Statistical Analysis Plan (SAP)

FLE-002 (INSTANT) – Final Analysis

A prospective, randomized, multicenter study of flecainide acetate oral inhalation solution in single and repeat dose regimens for acute conversion to sinus rhythm (SR) in subjects with recent onset of symptomatic paroxysmal atrial fibrillation (AF)

Protocol FLE-002 Revision History

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Signature Page

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This Statistical Analysis Plan (SAP) is based upon protocol FLE-002 version 8.0 / EU-1 dated 16-FEB-2021 and protocol FLE-002 version 8.0/US-1 dated 26-FEB-2021.

The undersigned have reviewed this analysis plan and approve of it in its entirety.

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SAP Version History

Date	Change	Reason
20-Dec-2019	V2.0 updates SAP V1.0 to include modifications in the efficacy endpoints and dose cohorts. This SAP only includes Part A of the study.	Protocol amendments 2.0-5.0 EU-2 necessitated modification of SAP V1.0
7-Apr-2020	V2.1 updates V2.0	V2.1 updated SAP for Part A, incorporating comments by reviewers on V2.0
9-Jul-2020	V3.0 updates V2.1	Revision to expand on analysis populations and endpoints to take into consideration exposure to study medication relative to conversion of AF to SR
30- Mar-2021	V4.0 is first SAP for Part B	Revision to describe the analysis of Part B
01-July-2021	V4.1 updates V4.0	Revision in PK population, mITT population, source data for Adverse Event reporting of Part A FlecIH-103 subjects
06-July-2022	V5.0 is the SAP for the final analyses	Revision to describe the analyses of Parts A, B and C

Table of Contents

1 Introduction 9
1.1 Final Analysis Report 9
1.1.1 Medically-Led Cardioversion Study (Part C MLS study) 9
1.1.2 Patient-Led Under Medical Supervision Cardioversion Study Patient-Led Cardioversion Study (PLS) 10
1.2 Brief description of Part C of the trial 10
1.3 Handheld Echo (HHE) 10
1.4 Study Design 11
1.5 Study Population 12
1.6 Study procedures 12
1.7 Screen Failures 13
2 Study objectives Part C 13
3 Definitions and Terminology 14
3.1 Conversion to SR, recurrence of AF 14
3.2 Methods for Cardioversion 14
3.3 Reported periods 15
3.4 Adverse Events 16
3.5 Other definitions 17
4 Study Medication 18
5 Source Data 19
5.1 Investigator reported information 20
5.2 Rhythm monitoring assessment (Holter) 20
5.3 Rhythm status assessments (Remote ECG) 20
5.4 Pharmacodynamic (PD) Assessment 20
5.5 Pharmacokinetics (PK) assessment 21
5.6 Safety results 21
5.6.1 Investigator (Part B and Part C) 21
5.6.2 Cardialysis (Part A) 22
5.6.3 Analysis Dataset Part B and Part C 22
5.6.4 Analysis Dataset Report Part A 23
5.6.5 Additional AESI and SAESI information 23
5.7 Handheld Echo (HHE) 24
5.8 Protocol Deviations 24

6 Study Endpoints: definition and availability of information 25
6.1 Time to conversion 26
6.1.1 Time between initiation of study drug and conversion to SR (in minutes) 26
6.1.2 Time between completion of study drug and conversion to SR (in minutes) 26
6.2 Endpoints, Adverse Events and other assessments 26
6.2.1 Primary endpoint 27
6.2.2 Secondary efficacy endpoints 27
6.2.3 Secondary safety endpoint 27
6.2.4 Exploratory endpoints (HHE) 28
6.2.5 Additional Assessments 28
6.2.6 Exploratory Endpoints for Part C PLS 32
7 General Statistical Considerations 33
7.1 Sample Size and Power 33
7.1.1 Treatment Allocation 33
7.1.2 Blinding and Unblinding 33
7.2 Handling of Data 34
7.2.1 Strata 34
7.2.2 Examination of Patient Subgroups 34
7.2.3 Multiple Testing and Comparisons 34
7.2.4 Visit Windows 34
7.2.5 Imputation of Missing Data 34
8 Study Populations 35
8.1 Population of Consented Subjects 36
8.2 Intention-To-Treat Population (ITT) 36
8.3 Safety Population 36
8.4 PK Population 36
8.5 Modified Intention-To-Treat Population (mITT) 38
8.6 Handheld Echo (HHE) Population 38
8.7 MLS Study Population Cohorts 38
8.7.1 Part C MLS Cohort (Cohort 1) 38
8.7.2 Pooled MLS Cohort (Cohort 2) 38
8.7.3 Pooled MLS No Predose Flecainide Cohort (Cohort 3) 383839
8.7.4 Pooled MLS Predose Flecainide Cohort (Cohort 4) 39
8.8 Patient-Led (PLS) Population 39
9 Statistical Methods 40

9.1 Patient Disposition, Demographic and Baseline Characteristics 40
9.2 Specification of Analyses 40
9.2.1 Primary efficacy endpoint 40
9.2.2 Secondary efficacy endpoints and other assessments analyses 41
9.2.3 Additional Analyses 51
9.2.4 Exploratory endpoints: Handheld Echo 55
9.2.5 Exploratory endpoints for Part C PLS study 60
9.3 On Pooled results (Part A, Part B and Part C MLS Subjects (120 mg FlecIH-103)) 63
10 Difference between protocol and SAP 63
11 Changes in the Planned Analyses 64
12 Programming Conventions 64
13 References 65
14 Tables, Figures and Listings 65
15 Programming Specifications 67
Annex A: FLE-002 Sponsor Review of Adverse Events of Special Interest 68
1. Background and Justification 68
2. Purpose 68
3. Responsibilities 69
4. Definitions 69
5. Procedure 71

Glossary of Abbreviations

Abbreviation	Definition
AE	Adverse Event
AESI	AE of Special Interest
AECG	Ambulatory Electrocardiogram
AF	Atrial Fibrillation
BLQ	Below the Limit of Quantification
C_{max}	Maximum Plasma Concentration
CV	Coefficient of Variation
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ECV	Electrical Cardioversion
EOS	End-Of-Study
eTLD	Estimated total lung dose
FlecIH	Flecainide acetate inhalation solution
HHE	Handheld Echo
IC	Informed Consent
ITT	Intent-To-Treat
IV	Intravenous
JTc	Corrected JT interval
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction (%)
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent To Treat
MLS	Medically-Led Cardioversion Study
PD	Pharmacodynamic
PK	Pharmacokinetic
PLS	Patient-Led Under Medical Supervision Cardioversion Study
PR	PR interval - measured from the beginning of the P wave to the beginning of the QRS complex
TdP	Torsades de Pointes
Q_1	First Quartile
Q_3	Third Quartile
QRS	QRS duration (complex) - a structure on the ECG that corresponds to the depolarization of the ventricles
QTc	QT interval corrected for heart rate
RR	RR interval - time between QRS complexes
SAE	Serious Adverse Event
SAESI	Serious Adverse Event of Special Interest
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System, software
SD	Standard Deviation
SOP	Standard Operating Procedure
SPAESI	Sponsor assessed (S)AESI
SR	Sinus rhythm

Abbreviation	Definition
T_{max}	Time (of maximum concentration)
TEAE	Treatment Emergent Adverse Event
TFLs	Tables, Figures, and Listings
TTM	Transtelephonic Monitoring
ULN	Upper Limit of Normal
VF	Ventricular Fibrillation
VT	Ventricular Tachycardia

1 Introduction

1.1 Final Analysis Report

This SAP describes the final analysis of the INSTANT trial (Parts A, B and C for patients receiving 120 mg dose of FlecIH-103).

Parts A and B, consisted of a Medically-Led Cardioversion (MLS) only, whereas, Part C consists of a Medically-Led Cardioversion Study (MLS) and a Patient-Led Under Medical Supervision Cardioversion Study (PLS). Refer to SAP Section 1.4. for a description of the study design for Part C of the trial.

This final Report will primarily focus on data for the MLS populations in the 120 mg FlecIH-103 using the prespecified definitions described in Section 8.1 through 8.6. Data for each MLS population will be presented for several cohorts, as described in Section 8.0.

Due to the low number of subjects who participated in the PLS, a more limited analysis will be conducted on the PLS populations described in Section 8.8. Data for the PLS will only be presented for the overall study populations as defined in Section 8.8, with no additional cohort analyses.

Details of all planned analyses for the INSTANT trial are specified in this SAP. Background information is provided for the overall study design. The reader is referred to the study protocols for details of study conduct.

The statistical analysis that will be performed for the final report will be based on this version of the SAP; Flowcharts, Tables, Figures, and Listings (TFLs) will be created. The report will be accompanied by an overview of all TFLs that are included in the report.

1.1.1 Medically-Led Cardioversion Study (Part C MLS study)

Study procedures for subjects enrolled in the PART C MLS are identical to those in Part B; subjects receive 120 mg (2*60 mg), using the FlecIH-103 inhalation solution. Results for the Medically-Led administration will be presented for the prespecified analysis populations (e.g., safety, mITT) for the Part C MLS cohort only, and for several pooled cohorts consisting of subjects receiving 120 mg FlecIH-103 in Part A, Part B and Part C (i.e., the dose/formulation selected for Phase 3). Refer to SAP sections 8.7 for the definition of the pooled MLS cohorts.

Statistical tables, figures and listings will be created. The tables will show study results for MLS Part C and for one or two pooled population, refer to SAP section 9.2 for a detailed description. Study procedures for the Part A subjects included in the pooled analysis were identical to those in Part B and Part C MLS.

In the final analysis all endpoints will be reported that were included in the final report for Part B. However, unlike in Part B, all endpoints in Part C are exploratory; no formal hypothesis testing is planned for Part C. Summary statistics will be generated, including estimates of the endpoints and for the primary efficacy endpoint (refer to SAP section 9.2.1) its 90% confidence interval.

Part C MLS subjects were enrolled in sites in Europe under Protocol Version 7.0 / EU-1 or later. This version of the SAP follows the text of the European Protocol Version V8.0 EU-1 as the basis for all

analyses, except where additional information from the US Protocol Version V8.0/ US-1 is required (e.g., for differences in screening requirements). Enrollment in the MLS cohort of Part C was stopped on 31 December 2021, the last subject signed informed consent and received study medication on 07 December 2021.

All analyses will be conducted with the EU and US subjects in a combined study population.

1.1.2 Patient-Led Under Medical Supervision Cardioversion Study Patient-Led Cardioversion Study (PLS)

At sites in the EU, Part C includes an open-label Patient-Led Under Medical Supervision Cardioversion Study (PLS), whereby subjects who specifically consent and whose AF episode was previously converted to SR following an oral inhalation of flecainide solution in Part A, Part B and/or MLS Part C may be eligible to participate.

Part C PLS will serve as a feasibility study to assess the ability of subjects to independently assemble the nebulizer, dispense the study medication, and self-administer the study medication with minimal supervision during a recurrent episode of recent-onset AF.

Due to the small number of subjects enrolled in the PLS study (18 enrolled, 3 treated), summary tables will only be created for a limited amount of data (e.g., primary efficacy endpoint and disposition) and no confidence intervals will be reported. A flowchart and a summary table will show the main results for the study and all PLS results will be presented in listings. If needed, results from the initial MLS (Part A, Part B or MLS study of Part C) may be presented in listings for these PLS subjects.

Three (3) out of 18 PLS subjects received a second treatment of 120 mg (2*60 mg) using the FlecIH-103 inhalation solution. The last subject in the PLS study signed Informed Consent for the PLS study on 14 December 2021 and last subject was treated 19 August 2021.

1.2 Brief description of Part C of the trial

Part C consists of a MLS and PLS part, refer to SAP Section 1.4 for a further description of the study design for Part C of the trial.

1.3 Handheld Echo (HHE)

At selected sites in the EU, subjects in Part B and MLS Part C (Protocol Version 7.0 / EU-1 or later) could consent to participate in an optional Handheld Echo (HHE) sub-study and undergo an echocardiogram using the HHE during screening to confirm eligibility.

In the US (Protocol Version V8.0/ US-1), an echocardiogram with LVEF within 6 months of screening was required to demonstrate eligibility. If no echocardiogram was available, subjects were required to undergo an echocardiogram using the HHE during screening to confirm eligibility.

HHE images were also reviewed and analyzed by an independent reviewer at a later date.

A HHE was performed for 6 subjects; the last HHE was performed on 11 November 2021.

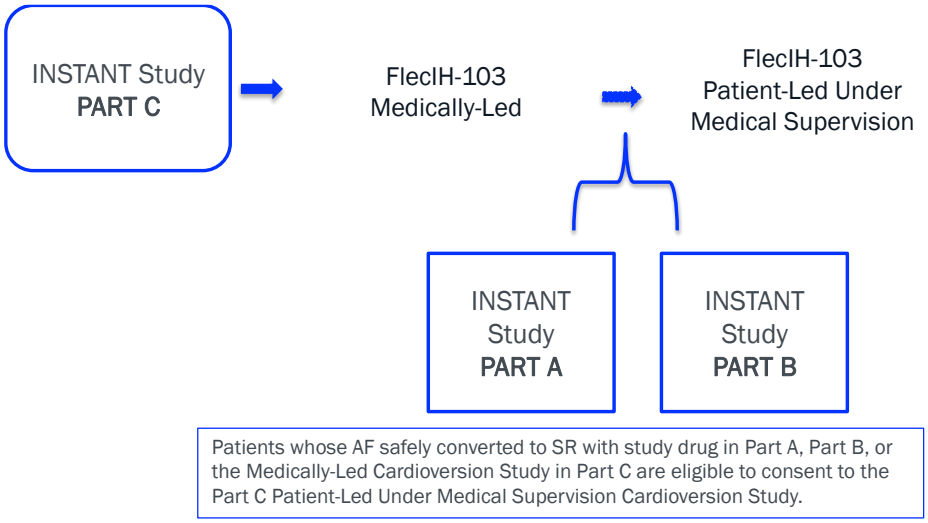
The flowchart of the statistical report for INSTANT will show the number of subjects who signed IC for the HHE sub-study (EU) or for whom an HHE was required at screening (US).

The full statistical analysis of the HHE sub-study is described in this version of the SAP. This analysis requires complete information from the HHE, as performed by the investigator and of the HHE analysis and as performed by the independent reviewer.

1.4 Study Design

An overview of Part C of the INSTANT trial is shown in Figure 1 below.

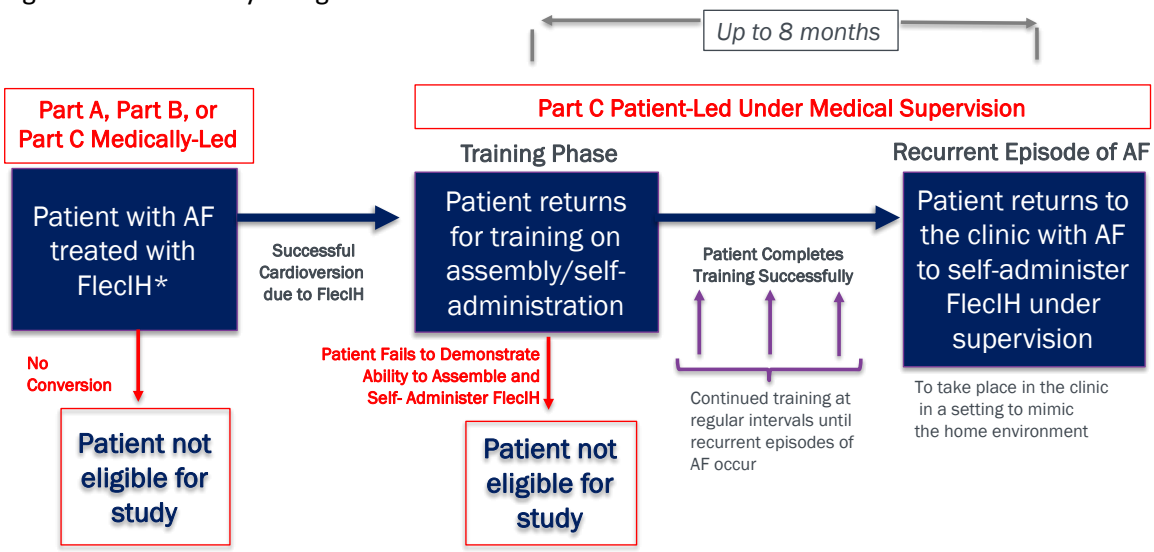
Figure 1. Schematic for Part C: 120 mg Dose



For Part C (both the MLS and PLS) subjects if treated receive a repeat dose regimen of 120 mg eTLD (2 x 60 mg) FlecIH-103 inhalation solution.

