Trial Statistical Analysis Plan

c09087498-01

BI Trial No.:	1160.248
Title:	RE-SPECT CVT: a randomised, open-label, exploratory trial with blinded endpoint adjudication (PROBE), comparing efficacy and safety of oral dabigatran etexilate versus oral warfarin in patients with cerebral venous and dural sinus thrombosis over a 24-week period (Including protocol amendment 1 [c03714648-02])
Investigational Product(s):	Pradaxa®, dabigatran etexilate
Responsible trial statistician(s):	Tel.:
Date of statistical analysis plan:	05 MAR 2018 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
AC	Adjudication committee
ADS	Analysis Datasets
AE	Adverse event
BRPM	Blinded report planning meeting
CI	Confidence interval
CrCl	Creatinine clearance
CRNMBE	Clinically relevant non-major bleeding event
CTP	Clinical trial protocol
CTR	Clinical trial report
CVT	Cerebral venous or dural sinus thrombosis
DBL	Database lock
DMC	Data Monitoring Committee
DVT	Deep vein thrombosis
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
EOT	End of treatment
FAS	Full analysis set
HI	Haemorrhagic infarction
HR	Hazard ratio
ICH	International Conference on Harmonisation
“ICH”	Intracranial haemorrhage
INR	International normalised ratio
IPV	Important protocol violation
IRT	Interactive response technology
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intent-to-treat
LMWH	Low molecular weight heparin
MBE	Major bleeding event
MedDRA	Medical Dictionary for Regulatory Activities

Term	Definition / description
MRI	Magnet resonance imaging
NIHSS	National Institutes of Health Stroke Scale
PE	Pulmonary embolism
PH	Parenchymatous haematoma
PN	Preferred name
PPS	Per protocol set
PROBE	Prospective, randomised, open label, blinded endpoint
PSTAT	Project statistician
PT	Preferred term
PV	Protocol violation
Q1	Lower quartile
Q3	Upper quartile
REP	Residual effect period
SA	Statistical analysis
SCR	Screened set
SD	Standard deviation
SMQ	Standardised MedDRA query
SOC	System organ class
TCM	Trial clinical monitor
TSAP	Trial statistical analysis plan
TTR	Time in therapeutic range
UFH	Unfractionated heparin
VKA	Vitamin K antagonist(s)
VTE	Venous thrombotic event
WHO-DD	World Health Organisation – Drug Dictionary

3. INTRODUCTION

As per ICH E9 [2], 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 (SA) of the primary and secondary variables and other data.

This trial statistical analysis plan (TSAP) assumes familiarity with the clinical trial protocol (CTP) [11], 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 data review by the Data Monitoring Committee (DMC). A separate DMC SAP was produced for this purpose.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

In the CTP version 1 only three analysis populations have been defined: treated set (TS), full analysis set (FAS) and per protocol set (PPS). A screened set (SCR) as described in CTP version 2 (01FEB2017) will also be created for display of disposition tables, etc., see Section 6.3.

5. ENDPOINT(S)

5.1 PRIMARY ENDPOINT(S)

The primary endpoint for this trial is the number of patients with the composite of major bleeding event (MBE) according to International Society on Thrombosis and Haemostasis (ISTH) criteria or venous thrombotic event (VTE: recurring cerebral venous or dural sinus thrombosis (CVT), deep vein thrombosis (DVT) of any limb, pulmonary embolism (PE), splanchnic vein thrombosis) up to 24 weeks.

All components of the primary endpoint will be adjudicated by an independent adjudication committee (AC). Details of the adjudication criteria can be found in the adjudication charter. All endpoints are either explicitly collected in the electronic case report form (eCRF) or captured in the database following adjudication. Adjudicated data takes precedence over eCRF data where both are available.

ISTH definition of an MBE:

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

and/or

- Bleeding associated with a reduction in haemoglobin of at least 2g/dL (1.24mmol/L) within 24 hours, or leading to transfusion of two or more units of blood or packed cells

and/or

- Fatal bleed

5.2 SECONDARY ENDPOINT(S)

5.2.1 Key secondary endpoint(s)

Not defined.

