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CLINICAL STUDY REPORT

EFFICACY AND SAFETY STUDY OF F373280 FOR MAINTENANCE OF SINUS RHYTHM AFTER ELECTRICAL CARDIOVERSION IN PATIENTS WITH PERSISTENT ATRIAL FIBRILLATION AND CHRONIC HEART FAILURE

16. APPENDICES (continued)

16.1. STUDY INFORMATION (continued)

16.1.9 DOCUMENTATION OF STATISTICAL METHODS

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1. TITLE PAGE

STATISTICAL ANALYSIS PLAN

Reference :	**F373280 CA 201**
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Title	**Project statistician**
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2. SIGNATURES

	Title	Name (First & Last name)	Consistency between SAP and study protocol	Date	Signature
Author	**Project Statistician**	**Mélanie GROC**	**NA**	**15/06/2017**	
Reviewer	**Head of Medical Unit**	**Karim KEDDAD M.D.Ph.D.**	**NA**	15 JUN 2017	
Approving Officer	**Head of Statistical Department**	**Stéphanie JEAN-ALPHONSE**	☒ **Confirmed**	15 June 2017	

3. VERSIONING

Version	Date	Author (First & Last name)	Pages or sections concerned	Nature(*)	Reason(s) for change (**)
1	14/06/2017	Mélanie GROC	All	C	
2	**15/06/2017**	Mélanie GROC	Section 2	M	Responsibility "Auditor" changed into "Reviewer"
2	**15/06/2017**	Mélanie GROC	Section 14.1.4	M	Modification of patients subgroups with vascular or cardiac therapeutic procedures (deletion of onset restriction "<3months")

(*) *C: Creation, M: Modification, A: Addition, D: Deletion*

(**) *If the modifications are requested by external representatives (authorities), specify the organism name.*

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5. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

aPTT :	aPTT : Activated partial thromboplastin time
AE	Adverse Event
AF	Atrial Fibrillation
AP	Alkaline Phosphatase
ATC	Anatomical Therapeutic Chemical classification
BP	Blood Pressure
BSA	Body Surface Area
CNALV	Clinically Noteworthy Abnormal Laboratory Value
CRF	Case Report From
DBP	Diastolic Blood Pressure
DHA	Docosahexaenoic acid
eCRF	Electronic case report form
ECG	Electrocardiogram
ECV	Electrocardioversion
FDA	Food and Drug Administration
HLGT	High-Level Group Term
HLT	High-Level Term
HR	Heart Rate
ICH	International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use
IDMC	Independent Data Monitoring Committee
INR	International normalized ratio
IVRS	Interactive voice response system
JNC	Joint National Committee
MedDRA	Medical Dictionary for Regulatory Activities
NYHA	New York Heart Association
PSC	Predefined Potentially Clinically Significant Change
PSCV	PSC leading to Clinically Significant Value
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SBP	Systolic Blood Pressure
SD	Standard Deviation
SEM	Standard Error of Mean
SOC	System Organ Class
TB	Total Bilirubin
TCT	Thrombin clotting time
TE AE	Treatment Emergent Adverse Event
TTEM	TransTelephonic ECG monitoring
WBC	White Blood Cells
WHODrug	World Health Organisation Drug

6. INTRODUCTION

This document describes the final statistical analysis of the study that will be performed after the lock of the clinical database and the randomisation code release on the total number of study patients.
This statistical analysis plan will be approved before the final Data Review Meeting, and finalised and signed prior to the final randomisation code release.

Study design
This phase IIa trial is conducted as an international, multicentric, 24 weeks, double-blind, placebo-controlled, randomised, parallel group design, study on patients suffering from persistent AF and chronic heart failure.

Study objectives
The primary objective of the study is to assess the efficacy of F373280 on the maintenance of sinus rhythm after direct ECV in patients with persistent AF and chronic heart failure.

The secondary objectives of the study are to assess:
- the efficacy of F373280 on the efficiency of direct ECV
- the effect of F373280 on echocardiographic parameters
- the safety and tolerability of F373280

Study treatment
After a 1 to 4-week run-in period, patients are randomised into one of the following treatment groups: F373280 1g or placebo 1g for 24 weeks. The treatment starts 4 weeks before ECV and ECV is performed in patients with no spontaneous cardioversion and with INR levels stabilized as mentioned in the protocol. The follow-up is of 20 weeks after a successful ECV (at visit 3 – cardioversion visit) or after a spontaneous CV.

Primary efficacy criterion
The primary criterion is the time to first Atrial Fibrillation recurrence or Atrial Flutter emergence defined by the time to first episode of Atrial Fibrillation or atrial flutter lasting for at least 10 minutes during the follow up of 20 weeks after visit 3 (ECV visit).

The cardiac monitoring is performed using:
- A 7-day continuous ECG ambulatory recording (Holter ECG) between visit 3 (ECV visit) and visit 4 (week 5) in patients cardioverted to sinus rhythm.
- A Trans Telephonic ECG Monitoring (TTEM):
  * before protocol amendment PA05: with a daily transmission from week 6 to week 8; then every two days from week 9 to week 24, and at anytime in case of AF symptoms
  * after protocol amendment PA05: with one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24).

Sample size
Assuming an AF recurrence rate of 85% under placebo and 65% under active group, i.e. a clinically relevant difference Δ of 20%, a sample size of 64 assessable patients per group is

required, using a log-rank test of survival curves with a 80 % power and a 5 % two-sided significance level. According to the previous assumptions and assuming a rate of not assessable patients of 15%, a minimum of 76 patients have to be randomised per group.
Due to low recruitment, it was decided to stop prematurely the study. 135 patients were finally randomised (instead of 152 initially planned).

Interim Safety reviews/IDMC recommendations
Three IDMC were planned to provide independent safety review and trial guidance during the course of the ongoing trial (after the first 30 randomised patients, when the first 80 patients have terminated their study participation and then 130 patients). Due to the premature stop of the recruitment, only the first two meetings took place with IDMC recommendations to continue the study.

STUDY FLOW-CHART (PROTOCOL VERSION 9 28/09/2016)

F373280 CA 201	V1	V2	V3	V4		V6	V7		V9
Weeks	**W-4 to W-1**	**D1**	**W4 (28 -2D/+7 D)**	**W5 (35 -2D/+7 D)**		**W12 (84+/-7D)**	**W16 (112+/-7D)**		**W24 (168+/-7D)**
Outpatient or Hospitalization (1)			X						
Informed consent	X								
Demographic characteristics	X								
Medico-surgical history	X								
Concomitant disease	X								
Concomitant treatment	X	X	X	X	X	X	X	X	X
Habits	X								
Global physical examination (body weight)	X	X	X		X	X	X	X	X
Echocardiography	X	X		X		X			X
Eligibility criteria check	X	X							
Blood pressure, heart rate	X	X	X	X	X	X	X	X	X
12-Lead ECG Recording	X	X	X		X	X	X	X	X
INR	←	—	—	—	X	—	—	X	→ (2)
aPTT, TCT	X	X	X		X	X	X	X	X
Biochemistry	X								X
Haematology	X		X			X			X
Urinary pregnancy test		X							X
Red Blood Cell concentrations of DHA		X	X			X			X
Treatment number allocation		X				X			
IVRS/IWRS	X	X				X			
ECV (3)			X						
Drug administration		←	—	—	—	—	—	—	→
Adverse events recording		X	X	X	X	X	X	X	X
Holter ECG	↔ (4)		↔	→ (5)					
TTEM (6)				←	—	—	—	—	→

(1) Outpatient or hospitalization according to clinical practice of the centre (less or more than 24 hours)
(2) In case of VKA introduction: INR 2 to 3 times a week until stabilization, then weekly until the ECV, then every 4 weeks after ECV
(3) In patients with AF
(4) 24-hour Holter ECG
(5) 7-day Holter ECG
(6) TTEM: one transmission per week from the day of visit 4 (end of week 5) to visit 9 (week 24) and at any time in case of AF or atrial flutter symptoms.
TTEM once a week even in case of AF recurrence or atrial flutter emergence for at least 10 minutes.

