at permanent discontinuation of initial antithrombotic treatment for stroke prevention (intention to treat (ITT) approach). KM curves will be plotted.

Dependent on the number of patients receiving different antithrombotic treatment for stroke prevention and dependent on comparability of important baseline characteristics, restricted and matched patient sets may be considered for other pairwise treatment regimes. In this case, the analyses defined here for dabigatran and VKA could be performed for other treatment groups.

Further outcome events

For the further outcome events such as transient ischemic attack (TIA) or stroke (instead of TIA alone), ischemic stroke and hemorrhagic stroke incidence rates, KM estimates and KM curves will be calculated on the eligible patient sets for all main treatment groups(see Table 6.1: 1). For patients initiating VKA at baseline and patients initiating Dabigatran at baseline, above analyses will be performed on the restricted and matched patient sets on the first treatment period only.

Dependent on the number of patients receiving different antithrombotic treatment for stroke prevention and dependent on comparability of important baseline characteristics, for further outcomes mentioned above, the incidence rates, KM estimates and KM curves might be calculated on the restricted and matched patient sets for other pair-wise treatment regimes, similar to the analysis as outlined for Dabigatran and VKA.

Technical specifications

Incidence rates per 100 patient years with 95%-confidence intervals for important outcome events (single and composite outcome) will be calculated the following way. In addition these analyses will be done stratified by chronic antiplatelet treatment at baseline. Recurrent events will be disregarded for calculation of incidence rates. Incidence rate λ is defined as

$$\text{Incidence rate } \lambda\left[\frac{1}{100}\,\text{pt.yrs}\right]: = 100 * \frac{\text{number of patients with event}}{\frac{1}{365.25} * \sum_{\text{patients}} \text{person time at risk (event)[days]}}$$

where the denominator is the patient years under risk. The 2-sided 95% CI of λ will be calculated based on the Poisson distribution and its relation with the Chi-square distribution according to the following formula [7]:

$$[\lambda_{lower}, \lambda_{upper}] = [\ \{0.5\ \chi^2(\alpha/2;\ 2x)\}/n\ ,\ \{0.5\ \chi^2(1-\alpha/2;\ 2x+2)\}/n\ ],$$

where $\chi 2(\gamma, r)$ is the 100γth percentile of a chi-square distribution with r degrees of freedom, n is the patient years under risk for the event, x is the number of patients with event, and α for (1- α) % 2-sided CIs.

Cumulative risk is defined as cumulative proportion of patients with event and will be calculated as the Kaplan-Meier estimate for failure. The Kaplan-Meier curve will be plotted. The proportion of patients with event, as well as the proportion of censored patients falling into specified intervals and the Kaplan-Meier estimate for failure will be computed for the following categories:

- <=3 months
- 3< and <=6 months
- 6< and <=12 months
- 12< and <=18 months
- 18< and <=24months
- 24 < and <=30 months
- >30 months

In the following if not stated otherwise for all analyses only patients from the restricted patient set are considered. Furthermore only the first treatment period is included (i.e. as-treated analysis) if not mentioned otherwise (like e.g. for ITT analyses).

1) Main analysis of composite outcome (Stroke, systemic embolism, myocardial infarction, life-threatening bleeding events and vascular death)

Acknowledging the limited precision given the sample size and the potential limitations, for the main comparison of the two treatment groups, Dabigatran and VKA, with regards to the composite outcome a multivariable Cox regression model (according to the 1160.129 and 1160.136 protocols) will be performed if those patient groups are determined to be comparable in terms of the PS analysis. The multivariable Cox regression model will include the following variables as core variables: treatment, age (<65, 65-75, >=75), gender and the following main stroke and bleeding risk factors: prior bleed, previous stroke/TIA, previous myocardial infarction, abnormal kidney function and concomitant antiplatelets use. The following further covariates will be investigated within a model selection procedure: (sub)region, congestive heart failure, left ventricular

hypertrophy, systemic embolism, complex aortic plaque, hypertension, diabetes mellitus, PAD, CrCl, NSAID use type of AF, hepatic disease, alcohol abuse, any drug (HAS-BLED), previous OAC use (within 3 months), smoking status, and concomitant medication like antipsychotics.