The PLS requires subjects to return to the clinic for training, pass an assessment of their ability to self-administer the study drug, and then return to the clinic within 48 hours of the onset of symptoms when they experience a recurrent episode of paroxysmal AF to self-administer the study drug. Subjects may return and self-administer study drug for one recurrent episode of AF.

Figure 2. Part C Study Design



*Potentially eligible patients from Part A, Part B, and the Medically-Led Cardioversion Study in Part C may provide Informed Consent for the Part C Patient-Led Under Medical Supervision Cardioversion Study.

1.5 Study Population

Protocol indicates that Part C does not have an enrollment target; enrollment will continue in the Part C MLS at the discretion of the Sponsor to support rollover participation in the Part C Patient-Led Under Medical Supervision Cardioversion Study. Enrollment in Part C MLS was stopped by Sponsor December 31, 2021.

For subjects to be included in the PLS Study, they must undergo rescreening to confirm their eligibility according to the same criteria in Part B prior to each treatment of a recurrent AF episode with the study drug. Safety labs and a symptom-driven physical examination may be performed at the discretion of the PI (e.g., due to changes in recent medical history); except for those required to confirm the subject's eligibility, which must be performed.

If a subject is not eligible, they may be treated as per institutional standard of care and are allowed to return in the future for a different recurrent episode of AF.

1.6 Study procedures

Study procedures for Part C are performed as described in the Schedule of Assessments (Appendix 4 protocol).

Study procedures are identical in Part C MLS compared to Part B. The Part A subjects analyzed in the final report also followed these study procedures. Vital signs and blood samples for PK analysis are collected at multiple serial time points just before, during, and after the inhalation regimen, and at the time of conversion to SR as detailed in the Schedule of Assessments. AECG (12-lead Holter) data are collected from 45 minutes pre-dose until 90 minutes post dose in order to identify the time of conversion to SR and to monitor the safety of the study subjects. Additionally, 12-lead ECGs are

extracted in triplicate from the AECG recording at multiple time points. Discharge at or after 90 minutes post dose (a -10 minute window is allowed).

If a subject's AF does not convert to SR after treatment with the study drug, they may be given an alternate therapy in accordance with standard of care after 90 minutes post completion of dosing. Only if deemed medically necessary by the investigator, an alternate therapy may be given as early as 60 minutes post completion of dosing; however, IV flecainide and propafenone may only be given after 90 minutes post completion of dosing.

All subjects have a Day 2 and a Day 5 (± 1 day) telephone assessment (Visit 1 and Visit 2, respectively). All enrolled subjects are followed for 5 days, and every effort should be made to maintain a subject's follow-up. End-of-study activities are completed for all enrolled subjects who received study drug. Study follow-up is only terminated at the explicit request of the subject. The overall duration of subject participation from screening through follow-up is 5 days.

When compared to Part C MLS, in Part C PLS less information is collected, refer to section 6C of the study protocol.

1.7 Screen Failures

Subjects are pre-screened based on the information available from the institutional standard of care. For subjects who appear to be candidates for the study based on this available information, IC signature and other study-specific screening procedures take place prior to enrollment. A subject who withdraws IC before enrollment or who fails the inclusion/exclusion criteria before enrollment is defined as a screen failure. No further clinical follow-up is performed for screen failed subjects unless they are re-screened and are enrolled.

Subjects who are enrolled but who do not receive study drug (e.g., due to spontaneous conversion of their AF to SR prior to dosing) are considered early terminations and may be replaced; refer to protocol Section 5.5.

2 Study objectives Part C

All Part C objectives are exploratory; no formal testing is performed. Study objectives are:

- To explore the feasibility of patient-led self-administration of flecainide acetate inhalation solution in a hospital setting under medical supervision
- To explore the PK/PD of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF for Patient-Led administration relative to Medically-Led administration
- To explore the feasibility of implementing a portable cardiac ultrasound (HHE) at screening in an emergent setting

3 Definitions and Terminology

3.1 Conversion to SR, recurrence of AF

This section defines conversion from AF to SR and recurrence of AF after conversion to SR. All information will be derived from AECG (Holter) Core Laboratory analysis if available. If AECG information is not available or is incomplete, then investigator-reported information (e.g., 12-lead ECG and/or telemetry) will be used for the missing Core Lab information.

Conversion from AF to SR
Conversion of AF to SR is defined as the presence of SR, derived from AECG, lasting for ≥ 1 minute.

Index Conversion
The first conversion of AF to SR that lasts for ≥ 1 minute is referred to as the index conversion.

Start Time of First Conversion from AF to SR
Start time of the index conversion

Time to First Conversion from AF to SR (from initiation of study drug)
Time from the initiation of study drug to the start time of the index conversion, measured as minutes and seconds.

Time to First Conversion from AF to SR (from conclusion of study drug)
Time from the conclusion of study drug dosing to the start time of the index conversion, measured as minutes and seconds. Index conversions that start prior to the end of dosing result in a negative value.

Recurrence of AF
Recurrence of AF is defined as the return of a subject's heart rhythm to AF for ≥ 1 minute after the index conversion.

Start Time of Recurrence of AF
Start time of the first recurrence of AF occurring after the index conversion.

3.2 Methods for Cardioversion

Conversion of AF to SR by the study drug
Index Conversion occurred ≤ 90 minutes after initiation of study medication, without the administration of any other intervention to induce conversion of AF to SR (e.g., IV flecainide, electrical cardioversion [ECV]).

Spontaneous conversion
Index Conversion occurred > 90 minutes after initiation of study medication, without administration of any other intervention to induce conversion of AF to SR (e.g., IV flecainide, ECV).

Conversion due to adjunct medication
Index Conversion occurred following administration of an adjunct medication (e.g., IV flecainide) to induce cardioversion.

Conversion due to adjunct procedure
Index Conversion occurred following ECV to induce cardioversion.

3.3 Reported periods

-T_{Pre}: Pre-dose

–T_{Admin}: Just before the start of inhalation

-$T_{between\ admin}$: In the 1-min break between inhalations

-T_0: Time zero is the initiation time of study drug.

-T_x: Time after initiation of study drug

T_{SR}: At the time of index conversion, which requires at least 60 seconds of SR. The time of index conversion is defined as the start time of this 60-second period.

Data related to the T_{SR} time point will either be reported at the start time of the index conversion (e.g., time of conversion reported from continuous ECG monitoring), or at the nearest time after the start of the index conversion (e.g., PK values that may have been obtained within or just after the 60-second period).

Time points measured after initiation of study drug are compared with T_0, e.g., 11 minutes post initiation of study drug (T_{11}) is recorded as 11 minutes after T_0.

In case time points are measured post dose, time points are compared with the conclusion of study drug administration. Note, all assessment time points after dosing in the Protocol Schedule of Assessments are calculated post the completion of study drug administration.

Day 1
Day 1 is the date of study enrollment (day of dosing). All values for Study Day are defined relative to Day 1.

3.4 Adverse Events

Adverse Event
An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding for example), symptom, or disease temporally associated with the use of a (investigational) medicinal product, whether or not considered related to the (investigational) medicinal product.

All adverse events will be recorded on the Adverse Event electronic case report form (eCRF). For the purposes of this study, a recurrence of AF will not be reported as an adverse event. AF recurrence will be collected in a specific eCRF designed to capture this data. However, recurrences of AF that meet the definition of a serious adverse event (SAE) will be captured on the AE CRF.

For the definition of an SAE, please refer to protocol Section 17.2.1.2.

Treatment-emergent Adverse Event
A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pre-treatment), or an AE that existed pre-treatment and worsened on treatment (relative to the pre-treatment state) through Day 5 (end of study).

Adverse Events of Special Interest (AESI)
Protocol 8.0/EU-1 uses a new definition of AESI, meaning in the data used for the final report, more than one AESI definition is used.

Protocol 8.0/EU-1 additionally introduces a new category: Serious Adverse Events of Special Interest (SAESI), meaning SAESI was not captured for AESIs reported prior to the introduction of Protocol 8.0/EU-1. The secondary safety endpoint (refer to SAP section 6.2.3.) reports on Serious AESI.

In order to be able to report all AESI and SAESI using the Protocol 8.0/EU-1 definitions, additional source data will be provided by the Sponsor (refer to SAP sections 5.6.5 and Annex A). These data will use a slightly adjusted definition than in protocol 8.0/EU-1 definition for AESI and SAESI, refer to SAP section Annex A .

The protocol 8.0/EU-1 definition of AESI and SAESI is as follows:

Four categories of adverse events of special interest (AESI) are defined. The fourth category described is a subcategory of the third type. For the complete definition of these AESI refer to protocol Section 9.1.2 B:

1. AEs related to inhalation device
Events related to the inhalation device (AeroEclipse® II BAN)

2. Pregnancies
Any female study subject or female partner of a study subject that becomes pregnant

3. *AEs known to be related to other flecainide formulations (i.e., IV and oral)*
The following events are known to be related to other formulations of flecainide (i.e., IV and oral) and are considered AESI if they occur after the initiation of study drug.

- Hypotension- an acute hypotensive episode (AHE) is a sudden drop in BP resulting in a BP < 90/60 mmHg (MAP < 70 mmHg) that lasts for at least 5 minutes and is based on multiple sequential readings (≥ 3). MAP is calculated as 1/3 (SBP – DBP) + DBP.
- Ventricular tachycardia ≥ 3 beats
- Bradycardia- an ECG derived rate < 50 bpm for ≥1 minute
- Sinus pauses post conversion of AF to SR- an ECG-derived pause > 3 seconds
- Atrial flutter with 1:1 conduction with fast ventricular response (ventricular heart rate ≥ 200 bpm)

4. Serious Adverse Events of Special Interest (SAESI)

The following potential Serious AESI are defined for study purposes:

- Hypotension, with symptoms/signs of clinical instability (i.e., severe chest pain/dyspnea or altered mental status), requiring vasopressor or inotropic agent
- Ventricular tachycardia, sustained (> 30 seconds or requiring intervention before that time) VT, TdP or VF
- Bradycardia, with symptoms/signs of clinical instability (i.e., severe chest pain/dyspnea, altered mental status or hypotension) requiring pacing or chronotropic agent
- Sinus pauses post conversion of AF to SR, causing syncope, or requiring pacing or CPR
- Atrial flutter with 1:1 conduction with fast ventricular response (ventricular heart rate ≥ 200 bpm), requiring intervention (DC cardioversion) for termination, or an IV AV nodal blocking agent (β-blocker or Ca2+-channel blocker) to slow the ventricular rate
- Any arrhythmia with symptoms/signs of clinical instability (i.e., severe chest pain/dyspnea, altered mental status or hypotension) and requires DC cardioversion, defibrillation, pacing, or vasopressor, inotropic or chronotropic agent. SAESIs in this category will also be included in the broader category of AESI described above.

3.5 Other definitions

AECG (Holter)
Ambulatory ECG device used to collect heart rhythm monitoring data over an extended period of time

PD
Pharmacodynamics; quantitative characteristics of ECGs

PK
Pharmacokinetics; concentration of flecainide in the blood plasma

Remote ECG (TTM)
Event recording ECG device used to collect heart rhythm status assessments over a brief period of time

Concomitant Medications
Medications taken during the study after signing IC

Prior Medications
Medications taken prior to signing informed consent for the study; captured for at least 30 days prior to enrollment

Baseline Value
Measurement(s) taken prior to initiation of study drug. If at a specific planned time point multiple measurements are taken (e.g., 3 ECGs analyzed at 15 minutes prior to study drug initiation) then the mean of these measurements will be used to represent the baseline value for the specific time point.

Baseline (seated)
The mean of all available Baseline Values at these time points: 15 minutes pre-initiation of study drug and just before initiation of study drug (T_0)

Baseline (semi-recumbent)
The mean of all available Baseline Values at these time points: 45 and 30 minutes pre-initiation of study drug

C_{max}
C_{max} is defined as the peak plasma level of flecainide after initiation of study medication and prior to administration of any alternative pharmacological agent (e.g., IV flecainide).

t_{max}
t_{max} is Protocol defines tmax as the time to Cmax (from the time of the start of dosing).

4 Study Medication

The study drug dose and regimen are: 120 mg FlecIH-103 (75 mg/mL) administered in 1 single AeroEclipse® II breath-actuated nebulizer in 2 inhalation stages of 3.5 seconds each, separated by a 1-minute break (2 x 60 mg).

Subjects continue to inhale according to the assigned regimen until the conversion of AF to SR is observed, or until the assigned dose is completed, whichever comes first ("dose/inhale to conversion").

5 Source Data

This section describes all source data used for the final statistical report.
For each data source is indicated which information is available for the MLS part of the trial and which information is available for the PLS part of the trial.
The data collection tool for this study is a validated electronic data capture (EDC) system called MARVIN (from XClinical). Data required according to this protocol are recorded by Investigator/study site personnel via data entry into the EDC. All eCRF data used in the statistical analysis are downloaded from the EDC system in the form of XML files and are converted into SAS datasets and formats.

Depending on the EDC version, different information can be required to be filled out by investigator for the enrolled subjects. For instance: SAESI is only included in the EDC since Protocol 8.0/EU-1.

For subjects enrolled in Part C of the trial EDC version 21 (or later) is applicable, the final EDC version for these subjects was version 25. The final EDC version for subjects enrolled in Part A of the trial was EDC version 16. The final EDC version for subjects enrolled in Part B of the trial was EDC version 20. When pooling MLS results from Part A, B and C, the information will be reported as defined in EDC version 25. For Part C the EDC captures information for both the PLS and the MLS part of the trial.

5.1 Investigator reported information

All investigator reported data for the PLS and MLS study are entered into the EDC.

5.2 Rhythm monitoring assessment (Holter)

The Holter analysis is performed by a Core Laboratory. Heart rhythm information is provided in two SAS datasets to the statistical department of Cardialysis. The first dataset shows summary data for the complete monitoring period, including if subject converted to SR during the Holter recording and if so: time of conversion and if recurrence of AF was observed. If recurrence of AF was observed the time of first recurrence of AF is indicated.

The second dataset shows details for separate phases in the recording being:
-If a subject converted to SR: Pre-Dose, start of dosing to time of conversion, time of conversion to End of Recording
-If a subject did not convert to SR: Pre-Dose, Dosing, Post-Dose

Information is available for Part A, Part B and Part C MLS subjects and for Part C PLS subjects.

Additionally, in Part A, Part B and Part C MLS Heart Rates (BPM) recorded for each rhythm strip within the Holter Report are entered by the Core Laboratory directly into the EDC, as these data cannot be provided within the SAS datasets. In the Part C PLS, the Heart Rate data from the rhythm strips was not collected in the EDC.

5.3 Rhythm status assessments (Remote ECG)

ECG analysis is performed by a Core Laboratory and results are provided to the statistical department of Cardialysis as a single cumulative SAS dataset. The length of each recording is expected to be 30 seconds.
Additionally, the duration (seconds) that a subject has been in:
- Sinus Rhythm,
- Atrial Fibrillation,
- Atrial Flutter,
- Atrial Tachycardia,
- Ventricular Tachycardia.

Results include a flag (Yes/No) indicating if subject is or is not in SR. Subject is defined by the Core Laboratory as being in SR if the number of seconds the subject is in Sinus Rhythm is greater than the number of seconds the subject is in any other rhythm, listed above. Refer to SAP section 6.2.2 for the secondary endpoints for which the Remote ECG information is used and to SAP section 9.2.2. for the statistical analysis of these endpoints.

Information is only available for Part A, part B and Part C MLS, not for Part C PLS.

