I. Clinical study title page

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).

Short title:	**IN**halation of flecainide to convert recent onset **S**ymp**T**omatic **A**trial fibrillation to si**N**us rhy**T**hm. (INSTANT)		
Test drug(s):	FlecIH-101, FlecIH-102, and FlecIH-103 (flecainide acetate inhalation solution) (INN - Flecainide Acetate)		
Study no.:	FLE-002		
IND no.:	147305		
EudraCT no.:	2018-000094-76		
Version no.:	8.0 EU-1	Date:	16 FEB 2021
Previous version no.(s):	7.0 / EU-2	Date(s):	03 NOV 2020
	7.0 / US-1		14 AUG 2020
	7.0 / EU-1		28 JUL 2020
	6.0*		06 MAR 2020 (**not implemented*)
	5.0 / EU-2		01 NOV 2019
	5.0 / EU-1		13 AUG 2019
	5.0		15 JUL 2019
	4.0		02 MAY 2019
	3.0		12 DEC 2018
	2.0		10 OCT 2018
	1.0		21 FEB 2018

Sponsor: InCarda Therapeutics, Inc.
39899 Balentine Drive, Suite 185
Newark, CA, USA

Sponsor's medical expert: Luiz Belardinelli, MD
Chief Medical Officer
39899 Balentine Drive, Suite 185
Newark, CA 94560, USA
Tel: +1 (650) 704-2805

II. Protocol Approval Page

Study title:	**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).**
Short title:	**IN**halation of flecainide to convert recent onset **S**ymp**T**omatic **A**trial fibrillation to si**N**us rhy**T**hm. (INSTANT)
Study no.:	FLE-002
Version:	8.0 EU-1 (16 FEB 2021)

We, the undersigned, have read and approved the protocol specified above, and agree upon the contents:

Sponsor

Name: Luiz Belardinelli, MD Role: Chief Medical Officer InCarda Therapeutics, Inc.

Date: February 19th, 2021 Signature: Luiz Belardinelli

Legal representative

Name: ERNEST Spitzer, MD Role: Medical Director Cardialysis B.V.

Date: March 2nd, 2021 Signature: E. Spitzer

III. Signature Page Principal Investigator

Study title:	**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).**
Short title:	**IN**halation of flecainide to convert recent onset **S**ymp**T**omatic **A**trial fibrillation to si**N**us rhy**T**hm. (INSTANT)
Study no.:	FLE-002
Version:	8.0 EU-1 (16 FEB 2021)

I have read this protocol and/or amendment and appendices and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to the study personnel under my supervision. I will discuss this material with them and ensure they are fully informed regarding the investigational product and the conduct of the study.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Conference on Harmonization guidelines on Good Clinical Practice (ICH E6), and applicable regional regulatory requirements.

Name:	Role:
Date:	Signature:

IV. Protocol Synopsis

Study Title	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). **Note**: Part A included a randomized phase; Part B and Part C are not randomized.
Short Title	**IN**halation of flecainide to convert recent onset **S**ymp**T**omatic **A**trial fibrillation to si**N**us rhy**T**hm. (INSTANT)
Study Phase	Phase 2
Study Objective(s)	To evaluate the safety, tolerability and efficacy of single and repeat doses of flecainide acetate oral inhalation solution in subjects with paroxysmal AF.
PART A Objective(s)	Part A was completed on 05Mar2020. The objective in Part A was to evaluate the feasibility of single and repeat administration of flecainide acetate inhalation solution (30, 60, 90 and 120 mg estimated total lung dose [eTLD]) for acute conversion of recent onset of paroxysmal AF to SR. Other objectives were exploratory in nature.
PART B Objective(s)	**Efficacy objective(s):** To evaluate the conversion of AF to SR and symptom relief by flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF. **Safety objective(s):** To assess the safety and tolerability of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF. **Pharmacokinetic (PK) and pharmacodynamic (PD) objective(s):** • To evaluate the pharmacokinetics of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF.

- To evaluate the electrocardiographic effects (PD) of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF.

Exploratory objective:
To explore the feasibility of implementing a portable cardiac ultrasound (handheld echocardiogram [HHE]) at screening in an emergent setting

PART C Objective(s)

All Part C objectives are exploratory:

- 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, including resumption of SR
- To explore the feasibility of implementing a portable cardiac ultrasound (HHE) at screening in an emergent setting

Study Design

Subjects eligible to participate in the study must provide written informed consent (IC) before enrollment or undergoing any study-specific procedures.

The study consists of 3 parts (Part A, Part B, and Part C) as described below. The optimal dose identified in Part A will be used for Part B and Part C.

PART A was an open-label, multicenter design and studied the feasibility of administration of inhaled flecainide in four dosing regimens (30, 60, 90, and 120 mg). Part A was closed to enrollment on 05Mar2020, after a total of 101 subjects were treated with the study drug (10 with 30 mg, 22 with 60 mg, 21 with 90 mg, and 48 with 120 mg). The final dose in Part A (120 mg FlecIH-103) was selected as the dose to continue evaluating in Part B.

PART B is an open-label, multicenter design to confirm the safety (including tolerability) and to provide a more precise estimate of efficacy of the optimal inhaled flecainide dose

determined from Part A (120 mg, using the FlecIH-103 inhalation solution). Subjects are enrolled to receive a repeat dose regimen of 120 mg eTLD (2 x 60 mg); N = approximately 25 subjects.

PART C consists of two distinct studies: 1) a Medically-Led Cardioversion Study (study procedures are identical to those in Part B), and 2) a Patient-Led Under Medical Supervision Cardioversion Study (study procedures include the subject self-preparing and self-administering the study drug under medical supervision in the clinic). Part C is only conducted in Europe (EU).

Subjects with recent-onset AF who have not been previously treated with flecainide acetate inhalation solution will first be enrolled into the Medically-Led Cardioversion Study to determine eligibility for the Patient-Led Under Medical Supervision Cardioversion Study.

Subjects that complete Part A, Part B, or the Part C Medically-Led Cardioversion Study may be eligible to enroll in the Part C Patient-Led Under Medical Supervision Cardioversion Study if their AF safely converted to SR due to study drug and they did not experience any difficulties or issues with inhalation (in the opinion of the investigator), serious AEs, or serious AESIs.

The Patient-Led Under Medical Supervision Cardioversion Study will require all subjects to return to the clinic for training and pass an assessment on their ability to self-administer the study drug. Subjects will then return to the clinic within 48 hours of the onset of a recurrent episode of paroxysmal AF to self-administer the study drug.

Part B and Part C:
Part B and the Part C Medically-Led Cardioversion Study also have an optional Handheld Echo (HHE) Sub-Study (only at select EU sites), where subjects who specifically consent will undergo an additional screening procedure using a portable hand-held ultrasound device to obtain an echocardiogram. Additional details on the HHE Sub-Study can be found in Appendix 6.

All Parts:
Study procedures are performed as described in the Schedule of Assessments (Section 17.4). If by 90 minutes post dose, no conversion to SR is observed, the Investigator may offer the subject another appropriate therapy, as per institutional standard (with exceptions; refer to Section 5.4.2 B). Discharge of the subject is at the discretion of the treating physician but may not be scheduled prior to 90 minutes after initiation of dosing.

An independent Data and Safety Monitoring Board (DSMB) is responsible for monitoring safety during the study. The Sponsor may discontinue a treatment dose cohort due to safety/tolerability concerns, change in the benefit/risk to the subject.

Enrollment occurs on Day 1 and the start of the first inhalation is considered time zero (T_0).

Dosing regimen(s)

Part A:
Four dosing regimens were evaluated in Part A: 30 mg eTLD, 60 mg eTLD, 90 mg eTLD, and 120 mg eTLD.

Part B and Part C:
One 'dose/inhale to conversion' regimen will be tested using FlecIH-103 inhalation solution:

- 120 mg eTLD (2 x 60 mg) repeat dose regimen (75 mg/mL): a first 60 mg inhalation is administered using an AeroEclipse® II BAN. The second 60 mg inhalation is administered using the identical AeroEclipse® II BAN.

Dosing in a 'dose/inhale to conversion' regimen shall continue according to the assigned regimen until the conversion of AF to SR is observed for ≥ 1 minute, or until the assigned dose is completed, whichever comes first.

Study duration

The study duration for Part A, Part B, and the Medically-Led Cardioversion Study of Part C lasts for a total of 5 days. In Part B, subjects are monitored for up to approximately 2 hours and 23 minutes (for 45 minutes before dosing, up to 8 minutes during dosing, and for 90 minutes after dosing) on Day 1.

	Subjects receive two outpatient telephone contacts, one on Day 2 and one on Day 5. The telephone contact on Day 5 is the final study contact and marks the end-of-study (EOS) for each subject, unless they consent to participate in the Part C Patient-Led Under Medical Supervision Cardioversion Study. The duration of the Part C Patient-Led Under Medical Supervision Cardioversion Study will continue through the Day 5 telephone contact after a recurrent episode of AF is treated, or approximately 8 months after consent, whichever comes first.
Indication	Flecainide acetate inhalation solution is indicated for rapid cardioversion of recent onset atrial fibrillation (AF) in patients with symptomatic paroxysmal AF when the need for treatment has been established. Flecainide acetate inhalation solution shall only be used in the absence of any contraindication to flecainide.
Investigational drug(s)	FlecIH-101, FlecIH-102, and FlecIH-103 (flecainide acetate inhalation solution)
Name of active ingredient	Flecainide Acetate
Dose(s)	**Part A:** Four doses were evaluated in Part A: 30 mg eTLD, 60 mg eTLD, 90 mg eTLD, and 120 mg eTLD. Each dose was administered using the hand-held inhaler device AeroEclipse® II BAN. **Part B and Part C:** FlecIH-103 (75 mg/mL): - 120 mg (repeat dose regimen): 2 consecutive inhalations of 60 mg eTLD Each dose is administered using the hand-held inhaler device AeroEclipse® II BAN.
Route of administration	Oral inhalation
Reference drug(s)	Not applicable
Part A Eligibility Criteria	Refer to a previous version of the Protocol.

Part B and Part C Eligibility Criteria	Subjects to be included in the study must meet the following <u>inclusion criteria</u>: 1) Subjects with recent-onset symptomatic AF at presentation. 2) With a duration at onset of symptoms from 1 hour to 48 hours 3) And from one of the following categories: a) First detected episode of paroxysmal AF b) Recurrent episode of paroxysmal AF c) Episode post-cardiac ablation for paroxysmal AF 4) **Part C Patient-Led Under Medical Supervision Cardioversion Study only:** Subjects whose AF converted to SR with inhaled flecainide and without difficulties or issues with inhalation (in the opinion of the investigator), serious AE(s), or serious AESI(s) in Part A, Part B, or the Part C Medically-Led Cardioversion Study NOTE: Subjects who: - are prescribed a pill-in-the-pocket regimen (flecainide or propafenone) for paroxysmal AF, or - are within 3 months of having undergone ablation of paroxysmal AF, or - have experienced an episode of new AF but are not currently experiencing an episode of recent-onset paroxysmal AF, or - are known to have paroxysmal AF (or previously diagnosed with paroxysmal AF) and have one or more previous symptomatic episodes but are not currently experiencing an episode of recent-onset paroxysmal AF may consent to pre-study screening prior to presenting with recent-onset symptomatic AF. These subjects will be eligible to receive study drug only when presenting with symptomatic paroxysmal AF of recent-onset (i.e., ≤ 48 hours), consenting to the full study, and after meeting all eligibility criteria.

Subjects are NOT eligible to participate in this study if they meet ANY of the following exclusion criteria:

General

1) Subject < 18 or > 85 years of age
2) Hemodynamic and/or cardiac instability, with systolic blood pressure < 100 mmHg or > 150 mmHg, and/or ventricular heart rate < 80 bpm or > 160 bpm. For subjects to meet eligibility criteria for Part B or the Part C Medically-Led Cardioversion Study C, at least 2 of the 3 measurements of vital signs during screening (45, 30, and/or 15 minutes prior to dosing) must meet the stated criteria. For subjects to meet eligibility criteria for the Part C Patient-Led Under Medical Supervision Cardioversion Study, the measurement of vital signs taken within 10 minutes prior to dosing must meet the stated criteria.
3) Current AF episode treated with Class I or Class III antiarrhythmic drugs or electrical cardioversion. Subjects whose current AF episode has been treated with flecainide are eligible if their total cumulative exposure to flecainide (including the study drug to be administered in this study) does not exceed 320 mg within a 24-hour period, per site standard of care.

Relevant structural heart disease

4) History of acute decompensated heart failure (HF)
5) Evidence of significant HF defined as any of the following:
   a) Hospitalization in the last 12 months for HF or suspected HF event
   b) Most recent assessment of left ventricular ejection fraction (LVEF) < 45%
      i) For subjects in the US, a standard diagnostic echocardiogram assessed ≤ 180 days prior to screening is required to ascertain eligibility. If none is available, the subject must undergo a standard diagnostic echocardiogram or a diagnostic echocardiogram using a portable ultrasound device (handheld echocardiogram [HHE]) during screening to confirm eligibility.

ii) For subjects in the EU who are participating in the optional HHE Sub-Study, the subject must undergo an HHE during screening to confirm eligibility.

c) New York Heart Association (NYHA) Class II-IV symptoms

d) Medication history suggestive of HF per the Investigator's discretion

6) Evidence of current ongoing myocardial ischemia, such as signs (e.g., significant [e.g., > 2 mm] ST segment elevation or depression on ECG, echocardiographic findings suggestive of acute myocardial infarction), symptoms (e.g., angina pectoris, atypical angina pectoris), and/or being medicated with anti-anginal medication. In addition, subjects with signs of prior myocardial infarction (such as pathological Q waves) who are also taking concomitant medications for angina pectoris should be evaluated for presence of ongoing ischemia.

7) History of myocardial infarction (MI) within 3 months of screening

8) Known uncorrected severe aortic or mitral valve stenosis. For subjects receiving an HHE assessment at screening (refer to exclusion criterion 5), any moderate or severe valvular disease noted during the HHE assessment is considered exclusionary.

9) Hypertrophic cardiomyopathy with outflow tract obstruction. For subjects receiving an HHE assessment at screening (refer to exclusion criterion 5), any moderate or severe hypertrophy noted during the HHE assessment is considered exclusionary.

Other cardiac conditions

10) Current diagnosis of persistent AF

11) One or more episodes of atrial flutter within 6 months prior to screening or atrial flutter at presentation, except subjects who received ablation for atrial flutter at least 3 months prior to screening and had no subsequent recurrence of atrial flutter prior to enrollment

12) History of any of the following heart abnormalities:

a) Long QT syndrome

b) Conduction disease (e.g. second- or third-degree heart block, bundle branch block)

c) Diagnosed with sinus node dysfunction (e.g., sick sinus syndrome) and/or one of the following:
(i) history of unexplained or cardiovascular syncope,
(ii) known bradycardia suggestive of sinus node dysfunction, and/or
(iii) prior electrical or pharmacological cardioversion associated with prolonged sinus or ventricular pause (e.g., >3 seconds) and/or slow ventricular rhythm (e.g., <45 bpm) at time of conversion
Note: Sinus node dysfunction in AF is more prevalent in subjects >75 years old.[2]
d) Brugada Syndrome
e) Torsades de pointes (TdP)

13) Any of the following ECG-related features:
a) QTc interval > 480 msec at screening (estimated by the Fridericia's formula[1])
b) QRS duration ≥ 120 ms or history of previous documented wide QRS tachycardia
c) Predominantly (i.e., > 30 %) paced heart rhythm
d) Ventricular tachycardia (VT, sustained or non-sustained), or excessive premature ventricular complexes (PVCs, > 20 multifocal PVCs per hour), prior to dosing as per site telemetry. Site telemetry should be equipped with an alarm system for VT and PVCs or be continuously visually observed prior to dosing

Concomitant conditions

14) Severe renal impairment (eGFR < 30 mL/min/1.73 m2) or on dialysis
15) Known medical history of abnormal liver function prior to enrollment
16) Uncorrected hypokalemia (defined as serum potassium < 3.6 mEq/L) at screening. If serum potassium result is < 3.8 mEq/L at screening, therapeutic correction (e.g., potassium supplementation) is strongly encouraged, although reassessing the serum potassium level is not required as long as a value of ≥ 3.6 mEq/L is documented at screening.
17) Subjects with established pulmonary disease in need of inhalation medication. Subjects with COPD are excluded. Subjects with mild to moderate asthma that are not experiencing active symptoms at screening and whose

asthma is well controlled with steroids and/or as-needed administration of a bronchodilator are eligible for the study.

