Trial Statistical Analysis Plan

c17384787-01

BI Trial No.:	1160.186
Title:	A prospective **R**andomised, open label, blinded endpoint (PROBE) study to **E**valuate **DUAL** antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAF) that have undergone a percutaneous coronary intervention (**PCI**) with stenting **(RE-DUAL PCI)** Including Protocol Amendment 3 [c02214385-09]
Investigational Product:	Pradaxa®, dabigatran etexilate
Responsible trial statistician:	[redacted] Phone [redacted] Fax:
Date of statistical analysis plan:	9 June 2017 SIGNED
Version:	Final

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2. LIST OF ABBREVIATIONS

Term	Definition / description
ACS	Acute Coronary Syndromes
ACEF	Age, creatinine and left ventricular ejection fraction
ADS	Analysis Dataset
AE	Adverse Event
AF	Atrial Fibrillation
ALT	Alanine aminotransferase
AP	Alkaline Phosphatase
ASA	Acetylsalicylic acid (Aspirin)
AST	Aspartate transaminase
BARC	Bleeding Academic Research Consortium
BI	Boehringer Ingelheim
b.i.d.	Twice a day
BMI	Body Mass Index
BMS	Bare Metal Stent
CABG	Coronary Artery Bypass Graft
CAD	Coronary Artery Disease
CHA_2DS_2 VASC	Congestive heart failure, Hypertension, Age, Diabetes mellitus, prior Stroke or TIA or Thromboembolism, Vascular disease, Sex
CI	Confidence Interval
CrCl	Creatinine Clearance
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DAPT	Dual Antiplatelet Therapy
DAT	Dual Antithrombotic Therapy
DBL	Database Lock
DBLM	Database Lock Meeting
DES	Drug Eluting Stent
DMC	Data Monitoring Committee
DTE	Death or Thrombotic Event

Term	Definition / description
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMA	European Agency for the Evaluation of Medicinal Products
EOT	End of Treatment
EU	European Union
FAS	Full Analysis Set
GI	Gastrointestinal
HAS-BLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol
HF	Heart Failure
HR	Hazard Ratio
IAC	Independent Adjudication Committee
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
IPV	Important Protocol Violation
IRT	Interactive Response Technology
ISTH	International Society of Thrombosis and Haemostasis
LAD	Left Anterior Descending Coronary Artery
LM	Left Main Coronary Artery
LVEF	Left Ventricular Ejection Fraction
MBE	Major Bleeding Event
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligrams
MI	Myocardial Infarction
mRS	modified Rankin Scale
NI	Non-Inferiority
NOAC	New Oral Anticoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSTEMI	Non-ST Elevation Myocardial Infarction
NVAF	Non Valvular Atrial Fibrillation
NYHA	New York Heart Association

Term	Definition / description
OAC	Oral Anticoagulant
OE	Outcome Event
PCI	Percutaneous Coronary Intervention
P-gp	P-glycoprotein
PPI	Proton Pump Inhibitor
PPS	Per Protocol Set
PROBE	Prospective, Randomised, Open-label, Blinded Endpoint
PT	Preferred Term
PV	Protocol Violation
Q1	Lower quartile (25^{th} percentile)
Q3	Upper quartile (75^{th} percentile)
REP	Residual Effect Period
ROW	Rest of World
RPM	Report Planning Meeting
SCR	Screened Set
SD	Standard Deviation
SE	Systemic Embolism
SOC	System Organ Class
STEMI	ST Elevation Myocardial Infarction
TAT	Triple Antithrombotic Therapy
TIA	Transient Ischaemic Attack
TIMI	Thrombolysis In Myocardial Infarction
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
TTR	Time in Therapeutic Range
UA	Unstable Angina
ULN	Upper Limit of Normal
VKA	Vitamin K Antagonist
WHO	World Health Organisation

3. INTRODUCTION

As per ICH E9 [4], 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 Trial Statistical Analysis Plan (TSAP) assumes familiarity with the Clinical Trial Protocol (CTP) [5], 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.

SAS® Version 9.2 (or a later version) will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

During the course of the study, the DMC may advise to stop enrolment into certain treatment arms or to stop the study completely. For further information, see CTP [5], Section 7.3.4. Changes to the planned analysis were introduced in protocol amendments 1 and 2. In addition, some further changes were implemented as follows.

Due to the Japanese local amendment (where the randomisation age group stratification factor was changed from <80 or ≥80 years old to <70 or ≥70 years old for Japanese patients), it will be necessary to change the way the age group stratification factor is defined in the analysis. Instead age group will be changed to be non-elderly vs. elderly and this will be used as the stratification factor in some analyses.

Due to the relatively few numbers of elderly patients finally recruited in the US region, it will not be possible to fit an age-group stratified Cox proportional hazards regression model for the 150mg DE-DAT versus warfarin-TAT comparison for any of the endpoints. Instead an unstratified model will be applied comparing 150mg DE-DAT versus warfarin-TAT. (excluding elderly EU/ROW patients in the warfarin-TAT group). In addition, unstratified sensitivity analyses of the non-elderly stratum only will be conducted.

GI bleeds, MBEs (ISTH), CRNMBEs, life-threatening bleeds and fatal bleeds were added as other safety endpoints.

The further endpoint of hospitalisation and the further composite endpoint of all-cause death or hospitalisation were added at the request of the Executive Steering Committee on 22nd November 2016.

The sensitivity analysis that censors patients who switch from study dabigatran to non-study NOAC/VKA or from study warfarin to non-study NOAC/VKA, at the time of the switch plus the Residual Effect Period (REP) of 6 days will not be performed because it will be virtually identical to the on-treatment sensitivity analysis already planned.

5. ENDPOINTS

5.1 PRIMARY ENDPOINTS

The primary endpoint for this study is a safety endpoint:

- Time to first International Society of Thrombosis and Haemostasis (ISTH) Major Bleeding Event (MBE) or Clinically Relevant Non-Major Bleeding Event (CRNMBE). Please refer to the CTP for the ISTH criteria.

The primary endpoint will be adjudicated by an Independent Adjudication Committee (IAC). Details of adjudication criteria can be found in the Adjudication Charter.

5.2 SECONDARY ENDPOINTS

5.2.1 Key secondary endpoints

Not applicable.