V5 et V8 were cancelled in the amendment PA05

7. ANALYSIS SETS

The following analysis sets will be defined:

- **The Screened patients Set** which consists of all patients who have signed an informed consent,
- **The Randomised Patients Set** which consists of all patients who have signed an informed consent, and are assigned a treatment number,
- **The Safety Set** composed of all randomised patients having taken at least one dose of the study treatment. This set will be used to perform analyses of Safety.
- **The Full Analysis Set (FAS)** composed of all randomised patients having received at least one dose of the study treatment and with a successful cardioversion observed at visit 3. A successful cardioversion will be defined as either spontaneous cardioversion beforeV3 or successful ECV performed at V3 (early relapse within the observation period after ECV will be considered as non successful).This set will be used to perform analyses of Efficacy.
- **The Per Protocol Set (PP)** which is the subset of the Full Analysis Set composed of all FAS patients without any major protocol deviation or other source of bias for primary criteria analyses. This set will be used to perform the supportive analysis of the primary efficacy criterion.

Patients from Randomised Patients Set, Safety Set, Full Analysis Set or PP set will be analysed as treated (*ie* as treatment actually received at the randomisation). In case of error of treatment dispensation during the study period, the assignment of patient treatment group will be discussed during the data review meeting.
Randomised patients not treated will be analysed as randomised (*ie* as treatment allocated at the randomisation).

8. INFERENTIAL PRINCIPLES

Only the test on the primary criterion, on which is based the sample size justification, may lead to a causal interpretation. All other statistical results are to be regarded as exploratory.
Statistical tests will be two-sided and the significance level will be set to 5 %.

In order to obtain statistical modelling convergence and balance number of randomised patients, Poland (with only four randomised patients) will be grouped with the country that randomised the second lowest number of patients (Hungary). Categorical variable “Country” will be analysed with 4 levels for stratified statistical tests and statistical modeling: Italy, Spain, Czech Republic and Hungary.

9. DEVIATIONS

A final data review meeting will be held, prior to database lock, in order to review protocol deviations. These will be classified as minor or major.
A protocol deviation will be considered as major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.
Major protocol deviations and other sources of bias for primary criterion analyses, as well as additional reasons of exclusion from analysis sets will be identified using the list of pre-defined reasons for exclusion from analysis sets for the study described in a specific document "Predefined reasons for exclusion from analysis sets" separately from the statistical analysis plan.

A listing of all deviations and a listing of additional reasons for exclusion from statistical analysis will be provided for all randomised patients, including the type (major/minor) as validated during the data review meeting. This listing should be provided prior to the database lock and the randomisation code release.
The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the randomised patients set defined in section 7. The number and percentage of patients with minor protocol deviations will be also tabulated by treatment group and type of minor deviations on the randomised patients set.

The number and percentage of patients with reason of exclusion from analysis sets will be tabulated by treatment group and type of reason of exclusion on the randomised patients set.

10. HANDLING OF MISSING DATA AND ANALYSIS OF DROP-OUTS

10.1. DROP-OUTS

Results of criteria reported over time will be presented on the observed cases (OC).

10.2. REPOSITIONING OF VISITS

For premature withdrawals, patients' data at the end of study visit will be imputed to the next expected visit (Observed Case approach). For example, if a patient drops out of the study after Visit 6 (Week 12), then the end of study visit will implement the visit 7 (Week 16).

Unscheduled measurements will be taken into account for analysis in case of missing original measurement.

Unscheduled measurements will be taken into account for individual detection of abnormalities.

In case of several post-baseline retests around a same visit, the first available measurement at the visit will be kept for all analyses.

10.3. MISSING DATA (OTHER THAN DROP-OUT)

- **For Safety analyses:**

For safety analyses, missing values will be replaced by corresponding value of repositioned unscheduled measurement if any.

For laboratory data, in the case that an upper limit is mentioned in the associated character variable, missing numerical value will be replaced by the limit mentioned in the character variable. (For lower limit, missing numeric value will be replaced by the lower limit).
Example: for a measure of ALAT with a character variable "<6", missing numeric value will be replaced by 6.

Missing body weight: for creatinine clearance estimation, missing body weight will be replaced by the body weight measured at the nearest visit.

Replacement of missing or incomplete dates presented hereafter is defined in a conservative approach.

- **Missing dates of first or last trial drug intake**

Missing dates of the first trial drug intake will be considered equal to the inclusion day.
Missing dates of last trial drug intake will be discussed by the members of the data review meeting and extrapolated using all information recorded.

- **Missing dates of start of adverse event**

In case of completely missing date, it will be estimated by the date of first intake of study drug

If the day and the month are missing,
- If the year is the same as the year of first intake, it will be estimated by the date of first intake of study drug
- If the year is prior to the year of first intake, it will be estimated by the 31 December
- If the year is after the year of first intake, it will be estimated by the 1st January

If only the day is missing,
- If the month/year are the same as the month/year of first intake, it will be estimated by the date of first intake of study drug

- If the month/year are prior to the month/year of first intake, it will be estimated by the last day of the month
- If the month/year are after to the month/year of first intake, it will be estimated by the first day of the month

If after imputation, the estimated start date is after the end date of the adverse event, it will be replaced by the end date of the adverse event

- **Missing dates of end of adverse event**

For adverse events that are not "ongoing" at the end of the study (i.e. with an outcome other than "Not recovered/not resolved" or "Recovering/resolving"):
In case of missing date, it will be estimated by the last available date (last visit or last unscheduled exam date)

If the day and the month are missing,
- If the year is the same as the year of last available date, it will be estimated by the last available date
- If the year is prior to the year of last available date, it will be estimated by the 31 December

If only the day is missing,
- If the month/year are the same as the month/year of last available date, it will be estimated by the last available date
- If the month/year are prior to the month/year of last available date, it will be estimated by the last day of the month

If after imputation, the estimated end date is before the start date of the adverse event, it will be replaced by the start date of the adverse event

- **Missing severity or relationship to study drug of an adverse events**

If the maximal severity of an AE, as reported by the investigator, is missing, a maximal severity "severe" will be imputed.

If the relationship to study drug, as reported by the investigator, is missing, a relationship "suspected" will be imputed.

- **Concomitant medications**

When the start date is partially or completely missing, the same rules as for start and end date of adverse event will be applied, except in case of confirmation of previous medication in the CRF (ticked box) that will be estimated at the earliest date.

11. DESCRIPTIVE STATISTICS

Summary statistics will be presented by treatment group and visit when appropriate, and will consist of values for:
- quantitative parameters: number of missing data, number of patients, mean, standard deviation (sd), median, lower and upper quartiles, minimum and maximum, 95% confidence interval around the mean (when relevant)
- qualitative parameters: number of missing data, and number and percentage of patients.

Mean changes and standard error of mean (SEM) will be also represented graphically from baseline over time for relevant criteria.

Calculated statistics (mean, sd, median, lower and upper quartiles and 95% confidence interval) will display at most one more significant figure than the observed data.

For percentages, one decimal digit will be given.

Individual data listings will be provided for all analysed criteria.

12. DISPOSITION OF PATIENTS

The number of screened patients (who have signed an informed consent) and randomised patients, and reasons for non randomisation will be provided on the Screened patients set.
The number of patients in each analysis set detailed in section 2 will be provided by treatment group and by country and centre for randomised patients.
The number of randomised patients by visit done will be also tabulated by treatment group for randomised patients.

The number and percentage of patients who withdrew prematurely from the study after their randomisation will be provided by treatment group and reasons of drop out on the randomised patients set.

13. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Before the first trial drug intake, medical and surgical history, demographic data (gender, age, weight, height and BSA) and disease characteristics (left atrial area in cm^2, left ventricular ejection fraction in %, duration of current AF up to selection visit (days), time from first

documented persistent AF up to selection visit, time from heart failure diagnosis up to selection visit, NYHA grade) will be described by treatment group on the Full Analysis Set.

These data, except disease characteristics and baseline efficacy criteria will also be described on the Safety set.

If more than 10.0% patients of the FAS are excluded from the Per Protocol Set, demographic data, disease characteristics and baseline efficacy criteria will be repeated on the PP Set.

The age in years will be calculated as the integer part of [(reference start date* - date of birth)/365.25].*See appendix 1*

For listings of individual data, the age presented for randomised and non treated patients will be (date of randomisation - date of birth) and the age for not randomised patients will be (date of informed consent signature dates - date of birth).

The BMI will be calculated as weight (kg) / [height (m)]^2 rounded to 1 decimal place.