Concomitant and study medication

18) Known hypersensitivity to flecainide acetate or any of its active metabolites
19) Concomitant therapy with systemic drugs that are strong inhibitors of CYP 2D6 (e.g. antidepressants, neuroleptics, ritonavir, some antihistamines) or CYP 2D6 inducers (e.g. phenytoin, phenobarbital, carbamazepine)
20) Treatment with Class I or Class III antiarrhythmic drugs within the last week. Subjects whose current AF episode has been treated with flecainide are eligible if their total cumulative exposure to flecainide (including the study drug to be administered in this study) does not exceed 320 mg within a 24-hour period, per site standard of care.
21) Treatment with amiodarone within the last 12 weeks

Other

22) Subject is deemed unsuitable for the trial by the Investigator (including but not limited to: patients who are considered at high risk for stroke based on medical history (e.g., CHA2DS2-VASc score); patients with congenital heart disease; patients with history of AF refractory to pharmacological or electrical cardioversion; patients whose AF is secondary to electrolyte imbalance, thyroid disease, or other reversible or non-cardiovascular cause; patients with any serious or life threatening medical condition; patients with any acute infection). The subject may be deemed unsuitable for the trial by the Investigator if the subject is not able or willing to inhale the study drug.
23) Known drug or alcohol dependence within the past 12 months as judged by the Investigator
24) A body mass index > 40 kg/m^2
25) Legally incompetent to provide informed consent (IC)
26) Previous treatment in this study (this does not apply to enrollment in the Part C Patient-Led Under Medical Supervision Cardioversion Study) or previous treatment with any other investigational drug within 30 days from screening or 5 half-lives of the drug, whichever is longer

27) Female of childbearing potential
    a) Who are not surgically sterile, or post-menopausal (defined as no menses for 2 years without an alternative cause), or
    b) For whom a negative pregnancy test is unavailable before study entry, or
    c) Who are pregnant or breast feeding at study entry
28) Previous administration of flecainide for an episode of paroxysmal AF or new AF did not result in conversion of AF to SR (i.e., subject is considered a non-responder to flecainide)
29) Cardiac surgery for any of the exclusionary conditions (e.g., valvular disease, hypertrophy, coronary artery disease [CAD], etc.) within the last 6 months prior to screening
30) Respiratory rate of > 22 breaths per minute

Study endpoint(s) PART A

Feasibility was assessed in terms of the following performance characteristics:

a) Rates of study enrollment, screen failures and refusals of IC;
b) The rate of technically successful administration of study inhalation regimens;
c) Successful capture of study data according to the schedule of study assessments;
d) Successful remote capture of AF-status at follow-up contacts

Conversion of AF to SR and safety/tolerability were compared in an exploratory manner.

Study endpoint(s) PART B

The primary efficacy endpoint is the proportion of subjects whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing. For the definition of the endpoint *conversion to SR* refer to Section 10.2.1.1 B.

Secondary efficacy endpoints include:

- 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 by inhaled flecainide 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 dosing and completion of dosing.

The secondary safety endpoint is the incidence of treatment emergent serious adverse events of interest for flecainide.

Exploratory endpoints (HHE):
- 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 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 if site staff made a successful assessment of subject eligibility using the HHE data obtained during screening.

Study Endpoint(s) Part C	All endpoints in Part C are exploratory:
	- 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
	- Feasibility of patient-led self-administration of study drug, including:
	  ○ 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
	- Proportion of subjects whose AF converted to SR
	- 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

Study centers	Part A: 14 clinical sites in Europe Part B and Part C: approximately 20 clinical sites in Europe and North America
Planned sample size	Approximately 126 subjects with recent onset of symptomatic paroxysmal AF are planned to be enrolled in the study. This includes the 101 subjects treated in Part A (N = 10 evaluable subjects for 30 mg dose cohort; N = 22 evaluable subjects for 60 mg dose cohort; N = 21 subjects for 90 mg dose cohort; N = 48 subjects for 120 mg dose cohort) and the approximately 25 subjects planned for Part B. In Part B, subjects who enroll but are not treated with study drug will not count towards the planned sample size. Part C (EU only) does not have an enrollment target. However, enrollment will continue in the Part C Medically-Led Cardioversion Study at the discretion of

the Sponsor to support rollover participation in the Part C Patient-Led Under Medical Supervision Cardioversion Study (refer to description above).

All subjects enrolled and treated with study drug will be analyzed within the safety population. For the modified intention-to-treat population (mITT), for any subject who was not in AF at the time of dosing and who does not complete inhalation of the full assigned dose will be replaced to keep the sample size needed.

In Part B, the estimated sample size of 25 subjects for the 120 mg dose cohort is based upon the evaluation of the following statistical hypotheses using an exact binomial test,

H_0: $\rho = 20\%$ versus H_A: $\rho > 20\%$ ($\alpha = 0.05$).

Given the actual conversion rate for the Part A 120 mg dose cohort (FlecIH-103 inhalation solution) is 48%, a sample size of 25 subjects has at least 92% power to reject the null hypothesis (H_0) in favor of the alternative (H_A) with a one-sided significance level of 0.05. The null hypothesis is rejected when at least 9 subjects' AF converts to SR within 90 minutes after initiation of dosing.

For example, with 25 subjects enrolled in Part B, if 9 of them have their AF converted to SR, the resulting conversion rate is 36% with a 90% exact binomial confidence interval of [20.24%, 54.39%]. If 9 or more subjects' AF converts to SR, the lower bound of the 90% exact binomial confidence interval will be greater than 20.24%. When the lower bound of the 90% confidence interval for conversion rate is greater than 20%, there is sufficient support for the rejection of the null hypothesis in favor of the alternative.

It is expected approximately 20 subjects will participate in the HHE Sub-Study in Europe (Part B and the Part C Medically-Led Cardioversion Study); however, the HHE Sub-Study does not have a minimum or maximum enrollment target.

Statistical analyses

PART A:
The main feasibility, efficacy and safety parameters were presented in a descriptive manner. Data on PK, PD and other assessments were presented in a similar manner.

PART B:
All (primary and secondary) efficacy endpoints are analyzed with the *modified Intention-to-treat (mITT) population*. The mITT population is defined as all enrolled subjects who were in AF at the time of dosing and completed the full assigned dose of study drug.

The primary endpoint analyses of Part B will be based on Part B subjects alone. If the Part B primary endpoint analysis meets the pre-specified criteria for significance and is not substantially different from Part A 120 mg FlecIH-103, the two dose cohorts (120mg FlecIH-103 cohorts from Part A and Part B) will be combined for the overall analysis of Part B to provide a more precise estimate of efficacy, safety, and PK/PD.

The primary efficacy analyses will compute the proportion of subjects whose AF converted to SR within 90 minutes after initiation of dosing. For Part B, the primary analysis will be based upon one-sided testing (i.e., $\rho > 20\%$) via an exact binomial test. One-sided testing is being undertaken based on the results from Part A with the same dose showing a conversion rate of 48%. A one-sided binomial exact test will be used to determine whether the null hypothesis of equality may be rejected in favor of a conversion rate of greater than a historical placebo rate of approximately 20%, a value higher than reported for placebo in the literature (16%)[3] and in the more recent randomized, placebo-controlled trials with vernakalant (approximately 5%)[4].

PART C:
No formal hypothesis testing is planned for Part C. Summary statistics will be generated, including estimates of the endpoints with their associated 90% confidence intervals.

All statistical analyses performed in the evaluation of the INSTANT Study data are described in the statistical analysis plan (SAP).

V. Table of contents

VI. List of tables

VII. List of in-text figures

VIII. List of Abbreviations

AE	adverse event
AECG	ambulatory ECG
AESI	adverse event of special interest
AF	atrial fibrillation
AHE	acute hypertensive episode
BP	blood pressure
CE	Conformite Europeene
C_{max}	maximum serum concentration
CRF	case report form
CRO	contract research organization
d	day(s)
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic CRF
EDTA	ethylenediaminetetraacetic acid
e.g.	exempli gratia (for example)
EMA	European Medicines Agency
EOS	end-of-study
et al.	et alia (and others)
etc.	et cetera (and so on)
EudraCT	European Clinical Trials Database
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice (refers to ICH)
GMP	Good Manufacturing Practice
GP	General Practitioner
h	hour(s)
HHE	handheld echocardiogram
HR	hazard ratio
IB	Investigator's Brochure
IC	informed consent
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IRB	institutional review board
ITT	intent-to-treat
JTc	corrected JT interval
LVEF	left ventricular ejection fraction
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
min	minutes
mITT	modified ITT
MPI	myocardial perfusion imaging
PD	pharmacodynamic
PDF	Portable Document Format
PI	Principal Investigator
PK	pharmacokinetic
PQ	on an ECG, the time between the beginning of the P wave and the beginning of the next QRS complex
PR	on an ECG, the time between the beginning of the P wave and the beginning of the next QRS complex (interchangeable with PQ)
PT	prothrombin time
QA	quality assurance
QoL	quality of life
QRS	on an ECG, a structure that corresponds to the depolarization of the ventricles
QT	on an ECG, the time between the start of the Q wave and the end of the T wave
QTc	on an ECG, QT interval corrected for heart rate
QTcF	on an ECG, QT interval corrected for heart rate using Fridericia's formula
RR	on an ECG, the time between QRS complexes
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDV	source data verification
SID	subject identification
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SpO_2	peripheral capillary oxygen saturation
SR	sinus rhythm
SUSAR	suspected unexpected serious adverse reaction
TDP	torsades de pointes
T_{max}	time at which C_{max} is observed
T_x	time point at time X
VT	ventricular tachycardia

IX. Introduction

1 Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice, with an estimated global prevalence of 33.5 million[5], and is projected to affect 3 million people in the United States by 2020[6]. Once a person reaches the age of 40 years, the lifetime risk of AF is 1 in 4[5]. In patients with AF, systemic thromboembolic events, hemodynamic instability, demand-induced ischemia, and ventricular arrhythmias contribute to a significant increase in morbidity, mortality and frequent hospitalizations.

Atrial fibrillation is classified into four different subtypes based primarily on the duration of the AF episodes[7-9]. Paroxysmal AF terminates spontaneously or with intervention within 7 days; episodes may recur with variable frequency. Persistent AF is sustained longer than 7 days and requires cardioversion to restore sinus rhythm (SR). Long-standing persistent AF has a duration of more than 12 months. The term permanent AF is used when there has been a joint decision by the patient and clinician to give up on attempts to maintain normal SR; acceptance of AF represents a therapeutic approach on the part of the patient and clinician rather than an inherent pathophysiological attribute of the AF.

The pathophysiology and mechanisms of AF are complex and multifactorial. Etiological factors associated with AF include hypertension, diabetes, heart failure, obesity, obstructive sleep apnea (major risk factor), coronary artery disease, ageing, and genetic predisposition. They contribute to a complex array of pathophysiological changes in the atrial myocardium, including stretch-induced atrial fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodeling, ischemia, ion channel dysfunction, and dysregulation of intracellular Ca^{2+} homeostasis. These changes enhance both ectopy and conduction disturbances, that increase the susceptibility of the atria to develop or maintain AF[8].

The management of AF depends on the type of AF, but the general objectives are to provide symptom relief, rate control (aimed at slowing the ventricular rate), and/or rhythm control (aimed at restoring SR), antithrombotic therapy (aimed at reducing risk of thromboembolic events, and treatment of the comorbidities. Due to its debilitating consequences, stroke prevention is critical. The choice of antithrombotic therapy is guided by risk factors for stroke, regardless of the presence or absence of symptoms or classification of AF. Currently, the CHA_2DS_2-VASc scoring system is used to determine both the need and the selection of anticoagulation strategies[7, 8, 9]. Selection of a primary therapeutic strategy of rhythm control or rate control is a multifactorial decision depending on the patient's age, symptoms, and importance of maintaining SR.

Current therapies for rhythm control include antiarrhythmic drugs (AADs), electrical cardioversion (ECV), or invasive electrophysiological procedures (e.g., AF catheter ablation). The efficacy, safety, tolerability and contraindications of the current therapeutic options have been extensively described in numerous reviews[10, 11] and in the relevant medical guidelines[8, 9]. With regard to the acute management of recent-onset AF, the current guideline recommendations are based on various factors that include the duration of the AF episode, the presence or absence of existent heart disease(s) such as ischemic heart disease, heart failure, left ventricular (LV) function, and the hemodynamic status of the patient[12].

For the acute management of AF, restoration of SR is a therapeutic choice in order to reduce symptoms, shorten hospitalization, and improve quality of life, with the long-term goal of preventing the detrimental effects of prolonged AF and avoiding subsequent hospitalization[13-17]. Both ECV and pharmacological cardioversion (PCV) are considered safe in patients in whom the AF episode duration is known to be less than 48 hours, or who have been previously maintained on oral anticoagulant therapy for at least 3 weeks. Electrical cardioversion is most effective but requires sedation or anesthesia, with the associated requirements for specialized medical personnel and appropriate facilities, and patients must be in a fasting state[8, 9, 14, 18]. In general, ECV is reserved for patients who are hemodynamically unstable and/or refractory to PCV[12]. The decision to use PCV is based mainly on whether or not the patient has demonstrable (moderate or severe) underlying cardiac disease (e.g., ischemic heart disease, HF, valvular heart disease, cardiomyopathy), and on the status of the LV systolic function[12]. Currently available oral and intravenous (IV) AADs for PCV are limited by their delayed onset of action, slow metabolism, and potential to cause hypotension and/or proarrhythmia, all of which may require or prolong hospitalization[8, 9, 13, 19, 20].

Approximately 60% of patients presenting with recent-onset AF in the Emergency Department (ED) in the US are admitted to the hospital (~ 300,000 patients per year [2014])[21]. This represents a major burden (resource utilization and costs) to the US healthcare system and has a significant negative impact on patient quality of life. Furthermore, because of the lack of an available pharmacological agent that is safe, effective and rapid-acting (minutes), requires minimal set up time and skills to administer, and a short monitoring time post-administration, PCV is not attempted in many patients whose AF could be successfully converted to SR. Thus, a pharmacological agent with the aforementioned properties would represent an important advancement in the acute management of patients with symptomatic recent-onset of AF presenting in the ED, which would also markedly reduce healthcare utilization.

1.1 Flecainide acetate

Flecainide is a potent cardiac sodium channel blocker that belongs to the AAD Class Ic. Flecainide has been in use since the mid-1980s for the management of patients with ventricular and atrial tachyarrhythmias[10]. Over the last three decades, a large body of clinical data and experience has been gathered using flecainide acetate. This data has strongly established

flecainide's efficacy and its safety profile[10, 11]. Both oral and IV flecainide are recommended by US and European Medical Society Guidelines as a first line therapy (class-1, level A) for PCV of recent-onset AF (< 48 hours' duration) in patients without structural heart disease[8, 9, 12, 22], although oral flecainide is not approved by health authorities for this use. The adverse effects of IV flecainide (2 mg/kg delivered over 10 minutes) when used according to guidelines for acute cardioversion of recent-onset AF are for the most part limited to the cardiovascular system and include rapid atrial flutter with 1:1 atrioventricular (AV) conduction and wide QRS complex, hypotension, and bradycardia.

Flecainide's inhibition of peak (transient) sodium current (peak I_{Na}) is responsible for slowing of electrical impulse conduction through the myocardium and specialized conduction system. This action of flecainide in the heart is detectable on a 12-lead ECG as dose-dependent prolongation of the PR and QRS intervals[23, 24]. The prolongation of the QTc interval by flecainide is relatively small (or not observed) and is mainly a consequence of the increase in QRS interval duration[10]. Thus, flecainide causes a small, generally insignificant prolongation of the JTc interval, a measure of ventricular repolarization[10].