5.2.2 (Other) Secondary endpoints

The other secondary endpoints of efficacy are (all time to first event endpoints):

1. Composite endpoints of:
    - DTE and unplanned revascularisation by PCI/CABG.
      (DTE = all death, Myocardial Infarction (MI), stroke/Systemic Embolism (SE))
    - DTE
2. Individual outcome events:
    - All death (and the following sub-categories separately)
        - Cardiovascular death
        - Non-cardiovascular death
        - Undetermined
    - MI
    - Stroke
    - SE
    - Stent thrombosis (definite)

3. Composite endpoint of death + MI + stroke

4. Unplanned revascularisation by Percutaneous Coronary Intervention (PCI)/Coronary Artery Bypass Graft (CABG)

All secondary endpoints will be adjudicated by an IAC. Details of adjudication criteria can be found in the Adjudication Charter.

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENTS

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

- Screening: date of informed consent to date of randomisation.
- Post-randomisation: Date of randomisation to time-point of first intake (date and time) of randomised study drug.
- On-treatment (ignoring temporary interruptions): first intake (date and time) of randomised study drug to last intake (date and time) of randomised study drug. The REP of 6 days will be added to the end of this period. Intermittent off-treatment periods will be ignored in cases of any temporary interruptions in study medication.
- Post-treatment: End of on-treatment period (including the REP) until date of trial completion. This is the date given on the termination (TERM) page of the electronic Case Report Form (eCRF).
- Post-study: day after date of trial completion onwards.

The REP is the time period after the last administration of trial medication when measurable drug levels or PD effects are still likely to be present. Events occurring in the REP are handled as occurring on-treatment (for the Treated Set). The REP is defined as 6 days after last intake of trial medication. Data from the post-study period will only be listed.

For rules on censoring, refer to Section 7.4.

Despite the trial being open label, all activities conducted by the trial team will be performed in a blinded manner (where possible) until database lock (DBL). For example, data tabulations and listings will be presented using dummy treatment group information instead of actual treatment group allocations.

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 Per Protocol analysis Set (PPS), the Full Analysis Set (FAS) or "None" of the analysis sets. Refer to Section 6.3 for more details. Most IPVs will be identified by the trial team prior to DBL, where possible in a blinded manner. Some programmatically-identified IPVs (e.g. treatment switching) will need to be identified after DBL.

Table 6.2: 1 Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
A		**Entrance criteria not met**		
	A1.1	Male or female patients aged ≥18 years or ≥20 years in Japan.	Inclusion criterion 1 not met	PPS
	A1.2	Patients with NVAF that have been receiving oral anticoagulant (OAC) treatment (either with warfarin, another Vitamin K Antagonist (VKA) or other novel oral anticoagulant), or were treatment naïve prior to PCI. Atrial Fibrillation (AF) may be paroxysmal, persistent or permanent, but must not be secondary to a reversible disorder such as MI, pulmonary embolism, recent surgery, pericarditis or thyrotoxicosis	Inclusion criterion 2 not met	PPS
	A1.3	Patients presenting with: • An Acute Coronary Syndrome (ACS) [ST elevation MI (STEMI), NSTEMI or unstable angina (UA)] that was successfully treated by PCI and stenting [either Bare Metal Stent (BMS) or Drug Eluting Stent (DES)] Or • Stable Coronary Artery Disease (CAD) with at least one lesion eligible for PCI that was successfully treated by elective PCI and stenting (either BMS or DES)	Inclusion criterion 3 not met	PPS
	A2.1	Patients with a mechanical or biological heart valve prosthesis	Exclusion criterion 1 met	PPS
	A2.2	Cardiogenic shock during current hospitalisation	Exclusion criterion 2 met	PPS
	A2.3	Patients who have used fibrinolytic agents within 24 hours of randomisation that, in the opinion of the Investigator, will put the patient at high risk of bleeding	Exclusion criterion 3 met	PPS
	A2.4	Stroke within 1 month prior to screening visit (Additionally in Japan: a haemorrhagic stroke, 6 months prior to administration of study treatment)	Exclusion criterion 4 met	PPS
	A2.5	Patients, who in the opinion of the Investigator, have had major surgery within the month prior to screening	Exclusion criterion 5 met. Nature and timing of surgery to be reviewed at Report Planning Meeting (RPM).	None
	A2.6	Patient has received an organ transplant or is on a waiting list for an organ transplant	Exclusion criterion 6 met	PPS
	A2.7	History of intraocular, spinal, retroperitoneal or a traumatic intra-articular bleeding unless the causative factor has been permanently eliminated or repaired (e.g. by surgery)	Exclusion criterion 7 met	PPS

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
	A2.8	Gastrointestinal (GI) haemorrhage within one month prior to screening, unless, in the opinion of the Investigator, the cause has been permanently eliminated (e.g. by surgery)	Exclusion criterion 8 met	PPS
	A2.9	Major bleeding episode (reduction in the haemoglobin level of at least 2g/dL, transfusion of at least two units[1] of blood, or symptomatic bleeding in a critical area or organ) including life-threatening bleeding episode (symptomatic intracranial bleeding, bleeding with a decrease in the haemoglobin level of at least 5g/dL or bleeding requiring transfusion of at least 4 units[2] of blood or inotropic agents or necessitating surgery) in one month prior to screening visit	Exclusion criterion 9 met	PPS
	A2.10	Haemorrhagic disorder or bleeding diathesis (e.g. von Willebrand disease, haemophilia A or B or other hereditary bleeding disorder, history of spontaneous intra-articular bleeding, history of prolonged bleeding after surgery/intervention)	Exclusion criterion 10 met	PPS
	A2.11	Anaemia (haemoglobin <10g/dL) or thrombocytopenia including heparin-induced thrombocytopenia (platelet count <100 × 109/L) at screening (Visit 1)	Exclusion criterion 11 met	PPS
	A2.12	Severe renal impairment (estimated CrCl calculated by Cockcroft-Gault equation) <30mL/min at screening (Visit 1)	Exclusion criterion 12 met	PPS
	A2.13	Active liver disease as indicated by at least one of the following: • Prior and persistent alanine aminotransferase (ALT) **or** Aspartate transaminase (AST) **or** alkaline phosphatase (AP) >3 × upper limit of normal (ULN) • Known active hepatitis C • Known active hepatitis B • Known active hepatitis A	Exclusion criterion 13 met	PPS
	A2.14	Recent malignancy or radiation therapy (≤6 months) unless, in the opinion of the Investigator, the estimated life expectancy is greater than 36 months	Exclusion criterion 14 met	PPS
	A2.15	Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine or St. John's Wort.	Exclusion criterion 15 met	PPS