Time from first documented persistent AF and time from heart failure diagnosis up to selection visit will be calculated in months as (selection visit date – event date +1)/30.4, rounded to one decimal place.

Body weight, BSA, left atrial area and left ventricular ejection fraction at screening and inclusion visits will be described by treatment group only for baseline values (*i.e.* last values measured before the first application of study drug).

Concomitant diseases at selection, as well as medical and surgical history will be tabulated descriptively by treatment group using the MedDRA System Organ Classes and preferred terms on the Safety Set.

Concomitant treatments taken before first study drug intake date will be tabulated descriptively (number and percentage of patients) by treatment group on the Safety Set. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification, by WHO-DRUG ATC1 and ATC2 codes.
Concomitant treatments taken before first study drug intake date and linked to the study pathology will be also tabulated as above.

Any factor which could bias the treatment effect estimate, like demographic data or any other baseline characteristics will be cautiously examined in order to determine whether the randomisation failed and affect the interpretation of the primary results. If this descriptive analysis provides any clues on potential imbalances, further statistical investigations will be carried out.

14. ANALYSIS OF EFFICACY

Unless otherwise specified, the efficacy analysis will be performed on the FAS.
Baseline values will be the latest value measured before the first study drug intake.

14.1. PRIMARY CRITERION

The primary efficacy criterion is the time to first recurrence of AF or atrial flutter emergence.
The time to first recurrence of AF or atrial flutter emergence is defined by the time between the date of ECV visit (visit 3) and the date of the first recurrence of AF or atrial flutter emergence over the period V3-V9.
The first recurrence of AF or atrial flutter is defined as the first episode of AF (symptomatic or not) or atrial flutter emergence lasting for at least 10 minutes from visit 3.

For randomised patients with spontaneous cardioversion before ECV, the recurrence of AF or the emergence of atrial flutter will be assessed from visit 3 (week 5).

The primary efficacy criterion will be calculated in a conservative approach:

- If first TTEM measurement is the first confirmed AF/flutter alert then the day after the end date of Holter will be considered as the onset day of first AF recurrence or atrial flutter emergence.
- If TTEM measurement is not available the day before the first confirmed AF/flutter alert, then the day after the previous TTEM will be considered as the onset day of first AF recurrence or atrial flutter emergence.
- If an AF/flutter alert in TTEM measurement was not checked at least 10 minutes after on the same day, it will be considered as the onset day of the first AF/flutter only if AF/flutter is confirmed with the next measurement.

If the patient has a premature EOT at a visit X (or in between visits X-1 and X), the censoring time will be at visit X. If the patient took prohibited treatment leading to non recurrence/non emergence prior to premature EOT, the censoring time will be the start date of the prohibited treatment.

If no recurrence of AF or atrial flutter emergence can be ascertained by last measurement day and the patient has not already been censored according to the rule described above, the patient will be right-censored at the last measurement day.

14.1.1. Primary Analysis

The primary criterion, time to first recurrence of AF or atrial flutter emergence, will be described using survival curves according to the Kaplan Meier method. Survival curves will be performed by treatment group. The time to first recurrence of AF or atrial flutter emergence will be compared between treatment groups using with the Log rank test.

The distribution of time to first recurrence of AF or atrial flutter emergence will be described by treatment group using Kaplan-Meier methods, reporting Q1, Q3, median, and the 95% confidence interval (CI).

Survival rates (patients still in sinusal rhythm) will be described by treatment group at several time points (including 1 week, 1, 2, 3 and 4 months).

Hazard ratios and 95% confidence intervals (based on the Wald test) will be estimated with a Cox regression model. The PHREG procedure in SAS with option TIES=EXACT will be used to fit the Cox proportional hazards model.

14.1.2. Supportive Analysis

The primary analysis will be repeated on the PP set.

14.1.3. Additional Analyses

To take into consideration the sample size reduction, the predictive probability of success with the expected sample size based on observed data, and the conditional power will be provided to support the statistical decision. Different possible true treatment effects will be assumed for the calculations of conditional power (expected clinically relevant difference of 20%, and observed difference).

14.1.4. Sensitivity Analyses

Primary analysis of the main criterion (see section 14.1.1) will be conducted on the subgroups of patients defined as:

- FAS patients with a DHA baseline <= median of the DHA at baseline
- FAS patients with a DHA baseline > median of the DHA at baseline
  Note: The medians separating subgroups will be calculated on the FAS.

- FAS patients with vascular or cardiac therapeutic procedures identified in the data review meeting report
- FAS patients without vascular or cardiac therapeutic procedures identified in the data review meeting report

Other Cox models will be used to investigate the influence of Treatment * country, Treatment * Baseline interactions (DHA baseline), and to evaluate the influence of some prognostic or demographic factors (gender, age, BSA), baseline characteristics of the disease (duration of current AF up to selection visit, time from first documented persistent AF up to selection visit, Time from heart failure diagnosis up to selection visit, NYHA grade, left atrial area, Left ventricular ejection fraction on the Full Analysis Set.

ROC curves will be also constructed according to DHA and time to first recurrence thresholds (for example, positive/negative DHA vs first recurrence <=/> 1 week).

14.2. SECONDARY CRITERIA

All secondary analyses will be performed on the FAS.

14.2.1. Numbers of Atrial Fibrillation/ Flutter Episodes in the first week following V3

The total number of AF/flutter episodes (symptomatic or not, lasting for at least 10 minutes or less than 10 minutes) during the 7-day holter monitoring will be described by treatment group and compared by the Cochran-Mantel-Haenszel test adjusted by country.

14.2.2. Duration of Atrial Fibrillation/ Flutter Episodes in the first week following V3

The duration of all AF/flutter episodes during the 7-day holter monitoring will be described by treatment group and compared using a non-parametric analysis of covariance (based on ranks) adjusted for country.

14.2.3. Time to first AF recurrence / flutter emergence less than 10 minutes during TTEM period

The time to the first AF recurrence / flutter emergence less than 10 minutes will be analysed as the primary analysis.

14.2.4. Time to first symptomatic AF recurrence / flutter emergence during TTEM period

The time to the first symptomatic AF recurrence / flutter emergence* will be analysed as the primary analysis.

** Symptomatic AF recurrence/Flutter emergence will be defined as AF recurrence/Flutter emergence associated with at least one symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) in EHRA evaluation.*

14.2.5. Clinical parameters evaluation

14.2.5.1. EHRA score

AF related symptoms were evaluated by the EHRA (European Heart Rhythm Association) score. The following items “during presumed arrhythmia episodes" are checked to determine the score: palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety.

Classification of AF-related symptoms (EHRA score) are as follows:

- EHRA I - ‘No symptoms’

- EHRA II - 'Mild symptoms'; normal daily activity not affected
- EHRA III - 'Severe symptoms'; normal daily activity affected
- EHRA IV - 'Disabling symptoms'; normal daily activity discontinued

The maximum EHRA score will be described by treatment group and analysed using the Cochran-Mantel-Haenszel statistics (row mean scores) stratified by country effect using modified ridit scores.

In addition to this score, the frequency of symptoms will be classified in three groups, namely occasionally (less than once per month), intermediate (1/month to almost daily) and frequent at least daily, and will be described by treatment group.

14.2.5.2. Presumed arrhythmia

A presumed arrhythmia will be defined as an EHRA score equal to II, III or IV.

The frequency of presumed arrhythmia (will be described by treatment group.

14.2.5.3. Recurrence of symptomatic AF

The number of recurrences of symptomatic AF consists of the number of AF recurrences during TTEM period associated with at least one symptom (palpitation, fatigue, dizziness, dyspnea, chest pain and anxiety) in EHRA evaluation.

The number of recurrence of symptomatic AF will be described by treatment group and compared using the Cochran-Mantel-Haenszel test stratified by country.

14.2.5.4. Number and duration of hospitalizations

Hospitalizations for cardiovascular events will be characterised by:

- Hospitalization for AF treatment
- Hospitalization for worsening of heart failure
- Hospitalization for myocardial infarction

The number of hospitalizations (for cardiovascular events, for thromboembolic stroke and for all causes) will be described by treatment group and compared using Cochran-Mantel-Haenszel test stratified by country.