The mechanism underlying the anti-AF activity of class Ic agents has been extensively investigated using various experimental cardiac preparations and models of AF[25-27]. Some key electrophysiological effects of flecainide that are likely to contribute to its anti-AF activity are: (1) induction of post-repolarization refractoriness (greater prolongation of atrial refractory period than the action potential duration [APD])[28], (2) decrease in excitability[29, 30], (3) rate-dependent prolongation of atrial refractoriness[31, 32], and (4) suppression of spontaneous diastolic SR Ca^{+2} release[33].

Class Ic AADs (such as flecainide) are also well known to be arrhythmogenic properties. The same or similar ion channel and electrophysiological effects that explain the therapeutic effects of flecainide are considered to be responsible for its proarrhythmic activity. The inhibition by flecainide of peak I_{Na} is exacerbated in depolarized myocytes and at high frequencies of depolarization (i.e., fast heart rates). Consequently, inhibition of peak I_{Na} in diseased myocardium may cause marked rate-dependent slowing of conduction and facilitate the initiation of re-entrant wave fronts around lines of functional conduction block such as infarcted or fibrosed tissue, leading to life-threatening ventricular arrhythmias and sudden cardiac death. It is important to recognize that the proarrhythmic effects of flecainide have been observed primarily in patients with ischemic heart disease, depressed LV function (e.g., HF), electrolyte disturbances, congenital (genetic) and acquired diseases/conditions resulting in conduction abnormalities. The results of the Cardiac Arrhythmia Suppression Trial (CAST)[34] demonstrated that flecainide, like other Class Ic AADS, caused serious malignant arrhythmias that led to a 3.6% (95% CI, 1.7 to 8.5) increase in risk of non-fatal cardiac arrest and death from arrhythmia compared to placebo. Due to this proarrhythmic potential, patients with depressed LV function, ventricular scar tissue and ischemic myocardium should not be treated

with flecainide. In addition, the negative inotropic effect of flecainide is greater in patients with LV dysfunction. Directly related to the proarrhythmic effects of flecainide caused by marked inhibition of peak I_{Na}, is the excessive widening of the QRS interval and/or slowing of the AV nodal conduction (PR prolongation or AV nodal block). These are important premonitory signs of the impending arrhythmogenic effects of flecainide.

Flecainide undergoes renal elimination[35] and CYP-mediated biotransformation. Hepatic oxidative metabolism via cytochrome CYP2D6 and CYP1A2[36] results in two major metabolites which display minimal/no cardiac activity. Both flecainide (~ 30%) and its major inactive metabolites are primarily excreted in the urine[37, 38]. Although the elimination half-life of a single dose of flecainide is likely to be increased in patients with severe renal and/or hepatic impairment, these conditions should not alter the initial C_{max} and tissue distribution kinetics of flecainide and are not likely to affect the pharmacodynamics associated with acute inhalation use.

1.2 Flecainide acetate inhalation solution (FlecIH)

An inhaled version of flecainide acetate is being developed for the acute conversion of recent-onset AF to SR in symptomatic patients without structural heart disease. The inhalation solution formulation for the 30 mg (35 mg/mL), 60 mg (35 mg/mL) and 90 mg (45 mg/mL) dose cohorts contained 90 mM acetic acid (FlecIH-101). To continue with dose escalation above the 90 mg dose cohort, e.g., 120 mg, the flecainide concentration in the inhalation solution was increased to 75 mg/mL by adding the excipient hydroxypropyl β-cyclodextrin in an acetic acid formulation, without (FlecIH-102) or with the addition of sodium saccharin (FlecIH-103). The current investigational product is the FlecIH-103 inhalation solution.

1.2.1 Non-clinical studies

The following non-clinical pharmacology studies in dogs and pigs have been completed for inhaled flecainide; they are:

- Pharmacokinetics (PK), pharmacodynamics (PD) and cardiovascular safety of intratracheal instillation of flecainide in pigs (study No: TRE-0022 and Study No. RPT-002)
- PK and PD of intratracheal instillation of flecainide in dogs (study No. SPD16-013)
- Cardiovascular Safety Pharmacology in dogs (Non-GLP study No. SPD12-003)

The two pilot PK studies in pigs and dogs mentioned above indicate that intratracheal instillation of flecainide can yield plasma concentrations within or in excess of the therapeutic concentration range of 200–1000 ng/mL[35]. In addition, the concentrations of flecainide achieved following intratracheal instillation are comparable to those observed when flecainide is given by the IV route (2 mg/kg infused over 10 minutes) for rapid cardioversion of AF.

In line with literature data[39, 40], a significant correlation between venous peak plasma concentrations of flecainide and the magnitude of the increases in QRS interval duration irrespective of the route of administration, either IV or intratracheal instillation, was observed. Moreover, there was a linear relationship between the peak plasma levels of flecainide and QRS interval durations pooled across the IV and intratracheal routes of administration with these two routes yielding equivalent relationships between peak plasma levels of flecainide and QRS interval durations.

The increase in QRS interval following intratracheal instillation of flecainide indicates that the plasma levels of flecainide achieved following pulmonary delivery are sufficient to elicit the expected "signature" pharmacologic effect of flecainide, consistent with inhibition of peak I_{Na}. More importantly, flecainide administered by intratracheal instillation at single or cumulative doses of 0.75 or 1.0 mg/kg was effective in rapidly (< 147 seconds) converting AF to SR in dogs. Flecainide administered by IV at doses 0.75–1.25 mg/kg was also effective in converting AF to SR, whereas administration of placebo vehicle (intratracheal or IV) to dogs had no effect on AF.

An additional non-clinical pharmacology study in pigs has been completed to evaluate the modified inhalation solution (FlecIH-102), containing hydroxypropyl β-cyclodextrin as an excipient. This PK and PD study comparing FlecIH-101 and FlecIH-102 inhalation solutions following intravenous infusion or intratracheal instillation in pigs (study No. RPT-002) revealed the following: the plasma-concentration-time profile and PD effects (electrocardiographic and hemodynamic) were comparable for the FlecIH-101 and FlecIH-102 inhalation solutions following IV infusion or intratracheal instillation showing that the addition of the cyclodextrin to the inhalation solution had no effect on the systemic distribution or pharmacologic activity of flecainide.

The following toxicology studies in rats and dogs have been completed for inhaled flecainide; they are:

- Maximum Tolerated or Maximum Feasible Dose of Flecainide in Rats by Nose Only Inhalation. Non-GLP study No. FY16-027A;
- Maximum Tolerated or Maximum Feasible Dose of Flecainide in Beagle Dogs by Face Mask Inhalation. Non-GLP study No. FY15-092A;
- 14-Day Repeated-dose Toxicity with 14-day Recovery and cardiovascular safety in Beagle Dogs via Face Mask Inhalation. GLP study No. FY15-092B and study No. FY19-020A;
- 14-day Nose Only Inhalation Toxicology Study in Rats with 14-day Recovery. GLP study No. FY16-027B, study No. FY19-019A, and study No. FY19-019B.

The results of the preclinical toxicology screening showed that flecainide administered via the lungs did not result in proarrhythmia, cardiac depression or hemodynamic instability; that is, no safety issues were observed. The initial 14-day toxicity study in dogs established a

No-Observed-Adverse-Effect-Level (NOAEL) dose of 8.03 mg/kg/day (FY15-092B). The initial 14-day rat inhalation toxicology study established a NOAEL dose of 28.7 mg/kg/day (FY16-027B).

Additional toxicology studies in dogs and rats were completed for inhaled flecainide using the modified inhalation solution formulation containing hydroxypropyl β-cyclodextrin (FlecIH-102), and using the inhalation solution formulation containing sodium saccharin (FlecIH-103). The results of the 14-day toxicity studies confirmed a NOAEL dose of approximately 9.87 mg/kg/day in dogs and of approximately 67.7 mg/kg/day in rats for FlecIH-102 (similar to that reported for FlecIH-101 in GLP study No. FY15-092B and FY16-027B, respectively) and provide a bridge to the non-clinical safety data obtained with the original acetic acid formulation. The additional excipient in the FlecIH-103 inhalation solution, sodium saccharin, was added to improve the sensory quality (organoleptic properties) of the inhalation solution. GLP study No. FY19-019B was conducted with the FlecIH-103 inhalation solution to bridge to the non-clinical safety data obtained with the FlecIH-101 and FlecIH-102 inhalation solutions and the results support its safety for clinical use. Sodium saccharin has been used previously in marketed inhalation solutions (see Investigator's Brochure [IB], Section 4.4.2.2.2).

Additional details on the non-clinical studies conducted are available in Section 4 of the IB[41].

1.2.2 Clinical experience

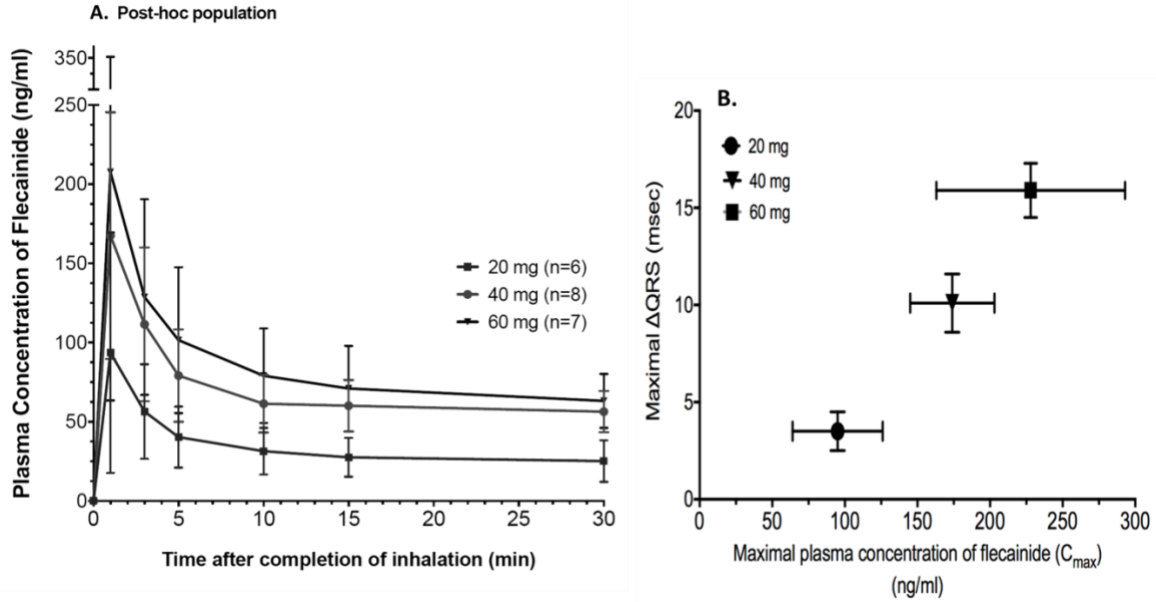
Two Phase 1 studies[41] have been conducted in healthy volunteers to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of inhaled flecainide, FLE-001 (completed), and FLE-003 (completed). FLE-001 was a single center study comprised of two parts: 1) a double-blind, randomized, placebo-controlled, three single ascending doses (20, 30 and 60 mg estimated total lung dose [eTLD]) part; and 2) an open-label, two period IV flecainide (2mg/kg ≈ 150 mg) vs. IH flecainide (30 mg eTLD) cross-over part. FLE-003 was a single center study comprised of two parts: 1) a double-blind, randomized, placebo-controlled, two single ascending doses (75 and 90 mg eTLD) part; and 2) an open-label, cross-over cohort comparing two different compressed air flow rates (8 vs 5 L/min) for delivering the aerosolized dose (90 mg eTLD).

In FLE-001, a total of 40 subjects completed the study; in the ascending dose first part of the study, subjects received doses of 20 mg (8 subjects: 2 placebo and 6 IH flecainide), 40 mg (14 subjects: 4 placebo and 10 IH flecainide), 60 mg (12 subjects: 3 placebo and 9 IH flecainide), and in the cross-over part, 6 subjects received 30 mg IH flecainide and 2 mg/kg (approx. 150 mg) IV flecainide infused over 10 minutes.

The results of the FLE-001 ascending doses study demonstrated that inhalation doses of flecainide, in the range of 30 to 60 mg, are safe, well-tolerated and delivers flecainide into the systemic circulation, within 1 to 3 minutes after the completion of inhalation, in sufficient

amounts to elicit the expected electrophysiological effect of flecainide, such as prolongation of QRS interval (**Figure 1**).

Figure 1. FLE-001 study: Single ascending inhaled flecainide doses



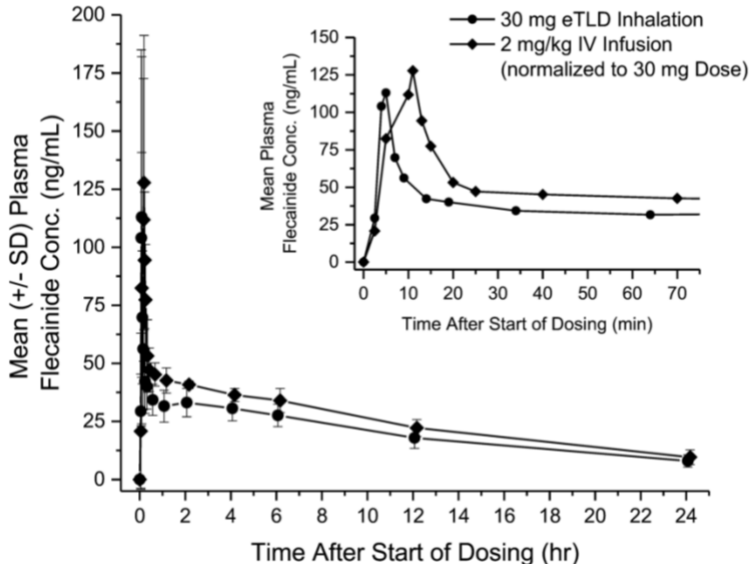
Panel A: Mean plasma flecainide concentration vs. time for 20, 40 and 60 mg eTLD of flecainide from the post-hoc dataset. Values are Mean ± SD.
Panel B: Relationship between peak venous plasma concentrations of flecainide (C_{max}) and the magnitude of maximal QRS prolongation. Data are from lead V4 of the 12-lead ECG recordings. Each data point represents the mean (± SEM) of the flecainide concentration (horizontal error bars) and QRS interval (vertical error bars).
The data in both these plots includes only the post-hoc population which excludes 4 subjects in which T_{max} was ≥ 15 min.

In both parts of the FLE-001 study, inhaled flecainide displayed a rapid distribution phase lasting ≈10-15 minutes, with an estimated $t_{1/2\alpha}$ of 3.5-4.2 minutes and elimination $t_{1/2\beta}$ of 9-12 hours. The distribution phase and elimination half-life were independent of the doses of inhaled flecainide whereas the C_{max} and AUC_{last} were dose-dependent. In the cross-over study, the distribution phase and elimination half-life were nearly identical for intravenous infusion and inhalation: 4.7±01.4 min and 10.0±1.8h for intravenous, and 4.3±1.5 min and 10.1±2.0h for inhalation. The relevancy of this finding is linked to the fact that flecainide given via IV at the approved dose of 2 mg/kg is an established agent for acute pharmacological cardioversion of recent onset AF (efficacious and safe dose).

In the FLE-001 cross-over study, a within subject comparison of the PK, PD, safety and tolerability of 30 mg eTLD of flecainide given via oral inhalation was made with that of a 10 min IV infusion dose of 2 mg/kg of flecainide (≈ 150 mg). To directly compare the PK profiles of flecainide given via IV infusion and oral inhalation, the mean ± SD plasma flecainide

concentration vs time for the IV dose was normalized to 30 mg in order to match the 30 mg oral inhalation dose (Figure 2). The resulting concentration-time profile curves are near-identical, indicating comparable pharmacokinetics by these two routes of administration. The results of the cross-over comparison between IV and inhaled flecainide also clearly demonstrated that the reported adverse events were far fewer and less intense following inhalation of a lower dose of flecainide (30 mg eTLD) than the 10 min IV infusion of 2 mg/ml of flecainide.