5.2.2 (Other) Secondary endpoint(s)

All secondary endpoints will be based on adjudicated data (except for any bleeding event).

The secondary efficacy endpoints are:

- Number of patients with recurring VTE (CVT, DVT of any limb, PE or splanchnic vein thrombosis) up to 24 weeks
- Cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses up to 24 weeks

The secondary safety endpoints are:

- Number of patients with MBE according to ISTH criteria up to 24 weeks
- Composite endpoint of number of patients with new intracranial haemorrhage (also abbreviated as “ICH”) or worsening of the haemorrhagic component of a previous lesion up to 24 weeks (categorisation see Table 5.2.2: 1)

- Number of patients with clinically relevant non-major bleeding event (CRNMBE) up to 24 weeks
- Number of patients with MBE according to ISTH criteria or CRNMBE up to 24 weeks
- Number of patients with any bleeding event up to 24 weeks

Recanalisation will be assessed as described below, analogous to the calculations made by Miranda et al [12].

1. At baseline and at the end of treatment EOT, occlusion of cerebral veins and sinuses will be scored as follows:
   1 = full occlusion
   0 = no occlusion or partial occlusion
2. This score will be applied to each of the veins and sinuses using the below conventions:
   - Superior sagittal sinus, straight sinus, cavernous sinus, left jugular vein, right jugular vein will each be scored individually (i.e. each will be scored as either 0 or 1)
   - Right lateral transverse and sigmoid sinus will be scored together (i.e. 0 points if neither is fully occluded; 1 point if at least one of them is fully occluded)
   - Left lateral transverse and sigmoid sinus will be scored together (i.e. 0 points if neither is fully occluded; 1 point if at least one of them is fully occluded)
   - Superior petrous sinus and inferior petrous sinus will be scored together (i.e. 0 points if neither is fully occluded; 1 point if at least one of them is fully occluded)
   - Deep venous system will be scored as system, irrespective of the number of occluded veins (i.e. 0 points if none is fully occluded; 1 point if at least one is fully occluded)
   - Superficial cortical veins will be scored as system, irrespective of the number of occluded veins (i.e. 0 points if none is fully occluded; 1 point if at least one is fully occluded)
   - Cerebellar veins will be scored as system, irrespective of the number of occluded veins (i.e. 0 points if none is fully occluded; 1 point if at least one is fully occluded)
3. For each individual patient a total score will be calculated at baseline and at the EOT.
4. A recanalisation score will subsequently be calculated for each patient as the difference between the baseline total score and the EOT total score.

Table 5.2.2: 1 Categorisation of haemorrhagic brain lesions (Von Kummer et al [13])

Class	Type	Description
1	Haemorrhagic transformation of infarcted brain tissue	
1a	HI-1*	Scattered small petechiae, no mass effect
1b	HI-2	Confluent petechiae, no mass effect
1c	PH-1*	Haematoma within infarcted tissue, occupying <30%, no substantive mass effect
2	Intracerebral haemorrhage within and beyond infarcted brain tissue	
	PH-2	Haematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3	Intracerebral haemorrhage outside the infarcted brain tissue or intracranial-extracerebral haemorrhage	
3a	Parenchymal haematoma remote from infarcted brain tissue	
3b	Intraventricular haemorrhage	
3c	Subarachnoid haemorrhage	
3d	Subdural haemorrhage	

* HI: haemorrhagic infarction; PH: parenchymatous haematoma

Any new haemorrhagic brain lesion will be categorised as Class 3 (Intracerebral haemorrhage outside the infarcted brain tissue or intracranial-extracerebral haemorrhage). If there is more than one haemorrhagic lesion present on imaging, the category of the most severe lesion is assigned.

For each patient, intracranial haemorrhage will be classified at baseline and EOT (in case there is no EOT visit, the classification based on the last on-treatment images up to 6 days after last study drug intake will be taken for the determination of worsening).