The duration of hospitalizations for cardiovascular events, for thromboembolic stroke and for any cause will be described by treatment group and compared using a non-parametric analysis of covariance (based on ranks) adjusted for country.

14.2.5.5. Cardioversion assessment

The number of spontaneous cardioversion before visit 3, of successful cardioversion (including number of shocks distribution) at visit 3 and the number of patients needing another cardioversion after initial ECV will be described by treatment group and compared using Cochran-Mantel-Haenszel test stratified by country.

14.2.5.6. Evolution of echocardiographic parameters

The following echocardiographic parameters were assessed: Left atrial diameter (mm), LAA (cm^2), Left atrial volume (ml), Left atrial volume/BSA (ml/m^2), LVEF (%), Left ventricular end diastolic volume/BSA (ml/m^2), Left ventricular end systolic volume/BSA (ml/m^2), Left ventricular end diastolic diameter (mm), Left ventricular end diastolic volume (ml), Left ventricular end systolic diameter (mm) and Left ventricular end systolic volume (ml).

The echocardiographic parameters values will be described at each time (V1, V2, V4, V6 and V9) and changes described from V4 to last value (V9) and from V2 to last value (V9).

15. COMPLIANCE

Estimation of compliance will be presented by treatment group on the Full Analysis Set. The analysis of compliance will be purely descriptive.

Only the global compliance (*ie for the whole duration of study*) will be estimated.

Trial drug compliance will be evaluated, for each patient, by treatment group, by calculating: (estimated number of tablets actually taken divided by theoretical number of tablets to be taken) x 100 (rounded at 1 digit).
The number of tablets actually taken during the study will be estimated as: number of tablets delivered minus number of tablets returned.
In case of trial drug boxes not returned or partially brought back, trial drug compliance will be considered unknown and missing.
The theoretical number of tablets to be taken will be calculated taking into account the actual number of days between dates of visits V2 and V9 considering the daily dose stable

Compliance will be tabulated using continuous scale and according to a 3-scale as: < 80, [80 – 100], and > 100 %.

An extrapolation of the compliance will be also calculated considering the not returned blisters as taken.

16. BIOMARKER ANALYSIS

16.1. RED BLOOD CELL CONCENTRATIONS OF DHA

Values and changes from baseline for red blood cell concentration of DHA will be performed by treatment group and assessment time on the FAS.

17. SAFETY ANALYSIS

The safety analysis will be presented on the Safety Set and will be descriptive.
Baseline Measures: The baseline will be the last value measured before the first intake of study drug. In particular, in case of retest, this retest will be used.

Values measured the same day as the first intake will be considered before the first intake of study drug (planned in the evening with dinner).
Results of retests performed post-trial drug administration will not be analyzed and tabulated (except in case of missing value for technical problem). They will only be displayed in individual data listings.

17.1. EXTENT OF EXPOSURE

Extent of exposure to the trial drug expressed in days will be tabulated as quantitative data, by treatment group and globally.
Extent of exposure to the trial drug is defined as the time interval between the actual date of first trial drug administration *(included)* and the actual date of last trial drug administration *(included)*, *i.e.*, as the quantity "date of last trial drug administration – date of first trial drug administration + 1 day". (*Incomplete or unknown dates of first and last trial drug* applications will be substituted as detailed in section 10.3*)*.

17.2. ADVERSE EVENTS

Any adverse event having been reported during the study for a given subject/patient will be classified using the MedDRA terminology on the Safety Set.

Any recorded AE will be regarded as Treatment Emergent (TE AE) if it occurs or worsens after the first administration (included) of the study drug.

The occurrence of an adverse event will be defined by the appearance of a new single event, the reappearance of a previously recovered event or the worsening of a persistent event (relative to its previous status).

If the severity is missing, a severity of "severe" will be assigned.

Missing or incomplete dates will be imputed for the calculation of TEAE as described in section 10.3, but will be presented as reported in the eCRF in the data listings.

A summary table will be produced giving the number (and percentage for patient) of:
- Patients with at least one AE
- Patients with at least one TE AE
- Patients with at least one related TEAE (i.e. relationship to the study drug other than "Not suspected")
- Patients with at least one AE leading to definitive study drug discontinuation
- Patients with at least one Serious AE (SAE)
- Occurrences of AEs
- Occurrences of TEAEs

- Occurrences of related TE AEs
- Occurrences of AEs leading to definitive study drug discontinuation
- Occurrences of SAEs

The number and percentage of patients with at least one AE occurred before first administration will be tabulated by MedDRA System Organ Class (SOC), Preferred Term (PT) and Treatment Group.

Numbers and percentages of subjects with at least one reported treatment emergent adverse event will be tabulated by treatment group (by decreasing order of frequency in the verum group). and:

- By system organ class and preferred term
- By system organ class, preferred term, and the most severe intensity
- And by system organ class, preferred term and the most severe relationship to the study drug.

"The number and percentage of patients with at least one drug related TE AE (i.e. relationship to the study drug other than “Not suspected") will be tabulated by SOC, Preferred Term and Treatment group in decreasing order for the treatment group (by decreasing order of frequency in the verum group).

The number and percentage of patients with at least one TEAE, and the number of occurrences of TEAEs, will be tabulated by MedDRA SOC, Preferred Term, seriousness and Treatment Group (by decreasing order of frequency in the verum group).
The number and percentage of patients with at least one related TEAE, and the number of occurrences of related TEAEs, will be tabulated by MedDRA SOC, Preferred Term, seriousness and Treatment Group (by decreasing order of frequency in the verum group).

Serious Adverse Events (SAEs)

Serious adverse events will also be described on an individual basis: treatment group, patient’s code, sex and age, investigator's reported term, preferred term, date of onset according to the date of the first study treatment administration, duration, action taken regarding the study treatment administration, use of a corrective treatment, outcome and relationship to the study treatment in the investigator’s opinion.

AEs leading to the definitive discontinuation
All AEs having led to the definitive discontinuation of the trial drug will be listed and exhaustively described, on an individual basis, by treatment group, in exactly the same way as serious adverse events previously described, during the study (from the date of the first trial drug intake onwards).

Deaths
Deaths will be also listed and exhaustively described, on an individual basis.

All AEs will be included in the listings of individual data.

17.3. VITAL SIGNS

Descriptive statistics over time of values and changes from baseline of supine Systolic Blood Pressure (SBP mmHg), Diastolic Blood Pressure (DBP mmHg) and Heart Rate (HR bpm) will be tabulated by treatment group and assessment time.
Figures: mean changes and standard error of mean (SEM) will be represented graphically from baseline over time.
The scales of vertical axis will be:

SBP mmHg	DBP mmHg	HR bpm
From -15 to +15	From -10 to +10	From -15 to +15

PSC and PSCV for supine parameters

The number and percentage of patients with at least one Predefined Potentially Clinically Significant Change (PSC) and with at least one PSC Leading to Clinically Significant Value (PSCV) will be tabulated by treatment group (cf Appendix 2, Table 1).

Orthostatic Hypotension

The number and percentage of patients experiencing at least one post-baseline orthostatic hypotension (cf Appendix 2, Table 2) will be tabulated by treatment group. Vital signs not measured according to protocol were identified during data review meeting. Measures performed first in standing position and then in supine position will not be taken into account for the analysis of orthostatic hypotension.

17.4. LABORATORY DATA

Clinically noteworthy abnormal laboratory values (CNALV) (See Appendix 4) will be identified and described on an individual basis. Five separate individual data listings by treatment group will be provided:

- for haemoglobin (including corresponding individual results of erythrocytes and haematocrit),
- for platelets (including corresponding individual results of erythrocytes and leucocytes),
- for liver function parameters (including corresponding individual results of gamma-GT),

- for neutrophils or leucocytes (including corresponding individual results of basophils, eosinophils, lymphocytes and monocytes)
- for serum creatinine

Estimated creatinine clearance (ml/min) will be calculated using Cockroft and Gault method as

$$\frac{[140 - \text{age (in years)}] \times \text{body weight (in kg)}}{\text{serum creatinine (in µmol/L)} \times 0.814} \times \text{(0.85 for female)}$$

Patients with estimated creatinine clearance (Cockroft method) < 30 ml/min will be also described on an individual basis. Values of estimated creatinine clearance (Cockroft method) will be classified as following:

Creatinine clearance categories (ml/min)
<15
[15-30[

For each laboratory parameter, values and changes from baseline will be tabulated by treatment group and assessment time.