Figure 2. Venous plasma concentration- time curve following flecainide IV (normalized to 30 mg dose) and oral IH



Values are mean ± SD. Inset shows the first 70 minutes after start of dosing. The Least Square Mean C_{max} value for the IV infusion was 143 ng/ml and that for the inhalation was 102 ng/ml. Note that the estimated bioavailability of flecainide given via IH is ≈75% compared to the 100% given via IV.

The changes in heart rate (HR), arterial systemic blood pressure (BP), and pulmonary function test parameters associated with administration of flecainide or placebo were assessed. Transient (5 to 10 mins) increases in both HR and systolic and diastolic BPs were noted in subjects that were given inhaled flecainide and placebo. These changes were not dose-dependent, and are, in part, due to the sympathetic reflex responses associated with postural changes (from semi-recumbent to seated) and are also, likely, due to the oral inhalation procedure.

All standard lung spirometry measurements and peripheral oxygen saturations (pulse oximetry) values were normal before and after flecainide or placebo. No SAEs were reported and no subject had to interrupt the inhalation of flecainide acetate or placebo. The changes in vital signs (HR, BP, respiratory rate) and pulmonary function are described in detail in the IB (IB Section 5.2.1.2.3)[41].

Therefore, inhaled flecainide at eTLD ≥ 30 mg was found to yield venous plasma flecainide concentrations and cause QRS interval prolongation within the range, albeit in the lower end of the range, reported to convert AF to SR by IV flecainide[42-44]. Based on the PK and PD of flecainide reported in the literature, inhaled flecainide at eTLDs ≥ 30 mg are considered likely to be effective in converting recent-onset AF to SR within minutes of administration; the 30 mg dose was used as the starting dose for the INSTANT study.

The FLE-003 study consisted of two Parts. Part 1 of the study was a single-center, double-blind, randomized, placebo-controlled design. A total of 21 subjects were enrolled in Part 1 (of 2) with ascending eTLDs of 75 mg (6 subjects: 2 placebo and 4 IH flecainide) and 90 mg (15 subjects: 3 placebo and 12 IH flecainide). A dose-dependent increase in plasma flecainide concentrations was observed for the 75 and 90 mg eTLDs, along with a transient (~ 3 minutes) increase in QRS and PR interval durations. C_{max} values reported for the 75 mg and 90 mg doses were 301 ng/mL and 347 ng/mL, respectively; whereas, the mean maximum change in QRS interval were generally small and ranged up to 8 msec at the 90 mg eTLD. Part 2 was an exploratory, open-label study, in which 6 subjects (5 from Part 1 and 1 naïve subject received 1 or 2 doses of inhaled flecainide. The main goal was to compare the PK of a 90 mg eTLD given to the same subjects at two compressed air flow rates. There were no significant differences in C_{max} values following inhalation of the 90 mg dose using compressed air pressure of 8 L/min (340 ng/mL) or 5 L/min (313 ng/mL) in the same 5 subjects, indicating no clear trend for effect of compressed air flow rate on C_{max} (or any PK parameter). Overall, inhaled flecainide at eTLDs of 75 and 90 mg was safe and well tolerated. The most frequently reported adverse events were headache, oropharyngeal pain, and throat irritation; all adverse events were mild and resolved spontaneously, and no serious adverse events were reported.

Additional information on the results of the Phase 1 studies conducted are provided in Section 5 of the IB[41].

The results of the Phase 1 studies warrant further development of inhaled flecainide, i.e., justify a Phase 2 study in patients with recent-onset paroxysmal episodes of AF. The rationale and objectives for the development of this route of administration of flecainide are described below.

1.3 Rationale for the study

The aim of inhaled flecainide (in patients that have no contraindications for IV or oral flecainide) is the restoration of SR in symptomatic patients with recent onset AF (of < 48 hours) in a manner that is safe, rapid (in minutes) and convenient. Minimizing the time spent in AF is consistent with the concept that “sinus rhythm begets sinus rhythm” and may decrease the frequency of recurrences, and thereby slow/delay the progression of paroxysmal to persistent and/or permanent AF.

Part A - Initial data for inhaled flecainide suggest that cardioversion of subjects with recent onset of paroxysmal AF may be achieved within minutes with the possibility to eliminate the in-hospital administration in the long term. Before embarking on further stages of the clinical development plan for inhaled flecainide, it was important to ascertain that flecainide, at the dose and regimens to be tested, is well tolerated and that the study is feasible. Therefore, Part A of the current study was devised as an open-label, dose-escalation investigation to evaluate the feasibility and tolerability of several inhalation regimens of inhaled flecainide.
Although no conclusions about the effectiveness of inhaled flecainide can be drawn from the results of Part A, the aims of the study were to provide supportive data on the viability, acceptability and tolerability of the study design and procedures prior to proceeding into Part B to confirm the efficacy of the selected dose using an open-label study design.

Part B is an open-label multi-center design to confirm the safety (including tolerability) and to provide a more precise estimate of efficacy of the optimal inhaled flecainide dose regimen determined from Part A. The planned dose is an eTLD of 120 mg given as two sequential inhalations (repeat regimen, 2 x 60 mg eTLD = 120 mg eTLD). Subjects will 'dose/inhale to conversion'; dosing in a 'dose/inhale to conversion' regimen continues according to the assigned regimen until the conversion of AF to SR is observed for ≥ 1 minute, or until the assigned dose is completed, whichever comes first. The study drug is administered to subjects with a recent onset of symptomatic AF without relevant structural heart disease.

Part C (EU only) includes an open-label Patient-Led Under Medical Supervision Cardioversion Study, 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 a Medically-Led Cardioversion Study in Part C may be eligible to participate. Part C 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.

1.4 Rationale for dose selection

A 14-day repeat dose inhaled toxicology program has been conducted in rats and dogs. The study showed that inhaled flecainide resulted in no new or unusual toxicology associated with inhalation of flecainide compared with the marketed IV and oral flecainide dosage forms. The NOAEL weight-based doses were in excess of the proposed Phase 2 clinical doses of 30 mg, 60 mg, 90 mg, and 120 mg. The weight-based doses for inhaled flecainide assuming a 70 kg subject are also lower than the 2 mg/kg dose recommended for IV flecainide in the summary of product characteristics. The weight-based doses to be examined in this study are (assuming 70 kg subject): 0.43 mg/kg for 30 mg inhaled flecainide dose, 0.86 mg/kg for 60 mg inhaled flecainide dose, 1.29 mg/kg for 90 mg inhaled flecainide dose, and 1.71 mg/kg for 120 mg inhaled flecainide dose.

Based on the results of the FLE-001 and FLE-003 studies, the overall safety profile for doses of 20, 30, 40, 60, 75, and 90 mg of inhaled flecainide solution was favorable; adverse events (AEs) were transient and mostly mild in severity. The most frequently reported AE was oropharyngeal discomfort, a common side effect of medications administered via inhalation. However, none of the subjects discontinued the inhalation.

Doses of 30 mg (1 x 30 mg), 60 mg (2 x 30 mg), and 90 mg (2 x 45 mg) and 120 mg (2 x 60 mg) have been under evaluation in this study based on PK and PD data (QRS prolongation) from FLE-001 and FLE-003 showing that doses ≥ 30 mg had the potential to convert AF to SR. Part A concluded after enrolling 101 subjects, as follows: 10 subjects treated with 30 mg eTLD, 22 subjects treated with 60 mg eTLD, 21 subjects treated with 90 mg eTLD, and 48 subjects treated with 120 mg (19 with FlecIH-102 and 29 with FlecIH-103. Enrollment in the 120 mg dose cohort was completed on 05Mar2020 and Part A was concluded. The rate of conversion from AF to SR observed to date for the dose cohorts is as follows: 30 mg, 1/10 (10%); 60 mg, 6/18 (33%; 2 subjects were excluded from analysis as they were not in AF at time of dosing); and 90 mg, 7/21 (33%); For the 120 mg dose, the conversion rate was 7/17 (41%) for the FlecIH-102 cohort (2 subjects were excluded from efficacy analysis because they did not receive the full dose of study drug) and 13/27 (48%) for the FlecIH-103 cohort (2 subjects were excluded from the efficacy analysis because they did not receive the full dose of study drug).

The majority of subjects had AEs that were mild in severity and the most commonly reported AEs were those associated with the inhalation route of administration, e.g., cough and throat irritation. All non-serious AEs of bradycardia and hypotension were minor, transient and resolved without drug treatment. A total of four subjects experienced serious AEs (SAEs) that were considered possibly related to study drug by the Investigator or Sponsor. The SAEs considered related to inhaled flecainide included the following: two cases of prolonged sinus pauses at the time of conversion of AF to SR (one mild and one moderate, as per the Investigators), one case of bradycardia (severe, as per the Investigator), and one case of atrial flutter with 1:1 conduction with fast ventricular response (severe, as per the Investigator). All SAEs were transient in nature, resolved without intervention, and had no sequelae.

Based on the feasibility, safety, tolerability and efficacy results from Part A using the FlecIH-103 inhalation solution, Part B and Part C of the study will use the 120 mg dose of flecainide to further evaluate the cardioversion of recent onset AF.

1.5 Benefit/Risk assessment

This is the first study investigating inhaled flecainide acetate for acute conversion of recent onset of paroxysmal AF to SR. Based on the data from Part A of the study, the doses of flecainide acetate inhalation solution (30 mg eTLD, 60 mg eTLD [2 x 30 mg eTLD], 90 mg eTLD [2 x 45 mg eTLD], and 120 mg eTLD [2 x 60 mg eTLD]), were safe in 101 subjects. The 120 mg eTLD selected for Part B provides an acceptable benefit/risk in this population:

a) The potential cardiovascular risks of oral and IV flecainide are monitored closely in clinical studies of oral inhaled flecainide (AEs of special interest): ventricular tachycardia (VT), hypotension, bradycardia, sinus pause post conversion of AF to SR, and atrial flutter with 1:1 conduction with fast ventricular response (ventricular heart rate ≥ 200 bpm).
   i) Ventricular tachycardia (VT) is rare in subjects without structural heart disease, electrolyte disturbances and coronary artery disease. Ventricular proarrhythmia manifests either as monomorphic or polymorphic VT not only early but also late after the initiation of chronic therapy[34]. The incidence of VT in patients receiving flecainide for acute cardioversion of atrial fibrillation is less than 3%[45]. These potential risks have been mitigated by excluding subjects who have structural heart disease, myocardial ischemia, and LV systolic dysfunction, populations in which these adverse effects are more commonly encountered.
   ii) Due to a negative inotropic effect, flecainide is contraindicated in subjects with congestive heart failure and reduced LV ejection fraction (LVEF)[46, 47]. Therefore, these subjects have been excluded from the current study population.
   iii) Clinically significant slowing of electrical conduction have been reported with chronic oral flecainide therapy, including exacerbation/unmasking of conduction system disturbances, such as sinus node dysfunction (1.2%; i.e., sinus pause, sinus arrest or symptomatic bradycardia). Flecainide alone may cause bradycardia, second-degree AV block (0.5%) or third-degree AV block (0.4%).[48] Flecainide slows cardiac electrical conduction because it inhibits peak I_{Na}, which is the basis for the contraindication for its use in patients with conduction system disturbances.
   iv) Conversion of AF into atrial flutter, has been occasionally reported with flecainide, resulting in rapid ventricular rates (200 bpm) in cases of 1:1 atrioventricular conduction[49]. Although the frequency of this proarrhythmic effect is low (3.5% - 5.0%) and its occurrence has been associated with conditions whereby sympathetic (adrenergic) activity is increased[50], the potential risks have been mitigated by allowing concomitant use of drugs with atrioventricular nodal blockade properties, such as β-blockers, and calcium channel blockers, lowering the risk of rapid ventricular rate and atrial flutter.
b) Other AADs used as part of the standard of care for pharmacological cardioversion (e.g., flecainide, propafenone, ibutilide, and dronedarone), have a similar pattern of expected cardiac adverse effects.
c) The study is being conducted under cardiac monitoring in a hospital setting in order to safeguard subject safety.
d) The potential benefits of subjects in need of treatment for recent onset symptomatic AF, participating in this trial include:

i) Between approximately 1.25- to 2.5-fold lower dose for inhaled flecainide, than the maximum doses for either oral (300 mg) or IV (~150 mg) flecainide. The rationale for the potential efficacy of a lower dose with the oral inhalation route of administration may be due to:
   (1) Delivery to the site of action within minutes, given the proximity of the pulmonary venous circulation to the left atrium, and then to the coronary circulation without systemic circulation dilution;
   (2) C_{max} being achieved rapidly without the requirement for steady state plasma concentration to be reached.
ii) Rapid conversion of AF to SR, enabling a relatively short time period for medical monitoring/follow up.
iii) The duration of elevated plasma flecainide concentrations > 200 ng/mL, and consequent pharmacological effects of orally inhaled flecainide, are significantly shorter (~15 min for 120 mg eTLD) than those of IV flecainide (~ 120 min for ~150 mg dose). Therefore, the lower inhaled dose is expected to have fewer, milder, short-lived acute adverse effects and an improved overall safety profile.

Overall, the population selected for this study is appropriate for evaluation of the efficacy and safety of flecainide acetate inhalation solution for rapid cardioversion of recent onset symptomatic AF in patients with paroxysmal AF with disabling symptoms when the need for treatment has been established.

The available safety data for 30 mg, 60 mg, 90 mg, and 120 mg cohorts support the safety of treatment with the current dose of 120 mg eTLD (2 x 60 mg). A total of four SAEs that were considered possibly related to study drug by the Investigator or Sponsor have been reported; all were transient in nature, resolved without intervention, and had no sequelae (see Section 1.4, above). Based on the safety profile of inhaled flecainide observed in Part A, the Sponsor and DSMB have reviewed safety/tolerability, and determined that the 120 mg eTLD (2 x 60 mg) dose cohort is acceptable for continued use in Part B and Part C of the study.

X. Study protocol (PART A)

Part A was an open-label, multicenter design and studied the feasibility of administration of inhaled flecainide in four dosing regimens (30, 60, 90, and 120 mg). Part A included a randomized phase.

Part A was closed to enrollment on 05Mar2020, after a total of 101 subjects were treated with the study drug (10 with 30 mg, 22 with 60 mg, 21 with 90 mg, and 48 with 120 mg). The final dose in Part A (120 mg FlecIH-103) was selected as the dose to continue evaluating in Part B and Part C.

In this protocol version, Part A procedures have been removed for clarity. Preliminary Part A data are summarized in the IB[41].

XI. Study protocol (PART B)

2 B - Study objectives

2.1 B – Efficacy objective(s)

The efficacy objective is to evaluate the conversion of AF to SR and symptom relief by flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF.

2.2 B - Safety objective(s)

The safety objective is to assess the safety and tolerability of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF.

2.3 B – Pharmacokinetic (PK) and pharmacodynamic (PD) objective(s)

The PK and PD objectives in Part B include:

- To evaluate the PK of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF
- To evaluate the electrocardiographic effects (PD) of flecainide acetate inhalation solution in subjects with recent onset of paroxysmal AF

2.4 B - Exploratory objective:

The exploratory objective in Part B is to explore the feasibility of implementing the use of a portable cardiac ultrasound to record a diagnostic echocardiogram at screening. This is applicable to all US sites, and to select EU sites participating in the optional HHE Sub-Study.