The correlation of covariates will be assessed and in case of a high correlation between two or more covariates the exclusion of at least one covariate might need to be discussed. Exclusion of covariates with high proportion of missing values might be considered.

The further covariates selection procedure will start with the baseline model including all core variables and will add only one of the further variables at a time. Only the variable which has the largest effect on the treatment estimate will be included in the next step model and only if the treatment effect estimate (hazard ratio) is relatively changed by more than 10% in comparison to the model with the core variables only. This step is repeated on the new model until none of the other variables change the treatment effect estimate by more than 10% in comparison to the resulting model from the previous step. To account for model overfitting, another restriction will be the number of events in comparison to the number of degrees of freedom required to represent all of the variables in the model. For example, a three-level categorical variable would require two degrees of freedom. The number of degrees of freedom for all variables*10 shall not exceed the number of events reported for the composite outcome. For example if 200 events are reported for an outcome, than the number of degrees of freedom summing up over all covariates included in the model is not allowed to exceed 20. If so the last covariate resulting from the last step of the model selection procedure process which was about to be included in the main model needs to be excluded from the final model and the selection process is stopped and the previous model resulting from the previous step is checked in the same way. Generally the selection procedure will be stopped as soon as the number of degrees of freedom for all covariates in the model multiplied by 10 exceeds the number of events.

Patients who discontinue initial antithrombotic treatment for stroke prevention permanently will be censored at date of last drug intake + 3 days (for dabigatran and non-VKA treatments) and +6 days (for VKA treatment or combinations of VKA with other antithrombotic treatments) or at first intake of other relevant chronic antithrombotic treatment for stroke prevention, whichever comes first (unless the event occurred prior to the time of censoring). A patient is considered to have permanently stopped initial antithrombotic treatment for stroke prevention, if another relevant chronic antithrombotic treatment is initiated for stroke prevention (switch) or depending on the duration of treatment interruption (see Section 6.1.2). Treatment effects and subgroup variable effects will be reported.

Multiple imputation methods (e.g. the fully conditional specification method) will be used to impute both continuous and categorical variables appropriately with arbitrary missing patterns. Each single step of the variable selection procedure above should be based on the combined estimates of the parameter estimates from all the models using the multiple imputed datasets.

2) Sensitivity analyses for composite outcome (Stroke, systemic embolism, myocardial infarction, life-threatening bleeding events and vascular death)

For 1160.136, only the sensitivity analyses on the ITT approach (d) and the sensitivity analyses on other multivariate models (f) will be performed.

a. **The primary sensitivity analysis** for the comparison between dabigatran and VKA treatment groups in terms of the composite outcome of stroke, SEE, vascular death, MI, life-threatening bleeds will be a **stratified analysis based on propensity scores and stratified by region**. For the stratification process the PS will be categorized by e.g. deciles or quintiles based on the smaller treatment group and depending on the number of patients per region. A Cox model with treatment as the only independent variable will be used. The stratified results will be combined to end up with one final effect estimate.

b. The main analysis will be repeated using a different variable selection procedure resulting in a potentially different model. Here the variable selection will be based on a forward likelihood ratio selection procedure based on p-values (e.g. cut-off p>0.2). The core variables will be fixed and the selection procedure will only be performed for the set of further covariates listed above. Again, to account for model overfitting, another restriction will be the number of events in comparison to the overall number of degrees of freedom for all covariates included in the model. The number of degrees of freedom* 10 shall not exceed the number of events reported for the composite outcome.