Worsening is defined as follows:

- Class 3 is worse than class 2, which is worse than class 1.
- Within class 1, type PH-1 (1c) is worse than type HI-2 (1b), which is worse than type HI-1 (1a).
- Within class 3 (a, b, c, d), an increase of at least 25% in volume is considered a worsening.

Patients who died during the trial before an EOT scan is made and patients for whom for other reasons no EOT or on-treatment scan is available or analysable will not be included in the analysis of number of patients with new intracranial haemorrhage or worsening of the haemorrhagic component of a previous lesion.

ISTH definition of a CRNMBE:
A CRNMBE is a clinically overt bleed that does not meet the criteria for an MBE but prompts a clinical response, in that it leads to at least one of the following:

- A hospital admission (i.e overnight stay in the hospital) for bleeding

or

- A physician guided medical or surgical treatment for bleeding

or

- A physician guided change, interruption or discontinuation of trial medication

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

The following treatment periods based on actual start and stop dates/times of randomised study drug administration are defined:

- Screening: date of informed consent (time "0:00:00") to date of randomisation (time "0:01:00")
- Post-randomisation: date of randomisation (time "0:01:00") to time-point of first intake (date and time, "0:02:00" if time is missing) of randomised study drug.
- On-treatment: first intake (date and time)/date restarted of randomised study drug to date stopped/last intake (date and time) of randomised study drug. The residual effect period (REP) of 6 days will be added to this period.
- Off-treatment: date randomised study drug stopped + REP to date randomised study drug restarted
- Post-treatment: last intake (date/time) of randomised study drug + REP until date of trial completion. This is the date given on the termination page (trial completion page) of the eCRF. If date of trial completion is before last intake + REP, REP will be cut accordingly.
- Post-study: day after date of trial completion to database lock (DBL) + 1 day (time "0:00:00").

The REP is the time period after the last administration of trial medication when measurable drug levels or pharmacodynamic effects are still likely to be present. Events occurring in the REP are handled as occurring on-treatment. Data from the post-study period will only be listed.

For the analysis two observation periods are defined:

- Full observation period: from date of randomisation until the end of the trial, including all observed time on and off trial medication until the last known alive date (or date of death)
  This observation period will be used for the efficacy analysis.

- On-treatment: from date of first intake of trial medication until discontinuation of trial medication + REP
  This observation period will be used for the safety analysis.

Despite the trial being open label, all activities conducted by the trial team will be performed in a blinded manner (as much as possible) until DBL. For example, data tabulations and listings will be presented using dummy treatment group information instead of actual treatment group allocations. The planned data review will be handled by the DMC in an unblinded manner (refer to the DMC SAP for more information).

6.2 IMPORTANT PROTOCOL VIOLATIONS

The following table defines the different categories of important protocol violations (IPVs). The final column describes which IPVs will be used to exclude patients from the different patient analysis sets. In this study, patients are either excluded from "All" analysis sets, the

PPS, the FAS or "None" of the analysis sets. Refer to Section 6.3 for more details. IPVs will be identified by the trial team prior to DBL in a blinded manner [4].