3 B - Study design

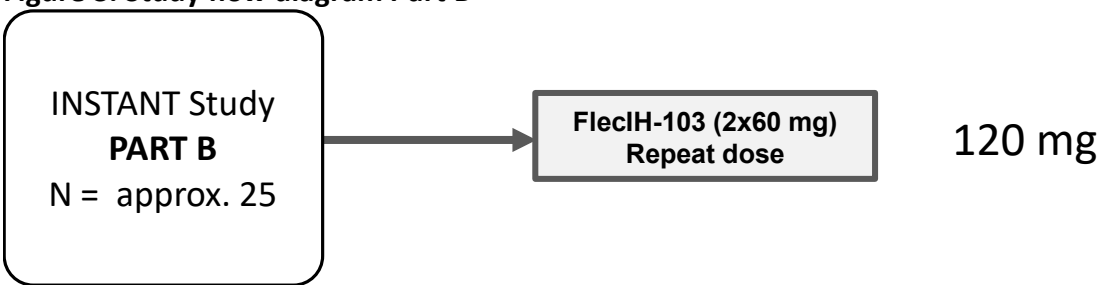
Part B is an open-label, multicenter design to confirm the safety (including tolerability) and efficacy of the optimal inhaled flecainide dose determined from Part A. Subjects are enrolled to receive a repeat dose regimen of 120 mg eTLD (2 x 60 mg) FlecIH-103 (N = approximately 25 subjects). The dose regimen is described in Section 5.1 B and 5.3.4 B.

The study design for Part B is described below in Figure 3. Subjects presenting with a symptomatic AF episode of recent onset (from 1 hour to 48 hours in duration) and without known relevant structural heart disease are candidates for the study. To qualify, subjects must also correspond to one of these categories: the first detected AF episode, a recurrent paroxysmal AF episode, or an episode post-cardiac ablation for paroxysmal AF.

Additionally, select subjects who may not be eligible to participate until a future date (e.g., not currently experiencing a symptomatic episode of paroxysmal AF) may sign a pre-study

screening consent to determine their eligibility to participate in the study by performing screening assessments (refer to Section 6.1.2.1 B).

Figure 3. Study flow diagram Part B



After written IC has been obtained for Part B, the subject is connected to cardiac telemetry and study ECG devices to evaluate the stability of AF during for at least 45 minutes prior to dosing (subject must remain predominantly in AF to be eligible for treatment with the study drug and must be in AF immediately prior to dosing).

The subject's right to early terminate inhalation of study drug, for whatever reason, shall not be infringed upon.

Enrollment (study drug allocation) occurs on Day 1 (day of dosing) and the start of the first inhalation is time zero (T_0).

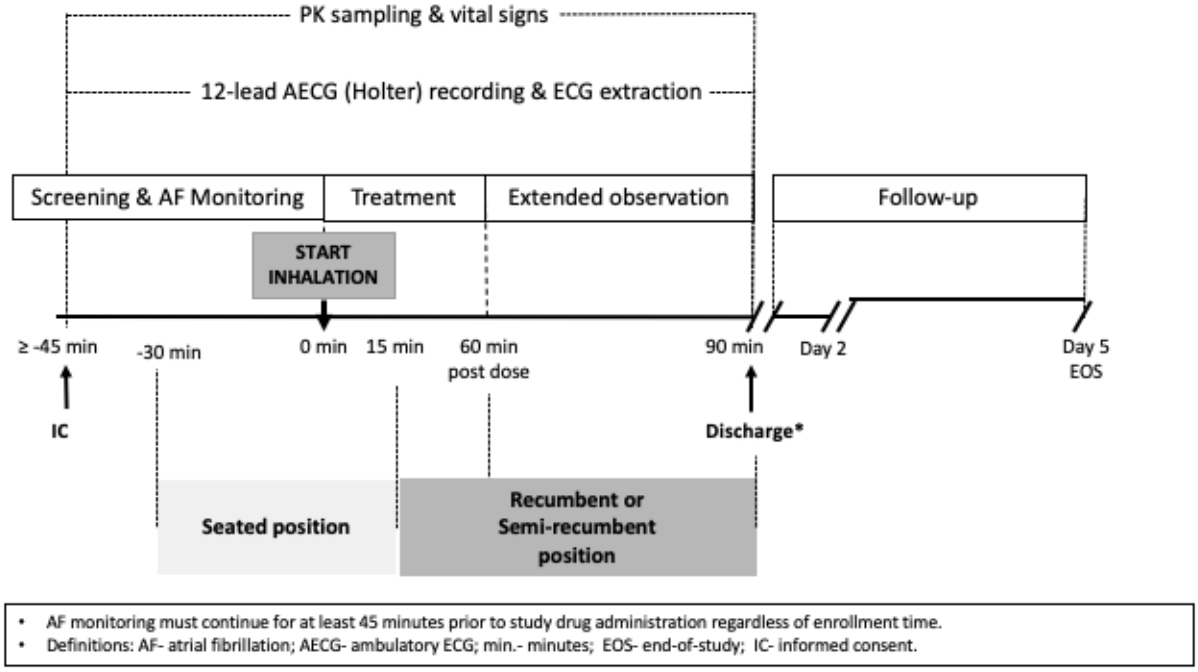
An overview of study assessments is shown in Figure 4. Vital signs, triplicate 12-lead ECGs, and blood samples for PK analysis are collected at multiple serial time points just before, during, and after the inhalation regimen, and at the time of conversion of AF to SR as detailed in the Schedule of Assessments. 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 of AF to SR and to monitor the safety of the study subjects. Time to discharge of the subject is left to the discretion of the treating physician but may not be scheduled prior to 90 minutes post dose (a — (minus) 10-minute window is allowed).

If conversion of AF to SR does not occur within 90 minutes post dose, the Investigator may offer another appropriate therapy, as per institutional standard, except for IV ibutilide, procainamide, or sotalol which are not allowed. See Section 5.4.2 B for specific requirements.

All subjects have a Day 2 (+1 day) and a Day 5 (± 1 day) telephone assessment (Visit 1 and Visit 2, respectively). ECG recordings are also obtained by the subject on Day 2 and Day 5 using an Event Recorder. All enrolled subjects are followed for 5 days and every effort shall be made to maintain the scheduled follow-up of the subject. 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.

Figure 4. Study assessments diagram Part B



The study organization is described in Section 17.3. An independent DSMB periodically reviews pertinent study data to protect the safety of the subjects participating in the study.

Part B and the Part C Medically-Led Cardioversion Study also include an optional sub-study (only at select EU sites): a Handheld Echo (HHE) Sub-Study, where subjects who consent will undergo an additional screening procedure that is a diagnostic echocardiogram using a portable HHE device. Details on the HHE Sub-Study can be found in Section 17.5.

Upon completion of Day 1 in Part B, EU subjects whose AF converted to SR with inhaled flecainide and without difficulties or issues with inhalation (in the opinion of the investigator), serious AE(s), or serious AESI(s) are potentially eligible to consent to participate in the Part C Patient-Led Under Medical Supervision Cardioversion Study.

4 B - Study population

In Part B, approximately 20 sites will participate to enroll approximately 25 subjects who have met all of the inclusion and none of the exclusion criteria as described under Sections 4.1 B and 4.2 B below.

4.1 B - Inclusion criteria

Subjects to be included in the study must meet the following inclusion criteria:

1) Subjects with recent-onset symptomatic AF at presentation.
2) With a duration at onset of symptoms from 1 hour to 48 hours
3) And from one of the following categories:
   a) First detected episode of paroxysmal AF
   b) Recurrent episode of paroxysmal AF
   c) Episode post-cardiac ablation for paroxysmal AF
4) **Part C Patient-Led Under Medical Supervision Cardioversion Study only**: Subjects whose AF converted to SR with inhaled flecainide and without difficulties or issues with inhalation (in the opinion of the investigator), serious AE(s), or serious AESI(s) in Part A, Part B, or the Part C Medically-Led Cardioversion Study

NOTE: Subjects who:

- are prescribed a pill-in-the-pocket regimen (flecainide or propafenone) for paroxysmal AF, or
- are within 3 months of having undergone ablation of paroxysmal AF, or
- have experienced an episode of new AF but are not currently experiencing an episode of recent-onset paroxysmal AF, or
- are known to have paroxysmal AF (or previously diagnosed with paroxysmal AF) and have one or more previous symptomatic episodes but are not currently experiencing an episode of recent-onset paroxysmal AF

may consent to pre-study screening prior to presenting with recent-onset symptomatic AF. These subjects will be eligible to receive study drug only when presenting with symptomatic paroxysmal AF of recent-onset (i.e., ≤ 48 hours), consenting to the full study, and after meeting all eligibility criteria.

4.2 B - Exclusion criteria

Subjects are NOT eligible to participate in this study if they meet ANY of the following exclusion criteria:

General

1) Subject < 18 or > 85 years of age
2) Hemodynamic and/or cardiac instability, with systolic blood pressure < 100 mmHg or > 150 mmHg, or ventricular heart rate < 80 bpm or > 160 bpm. For subjects to meet eligibility criteria for Part B or the Part C Medically-Led Cardioversion Study, at least 2 of the 3 measurements of vital signs during screening (45, 30, and/or 15 minutes prior to dosing) must meet the stated criteria. For subjects to meet eligibility criteria for the Part C Patient-Led Under Medical Supervision Cardioversion Study, the measurement of vital signs taken within 10 minutes prior to dosing must meet the stated criteria.

3) Current AF episode has been treated with Class I or Class III antiarrhythmic drugs or electrical cardioversion. Subjects whose current AF episode has been treated with flecainide are eligible if their total cumulative exposure to flecainide (including the study drug to be administered in this study) does not exceed 320 mg within a 24-hour period, per site standard of care.

Relevant structural heart disease

4) History of acute decompensated heart failure (HF)
5) Evidence of significant HF defined as any of the following:
   a) Hospitalization in the last 12 months for HF or suspected HF event
   b) Most recent assessment of left ventricular ejection fraction (LVEF) < 45%
      i) For patients in the US, a standard diagnostic echocardiogram assessed ≤ 180 days prior to screening is required to ascertain eligibility. If none is available, the patient must undergo a standard diagnostic echocardiogram or a diagnostic echocardiogram using a portable ultrasound device (handheld echocardiogram [HHE]) during screening to confirm eligibility.
      ii) For patients in the EU who are participating in the optional HHE Sub-Study, the patient must undergo an HHE during screening to confirm eligibility.
   c) New York Heart Association (NYHA) Class II-IV symptoms
   d) Medication history suggestive of HF per the Investigator's discretion
6) Evidence of current ongoing myocardial ischemia, such as signs (e.g., significant [e.g., > 2 mm] ST segment elevation or depression on ECG, echocardiographic findings suggestive of acute myocardial infarction), symptoms (e.g., angina pectoris, atypical angina pectoris), and/or being medicated with anti-anginal medication. In addition, subjects with signs of prior myocardial infarction (such as pathological Q waves) who are also taking concomitant medications for angina pectoris should be evaluated for presence of ongoing ischemia.
7) History of myocardial infarction (MI) within 3 months of screening
8) Known uncorrected severe aortic or mitral valve stenosis. For subjects receiving an HHE assessment at screening (refer to exclusion criterion 5), any moderate or severe valvular disease noted during the HHE assessment is considered exclusionary.
9) Hypertrophic cardiomyopathy with outflow tract obstruction. For subjects receiving an HHE assessment at screening (refer to exclusion criterion 5), any moderate or severe hypertrophy noted during the HHE assessment is considered exclusionary.

Other cardiac conditions

10) Current diagnosis of persistent AF
11) One or more episodes of atrial flutter within 6 months prior to screening or atrial flutter at presentation, except subjects who received ablation for atrial flutter at least 3 months prior to screening and had no subsequent recurrence of atrial flutter prior to screening

12) History of any of the following heart abnormalities:
    a) Long QT syndrome
    b) Conduction disease (e.g., second- or third-degree heart block, bundle branch block)
    c) Diagnosed with sinus node dysfunction (e.g., sick sinus syndrome) and/or one of the following:
    (i) history of unexplained or cardiovascular syncope,
    (ii) known bradycardia suggestive of sinus node dysfunction, and/or
    (iii) prior electrical or pharmacological cardioversion associated with prolonged sinus or ventricular pause (e.g., > 3 seconds) and/or slow ventricular rhythm (e.g., < 45 bpm) at time of conversion
    Note: Sinus node dysfunction in AF is more prevalent in patients >75 years old.[2]
    d) Brugada Syndrome
    e) Torsades de pointes (TdP)

13) Any of the following ECG-related features:
    a) QTc interval > 480 msec at screening (estimated by the Fridericia's formula[1])
    b) QRS duration ≥ 120 ms or history of previous documented wide QRS tachycardia
    c) Predominantly (i.e., > 30%) paced heart rhythm
    d) Ventricular tachycardia (VT, sustained or non-sustained), or excessive premature ventricular complexes (PVCs, > 20 multifocal PVCs per hour), prior to dosing as per site telemetry. Site telemetry should be equipped with an alarm system for VT and PVCs or be continuously visually observed prior to dosing

Concomitant conditions

14) Severe renal impairment (eGFR < 30 mL/min/1.73 m^2) or on dialysis
15) Known medical history of abnormal liver function prior to enrollment
16) Uncorrected hypokalemia (defined as serum potassium < 3.6 mEq/L) at screening. If serum potassium result is < 3.8 mEq/L at screening, therapeutic correction (e.g., potassium supplementation) is strongly encouraged, although reassessing the serum potassium level is not required as long as a value of ≥ 3.6 mEq/L is documented at screening.
17) Subjects with established pulmonary disease in need of inhalation medication. Subjects with COPD are excluded. Subjects with mild to moderate asthma that are not experiencing active symptoms at screening and whose asthma is well controlled with steroids and/or as-needed administration of a bronchodilator are eligible for the study.

Concomitant and study medication

18) Known hypersensitivity to flecainide acetate or any of its active metabolites
19) Concomitant therapy with systemic drugs that are strong inhibitors of CYP 2D6 (e.g. antidepressants, neuroleptics, ritonavir, some antihistamines) or CYP 2D6 inducers (e.g. phenytoin, phenobarbital, carbamazepine)

20) Treatment with Class I or Class III antiarrhythmic drugs within the last week. Subjects whose current AF episode has been treated with flecainide are eligible if their total cumulative exposure to flecainide (including the study drug to be administered in this study) does not exceed 320 mg within a 24-hour period, per site standard of care.
21) Treatment with amiodarone within the last 12 weeks

Other

22) Subject is deemed unsuitable for the trial by the Investigator (including but not limited to: patients who are considered at high risk for stroke based on medical history (e.g., CHA2DS2-VASc score); patients with congenital heart disease; patients with history of AF refractory to pharmacological or electrical cardioversion; patients whose AF is secondary to electrolyte imbalance, thyroid disease, or other reversible or non-cardiovascular cause; patients with any serious or life threatening medical condition; patients with any acute infection). The subject may be deemed unsuitable for the trial by the Investigator if the subject is not able or willing to inhale the study drug.
23) Known drug or alcohol dependence within the past 12 months as judged by the Investigator
24) A body mass index > 40 kg/m^2
25) Legally incompetent to provide informed consent (IC)
26) Previous treatment in this study (this does not apply to enrollment in the Part C Patient-Led Under Medical Supervision Cardioversion Study) or previous treatment with any other investigational drug within 30 days from screening or 5 half-lives of the drug, whichever is longer
27) Female of childbearing potential
    a) Who are not surgically sterile, or post-menopausal (defined as no menses for 2 years without an alternative cause), or
    b) For whom a negative pregnancy test is unavailable before study entry, or
    c) Who are pregnant or breast feeding at study entry
28) Previous administration of flecainide for an episode of paroxysmal AF or new AF did not result in conversion of AF to SR (i.e., subject is considered a non-responder to flecainide)
29) Cardiac surgery for any of the exclusionary conditions (e.g., valvular disease, hypertrophy, coronary artery disease [CAD], etc.) within the last 6 months prior to screening
30) Respiratory rate of > 22 breaths per minute

4.3 B - 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 to meet

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 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; refer to Section 5.5 B.

5 B – Treatment

5.1 B - Study treatments

Study treatment in Part B consists of a 120 mg eTLD (2 x 60 mg) FlecIH-103 inhalation solution repeat dose regimen. Specific instructions for the administration of study treatments are provided to the sites in the Instructions for Use (IFU). Also refer to Section 5.3.4 B for more treatment guidelines.