5.4 Pharmacodynamic (PD) Assessment

PD analysis is performed by a Core Laboratory conducting rhythm monitoring and status assessments. 12-lead ECG recordings are extracted by the Core Laboratory from the Holter (AECG) recordings (refer to SAP section 5.2). Consequently, if the Holter data are not analyzed, the PD information will be missing.
Each time point will have triplicate measurements performed with data provided as a cumulative

SAS dataset. Results are provided to the statistical department of Cardialysis as a single SAS dataset.

Information is available for Part A, Part B and Part C MLS subjects and for Part C PLS subjects.

5.5 Pharmacokinetics (PK) assessment

Blood plasma samples are analyzed by a single Core Laboratory, reporting plasma concentrations of flecainide (ng/mL) at pre-specified time points. Results are provided to the statistical department of Cardialysis in the form of a single, cumulative csv file.

Information is available for Part A, Part B and Part C MLS subjects and for Part C PLS subjects, however, for Part C PLS plasma concentrations are measured at only a limited number of time points.

5.6 Safety results

5.6.1 Investigator (Part B and Part C)

For subjects enrolled under Part B and Part C of the trial, investigator reported information is used in the analysis. Refer to section 5.6.2 for the source data for subjects enrolled under Part A of the trial.

For investigator assessments of AEs that were reported in Part B and Part C of the trial, the verbatim term is entered into the EDC, as well as an indication if event is related to inhaled flecainide, if event is related to study device, if event is an adverse event of special interest (AESI) and if event is a Serious Adverse Event of Special Interest (SAESI).

Protocol 8.0/EU-1 uses a new definition of AESI, meaning in the data used for the final report more than one AESI definition is used. SAESI is introduced in Protocol 8.0/EU-1, meaning in the data used for the final report SAESI is not captured for AESI events reported prior to the introduction of Protocol 8.0/EU-1. In the final report AESI and SAESI will however be reported using a uniform definition that differs slightly form the study protocol. Refer to SAP sections 5.6.5. and Annex A for the source data that enable reporting AESI and SAESI according to the Protocol 8.0/EU-1 definition for all AE included in the final report. Refer to SAP section Annex A and to section 3.4. for the Protocol 8.0/EU-1 definitions of AESI and SAESI.
Based on answers to below questions, the EDC concludes if the AE is a Serious Adverse Event (SAE):
Did the adverse event result in the following:
- Death?
- Life-threatening event?
- Hospitalization or prolongation of hospitalization?
- Persistent or significant disability or incapacity?
-Congenital anomaly/birth defect?
-Other medically important event?

If any of these six questions is answered with “Yes” the EDC automatically indicates AE is an SAE. Protocol indicates that recurrent AF is not considered an adverse event as it is an expected event in this patient population and is not considered to be related to study drug. AF recurrence is captured in a separate form in the EDC, will be reported in a separate listing in the statistical report, and will be excluded from AE summary tables in the statistical report. However, AF recurrences that meet

the definition of an SAE (e.g., death, hospitalization, life-threatening, etc.) will be captured on the AE eCRF as an SAE and will be included in the relevant summary tables reporting on AEs.

For the HHE population compared to other subjects, an additional HHE analysis is performed. Any new findings on the HHE determined by the Investigator to be clinically significant will be reported as AEs in the EDC. The independent reviewer will not make a determination of clinical significance on HHE abnormalities. Findings from the independent reviewer will be documented in their analysis and presented in a listing for the HHE population.

5.6.2 Cardialysis (Part A)

Cardialysis assigns MedDRA coding to all investigator reported AEs. The verbatim terms used in the EDC by Investigators to identify AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1 or higher) by System Organ Class (SOC) and Preferred Term, additionally is indicated if Adverse Event was an Adverse Event of Special Interest (AESI).

The definition used for AESI differs from the Protocol 8.0/EU-1 definition of AESI and SAESI was not defined yet. Refer to SAP section 5.6.5. for the source data that enable reporting AESI and SAESI according to the Protocol 8.0/EU-1 definition for all AE included in the final report. Refer to SAP section 3.4. for the Protocol 8.0/EU-1 definitions of AESI and SAESI.

Results of the MedDRA coding by Cardialysis are provided in a single SAS dataset; by combining these with the investigator reported AE results in the EDC the complete AE analysis dataset is created. In the remainder of the SAP the resulting analysis dataset is indicated as “Clinical AE database”.

5.6.3 Analysis Dataset Part B and Part C

PrimeVigilance (PVL) is responsible for providing drug safety and Pharmacovigilance (PVG) support, in relation to the FlecIH investigational medicinal product (IMP) clinical development program by InCarda.

The PVL safety database only contains SAEs, AESIs, and Serious AESIs.

The verbatim terms used in the EDC by Investigators to identify AEs are coded using MedDRA by SOC and Preferred Term. Seriousness of the event and relationship to inhaled flecainide are assessed.

The statistical report for Part C will report information as follows for Parts B and C:
The Clinical AE database (refer to section 5.6.2 of SAP) is the only source when reporting the AE results in the Tables in the statistical report for Part B and Part C MLS subjects of the trial.

Before the Clinical AE database of Part C is considered final, a reconciliation will take place with results as reported by PVL. Part B has already been reconciled and is considered final.

In case of differences relating to information filled out by investigator in the EDC, queries can be added in the EDC, requesting investigator to re-assess the AE. All these queries need to be answered before the Clinical AE database is considered final.

In case of differences relating to MedDRA coding by Cardialysis, Cardialysis can be requested to re-evaluate the assigned MedDRA codes. Re-evaluation needs to be final before the Clinical AE

database is final.

Information is available for Part B and Part C MLS subjects and for Part C PLS subjects.

5.6.4 Analysis Dataset Report Part A

The statistical report for the INSTANT study will include AE results for subjects enrolled in Part A of the trial (2*60 mg, FlecIH-103). The statistical report for Part A reported AE by using the Safety Database maintained by Cardialysis, not by using the clinical AE database. The same database will be used in the final statistical report when showing results for FlecIH-103 subjects enrolled in Part A of the trial.

This implies that for subjects enrolled in Part A (2*60 mg, FlecIH-103 subjects) the AE results that were reported in the statistical report for Part A are identical to the AE results as reported in the final statistical report.

In the Cardialysis safety database some Adverse Events were reported twice: as the original AE and as “Condition Aggravated”. In these cases, there was no MedDRA coding available for the worsening of the event, the worsening was registered under a general MedDRA coding:

-“General disorders and administration site conditions”
- Preferred Term: “Condition Aggravated”.

In total this occurred 2 times for subjects receiving 2*60 mg, FlecIH-103

In the statistical tables these cases are reported twice:

-under the MedDRA coding of the original event
-under the “Condition Aggravated” coding

To prevent double counting of these events, in summary tables when showing the total number of AE, these AEs are counted only once.

5.6.5 Additional AESI and SAESI information

In order to be able to report AESI and SAESI according to the Protocol V8.0/EU-1 definition, AEs that were reported using a previous AESI definition need to be re-assessed to see if the AE is an AESI according to the new definition. Additionally, these AEs must be reviewed to determine if they met the criteria for a SAESI, as before Protocol V8.0/EU-1, SAESI was not yet defined. Refer to SAP section 3.4. for the Protocol 8.0/EU-1 definitions of AESI and SAESI.

Sponsor will provide a file showing for all AEs:
-Is AE an AESI (yes/no) according to the Protocol 8.0/EU-1 definition?
-If yes: is AESI Cardiovascular (Y/N)
-Is AE a SAESI (yes/no) according to the Protocol 8.0/EU-1 definition?
-If yes: is SAESI Cardiovascular (Y/N)

Additional relevant information may also be included.
Sponsor uses a slightly adjusted definition than protocol for AESI and SAESI to better align with FDA-

agreed terms for Phase 3, which may facilitate pooling of these data across multiple studies. Please refer to SAP section Annex A for final Sponsor definitions.

Refer to SAP section Annex A for the definition of *Cardiovascular.*

When reporting AESI and SAESI in the final report, an analysis dataset will be used that combines:

- AESI (Y/N) filled out by investigator
- SAESI (Y/N) filled out by investigator
- (S)AESI information assessed by Sponsor with 5 options:
    1. Non-AESI
    2. Non-Cardiovascular Non-Serious AESI
    3. Non-Cardiovascular Serious AESI
    4. Cardiovascular Non-Serious AESI
    5. Cardiovascular Serious AESI

Refer to SAP Annex A for a specification of the process used by Sponsor to create the Sponsor assessments for AESI information.

5.7 Handheld Echo (HHE)

For subjects who are included in the EU HHE Sub-Study the HHE is used by the investigator to assess if subject is eligible for enrollment. Additionally, for subjects who are enrolled in the US, an HHE is required if an echocardiogram with LVEF within 6 months of screening required to demonstrate eligibility is not available. HHE assessments are entered into the EDC by investigator.

The HHE images will also be analyzed by an independent reviewer at a later date, and the statistical analysis will compare the HHE results between the investigator and the independent reviewer.

Results from the independent reviewer are provided to the statistical department of Cardialysis in the form of a single, cumulative Excel file.

The HHE sub-study was not included in the PLS.

5.8 Protocol Deviations

Protocol Deviations are registered in the CTMS system. After eCRF database lock and after approval by InCarda, the final listing of Protocol Deviations will be provided to STAT in the form of an Excel file. This file will include: an indicator if Protocol Deviation is major or minor, and the type of Protocol Deviation (e.g. ECGs).

Information is available for Part A, Part B, Part C MLS subjects and for Part C PLS subjects.

6 Study Endpoints: definition and availability of information

The final report will be in line with the final statistical report for Part B, reporting all endpoints that were included in the final report of Part B of the trial. As in the Part B report all Part A and Part B subjects receiving 2*60 mg FlecIH-103 are included in the analysis, in the final report these subjects are pooled with the Part C MLS subjects. Sections 6.1 to 6.2.5 describe these study endpoints as defined in version 8.0/EU-1 of the protocol. Section 6.2.6 describes the additional exploratory endpoints for the Part C PLS.

For the endpoints *Conversion from AF to SR* and *Recurrence of AF,* in principle, only Core Laboratory information will be used, this applies for the Holter and TTM AF monitoring period.

In Core Laboratory results, Conversion of AF to SR is reported by filling out column SRTM (Date and Time Rhythm Switched to SR). In the statistical analysis then is reported: Subject did convert, time of conversion is the Date and Time shown in SRTM. Refer to section 3.1. of the SAP for the definition of Conversion (Rhythm Switch) to SR. If data in the column SRTM is missing, subject did not convert during the period analyzed by the Core Laboratory.

For subjects who converted from AF to SR, the column AFIBAFTER (Atrial Fibrillation Recurrence Post-Rhythm Change) indicates if AF recurred (value: “YES”) or did not recur (value: “NO”). If AF did recur, column AFIBRTM (Atrial Fibrillation Recurrence Time) shows the Date/time of the first AF recurrence.

Investigator reported information on conversion and recurrence of AF is also reported for the 90 minutes after the end of dosing. This information will not be used in the statistical analysis unless Core Laboratory information is Completely Missing (no analysis at all) or Partly Missing (e.g., analyzed only up to only 28 minutes of the planned 90 minutes post dose).

If Core Laboratory information is Completely Missing then only investigator reported information will be used. The following information is used, as filled out by investigator in the EDC:
- Did the patient convert to SR? (SAS dataset: DSCONV, column CONVYN, values 1 (Yes), 0(No)
-If subject did convert to SR:
-Date/Time of Conversion to SR (SAS dataset: DSCONV, column DSSTDAT/DSSTTIM, measured in seconds)
- Was AF recurrence observed? (SAS dataset RECURYN, value 1=Yes, 0=No)
-If AF recurrence was observed, per AF recurrence the Date/Time of the AF recurrence (SAS dataset: DSCONVAF, column: RECURDAT/RECURTIM, measured in seconds), the date and time of the first AF recurrence is used in the analysis.

If Core Laboratory information is Partly Missing then available Core Laboratory information (e.g. up to 28 minutes post end of dose) will be supplemented with Investigator Reported information for the period that was not analyzed by the Core Laboratory (e.g. from 28 to 90 minutes post dose). The final report will indicate the reason(s) why Core Laboratory analysis was Partly Missing. Before combining the information, the Core Laboratory and investigator reported information will be checked for consistency on a case-by-case basis. Afterwards these rules will be followed for *Conversion of AF to SR*:

-If Core Laboratory did not report Conversion of AF to SR, then the investigator reported information is used for the period for which no Core Laboratory information is available.

-If Core Laboratory reported Conversion of AF to SR, then the investigator reported information is not used. Subject already converted within the period analyzed by Core Laboratory.

These rules will be followed for *recurrence of AF:*

-If Core Laboratory did not report Recurrence of AF, then the investigator reported information is used for the period for which no Core Laboratory information is available.

-If Core Laboratory reported Recurrence of AF, then the investigator reported information is not used. This applies for recurrences during the Holter or TTM monitoring period. If AF recurrence occurs outside of the monitoring period but prior to Day 5, the event will be entered in the EDC as a recurrent AF episode by the investigator.

6.1 Time to conversion

The protocol indicates that all endpoints reporting on time to conversion need to be reported in the following two ways.

6.1.1 Time between initiation of study drug and conversion to SR (in minutes)

Subject should be in AF at the initiation of study medication (if not, the subject is not included in the population for which the endpoints are measured); conversion should thus not occur before initiation of study drug. The time between initiation of study drug and conversion to SR (in minutes) is thus expected to be non-negative.

6.1.2 Time between completion of study drug and conversion to SR (in minutes)

Study drug inhalation is discontinued after conversion from AF to SR is observed, or once the entire dose is completed, whichever comes first.

Subject should be in AF at the initiation of study medication (if not, the subject is not included in the population for which the endpoints are measured); conversion should thus not occur before initiation of study drug. Subject may however convert prior to completing inhalation of study drug.

The time of conversion will be compared with the end of dosing time. If conversion occurred prior to the end of dosing, for the time to conversion a negative value will be calculated and reported.

6.2 Endpoints, Adverse Events and other assessments

The final report will include all endpoints that were included in the final Part B report. However, unlike in the Part B report, no formal testing will be performed for the primary efficacy endpoint. Additionally, the exploratory endpoints for Part C as indicated in the protocol will be reported.

Section below first report the endpoints reported for Part B of the trial (as indicated in section 7.5 B of the Protocol). Additionally, Adverse Events, PK assessments and PD assessments as indicated in

section 8 B and 9.1 B of the protocol are described. These should be considered as (exploratory) endpoints. Finally, section 6.2.6. lists the exploratory endpoints for the Part C PLS Study.

Section 9 of the SAP describes the statistical analyses of the endpoints, Adverse Events and other assessments.

6.2.1 Primary endpoint

The primary efficacy endpoint is:

The proportion of subjects whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing.

The first conversion to SR that lasts for at least 1 minute is referred to as the index conversion and is reported in endpoints measuring conversion. Any conversion not lasting for at least one minute is not considered an index conversion. Refer to SAP section 9.2.1 for the analysis of the endpoint.

6.2.2 Secondary efficacy endpoints

Refer to SAP section 9.2.2 for the statistical analysis of these endpoints.

- The proportion of subjects with C_{max} values ≥ 200 ng/mL (e.g., 200, 300, 400, and 500 ng/mL) post inhalation with inhaled flecainide (excluding plasma levels associated with IV flecainide infusion) whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing.
- The time to conversion of AF to SR from initiation of dosing up to 90 minutes after initiation of dosing
- The proportion of subjects in SR on Day 2;
- The proportion of subjects with reduced or no AF symptoms at 30 minutes post dose;
- The proportion of subjects with reduced or no AF symptoms at 60 minutes post dose;
- The proportion of subjects with reduced or no AF symptoms at 90 minutes post dose;
- The proportion of subjects who had their AF converted to SR within 90 minutes after initiation of dosing and had no AF recurrence requiring electrical or pharmacological cardioversion or rate control intervention, up to discharge;
- The proportion of subjects in SR on Day 5

Time to conversion will be reported in statistical analyses from both initiation of study drug and completion of study drug.

The analysis of the primary and secondary efficacy endpoints will be performed on the mITT population (refer to section 8.5 SAP). If applicable, methods for conversion (e.g., Conversion to SR by inhaled flecainide, refer to section 3.2 SAP) will be specified in the overview of TFLs.