Table 6.2: 1 Important protocol violations

Category / Code		Description	Requirements	Excluded from
A		**Entrance criteria not met**		
	A1.1	Male or female patients. Women of childbearing potential must be ready and able to use highly effective methods of birth control	Inclusion criterion 2 not met as specified in the protocol.	None
	A1.2	Age ≥ 18 years and < 79 years at Visit 1	Inclusion criterion 3 not met as specified in the protocol.	PPS
	A1.3	Confirmed diagnosis of CVT, with or without ICH	Inclusion criterion 4 not met as specified in the protocol.	PPS
	A1.4	Patient has achieved clinical stability after having received standard acute CVT treatment as required, including anticoagulation therapy for 5-15 days which has been administered until randomisation.	Inclusion criterion 5 not met as specified in the protocol.	PPS
	A1.5	Eligibility for treatment with an oral anticoagulant for their CVT, based on Investigator judgment. Based on risk assessment and clinical condition, patient should be a candidate for at least 24 weeks of oral anticoagulation	Inclusion criterion 6 not met as specified in the protocol.	PPS
	A1.6	Availability for external review of the imaging that was used to diagnose the CVT	Inclusion criterion 7 not met as specified in the protocol.	None
	A2.1	Inability to swallow trial medications	Exclusion criterion 1 met as specified in the protocol	PPS
	A2.2	CVT associated with central nervous system infection	Exclusion criterion 2 met as specified in the protocol	PPS
	A2.3	CVT due to head trauma	Exclusion criterion 3 met as specified in the protocol	PPS
	A2.4	Planned for surgical treatment for CVT	Exclusion criterion 4 met as specified in the protocol	PPS
	A2.5	Patient with conditions associated with increased risk of bleeding	Exclusion criterion 5 met as specified in the protocol	PPS
	A2.6	Life-threatening or major bleeding (per ISTH criteria) other than intracranial bleeding due to inclusion CVT, during the 6 months prior to randomisation or while on anticoagulants during the acute phase of CVT	Exclusion criterion 6 met as specified in the protocol	PPS
	A2.7	History of symptomatic non-traumatic ICH with risk of recurrence (including haemorrhagic stroke within 6 months prior to Visit 1)	Exclusion criterion 7 met as specified in the protocol	PPS

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Requirements	Excluded from
	A2.8	Severe renal impairment defined as CrCl (calculated by Cockcroft-Gault equation) <30mL/min at screening, or if the Investigator expects CrCl is likely to drop below 30mL/min during the course of the trial	Exclusion criterion 8 met as specified in the protocol	PPS
	A2.9	Patients who are taking any of the drugs listed as restricted in CTP section 4.2.2.1 while on active treatment with study drug	Exclusion criterion 9 met as specified in the protocol	PPS
	A2.10	Patients receiving treatment with warfarin, dabigatran etexilate or other antithrombotic regimen (i.e. anticoagulants or anti-platelet medication) for an indication other than CVT and requiring continuation of that treatment for the original diagnosis without change in the regimen	Exclusion criterion 10 met as specified in the protocol	None
	A2.11	Patients with prosthetic heart valves	Exclusion criterion 11 met as specified in the protocol	PPS
	A2.12	Known hypersensitivity to dabigatran etexilate or warfarin or to any of the excipients of either product	Exclusion criterion 12 met as specified in the protocol	None
	A2.13	Any current or recent malignancy (≤ 6 months prior to Visit 1) unless the malignancy was a basal cell carcinoma that was completely removed	Exclusion criterion 13 met as specified in the protocol	PPS
	A2.14	Concomitant disease that increases the risk of an adverse reaction to trial interventions or with life expectancy < 6 months (for any reason) per Investigator judgment	Exclusion criterion 14 met as specified in the protocol	PPS
	A2.15	Pre-menopausal women (last menstruation ≤ 1 year prior to Visit 1) who are pregnant, nursing, or who plan to become pregnant while in the trial.	Exclusion criterion 15 met as specified in the protocol	None
	A2.16	Patients who have participated in another trial with an investigational drug or device within the past 14 days preceding Visit 1 or who currently are participating in another trial. Patients who are still experiencing a clinical effect from an investigational drug or device.	Exclusion criterion 16 met as specified in the protocol	None
	A2.17	Patients considered unreliable by the Investigator concerning the requirements for follow-up during the trial or at the end of the trial.	Exclusion criterion 17 met as specified in the protocol	None
	A2.18	Any condition the Investigator believes would not allow safe participation in the trial.	Exclusion criterion 18 met as specified in the protocol	None
	A2.19	Active liver disease	Exclusion criterion 19 met as specified in the protocol	None