5.1.1 B - Repeat dose regimen

'Dose/inhale to conversion':
2 x 60 mg eTLD (FlecIH-103) for 120 mg eTLD (75 mg/mL concentration)

Dosing in a 'dose/inhale to conversion' regimen continues until the conversion of AF to SR is observed for ≥ 1 minute, or until the assigned dose is completed, whichever comes first.

5.2 B - Treatment assignment

After the IC has been signed, the investigational site enters the subject in the eCRF to obtain a unique subject identification number (SID) (if not already obtained during pre-study screening). Subjects may be enrolled at the end of the AF monitoring period provided they meet all the inclusion criteria and none of the exclusion criteria (note, AF monitoring must continue for at least 45 minutes prior to dosing, regardless of enrollment time).

Subjects are assigned to a 120 mg eTLD (2 x 60 mg) FlecIH-103 repeat dose regimen (N = approximately 25 subjects).

5.3 B - Identity of study drug(s)

5.3.1 B – Description

Study drug is supplied as a 4.7 mL of sterile FlecIH-103 (75 mg/mL flecainide acetate) in a 6-mL clear glass vial, with a grey rubber stopper, and sealed with an aluminum crimp.

5.3.2 B - Labeling and packaging

FlecIH-103 is labeled according to the requirements of local regulatory guidelines. Label text is approved according to the Sponsor's procedures. A description of FlecIH-103 is given in Table 1 below.

A system of numbering in accordance with all requirements of Good Manufacturing Practice (GMP) is used, ensuring that each dose of FlecIH-103 can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels are maintained by the Sponsor. A complete record of batch numbers and expiry dates of FlecIH-103 as well as the labels is maintained in the Sponsor's study file.

Table 1 - Identity of investigational drug: FlecIH-103

	75 mg/mL concentration
Active ingredient or INN	Flecainide acetate
CAS No.	54143-56-5
Material name	FlecIH-103 (flecainide acetate inhalation solution)
Dosage(s)	120 mg: 2 x 60 mg eTLD
Color of the vial	Clear
Composition	Active ingredient: Flecainide acetate Excipients: water for injection, Glacial Acetic Acid, hydroxypropyl β-cyclodextrin, Sodium Saccharin, and Sodium Hydroxide
Concentration	75 mg/mL
Type of packaging	Glass vial
Content	1 sealed vial of 4.7 mL

5.3.3 B – Preparation

The FlecIH-103 is supplied in glass vials. The clinical site will prepare the dose to be administered by withdrawing the required volume of the study drug from the vial(s) using a syringe with needle and then dispensing the study drug into the nebulizer cup(s). In order to maintain sterility, the study drug must be administered within 4 hours of dispensation into the nebulizer cup. Detailed instructions for dose preparation are outlined in the Pharmacy Manual.

5.3.4 B – Administration

Subjects will be dosed with 120 mg eTLD (2 x 60 mg) FlecIH-103 (75 mg/mL) inhalation solution: 2 inhalations of 3.5 minutes each, separated by a 1-minute break ('dose/inhale to conversion'). Dosing in a 'dose/inhale to conversion' regimen continues until the conversion of AF to SR is observed for ≥ 1 minute, or until the full dose is completed, whichever comes first.

For the administration of study drug, the following procedures are to be performed:

1. The subject must be seated in an upright position in a chair or adjustable bed from approximately 30 minutes prior to the start of inhalation up to completion of dosing, at which point subjects may return to a semi-recumbent position. A height-adjustable table must be placed in front of the subject (e.g., overbed table on casters), whereby the subject can rest his/her arms during the inhalation regimen. The set up at the site will allow for subject to remain in this upright sitting position while connected to the cardiac monitoring system and while blood samples are collected during the self-administration of the inhalation solution.
   NOTE: Subjects may be placed in a semi-recumbent, supine, or other position as needed for an adverse event, at the discretion of the investigator. These occurrences will not constitute a protocol deviation.
2. The subject is given instructions from study personnel on how to inhale the study drug according to the IFU.
3. The subject is required to use a nose clip to seal off their nostrils during inhalation, unless the subject refuses.
4. The subject may practice the inhalation procedure (without flecainide) prior to starting the inhalation of study drug.
5. The inhaler must be connected to medical compressed air that is set at a steady flow rate of 5 L/min.
6. The subject shall be informed prior to the start of the inhalation about the potential to experience throat discomfort, bad taste, and the impact of the sensation caused by the vapors being inhaled.
7. If not contraindicated, a topical oral anesthetic (e.g., containing lidocaine or phenol) spray (e.g., Medica, Chloraseptic) or lozenge (e.g., Trachitol, Cepacol) may be used by the subject to prophylactically mitigate the discomfort or pain associated with the inhalation and thereby improve the tolerability.
8. The subject inhales the study drug using a fully assembled AeroEclipse® II BAN provided by the study nurse.
9. Site staff shall closely observe the subject during inhalation to ensure that the subject only inhales and exhales through the mouth.
10. Once the inhalation rhythm is established, the subject should not remove the mouthpiece of the inhaler from the mouth during the entire inhalation time. If the subject removes the mouthpiece of the inhaler from their mouth for any reason/cause (e.g., cough, excessive saliva, etc.) and the inhalation is interrupted for > 30 seconds, then the inhalation time may be extended by the duration of the interruption if conversion of AF to SR is not achieved during inhalation. During the entire inhalation procedure, the nurses shall remain vigilant and ready to assist the subjects to successfully complete each inhalation period.
11. Once conversion of AF to SR is observed on telemetry, the time of the observation should be recorded as the time of conversion; however, the subject must continue dosing for at least 1 minute to confirm that SR is stable. If SR does not remain stable

for ≥ 1 minute, the subject should continue dosing according to the assigned regimen and conversion to SR will not be reported.

12. The subject's right to early terminate inhalation of study drug, for whatever reason/cause, shall not be infringed upon.
13. If a subject experiences difficulty in following the instructions for the inhalation procedure, this must be recorded in the eCRF along with the reason.
14. If an unexpected event is observed during the inhalation procedure, this event/observation must be recorded in the eCRF (e.g., liquid dripping from the inhaler, fugitive aerosol, etc.).

Additional instructions for the inhalation of the study drug are provided to the sites in the IFU.

5.3.5 B – Shipment, receipt and storage

When a drug shipment is received, the Investigator or designee must check the amount and condition of the drug, check for appropriate local language on the label, check the drug expiration date, and provide confirmation of receipt of the study drug. Problems with drug shipments must be reported to the site Monitor as soon as possible.

Drug supplies are stored at the investigational site in accordance with GCP and GMP and must be stored in a secure, limited-access storage area protected from light and under the recommended storage conditions. All drug supplies shall be stored at 15°C to 25°C (59°F to 77°F) as measured by a min/max thermometer. Excursions to 2°C to 40°C (36°F to 104°F) shorter than a week in duration are permitted. Excursions to 30°C at the site are allowed in accordance with USP <659> guidance. Temperature measurement shall be recorded daily on a temperature log, excluding weekends and holidays. The Sponsor must be notified as soon as possible in the event of any temperature excursion, with the exception of those permitted as described above. The site-relevant elements of special storage conditions, complete batch numbers, and expiry dates are available in the Investigator site file.

5.3.6 B - Drug accountability

Inhalation of study drug is performed under Principal Investigator (PI) or designee supervision. Pertinent information and data on the administration of study drug shall be captured by the site staff in the eCRF. All materials supplied, namely study drug and hand-held inhaler device (AeroEclipse® II BAN), are intended for use in this study only and shall not be used for any other purpose.

The PI or designated trained site staff are responsible for assuring the retrieval of all study supplies needed for the subjects. The pharmacy dispenses the study drug and the Investigator oversees the subject's inhalation and ensures the study drug is only administered according to the procedures described in this study protocol.

Study drug administration is documented in the relevant module of the eCRF and other study drug records. The PI at the site is responsible for oversight of the investigational product accountability, reconciliation and record maintenance at the investigational site. In accordance with all applicable regulatory requirements, the PI and/or designated trained staff at each site must maintain investigational product accountability records throughout the course of the study. The amount of investigational product received, administered to study subjects and unused must be documented in study records. Following drug accountability and reconciliation by the Monitor, destruction (if any) of study drugs must be properly documented according to the Sponsor's specified procedures. Re-supply of study drug is made upon request to the investigational product supply vendor. The drug accountability process is described in further detail separately in the Pharmacy Manual. Written instructions on medication destruction are made available to the clinical sites as applicable.

5.4 B – Non-study therapy

5.4.1 B - Prior and concomitant medication

Prior medications that the subject has taken within 30 days of enrollment and the subject's alcohol use are recorded in the eCRF. Medications taken by the subject prior to enrollment or at any time during the study, including adjunct therapy or medical devices, are regarded as prior and/or concomitant medications/treatments and must be documented on the appropriate pages of the eCRF throughout the study and until the final contact with the subject, i.e., EOS.

If the subject experiences an AE, information on concomitant medications taken within the past 30 days needs to be evaluated when considering causal relationship (Section 17.2.2.3).

The concomitant use of Class II and Class IV AADs, i.e. beta-blockers and calcium channel blockers *is allowed* throughout the study.

Concomitant use of the following therapies is *not allowed*:

- Treatment with Class I and any Class III AADs within 1 week before enrollment (except Amiodarone, which is not allowed within 12 weeks before enrollment);
- Concomitant pharmacological or electrical cardioversion up to 90 minutes post completion of dosing; refer to Section 5.4.2 B;
- Concomitant treatment with sotalol, procainamide or ibutilide is *not allowed* throughout the study;
- Concomitant systemic treatment with drugs that are strong inhibitors of CYP2D6 (e.g., antidepressants, neuroleptics, propranolol, ritonavir, some antihistamines) or CYP 2D6 inducers (e.g., phenytoin, phenobarbital, carbamazepine);
- Investigational drugs (other than the study treatment regimen)
- Bronchodilators from time of consent to start of inhalation of the study drug

5.4.2 B - Post-dose regimen therapy and medication

The Investigator may offer an alternative treatment after 90 minutes post dose, within the institutional standard of care and in accordance with Section 5.4.1 B above, to subjects without conversion of AF to SR. The choice of the treatment is guided by subject-specific factors and subject preferences and is left at the discretion of the treating physician and to subject's approval with the exception of sotalol, procainamide or ibutilide, which are not allowed throughout the study. Alternate therapy in accordance with the guidelines above may be given as early 60 minutes pose dose only if deemed medically necessary by the investigator not to wait until 90 minutes post dose; however, IV flecainide and propafenone may not be administered until at least 90 minutes post dose.

5.4.3 B – Other recommendations

Exercise: Subjects shall refrain from strenuous activity for the duration of the study (i.e., until completion of Day 5 assessments [EOS]).

Caffeine and alcohol: Subjects are instructed to abstain from caffeine and alcohol for the duration of the study (i.e., until completion of Day 5 assessments [EOS]).

Fasting: After providing IC, subjects should remain fasting in order to facilitate anesthesia care, if deemed necessary if no conversion to SR occurs within 90 minutes post dose. This is particularly relevant for sites that may consider performing an electrical cardioversion, as per their institutional standard of care.

5.5 B – Discontinuation Criteria

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. The subjects may be replaced and can re-screen for the study.

At any time during the study and without giving reasons, a subject may decline completion of the assigned study treatment. Study treatment may also be discontinued at the discretion of the Investigator as deemed appropriate for safety and/or if the subject's medical condition contraindicates further study treatment.

Follow-up and data collection continue until EOS for all enrolled subjects who received study drug, unless the subject explicitly withdraws consent for further clinical follow-up and data collection. If a subject withdraws consent for further collection of study data, their data up to that point are evaluated, and the reason for the termination is recorded in the eCRF. If termination of treatment or of clinical follow-up is a result of an AE or death, the AE must be recorded in the eCRF, including any changes in concomitant medications.

For subjects who cannot be located for their follow-up contacts, every reasonable effort must be made to make contact. The subject is considered "lost to follow-up" when contact with the subject has been lost without completing Day 5, and every attempt to contact has failed. Final documentation regarding all attempts to contact the subject shall be documented in the subject source records. All premature terminations of either study treatment or of clinical follow-up are tabulated and reported.

A subject's decision to withdraw from the study and/or to disallow further clinical follow-up is acceptable for any reason, without prejudice or detriment to their medical care, and the subject will not suffer any disadvantage as a result.

An excessive rate of subjects who withdraw consent or subjects lost-to-follow-up could render the study difficult to interpret. Hence, unnecessary withdrawal of subjects shall be avoided. Should a subject withdraw or be withdrawn, every effort must be made to contact the subject for a final follow up.

The Sponsor has the right to terminate the study, any part of the study, or the HHE Sub-Study at any time. In this event, the investigator(s) and relevant authorities will be informed of the reason for study termination.

6 B - Study procedures

The study is divided into the following periods: screening, treatment, extended observation, and follow-up. Subjects with an episode of recent onset, symptomatic AF (either their first episode, a recurrent episode of paroxysmal AF, or an episode post-ablation for paroxysmal AF) that requires acute conversion of AF to SR, without known relevant structural heart disease, and without contraindications to flecainide, are evaluated for potential participation in this study (included in screening). Additionally, select subjects who are not currently experiencing an episode of recent onset, symptomatic AF may sign a pre-study screening consent to determine their eligibility to participate in the study in the future (a recurrent episode of AF) by performing screening assessments (refer to Section 6.1.2.1 B).

Part B and the Part C Medically-Led Cardioversion Study also contain an optional Handheld Echo Sub-Study (only at select EU sites). Subjects who consent will have an additional screening procedure and will be evaluated with a portable ultrasound device to obtain an HHE. More details on the Handheld Echo Sub-Study can be found in Section 17.5.

All medications used in the study and the hand-held inhaler device are provided by the Sponsor. Details on drug accountability are provided in Section 5.3.6 B.

Windows for PK blood draws and vital signs assessments

Where PK blood draws and vital signs assessments coincide at scheduled time points, PK blood draws are prioritized and must occur at the protocol-specified time point (with the exception of the 60 minutes post dose time point, which may be collected within a ± 5-minute window, and the 90 minutes post dose time point, which may be collected within a ± 10-minute window). Vital signs shall be collected as close as possible to the scheduled time point after the PK blood draw is completed. As vital signs assessments coincide with PK blood draws, any deviations from the protocol-required time points for vital signs will not be recorded as protocol deviations. Any missed vital signs assessments will be recorded as protocol deviations.

Discharge window

Discharge is left to the discretion of the Investigator, but may not occur before 90 minutes post dose, with a -10-minute window allowed. Because discharge may occur, at the earliest, at 80 minutes post dose due to the window, all 90-minute post dose study assessments also have a ±10-minute window (may be performed between 80 and 100 minutes post dose, inclusive).

For the Schedule of Assessments please refer to Appendix 4.

6.1 B – Screening period

6.1.1 B - Screening

The Investigator or designee identifies patients who may be potential candidates for the study by reviewing:

- Recent history of paroxysmal AF;
- Other targeted medical/surgical history;
- Medication history over the past 30 days, including prescription drugs and alcohol use;
- Other inclusion and exclusion criteria assessable by routinely available clinical information.

This review is based on clinical information routinely available at the time of screening.

6.1.2 B - Informed consent (IC)

6.1.2.1 B - Pre-study screening IC (for select subjects)

Subjects who:

- are prescribed a pill-in-the-pocket regimen (flecainide or propafenone) for paroxysmal AF, or
- are within 3 months of undergoing ablation for paroxysmal AF but who are not currently experiencing an episode of recent-onset paroxysmal AF, or

- have experienced an episode of new AF but are not currently experiencing an episode of recent-onset paroxysmal AF, or
- are known to have paroxysmal AF (or previously diagnosed with paroxysmal AF) and have one or more previous symptomatic episodes but are not currently experiencing an episode of recent-onset paroxysmal AF

may sign a pre-screening consent to determine their eligibility to participate in the study by performing selected screening assessments. The selected assessments include a review of medical history to confirm that the subject does not meet certain exclusion criteria. The subject will also receive training and practice with the inhaler without any study drug. The subject may withdraw or be withdrawn from pre-study screening at any time.