[1] Equivalent to 4.5 units in Japan
[2] Equivalent to 9 units in Japan

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
	A2.16	Patients who, in the Investigator's opinion, need continuous treatment with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)	Exclusion criterion 16 met	PPS
	A2.17	Patients with a known allergy to dabigatran etexilate or to the excipients used for the capsule of the drug	Exclusion criterion 17 met	PPS
	A2.18	Patients with a known allergy to warfarin tablets or to the excipients	Exclusion criterion 18 met	PPS
	A2.19	Patients who, in the Investigator's opinion, should not be treated with OAC	Exclusion criterion 19 met	PPS
	A2.20	Patients with a contraindication to clopidogrel, ticagrelor or aspirin (ASA)	Exclusion criterion 20 met	PPS
	A2.21	Pre-menopausal women (last menstruation ≤1 year prior to screening) who: • Are pregnant or breast feeding or • Are not surgically sterile or • Are of child bearing potential and not practising two acceptable methods of birth control, or do not plan to continue practising an acceptable method of birth control throughout the trial. Acceptable methods of birth control are oral or parenteral (patch, injection, implant) hormonal contraception which has been used continuously for at least one month prior to the first dose of study medication, intrauterine device or intrauterine system, double-barrier method of contraception (condom and occlusive cap or condom and spermicidal agent), male sterilisation and complete sexual abstinence (if acceptable by local authorities). Periodic abstinence is not an acceptable method of contraception.	Exclusion criterion 21 met. Pregnant patients will be excluded from the PPS.	None
	A2.22	Patients who have participated in another trial with an investigational drug or device within the past 30 days preceding the screening visit or are participating in another trial (patients participating in an observational study only will not be excluded)	Exclusion criterion 22 met	PPS
	A2.23	Patients not willing or able to comply with the protocol requirements or considered unreliable by the Investigator concerning the requirements for follow-up during the study and/or compliance with study drug administration, who have a life expectancy less than the expected duration of the trial due to concomitant disease, or who have any condition which in the opinion of the Investigator, would not allow safe participation in the study (e.g. drug addiction, alcohol abuse).	Exclusion criterion 23 met	PPS

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
B		**Informed consent**		
	B1	Informed consent not given	Inclusion Criterion 4	All
	B2	Informed consent given too late or the dates of the investigator's and patient's signatures do not match		None
	B3	Informed consent withdrawn	Only applies from the date at which consent is withdrawn.	All
C		**Trial medication and randomization**		
	C1	Incorrect trial medication taken	Medication kit assigned not matching treatment patient was randomised to (e.g. patient randomized to warfarin-TAT but received 110mg DE-DAT)	PPS
	C2	Randomisation order not followed	e.g. forced randomization, mis-stratification	PPS
	C3	Non-compliance	Compliance <80% or >120% over the course of the study for dabigatran patients (determined on a visit-wise basis), or time in therapeutic target range for warfarin patients <45% (also on a visit-wise basis). See Section 7.3 for details on compliance calculations. Patients will be flagged if they exhibit non-compliance for two consecutive visits or more (for both dabigatran and warfarin patients). Non-compliance caused by temporary interruption of treatment due to a procedure or a drop in CrCl to less than 30mL/min should not be classified as a protocol violation.	PPS, but only from start of non-compliance onwards
	C4	Trial medication taken at the wrong time	First dose of study drug not administered at the correct time (should be between 6 hours after sheath removal and up to 120 hours post PCI)	PPS
D		**Concomitant medication**		

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
	D2.1	Prohibited medication use	The following treatments should not be taken during the active treatment period of the trial (at least one on-treatment use, unless otherwise stated: 1. Treatment with ticlopidine or prasugrel 2. Fibrinolytic agents (see Section 4.2.1.4 of the protocol for exceptions) 3. GPIIb/IIIa antagonists (e.g. abciximab, tirofiban) 4. Treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone and rifampicin, phenytoin, carbamazepine or St. John's Wort (only applicable to patients randomised to dabigatran etexilate) 5a. Dipyridamole (although it is allowed for exceptional cases based on CTP Section, 4.2.1.4; for the PPS analyses all patients with on-treatment use will be excluded), 5b. Other oral anticoagulants (e.g.VKAs) Commercial NOACs (dabigatran, rivaroxaban, apixaban and edoxaban): Warfarin Patients: At the end of the treatment, flag patients with more than 2 days of overlap of warfarin and commercial NOAC + flag any days of overlap during the treatment period (except for washout of previous treatment/titration at study start (see IPV C4)) Dabigatran patients: At the end of treatment, flag patients with more than 1 day of overlap of dabigatran and commercial NOAC + flag any days of overlap during the treatment period (except for washout of previous treatment/titration at study start (see IPV C4)) Commercial VKAs: Dabigatran patients: At the end of treatment, flag patients with more than 5 days of overlap of dabigatran and commercial VKA +flag any days of overlap during the treatment period (except for washout of previous treatment/titration at study start (see IPV C4)) Warfarin patients: At the end of treatment, flag patients with more than 1 day of overlap of warfarin and commercial VKA. +flag any days of overlap during the treatment period (except for washout of previous treatment/titration at study start (see IPV C4)) 6. ASA in the first 12 months for all patients – except for in the first month for warfarin patients with a BMS or the first three months for warfarin patients with a DES (consecutive use of more than 14 days)	PPS

Table 6.2: 1 (continued) Important protocol violations

Category/ Code		Description	Example/Comment	Excluded from
	D2.2	Prohibited use of heparin	Any on-treatment use of heparin where no medical indication is given.	PPS
	D3.1	Mandatory medication not taken per protocol (ASA)	ASA not taken for the first month for warfarin patients with a BMS or for the first three months for patients with a DES as indicated on the *Trial Medication Compliance* eCRF page (exclude if at least one visit is ticked "No").	PPS, but only from start of non-compliance onwards
	D3.2	Mandatory medication not taken per protocol (clopidogrel/ticagrelor)	Clopidogrel/ticagrelor non-compliance during the first 12 months of treatment as indicated on the *Trial Medication Compliance* eCRF page (exclude if at least one visit is ticked "No").	PPS, but only from start of non-compliance onwards
G		Trial Specific Protocol Violations		
	G1	Patient not withdrawn from treatment if CrCl drops to <30mL/min at two different occasions during the trial	As per study protocol, this only applies to patients randomised to dabigatran etexilate.	PPS

KEY: PPS – Per Protocol Set

6.3 PATIENT SETS ANALYSED

The following analysis sets will be defined for this trial:

- SCR – Screened Set
  All patients who signed informed consent and completed at least some screening procedures.