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Requirements	Excluded from
	A2.20	Previous randomisation in this trial	Exclusion criterion 20 met as specified in the protocol	PPS
B		**Informed consent**		
	B1	Informed consent not available/not done	Inclusion criterion 1 not met as specified in the protocol.	All
	B2	Informed consent too late	Informed consent date was after Visit 2 date	None
C		**Trial medication and randomisation**		
	C1	Incorrect trial medication taken	Medication kit assigned not matching treatment patient was randomised to (cross-treatment) and/or not matching IRT assignment	PPS
	C2	Randomisation order not followed, e.g. forced randomization, misstratification	Cases will be identified from IRT reports and read in via the manual PV spreadsheet	PPS
	C3	Non-Compliance	Compliance <80% or >120% over the course of the study for dabigatran patients, or time in therapeutic target range for warfarin patients <45%. See Section 7.3 for details on compliance calculation. Non-compliance caused by temporary interruption of the treatment due to a procedure or a drop in CrCl to less than 30 mL/min should not be classified as a protocol violation.	PPS
D		**Concomitant medication**		
	D1	Prohibited medication use	See CTP section 4.2.2.1 Those treatments should not be taken during the active treatment phase of the trial: - Fibrinolytic agents (refer to CTP section 4.2.1.5 for exceptions) - GPIIb/IIIa antagonists (e.g. abciximab, tirofiban) - Rivaroxaban, apixaban and edoxaban, or other oral anticoagulants (e.g. VKAs) - Treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus and dronedarone, and rifampicin, carbamazepine, phenytoin and St. John's Wort Medications will be identified through medical review and details will be provided in the technical TSAP.	PPS

Table 6.2: 1 Important protocol violations (continued)

Category / Code		Description	Requirements	Excluded from
G		**Trial Specific Protocol Violations**		
	G1	Patient randomized to dabigatran etexilate not withdrawn from trial treatment if CrCl drops to <30mL/min at two different occasions during the trial or drops to <30mL/min and does not recover to above 30 within 7 days		PPS
	G2	Creatinine clearance not measured / not reviewed prior to start of treatment		PPS
	G3	Woman of child bearing potential and pregnancy test not confirmed to be negative prior to start of trial treatment		None
	G4	Woman become pregnant during the trial		None
	G5	Patient on VKA prior to randomization, randomized to dabigatran etexilate and treated although INR not confirmed to be <2.0		PPS
	G6	Patient on VKA prior to randomization, randomized to warfarin and treated although INR not confirmed to be <3.0		PPS
	G7	Patient randomized to warfarin and treated and UFH / LMWH stopped although INR not confirmed to be >= 2.0		PPS

The following IPV are programmed automatically: all from A and B, C3, D1, G1, G3-G7.

The remaining IPV are manual IPVs and need to be identified at a site level on the manual PV log.

The frequency of patients with IPVs will be presented. Those which lead to a patient being excluded from the PPS will be presented separately to those which do not.

6.3 PATIENT SETS ANALYSED

The following analysis sets will be defined for this trial:

- Screened set (SCR)
  All patients who signed informed consent; these patients will have completed routine procedures to establish the diagnosis of CVT.

- Treated set (TS):
  The set includes patients who received at least one dose of study medication.

- Full analysis set (FAS):
  This set includes all patients randomised.

- Per protocol set (PPS):
  This is a subset of the TS, restricted to patients without relevant important protocol violations as defined in Table 6.2: 1.

The efficacy analysis (i.e. analysis of primary and secondary efficacy endpoints, as well as further endpoints based on the FAS will follow the intent-to-treat (ITT) principle. Patients will be allocated to the randomised treatment groups regardless of actual medication taken.

The safety analysis (including analysis of secondary safety endpoints as well as adverse event analysis) will be based on the TS, and patients will be analyzed according to the treatment they have received.

Secondary efficacy analysis on the PPS may not be conducted if the number of patients excluded from the patient set is small (i.e. <10% of the TS).

Disposition data on the SCR will be presented according to the randomized treatment groups. For patients not entered/randomised on the total number will be presented.