The care of these pre-study screening subjects should be as per institutional standard of care. During the pre-study screening, to be eligible, subjects cannot be treated with Class I or Class III AADs within the last week, or with amiodarone in the last 12 weeks, as per the protocol (refer to Section 5.4.1 B). Subjects whose current AF episode has been treated with flecainide are eligible if their total cumulative exposure to flecainide (including the study drug to be administered in this study) does not exceed 320 mg within a 24-hour period.

The subject may use their own or a site-provided personal cardiac monitoring device to self-monitor for recurrence of AF as per institutional standard of care and if permitted by local regulations. Site staff is encouraged to contact the subject approximately monthly to review the subject's status. AEs will not be collected for pre-study screening subjects. If the subject returns to clinic for a visit with the Investigator (related or unrelated to the study), repeat training and practice with the inhaler should be performed if possible.

When the subject presents with recent-onset (≥ 1 to ≤ 48 hours) symptomatic AF, they may sign the IC for Part B and complete all remaining screening assessments (e.g., laboratory tests, AF monitoring, etc.) to determine eligibility criteria prior to study enrollment on Day 1. Only after confirming that they fulfill all the inclusion and exclusion criteria, may the subject be enrolled in the study to receive study drug.

6.1.2.2 B - Study IC (for all symptomatic subjects presenting with paroxysmal AF)

Signature of IC is always preceded by subject's qualification during screening which is based on clinical information routinely available. Only after the IC is signed does the subject undergo any study-specific procedures. Informed consent for Part B may only be obtained after the subject presents with symptomatic AF.

6.1.2.3 B - Handheld Echo Sub-Study IC

Only at select EU sites, subjects may consent to an optional Handheld Echo Sub-Study during screening on Day 1 after consenting to participate in Part B or the Part C Medically-Led Cardioversion Study. Refer to Section 17.5 for details on the Sub-Study.

6.1.2.4 B – Optional Part C Patient-Led Under Medical Supervision Cardioversion Study IC

Subjects in EU whose AF is converted to SR within 90 minutes of inhalation of study drug without an alternative therapy in Part B and who did not experience difficulties or issues with inhalation (in the opinion of the investigator), serious AE(s) or serious AESIs may be eligible for participation in the Part C Patient-Led Under Medical Supervision Cardioversion Study. Eligible subjects may consent to the study after successful conversion of AF to SR during Part B.

6.1.3 B - AF-monitoring

The AF-monitoring period is part of screening. The following procedures are performed by the Investigator or trained and qualified study staff after IC for the study has been obtained to determine subject eligibility for enrollment:

- A physical exam including auscultation of the heart and of the lungs is performed and height, weight, and temperature are recorded;
- A diagnostic echocardiogram is obtained using a handheld portable ultrasound device if:
  - (US subjects only) the subject does not have results from a standard diagnostic echocardiogram (including LVEF) within 180 days prior to screening
  - (EU subjects only) the subject has consented to the HHE Sub-Study;
- An IV catheter/cannula for blood sample draws is placed (please refer to detailed instructions of sample collection in the Laboratory Manual);
- Blood samples are drawn for clinical local laboratory assessment including: hematology panel, comprehensive metabolic panel, coagulation panel and a serum pregnancy test for women of childbearing potential (a urine pregnancy test may be collected instead of serum; see details under Section 9.2 B). A blood draw for assessment of potassium must always be drawn after informed consent and prior to enrollment; however, if results are available for any or all other parameters from a blood draw prior to screening (up to 24 hours prior to IC), there is no need for a new blood draw for those parameters;
- A single source for the time of all assessments shall be utilized for each patient. For example, if telemetry is used, all assessments for that patient must be recorded from the same telemetry unit. All times shall be reported in a 24-hour format. **NOTE:** The date and time displayed on study Holter monitor AECG must be set to

match the date and time of the device used for capturing the time of all assessments, for each subject;

- A baseline remote ECG event recording is obtained prior to connecting the subject to the AECG (12-lead Holter);
- The subject is connected to site cardiac telemetry and study AECG (12-lead Holter) approximately 45 minutes prior to the planned start of study drug administration, if not already connected;
- The subject is seated in an upright position approximately 15 minutes prior to the start of inhalation and after the 30-minute pre-dose time point assessments are completed (refer to Section 5.3.4 B);
  NOTE: For the medication to be effectively delivered into the lungs, the subject must be seated in an upright position;
  NOTE: When subject changes their position from seated to semi-recumbent or vice versa, the subject must be allowed time to stabilize in the new position for about 10 minutes for PD assessments;
- Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min) and oxygen saturation) are collected from telemetry at 45 (semi-recumbent), 30 (semi-recumbent), and 15 (seated upright) minutes prior to the start of study drug.
  - For vital signs where 3 measurements are required during screening, at least 2 of the 3 assessments during screening must be within the eligibility requirements. Additionally, these criteria shall be rechecked at T_0 for confirmation of eligibility prior to dosing. If the T_0 assessment is not within eligibility requirements, subject is not eligible to receive the study drug and will be early terminated.

Triplicate 12-lead ECG readings are extracted from the AECG (12-lead Holter) recording by the ECG Core Laboratory for the 45-, 30-, and 15-minute pre-dose time points after receipt of the data.

Adverse events and concomitant medications are continually assessed and recorded from time of IC through EOS.

6.1.4 B – Allocation

Refer to Section 5.2 B for a description of the treatment assignment process.

While the study drug is being retrieved, the Investigator or designee shall train the subject in the use of the inhaler (AeroEclipse II BAN) as described in the IFU. The subject shall remain seated in an upright position in a chair or adjustable bed with a height-adjustable table on wheels in front (e.g., overbed table on casters).

6.2 B – Treatment period

The Treatment Period comprises the time from T_0 (start of the first inhalation) to 60 minutes post dose.

6.2.1 B - Study treatment

Before dosing
The subject must be predominantly in AF (i.e., no other arrhythmias [e.g., VT, atrial flutter] and no conversion to SR ≥ 1 minute) during the 45-minute AF monitoring period. Once this is confirmed and just before the subject is ready to initiate the inhalation of the study drug (T_0), the following baseline measurements are performed:

- a PK blood sample is drawn (this may be drawn up to 45 minutes prior to initiation of study drug after enrollment);
- vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate [breaths/min] and oxygen saturation) are collected from telemetry;
  - If the T_0 vital signs assessment is not within eligibility requirements, subject is not eligible to receive the study drug and will be early terminated.
- The subject's AF-related symptoms are recorded;

Triplicate 12-lead ECG readings are also extracted from the AECG (12-lead Holter) recording by the ECG Core Laboratory after receipt of the data.

The Investigator or designee prepares the inhaler.

After completion of the baseline measurements as described above, the Investigator verifies whether the subject is still in AF. Study inhalation is not started in subjects who have spontaneously converted to SR or are in a heart rhythm other than AF.

During dosing
Subjects will 'dose/inhale to conversion'.

The following procedures are performed during the 1-minute break in between inhalations:

- a PK blood sample is drawn;
- Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min) and oxygen saturation) are collected from telemetry;
- Triplicate 12-lead ECG readings are extracted from the AECG (12-lead Holter) recording by the ECG Core Laboratory after receipt of the data.

Used inhalers are disposed according to local hospital procedures.

The Investigator may terminate the subject's inhalation of study drug earlier in the event of any clinically significant arrhythmias (e.g., bradycardia, frequent PVCs, non-sustained VT, or sustained VT or ventricular fibrillation [VF]) or other life-threatening or serious adverse reactions (e.g., hypotension). The subject may also stop the inhalation of study drug early as defined under Section 5.5 B.

No other pharmacological or electrical cardioversion may be attempted until at least 90 minutes post dose. Alternate therapy may be given as early 60 minutes pose dose only if deemed medically necessary by the investigator not to wait until 90 minutes post dose; however, IV flecainide and propafenone may not be administered until at least 90 minutes post dose. An exception to the above guidance is in case of an SAE, that requires an immediate treatment as per the discretion of the Investigator. Subjects remain on rhythm monitoring (i.e., cardiac telemetry and study AECG [12-lead Holter]) during dosing and for the entire duration of Day 1, including the observation period.

After dosing
After administration of the study drug regimen is complete, the following procedures are performed:

- a PK blood sample is drawn;
- vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min) and oxygen saturation) are collected from telemetry;
- Triplicate 12-lead ECG readings are extracted from the AECG (12-lead Holter) recording by the ECG Core Laboratory after receipt of the data.

The procedures above are performed at: T_X (1, 3, 10, and 30 minutes post dose) and at conversion to SR.

The subject may return to a semi-recumbent position after completion of dosing.

The subject's AF-related symptoms at 30 minutes post dose are recorded.

6.2.1.1 B - Subjects without conversion of AF to SR

The Investigator may offer an alternative treatment, within the standard of care, to subjects without conversion of AF to SR, in accordance with Section 5.4.2 B.

6.3 B – Extended observation period

The extended observation period starts at 60 minutes post dose and lasts until 90 minutes post dose. During this period, subjects remain connected to rhythm monitoring (i.e., cardiac telemetry and study AECG [12-lead Holter]).

After administration of the study drug regimen is complete, vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min) and oxygen saturation) are collected from telemetry at 60 and 90 minutes post dose.

Triplicate 12-lead ECG readings are extracted from the AECG (12-lead Holter) recording by the ECG Core Laboratory for the time points above after receipt of the data.

A PK blood sample is drawn at 60 and 90 minutes post dose.

A comprehensive metabolic panel blood sample is drawn for the clinical local laboratory assessment at 90 minutes post dose.

The subject's AF-related symptoms are recorded at 60 and 90 minutes post dose.

After 90 minutes post dose and prior to discharge, subjects whose AF converted to SR due to the study drug (converted within 90 minutes post dose without any alternative treatment) will be asked questions about their treatment satisfaction (refer to Section 7.4 B).

6.3.1 B - Discharge

Discharge is left to the discretion of the treating physician 90 minutes post dose (— (minus) 10-minute window). At discharge a plan for the Day 2 and Day 5 follow-up study contacts is made with the subject.

Once the study AECG (12-lead Holter) has been disconnected, a single reading using the remote ECG Event Recorder is performed. Before discharge, the Investigator trains each subject in the use of the remote ECG Event Recorder as described in Section 7.2 B.

The subject's primary care provider (PCP) is informed of the subject's participation in the trial by means of a letter from the Investigator. Information is included on the subject's treatment regimen as well as on specific clinical assessments (i.e., medical contacts for AF-related complaints) that must come to the attention of the investigational study center until EOS.

6.4 B - Follow-up period

6.4.1 B – Telephone assessment (Visit 1): Day 2

The following procedures are completed during a pre-scheduled Day 2 telephone contact:

- Review of concomitant medications/treatments;
- Assessment of AEs;
- Assessment of AF-status (any recurrence);
- Assessment of the status of the subject's AF symptoms;
- Reminder to the subject to collect a remote ECG recording.

6.4.2 B – Telephone assessment (Visit 2): Day 5 ± 1 day

Day 5 is the final subject contact and marks the EOS for Part B and may be completed within a ± 1 day window. The following procedures are completed during a pre-scheduled Day 5 telephone contact.

- Review of concomitant medications/treatments;
- Assessment of AEs;
- Assessment of AF-status (any recurrence);
- Assessment of the status of the subject's AF symptoms;
- Reminder to the subject to collect a remote ECG recording;
- Instruction of the subject to return the remote ECG device to the site using the courier service or return instructions provided.

6.4.3 B – End-of-study (EOS) definition

All subjects in Part B have a final visit (telephone contact) planned at approximately 4 days after enrollment (Day 5 = EOS). For EU subjects continuing into the Part C Patient-Led Under Medical Supervision Cardioversion Study, EOS occurs on Day 5 following treatment of a recurrent episode of AF, or 8 months following informed consent for the Patient-Led Under Medical Supervision Cardioversion Study, whichever comes first.

7 B - Efficacy assessments and endpoints

7.1 B – Rhythm monitoring assessments

Subjects are connected to the AECG system (12-lead Holter) after signature of IC is obtained and at least 45 minutes prior to dosing until 90 minutes post dose. Remote ECG Event Recordings are performed according to the Schedule of Assessments. Anonymized ECG recordings are analyzed centrally by the ECG Core Laboratory. Further detail may be found in separate instructions provided.

7.2 B – Rhythm status assessments

Remote ECG event recordings are performed according to the ECG Core Laboratory acquisition manual and following the study Schedule of Assessments.

- Recording #1: at the start of AF monitoring period before the AECG system is connected;
- Recording #2: at the end of the extended observation period after the AECG system is disconnected;
- Recording #3: on Day 2 (+1 day) at home (e.g., during the follow-up telephone assessment [Visit 1]);
- Recording #4: on Day 5 (± 1 day) at home (e.g., during the follow-up telephone assessment [Visit 2])

The site staff will train each subject in the use of the remote ECG Event Recorder according to separate instructions provided.

7.3 B - AF-related symptoms

Before enrollment, subjects are queried about the absence or presence of each of the following AF-related symptoms:

- Palpitations, i.e., sensation of a racing, uncomfortable, irregular heartbeat or a flip-flopping in your chest
- Lightheadedness or dizziness
- Shortness of breath or dyspnea
- Chest discomfort

At 30, 60, and 90 minutes post dose, subjects are again queried about each of these individual symptoms in terms of "no symptoms, improved, unchanged or worsened" as compared to baseline.

During the Day 2 and Day 5 telephone assessments, the subject is again queried on the status of each of these individual AF symptoms as compared to baseline.

7.4 B - Treatment satisfaction questions

After 90 minutes post dose and prior to discharge, subjects whose AF converted to SR due to study drug (i.e., converted within 90 minutes post dose without any alternative treatment) are asked the following questions regarding their treatment satisfaction:

- If offered, would you take the study treatment again in the future?
- On a scale of 1 to 10 (1 being very dissatisfied and 10 being very satisfied), how satisfied were you with the study treatment?

7.5 B - Study endpoint(s)

7.5.1 B - 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. Conversion of AF to SR is defined as the presence of SR lasting for at least 1 minute.

7.5.2 B - Secondary endpoints

The secondary efficacy endpoints are:

- 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 secondary safety endpoint is the incidence of treatment emergent serious adverse events of interest for flecainide

7.5.3 B - Exploratory endpoints

The exploratory endpoints (for the HHE) are:

- 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 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 if site staff made a successful assessment of subject eligibility using the HHE data obtained during screening.

8 B - Other assessments

8.1 B - Pharmacokinetic (PK) assessment(s)

Whole blood samples of about 4.0 mL are collected for measurement of plasma concentrations of flecainide acetate components as specified in the Schedule of Assessments (Section 17.4). Dense sampling occurs only over a 90-minute period on Day 1 (day of dosing).

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 shall 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 the study drug regimen is complete: T_x (1, 3, 10, 30, 60 and 90 minutes post dose).

When time points coincide for blood draw and vital signs assessments, procedures should be performed in said order.

Instructions for the collection, processing, storage and shipping of biological samples are provided in the Laboratory Manual.

Plasma samples are assayed by a validated LC/MS/MS method, which is specific for the determination of flecainide acetate components and used to evaluate the PK parameters.

No genetic analyses are to be performed on these plasma/whole blood samples.

Subject confidentiality is maintained at all times.
The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) are informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the IC.

8.2 B - Pharmacodynamic (PD) assessment(s)

To evaluate the electrocardiographic effects of inhaled flecainide under oral inhalation dosing regimens in subjects with recent onset of paroxysmal AF, which are detectable on 12-lead ECG recordings mainly by assessing the following PD variables: PR, QRS, and QT intervals.

ECGs are reviewed by an independent ECG Core Laboratory. Triplicate ECGs will be extracted from the recorded AECG (Holter) data transmitted by the site to the ECG Core Laboratory according to the Schedule of Assessments (Section 17.4). 12-lead ECGs will be extracted at or after each specified time point (up to 5 minutes after the specified time point or up to the next scheduled time point, whichever comes first). The triplicate 12-lead ECG extractions are over-read on the same lead by the same ECG Core Laboratory reader.