For all biochemistry parameters, scatter plots highlighting individual results will display the baseline and last value of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively last value in the ordinate.

For all haematology parameters, scatter plots highlighting individual results will display the baseline and week 4, week 12 and week 24 of the laboratory measurements for each patient by locating the point defined by the baseline value on the abscissa and respectively week 4, week 12 and week 24 value in the ordinate.

Each treatment group will be differently identified. The first bisecting line (45° line), the lines of lower and upper normal range, the lines of Potentially Clinically Significant Change (PSC) range and Clinically noteworthy abnormal laboratory value (CNALV) range added on the plots (see Appendices 3 and 4).

For all blood laboratory parameters, shift tables will be provided to depict the numbers of patients with post-trial drug administration variations at each assessment time as compared to the baseline

values (measured on the last blood sample collected before the first trial drug administration) by treatment group. A 3-point scale (low, normal, high) will be used as defined by the normal ranges in use in the laboratory in charge of the assays.

Note: zero laboratory values without clinical significance will have to be considered as missing for statistical analysis.

17.5. COAGULATION PARAMETERS

For coagulation parameters, values and changes from baseline will be tabulated by treatment group and assessment time.

Scatter plots highlighting individual results for coagulation parameters (prothrombin time/INR, activated partial thromboplastin time and thrombin clotting time) before and after study treatment administration (last value) will be produced.

17.6. ECG

Individual tabulated data for ECG abnormalities will be displayed.

17.7. PHYSICAL EXAMINATION

Descriptive statistics over time of body weight values and changes from baseline will be tabulated by treatment group and assessment time.

The results on global physical examination will never be tabulated because it's only used to detect potential AE. They will be only listed in appendix 16 of the ICH report.

17.8. CONCOMITANT MEDICATIONS

Concomitant medications will be tabulated by treatment group and according to the first study drug intake and V9 (Taken at least once before first study drug administration, taken at least once after first-study drug administration and not started at V9, started at V9) within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" classification on the safety set.

Note: a concomitant medication which begins before first study drug administration and is on-going after first study drug administration, is counted in both periods "Taken at least once before first study drug administration" and "taken at least once after first-study drug administration and not started at V9".

18. CHANGES SINCE PROTOCOL REDACTION

The following modifications were made to statistical analyses compared to those envisaged in the Version 9 of the protocol dated December 6th, 2016:
- predictive probability of success and conditional power for primary efficacy criterion will be added
- subgroups analyses for primary criterion will be added
- ROC curves for primary criterion exploratory analyses according to DHA will be added
- the secondary criteria analyses repeated on the PP set will not be performed
-the secondary criteria were extended to the flutter detection as the primary efficacy criterion
- VS parameters in standing positions will not be analysed (only provided in individual data listngs)
- Frequencies on the ECG clinical interpretation will not be presented (not collected)- Analysis of TEAEs occurences by MedDRA SOC, PT, seriousness and Treatment Group will be added as per EudraCT requirement

Note: the Full Analysis Set definition was clarified with the definition of successful cardioversion as either spontaneous cardioversion beforeV3 or successful ECV performed at V3.

19. DATA PROCESSING

Version 9.4 of SAS Software for windows will be used to perform the statistical procedures.

20. APPENDIX

Appendix 1: Conventions related to reference dates and analysis study day variables

Appendix 1 **CONVENTIONS RELATED TO REFERENCE DATES AND ANALYSIS STUDY DAY VARIABLES**	**page 1/1**

Reference dates are usually equivalent to:

- For the Reference Start Date: the date of first study drug intake for treated patients, the date of randomisation for randomised and non treated patients and the date of informed consent date in other case (for listings of individual data)
- For the Reference End Date: the date of last intake of study treatment.

Some analysis may require the computation of duration from a reference day to a post-reference day. Duration will be defined as following:

⇨ Duration (in days) = Date - Reference date +1 day

⇨ Duration (in minutes) = (Date/time) – (Reference date/time)

Appendix 2 **CARDIOVASCULAR SAFETY**	**page 1/1**

Table 1: Predefined Limits for Potentially Clinically Significant Changes (PSC) and PSC Leading to Clinically Significant Values (PSCV)

Parameter	PSC	PSCV
SBP	*Increase ≥ 20 mmHg* *Decrease ≥ 20 mmHg*	*SBP ≥ 160 mmHg and increase ≥ 20 mmHg* *SBP ≤ 90 mmHg and decrease ≥ 20 mmHg*
DBP	*Increase ≥ 10 mmHg* *Decrease ≥ 10 mmHg*	DBP ≥ 100 mmHg and increase ≥ 10 mmHg *DBP ≤ 50 mmHg and decrease ≥ 10 mmHg*
HR	Increase ≥ 20 bpm *Decrease ≥ 20 bpm*	HR ≥ 120 bpm and increase ≥ 20 bpm *HR ≤ 50 bpm and decrease ≥ 20 bpm*

Table 2: Definition of orthostatic hypotension

Orthostatic Hypotension *
SBP Decrease ≥ 20 mmHg or DBP Decrease ≥ 10 mmHg between supine and standing positions

The Consensus Committee of the American Autonomic Society and the American Academy of Neurology. Consensus statement on the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology 1996;46:1470-3.

Appendix 3 **LIST OF PREDEFINED POTENTIALLY CLINICALLY SIGNIFICANT CHANGE FOR LABORATORY VALUES(¤)**	**page 1/1**

PARAMETERS		**UNIT**	**PSC**	
			Decrease	**Increase**
MUSCLE	Creatine Phosphokinase	U / l	-	236
KIDNEY	Creatinine	µmol/l	-	35
	Urea	mmol/l	-	3.2
	Uric acid	µmol/l	-	119
	Phosphate	mmol/l	0.39	0.39
	Calcium	mmol/l	0.30	0.30
ELECTROLYTES	Sodium	mmol/l	8	8
	Potassium	mmol/l	1.1	1.1
	Chloride	mmol/l	8	7
	Bicarbonate	mmol/l	7	8
METABOLISM/ NUTRITIONAL	Glucose (random)	mmol/l	3	3.7
	Albumin	g/l	6	6
	Protein	g/l	11	10
	Cholesterol	mmol/l	-	1.97
	HDL cholesterol	mmol/l	0.91	0.85
	LDL cholesterol	mmol/l	2.17	2.04
	Triglycerides	mmol/l	-	2.91
ERYTHROCYTES	Erythrocyte count	T/l	0.7	0.7
	Haemoglobin	g/l	20	-
	Haematocrit	1	0.06	0.06
	MCV	fl	7	7
	MCH (Fe)	fmol	0.19	0.19
	MCHC (Fe)	mmol/l	2	2
LEUKOCYTES	Leukocyte count	G/l	4.2	3.8
DIFFERENTIAL COUNT	Neutrophils	G/l	3.47	3.19
	Lymphocytes	G/l	1.76	1.63
	Monocytes	G/l	-	0.49
	Eosinophils	G/l	-	0.41
	Basophils	G/l	-	0.14
URINE	Specific gravity	-	0.017	0.015
	pH	-	2	2
LIVER	Total bilirubin	µmol/l	-	10
	ASAT (SGOT)	U/l	-	N x (23/36)
	ALAT (SGPT)	U/l	-	N x (28/45)
	Gamma GT	U/l	-	N x (25/38)
	Alkaline phosphatase	U/l	--	N x (30/95)

N = upper limit of normal range

(¤) Delta-limits from « Routine Laboratory Tests in Clinical Trials » W. Leigh Thompson, Rocco L. Brunelle, Gregory G. Enas, Patrick J. Simpson and Randy L. Walker Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, Indiana in « Clinical Trials and Tribulations » 1988.