Table 6.3: 1 Patient sets analyzed

	Patient set			
Class of endpoint/data	SCR	TS	FAS	PPS
Primary endpoint (Section 5.1)			primary analysis	secondary analysis
Secondary and further efficacy endpoints (Section 5.2.2 and 5.3)			X	
Safety endpoints (Section 7.8)		X		
Demographic/baseline data (Section 7.1)		X	(X)	
Disposition	X			

(X) An additional FAS presentation of the demographic/baseline data may be provided in the End of Text section of the clinical trial report (CTR) if patient numbers for FAS and TS are clearly different, i.e. if ≥10% of the TS are excluded from the FAS.

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6 “Handling of missing data and outliers”.

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

A major goal of the trial is to obtain virtually complete follow-up of vital status and full collection of outcome event data. For the primary and secondary endpoints no general imputations are planned. In case of early discontinuation of patients with no follow-up and no events, those will be handled as imputed no event.

Missing or incomplete AE dates are imputed according to BI standards (see "Handling of missing and incomplete AE dates" [5]). The same philosophy will be applied to missing or incomplete outcome event and concomitant medication dates/times.

Other missing data will not be imputed.

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

The baseline assessment is the last measurement made (or sample taken) prior to first study drug administration. The first study drug administration should occur at Visit 2. Any assessments made on this day, where time is not collected, are assumed to be prior to study

drug administration. This does not apply to adverse events (AEs) and outcome events where it will be assumed that events occurred on-treatment.

Actual dates will be used for assigning AEs and outcome events to the appropriate treatment period as defined in Section 6.1. Windowing with regard to visits will not be applied as the main objective of this trial is the collection of outcome events, which are not necessarily associated with clinic visits.

7. PLANNED ANALYSIS

Patient disposition (number of patients screened, randomised, treated, discontinued, etc...) will be presented for all patients.

Disposition as well as demographic and baseline data will be displayed by treatment group and overall. Primary, secondary and further as well as safety endpoints will be displayed by treatment group.

Descriptive statistics for continuous variables will generally be N (number of patients with non-missing values), mean, standard deviation (SD), minimum, Q1 (lower quartile), median, Q3 (upper quartile), maximum. In general, means, medians, Q1 and Q3 will be presented to one more decimal place than the raw data and SDs will be presented to two more decimal places. Minima and maxima will be presented to the same number of decimal places as the raw data.

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. Percentages will be rounded to one decimal place. A missing category will be displayed if and only if there are actually missing values. Percentages will be based on all patients in the respective patient set whether they have non-missing values or not.

For calculations, 7 days will be considered 1 week, 30 days will be considered 1 month.

Generally, displays will follow [1], [3] and [6].

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only descriptive statistics are planned for this section of the report. Data from the demographic, as well as medical and surgical history eCRF pages will be presented, including details on CVT history.

With regard to demographic data the following categorisations will be considered, in addition to the continuous data:

- Age class (years): <30, ≥30-<40, ≥40-<50, ≥50-<60, ≥60-<70, ≥70-<80, ≥80
- Weight class (kg): <30, ≥30 - <60, ≥60 - <90, ≥90
- Body mass index (BMI) class (kg/m^2): < 18.5, ≥18.5-<25, ≥25-<30, ≥30

The National Institutes of Health Stroke Scale (NIHSS) will be recorded, if it had been collected at the time of qualifying (index) CVT. In patients, where NIHSS has not been done at the time of index CVT, it will be performed at study entry (at Visit 1). It is a tool used by healthcare providers to objectively quantify the impairment caused by a stroke. The NIHSS is composed of 11 items, and for each item a score of 0 typically indicates normal function in that specific ability, while a higher score is indicative of some level of impairment. The individual scores from each item are summed in order to calculate a patient's total NIHSS score. The maximum possible score is 42, with the minimum score being a 0 ([16], [17]).

Table 7.1: 1 NIHSS score

Score	Stroke Severity
0	No Stroke Symptoms
1-4	Minor Stroke
5-15	Moderate Stroke
16-20	Moderate to Severe Stroke
21-42	Severe Stroke

7.2 CONCOMITANT DISEASES AND MEDICATION

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

Baseline conditions will be coded according to the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by ATC class 3 and preferred name (PN). The frequency of patients with different baseline conditions will be presented.