c. One further sensitivity analysis for the composite outcome will be a PS matched pair analysis (1:1 greedy nearest neighbour matching using calipers equal to, e.g. 0.2 standard deviations of the logit of the estimated propensity score, matching will be performed within region). The Cox regression model to analyse the matched data with regards to the composite outcome will be performed with only treatment as the independent variable but taking into account the dependencies within the matched pairs by including a frailty parameter into the Cox model. The balance in measured covariates will be assessed using standardized mean differences. A covariate with a difference > 10% (in absolute value) will be considered unbalanced between the two treatment groups. For these unbalanced covariates, another Cox model will be optionally performed including treatment and the residually imbalanced variables. Furthermore baseline characteristics of the matched cohort after matching will be provided.

d. In addition, Cox regression analysis (based on the main analysis model) will be performed **without censoring at permanent discontinuation of initial antithrombotic treatment for stroke prevention (intention to treat (ITT) approach)**.

e. Regarding the main model for the composite outcome: **An additional sensitivity analysis will be conducted to assess the effect of telephone visits on outcome event reporting rates.** For this analysis, patients will be censored if they miss more than 1

consecutive physical visit (censoring date will be the last physical visit prior to the consecutive telephone/missed visits). In addition, patients who had their last study visit as telephone visit will be censored at their last physical visit. An event will only be counted for this analysis if it occurs during the initial treatment regimen episode of the antithrombotic therapy selected at baseline (as defined in Section 6.1.2) and prior to the time point of censoring. Start dates for calculation of time to event and time to censoring are defined as for the main analysis.

f. In order to explore which factors potentially modify the effect of dabigatran vs. VKA in terms of occurrence of the composite outcome, additional interaction terms (treatment*(factor potentially impacting safety and effectiveness)) might be included in multivariable regression models similar to the final main model. Factors to be explored include stroke risk factors as those might impact safety and effectiveness of dabigatran. Forest plots will be used to graphically summarize the treatment effects in the different subgroups.

g. Another sensitivity analysis on the main model might be performed using treatment-naïve patients only, i.e. patients without any OAC treatment within the last 3 months prior to the baseline visit.

h. An imputation method similar to Phase II for the multivariable regression analyses might be performed on the main model. Missing information on risk factor variables (binary variables) with a frequency (prevalence) below 50% in patients with data will be treated as absence of risk factor. Missing information on intake of co-medication at baseline will be considered as no intake of the co-medication. The risk scores (derived variables e.g. Has-Bled score) will be calculated from the (possibly imputed) components. For missing variables that have not been described as risk factors for stroke or major bleeding in the literature nor have a known impact on PK/PD of the treatments analyzed, a value will be randomly assigned based on the distribution of patients with values.

i. To explore the impact of the primary imputation approach for unknown cause of death, the following two alternative approaches will be considered: (1) Unknown cause of death will be imputed as a vascular cause; (2) Unknown cause of death will be imputed as a non-vascular cause.

j. The main analysis might be repeated using a different composite outcome definition: replacing vascular death with all cause death in the composite outcome

k. One more sensitivity analysis might be performed by repeating the main analysis using different definitions of washout and gap for treatment discontinuation

3) Analyses of other outcome events

The following Cox models will only be performed if enough events are reported such that the number of events is roughly proportional to the number of degrees of freedom for all the covariates included in the Cox model. If for other kind of outcome events not listed below

enough events are reported a similar kind of analysis might be performed. The same model selection procedure approach as used for the composite outcome will be used. For all models below the following rule of thumb applies as in the main model used for the composite outcome. The number of degrees of freedom for all covariates in the model * 10 roughly shall not exceed the number of events reported for the composite outcome. The PS matched pair analysis on the specific outcome event might be performed for all outcomes. Additional sensitivity analyses for the single outcome events similar to the ones described for the composite outcome under 2) a),c),f) will be performed if the number of events reported is large enough and additional above mentioned sensitivity analysis will be considered.

- *Composite vascular outcome*
  Using the same methods as described above for the composite outcome under 1), VKA and Dabigatran treated patients will be compared in terms of the vascular composite outcome using the same approach for the main analysis and the same sensitivity analyses a), c), f), and i) as outlined for the composite outcome above. Additional above mentioned sensitivity analysis might be considered.