- FAS – Full Analysis Set
  All consenting patients randomised will be analysed in the treatment group to which they are randomised regardless of whether they took study medication. The start date of the observation period for this analysis set is the date of randomisation. This follows the intent-to-treat principle. All patient listings will be based on the FAS except where specified otherwise. Refer to the technical TSAP for more detail.

- TS – Treated Set
  The set of patients who receive at least one dose of study medication will be analysed according to the treatment they have received. The start date of the observation period for this analysis set is the date of first intake of trial medication.

- PPS – Per-Protocol Set
  Patients will be included in the PPS, if they are already included in the TS and if they adhere to the trial protocol without any IPVs. IPVs are defined in Section 6.2.

For rules on censoring, refer to Section 7.4.

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, where possible and will be documented in the minutes of the RPM or Database Lock Meeting (DBLM). Some decisions may need to be taken after DBL (e.g. treatment switching). If the number of patients excluded from the PPS is small (<10% of the TS), then analyses on this set may not be conducted. This decision will also be documented in the minutes of the RPM or DBLM.

The following table identifies which patient set is used for which category of endpoints.

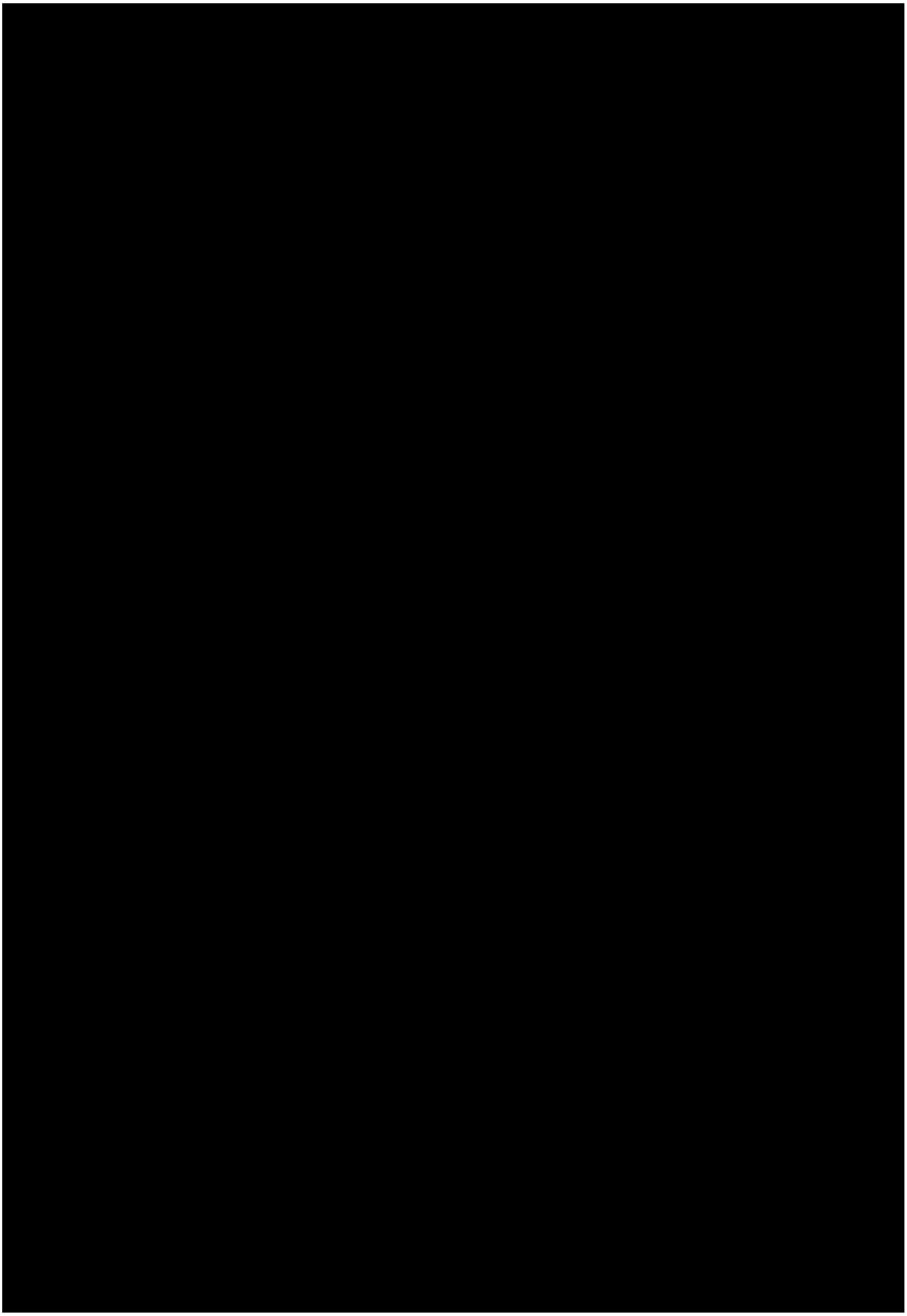
Table 6.3: 1 Patient sets analysed

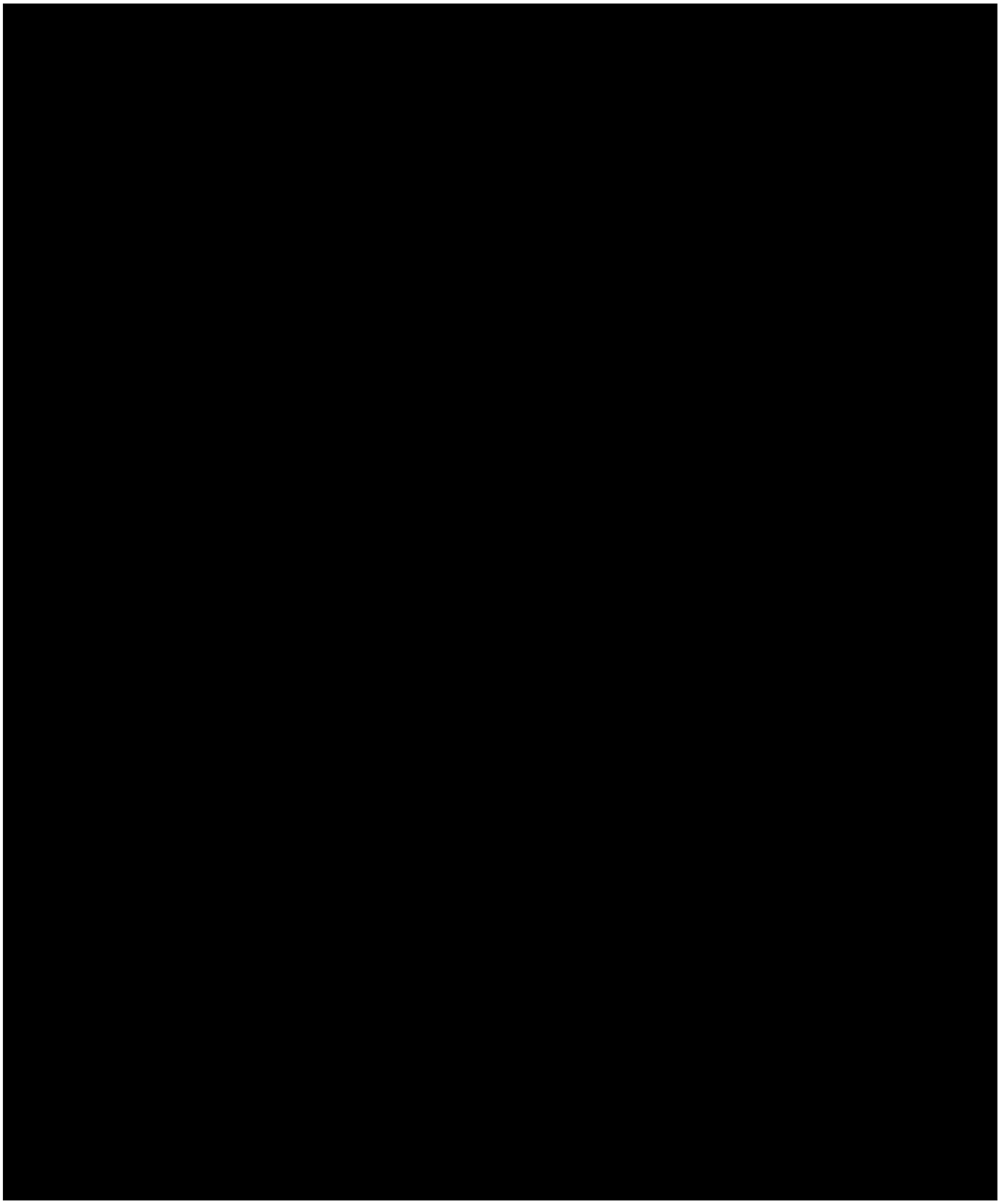
	Patient set		
Class of endpoint	FAS*	TS	PPS#
Primary endpoint (see Section 5.1)	X	X	X
Secondary endpoints (see Section 5.2.2)	X	X	
Further endpoints (see Section 5.3)	X	X	
Safety endpoints other than the primary endpoint (see Section 7.8)	X	X	
Other safety endpoints (see Section 7.8.5)	X	X	
Demographic/baseline endpoints (see Section 7.1)	X		X

Note that the number of patients with available data for an endpoint may differ. For details, see Section 6.6.

* The FAS will be the main analysis set for the summary of clinical outcome event data. Other analysis sets will be used for sensitivity purposes.

If the number of patients excluded from the PPS is small (<10% of the TS), then analyses on this set may not be conducted





6.5 POOLING OF CENTRES

This section is not applicable because centre/region is not included in the statistical model. However, consistency of treatment effects across regional subgroups will be investigated (see Section 6.4).

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. As mentioned in Section 7.4, all patients lost to follow-up will be treated as censored at the time of last known vital status. This section contains details of how censoring will be performed for patients who do not experience outcome events.

The CTR will contain a summary of the number and percentage of patients with (and without) complete follow-up of vital status in each treatment group.

Due to the nature of the adjudication process, it may not be possible to classify bleeds under every bleed definition (i.e. TIMI and BARC). In these instances, the bleed classification will be left missing and no imputation will be attempted. Classification of bleeds under the ISTH definitions should not be left missing by the IAC.

