Trial Statistical Analysis Plan

c02583764-04

BI Trial No.:	1160.189
Title:	**R**andomized, double-blind, **E**valuation in secondary **S**troke **P**revention comparing the **E**ffica**C**y and safety of the oral **T**hrombin inhibitor dabigatran etexilate (110 mg or 150 mg, oral b.i.d.) versus acetylsalicylic acid (100 mg oral q.d.) in patients with **E**mbolic **S**troke of **U**ndetermined **S**ource (RESPECT ESUS) Including Protocol Amendment 1 <1160.189>-protocol-amendment-1 [c02244185-02] and Protocol Amendment 2 <1160.189>-protocol-amendment-2 [c02244185-04]
Investigational Product:	Pradaxa®, Dabigatran etexilate
Responsible trial statistician:	Phone Fax:
Date of statistical analysis plan:	10 APRIL 2018 REVISED
Version:	Revised

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AE	Adverse event
ASA	Acetylsalicylic Acid
BRPM	Blinded report planning meeting
CTC	Common Terminology Criteria
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DE	Dabigatran etexilate
DM&SM	Boehringer Ingelheim Data Management and Statistics Manual
DRA	Drug Regulatory Affairs
DMG	Dictionary Maintenance Group
EMA	European Medicines Agency
FAS	Full analysis set
ICH	International Conference on Harmonisation
IPV	Important protocol violation
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
MoCA	Montreal Cognitive Assessment
MQRM	Medical Quality Review Meeting
mRS	Modified Rankin Scale
O*C	Oracle Clinical
PK	Pharmacokinetics
PPS	Per protocol set
PSTAT	Project Statistician
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
RS	Randomized set
SA	Statistical analysis
SD	Standard deviation

Term	Definition / description
SMQ	Standardised MedDRA query
SOC	System organ class
TCM	Trial Clinical Monitor
TESS	Treatment emergent signs and symptoms
TOC	Table of contents
TMW	Trial Medical Writer
TS	Treated set
TSAP	Trial statistical analysis plan

3. INTRODUCTION

As per ICH E9 [1], the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This TSAP assumes familiarity with the Clinical Trial Protocol (CTP), including Protocol Amendments. In particular, the TSAP is based on the planned analysis specification as written in CTP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, TSAP readers may consult the CTP 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, randomization.

This TSAP does not cover the planned analyses by the Data Monitoring Committee (DMC). A separate DMC TSAP will be produced for this purpose.

This document is developed by using “TSAP annotations” [2]. SAS® Version 9.4 (or later version) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

Changes added to the TSAP since the protocol are:

- Addition of Screened Set to the Patients sets analysed (see Section 6.3)
- Missing data rules for National Institutes of Health stroke scale (NIHSS), baseline creatinine clearance, modified Rankin Scale, and disabling stroke were added (see Section 6.6)

Additional changes added to the TSAP as a result of Amendment 1 are:

- Important protocol violation (IPV) clarified, separating atrial fibrillation > 6 minutes and cardiac monitoring < 20 hours into distinct IPVs (A1.1, A1.2) (see Table 6.2: 1)
- ECG analyses were modified based on changes to data collection (see Section 7.8.4)

Additional changes added to the TSAP as a result of Amendment 2 are:

Additional changes added to the TSAP as a result of local Japanese Amendment are:

- Clarification that in Japan, the criteria for major bleed includes transfusion of 4.5 units or more of blood (text added to Section 5.4 that includes those details, but does not change original protocol definition of major bleeds)

5. ENDPOINTS

5.1 PRIMARY ENDPOINT

The primary endpoint, as defined in the CTP, Section 5.1, is time to first recurrent stroke (ischemic, hemorrhagic and unspecified).

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

The key secondary efficacy endpoints are (both time to event endpoints):

- Ischemic stroke
- Composite endpoint of non-fatal stroke, non-fatal MI and cardiovascular death

5.2.2 (Other) Secondary endpoints

Other Secondary efficacy endpoints (all time to event endpoints):

- Disabling stroke (modified Rankin Scale ≥ 4, as determined 3 months after recurrent stroke)
- All-cause death

5.4 OTHER VARIABLES

Safety endpoints will be used as defined in the CTP, Section 5.2.1.

Major bleeds will be defined according to the ISTH definition of a major bleed, as follows (R05-0344).

- Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome,

and/or

- Bleeding associated with a reduction in hemoglobin of at least 2g/dL (1.24mmol/L), or leading to transfusion of two or more units of blood or packed cells (equivalent to 4.5 or more units in Japan) (Bleeding should be overt and the hemoglobin drop should considered to be due to and temporally related to the bleeding event)

and/or

- Fatal bleed

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

Treatment periods are the on-treatment period, defined to start on the first day of treatment and end on the last day of study medication intake plus 6 days or date of death, if earlier, and the post-treatment period, defined to start 7 days after last intake of randomized study drug and end on the date of trial completion, or death, whichever comes first. If no data indicating that the patient is alive are recorded after the last day of study medication intake plus 6 days, then there is no post-treatment period. The screening period is defined as the date of informed consent until the day before first intake of study medication.

Patients will be analyzed in the treatment group as randomized regardless of treatment misallocations. Randomized treatment groups are dabigatran etexilate (merged group of both 110 mg and 150 mg) and acetylsalicylic acid (ASA).

Additional treatment comparisons using baseline assigned dose (DE 110, DE 150, ASA) will be analyzed for primary and secondary efficacy endpoints (and components) plus Safety endpoints will also be compared by baseline assigned dose (DE 110, DE 150, ASA). These analyses will be descriptive and will include the main safety endpoint major bleeding, as well as life-threatening, fatal, any bleed, intracranial hemorrhage, Descriptive statistics will be used for these analyses because these dose groups are not randomized.

6.2 IMPORTANT PROTOCOL VIOLATIONS

Table 6.2: 1 contains important protocol violations that will be listed in the clinical trial report.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1.1	Atrial fibrillation duration > 6 minutes	AFib duration > 6 minutes	None
	A1.2	Cardiac monitoring < 20 hours	Cardiac monitoring < 20 hours	None
	A2.1	Conditions not consistent with diagnosis of ESUS	Inclusion criteria 2A, 3 (IN2A, IN3), Exclusion criterion 1,2,4,5,21 (EX1, EX2, EX4, EX5, EX21), and IN2 (programmed for patients without ESUS)	None
	A2.2	Any indication that requires treatment with anticoagulant	EX3	None
	A2.3	Primary intracerebral hemorrhage on qualifying neuroimaging	EX6	None
	A2.4	Conditions associated with risk of bleeding	EX7, EX7A	None
	A2.5	History of symptomatic intracranial hemorrhage	EX8, EX8A	None
	A2.6	Renal impairment; CrCL<30mL/min	EX9	None
	A2.7	History of hypersensitivity to dabigatran or ASA	EX10	None
	A2.8	Participation in another trial with investigational drug or device within past 14 days	EX16, EX16A	None
	A2.9	Conditions that would not allow safe trial participation	EX18, EX18A	None
	A2.10	Active liver disease	EX19	None
	A2.11	Severe glucose-6-phosphate dehydrogenase deficiency	EX20	None
	A2.12	Previous participation (receipt of randomized treatment) in this trial	Manual PV	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent date missing	All
	B2	Informed consent too late	Informed consent date was after Visit 1 date	None

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
C		**Trial medication and randomization**		
	C1	Incorrect trial medication taken	Medication kit assigned not matching treatment patient was randomized to (cross-treatment) and/or not matching IVRS assignment	None
	C2	Randomization not followed	Date of first trial medication before date of randomization	None
	C3.1	Treatment not interrupted when required	Study drug not interrupted when AF diagnosed or CrCL < 30 mL/min	None
	C3.2	Non-compliance	Cumulative compliance <80% or >120% (see Section 7.3)	None
	C4	Medication code broken inappropriately	Manual PV	None
	C5	Incorrect dose adjustment (on wrong medication > 50% of the time)	Patient on incorrect dose according to age, renal criteria, in-trial GI bleed	None
D		**Concomitant medication**		
	D2	Prohibited medication use	See CTP Section 4.2.2.1	None

6.3 PATIENT SETS ANALYSED

- Screened set (SCR):
  This patient set includes all patients who signed informed consent and completed at least some screening procedures.

- Randomized set (RS)
  This patient set includes all randomized patients, whether treated or not.

- Treated set (TS):
  This patient set includes all patients who were documented to have taken at least one dose of investigational treatment. The start date of the observation period for this analysis set is the date of first intake of trial medication.

The final decision as to whether a patient is included in or excluded from each analysis set will be taken before database lock in a blinded manner and will be documented in the minutes of the Blinded Report Planning Meeting (BRPM) or Database Lock Meeting.