Therapies will be classified using the most recent version of the World Health Organisation – Drug Dictionary (WHO-DD), and the frequency of patients with therapies will be presented according to whether these were concomitantly taken during the on-treatment period defined in Section 6.1, or whether these are prior or post therapy.

Details on administration of commercially available idarucizumab – including indication, information on surgery / invasive procedures and bleeding – will additionally be listed.

7.3 TREATMENT COMPLIANCE

Cumulative days of temporary treatment interruptions will be summarized in classes (0, 1 - <5, 5 - <10, 10 - <20, 20 - <30, ≥30). Frequency of patients with treatment interruptions for AEs as well as for other reasons will be presented. Additionally, time to first temporary treatment interruption will be analyzed. For this purpose, patients who permanently discontinue from treatment before having had a temporary treatment interruption will be censored at time of treatment discontinuation.

Treatment compliance will be calculated as follows:

7.3.1 Dabigatran Compliance

Based on capsule counts, treatment compliance (%) will be calculated as:

$$\text{Dabigatran compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

This value will be entered directly into the eCRF.

Only treatment interruptions not due to AE will be considered as a compliance issue and will be taken into account in the calculation (duration of interruptions due to AE will be subtracted from the duration of the study period).

Dabigatran compliance will be summarised continuously and in classes (<80%; 80-120%; >120%).

A patient will be considered as non-compliant if the number of doses taken is not between 80-120% of the expected number of doses.

7.3.2 Warfarin Compliance

Warfarin compliance will be monitored by means of the international normalised ratio (INR) rather than by pill counts as it is a more accurate and biologic measure of pharmacodynamic effect. The quality of warfarin therapy for each patient will be assessed by reporting the number of INR values within the indicated therapeutic target range (2.0 – 3.0) as well as those above and below this range. The Rosendaal method [10] will be used to evaluate the percentage of time that a patient's INR is in range (i.e. time in therapeutic range [TTR]). For each calendar month, the mean of all INR values will be reported. This will be calculated for each patient, for each centre, for each country and for the whole study. The mean percentage of time of INR in range will be calculated for each centre and each country during the trial conduct to monitor the INR control. The percentage of time of INR in range for each country and for the trial will be reported at study end.

For patients who had a temporary discontinuation of study warfarin, INR values taken in the time interval between the day after the temporary discontinuation and restart of medication will not be counted. If INR is evaluated during the first week after randomisation, those INR values will not be used in calculating TTR.

The Rosendaal method: assume the INR value between two measurements will vary linearly from the value of the first to the value of the second measurement, divide the time between two measurements in days, fit a linear equation using the two measured INR values, and then calculate the INR for each day in the interval. The percentage of time when INR is in target range is calculated for each patient.

Furthermore, the number and frequency of patients with percentage of time in INR target range by cutpoints 45, 55 and 65%, as well as 60 and 75% will be presented for the trial.

Descriptive statistics will be provided for the number of INR measurements per months.

7.4 PRIMARY ENDPOINT(S)

This is a prospective, randomised, open label, blinded endpoint (PROBE), active comparator trial and the clinical endpoints are being adjudicated by an AC in a blinded fashion. All analyses are exploratory, no statistical hypothesis will be tested.

The number and frequency of patients by treatment as well as by subgroup will be displayed along with the 95% confidence intervals (CIs). No difference between the treatments dabigatran etexilate versus warfarin will be tested.

Hazard ratios (HR) and 95% CI will be calculated as well; however the result will only be considered interpretable if the CI is not too wide, i.e. (lower limit of CI) ≥ (estimate of HR / 4) and (upper limit of CI) ≤ (4 * estimate of HR). A Cox proportional hazard model stratified by ICH at baseline will be applied.

7.5 SECONDARY ENDPOINT(S)

7.5.1 Key secondary endpoint(s)

This section is not applicable as no key secondary endpoint has been specified in the protocol.