Appendix 4 **DEFINITION OF CLINICALLY NOTEWORTHY ABNORMAL LABORATORY VALUES (CNALV)**	**page 1/1**

PARAMETERS	**Baseline value**	**CNALV**
HAEMOGLOBIN	Not missing	Decrease of at least 2g/dl and value < 10 g/dl
	Missing	Value <10g/dl
NEUTROPHILS	-	< 1 500/mm3
WBC (if missing value for neutrophils)	-	< 3 000/mm3
PLATELETS	-	< 100 000/mm3
SERUM CREATININE	Not missing	Increase of at least 30 % as compared to baseline value and value > 150 µmol/l
	Missing	Value > 150 µmol/l
LIVER FUNCTION TESTS		
ALAT	Normal	ALAT > 2 N
	≤ 2.5 N	Increase of at least 100 % as compared to baseline value
	> 2.5 N	value > 5 N
and/or **ASAT**	Normal	ASAT > 2 N
	≤ 2.5 N	Increase of at least 100 % as compared to baseline value
	> 2.5 N	value > 5 N
and/or **Alkaline phosphatase (AP)**	Normal	AP > 1.25 N
	Abnormal	AP > 2 N
and/or **Total bilirubin (TB)**	Normal	TB > 1.5 N
	Abnormal	TB > 2 N

N=upper limit of normal range

International consensus Meeting. International Journal of Clinical Pharmacology, Therapy and Toxicology, 1990;28:317-322
Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced liver disorders: report of an Standardisation of definitions and criteria of causality assessment of adverse drug reactions: drugs-induced cytopenia. Intenational Journal of Clinical Pharmacology, Therapy and Toxicology, 1991;29:75-81

Appendix 5: TABLES, FIGURES AND LISTINGS

SECTION	Title	RTF reference
10.1	Number of screened and randomised patients, and reasons for non randomisation [Screened patients set]	10_1a_randtrt.RTF
10.1	Number of patients with study discontinuation and reason for discontinuation [Randomised patients set]	10_1d1_pwstudy_ov.RTF
10.2	Number of Patients with Major protocol Deviations [Randomised Patients Set]	10_2a_maj_dev.RTF
10.2	Number of Patients excluded from analysis sets and reasons [Randomised Patients Set]	10_2b_reas_excl.RTF
11.1	Number of patients in each analysis set [Randomised patients Set]	11_1_aset.RTF
11.1	Number of patients by study visit [Randomised patients sets]	11_1b_byvisit.RTF
11.2	Demographic characteristics [FAS]	11_2a_demo.RTF
11.2	Disease characteristics at baseline [FAS]	11_2c_dischar.RTF
11.3	Treatment Compliance [FAS]	11_3a.RTF
11.3	Extrapolated treatment compliance [FAS]	11_3b.RTF
11.4.1.1	Time to first recurrence of AF or atrial emergence - Survival curves and Logrank test [FAS]	11_4_1_1_1_primana_KM.gif
11.4.1.1	Time to first recurrence of AF or atrial emergence - KM summary [FAS]	11_4_1_1_2_primana_KM.RTF
11.4.1.1	Time to first recurrence of AF or atrial emergence - Cox analysis [FAS]	11_4_1_1_3_primana_cox.RTF
11.4.1.1	Time to first recurrence of AF or atrial emergence - Survival curves and Logrank test [PP]	11_4_1_2_1_supana_KM.gif
11.4.1.1	Time to first recurrence of AF or atrial emergence - KM summary [PP]	11_4_1_2_2_supana_KM.RTF
11.4.1.1	Time to first recurrence of AF or atrial emergence - Cox analysis [PP]	11_4_1_2_3_supana_cox.RTF
	Time to first recurrence of AF or atrial emergence - Survival curves and Logrank test [FAS patients with a DHA baseline <= median of the DHA at baseline]	11_4_1_4_1_sensana_DHA1_KM.gif
	Time to first recurrence of AF or atrial emergence - KM summary [FAS patients with a DHA baseline <= median of the DHA at baseline]	11_4_1_4_2_sensana_DHA1_KM.RTF
	Time to first recurrence of AF or atrial emergence - Cox analysis [FAS patients with a DHA baseline <= median of the DHA at baseline]	11_4_1_4_3_sensana_DHA1_cox.RTF
	Time to first recurrence of AF or atrial emergence - Survival curves and Logrank test [FAS patients with a DHA baseline > median of the DHA at baseline]	11_4_1_4_4_sensana_nonDHA2_KM.gif
	Time to first recurrence of AF or atrial emergence - KM summary [FAS patients with a DHA baseline > median of the DHA at baseline]	11_4_1_4_5_sensana_DHA2_KM.RTF
	Time to first recurrence of AF or atrial emergence - Cox analysis [FAS patients with a DHA baseline > median of the DHA at baseline]	11_4_1_4_6_sensana_DHA2_cox.RTF

SECTION	Title	RTF reference
	Time to first recurrence of AF or atrial emergence - Survival curves and Logrank test [FAS patients with vascular or cardiac therapeutic procedures that will be identified in the data review meeting report<3months]	11_4_1_5_1_sensana_surg1_KM.gif
	Time to first recurrence of AF or atrial emergence - KM summary [FAS patients with vascular or cardiac therapeutic procedures that will be identified in the data review meeting report<3months]	11_4_1_5_2_sensana_surg1_KM.RTF
	Time to first recurrence of AF or atrial emergence - Cox analysis [FAS patients with vascular or cardiac therapeutic procedures that will be identified in the data review meeting report<3months]	11_4_1_5_3_sensana_surg1_cox.RTF
	Time to first recurrence of AF or atrial emergence - Survival curves and Logrank test [FAS patients without vascular or cardiac therapeutic procedures that will be identified in the data review meeting report<3months]	11_4_1_5_4_sensana_surg2_KM.gif
	Time to first recurrence of AF or atrial emergence - KM summary [FAS patients without vascular or cardiac therapeutic procedures that will be identified in the data review meeting report<3months]	11_4_1_5_5_sensana_surg2_KM.RTF
	Time to first recurrence of AF or atrial emergence - Cox analysis [FAS patients without vascular or cardiac therapeutic procedures that will be identified in the data review meeting report<3months]	11_4_1_5_6_sensana_surg2_cox.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and interaction treatment group by country– Cox analysis [FAS]	11_4_1_5_1_inter_country.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and interaction treatment group by DHA baseline – Cox analysis [FAS]	11_4_1_6_1_inter_DHA.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and gender – Cox analysis [FAS]	11_4_1_7_1_gender.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and age – Cox analysis [FAS]	11_4_1_8_1_age.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and BSA – Cox analysis [FAS]	11_4_1_9_1_BSA.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and duration of current AF up to selection visit – Cox analysis [FAS]	11_4_1_10_1_current.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and time from first documented persistent AF up to selection visit– Cox analysis [FAS]	11_4_1_11_1_firstFA.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and Time from heart failure diagnosis up to selection visit – Cox analysis [FAS]	11_4_1_12_1_heartfail.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and NYHA grade – Cox analysis [FAS]	11_4_1_13_1_NYHA.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and left atrial area – Cox analysis [FAS]	11_4_1_14_1_leftatrial.RTF
11.4.1.1	Primary criterion - Time to first recurrence of AF or atrial emergence and Left ventricular ejection fraction – Cox analysis [FAS]	11_4_1_15_1_leftventri.RTF