6.2.3 Secondary safety endpoint

The secondary safety endpoint is:

Incidence of treatment emergent serious adverse events of special interest for flecainide (SAESI)

The analysis of the secondary safety endpoints will be performed on the Safety population (refer to section 8.3 SAP). Refer to SAP section 5.6 for the source data of the SAESI information. Refer to section 3.4 SAP for the definition of SAESI.

6.2.4 Exploratory endpoints (HHE)

The HHE data will be submitted to an independent reviewer to compare with the HHE assessments made by the site staff during the screening period; however, this independent review will not be used for the assessment of subject eligibility during screening. This independent review will only be used to explore whether site staff made a successful assessment of subject eligibility using the HHE data obtained during screening.

The exploratory endpoints for the Handheld Echo are:

- Proportions of subjects for whom capture and assessment of a diagnostic echocardiogram using a HHE at screening was successful.

These characteristics are assessed:
-LV size
-LVEF
-LV hypertrophy
-Valvular disease
-Other clinically significant findings

- Percentage of subjects who are considered ineligible for enrollment as a result of the HHE assessment

- Time from HHE administration to availability of HHE report/results

The analysis of these exploratory endpoints will be performed on the HHE population (refer to SAP section 8.6).

All except the last endpoint listed above (being "Time from HHE administration to availability of HHE report/results") will be analyzed for both the Investigator reported results as well as the results of the independent reviewer.

In the SAP this endpoint is added:

- Agreement between subject eligibility between site staff and independent reviewer.

Refer to SAP section 9.2.4 for the analysis of the HHE endpoints.

6.2.5 Additional Assessments

In the final report the following additional assessments are reported but are not associated with an endpoint.

6.2.5.1 *Pharmacokinetic (PK) assessment(s)*

Whole blood samples of about 4.0 mL are collected for measurement of plasma concentrations of flecainide acetate components. PK sampling occurs only over a 90 min period on Day 1 (day of dosing).

For all reported subjects (i.e., Part A (2*60 mg FlecIH-103 subjects) Part B, and Part C MLS) sample collection times are as follows:

1. Pre-dose inhalation –T_{Pre} (any time up to 45 minutes prior to dosing and after treatment assignment)
2. During dose regimen administration – $T_{between\ admin}$ (in the 1-minute break in between inhalations), if applicable
3. At the time of conversion to SR – T_{SR}. A PK sample should be taken at SR regardless of method of conversion. If conversion is, for example, by ECV, the PK sample should be taken at the earliest time feasible.
4. After administration of study drug regimen is complete – T_x (1, 3, 10, 30, 60 and 90 minutes post dose).

All available information will be reported. The analysis will be performed for the PK population (refer to SAP section 8.4).

For the subjects in Part C PLS who received study medication only three samples are collected: pre-dose, at 3 minutes post end of dose and at 90 minutes post end of dose, additionally at the time of conversion to SR – T_{SR} a PK sample should be taken regardless of method of conversion. If conversion is, for example, by ECV, the PK sample should be taken at the earliest time feasible.

6.2.5.2 *Pharmacodynamic (PD) assessment(s)*

Electrocardiographic effects of the study drug will be evaluated based on 12-lead ECG recordings. An independent central review of ECGs is conducted. The ECG recordings will be extracted in triplicate from the recorded AECG data by the ECG Core Laboratory after receiving the data. 12-lead ECGs will be extracted at or after each specified time point within up to 5 minutes or up to the next scheduled time point, whichever comes first.

Triplicate 12-lead ECG readings are collected at pre-defined collection time points for a given subject and are over-read on the same lead by the same ECG Core Laboratory reader.

Extraction times for ECG recordings under both regimens are as follows:

1. Pre-dose inhalation – T_{Pre} - at -45, -30 and -15 minutes
2. Just before the start of inhalation – T_{Admin}
3. During dose regimen administration – $T_{between\ admin}$ (in the 1-minute break in between inhalations)
4. At the time of conversion to SR – T_{SR} (if applicable)
5. After administration of study drug regimen is complete – T_x (1, 3, 10, 30, 60, and 90 minutes post dose)

The following ECG parameters are determined:
-Heart rate (HR)
-RR interval
-PR interval
-QRS duration
-QTcF duration
-JTc duration (QTc-QRS)

This analysis will be performed for the Safety population (refer to SAP section 8.3). However, for QRS and ΔQRS, additional analyses will be performed using the PK population (refer to SAP section 8.4).

Results for the PLS subjects will be listed, but not summarized.

6.2.5.3 *Adverse Events*

Adverse events will be reported for the safety population (refer to SAP section 8.3).
Refer to SAP section 3.4 for the definitions for AEs, SAEs, AESI and SAESI. The clinical safety of inhaled flecainide is evaluated by the frequency of treatment emergent AEs and SAEs. Treatment emergent SAEs (TESAE) are those SAEs defined as following dose administration. AESIs and Serious AESIs are reported. Adverse events are reported from time of IC through EOS (Day 5).

6.2.5.4 *Clinical laboratory evaluation analyses*

Section 9.7.2.1.B of the protocol indicates statistical analysis will be performed for laboratory data.

Laboratory analysis is performed twice: (i) at screening (Day 1) and (ii) at 90 minutes after initiation of dosing or at discharge. Tests can be repeated.
For the subjects treated with inhaled flecainide in Part C PLS the laboratory analysis is only performed at screening.

The following laboratory safety variables can be measured and analyzed at the local laboratory and are registered in the EDC:

Panel	Variable
Hematology Panel	White blood cell (WBC) count
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
	Red Blood Cell (RBC) count
	Hemoglobin
	Hematocrit
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	Mean corpuscular hemoglobin concentration (MCHC)
	Red cell distribution width (RDW)
	Platelet count
	Mean Platelet Volume (MPV)
Comprehensive Metabolic Panel (CMP)	Glucose
	Calcium
	Serum Creatinine
	Creatinine Clearance (derived in EDC)
	BUN (blood urea nitrogen)
	Total Protein
	Albumin (Protein)
	Potassium
	Sodium
	Chloride
	Bicarbonate
	Total Bilirubin (TBL)
	Conjugated Bilirubin
	Aspartate Aminotransferase (AST)
	Alanine Aminotransferase (ALT)
	Alkaline Phosphatase (ALP)
Coagulation Panel	PTT
	PT
	TT
	Fibrinogen
Other	Pregnancy Test

Refer to SAP section 9.2.3.4 for the analysis of these characteristics.

6.2.6 Exploratory Endpoints for Part C PLS

Study protocol includes these exploratory endpoints for the Part C PLS:

6.2.6.1 *Proportion of subjects who achieved therapeutic dosing (≥ 200 ng/mL) with the study drug in the Part C Patient-Led Under Medical Supervision Cardioversion Study*

Endpoint will be reported, refer to SAP section 9.2.5. for the analysis of the endpoint

6.2.6.2 *Feasibility of patient-led self-administration of study drug, including:*

Feasibility is measured by:

- Percent of subjects who consent to the study
- Percent of subjects who withdraw from the study
- Percent of subjects who are certified for self-administration of study drug
- Percent of subjects who return to clinic with a recurrent episode of PAF within 8 months of signing consent, and the associated timeframe(s) to time(s) of recurrence
- Percent of subjects that independently set up and inhale study drug according to the provided instructions

Endpoint will be reported, refer to SAP section 9.2.5. for the analysis of the endpoint

6.2.6.3 *Proportion of subjects whose AF converted to SR*

Endpoint will be reported, refer to SAP section 9.2.5. for the analysis of the endpoint

6.2.6.4 *Hand Held Echo (HHE) endpoints*

Protocol includes HHE endpoints for Part C:

- Proportion of subjects for whom capture and assessment of a diagnostic echocardiogram using a HHE at screening was successful
- Percent of subjects who are considered ineligible for enrollment as a result of the HHE assessment

- Time from HHE administration to availability of HHE report/results

The HHE sub-study was not included in Part C PLS; hence the above endpoints will not be reported for this part of the trial.

7 General Statistical Considerations

7.1 Sample Size and Power

Part C MLS and PLS did not have an enrollment target; enrollment was planned to continue in the Part C MLS at the discretion of the Sponsor to support rollover participation in the Part C PLS. December 31, 2021 Sponsor decided to stop enrollment in Part C MLS.

No formal hypothesis testing is planned for Part C. Summary statistics will be generated, including estimate of the endpoints and for the primary efficacy endpoint (refer to SAP section 9.2.1) its 90% confidence interval.

7.1.1 Treatment Allocation

All subjects in the Part C MLS and in the Part C PLS study who are enrolled are assigned to a 120 mg eTLD (2 x 60 mg) FlecIH-103 dose regimen.

The site is permitted to enroll a subject before the monitoring period is finished. Thus, between time of enrollment and the end of the screening period, a subject can cease to be considered eligible if there is a change in the subject's status with regard to the study Inclusion or Exclusion criteria. In this case, the subject will not start study drug. These subjects are not reported as screen failures.

Subjects who are screened but did not start study drug (regardless of if the subject was enrolled or considered a screen failure) can re-enter the study when a new AF episode occurs. The statistical report will describe the reason(s) the subject did not start study drug when initially screened. Furthermore, the result of the secondary screening will be reported (e.g., if subject was enrolled and started study drug).

In the final report along with the Part C MLS subjects Part A and Part B subjects are reported who were assigned to a 120 mg eTLD (2 x 60 mg) FlecIH-103 dose regimen.

7.1.2 Blinding and Unblinding

This is an open-label trial of a single study drug treatment. Thus, the processes of blinding and unblinding are not applicable in this study.

7.2 Handling of Data

7.2.1 Strata

Subjects are not stratified to any criterion.

7.2.2 Examination of Patient Subgroups

For the HHE population (refer to section 8.6) results will only be reported for the specific HHE endpoints.

7.2.3 Multiple Testing and Comparisons

There will be no multiplicity adjustments for the analyses outlined in this SAP.

7.2.4 Visit Windows

After discharge two follow-up visits are planned, both are telephone assessments.
The first visit is planned on Day 2, 1 day after study drug administration.
Visit 2 is planned on Day 5, which is 4 days after study drug administration and coincides with End Of Study. Visit 2 may be completed within a ± 1 day window, meaning the visit can take place on Day 4, 5 or 6.

The statistical report will not take into account whether the visit occurred on the planned day or within the specified window; all visits will be reported, and visit dates will be included, along with the name of the corresponding visit (e.g., Visit 1, Visit 2) and its defined visit window.

If multiple assessments occur within a visit window, then the average of those assessments will be used for summarization and analysis.

For PLS subjects, Day 5 assessments of the Part C MLS study are not considered for the End of Study visit. Subjects who receive inhaled flecainide in the PLS part of the study are followed until Visit 2 (Day 5) of the PLS treatment. For PLS subjects who are enrolled for follow-up but do not receive inhaled flecainide, the End of Study form will show the reason why EOS was reached for the PLS.

7.2.5 Imputation of Missing Data

Imputation of date and time values
Date and time values will only be imputed if the missing value impacts the reporting of Adverse Events, Conversion of AF to SR or recurrence of AF:

- For adverse events or recurrence of AF, the earliest possible date or time will be imputed. *Example: For AEs occurring after initiation of study medication for which the start time of the AE is missing, the time of initiation of study medication will be imputed to be the start time of the AE*
- In conversion from AF to SR, the last possible date or time will be imputed. *Example: If conversion to SR is known to have occurred between initiation of study medication and 60 minutes post initiation of study medication, but the time of conversion to SR is unknown: 60 minutes post initiation of study drug is imputed for time of conversion to SR.*
- For Treatment Emergent Adverse Events: a worst-case approach is used. If AE can be Treatment Emergent, event is assumed to be Treatment Emergent.
  For instance: if medication started at 12h:12m:45s and Adverse Event started at 12h:12m (seconds unknown) event is assumed to be Treatment Emergent

Conversion of AF to SR and recurrence of AF: frequency analysis.
No missing information is expected: if Core Laboratory analysis is missing or incomplete, then investigator reported information is available (refer to section 6 SAP) for analysis. Should however information regarding the status of conversion to SR or recurrence of AF be incomplete, then the subject is assumed to be free of the event between time of last available information and the end of the reported period.

Laboratory values below the limit of quantification
If a laboratory reports a value below the limit of quantification (e.g., "<0.1" or "BLQ") the value 0 will be imputed. Additionally, the value 0 will be imputed if the PK value for the sample taken just before initiation (at T_0) is not available unless additional information indicates otherwise (refer to SAP section 9.2.2.10).

Imputation of other missing values
No imputation is planned for other missing values, nor is any sensitivity analysis planned. Missing values are assumed to be Missing Completely at Random (MCAR).

8 Study Populations

The final analysis for the INSTANT study will primarily focus on data for the MLS populations (Part A, part B and Part C) receiving 2x60mg FleIH-103 formulation using the prespecified definitions described in Section 8.1 through 8.6. Data for each MLS population will be presented for several cohorts, as described below and further defined in Section 8.7.

Due to the low number of subjects who participated in the PLS, a more limited analysis will be conducted on the PLS populations described in Section 8.8. Data for the PLS will only be presented for the overall study populations as defined in Section 8.8, with no additional cohort analyses.

Cohorts of the MLS populations include the Part C MLS Cohort (Section 8.7.1) and a Pooled MLS Cohort (Section 8.7.2); the latter of which consists of all MLS subjects enrolled to receive 120 mg FlecIH-103 in Part A, Part B and Part C of the study. The Pooled MLS Cohort will be further subdivided into two additional sub-cohorts: 1) patients in the Pooled MLS Cohort with no evidence of flecainide present in their predose PK sample (Pooled MLS No Predose Flecainide Cohort; Section 8.7.3), and 2) patients in the Pooled MLS Cohort with flecainide present in their predose PK sample (Pooled MLS Predose Flecainide Cohort; Section 8.7.4).

A consort diagram will present the number of subjects included in each MLS population (i.e., safety, mITT etc.), including the overall number of subjects in the study population and the number of patients in each cohort of that population.

Individual tables will summarize data for each MLS population as described below in the table. The numbers in the table denote the 4 cohorts that will be analyzed. Each Cohort is defined in the table footnote below. The specified Cohorts will be presented as columns within each table for the study population analyzed. For example, for adverse events, the table will be based on the Safety population with columns for each Cohort specified in the table below (i.e., Cohorts 1, 2, 3, and 4).

Table 1: Analysis Populations by Characteristics

	MLS Populations		
Data Type	Safety[1]	PK[1]	mITT[1]
Demographics[2]	1,2,3,4	1,2,3,4	1,2,3,4
Efficacy	-	-	1,2,3,4
Safety	1,2,3,4	-	-
PK		2,3	
PD	1,2,3,4	2,3	
The numbers in the table denote each Cohort as follows (each are further defined in section 8.7): 1-Part C MLS Cohort; 2-Pooled MLS Cohort; 3-Pooled MLS No Predose Flecainide Cohort; 4-Pooled MLS Predose Flecainide Cohort.			

[1] Safety, PK and mITT populations are defined below in section 8 of the SAP
[2]Including medical history, prior and concomitant medications, patient characteristics, etc.

8.1 Population of Consented Subjects

The population of consented subjects includes all subjects who signed the informed consent form (IC) for the MLS. Population includes Part A, Part B and Part C MLS subjects receiving 120 mg FlecIH-103.

8.2 Intention-To-Treat Population (ITT)

The intention-to-treat (ITT) population includes all subjects that were enrolled (allocated). Compared to the Population of consented subjects, the ITT population excludes subjects who are not enrolled. Population includes Part A, Part B and Part C MLS subjects receiving 120 mg FlecIH-103.

8.3 Safety Population

The Safety population includes all enrolled subjects who started the inhalation of study medication, whether the subject was in AF or not and whether the subject received the full assigned dose of study medication or not. Compared to the ITT population, the Safety population excludes subjects who are enrolled but did not start the inhalation of study medication.
Population includes Part A, Part B and Part C MLS subjects receiving 120 mg FlecIH-103.