- *Stroke/SEE (optional)*
  For stroke/SEE events the multivariable Cox model will include the following variables as core variables as used for the composite outcome: treatment, age (<65, 65-<75, >=75), gender and stroke and bleeding risk factors: prior bleed, previous stroke/TIA, previous myocardial infarction, abnormal kidney function, and concomitant antiplatelet use.
  Further covariates will be selected within the model selection procedure: (sub)region, congestive heart failure, left ventricular hypertrophy, systemic embolism, complex aortic plaque, hypertension, diabetes mellitus, PAD, CrCl, NSAID use (including missing/unknown as a separate category), type of AF, complex aortic plaque, hepatic disease, alcohol abuse, any drug (HAS-BLED), smoking status, concomitant medication like antipsychotics, previous OAC use (within 3 months).

  A similar model might be run on stroke events alone if the number of events reported is large enough.

- *Major Bleeding*
  For the major bleeding outcome event the multivariable Cox model will include the following variables as core variables: treatment, age (<65, 65-<75, >=75), gender and the following bleeding risk factors: prior bleed, abnormal kidney function, any drug-HAS-BLED, and concomitant antiplatelet use. Further covariates will be selected within a model selection procedure: (sub)region, congestive heart failure, previous stroke/TIA, previous myocardial infarction, left ventricular hypertrophy, systemic embolism, complex aortic plaque, hypertension, diabetes mellitus, PAD, CrCl, NSAID use (including missing/unknown as a separate category), type of AF, complex aortic plaque, hepatic disease, alcohol

abuse, smoking status, concomitant medication like antipsychotics, previous OAC use (within 3 months).

- *All Cause Death (optional)*
  For death events the multivariable Cox model will include the following variables as core variables like used for the composite outcome: treatment, age (<65, 65-<75, >=75), gender and the following main stroke and bleeding risk factors: prior bleed, previous stroke/TIA, previous myocardial infarction, abnormal kidney function and concomitant antiplatelets use. Further covariates will be selected within a model selection procedure: (sub)region, congestive heart failure, left ventricular hypertrophy, systemic embolism, complex aortic plaque, hypertension, diabetes mellitus, PAD, CrCl, NSAID use (including missing/unknown as a separate category), type of AF, complex aortic plaque, hepatic disease, alcohol abuse, any drug (HAS-BLED), smoking status, concomitant medication like antipsychotics, previous OAC use (within 3 months).

- *Myocardial Infarction (optional)*
  For MI events the multivariable Cox model will include the following variables as core variables: treatment, age (<65, 65-<75, >=75), gender and the following MI risk factors (hypertension, diabetes mellitus, previous myocardial infarction) and concomitant antiplatelet use. Further covariates will be selected within a model selection procedure: (sub)region, left ventricular hypertrophy, systemic embolism, complex aortic plaque, congestive heart failure, PAD, CrCl, NSAID use (including missing/unknown as a separate category), type of AF, complex aortic plaque, hepatic disease, alcohol abuse, any drug (HAS-BLED), smoking status, concomitant medication like antipsychotics, previous OAC use (within 3 months).

If sample size allows, comparisons of other outcomes may be considered for either 1160.129 or 1160.136, if needed.

Dependent on the number of patients receiving different antithrombotic treatment for stroke prevention and dependent on comparability of important baseline characteristics, other pair-wise comparisons of the treatment regimes regarding outcome events might be performed similar to the analysis as outlined for Dabigatran and VKA if the total number of events does allow for a meaningful comparison.

7.8 EXPOSURE TIME

Exposure data will be summarized based on all eligible patients by antithrombotic treatments. Furthermore exposure data for all patients in the matched and restricted patient sets will be provided for Dabigatran and VKA patients. Prescribed but never taken patients will be excluded from all the analyses described in this section.