SECTION	Title	RTF reference
11.4.1.2	Number of AF/flutter episodes in the first week following V3[FAS]	11_4_1_2_1_nbAF.RTF
11.4.1.2	Duration of AF/flutter episodes in the first week following V3[FAS]	11_4_1_2_2_durAF.RTF
11.4.1.2	Time to first AF recurrence /flutter emergence less than 10 minutes - Survival curves and Logrank test [FAS]	11_4_1_2_4_1_AFless10_KM.gif
11.4.1.2	Time to first AF recurrence /flutter emergence less than 10 minutes - KM summary [FAS]	11_4_1_2_4_2_AFless10_KM.RTF
11.4.1.2	Time to first AF recurrence/flutter emergence less than 10 minutes - Cox analysis [FAS]	11_4_1_2_4_3_AFless10_cox.RTF
11.4.1.2	Time to first symptomatic AF/Flutter - Survival curves and Logrank test [FAS]	11_4_1_2_4_1_symptAF_KM.gif
11.4.1.2	Time to first symptomatic AF/Flutter - KM summary [FAS]	11_4_1_2_4_2_symptAF_KM.RTF
11.4.1.2	Time to first symptomatic AF/Flutter - Cox analysis [FAS]	11_4_1_2_4_3_symptAF_cox.RTF
11.4.1.2	Maximum EHRA score– CMH [FAS]	11_4_1_2_5_ehra.RTF
11.4.1.2	Frequency of symptoms - –[FAS]	11_4_1_2_6_symptfreq.RTF
11.4.1.2	Presumed arryhtmia - –[FAS]	11_4_1_2_7_arrhy.RTF
11.4.1.2	Number of symptomatic AF recurrence/Flutter emergence - [FAS]	11_4_1_2_8_nb_symptrecu.RTF
11.4.1.2	Number of hospitalizations- [FAS]	11_4_1_2_9_1_nb_hospit.RTF
11.4.1.2	Duration of hospitalizations- [FAS]	11_4_1_2_9_2_dur_hospit.RTF
11.4.1.2	Cardioversion assessment- [FAS]	11_4_1_2_10_cardiov_assess.RTF
11.4.1.2	Echocardiographic parameters values and changes over time- [FAS]	11_4_1_2_11_echoparam_assess.RTF
11.4.1.2	Values and changes from baseline for red blood cell concentration of DHA [FAS]	11_4_1_2_12_DHA.RTF
12.1	Total extent of exposure to the study drug [Safety Set]	12_1_a_expos.RTF
12.2.1	Summary of adverse events [Safety Set]	12_2_1_ae_overview.RTF
12.2.2	Number of patients with at least one treatment-emergent adverse event by MedDRA primary system organ class and preferred term [Safety Set]	12_2_2a_teae_socpt.RTF
12.2.2	Number of patients with at least one related treatment-emergent adverse event by MedDRA primary system organ class and preferred term [Safety Set]	12_2_2b_relteae_socpt.RTF
12.3.1.1	Listing of deaths [Safety Set]	12_3_1_1_deaths_list.rtf
12.3.1.2	Listing of serious adverse events [Safety Set]	12_3_1_2_sae_list.rtf
12.3.1.3	Listing of adverse events leading to definitive study treatment discontinuation [Safety Set]	12_3_1_3_aedefstoptrt_list.rtf
12.4.2.2	Hematology: Number of patients with variations over time [Safety Set]	12_4_2_2_1Hem.RTF

SECTION	Title	RTF reference
12.4.2.2	Biochemistry: Number of patients with variations over time [Safety Set]	12_4_2_2_1Bioch.RTF
12.4.2.3	CNALV: Patients with haemoglobin < 10 g/dL and decreased from baseline >=2 g/dL (if baseline was measured) [Safety Set]	12_4_2_3a_hemog.RTF
12.4.2.3	CNALV: Patients with neutrophils < 1.5 G/L or WBC < 3G/L (if neutrophils missing) [Safety Set]	12_4_2_3b_neutr.RTF
12.4.2.3	CNALV: Patients with platelets < 100 G/L [Safety Set]	12_4_2_3c_plat.RTF
12.4.2.3	CNALV: Patients with ALAT > 2N or ASAT > 2N or ALP > 1.25N or TB > 1.5N, and normal baseline value, or GGT > 3 N (if baseline<3N) [Safety Set]	12_4_2_3d_liver.RTF
12.4.2.3	CNALV: Patients with creatinine >150 µmol/L and increase by 30% from baseline value (if any) [Safety Set]	12_4_2_3e_creat.RTF
12.4.2.3	Patients with estimated creatinine clearance < 30 ml/min [Safety Set]	12_4_2_3f_clear.RTF
12.5.1	SBP Changes over Time [Safety Set]	12_5_1_1_figCH_SBP.gif
12.5.1	DBP Changes over Time [Safety Set]	12_5_1_1_figCH_DBP.gif
12.5.1	HR Changes over Time [Safety Set]	12_5_1_1_figCH_HR.gif
12.5.1	Supine VS measurements : Incidence of post-baseline PSCs and PSCVs [Safety Set]	12_5_1_2_SCVS.RTF
12.5.1	Supine BP measurements : Incidence of post-baseline PSCs and PSCVs [Safety Set]	12_5_1_2_SCBP.RTF
12.5.1	Supine HR measurements : Incidence of post-baseline PSCs and PSCVs [Safety Set]	12_5_1_2_SCHR.RTF
12.5.1	BP measurements : Number of patients with at least one post-baseline orthostatic hypotension [Safety Set]	12_5_1_2_OrthoBP.RTF
12.5.3	Patients with ECG abnormalities (Investigator's evaluation) [Safety Set]	12_5_3_1_2_ecg_abn.RTF
14.1	Number of patients per country and centre [Randomised patients]	14_1a_asetpercenter_all.RTF
14.1	Number of patients with minor deviations [Randomised Patients Set]	14_1b_minor_dev.RTF
14.1	Demographic characteristics [Safety Set]	14_1c_demoSaf.RTF
14.1	Demographic characteristics [PP]	14_1c_demoPP.RTF
14.1	Disease characteristics at baseline [PP]	14_1c_discharPP.RTF
14.1	Number (%) of patients with at least one medical or surgical history by MedDRA primary system organ class and preferred term [SafetySet]	14_1d_medhist_socpt_saf.RTF
14.1	Number (%) of patients with at least one concomitant disease at time of selection by MedDRA primary system organ class and preferred term [Safety Set]	14_1e_cdiseasesel_socpt_saf.RTF
14.1	Number (%) of patients with at least one medication taken before first study drug administration, by WHO-Drug ATC1and ATC2 [Safety Set]	14_1f_pmed_atc_saf.RTF
14.1	Number (%) of patients with at least one medication before first study treatment administration linked to the study pathology, by WHO-Drug ATC1and ATC2 [Safety Set]	14_1g_pmed_link_atc_saf.RTF
14.3.1	Number of patients with at least one AE occurred before first administration by MedDRA primary system organ class and preferred term [Safety Set]	14_3_1_ae_socpt.RTF
14.3.1	Number of patients with at least one treatment-emergent adverse event by MedDRA primary system organ class, preferred term and maximum intensity [Safety Set]	14_3_1a_teae_socptmaxi.RTF

SECTION	Title	RTF reference
14.3.1	Number of patients with at least one treatment-emergent adverse event by MedDRA primary system organ class, preferred term and most severe relationship to study drug [Safety Set]	14_3_1b_teae_socptmaxr.RTF
14.3.1	Number of patients with at least one non serious TEAE, and the number of associated occurrences, by MedDRA primary system organ class and preferred term [Safety Set]	14_3_1c_nsaeteae_socpt.RTF
14.3.1	Number of patients with at least one TEAE, and the number of occurrences of TEAEs by MedDRA SOC, Preferred Term, seriousness and Treatment Group [Safety Set]	14_3_1e_teae_occu_socpt.RTF
14.3.1	Number of patients with at least one related TEAE, and the number of occurrences of related TEAEs by MedDRA SOC, Preferred Term, seriousness and Treatment Group [Safety Set]	14_3_1f_relteae_occu_socpt.RTF
14.3.4	Hematology Values and changes over time [Safety Set]	14_3_4_1a_1Hem.RTF
14.3.4	Biochemistry Values and changes over time [Safety Set]	14_3_4_1a_2Bioch.RTF
14.3.4	Coagulation Values and changes over time [Safety Set]	14_3_4_1a_3Coag.RTF
14.3.4	Hematology Changes of values relative to normal ranges over time[Safety Set]	14_3_4_1c_1Hem.RTF
14.3.4	Biohemistry Changes of values relative to normal ranges over time [Safety Set]	14_3_4_1c_2Bioch.RTF
14.3.4	Lab scatter plot: haematocrit(Week 4) [Safety Set]	14_3_4_2hema_w4.gif
14.3.4	Lab scatter plot: haemoglobin (Week 4) [Safety Set]	14_3_4_2hemog_w4.gif
14.3.4	Lab scatter plot: RBC count (Week 4) [Safety Set]	14_3_4_2RBC_w4.gif
14.3.4	Lab scatter plot: WBC count (Week 4) [Safety Set]	14_3_4_2WBC_w4.gif
14.3.4	Lab scatter plot: reticulocytes (Week 4) [Safety Set]	14_3_4_2retic_w4.gif
14.3.4	Lab scatter plot: Platelets (Week 4) [Safety Set]	14_3_4_2plat_w4.gif
14.3.4	Lab scatter plot: haematocrit(Week 12) [Safety Set]	14_3_4_2hema_w12.gif
14.3.4	Lab scatter plot: haemoglobin (Week 12) [Safety Set]	14_3_4_2hemog_w12.gif
14.3.4	Lab scatter plot: RBC count (Week 12) [Safety Set]	14_3_4_2RBC_w12.gif
14.3.4	Lab scatter plot: WBC count (Week 12) [Safety Set]	14_3_4_2WBC_w12.gif
14.3.4	Lab scatter plot: reticulocytes (Week 12) [Safety Set]	14_3_4_2retic_w12.gif
14.3.4	Lab scatter plot: Platelets (Week 12) [Safety Set]	14_3_4_2plat_w12.gif
14.3.4	Lab scatter plot: haematocrit(Week 24) [Safety Set]	14_3_4_2hema_w24.gif
14.3.4	Lab scatter plot: haemoglobin (Week 24) [Safety Set]	14_3_4_2hemog_w24.gif
14.3.4	Lab scatter plot: RBC count (Week 24) [Safety Set]	14_3_4_2RBC_w24.gif
14.3.4	Lab scatter plot: WBC count (Week 24) [Safety Set]	14_3_4_2WBC_w24.gif
14.3.4	Lab scatter plot: reticulocytes (Week 24) [Safety Set]	14_3_4_2retic_w24.gif
14.3.4	Lab scatter plot: Platelets (Week 24) [Safety Set]	14_3_4_2plat_w24.gif
14.3.4	Lab scatter plot: ASAT (last value) [Safety Set]	14_3_4_2AST.gif
14.3.4	Lab scatter plot: ALAT (last value) [Safety Set]	14_3_4_2ALT.gif