In general, missing investigator INR ranges will be imputed with the standard guideline range for this patient population which is 2-3. The exception to this is for patients in Japan who are ≥70 years old. The guideline range for these patients is 2 – 2.6.

Missing or incomplete AE dates/times are imputed according to BI standards (see "Handling of missing and incomplete AE dates") [1]. The same philosophy will be applied to missing or incomplete outcome event and concomitant medication dates/times. Incomplete dates of temporary study medication discontinuation and restart will be imputed. See the TSAP Analysis Dataset (ADS) Plan for further details. Other special handling for missing/incomplete dates/times will be documented in the RPM.

Other missing data will not be imputed. If date of birth/age is missing for a patient, they will not be included in models that use age group as a stratifying factor.

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 and outcome events where it will be assumed that events occurred on-treatment.

Concomitant medication is considered a baseline medication, if taken on the day of randomisation.

Actual dates will be used for assigning adverse events and outcome events to the appropriate treatment period as defined in Section 6.1. Windowing 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.

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.

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 population. 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.

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Data from the demographic, medical history, PCI details and medication history eCRF pages will be presented descriptively by treatment group.

7.2 CONCOMITANT DISEASES AND MEDICATION

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

The frequency of patients with different concomitant diseases (baseline conditions) will be presented.

Medications will be classified using the World Health Organisation (WHO) dictionary (into e.g. antithrombotic therapies, bridging medications, P-gp inhibitors, P-gp inducers, etc...) and will be presented according to whether they were concomitantly taken during the on-treatment period (ignoring the REP) defined in Section 6.1 or whether they are prior (i.e. those taken at baseline (=randomization visit)) or post therapy. Additional pooling of medication categories may also be necessary.

The usage of each concomitant medication of special interest during the treatment period (ignoring temporary interruptions) will be categorised according to the % of time that patients used that medication:

- Never used (0%)
- Used at least one time
- 0% < and ≤50% of the time

□ 50% <and <100% of the time
□ Always used (100%)

Only medications in the following categories will be presented:

- Antiplatelet medication
- Thrombolytic agents
- Novel direct oral anticoagulants
- Parenteral anticoagulants
- Vitamin K antagonists
- GPIIb/IIIa antagonists
- Therapies for bleeding management

Medications may be combined or removed from the table, if too few patients have taken them during the treatment period.