8.4 PK Population

The PK population includes all enrolled subjects who received the full assigned dose of study drug irrespective of whether the subject was in AF or not at the initiation of dosing. Compared to the Safety population the PK population excludes subjects who did not receive the full assigned dose of study drug. The full 120 mg dose of study medication is defined as completing both inhalation stages, for a total dose of 120 mg eTLD (2 x 60 mg eTLD).

Population includes Part A, Part B and Part C MLS subjects receiving 120 mg FlecIH-103.

Subject is in PK population, thus receiving the "full 120 mg dose of study medication", if both conditions below apply:

Condition 1: Medication was administered for a sufficient period of time

According to protocol medication should be administered for at least 3.5 minutes in two inhalation stages, separated by a 1-minute break. To measure if subject completed study medication according to protocol the following information, as registered in the EDC, is used:

- Was first dose taken?
  SAS Dataset: EX, record for first dose, column: EXYN=1 (Yes) or 0 (No)
- If not: Reason first dose was not taken
  SAS dataset: EX, record for first dose, column: EXREASNS
- Was repeat dose started?
  SAS Dataset: EX, record for repeat dose, column: EXYN=1 (Yes) or 0 (No)
- If not: Reason repeat dose was not taken
  SAS dataset: EX, record for repeat dose, column: EXREASNS
- Start Time of First Dose
  SAS Dataset EX, record for first dose, column: EXSTTM (measured in seconds)
- End Time of First Dose
  SAS Dataset EX, record for first dose, column: EXENTM (measured in seconds)
- Start Time of Repeat Dose
  SAS Dataset EX, record for repeat dose, column: EXSTTM (measured in seconds)
- End Time of Repeat Dose
  SAS Dataset EX, record for first dose, column: EXENTM (measured in seconds)
- (Start) Time of Conversion to SR
  SAS dataset DSCONV, record for first or second dose, column: DSSTIM (measured in seconds) indicates the time of conversion. This is the start of the 60 second period of SR that is required for index conversion.
  These conditions must apply for subject to meet Condition 1:
- Was first dose taken: Yes
- Was repeat dose taken: Yes
- Total time of the administration of the First Dose and Second Dose is at least 6 minutes and 30 seconds (390 seconds), total administration time is measured as the sum of:
  - The difference between End Time of First Dose and Start Time of First Dose
  - The difference between End Time of Second Dose and Start Time of Second Dose.

Condition 2: The subject was not under-dosed

Study drug preparation instructions require 4.2 mL of study drug to be dispensed into a single nebulizer for administration of drug to the subject. If less than 4.2 mL is dispensed to a subject, then the subject is excluded from the PK population. If at least 4.2 mL is dispensed to a subject, the subject is included in the PK population.

Three subjects are indicated by sponsor to be under-dosed where investigator filled out below information in a comment column of the eCRF (quoted literally):

NL004-1009: "*dose lower than 4,2 ml administered*"

NL025-2006: "*patient was in panic and stopped the inhalation for a short moment*"

NL033-2006: "*not deeply breathing through nebulizer because of coughing*

Only these three subjects will be excluded from the PK-population due to under-dosing.

8.5 Modified Intention-To-Treat Population (mITT)

The modified ITT population includes all enrolled subjects who completed the full assigned dose of study drug and were in AF at the time of start of the inhalation of the study drug. Subjects whose AF converted to SR prior to completion of the assigned full dose of study drug will also be included in the mITT population.

Completing the assigned dose of study medication in accordance with the protocol (i.e., dose/inhale to conversion) is defined as completing both inhalation stages, for a total dose of 120 mg eTLD (2 x 60 mg eTLD), OR completing the dosing early due to conversion of AF to SR. All subjects who converted prior to completion of the assigned 120 mg dose of study medication will be included in the mITT population, regardless if they stopped dosing or continued.

The mITT population will be used to evaluate all primary and secondary efficacy endpoints. Population includes Part A, Part B and Part C MLS subjects receiving 120 mg FlecIH-103.

8.6 Handheld Echo (HHE) Population

At selected sites in the **EU,** subjects in Part B and Part C can participate in an optional Handheld Echo (HHE) Sub-Study, where subjects who specifically consent will undergo an additional screening procedure using a portable hand-held ultrasound device to obtain an HHE

In the US**,** an echocardiogram with LVEF within 6 months of screening is required to demonstrate eligibility. If no echocardiogram is available, subject must undergo an HHE during screening to confirm eligibility.

The HHE population (refer to SAP section 8.2.6) thus consists of EU subjects who signed the IC for participating in the HHE Sub-Study and of US subjects without an available recent echocardiogram at screening that contains an LVEF value.

For this population, the HHE exploratory endpoints as indicated in section 6.2.4 of the SAP will be reported. As HHE results are not available in Part A of the trial, the statistical report for Part C will only report subjects who were enrolled in Part B or MLS Part C of the trial.

8.7 MLS Study Population Cohorts

8.7.1 Part C MLS Cohort (Cohort 1)

This Cohort includes all subjects in the study population (i.e., safety, mITT etc.) who were enrolled in the Part C MLS. This Cohort will be referred to as Cohort 1.

8.7.2 Pooled MLS Cohort (Cohort 2)

This Cohort includes all subjects in the study population (i.e., safety, mITT etc.) who were enrolled to receive the 120 mg (2 x 60 mg) FlecIH-103 study medication in Part A, Part B or Part C of the MLS. This Cohort will be referred to as Cohort 2.

8.7.3 Pooled MLS No Predose Flecainide Cohort (Cohort 3)

This Cohort includes all subjects in the study population (i.e., safety, mITT etc.) who are part of the Pooled MLS Cohort (Cohort 2) and have no evidence of flecainide present in their predose PK sample. This includes subjects whose pre-dose PK sample had flecainide plasma concentrations = 0 ng/mL and subjects whose pre-dose PK sample was missing. This Cohort will be referred to as Cohort 3.

8.7.4 Pooled MLS Predose Flecainide Cohort (Cohort 4)

This Cohort includes all subjects in the study population (i.e., safety, mITT etc.) who are part of the Pooled MLS Cohort (Cohort 2) and have flecainide present in their predose PK sample (i.e., flecainide plasma concentrations > 0 ng/mL). This Cohort will be referred to as Cohort 4.

8.8 Patient-Led (PLS) Population

The PLS analysis will include all subjects who signed Informed Consent for the Part C Patient-Led Study (i.e., the PLS Population of Consented Subjects). All further PLS Populations (safety, mITT, etc.) will be based on the PLS Population of Consented Subjects and will use the population definitions described in Sections 8.2 through 8.6.

A consort diagram will present the number of subjects included in each PLS Population (i.e., safety, mITT etc.); however due to the small number of PLS subjects who received study drug, all PLS data will be presented for the overall study populations (i.e., no Cohort analysis).

All PLS subjects were previously successfully treated with inhaled flecainide earlier in Part A, B or C of the MLS.

9 Statistical Methods

Statistical programming and analyses will be performed using established statistical methods.

The study data will be reported using tables, figures, and data listings. Descriptive statistical methods will be used to summarize the data from this study.

Continuous variables will be descriptively summarized using number of subjects (n), mean and standard deviation (SD), additionally coefficient of variation (CV (%), as appropriate), median, minimum, maximum, and, as appropriate, geometric mean may be reported. If required, a 95% two-sided confidence interval will be reported for the mean, using Student's t-distribution.

Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category. If required, a 95% exact two-sided confidence interval will be reported for each proportion using the binomial distribution.

A selection of data collected during the study will be included in data listings. Unless otherwise noted, the data will be sorted by subject identifier, and (where applicable) by date within each subject identifier.

The statistical analyses will be conducted using SAS® System version 9.3 or higher. Validation will be performed in accordance with applicable Cardialysis SOPs.

9.1 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition will be presented for all subjects who signed Informed Consent, i.e., Population of Consented Subjects. The number of subjects who completed the study and discontinued from the study will be summarized. The reasons for early discontinuation at any time in the study will be described by dose cohort. Screen failures are defined as subjects who signed Informed Consent but were not enrolled (randomized or allocated).

Disposition, demographic and baseline characteristics data, including age, gender, race, ethnicity, etc. will be summarized in tables for each MLS population and cohort as described in Section 8, but no statistical testing will be performed.

Medical history and AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) (version 23.1 or higher) for the study period. Medical history and AEs may be summarized in tables and will be presented in data listings.

Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (version WHO September 2019 or later). Prior and concomitant medications may be summarized in tables and will be presented in data listings.

A separate consort diagram will be provided for the pooled analysis (Part A, part B and Part C MLS) and for Part C PLS.

9.2 Specification of Analyses

9.2.1 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of subjects whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing.

Analysis is performed for the mITT population. A Subject meets the endpoint if conversion occurred within 90 minutes after initiation of dosing without the use alternative medication (e.g., IV flecainide and propafenone) or procedures (e.g., ECV). If a subject's conversion status is unknown, then the analysis will assume that the subject did not convert.

The percentage is calculated as:

p= 100 * (number of converted subjects/number of subjects in mITT population)

A 90% exact binomial confidence interval will be calculated for the percentage.

No formal testing will take place. Analysis will not be performed for the PLS population.

9.2.2 Secondary efficacy endpoints and other assessments analyses

9.2.2.1 *The proportion of subjects with C_{max} values ≥ 200ng/mL (e.g., 200, 300, 400, and 500 ng/mL) post inhalation with inhaled flecainide (excluding plasma levels associated with IV flecainide infusion) whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing*

This endpoint is reported for the mITT population.

The definition of conversion is identical as used for the primary efficacy endpoint meaning that If subject converts due to alternative medication (e.g., IV flecainide and propafenone) or procedures (e.g. ECV) patient fails the endpoint.

For the purpose of this study, C_{max} is defined as the peak plasma level of flecainide prior to administration of any alternative pharmacological agent (e.g., IV flecainide).

The endpoint will be reported as percentages for eight different C_{max} cut-off values as will the corresponding 95% Clopper-Pearson two-sided Confidence Intervals.

The first percentage measures the conversion rate within 90 minutes after initiation of dosing, regardless of PK values, implying a C_{max} cut-off value of 0.

P_1=100% * (number of converted subjects/number of subjects in mITT population)

The other seven percentages measure the conversion rate within 90 minutes after initiation of dosing using a specific cut-off value of $C_{max.}$ In order to be included in the analysis for subject sufficient information must be available to calculate C_{max}. The proportions are defined as: 100* Numerator divided by Denominator.

Proportion	Numerator: number of converted subjects with:	Denominator: Number of subjects with
P_2	C_{max} <200	C_{max} <200
P_3	C_{max} ≥200	C_{max} ≥200

P_4	C_{max} ≥300	C_{max} ≥300
P_5	C_{max} ≥400	C_{max} ≥400
P_6	C_{max} ≥500	C_{max} ≥500
P_7	C_{max} ≥600	C_{max} ≥600
P_8	C_{max} ≥700	C_{max} ≥700

Analysis will not be performed for the PLS population.

9.2.2.2 *Statistical analysis of time-to-conversion to SR from initiation of dosing up to 90 minutes after initiation of dosing*

The Modified ITT Population will be used for this analysis.

The cumulative incidence for the time to conversion from initiation of study medication up to 90 minutes post dose will be determined using the Kaplan-Meier methods. Subjects who converted within 90 minutes post dose due to adjunct medication or procedure are reported as not converted and will not be censored at the time the subject converted due to the adjunct treatment. Results are shown in a Kaplan-Meier curve.

Kaplan-Meier figures will be created for the following:

-A figure with a single curve, showing results of Part C MLS Cohort (Cohort 1).

-A figure with a single curve, showing results of the Pooled MLS Cohort (Cohort 2)

- A figure with a single curve, showing results of the Pooled MLS No Predose Flecainide Cohort (Cohort 3)

- A figure with two curves, for the Pooled MLS Cohort (Cohort 2) and the Pooled MLS No Predose Flecainide Cohort (Cohort 3)

Analysis will not be performed for the PLS population.

9.2.2.3 *The proportion of subjects in SR on Day 2*

The Modified ITT Population will be used to determine the proportion of subjects in SR on Day 2. The rhythm status used for the evaluation of this secondary efficacy endpoint is derived from the remote ECG system, in which the subject's heart rhythm is recorded. A subject is considered in SR on Day 2 if the subject's sinus rhythm during the recording is longer in duration (in seconds) than any of the other reported rhythms (refer to SAS section 5.2). The variable is set to missing if no evaluable remote ECG recording is available for analysis.

The proportion is estimated by the number of subjects in SR on Day 2, divided by the total number of subjects with available data. The estimate for the proportion will be reported.

Analysis will be performed for:

- the complete Modified ITT population

- mITT subjects whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing (subjects meeting the primary efficacy endpoint)

- mITT subjects whose AF was not converted to SR by inhaled flecainide within 90 minutes after initiation of dosing (subjects not meeting the primary efficacy endpoint)

Analysis will not be performed for the PLS population.

9.2.2.4 *The proportion of subjects with reduced or no AF symptoms at 30 minutes post dose*

The Modified ITT Population will be used to determine the proportion of subjects with reduced or no AF symptoms (compared to baseline) at 30 minutes post dose.

The evolution of symptoms (no symptoms, improved, unchanged or worsened) is a categorical variable, a subject is considered to have reduced or no AF symptoms at 30 minutes post initiation of dose (compared to baseline) if the symptoms are reported as either 'no symptoms' or 'improved'.

The proportion is estimated by the number of subjects meeting the endpoint divided by the total number of subjects with available data. The estimate for the proportion will be reported. The variable is set to missing if no information is available.

Analysis will be performed for:

-the complete Modified ITT population

-miTT subjects whose AF converted to SR by inhaled flecainide within 30 minutes post dose

-mITT subjects whose AF was not converted to SR by inhaled flecainide within 30 minutes post dose

Analysis will not be performed for the PLS population.

9.2.2.5 *The proportion of subjects with reduced or no AF symptoms at 60 minutes post dose*

The Modified ITT Population will be used to determine the proportion of subjects with reduced or no AF symptoms (compared to baseline) at 60 minutes post dose.

The evolution of symptoms (no symptoms, improved, unchanged or worsened) is a categorical variable, a subject is considered to have reduced or no AF symptoms at 60 minutes post initiation of dose (compared to baseline) if the symptoms are reported as either 'no symptoms' or 'improved'.

The proportion is estimated by the number of subjects meeting the endpoint divided by the total number of subjects with available data. The estimate for the proportion will be reported. The variable is set to missing if no information is available.

Analysis will be performed for:

-the complete Modified ITT population

-mITT subjects whose AF converted to SR by inhaled flecainide within 60 minutes post dose

-mITT subjects whose AF was not converted to SR by inhaled flecainide within 60 minutes post dose

Analysis will not be performed for the PLS population.

9.2.2.6 *The proportion of subjects with reduced or no AF symptoms at 90 minutes post dose*

The Modified ITT Population will be used to determine the proportion of subjects with reduced or no AF symptoms (compared to baseline) at 90 minutes post dose.

The evolution of symptoms (no symptoms, improved, unchanged or worsened) is a categorical variable, a subject is considered to have reduced or no AF symptoms at discharge dose (compared to baseline) if the symptoms are reported as either 'no symptoms' or 'improved'.

The proportion is estimated by the number of subjects meeting the endpoint divided by the total number of subjects with available data. The estimate for the proportion will be reported. The variable is set to missing if no information is available.

Analysis will be performed for:

-the complete Modified ITT population

-mITT subjects whose AF converted to SR by inhaled flecainide within 90 minutes post dose

-mITT subjects whose AF was not converted to SR by inhaled flecainide within 90 minutes post dose

Analysis will not be performed for the PLS population.

9.2.2.7 *The proportion of subjects who had their AF converted to SR within 90 minutes after initiation of dosing and had no AF recurrence requiring electrical or pharmacological cardioversion or rate control intervention, up to discharge*

The Modified ITT MLS Population will be used to determine this endpoint.

This endpoint is derived from the primary efficacy endpoint at 90 minutes after initiation of dosing. The endpoint is met if the subject's AF converts to SR within 90 minutes after initiation of dosing without an alternative therapy and without subsequent AF recurrence up to discharge requiring additional intervention, either by electrical or pharmacological cardioversion or by rate control treatments.