A patient might receive several mono-/combined therapies during study conduct. Total exposure time will be calculated for each treatment group X based on all treatment periods (see Section 6.1 for definition of treatment groups) as:

$$\text{Exposure treatment X[days]} = \sum_{\text{treatment-period with treat= X}} (\text{treatment stop date} - \text{treatments start date} + 1).$$

The calculated days are converted to months (12*days/365.25) for summary tables.

In addition, total subject years will be calculated and presented:

$$\text{Total subject} - \text{years treatment X[years]} = \sum_{\text{subjects}} \text{Exposure treatment X [days]}/ 365.25.$$

Descriptive statistics of the (cumulative) treatment exposure in months and the percentage of patients falling into specified intervals will be provided. The following categories might be used

<=14 days

14 days < and <=1 month

1< and <=3 months

3< and <=6 months

6< and <=9 months

9< and <=12 months

12< and <=16 months

16< and <=20 months

20< and <=24 months

>24 months

7.9 SAFETY ANALYSIS

7.9.1 Adverse events

7.9.1.1 Death

See analysis of important outcome events and standard adverse event (AE) analyses respectively

7.9.1.2 Bleeding

See analysis of important outcome events and standard AE analyses respectively

7.9.1.3 Interventions

See additional analyses

7.9.1.4 Other standard AE analyses

Analyses for AEs will be based on all patients treated with an anticoagulant treatment at least once. The analysis of adverse events will be descriptive in nature and will be based on BI standards (see DM&SM: Handling and summarization of adverse event data for clinical trial reports and integrated summaries [4]). Adverse events will be coded with the most recent version of MedDRA. The summary of standard AE tables will be based on the AE/ SAE CRFs. According to the reporting procedures for this study, all SAEs and outcome events are to be documented on the SAE or OE form irrespective of causal relationship to antithrombotic treatment or any other BI drug. Non-serious AEs which are not deemed related to antithrombotic treatment or to any other BI drug should not be included in the CRF (see study protocol, Section 5.2.2.2).

For the analysis, only AEs which are considered treatment-emergent for antithrombotic treatment are included (see Section 6.1.2 for definition of analysis periods for AEs). AEs which are assigned to treatment other than the ones listed in Table 6.1:1 (besides the no treatment group), to post-study, or to pre-treatment will not be displayed in summary tables but will only be reported in listings (sorted by analysis period (pre-treatment, , post-study, on-treatment) and antithrombotic treatment).

For analysis of adverse drug reactions (ADRs), all AEs which are related to antithrombotic therapy according to the investigators judgment are to be included.

The following tables will be created by treatment group:

- Overall summary of ADRs and serious adverse events
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with SAEs
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with SAEs leading to death

- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with ADRs (related to antithrombotic therapy)
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with ADRs (events related to antithrombotic therapy prescribed at baseline)
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with ADRs (related to antithrombotic therapy) leading to discontinuation of antithrombotic treatment
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with ADRs (related to antithrombotic therapy) leading to hospitalization.
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with ADRs (related to antithrombotic therapy) leading to death
- Frequency [N (%)] and incidence rate (per 100 patient years) of patients with Serious ADRs (related to antithrombotic therapy)

Time at risk and incidence rates will be calculated according to BI standards (see DM&SM: Handling and summarization of adverse event data for clinical trial reports and integrated summaries [4]; especially the washout period will be included in calculation of time at risk up to the time point at which other relevant antithrombotic treatment is started).

Additionally a summary of patients with non-serious adverse events with overall occurrence above 5% will be created for the Appendix of the study report.

7.9.2 Laboratory data

Creatinine clearance and GFR (for definition see Section 9.2) will be included in baseline characteristics tables.

7.9.3 Vital signs

Blood pressure and heart rate is only collected at baseline and will be analysed descriptively.

7.9.4 ECG

ECG data is not collected in this study.