7.5.2 (Other) Secondary endpoint(s)

The analyses for the secondary endpoints as described in Section 5.2.2 will be mainly based on frequency counts and percentages along with 95% CIs.

Means and standard deviations will be displayed for the endpoint on cerebral venous recanalisation as measured by the change in number of occluded cerebral veins and sinuses after up to 24 weeks. Patients with missing or not analyzable MRI scans at EOT will be excluded from this analysis.

The frequency of patients with new intracranial haemorrhage (“ICH”) or worsening of the haemorrhagic component of a previous lesion will be presented, along with 95% CIs. The single components of this composite endpoint will be presented in the same way.

7.7 EXTENT OF EXPOSURE

The date of first administration is recorded at visit 2.

Days on treatment = date of last administration – date of first administration + 1 day

There will be one summary of duration of exposure [weeks] including treatment interruptions (i.e. they will not be substracted from days on treatment), and one excluding treatment interruptions (i.e. they will be substracted from days on treatment).

Duration of exposure class [weeks]: ≤8 weeks (56 days), >8 weeks (56 days) to ≤16 weeks (112 days), >16 weeks (112 days) to ≤24 weeks (168 days), >24 weeks (168 days)

Additionally, time to permanent discontinuation of trial medication will be analyzed.

7.8 SAFETY ANALYSIS

7.8.1 Adverse events

Adverse events (AEs) will be coded with the most recent version of MedDRA.

Unless otherwise specified, the analyses of AEs 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.

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 [5], [7].

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs occurring between first drug intake till 6 days after last drug intake will be assigned to the randomised treatment. For details on the treatment definition, see Section 6.1.

According to ICH E3 [8], AEs classified as ‘other significant’ needs to be reported and will include those non-serious and non-significant adverse events with
(i) ‘action taken = discontinuation’ or ‘action taken = reduced’, or
(ii) marked haematological and other lab abnormalities or lead to significant concomitant therapy as identified by the Clinical Monitor/Investigator at a Medical and Quality Review Meeting.

An overall summary of AEs will be presented.
The frequency of patients with AEs will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). Separate tables will be provided for patients with serious AEs, AEs leading to treatment discontinuation, AEs leading to death, other significant AEs according to ICH E3 and AEs considered to be drug-related by the investigator (any, as well as serious). Furthermore, AEs will be summarised by intensity. For data disclosure purposes, non-serious AEs will also be provided in separate tables.

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

The overall summary, as well as the frequency table of patients with any AEs by SOC and PT, will also be presented by stratification factor intracranial haemorrhage ("ICH") at baseline as assessed by investigator.

For the listings AEs will be presented per the period in which they occurred, for details see Section 6.1.

7.8.2 Laboratory data

The following safety laboratory parameters will be tested / collected:

- Chemistry: ALT (SGPT), AST (SGOT), Alkaline Phosphatase, Bilirubin total (fractionated if increased), GGT, Creatinine and Creatinine Clearance (CrCl, according to Cockcroft-Gault formula)

- Haematology: Erythrocytes, Haemoglobin, Haematocrit, Platelet count, WBC count

The analyses of laboratory data will be descriptive in nature and will be based on BI standards [9].

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

Additionally, potential Hy's Law cases will be presented graphically.

Thrombophilia testing is not a required trial procedure, but the results will be collected if it was performed as part of routine care at any time after randomisation. These data will only be listed.

7.8.3 Vital signs

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

Vital signs data – systolic and diastolic blood pressure, as well as pulse rate - observed at Visit 3 and 4, and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Weight (collected to calculate CrCl) will only be listed.

7.8.4 ECG

Frequency of patients with any clinically relevant ECG finding during screening period will be presented.

7.8.5 Others

Pregnancy test results will only be listed.

8. REFERENCES

1	
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10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
Initial	**16-NOV-16**		None	This is the initial TSAP with necessary information for trial conduct.
Final	**05-MAR-18**		All	This is the final TSAP, based on the initial one, with necessary information for the analysis for the CTR.