Analyses will be performed as outlined in Table 6.3: 1.

Table 6.3: 1 Patient sets analysed

	Patient set		
Class of endpoint	Screened set	Randomized set	Treated set
Primary endpoints		X	S[1]
Secondary endpoints		X	
Safety endpoints		S[1]	X
Patient disposition	X		

[1] S=Sensitivity analyses (see Section 7.4 and 7.8)

Two analysis periods are defined:

- Full follow-up: from date of randomization until the date of last contact (see Section 6.8), including all observed time on and off trial medication
- On-treatment: from the date of first treatment intake until the date of discontinuation of trial medication + 6 days (or death, if death occurs earlier)

6.5 POOLING OF CENTRES

This section is not applicable because centre/country is not included in the statistical model.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

For each time to event analysis, patients who do not experience the assessed outcome will be censored.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates") [3]. The same philosophy will be applied to missing or incomplete outcome event dates, index qualifying stroke date, concomitant medication dates (where applicable), and dates of temporary study medication discontinuation and restart, and trial completion date.

If prior is missing, it will be assumed that the patient did not have previous when used as a baseline covariate in the Cox model. If baseline creatinine clearance is missing, then the first on-treatment creatinine clearance will be used as a baseline covariate in the Cox model (and if there is no creatinine clearance in the database, then creatinine clearance ≥ 50 will be used as covariate in the model).

For NIHSS –if the score on any item is 9 or the ataxia item is missing, default these items to "0" (best case). Otherwise, for patients with up to 2 items missing, the worst case score for that item is imputed. For patients with 3 or more items missing, a total score will not be calculated and the NIHSS will be considered missing.

Other missing and incomplete data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The planned study period will include 14 visits conducted at Screening, Randomization (Day 0, i.e., baseline), and every 3 months thereafter during the first year. After year one, planned visits will be every 6 months starting month 18 with telephone follow ups at months 15, 21, 27 and 33.

If the trial is extended, planned visits will be extended at 3 month intervals. If a patient stops medication before the end of the trial, visits should still be made to the clinic (or by telephone). For patients that permanently stop study drug and choose not to continue visits, vital status will be checked during the trial closeout.

Table 6.7: 1 Visit schedule

Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Month	-	0	3	6	9	12	15	18	21	24	27	30	33	36

The actual number of visits that a patient will have depends on when the patient started the trial.

Time windows will not be used. Most analyses are collected in real time (e.g., time to death). Variables that are collected at visits will be analyzed by planned time point.

A patient will be considered to have completed follow-up if he/she has a date of last contact during the end of trial period, defined as within six months of the date of Last Patient Out.

6.8 CALCULATION OF TIME TO EVENT

The calculations of time to events and the time that patients without an event were in the study (under risk) are done according to procedures described in this section.

Date of randomization

The day of randomization is the reference for all RS analyses, regardless of when (or if) treatment started.

Date of event

For one-time events, like death, the date of event reported on the event case report form (CRF) will be used. For events with multiple episodes, such as MI and recurrent stroke, the onset date of the first episode will be used. For composite outcome, the onset date of the first occurring component will be used.

Date of last contact

This is determined as the latest date among the trial completion date (from CRF), last clinic visit/phone call, assessment date or last known alive date from the vital status CRF, and the maximum of the start dates of all adverse events. If a patient dies, then the date of death is the date of last contact.

Survival time for full follow-up analyses

For those *with an event*, the survival time is calculated as:

<date of event> - <date of randomization> + 1

For those patients *without an event*, the survival time is calculated as:

<date of last contact> - <date of randomization> + 1

Survival time for on-treatment analyses

For those *with an event*, the survival time is calculated as:

<date of event> - <treatment start date> + 1

For those *without an event*, the survival time is calculated as:

<min (date of last administration of trial medication + 6, date of last contact)> - <treatment start date> + 1

7. PLANNED ANALYSIS

For End-Of-Text (EoT) tables, the set of summary statistics is: N / Mean / SD / Min / Median / Max.

For tables that are provided for endpoints with some extreme data, median, quartiles and percentiles should be preferred to mean, standard deviation, minimum and maximum.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective treatment group (unless otherwise specified, all patients in the respective patient set whether they have non-missing values or not). Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values.