7.3 TREATMENT COMPLIANCE

Compliance will be summarised descriptively using the TS. The time period after permanent discontinuation from study medication and the time period during any temporary discontinuation of study medication will not be included in the calculation of the denominator.

Compliance to dabigatran etexilate
Based on capsule counts, treatment compliance (%) will be calculated as:

$$\frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken}}$$

This value will be entered directly into the eCRF.

For patients who had a temporary discontinuation of dabigatran etexilate, the time interval between the day after temporary discontinuation and restart of medication should not be used in the calculation of the denominator.

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

Descriptive statistics will be presented for patients' overall compliance with dabigatran etexilate during the treatment period. This will be assessed using information from the trial medication compliance eCRF page. Mean compliance will be calculated per patient by weighting their reported % compliance according to how long it has been since their last clinic visit.

The mean compliance and the percentage of patients with compliance <50%, 50- <80%, 80 - <120%, ≥ 120% will be summarised by visit and overall.

Time in therapeutic range (TTR, warfarin)

The quality of warfarin therapy for each patient will be assessed by reporting the number of International Normalised Ratio (INR) values within the investigator indicated therapeutic target range at the time of the measurement, as well as those above and below these ranges. The following additional ranges will be investigated: 2.0 to 3.0, 2.0 to 2.5 and 2.5 to 3.0. The Rosendaal method will be used to evaluate the percentage of time that a patient's INR is in range (i.e. time in therapeutic range, TTR). This will be calculated for each patient, for each centre, for each country and for the whole study. The mean and median percentage of time in target INR range will be calculated for each centre and each country during the trial conduct to monitor the INR control. The percentage of time in target INR range for each country and for the trial will be reported.

For patients who had a temporary discontinuation of study warfarin, 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. The intended target range for each patient is indicated by the investigator on the INR log page of the eCRF.

The frequency of the INR monitoring will be assessed using descriptive statistics.

Evaluation of INR measurements will include the following:

Mean and median percentage of time in target INR range over time

Frequency of patients with percentage of time in target INR range: < 45%, ≥45-<55%, ≥55-<65% and ≥65%

Frequency of patients with percentage of time in target INR range: <60%, ≥60-<75% and ≥ 75%

Medication interruptions:

The number of patients with temporary interruptions of study medications and the reasons for the interruptions will be summarised. In addition, the number of days with interruptions of study medications will be summarised descriptively. This will not include the addition of the REP (6 days). The number of patients with permanent interruptions of study medication are summarised in the patient disposition tables.

7.4 PRIMARY ENDPOINT

This is a prospective, randomised, open label, blinded endpoint (PROBE), active comparator trial and the clinical endpoints are being adjudicated by an IAC in a blinded fashion. The IAC

Charter contains details of the outcome event adjudication criteria. The study will employ a time to first event analysis (using a stratified Cox proportional hazards regression model) and it is assumed that all patients will be observed until first primary endpoint event or until the last patient entered has completed at least six months of treatment (up to an anticipated maximum duration of approximately 30 months for the first patient entered). The trial will be monitored by an independent DMC.

This study is designed to test two safety hypotheses in NVAF patients that have undergone a successful PCI (elective or due to ACS) with stenting and were treatment naïve or were receiving oral anticoagulant treatment (either with warfarin, another VKA or other novel oral anticoagulant) before the procedure.

The primary endpoint, measured from date of randomisation to end of observation period, is:

- Time to first ISTH MBE or CRNMBE

as determined by the IAC. Only positively adjudicated events will be included in the analyses. They will be analysed using the stratified Cox proportional hazards regression model including age group (non-elderly or elderly [<70 or ≥70 years old in Japan and <80 or ≥80 years old everywhere else]) as a stratifying factor and treatment arm (110mg DE-DAT vs warfarin-TAT and 150mg DE-DAT and 110mg DE-DAT combined vs warfarin-TAT). For the 150mg DE-DAT versus warfarin-TAT comparison, an unstratified model will be applied comparing 150mg DE-DAT versus warfarin-TAT (excluding elderly EU/ROW patients in the warfarin-TAT group). In addition, an unstratified sensitivity analysis of the non-elderly patients only will be conducted.

Models will be fitted for each comparison separately (110mg DE-DAT vs warfarin-TAT and 150mg DE-DAT vs warfarin-TAT). The Breslow method [9] will be used to handle tied failure times.

The primary analysis will be performed under the intention-to-treat framework on the FAS. Patients who discontinue study medication will be followed until the end of the trial for vital status, ECGs, AEs, OEs (including completion of the bleeding questionnaire) and concomitant medications. All patients will be analysed according to the treatment arm to which they were randomised.

Survival time

For those patients with an OE within the analysis period, the survival time will be calculated as:
<date of event> - <date of randomisation> + 1

For those patients without an OE within the analysis period, the censored survival time will be calculated as
<censoring date as per below> - <date of randomisation> + 1

When centres are informed about the study end, they will schedule EOT visits for those patients that did not already have their EOT visit. As this is the design of the study, those

patient's EOT visits do not relate to any patient conditions. Therefore, for the primary analysis, patients who did not prematurely stop trial medication (as documented on the "termination of trial medication" (TTM) CRF page) will be censored at their EOT visit. If such a patient who did not prematurely stop trial medication as per the TTM CRF page, based on the call of the centre for the EOT visit, has stopped study medication before the EOT, the date of last trial medication intake will be used for censoring purposes (if available), as it was triggered by the information on end of the study. For patients who already had their EOT visit (i.e. those who stopped treatment prematurely according to the TTM CRF page), they will be censored at the date of their final visit. Centres were asked to schedule final visits for any prematurely discontinued patients between 1st Feb 2017 and 30th April 2017. In order to account for patients for whom premature treatment discontinuation occurs rather late during the trial conduct, the first visit which occurs after the date of 1st Feb 2017 will be used to censor these patients.