7.9.5 Others

Nothing planned

7.10 INTERIM ANALYSES

The following interim analyses are specified in the 1160.129 study protocol:

1. Analysis of baseline characteristics during the conduct of Phase III on a regular basis in order to assess comparability of VKA and dabigatran treatment cohorts and potential other treatment groups (see Section 7.10.1)

2. Optional interim analysis on Phase III data prior to final database lock for Phase III to obtain preliminary results on safety, compliance/persistence, and outcome events of dabigatran and on baseline characteristics of AF population (see Section 7.10.2)

3. Optional interim analyses for Phase III on a regional level once enrolment and follow up for all patients within a region in Phase III is completed (see Section 7.10.3)

4. Interim analysis on baseline characteristics in Phase III (e.g. at least 15,000 eligible patients) (see Section 7.10.4)

In general, full patient listings as included in Appendix 16.2 of study report will not be created in context of these interim analyses.

As the planned analyses are to be interpreted on a descriptive level, no adjustment for multiplicity will be done.

Blinding issues

All analyses will be done in an unblinded fashion.

Access plan

The interim analysis reports will be stored in BI`s archiving and document management system and will therefore be accessible to BI employees. No additional restrictions of access rights are planned. Additionally the Steering committee will have access to the interim results and results from these analyses might be included in publications.

7.10.1 Analysis of baseline characteristics during the conduct of Phase III on a regular basis in order to assess comparability of VKA and dabigatran treatment cohorts and potential other treatment groups

These analyses are specified in a separate SEAP [5]. The interim analyses to compare the baseline characteristics of patients initiating dabigatran or VKAs will be continued during Phase III, in order to address the potential changing relevance of VKAs. Further comparisons of drugs may be added in order to reflect the possible approval of other new oral anticoagulants. Only one comparability assessment will be done including all enrolled patients in Phase III.

7.10.2 Optional interim analysis on Phase III data prior to database lock for Phase III to obtain preliminary results on safety, compliance/persistence, and outcome events of dabigatran and on baseline characteristics of AF population

Optionally, an interim analysis of cross-sectional and longitudinal data of patients enrolled in phase III might be conducted using the methodology as specified for the final analysis of phase III data. Once a reasonable number of dabigatran and VKA patients completed follow up, e.g. around 2000 patients in each group, this analysis might be conducted to obtain preliminary phase III results.

This analysis would be restricted to those analyses which are specified in the protocol. Analyses only added in this SEAP are not mandatory.

Timing and scope of work considerations

Scheduling of interim analysis:

The operations committee (OC) decides if and by when this interim analysis is to be conducted.

Format of the interim report: A brief textual summary or synoptic interim report will be used to summarize the results of the interim analysis.

Level of database clean-up and coordination of timing:

The cleaning requirements are the same as for the final analysis.

7.10.3 Optional interim analyses for Phase III on a regional level once enrolment and follow up for all patients within a region in Phase III is completed

For this optional interim analysis, all analyses which are planned to be provided as stratified displays by region for the final report of phase III will be created for the specific region. In addition standard AE tables will be provided.

Timing and scope of work considerations

Scheduling of interim analysis:

The OC decides if, for which region and by when this type of interim analysis is to be conducted. A pre-requisite for the snapshot of the database for this interim analysis to be taken is that enrolment and follow up for all patients within a region as well as data cleaning is completed.

Description of the data needed for the interim analysis:

All CRF pages from phase III for a region.

Format of the interim report: A brief textual summary or synoptic interim report will be used to summarize the results of the interim analysis.

Level of database clean-up and coordination of timing:

The cleaning requirements are the same as for the final analysis.

7.10.4 Interim analysis on baseline characteristics in Phase III (e.g. at least 15,000 eligible patients)

Within Phase III an interim analysis of baseline characteristics will be conducted after recruitment of e.g. at least 15,000 eligible patients in the registry is completed. Analyses on country level might be performed in addition based on the data snapshot used for these interim analyses and/or country-specific amendments.

For this interim analysis, all analyses specified for the final analysis of phase III data on demographics and baseline characteristics will be conducted as well as an overview of non-eligible patients and overall disposition.