When composite endpoints are evaluated as survival endpoints, the time to first onset date of any of the events listed in the composite endpoint will be used as the date of the event. For combined endpoints of non-fatal and fatal events, the time to the first event is taken. If the fatality is the first event, then the time to death (not the time to the event leading to death) is taken. For example, if a patient has a stroke at study day 100 and subsequently dies due to stroke (as adjudicated) on day 110. For the combined endpoint "Non-fatal stroke, non-fatal MI, CV death" the day of event would be day 110. In the analysis of stroke this patients enters the analysis with day 100; in an analysis of fatal stroke this patient should also be included with day 100. However in an analysis of CV death the relevant day is day 110.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics by treatment group (and total) are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Only descriptive statistics are planned for this section of the report. The frequency [N (%)] of patients with different concomitant diseases (baseline conditions) will be presented.

Concomitant medications of special interest will be collected for the following categories: antiplatelet medications, thrombolytic agents (fibrinolytics), novel direct oral anticoagulants, parenteral anticoagulants, vitamin K antagonists, GPIIb/IIIa antagonists, therapies for bleeding management. These medications will be classified using the World Health Organization (WHO) dictionary.

The remainder of concomitant medications will be collected by tickbox. All concomitant medications will be summarized according to category and displayed by treatment using descriptive statistics [N, (%)]. Separate tables for baseline, on-treatment, and post-treatment will be presented. Concomitant therapy during the treatment period will be indicated as used if used for at least one day during the treatment period (from the first on-treatment visit through termination of trial medication visit). A separate post-treatment display will be generated summarizing use from the end of treatment until last patient contact.

7.3 TREATMENT COMPLIANCE

Descriptive statistics, N / Mean / SD / 1st percentile / Q1 (lower quartile) / Median / Q3 (upper quartile) / 99th percentile / N missing, for patient mean compliance will be presented together with the N (%) of patients with compliance < 80%, between 80 and 120% and > 120%. Compliance percentage for each patient is based on *cumulative compliance per patient* (e.g., by taking average of each visit and weighting by the number of days between visits.

7.4 PRIMARY ENDPOINTS

The primary endpoint of time to first recurrent stroke (ischemic, hemorrhagic, or unspecified) as determined by the adjudication committee will be analyzed using the Cox proportional hazards regression model. Covariates included in the model will be age (binary, < or ≥ 75 years old), renal impairment (binary; creatinine clearance < or ≥ 50 mL/min), and stroke or TIA prior to index stroke (binary, "yes" or "no").

The primary analysis will be performed on the RS for the full follow-up period. Patients who discontinue study medication will be followed until the end of the trial for OEs including vital status. Patients who are lost to follow-up for vital status will be censored for the primary endpoint of recurrent stroke at the date of last contact (see Section 6.8).

The hypotheses for the primary (and key secondary endpoints) are:

$$H_o: HR_{Dabigatran/ASA} = 1 \qquad \text{vs.} \qquad H_a: HR_{Dabigatran/ASA} \neq 1$$

Tests will be performed at the two-sided $\alpha = 0.05$ level.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

Key secondary endpoints will be analyzed in a hierarchical manner to preserve the Type I error. If the test for the primary endpoint is successful, then testing will continue for the first

key secondary endpoint of time to ischemic stroke with two-sided α=0.05. If this test is statistically significant, then the second key secondary endpoint of time to non-fatal stroke, non-fatal MI, and cardiovascular death will be tested with two-sided α=0.05. If at any point, the null hypotheses for the primary or key secondary endpoints cannot be rejected, formal testing will stop.

Key secondary endpoints will be analyzed using the same Cox proportional hazards regression model (with covariates) as the primary endpoint. All secondary analyses as determined by the adjudication committee will be performed on the RS for the full follow-up period.

No multiplicity adjustments are planned for other secondary endpoints. Nominal p-values will be reported for descriptive purposes.

7.5.2 (Other) Secondary endpoints

Other secondary endpoints will be analyzed using the same Cox proportional hazards regression model (with covariates) as the primary endpoint. All secondary analyses will be performed on the RS for the full follow-up period.

No multiplicity adjustments are planned for other secondary endpoints. Nominal p-values will be reported for descriptive purposes.

7.7 EXTENT OF EXPOSURE

Extent of exposure to trial medication within the study will be displayed by treatment to the extent that data were collected for the TS. Both descriptive statistics and categorization by exposure intervals (e.g., cumulative exposure intervals <1, 1 - <3, 3 - <6, 6 - <12, 12 - <18, 18 - < 24, 24 - < 30, 30 - < 36 months, >36 months, if applicable) will be used.