This proportion of subjects that convert to SR without AF recurrence is estimated as the number of subjects who meet the endpoint, divided by the total number of mITT subjects. The estimate for the proportion and its associated 95% Clopper-Pearson CI will be derived.

The requirements for meeting the endpoint are thus as follows:
- the start time of the conversion of AF to SR is within 90 minutes (including 90 minutes) after the initiation of study drug, AND EITHER

-no recurrence of AF occurred between time of conversion and discharge, OR
-recurrence of AF occurred between time of conversion and discharge but for subject none of the indicated interventions (as reported by investigator) was started between initiation of dosing and discharge.

Discharge is left to the discretion of the treating physician 90 minutes post dose (-10 minute window).

Additionally, analysis is repeated for the proportion of subjects whose AF converted to SR within 90 minutes post dose.

No imputation will take place, i.e., the subject is assumed to be free of event (No Conversion, No AF Recurrence, None of the three Interventions) after the time last information is available.

Analysis will not be performed for the PLS population.

9.2.2.8 *Proportion of subjects in SR on Day 5*

The Modified ITT Population will be used to determine the proportion of subjects in SR on Day 5 (second follow-up visit).
The rhythm status used for the evaluation of this secondary efficacy endpoint is derived from the remote ECG system, in which the subject's heart rhythm is recorded.

A subject is considered in SR on Day 5 if the subject's sinus rhythm during the recording is longer in duration (in seconds) than any of the other reported rhythms (refer to SAS section 5.2). The variable is set to missing if no evaluable remote ECG recording is available for analysis.

The proportion is estimated by the number of subjects in SR on Day 5, divided by the total number of subjects with available data.

The Modified ITT Population will be used to determine the proportion of subjects with reduced or no AF symptoms (compared to baseline) at discharge. Discharge is left to the discretion of the treating physician 90 minutes post dose (-10 minute window).

Analysis will be performed for:

-the complete Modified ITT population

-mITT subjects whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing (subjects meeting the primary efficacy endpoint)

-mITT subjects whose AF was not converted to SR by inhaled flecainide within 90 minutes after initiation of dosing (subjects not meeting the primary efficacy endpoint)

Analysis will not be performed for the PLS population.

9.2.2.9 *Adverse Events*

Adverse events in the MLS will be reported for the Safety MLS population, meaning for subjects who started study medication, regardless of if subject was in AF when starting study medication.
Refer to SAP section 5.6.3. for the AE results reported for Part B and Part C MLS subjects, refer to SAP section 5.6.4 for the AE results reported for Part A subjects.

Adverse Events are coded as serious or non-serious, as related or not related to study medication, and as related or not related to study device. Adverse Events of Special Interest (AESI) and Serious Events of Special Interest (SAESI) are identified. Results are MedDRA coded (version 23.1 or higher).

In all tables the number of AEs, the number of subjects with at least one occurrence of the AE, and the percentage of subjects with at least one occurrence of the AE are reported by cohort (refer to SAP section 8.7).

If subject information is not complete up to the end of the planned End of Study (i.e., subject is lost to follow-up), subject is assumed to be free of events up to planned End of Study.

These results will be reported:

1. Any Adverse Event (AE)
   - overall
   - per combination of MedDRA System organ Class and MedDRA Preferred Term:
     - Any Event
     - Events occurring between IC and initiation of study medication
     - Events between study medication and 4 hours after initiation
     - Events between 4 hours after initiation and 24 hours after initiation
     - Events between 24 hours after initiation and end of observation period

2. Any Serious Adverse Event (SAE)
   - overall
   - per combination of MedDRA System organ Class and MedDRA Preferred Term:
     - Any Event
     - Events occurring between IC and initiation of study medication
     - Events between study medication and 4 hours after initiation
     - Events between 4 hours after initiation and 24 hours after initiation

- Events between 24 hours after initiation and end of observation period

- Any Treatment Emergent Adverse Event (TEAE)
  - overall
  - per combination of MedDRA System organ Class and MedDRA Preferred Term:
    - Any Event
      - By severity
      - By relationship to study medication
      - TEAEs that are moderate or severe and related to study medication
-
  - Events between study medication and 4 hours after initiation
  - Events between 4 hours after initiation and 24 hours after initiation
  - Events between 24 hours after initiation and end of observation period

3. Any Treatment Emergent Serious Adverse Event (TESAE)
   - overall
   - per combination of MedDRA System organ Class and MedDRA Preferred Term:
     - Any Event
     - Events between study medication and 4 hours after initiation
     - Events between 4 hours after initiation and 24 hours after initiation
     - Events between 24 hours after initiation and end of observation period

The end of the extended observation period is defined as Visit 2 (Day 5). Subjects enrolled in Part A, Part B or Part C MLS who are also included in the Part C Patient-Led sub-study will be followed until a recurrent episode of AF is treated, or approximately 8 months after consent (whichever comes first); events starting after Visit 2 will not be included in the MLS part of the final statistical report but will be included in the PLS part of the final statistical report.

4. Adverse Events of Special Interest (AESI)
   These results will be reported:
   - Listing of AESI
   -Overall number of AESI
   Specification (per type of AESI, refer to SAP section 3.4)

AESI will be reported only if starting on or after initiation of study medication (Treatment Emergent).

The definition for AESI was modified during the trial based on examination of the data and regulatory interactions with the US FDA. All AESIs will be tabulated using a slightly adjusted definition compared to the Protocol version 8.0\EU-1 AESI definition, results are provided by sponsor (refer to SAP section 5.6.5 and Annex A); in the listings all results will be included: as per the Cardialysis Safety Team (Part A, refer to SAP section 5.6.2), investigator (Part B and C, refer to SAP section 5.6.1) and by Sponsor (Parts A, B and C, refer to SAP section 5.6.5 and Annex A).
AESIs will be classified as Cardiovascular or non-Cardiovascular, refer to SAP section Annex A.

5. Serious Adverse Events of Special Interest (SAESI)
   These results will be reported:
   - Listing of SAESI

-Overall number of SAESI

SAESIs will be reported only if the event start time is on or after initiation of study medication (Treatment Emergent).

Only from Protocol version 8.0\EU-1 onwards SAESI was defined in study protocol. SAESI will be tabulated according to a slightly adjusted definition compared to the Protocol version 8.0\EU-1 SAESI definition, results are provided by Sponsor (refer to SAP section 5.6.5 and Annex A); in the listings all results will be included: as indicated by investigator and by Sponsor (Parts A, B and C, refer to SAP section 5.6.5 and Annex A).

SAESI will be classified as Cardiovascular or non-Cardiovascular, refer to SAP section Annex A.

Reporting of AE
All Adverse Events will be included in listings. AE occurring in the PLS part of the study will be listed separately. Listings will include flags indicating:

-Is reported event Treatment Emergent?
-Are reported events categorized by investigator (Parts B and Part C MLS) or Cardialysis Safety Team (Part A) as 'AESI'?
-Are reported events categorized by investigator as 'Serious AESI'?
-Are reported events categorized by sponsor as 'AESI'? (refer to Appendix A SAP)
-Are reported events categorized by sponsor as 'Serious AESI'? (refer to Appendix A SAP)

Adverse events tables will be reported as follows:

1) All AEs from time of MLS consent through MLS Day 5
2) Treatment Emergent AEs from start of MLS dosing through MLS Day 5

Tables will thus exclude AE that start in the PLS part of the study.

No tables will be reported for the PLS population, AEs will be listed only.

9.2.2.10 *Pharmacokinetic (PK) assessment(s): Flecainide plasma concentration over time*

PK results will be reported for all evaluable patients in the PK population. For each subject all available flecainide plasma (PK) values are reported in a listing and in a figure. The PK results are reported according to the time the blood sample was collected since initiation of study medication (minutes). If the PK value for the sample taken just before initiation (at T_0) is not available or is reported as 'BLQ' (Below Limit of Quantification) the value 0 will be imputed (unless additional information indicates otherwise).

Section 6.2.5.1 indicates the planned time points PK samples are taken.

Per cohort per planned PK time point the mean value and standard deviation of the flecainide values are reported in a table and in a figure. These tables and figures can be repeated for specific types of subjects, according to the specific type of conversion to SR (refer to SAP section 3.1, "definition of methods for cardioversion"), these additional analyses will be specified in the overview of TFLs that will accompany the final report.

No PK results will be tabulated for the PLS population, however for these subjects plasma concentrations of flecainide will be presented in listings.

PD results are reported for the PK population.

Summarizing PK statistics

These results are not planned to be included in the final report. The final report will however show information on C_{max} and t_{max}, based on the PK results that are indicated in SAP section 5.5.

Results will be calculated by Eurofins as: 1) per-subject results, and; 2) summary statistics for a selection of subjects. Statistics calculated are: number of observation, mean, standard deviation, coefficient of variance, geometric mean, minimum and maximum. Results will be sent by Eurofins to Sponsor.

Protocol (refer to section 10.2.3 B) additionally indicates reporting of summarizing statistics for PK parameters, which include:

$AUC_{0\text{-}10}$:	The area under the plasma concentration versus time curve from the start of dosing (time zero, T_0) to 10 minutes post completion of dosing
$AUC_{0–90}$:	The area under the plasma concentration versus time curve from the start of dosing (time zero, T_0) to 90 minutes post completion of dosing
C_{max}:	The peak (maximum) plasma concentration prior to the start time of any alternate pharmacological therapy, is to be obtained directly from the plasma concentration time profile
t_{max}:	The time to C_{max} (from the time of start of dosing) is obtained.
$t_{½}$ distribution:	The distributive half-life is calculated by the equation $t_{½} = \ln(2)/k_{dist}$

9.2.2.11 *Pharmacodynamic (PD) assessment(s): QRS and other 12-lead ECG parameters over time*

PD results will be reported for the safety, PK and mITT populations. Section 6.2.5.2 indicates the planned time points PD information is measured. Information is provided by the Core Laboratory performing the analysis by extracting 12-lead ECGs from the AECG (Holter) recording at pre-defined time points.
For each time point triplicate measurements take place, the second and third measurements are planned at approximately 30 seconds and approximately 60 seconds after the initial measurement, respectively. Per subject per time point the mean value is calculated for the ECG parameters; these

mean values are used in all PD analyses.

The following parameters will be reported:

- Heart Rate (bpm)
- QRS Interval Duration (msec)
- QT_c Interval Duration (msec)
- JT_c Interval Duration (msec)
- RR Interval Duration (msec)
- PR Interval Duration (msec)
  PR is only available if subject is in SR

Baseline Values will be summarized as Baseline (seated) and Baseline (semi-recumbent) (refer to SAP Section 3.5).
This information is reported per cohort per time period:
- a per subject listing of all PD values
- a per subject listing of the change of PD values compared to baseline value (seated) (delta).
  For ΔQRS interval (msec) additionally the maximum is shown.

- a per cohort table of mean and standard deviation of PD values
- a per cohort table of mean and standard deviation of change of PD values compared to baseline values (seated) (delta).
  For ΔQRS interval (msec) additionally the maximum is shown.
- a per cohort figure of ΔQRS interval (msec) and its standard error of mean.

Tables and figures can be repeated for specific reasons why subject Converted to SR (refer to SAP section 3.1, "definition of methods for cardioversion"), these additional analyses will be specified in the overview of TFLs that will accompany the final report.

PD results are reported for the Safety and the PK population.

Results for the Part C PLS study are available for 3 subjects only; results will only be listed, not tabulated.

9.2.2.12 *Secondary safety endpoint (MLS)*

The secondary safety endpoint, the incidence of treatment emergent serious adverse events of special interest for flecainide (SAESI, refer to section 3.4 SAP for definition) is reported by analyzing AEs that fulfill all of these conditions:

- Events starts between initiation of inhalation of study drug and Visit 2.
- AE is a SAESI according to sponsor provided information (refer to SAP section Annex A).

Results will be reported for the Safety Population, meaning all subjects who started inhalation of study medication.

The MLS statistical report will summarize results as:
-total number of serious AESI and mean number of serious AESI per subject

-total number of subjects with at least one serious AESI, percentage of subjects with at least one serious AESI

Additionally details of the Serious AESI will be shown in the listings in the statistical report.

Serious AESIs (SAESI) will be reported as follows:

1) All SAESIs from time of MLS consent through MLS End of Study (EoS)
2) MLS Treatment Emergent SAESIs from start of MLS dosing through MLS Day 5

9.2.2.13 *Safety endpoint (PLS)*

The secondary safety endpoint, the incidence of treatment emergent serious adverse events of special interest for flecainide (Serious AESI, refer to section 3.4 SAP for definition) is defined as follows:

- Adverse Events starts between initiation of PLS study drug and PLS Day 5 *and*
- AE is a SAESI according to sponsor provided information (refer to SAP section Annex A).

AEs reported from the time of PLS consent until the initiation of PLS study drug are thus not considered treatment emergent.

Endpoints will not be reported in statistical tables, but a listing will include all information required to derive endpoint. Refer to section 9.2.2.9 SAP for the information included in the listing.

Adverse events will be reported as follows:

1) PLS Treatment Emergent AEs from the initiation of PLS study drug through PLS Day 5 (End of Study)

2) All AEs from time of PLS consent through PLS End of Study

9.2.3 Additional Analyses

9.2.3.1 *Vital Signs*

The investigator reported values from vital sign measurements (heart rate, respiration rate, etc.) will be used. Vital sign values after initiation of inhalation will be compared with the semi-recumbent Baseline value at 30 minutes pre-initiation to study medication, in case this value is missing the semi-recumbent Baseline value at 45 minutes pre-initiation will be used. In case also the 45 minutes pre-initiation value is missing, the Baseless value nearest to initiation of study medication will be use as reference value.

For the MLS part of the study a table will report baseline values, a second table will report the post initiation results and the change compared to baseline.

All data will be provided in a listing, both for the MLS and PLS part of the study. For the PLS study results information is available only for subjects who started PLS study drug.

9.2.3.2 *Prior and concomitant medication*

In the MLS part of the trial prior and concomitant medications that were taken between 30 days of enrollment through Day 5 of the MLS part of the study is recorded by investigator. For subjects not participating in the PLS Part of the trial this Day 5 visit is the End of Study visit.

For subjects participating in the PLS trial, any additional medications are recorded up to the end of the PLS episode, being either Day 5 of the PLS study (for subject who started PLS study medication, this visit is the EOS visit for subject) or the EOS visit (for subjects who did not start PLS study medication).

All concomitant medications for the reported MLS subjects and Part C PLS subjects will be listed in the statistical report. Additionally, tables will be created to summarize the concomitant medications for the Cohorts defined Table 1 in SAP section 8. For the MLS study, in addition, tables will summarize the medication by type:

-Antiarrhythmics
-Antithrombotics
- Other cardiovascular medication
- Other medication

Additionally tables will summarize the medication by reporting all observed values (before and after start of dosing) of ATC class (e.g. B01AF=DIRECT FACTOR XA INHIBITORS) and within the specific ATC class by reporting all observed values for Standardized Medication name (e.g. Rivaroxaban, Apixaban).

9.2.3.3 *Treatment satisfaction for subjects meeting Primary Efficacy Endpoint*

According to protocol FLE-002 version 8.0 / EU-1 after 90 minutes post dose and prior to discharge, subjects whose AF converted to SR within 90 minutes post dose without any alternative treatment will be asked questions about their treatment satisfaction.

In the EDC for subjects who were enrolled according to an earlier version of the protocol the questions were asked after 60 minutes post dose and prior to discharge.

Two questions are asked:

1. *If offered, would you take the study treatment again in the future (No/Yes)*
All results will be listed in the statistical report, in the summary tables this percentage will be reported:

p= 100% * (Number of subjects who respond “Yes”)/(number of subjects with non-missing value)

2. On a scale of 1 to 10, how satisfied were you with the study treatment (1 being the worst and 10 being the best)
All results will be listed in the statistical report, the summary tables include these results:

-Number of non-missing values
-Frequency and percentage of all possible outcomes (1, 2, 3, 4, 5, 6, 7, 8, 9, 10)
-Number, mean, and standard deviation of the outcomes.

Results are not available for Part C PLS.