Timing and scope of work considerations

Scheduling of IA:

The data cut-off date for this analysis will be defined by the OC at least two months prior to the actual date. The OC needs to ensure that a minimum of 15000 eligible patients are in the database for phase III at the date of data cut-off.

Description of the data needed for the IA:

The baseline CRF forms (including the eligibility page) as well as the CT CRF pages and the End-of-study information (to check for eligibility status of patients) are required for the IA.

Format of the interim report:
A brief textual summary or synoptic interim report will be used to summarize the results of the interim analysis.

Level of database clean-up and coordination of timing

The data cut-off date as defined by the OC will be approximately 8 weeks prior to the date of snapshot creation.

The interim analysis will include all eligible patients who fulfil the following criteria:

- baseline visit <= data cut-off date
- All baseline CRF pages have a completion and approval flag, CT page marked as complete
- Number of manual (monitor) queries on baseline CRF and on CT page and end of study page <5

7.10.5 Optional interim analysis on Phase III data prior to final database lock for Phase III to obtain preliminary results on baseline characteristics and on follow up data of AF population (study 1160.129 only)

Optionally, an interim analysis of cross-sectional and follow up data may include analysis of treatment and/or clinical management decisions of patients enrolled in phase III when enough follow-up data is available and reasonably complete, e.g. 1 year follow up.

The results of this interim analysis will be incorporated in the interim report of interim analyses 7.10.1 and 7.10.4 (brief textual summary or synoptic interim report).

The interim analysis will include all eligible patients who fulfil the following criteria:

- No IPV leading to exclusion of eligible set present (see Table 6.2: 1)
- All forms are marked as complete where applicable (depending on how many visits have been completed, or whether there are forms that contain no data i.e. ‘blanked forms’ due to entry errors)

8. REFERENCES

1	ICH E9, Statistical Principles for Clinical Trials, 1998;
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3	*c02207362-02:* "1160.129 Interim Report"; BIRDS.
4	*001-MCG-156:* "DM&SM: Handling and summarization of adverse event data for clinical trial reports and integrated summaries"); current version, IDEA for CON.
5	*c01444255:* "1160.129 SEAP interim analyses – propensity scores"; BIRDS.
6	Til Stürmer,* Kenneth J. Rothman, Jerry Avorn, and Robert J. Glynn. Treatment Effects in the Presence of Unmeasured Confounding: Dealing With Observations in the Tails of the Propensity Score Distribution—A Simulation Study. Am J Epidemiol. Oct 1, 2010; 172(7): 843–854.
7	Hahn GJ, Meeker WQ. Statistical Intervals: A Guide for Practitioners. Wiley, New York/Chichester/Brisbane/Toronto/Singapore: John Willey and Sons; 1991.
8	Rosendaal FR, Cannegieter SC, van der Meer FJ, et al. A method to determine the optimal intensity of oral anticoagulant therapy. Thromb Haemost 1993; 69: 236-239.
9	Levey AS, Bosch JP, Breyer Lewis J, Greene T, Rogers N, Roth D. A., More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Annals of Internal Medicine 130(6), 461-470, 1999 [R02-2529]
10	National Kidney Foundation: K/DOQI Clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. Am J Kidney Dis. 39:1-266, 2002 [R02-1381]

10. HISTORY TABLE

Table 10: 1 History Table

Version No.	Date (dd Mmm yyyy)	Author	Sections changed	Brief description of change
Final	06 Apr 2017		None	This is the final SEAP without any modification
Revised	09 Nov 2018		6.3, 7.10	1) Specify the eligibility criteria in addition to important protocol violation in terms of the data cleaning status, i.e. the approval/completion status of case report forms, for the final Phase III analysis. Include 2 optional sensitivity analyses by adopting 2 different sets of additional criteria 2) Add an new subsection 7.10.5 for an optional interim analysis of cross-sectional and follow up data potentially including analysis of treatment and/or clinical management decisions of patients enrolled in Phase III when enough follow-up data is available