For patients where this data is not available, the censoring will be based on the date last seen. Dates used in determining the date last seen are:

- Date of EOT visit
- Date of last intake of study medication
- Date of follow-up visit
- Date of last known vital status, if available (including information obtained by a third party, where possible) if patients withdraw from the study [data collected on the vital status form and the TERM page]
- Date of withdrawal of consent by the patient (if applicable)
- Date of death (if a patient dies).
- Date of any event reported on the OE pages of the eCRF or dates confirmed by adjudication

For patients with DTEs and other OEs that include death (see Section 7.5.2), the date of death will not be used for censoring purposes, but instead will count as an event. In general, if the date last seen coincides with the date of any outcome event reported, this outcome event will be counted for the primary analysis.

These censoring rules determine the "time at risk" for counting of events for the primary analysis.

The robustness of the primary analysis will be assessed by an on-treatment analysis of the TS and the PPS. The same censoring rules as defined above will be used. However, for patients who already had their EOT visit (i.e. those who stopped treatment prematurely), they will be censored at the date of their last trial medication intake plus 6 days. It will also analyse patients by the actual treatment taken.

The censoring rules defined for the on-treatment analysis determine the "time at risk" for counting of events for the on-treatment analysis, i.e. the on-treatment analysis will only count events that occur while a patient is taking study medication (+ REP of 6 days, if study

medication is stopped prematurely before study end). The date of first intake of study medication will be used as the start of the analysis period in this analysis instead of the date of randomisation. Intermittent off-treatment periods will be ignored in cases of any temporary interruptions in study medication.

These analyses will be based on the TS and the on-treatment period.

The proportional hazards assumption will be investigated for the primary analysis only. The following techniques will be used:

- Plotting log (-log (survival function)) against the log of time by treatment group. Parallel curves are consistent with the proportional hazards assumption.

- Adding time-dependent variables to the Cox model
  For each variable in the model an interaction term is derived by multiplying by the log of time and adding to the model. Non-significance at the 5% level is consistent with the proportional hazards assumption.

A summary of adjudication will be presented showing the number of investigator-reported OEs along with whether they were positively or negatively adjudicated or whether they were non-assessable. Further analyses will be performed on investigator reported events (i.e. those that are positively and negatively adjudicated). A sensitivity analysis will be performed that includes any non-assessable events into the positively adjudicated MBE/CRNMBE category.

Two safety hypotheses (110mg DE-DAT vs. warfarin-TAT and 150mg DE-DAT vs. warfarin-TAT) will be tested:

1. 110mg DE-DAT is non-inferior to warfarin-TAT with respect to MBE/CRNMBE over the duration of the trial

2. 150mg DE-DAT is non-inferior to warfarin-TAT with respect to MBE/CRNMBE over the duration of the trial.

To control the Type I error rate at a one-sided 0.025 level, a hierarchical procedure for multiple testing will be used to test the above hypotheses. Additional testing for safety and efficacy endpoints will also be included in this hierarchical procedure. The following hierarchical procedure will be applied:

Step 1 – Non-inferiority of 110mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

Step 2 – Non-inferiority of 150mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

Step 3 – Non inferiority of 150mg DE-DAT and 110mg DE-DAT combined to warfarin-TAT in DTE and unplanned revascularisation by PCI/CABG is met at the one-sided 0.025 level of significance

Step 4 –Superiority of 110mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

Step 5 – Non inferiority of 150mg DE-DAT and 110mg DE-DAT combined to warfarin-TAT in DTE is met at the one-sided 0.025 level of significance

Step 6 – Superiority of 150mg DE-DAT to warfarin-TAT in MBE/CRNMBE is met at the one-sided 0.025 level of significance

If any of the steps above fail to meet statistical significance, the testing procedure will stop at that step and subsequent tests will not be performed.

The Non-Inferiority (NI) margin used will be 1.38 (on the relative hazard ratio (HR) scale). See Section 7.6 of the CTP for a clinical justification of this margin. The upper bound of the Wald confidence interval (CI) of the HR of DE-DAT vs. warfarin-TAT (one-sided 97.5%) will be compared to this NI margin for the NI testing.

Kaplan-Meier survival figures will be presented by treatment group/strata and by treatment group.

Frequency counts will be provided showing the number of patients experiencing recurrent events. In addition, the number of events will be presented as follows: the number of initial events, the number of additional events and the total number of events. ISTH MBEs and CRNMBEs will be presented separately and combined in these summaries.

7.5 SECONDARY ENDPOINTS

7.5.1 Key secondary endpoints

This section is not applicable as no key secondary endpoints have been specified in the protocol.

7.5.2 (Other) Secondary endpoints

Other secondary efficacy endpoints (all time to first event, measured from date of randomisation to end of observation period) are:

- A combined endpoint of DTE and unplanned revascularisation by PCI/CABG
- A combined endpoint of DTE
- Individual OEs:
    - All deaths
      - Cardiovascular death
      - Non-cardiovascular death
      - Undetermined
    - MI
    - Stroke
    - SE
    - Stent thrombosis (definite)

- Composite of death + MI + stroke
- Unplanned revascularisation by PCI /CABG

Time to first event endpoints will be analysed using the same methods as for the primary endpoint. However, comparisons will be for superiority of 110mg DE-DAT over warfarin-TAT, 150mg DE-DAT over warfarin-TAT and 150mg DE-DAT and 110mg DE-DAT combined over warfarin-TAT (for DTE/unplanned revascularisation and DTE, NI will be tested first). No multiplicity adjustments are planned for secondary endpoints, unless they are part of the hierarchical procedure (see Section 7.4). Nominal one-sided p-values will be reported for descriptive purposes. For analysis of stent thrombosis, Kaplan Meier plots will be provided additionally by stent type (DES, BMS,..) and by "Index PCI for ACS vs. elective index PCI (non-ACS)".

Only positively adjudicated events will be included in the analyses. Secondary analyses will also include presentations of number (%) of patients with events.

All secondary analyses will be performed on the FAS. The robustness of these analyses will be assessed by on-treatment analyses of the TS.

Further sensitivity analyses will be performed on investigator reported events (i.e. those that are positively and negatively adjudicated). Post-treatment events will also be summarised and a summary of adjudication will be presented showing the number of investigator-reported OEs along with whether they were positively or negatively adjudicated or whether they were non-assessable.

Frequency counts will be provided showing the number of patients experiencing recurrent events by endpoint. The number of events will be presented as follows: the number of initial events, the number of additional events and the total number of events. Individual outcome events (with the exception of death), as described above, will be presented in these summaries.

7.7 EXTENT OF EXPOSURE

Duration of exposure is calculated in days as:

Date of last administration of trial medication – date of first administration of trial medication + 1.