SECTION	Title	RTF reference
14.3.4	Lab scatter plot: Alkaline phosphatase (last value) [Safety Set]	14_3_4_2Alkaline_phosgif
14.3.4	Lab scatter plot: Conjugated bilirunin (last value) [Safety Set]	14_3_4_2Conjugated_Bili.gif
14.3.4	Lab scatter plot: Total bilirunin (last value) [Safety Set]	14_3_4_2Total_Bili.gif
14.3.4	Lab scatter plot: Gamma GT (last value) [Safety Set]	14_3_4_2GGT.gif
14.3.4	Lab scatter plot: Total Cholesterol (last value) [Safety Set]	14_3_4_2Total_Chol.gif
14.3.4	Lab scatter plot: HDL Cholesterol (last value) [Safety Set]	14_3_4_2HDL_Chol.gif
14.3.4	Lab scatter plot: LDL Cholesterol (last value) [Safety Set]	14_3_4_2LDL_Chol.gif
14.3.4	Lab scatter plot: Sodium (last value) [Safety Set]	14_3_4_2Sod.gif
14.3.4	Lab scatter plot: Potassium (last value) [Safety Set]	14_3_4_2Pota.gif
14.3.4	Lab scatter plot: Bicarbonate (last value) [Safety Set]	14_3_4_2Bicar.gif
14.3.4	Lab scatter plot: Chloride (last value) [Safety Set]	14_3_4_2Chlo.gif
14.3.4	Lab scatter plot: Albumin (last value) [Safety Set]	14_3_4_2Albu.gif
14.3.4	Lab scatter plot: Creatinine (last value) [Safety Set]	14_3_4_2Creat.gif
14.3.4	Lab scatter plot: Fasting glucose (last value) [Safety Set]	14_3_4_2Gluc.gif
14.3.4	Lab scatter plot: Triglycerides (last value) [Safety Set]	14_3_4_2Trig.gif
14.3.4	Lab scatter plot: Fibrinogen (last value) [Safety Set]	14_3_4_2Fibri.gif
14.3.4	Lab scatter plot: prothrombin time/INR (last value) [Safety Set]	14_3_4_2coag1.gif
14.3.4	Lab scatter plot: Activated partial thromboplastin time (last value) [Safety Set]	14_3_4_2coag2.gif
14.3.4	Lab scatter plot: Thrombin clotting time (last value) [Safety Set]	14_3_4_2coag3.gif
14.3.5	Supine Systolic Blood Pressure Measurements Over Time [Safety Set]	14_3_5_1_sbp.GIF
14.3.5	Supine Diastolic Blood Pressure Measurements Over Time [Safety Set]	14_3_5_1_dbp.GIF
14.3.5	Supine Blood Pressure Measurements Over Time [Safety Set]	14_3_5_1_BP.RTF
14.3.5	Supine Heart Rate Measurements Over Time [Safety Set]	14_3_5_1_hr.GIF
14.3.5	Supine Heart Rate Measurements Over Time [Safety Set]	14_3_5_1_hr.RTF
14.3.5	Number of patients with Predefined Potentially Clinically Significant Change (PSC) and with PSC Leading to Clinically Significant Value (PSCV) in supine Systolic Blood Pressure [Safety Set]	14_3_5_1b_PSC_PSCV_sbp.RTF
14.3.5	Number(%) of patients with Predefined Potentially Clinically Significant Change (PSC) and with PSC Leading to Clinically Significant Value (PSCV) in supine Diastolic Blood Pressure [Safety Set]	14_3_5_1b_ PSC_PSCV _dbp.RTF
14.3.5	Number(%) of patients with Predefined Potentially Clinically Significant Change (PSC) and with PSC Leading to Clinically Significant Value (PSCV) in supine Heart Rate [Safety Set]	14_3_5_1b_ PSC_PSCV _hr.RTF
14.3.5	Body weight values and changes from baseline over time [Safety Set]	14_3_5_2_1_bodyw.RTF
14.3.5	Number (%) of patients with at least one concomitant medication, by WHO-Drug ATC1and ATC2 [Safety Set]	14_3_5_5_1_cmed_atc.RTF
16.1.7	16.1.7: Randomisation	16_1_7.RTF
16.2.1	16.2.1: Discontinued patients	16_2_1.RTF

SECTION	Title	RTF reference
16.2.2	16.2.2: Protocol deviations for randomised patients	16_2_2.RTF
16.2.3	16.2.3: Reasons for exclusion from analysis sets	16_2_3.RTF
16.2.4.1	16.2.4.1: Demographic data	16_2_4_1.RTF
16.2.4.2	16.2.4.2: Disease characteristics	16_2_4_2.RTF
16.2.4.3	16.2.4.3: Medical and Surgical History by patient	16_2_4_3.RTF
16.2.4.4	16.2.4.4: Concomitant Diseases by patient	16_2_4_4.RTF
16.2.4.5	16.2.4.5.1 Prior medications by Patient	16_2_4_5_1.RTF
16.2.4.5	16.2.4.5.2 Prior medications by ATC classification	16_2_4_5_2.RTF
16.2.4.6	16.2.4.6 Inclusion and non-inclusion criteria	16_2_4_6.RTF
16.2.5.1	16.2.5.1: Dates of Visit	16_2_5_1.RTF
16.2.5.2	16.2.5.2: Global Compliance	16_2_5_2.RTF
16.2.5.3	16.2.5.3 Exposure for randomised patients	16_2_5_3.RTF
16.2.6.1	16.2.6.1: Time to first recurrence of AF or atrial flutter	16_2_6_1.RTF
16.2.6.2	16.2.6.2: Holter measurements	16_2_6_2.RTF
16.2.6.3	16.2.6.3: TTTEM measurements	16_2_6_3.RTF
16.2.6.4	16.2.6.4: DHA measurements	16_2_6_4.RTF
16.2.7.1	16.2.7.1: Adverse Events Reported Term, Preferred Term and Dates	16_2_7_1.RTF
16.2.7.2	16.2.7.2: Adverse Events by Patient	16_2_7_2.RTF
16.2.7.3	16.2.7.3: Adverse Events by SOC, PT, LLT	16_2_7_3.RTF
16.2.8.1	16.2.8.1: Listing of individual laboratory measurements	16_2_8_1.RTF
16.2.8.2	16.2.8.2: Listing of individual coagulation parameters measurements	16_2_8_2.RTF
16.2.9.1	16.2.9.1: Listing of vital signs measurements	16_2_9_1.RTF
16.2.9.2	16.2.9.2: ECG measurements	16_2_9_2.RTF
16.2.9.3	16.2.9.3: Physical examination	16_2_9_3.RTF
16.2.10.1	16.2.10.1: Concomitant medications by Patient	16_2_10_1.RTF
16.2.10.2	16.2.10.2: Concomitant medications by ATC classification	16_2_10_2.RTF