Extent of observation time (defined as: date of randomization to date of last contact) will be summarized similarly. The same intervals will be used except for combining the first three intervals into 0-6 months.

7.8 SAFETY ANALYSIS

All safety analyses will be performed on the treated set as randomized.

The primary safety endpoint is time to first major bleed.

Secondary safety endpoints are:

- Time to first intracranial hemorrhage
- Time to life-threatening bleed
- Time to fatal bleed
- Time to first bleed (all severities)

Further safety endpoints are:

Only investigator-determined major and potentially major bleeds are adjudicated. Bleeding endpoints (as determined by the adjudication committee) that will be analyzed are: major bleeds, intracranial hemorrhage, life-threatening and fatal bleeds.

Time to event endpoints will be analyzed using the same Cox proportional hazards regression model as the primary endpoint. No multiplicity adjustments are planned for safety endpoints.

7.8.1 Adverse events

Analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number of patients with AEs and NOT on the number of AEs.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the CRF, will be collapsed into AE episodes provided that all of the following applies:

- The same MedDRA lowest level term was reported for the occurrences
- The occurrences were time-overlapping or time-adjacent (time-adjacency of 2 occurrences is given if the second occurrence started on the same day or on the day after the end of the first occurrence)

- Treatment did not change between the onset of the occurrences OR treatment changed between the onset of the occurrences, but no deterioration was observed for the later occurrence

For further details on summarization of AE data, please refer to the guideline 'Handling and summarization of adverse event data for clinical trial reports and integrated summaries' [5].

The analysis of adverse events will be based on the concept of treatment emergent adverse events. That means that all adverse events occurring between first drug intake until 6 days after last drug intake will be assigned to the randomized treatment. All adverse events occurring before first drug intake will be assigned to 'screening' and all adverse events occurring after last drug intake + 6 days will be assigned to 'post-treatment' (for listings only). For details on the treatment definition, see Section 6.1. In general, adverse events attributed to 'Screening' or 'Post-treatment' will be listed only.

An overall summary of adverse events will be presented.

Frequencies [N (%)] of patients with adverse events will be summarised by treatment, primary system organ class and preferred term (using MedDRA). Separate tables will be provided for patients with serious adverse events.

The system organ classes will be sorted according to the standard sort order specified by EMA, preferred terms will be sorted by frequency (within system organ class).

7.8.2 Laboratory data

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [6].

7.8.3 Vital signs

Only descriptive statistics are planned for this section of the report.

7.8.4 ECG

ECGs will be evaluated centrally by an external vendor. Summary statistics will be displayed at baseline. Additional summaries will be produced for patients who have abnormal ECG findings at baseline or during the study period.

7.8.5 Others

Duration of cardiac monitoring performed during the course of the trial and the observed duration of atrial fibrillation (from this monitoring) will be summarized using descriptive statistics.

8. REFERENCES

1 *CPMP/ICH/363/96*: “Statistical Principles for Clinical Trials”, ICH Guideline Topic E9; Note For Guidance on Statistical Principles for Clinical Trials, current version.

2 *001-MCG-160_RD-01*: "TSAP annotations", current version; IDEA for CON.

3 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

4 *001-MCS-36-472_RD-01*: "Noncompartmental Pharmacokinetic/Pharmacodynamic Analyses of Clinical Studies", current version; IDEA for CON.

5 *001-MCG-156*: "Handling and summarisation of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

6 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

10. HISTORY TABLE

This is a revised TSAP including the following modifications to the final TSAP.

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Final	29-JUL-14		None	This is the final TSAP without any modification.
Revised	14-NOV-14		6.2, 6.3,	Table 6.2: 1 (Important PVs) inserted.
Revised	11-AUG-15		4, 6.2, 6.3, 6.6, 7.8.5	Section 6.6 missing data rules added for NIHSS. Other changes due to Amendment 1 are summarized in Section 4.
Revised	10-APR-18		2, 4, 5.1, 6.1, 6.2, 6.3, 6.6, 6.7, 6.8, 7.3, 7.4, 7.5.1, 7.7, 7.8, 7.8.4	Section 6.8 added to specify time to event calculation rules. Rule to define full follow-up added to Section 6.7. Additional changes in 5.1, 6.1, 6.3, 7.3, 7.5.1, 7.7, 7.8 are wording clarifications.