If the date of the first intake of study medication is missing, the randomisation date will be used to calculate exposure.

Total treatment time therefore includes time when treatment was temporarily discontinued and subsequently reintroduced. Descriptive statistics and frequency counts as described in Section 7 will be presented for extent of exposure. Categorisations for total treatment time are defined as follows:

- < 3 months
- 3 months - < 6 months
- 6 months - < 12 months
- 12 months - < 18 months
- 18 months - < 24 months
- 24 months - < 30 months
- ≥ 30 months

In addition, extent of exposure taking into account any temporary discontinuations in study medication will be computed (REP not included).

7.8 SAFETY ANALYSIS

This section describes the analysis of standard safety data such as adverse events, laboratory data, vital signs, ECGs, etc. The analysis of bleeding outcome event data is covered in Section 7.6. All safety analyses will be performed on the TS (including the REP, where applicable).

7.8.1 Adverse events

The analyses of adverse events will be descriptive in nature. All analyses of AEs will be based on the number (and %) of patients with AEs and not on the number of AEs. In addition to the usual summaries of adverse events, some analyses will be based on the number of AEs per patient year.

Furthermore, for analysis of AE attributes such as duration, severity, etc. multiple AE occurrence data on the eCRF, 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' [2].

The analysis of adverse events will be based on the concept of treatment emergent adverse events. Refer to Section 6.1 for a full list of the different treatment periods to which adverse events will be assigned based on the onset date/time of the event. In general, adverse events attributed to 'Screening', 'Post-treatment' or 'Post-study' will be listed only.

An overall summary of adverse events will be presented.

Separate summaries will be created for patients with serious adverse events.

AEs will also be analysed with respect to drug relationship, worst intensity and discontinuations of study drug.

Adverse events per patient year will be summarised by treatment, primary system organ class (SOC) and preferred term (PT). The SOCs will be sorted according to the standard sort order specified by the European Agency for the Evaluation of Medicinal Products (EMA). The PTs will be sorted by descending incidence within SOC. The number of events per patient year is calculated per treatment arm as follows:

$$\frac{\text{total number of patients with AE} \times 365.25}{\text{number of days exposure}}$$

Further details will be provided in the technical TSAP (comprehensive list of tables, figures, and listings, example table and listing templates and ADS specifications).

7.8.2 Laboratory data

Changes in laboratory data will be reported descriptively and will be based on BI standards [3].

Only central laboratory data will be summarised. Local laboratory data will be listed separately. The following displays will be presented:

- Change from baseline in laboratory parameters over time (original values)
- Frequency of patients categorised by reference range at baseline and last value on-treatment, minimum value post-baseline or maximum value post-baseline
- Frequency of patients with transitions relative to the reference range

- Frequency of patients with possibly clinically significant abnormalities (as defined by the Investigator)
- Descriptive statistics for baseline, last value on-treatment, and difference from baseline
- Laboratory values over time by parameter

CrCl will be estimated based on serum creatinine and use of the Cockroft-Gault equation (see Section 5.2.3 of the CTP). CrCl will also be estimated using the MDRD and CKD-EPI equations.

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 and further summaries will be produced for the number of patients who develop significant Q waves, atrial flutter, atrial fibrillation, ST segment changes and other changes.

In addition, ECG abnormalities will be summarised in the AE or baseline conditions tables.

7.8.5 Others

Other safety endpoints are:

1. ISTH MBE
2. CRNMBE
3. Clinically relevant bleeding measured using the following definitions:
    - Bleeding Academic Research Consortium (BARC) ≥3
    - TIMI group – Major, Minor and Minimal
4. Minor and total bleeding (ISTH, BARC and TIMI)
5. Intracranial haemorrhage
6. Gastrointestinal bleeds
7. Life-threatening bleeds
8. Fatal bleeds

These endpoints will be analysed using the same methods as the primary endpoint. No multiplicity adjustments are planned for safety endpoints. Sensitivity analyses will only be done to a limited extent (see Table 6.3: 1) and model assumption checking will not be performed.

Modified Rankin Scale (mRS)

For patients with an outcome event of stroke, frequency counts will be presented for each grade of the mRS at each time point (at time of stroke and 90 days thereafter).

8. REFERENCES

1 *001-MCG-156_RD-01*: "Handling of missing and incomplete AE dates", current version; IDEA for CON.

2 *001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.

3 *001-MCG-157*: "Display and Analysis of Laboratory Data", current version, IDEA for CON.

4 *CPMP/ICH/363/96*: "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note for Guidance on Statistical Principles for Clinical Trials, current version.

5 Clinical Trial Protocol Version 4 [c02214385-09]

6 Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining Clinical Risk Stratification for Predicting Stroke and Thromboembolism in Atrial Fibrillation Using a Novel Risk Factor-Based Approach: the Euro Heart Survey on Atrial Fibrillation. Chest 137 (2), 263 - 272 (2010) [R10-5332]

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8 Mauri L, Kereiakes DJ, Normand SLT, Wiviott SD, Cohen DJ, Holmes DR, Bangalore S, Cutlip DE, Pencina M, Massaro JM. Rationale and design of the dual antiplatelet therapy study, a prospective, multicenter, randomized, double-blind trial to assess the effectiveness and safety of 12 versus 30 months of dual antiplatelet therapy in subjects undergoing percutaneous coronary intervention with either drug-eluting stent or bare metal stent placement for the treatment of coronary artery lesions. Am Heart J 160 (6), 1035 – 1041.e1 (2010) [R13-4137]

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10 Ranucci M, Castlevecchio S, Menicanti L, Frigiola A, Pelissero G. Risk of assessing mortality risk in elective cardiac operations: age, creatinine, ejection fraction, and the law of parsimony. Circulation 119 (24), 3053 - 3061 (2009) [R17-0503]

11 Gibson CM, Pinto DS, Chi G, Arbetter D, Yee M, Mehran R, et al. Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with 2 treatment strategies of rivaroxaban or a dose-adjusted oral vitamin K antagonist treatment strategy. Circulation 135 (4), 323 - 333 (2017) [R17-0610]

10. HISTORY TABLE

Table 10: 1 History table

Version	Date (DD-Mmm-YY)	Author	Sections changed	Brief description of change
1	**14-May-14**	[redacted]	None	This is the first TSAP without any modification
Final	**9-Jun-17**		All	Updated due to global protocol amendments 1,2 and 3.