9.2.3.4 *Clinical laboratory evaluation analysis*

The protocol indicates:

Laboratory data are summarized by type of laboratory test. Reference ranges and clinically significant abnormal results are depicted in the summary of clinical local laboratory data, as described in the SAP. Descriptive statistics are used for each laboratory parameter at screening (Day 1) and either at 90 min after initiation of dosing or at discharge.

MLS
Blood samples for determination of the hematology panel, the comprehensive metabolic panel and the coagulation panel are taken at two time points:
-Approximately 45 minutes preceding initiation of drug administration
-At 90 minutes post dose (comprehensive metabolic panel only)

PLS
For subjects who signed IC for the PLS Part C and receive inhaled flecainide in the PLS study, blood samples are taken at one time point. Blood samples as described in Part B may be obtained on Day 1 prior to self-administration of the study drug per the discretion of the treating physician.

For all MLS cohorts, all variables shown in SAP section 6.2.5.4 for the Safety Population results will be reported shown for two time points: at screening and at 90 minutes after initiation of dosing and/or at discharge.
Comparisons will be made for changes from baseline (screening) and 90 minutes after initiation of dosing or at discharge for all parameters.
The measuring unit will be shown in all cases.

1) Per Lab test characteristic (at screening, at discharge)
-Was Lab test performed (Yes/No)
Reported are: Number of analyzed subjects and the number and percentage of subjects for whom the Lab test was performed. The number of subjects for whom Lab test was performed is indicated below as: Number of subjects with Lab Test.

2) Per specific test
-Was the test performed
Reported are: Number of subjects with Lab Test, and the number and percentage of subjects for whom the specific test was performed.

-If test performed: outcome is reported as follows:

2.1) for Categorical characteristics
Pregnancy Test is only performed for female subjects, a Serum or Urine test can be performed, the result is categorized as “Negative” or “Positive”.

Reported are the number of female subjects for whom the overall Lab Test was performed. For these subjects the type of test (Serum/Urine) is shown by frequency and by percentage and the outcome (Negative/Positive) by frequency and percentage.

2.2) for Numeric characteristics
For all other tests a numeric outcome is to be indicated in the EDC. However, investigator can also fill out "NE" as value in the EDC indicating no exact numeric value is available. The results of the test are then specified in an open text field. This option is intended to fill out test results that are Below the Limit of Quantification (BLQ), meaning in the comment field e.g., "<0.1" is reported.
In these cases in the analysis value 0 will be imputed as numeric outcome, this result will be used in the analyses described in the remainder of this section of the SAP.

For the MLS study, statistical tables will show the number of subjects in each cohort for whom the specific test was performed and the number and percentage of subjects with missing results (after performing above indicated imputation of values BLQ). For the PLS study results will only be listed.

A test can be repeated either at screening (e.g., potassium can be measured twice to confirm eligibility) or when a test failed, and a second attempt was made to measure the characteristic. If more than one non-missing value is available at screening, only the value closest to dosing (i.e., last available non-missing value) will be used in the statistical analysis.

The statistical tables will show the number of subjects in each cohort for whom specific test resulted in a numeric value, mean value and standard deviation of the numeric results are reported.

If the numeric value indicated in the EDC is lower than the Lower Limit of Normal (LLN) or higher than the Upper Limit of Normal (ULN) a question pops up in the EDC requiring investigator to fill out if the reported value is Clinically Significant ("CS") or not ("NCS"). The statistical tables will show the number of subjects with a numeric result and the number and percentage of these subjects for whom this numeric result is classified in the EDC as Clinically Significant.

9.2.3.5 *Protocol Deviations*

Protocol deviations will be listed, a first listing will show the Major Protocol Deviations, a second listing the minor Protocol Deviations.

In tables per cohort the Protocol Deviations will be reported:
- by category of protocol deviation (all, major, minor),
- by type of protocol deviation (e.g. Vitals, ECGs),
- by combination of category and type of protocol deviation.

9.2.4 Exploratory endpoints: Handheld Echo

All HHE endpoints (refer to section 6.2.4 SAP) will be reported for the HHE population (refer to section 8.6 SAP) in listings.
This section describes the full analysis of the HHE assessments, including non-endpoints.

HHE data will be measured by investigator and filled out in the EDC. Only subjects with assessments that are normal, minimal, or absent, will be eligible for the study.

The HHE will also be submitted to an independent reviewer, at a later time, to compare with the assessments made by the site staff during the screening period. This independent review will not be used for the assessment of subject eligibility during screening.

HHE echo data are not available for the PLS Part C study.

9.2.4.1 *HHE characteristics*

The report for Part C will show HHE characteristics twice: once for the results reported by investigator and once for the results reported by an independent reviewer (refer to section 5.7 SAP).

The below characteristics are reported from both reviewers:

- Was HHE performed?
  The number of subjects in the HHE population is reported as is the percentage of subjects for whom the HHE was performed. If HHE is not performed, the reasons are reported.

- LV Size
  Size is classified as "Normal" or "Enlarged". For subjects for whom the HHE was performed, per category the number and percentages of subjects in the category is reported.
  Enlarged is defined as: LV end-diastolic internal dimension > 55 mm for men and > 50 mm for females

- LV-Function
  Size is classified as "Normal" or "Abnormal". For subjects for whom the HHE was performed, per category the number and percentages of subjects in the category is reported.

- LVEF
  For the LVEF value (%) is indicated:
  -Number and percentage of subjects for whom LVEF was not evaluable
  -Number and percentage of subjects for whom LVEF was evaluable
  -Mean and standard deviation of the LVEF value (for subjects for whom LVEF was evaluable)
  -Number and percentage of subjects with a LVEF <45% (for subjects for whom LVEF was evaluable)

- LV hypertrophy
  The number and percentage of subjects is indicated for whom the HHE was performed but information on LV hypertrophy is missing.
  LV Hypertrophy is classified as "Absent", "Mild", "Moderate" or "Severe". For subjects for whom the HHE was performed, and information is available, per category the number and percentages of subjects in the category is reported, as is the percentage of subjects with "Absent" or "Mild".
  Moderate or Severe: LV thickness > 12mm

  Aortic Valve Disease (stenosis or regurgitation)
  The number and percentage of subjects is indicated for whom the HHE was performed but information on Aortic Valve Disease is missing.
  Aortic Valve Disease is classified as "Absent", "Mild", "Moderate" or "Severe". For subjects for whom the HHE was performed, and information is available, per category the number and percentages of subjects in the category is reported, as is the percentage of subjects with "Absent" or "Mild".

- Mitral Valve Disease (stenosis or regurgitation)
  The number and percentage of subjects is indicated for whom the HHE was performed but information on Mitral Valve Disease is missing.

  Mitral Valve Disease is classified as "Absent", "Mild", "Moderate" or "Severe". For subjects for whom the HHE was performed, and information is available per category the number and percentages of subjects in the category is reported, as is the percentage of subjects with "Absent" or "Mild".

- Other Valve Disease (stenosis or regurgitation)
  The number and percentage of subjects is indicated for whom the HHE was performed but information on Other Valve Disease is missing.

  Other Valve Disease is classified as "Yes" or "No". For subjects for whom the HHE was performed, and information is available, per category the number and percentages of subjects in the category is reported. For subjects with Other Valve Disease, a listing will specify the valve disease (as filled out in a comment field in the EDC by investigator or the comment field in the dataset from the independent reviewer).

- Other Clinically significant findings
  The number and percentage of subjects is indicated for whom the HHE was performed but information on Other Clinically significant findings is missing.

  Other Clinically significant findings as "Yes" or "No". For subjects for whom the HHE was performed, and information is available, per category the number and percentages of subjects in the category is reported. For subjects with Other Clinically significant findings a listing will specify the finding (as filled out in a comment field in the EDC by investigator or the comment field in the dataset from the independent reviewer).

9.2.4.2 *Subject considered eligible based on HHE assessment*

Only If HHE was performed subject is included in the analysis of this endpoint.

Values are "No", "Yes" or "Not assessable". Per category the number and percentages of subjects in the category is reported.

Values are automatically derived in the EDC by evaluating the answers to four HHE characteristics (refer to SAP section 9.2.4.1) as indicated by investigator. For the evaluation of the results reported by the independent reviewer the same criteria will be applied in the statistical analysis.

Inclusion criteria 5 in section 4.2.B of the Protocol indicates

If participating in the optional Handheld Echo Sub-Study, the subject must have an LVEF ≥ 45%, absent or mild left ventricular hypertrophy, and absent or mild valvular disease (stenosis or regurgitation) to be considered eligible for the study.

Subject is thus considered eligible if all conditions below are applicable:

-LVEF is >=45%
- LV hypertrophy is “Absent” or “Mild”
- Aortic Valve Disease (stenosis or regurgitation) is “Absent” or “Mild”
- Mitral Valve Disease (stenosis or regurgitation) is “Absent” or “Mild”

Subject is considered non eligible if any condition below is applicable:
-LVEF is <45%
- LV hypertrophy is “Moderate” or “Severe”.
-Aortic Valve Disease (stenosis or regurgitation) is “Moderate” or “Severe”.
- Mitral Valve Disease (stenosis or regurgitation) is “Moderate” or “Severe”.

Subject is considered non assessable if all conditions below are applicable:
-None of the four conditions indicated in the category “non-eligible”, as indicated above, apply
-For at least one of the four characteristics used in the category “non-eligible” a missing value occurs.

9.2.4.3 *Subject considered ineligible as a result of HHE assessment*

The independent review will not be used for the assessment of subject eligibility during screening. For this endpoint therefore only investigator reported information is used.

As a result of is interpreted in the SAP as: the HHE assessment is the main reason for subject being non-eligible for enrollment. For all subjects who are ineligible for enrollment investigator fills out maximum three failed Inclusion/Exclusion Criteria in the EDC, the first one filled out is considered to be the *main reason*. Thus, if as first failed IC/EC Criteria Exclusion above cited Inclusion criteria 5 is indicated, the HHE is the main reason for subject.

The endpoint is thus met if these two conditions both apply:

-HHE analysis performed by investigator indicates subject is considered ineligible (refer to SAP section 9.2.5.2) *and*
-The HHE assessment is filled out by investigator in the EDC as being the main reason for subject being ineligible in the trial.

The endpoint is reported for subjects included in the HHE population for whom the HHE assessment resulted in the conclusion ‘Eligible’ or “Non Eligible’, meaning subjects are excluded if assessment resulted in “Not Assessable”.

For these subjects the number of and percentage of subjects who were classified as “Ineligible” are reported, as is the number and percentage of subjects who meet the endpoint (being “Ineligible” with the HHE Echo results as main reason for being Ineligible for enrollment).

9.2.4.4 *Time from HHE administration to availability of HHE report/results*

These three time points are registered by investigator in the EDC:

-Time of HHE assessment
(eCRF: dataset HHE, Column ECDAT)

-Time HHE report/results are available
Defined as: Time when results were completed in the source worksheets (eCRF: dataset HHE, column REPDAT)

-Analysis time
Defined as the time analysis was completed (eCRF: dataset HHE, Column ANALDAT)

All three are date-time variables, with number of seconds as measuring unit.

The time from HHE administration to availability of HHE report/results will be reported in minutes and will calculated as:

t_1= (Time HHE report/results available -/- Time of HHE assessment)/60

The number of available observations and the mean and standard deviation will be reported.

Additionally the time from HHE administration to time of Analysis will be calculated.

t_2= (Analysis Time -/- Time of HHE assessment)/60

The number of available observations and the mean and standard deviation will be reported.

9.2.4.5 *Agreement between eligibility based on HHE analysis investigator and independent reviewer*

Refer to section 9.2.4.3 for the assessment if subject was eligible according to investigator and according to independent reviewer. For both sources the result of the analysis can be: “Eligible”, “Non Eligible” or “Not Assessable”.

The statistical report will include a 3*3 table:

	Eligible according to independent review			Total
Eligible according to investigator	Yes	No	Not Assessable	
Yes	N11	N12	N13	N1.
No	N21	N22	N23	N2.
Not Assessable	N31	N32	N33	N3.
Total	N.1	N.2	N.3	N

The percentage agreement is reported in two ways:

The first percentages show agreement using all analyses, meaning also agreement is reached if both raters indicate eligibility is “Not Assessable”

p_1=100*(N11+N22+N33)/N.

The number of patients and the percentage agreement will be reported, if required a 95% two-sided Clopper-Pearson confidence interval will be shown.

The second percentages show agreement excluding analyses where raters indicate eligibility is Not Assessable, thus only including analyses where at least one rater concluded that subject was Eligible or Not Eligible.

p_2=100*(N11+N22/(N-N33).
The number of patients and the percentage agreement will be reported, if required a 95% two-sided Clopper-Pearson confidence interval will be shown.

Additionally, a listing will show a line per subject, indicating for both investigator as independent reviewer the conclusion on eligibility of the subject.

No other inter-rater comparison of HHE characteristics (e.g. LVEF %, LV hypertrophy, refer to section 9.2.4.1 of SAP) is planned.

9.2.5 Exploratory endpoints for Part C PLS study

These endpoints will be reported for the PLS population (refer to SAP section 8.8).

9.2.5.1 *Proportion of subjects who achieved therapeutic dosing (≥ 200 ng/mL) with the study drug in the Part C Patient-Led Under Medical Supervision*

Due to the small sample size (n=3), this endpoint will not be analyzed, per subject results will be listed.

9.2.5.2 *Feasibility of patient-led self-administration of study drug*

Below endpoints are defined in the protocol.

<u>1) Percent of subjects who consent to the PLS study</u>

A first overview shows if patient consented to the PLS study, three possible options:
-"Not applicable"
-"Yes"
-"No"

Only for subjects whose initial treatment was performed in <u>Part B</u> or the MLS <u>Part C</u> of the trial numbers and frequencies will be provided. The sample size is all subjects who received inhaled flecainide in Part B or in the MLS Part C.

For the "non applicable" category the reason is specified:
-Subject not Eligible
-Site does not participate in patient-Led study
-Other (Reason will be provided)

For the remaining subjects ("Yes", "No") the number and percentage of subjects who consented to the PLS study is reported. The sample size is the number of remaining subjects ("Yes", "No"). For subjects who did not consent the reason will be provided.

For subjects whose initial treatment was performed in Part A of the trial no information is available in the EDC for this endpoint. Only the number of subjects who consented to the PLS study will be provided.

2) Percent of subjects who withdraw from the study

For the subjects who consented to the PLS study the End of Study status will be reported. These categories are specified in the eCRF:

-Completed
-Subject received medication in PLS part of Part C due to recurrent AF
-Subject completed the 8 months follow-up period without treatment of recurrent AF
-Adverse Event
-Death
-Physicians Decision
-Lost to Follow-up
-Withdrawal by Subject
-Protocol Deviation
-Site Terminated by Sponsor
-Study Terminated by Sponsor
-Screen Failure
-Other (the reason will be specified)

Information is available for all subjects participating in the PLS study.

3) Percent of subjects who are certified for self-administration of study drug
The number of subjects who consented to the PLS study will be reported as is the number and percentage of subjects who completed training certification.

percentage=100*number of certified/number of consented subjects

Information is available for all subjects participating in the PLS study.

4) Percent of subjects who return to clinic with a recurrent episode of PAF within 8 months of signing consent, and the associated timeframe(s) to time(s) of recurrence
For subjects who consented to the PLS study all AF recurrences after Informed are reported in a listing.

If no AF recurrence occurred subject will be listing as having no AF recurrence.

If any AF recurrence occurred for subject all AF recurrences are shown, one line per recurrence. The line includes:

-Subject ID
-Visit when the AF recurrence was registered
-If more than one AF recurrence for the visit: sequence number
-Date and time of AF recurrence
-Did AF recurrence lead to treatment by inhaled flecainide
If AF recurrence did not lead to treatment by inhaled flecainide: reason why.
This is a comment field, e.g. “conversion with pill in the pocket”

Information is available for all subjects participating in the PLS study.

5) Percent of subjects that independently set up and inhaled study drug according to the provided instructions
For subjects receiving inhaled flecainide in the PLS trial investigator filled out:

“Did the subject self-administer the dose as instructed without assistance”

The number and percentage of subjects for whom “Yes” is filled out is reported. For subjects for whom “No” is filled out, a comment field lists the difficulties encountered during self-administration

Information is available for all subjects participating in the PLS study who received inhaled flecainide in the PLS trial.

9.2.5.3 *Proportion of subjects whose AF converted to SR*

For subjects receiving inhaled flecainide in the PLS trial the number of subjects who converted to SR within 90 minutes post end of dose is reported, as is the method of Cardioversion (refer to SAP section 3.2)

Information is available for all subjects participating in the PLS study who received inhaled flecainide in the PLS trial.

9.2.5.4 *Hand Held Echo (HHE) Endpoints*

1) Proportion of subjects for whom capture and assessment of a diagnostic echocardiogram using a HHE at screening was successful

2) Percent of subjects who are considered ineligible for enrollment as a result of the HHE assessment

3) Time from HHE administration to availability of HHE report/results

In the Part C PLS study no HHE was performed, endpoints will not be reported.

9.3 On Pooled results (Part A, Part B and Part C MLS Subjects (120 mg FlecIH-103))

In Part B, a formal homogeneity test was performed to assess if the primary endpoint results for part A subjects receiving the 120 mg FlecIH-103 inhalation solution could be pooled with the primary endpoint results for Part B subjects. If results could be pooled, as was the case, a Total column would be included in the statistical report showing results for the Pooled population of Part A and Part B 120 mg FlecIH-103 subjects.

In the final report MLS subjects from Part A, Part B and Part C MLS will be pooled without any formal test performed on heterogeneity. Refer to sections 8 and 8.7 of SAP for the definition of the pooled cohorts and for an indication per type of data for which pooled cohorts study information will be reported.

10 Difference between protocol and SAP

The SAP is in accordance with study protocol V8.0/ EU-1 except for the following deviations:

- The SAP adds Methods for Cardioversion (refer to SAP section 3.2)
- The SAP specifies cohorts of the pre-specified study populations to be analyzed (refer to Table 1 in Section 8.0)
- Only 3 subjects were treated with study medication in the PLS study, as a result for some endpoints results are only listed and no summarizing statistics will be reported
- No HHE data are available for the PLS study, the endpoints will thus not be reported
- The protocol indicates a 90% confidence interval will be created for endpoints, instead (refer to SAP sections 9.2) for a selection of endpoints a 95% confidence intervals will be created; only for the primary efficacy endpoint (refer to SAP section 9.2.1) a 90% confidence interval will be created.
- The protocol indicated tmax is measured as the time to Cmax (from the time of end of dosing), in the SAP definition $t_{\text{-max}}$ is measured as the time to Cmax (from the time of the start of dosing).
- Adverse Events of Special Interest (AESI) and Serious Adverse Events of Special Interest (SAESI) will be tabulated using results as indicted in SAP section Annex A, using a slightly different definition than the definition in protocol V8.0/EU-1.

11 Changes in the Planned Analyses

Additional analyses that may be included in the Clinical Study Report but are not mentioned in the SAP will be identified as such.

12 Programming Conventions

- Identification of analysis population: Every summary table and figure should clearly specify the analysis population being summarized.
- Group headers: In summary tables group headers will identify the summary group and the sample size for the indicated analysis population. The header's sample size does not necessarily equal the number of subjects actually summarized within any given summary module; some subjects in the analysis population may have missing values and thus may not be summarized.
- Presentation of sample sizes: All TFLs should indicate, in one way or another, the number of subjects actually contributing to the summary statistics presented in any given summary module. As mentioned above, this may be less than the number of subjects in the analysis population due to missing data.
  - In the quantitative modules describing continuous variables (and thus presenting sample size, means, and standard deviations), the sample size should be the number of non-missing observations. The number of missing observations, if any, should be identifiable in the module
  - For categorical variables that are presented in frequency tables, the module should present the total count in addition to the count in each category. Percentages should be calculated using this total as the denominator, and the percentage corresponding to the sum itself (that is, 100%) should be presented so as to indicate clearly to a reviewer the method of calculation. The number of missing observations, if any, will be noted.
- Sorting: Listings will be sorted by subject identifier and (where applicable) then by date within each subject identifier. If a listing is sorted in a different manner, a footnote will indicate as such.
- General formatting rules: Rounding for all variables will occur only as the last step, immediately prior to presentation in listings, tables, and figures. No intermediate rounding will be performed on derived variables. The standard rounding practice of rounding numbers ending in 0-4 down and numbers ending in 5-9 up will be employed.
- The presentation of numerical values will adhere to the following guidelines:
  - Raw measurements will be reported to the number of significant digits as captured in the source data
  - Mean, standard deviation, median, Q1 and Q3 will all be shown using 1 additional decimal compared to the source data, with a maximum of two decimals. Minimum and maximum will be shown using the number of decimals in the source data.

  - Calculated percentages will be reported to one decimal place.
- Dates will be formatted as DDMMMYYYY. Partial dates will be presented on data listings as recorded in the EDC.
- Time will be presented according to the 24-hour clock (HH:MM or HH:MM:SS as applicable).

13 References

This version of the SAP only uses references to the study protocol indicated at page 2 of SAP.

14 Tables, Figures and Listings

The Tables, Figures and Listings and Flowchart that are included in the final statistical analysis will be created using the analysis described in this SAP. The final report will include an overview of all TFLs that are included in the report.

Each table will reference an associated listing containing data used by the table. If applicable, the figures will reference an associated listing and/or an associated table used by the figure.

For the **MLS** part of the trial all data for subjects that received FlecIH-103 120 mg dose from Parts A, B and C will be included in the listings. If subject also participated in the PLS trial, the results of the PLS trial are not included in the MLS part of the final report.

For the **PLS** part of the trial, the tables and listings will only report on study results for this PLS part of the trial, not for the study results of the initial MLS treatment of subject in Part A, B or Part C MLS. However, for the PLS subjects the MLS study results can be found in these listings:

- If the MLS treatment took place in Part B or Part C MLS: results are listed in the final MLS report under the same subject identifier as in the PLS report
- If MLS treatment took place in Part A and in Part A subject received 2*60 mg FlecIH-103 (and is thus included in the pooled MLS analysis): results are listed in the final MLS report. Subject however received a new subject identifier in Part C PLS, the PLS report will include information showing the subject identifier in the PLS report and the corresponding subject identifier in the final MLS report
- If MLS treatment took place in Part A and in Part A subject received a different regimen than 2*60 mg FlecIH-103 (and is thus not included in the pooled MLS analysis): results were listed in the final report for Part A of the trial (as created July 24, 2020). Subject however received a new subject identifier in Part C PLS, the PLS report will include information showing the subject identifier in the Part C PLS report and the corresponding identifier in the final Part A report.

Refer to section 8.0 of the SAP for a description on the specific cohorts for which Part C MLS results and MLS pooled results will be reported.

15 Programming Specifications

If required, a separate document will provide details necessary to replicate the various data derivations outlined in the SAP.

Annex A: FLE-002 Sponsor Review of Adverse Events of Special Interest

1. Background and Justification

1.1 FLE-002 (INSTANT) is the first InCarda Phase 2 clinical study to assess the efficacy and safety of flecainide acetate inhalation solution (FlecIH-103), administered via oral inhalation in patients with recent onset, symptomatic atrial fibrillation (AF). The study is composed of 3 parts which was refined over time through successive protocol amendments (Parts A, B, and C). Part A examined different formulations of inhalation solutions and dosages, leading to the selection of the 120 mg estimated total lung dose (eTLD) of FlecIH-103 formulation administered as two 3.5-minute inhalations separated by a 1-minute break (8 minutes total administration time). This treatment regimen was further evaluated in Parts B and C of FLE-002 and was selected for evaluation in Phase 3.

1.2 One of the main objectives of the study, and the focus of the final analysis, is to assess the safety of 120 mg FlecIH-103 inhalation for acute cardioversion of AF. To address this objective, Adverse Events (AEs) were collected by the sites and entered in the Case Report Form (CRF), implemented in an Electronic Data Capture (EDC) system. The AEs were initially also entered in the CRO's Safety Database by the safety team as the MedDRA and WHODrug coding feature in the EDC system (Marvin) was not enabled (in Part A).

1.3 Several AEs of special interest (AESIs) were defined for FLE-002, which were progressively refined in subsequent protocol amendments. In February 2021, InCarda amended the FLE-002 protocol (v8.0 EU-1; 16 Feb 2021) with the final pre-defined AESI list and associated criteria, which included: 1) AEs related to the inhalation device; 2) Pregnancy, and; 3) AEs known to be related to other well characterized flecainide formulations (i.e., IV and oral). Criteria for these AESIs and serious AESIs are further defined in Section 5.

1.4 Because the definition of AESIs changed over time, and the process to collect them varied between the different parts of the study, InCarda will centrally review all AEs and provide a consistent assessment of AESIs per the criteria described in Section 4 below.

2. Purpose

2.1 This document outlines the steps required to review all AEs reported in patients who received 120 mg FlecIH-103 in Parts A, B and C of the FLE-002 study to determine if they meet the final AESI criteria as defined in the protocol.

2.2 This review will generate data that is to be used in the final analysis of the study, as described in the FLE-002 Statistical Analysis Plan (SAP).

3. Responsibilities

3.1 InCarda Data Management will provide the listing of all AEs, organize data entry, and prepare a memorandum that will record the process execution as per section 5.

3.2 InCarda Clinical Development will provide resources to review AEs, enter and verify the new assessments.

3.3 InCarda Clinical Operations will archive all relevant documentation in the study Trial Master File (TMF).

4. Definitions

4.1 Adverse Event (AE): Any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

4.2 AE of Special Interest (AESI): Any AE related to the inhalation device, any pregnancy that started while participating to the study, and AEs known to be related to other formulations of flecainide (i.e., IV and oral).

4.3 Non-Cardiovascular Adverse Event of Special Interest (Non-CV AESI): A subset of AEs coded in MedDRA within a System Organ Class (SOC) other than "Cardiac disorders" or "Vascular disorders, which includes AEs related to the inhalation device and any pregnancy that started while participating to the study as defined below:

- Pregnancy: Any female study subject or female partner of a study subject that becomes pregnant while participating in this study
- AE related to the inhalation device (nebulizer): AE considered directly related to the nebulizer

4.4 Serious Non-Cardiovascular Adverse Event of Special Interest: Non-CV AESI is considered serious if it meets the following criteria.

- Pregnancy: Any female study subject or female partner of a study subject that becomes pregnant while participating in this study
- AE related to the inhalation device: AE considered directly related to the nebulizer by the Investigator that meets the definition for a SAE

4.5 Cardiovascular Adverse Event of Special Interest (CV AESI): A subset of AEs coded in MedDRA within a System Organ Class (SOC) of "Cardiac disorders" or "Vascular disorders, which include AEs known to be related to flecainide as defined below.

- Hypotension: an acute hypotensive episode (AHE) is a sudden drop in BP resulting in a BP < 90/60 mmHg (MAP < 70 mmHg) that lasts for at least 5 minutes and is based on multiple sequential readings (≥ 3). MAP is calculated as 1/3 (SBP – DBP) + DBP

- Ventricular Tachycardia (VT): Ventricular tachycardia (i.e., an ECG-derived rate >100 bpm) > 3 beats (excludes triplets)

- Bradycardia: an ECG-derived rate < 50 bpm for ≥ 1 minute

- Sinus pause post conversion of AF to SR: an ECG-derived pause > 3 seconds

- Atrial flutter with 1:1 conduction with fast ventricular response: Atrial flutter with a ventricular heart rate ≥ 200 bpm

4.6 Serious Cardiovascular Adverse Event of Special Interest: A CV AESI is considered serious as defined below.

- Hypotension per AESI definition in Section 4.5 with symptoms/signs of clinical instability (i.e., severe chest pain/dyspnea or altered mental status) and requiring a vasopressor or inotropic agent

- Ventricular tachycardia per AESI definition in Section 4.5 that is sustained (> 30 seconds or requiring intervention before that time) VT, TdP, or VF

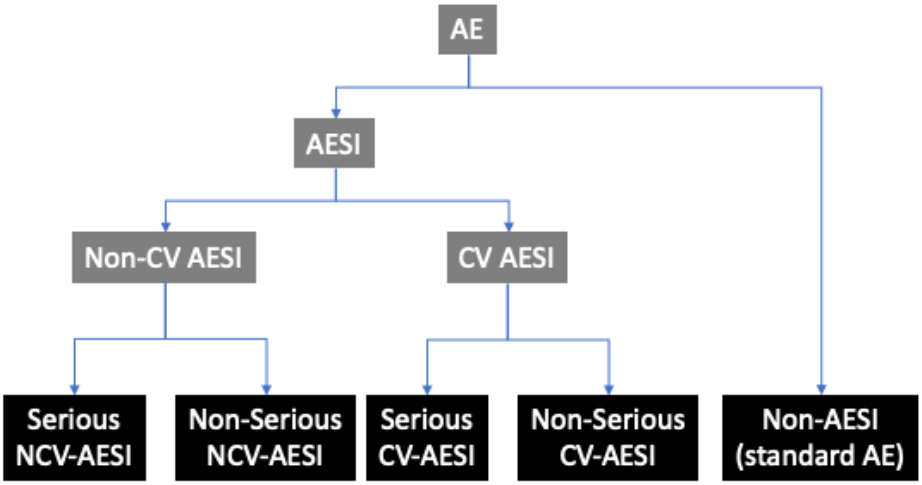
- Bradycardia per AESI definition in Section 4.5 with symptoms/signs of clinical instability (i.e., severe chest pain/dyspnea, altered mental status or hypotension) and requiring pacing or a chronotropic agent

- Sinus pauses post conversion of AF to SR per AESI definition in Section 4.5, causing syncope or requiring pacing or CPR

- Atrial flutter with 1:1 conduction with fast ventricular response per AESI definition in Section 4.5, and requiring intervention (DC cardioversion) for termination or an IV AV nodal blocking agent (β-blocker or Ca2+-channel blocker) to slow the ventricular rate

Any arrhythmia with symptoms/signs of clinical instability (i.e., severe chest pain/dyspnea, altered mental status or hypotension), and requiring DC cardioversion, defibrillation, pacing, or a vasopressor, inotropic or chronotropic agent. Serious AESIs in this category will also be included in the broader category of CV AESI described in Section 4.5.

4.7 Decision Tree



Non-CV AESI = Pregnancy and AEs related to the inhalation device (nebulizer)
CV AESI = Hypotension, ventricular tachycardia, bradycardia, sinus pause post-cardioversion, and atrial flutter with 1:1 conduction with fast ventricular response

5. Procedure

5.1 Listing Preparation

5.1.1 Data Management will generate a MedDRA coded AE listing, including Preferred Term (PT) and System Organ Class (SOC)and will ensure consistency with the database and previous study reports.

5.1.2 The listing will include all information in the safety database and the EDC for Part A for patients receiving 120 mg FlecIH-103 and safety data and all associated details from the EDC for Parts B and C.

5.1.3 The Listing will include the necessary columns for entering the review result and ensure traceability (see section 6.2.2).

5.1.4 Data Management will place the listing in a secure area and will grant access to designated Reviewers.

5.1.5 All versions of the listings will be easily accessible for review.

5.2 Listing Review

5.2.1 The designated person responsible for the review (Reviewer) is provided with AESI definitions from section 4 of the present document.

5.2.2 Each AE will be reviewed, and documented as follows:

- AE type (select only one option)
  - Non-AESI (standard AE)
  - Non-CV Non-Serious AESI
  - Serious Non-CV AESI
  - CV Non-Serious AESI
  - Serious CV AESI
- Initials
- Date
- Comment

5.2.3 The Reviewer initials and dates next to each recoded item and provides comments as necessary.

5.2.4 The Reviewer also signs a memorandum to record execution.

5.3 Listing Verification

5.3.1 A separate designated Clinical Development member will review all assessments and ensure completion and consistency.

5.3.2 Any issue(s) will be reported to the Reviewers for discussion, adjudication and possibly update. The comment field can be updated with initials and date.

5.3.3 The person in charge of the verification also signs the execution memorandum at completion of the process.

5.4 Archiving

5.4.1 Annotated listing sand the execution memorandum will be archived upon completion in the study TMF by the Clinical Operations team.