Extraction time points 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}
5. After administration of study drug regimen is complete: T_x (1, 3, 10, 30, 60, and 90 minutes post dose)

Details of the ECG Core Laboratory analyses are included in the Core Laboratory analysis plan. At a minimum, the following ECG parameters are determined for each ECG recording:

- Heart rate (HR)
- RR interval
- PR interval
- QRS duration
- QTcF duration
- JTc duration (QTc-QRS)

ECGs extracted from the 12-lead Holter are provided to Investigators for filing in the subject's source records. Any original ECG recordings obtained at the site must also be stored in the subject's source records.

9 B - Safety evaluation and reporting

9.1 B - Adverse events

Refer to the definitions for AEs and SAEs in Section 17.2.1. 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.

Safety and tolerability of inhaled flecainide is further evaluated by collection of the following measurements performed according to the Schedule of Assessments (Section 17.4):

- Monitoring of AEs, SAEs and AEs/SAEs of special interest (AESIs/SAESIs)
- Physical examinations
- Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate and oxygen saturation)
- Routine ECGs or 10-second printouts of telemetry rhythm strip performed for safety purposes are printed and reviewed on-site
- Continuous telemetry
- Pulmonary function by lung auscultation and oxygen saturation
- Clinical local laboratory assessment (including hematology, comprehensive metabolic and coagulation panel)

Recurrent AF will not be considered an AE as it is an expected event in this patient population. Recurrence of AF will be captured in a separate eCRF.

9.1.1 B - Adverse event collection and reporting

All AEs occurring after signature of the study IC and until the EOS are recorded in the eCRF according to the definitions and classifications described under Section 17.2.1. All AEs must be recorded and reported, including AEs that occur during the administration of other drugs. Even if the subject has not yet received the study drug, untoward medical occurrences shall be treated as AEs. After the EOS contact, there is no requirement to actively collect AEs, including deaths.

All laboratory results and vital signs are to be evaluated by the Investigator for clinical significance. Isolated abnormal laboratory results or vital signs findings that are not part of a diagnosis and are considered clinically significant shall be reported as AEs. Medical conditions (including laboratory values/vital signs that are out of range) that were diagnosed or known to exist prior to IC are recorded as medical history.

Adverse events may be directly observed, reported spontaneously by the subject, or reported by the subjects after being questioned by study staff. Holter, ECG and Event Recorder reports may also be used as source to identify AEs. Subjects shall be questioned in a general way, without asking about the occurrence of any specific symptoms. The Investigator must assess all AEs to determine seriousness, severity, and causality, in accordance with the definitions in Section 17.2.1. The Investigator's assessment must be clearly documented in the site's source documentation with the Investigator's signature.

All SAEs recorded on the AE eCRF page, that meet seriousness criteria (see Section 17.2.1.2) or that meet the criteria for AESI (serious or non-serious; see Section 9.1.2 B) must be reported within 24 hours of the Investigator's awareness. If all the required information is not available, the information which is available is to be recorded without delay (within 24 hours), and the outstanding data recorded as soon as available thereafter. Responses to queries related to the reported SAE or AESI must be provided as soon as possible.

In case of an occurrence of an AE, the Investigator must ensure appropriate medical treatment and shall decide whether to discontinue or interrupt the study drug, as applicable.

For each SAE, a separate assessment for expectedness, seriousness, and causal relationship to study drug is performed by the Sponsor in addition to the assessment from the Investigator.

The Investigator is responsible for continuous monitoring of all SAEs (whether or not related to study drug) until resolution or until the event is considered chronic and/or stable by the Investigator and/or other physician who has the responsibility for the subject's medical care. Follow-up SAE reports are reported according to the same timelines as initial reports, as soon

as new significant information becomes available and within 24 hours of the Investigator's awareness of the event.

For all EU subjects who consent to the Part C Patient-Led Under Medical Supervision Cardioversion Study, AEs will continue to be collected until the subject withdraws or is withdrawn, or until EOS (Day 5 after treatment for a recurrent episode of AF or 8 months after signing informed consent for the Part C Patient-Led Under Medical Supervision Cardioversion Study, whichever comes first).

9.1.2 B - Events of special interest

The following AESIs (even if classified as non-serious) will be reported *within 24 hours of the Investigator's awareness* by recording them on the AE page of the eCRF.

9.1.2.1 B – AEs related to inhalation device

Events related to the inhalation device (AeroEclipse® II BAN) are considered AESI. All AEs related to inhalation device are followed to conclusion to determine their outcome. Inhalation devices associated with AESIs are to be retained and returned to the Sponsor for further evaluation as appropriate.

9.1.2.2 B - Pregnancies

Any female study subject or female partner of a study subject that becomes pregnant while participating in this study must be reported within 24 hours of the Investigator's awareness. All pregnancies must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. The Investigator shall contact the Medical Monitor to discuss subject management.

9.1.2.3 B - 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. These events will be monitored closely and will be followed to conclusion to determine their outcome.

- 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 pause 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)

9.1.2.4 B – Serious Adverse Events of Special Interest (SAESI)

The following potential SAESIs are defined for study purposes:

- Hypotension, 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, 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), and requiring pacing or a 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), 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

9.1.3 B - Notification to Regulatory authorities, Investigators and IRBs

Detailed SAE processing, distribution and reporting is provided in the Safety Management Plan. Sponsor and/or CRO(s) inform Investigators, IRBs/IECs and regulatory authorities of any Suspected Unexpected Serious Adverse Event Reactions (SUSARs) occurring in the study or other Sponsor studies of the investigational product, as appropriate per local reporting requirements.

9.2 B – Clinical local laboratory assessments

Blood samples for determination of the hematology panel, the comprehensive metabolic panel and the coagulation panel are taken at the times indicated below and in the Schedule of Assessments. No fasting is required.

Sample collection times are as follows:

- During screening, approximately 45 minutes preceding initiation of study drug. Note, a blood draw for assessment of potassium must always be drawn after informed consent and prior to enrollment; however, if results are available for any or all other parameters from a blood draw prior to screening (up to 24 hours prior to IC), there is no need for a new blood draw for those parameters.
- At 90 minutes post dose

The following laboratory safety variables are measured and analyzed at the local laboratory:

Hematology panel: performed at screening and may include some or all of the following parameters (use the site's standard hematology panel, also known as complete blood count with differential):

- 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)
- White blood cell (WBC) count
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelet count
- Mean platelet volume (MPV)

***Comprehensive metabolic panel (CMP)*:** performed at screening and at 90 minutes post dose and may include some or all of the following parameters (use the site's standard comprehensive metabolic panel):

- Glucose and calcium
- Kidney function tests (serum creatinine*, to derive the estimated creatinine clearance [mL/min/1.73m^2], and blood urea nitrogen [BUN])
- Proteins (total protein and albumin)
- Electrolytes (potassium*, sodium, chloride, bicarbonate)
- Liver function tests (total bilirubin [TBL], conjugated bilirubin [e.g., if TBL is elevated], aspartate aminotransferase [AST], alanine aminotransferase [ALT], and alkaline phosphatase [ALP])

* = parameter is required for evaluation of eligibility and must be collected at screening

Coagulation panel: performed at screening and includes at least of the following parameters (use the site's standard coagulation panel):

- Partial thromboplastin time (PTT)
- Prothrombin time (PT)
- Thrombin time (TT)
- Fibrinogen

Pregnancy: female subjects of childbearing potential that undergo screening after IC signature need to have either a serum or urine pregnancy test.

Laboratory reports are filed with the source documents. The Investigator must review the laboratory reports, document this review, and record any clinically significant abnormal laboratory results occurring during the study as adverse events. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject's management or are considered clinically significant by the Investigator, then the results must be recorded in the eCRF.

9.2.1 B - Total blood volume

Blood samples for PK analysis (Section 8.1 B) and for laboratory safety assessments (Section 9.2 B) are collected for each subject periodically on Day 1, resulting in the following total blood volume, in mL, per subject per assessment type:

- Pharmacokinetic assessments (a maximum of 9 samples of 4.0 mL)	36.0 mL
- Clinical local laboratory assessment (screening)	12.5 mL
- Clinical local laboratory assessment (discharge)	7.0 mL
Total	55.5 mL

The total blood volume of 55.5 mL corresponds to approximately 3.75 tablespoons.

9.3 B - Vital signs

Heart rate, systolic and diastolic BP, respiratory rate (breaths/min), oxygen saturation (SpO_2), and body temperature are recorded from the cardiac telemetry monitoring according to the Schedule of Assessments (Section 17.4). Body temperature is only recorded at screening.

When time points coincide for blood draws and vital signs assessment, blood draws will be performed prior to vital signs assessments.

9.4 B – Other electrocardiograms

Other original routine ECGs obtained at the site or printouts of the telemetry rhythm strip performed according to local clinical practice are stored in the subject's medical record as source documentation.

9.5 B - Physical examination

A physical examination is performed by medically qualified individuals. The targeted examination includes general appearance, cardiovascular, respiratory (including lung auscultation), abdomen (liver and spleen) and neurological evaluations. Results are recorded as normal or abnormal per evaluation with a listing of abnormalities in the eCRF. Height, weight and derived BMI are also measured and recorded in the eCRF at screening.

9.6 B - Handheld echocardiogram (HHE)

To evaluate the subject's eligibility during screening (e.g., LVEF, valvular disease, structural heart disease), a diagnostic echocardiogram with a Sponsor-provided handheld portable ultrasound device will be required at screening for US subjects if the subject does not have results from a standard diagnostic echocardiogram (including LVEF) within the 6 months prior to screening. For information on the HHE Sub-Study available to EU subjects, refer to Section 17.5.

The following data will be recorded from the HHE in the eCRF:

- Date and time HHE is administered
- Who performed the HHE (e.g., professional title or study role)
- Date and time HHE report/results became available
- Who analyzed the echocardiogram obtained (e.g., professional title or study role)
- The following assessments will be recorded:
  - LV size
  - LVEF
  - LV hypertrophy
  - Valvular disease
  - Other clinically significant findings

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 Part B subject eligibility during screening. This independent review will only be used to explore if site staff made a successful assessment of subject eligibility using the HHE data obtained during screening.

10 B - Statistical methods

Statistical analyses for Part B will apply to all Part B subjects, including those EU subjects participating in the Handheld Echo Sub-Study (refer to Appendix 6). Data from the HHE Sub-Study are collected on a subset of the Safety Population for Part B and the Part C Medically-Led Cardioversion Study. The analysis for the additional echocardiogram data measured will be separate from the safety analyses of all Part B subjects and Part C subjects in the Medically-Led Cardioversion Study.

10.1 B - Study populations

10.1.1 B - Population of consented subjects

The population of consented subjects includes all subjects who signed the informed consent form.

10.1.2 B - Intention-to-treat population (ITT)

The intention-to-treat (ITT) population includes all subjects that were enrolled. Compared to the population of consented subjects, the ITT population excludes subjects who are not enrolled. The population does include subjects who were enrolled when re-entering the study for a new episode of AF.

10.1.3 B - Modified ITT population (mITT)

The modified ITT population includes all enrolled subjects who received 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.

10.1.4 B - 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.

10.1.5 B - Safety population

The Safety population includes all enrolled subjects who started the inhalation of study drug, whether the subject was in AF or not and whether the subject received the full assigned dose of study drug or not. Compared to the ITT population, the Safety population excludes subjects who are enrolled but did not start of the inhalation of study drug.

10.2 B – Statistical analyses

The primary endpoint analyses of Part B will be based on Part B subjects alone. If the Part B primary endpoint analysis meets the pre-specified criteria for significance and is not substantially different from Part A 120 mg FlecIH-103, the two dose cohorts (120mg FlecIH-103 cohorts from Part A and Part B) will be combined for the overall analysis of Part B to provide a more precise estimate of efficacy, safety, and PK/PD.

This protocol provides general aspects of the statistical methods. Specific details are outlined in the Statistical Analysis Plan (SAP).

10.2.1 B - Efficacy analyses

Modified ITT population
The mITT population will be used to evaluate all primary and secondary efficacy endpoints.

Statistical analyses of secondary efficacy endpoints
Hierarchical testing and adjustments for multiplicity will not be applied in the evaluation of efficacy.

10.2.1.1 B - Statistical analysis of the primary efficacy endpoint

The endpoint of conversion to SR is defined as the presence of SR, derived from the AECG, lasting for at least 1 minute. The first conversion to SR that lasts for at least 1 minute is referred to as the index conversion. Any conversion not lasting for at least 1 minute is not considered an index conversion.

The conversion rate (%) of recent onset of AF to SR, within 3 hours, ranges from 2 – 14% spontaneously[22] and with placebo[51, 52] approximately 16%[3]. In more recent studies such as those with vernakalant, the reported placebo conversion rate was ~5%[4]. For this study, we have selected a somewhat higher placebo conversion rate of 20%. In order to statistically evaluate whether the proportion of subjects whose AF converted to SR by inhaled flecainide within 90 minutes after initiation of dosing is > 20%, the following hypotheses are evaluated at a one-sided significance level of 0.05:

$H_0 : \rho = 20\%$

The one-sided alternative hypothesis is:

$H_A : \rho > 20\%$

The null hypothesis is tested with the use of an exact binomial test. A 90% Clopper-Pearson confidence interval is computed for the proportion of subjects who met the primary endpoint. If the lower bound of the 90% confidence interval is > 20% then the null hypothesis is rejected in favor of the alternative, i.e. there is sufficient evidence to conclude the percentage of subjects AF converting to SR is > 20%.

10.2.1.2 B - Statistical analysis of proportion of subjects who convert within 90 minutes after initiation of dosing and have C_{max} values ≥ 200ng/mL (e.g., 200, 300, 400, and 500 ng/mL)

This endpoint is defined as the number of subjects who meet the endpoint criteria, divided by the total number of subjects included in the analysis. The estimate for the conversion rate and its associated 95% Clopper-Pearson CIs will be derived.

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., oral flecainide).

10.2.1.3 B - Statistical analysis of time-to-conversion to SR from initiation of dosing up to 90 minutes after initiation of dosing

The cumulative incidence function for the time to conversion from initiation of study drug up to 90 minutes after initiation of dosing will be determined via Kaplan-Meier methods as described in the SAP.

10.2.1.4 B - 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 Event Recorder, in which the subject's heart rhythm is recorded. A subject is considered in SR on Day 2 if the remote ECG recording at the intended time shows SR. 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 and its associated 95% Clopper-Pearson CI will be derived.

10.2.1.5 B - The proportion of subjects with reduced or no AF symptoms at 30 minutes post dose

A subject is considered to have reduced or no AF symptoms at 30 minutes post dose based upon patient-reported outcomes (reported as either 'no symptoms' or 'improved').

The evolution of symptoms (no symptoms, improved, unchanged or worsened) is a categorical variable that will be summarized by the frequency and proportion of subjects within each category. The estimate for the proportion and its associated 95% Clopper-Pearson CI will be derived.

10.2.1.6 B - The proportion of subjects with reduced or no AF symptoms at 60 minutes post dose

A subject is considered to have reduced or no AF symptoms at 60 minutes post dose based on patient-reported outcomes (reported as either 'no symptoms' or 'improved').

The evolution of symptoms (no symptoms, improved, unchanged or worsened) is a categorical variable that will be summarized by the frequency and proportion of subjects within each category. The estimate for the proportion and its associated 95% Clopper-Pearson CI will be derived.

10.2.1.7 B - The proportion of subjects with reduced or no AF symptoms at 90 minutes post dose

A subject is considered to have reduced or no AF symptoms at 90 minutes post dose based on patient-reported outcomes (reported as either 'no symptoms' or 'improved').

The evolution of symptoms (no symptoms, improved, unchanged or worsened) is a categorical variable that will be summarized by the frequency and proportion of subjects within each category. The estimate for the proportion and its associated 95% Clopper-Pearson CI will be derived.

10.2.1.8 B - Descriptive statistics of proportion of conversion to SR within 90 minutes after initiation of dosing without AF recurrence requiring electrical or pharmacological cardioversion or rate control intervention up to discharge

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.

The 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.

10.2.1.9 B - The proportion of subjects in SR on Day 5

The rhythm status used for the evaluation of this secondary efficacy endpoint is derived from the remote ECG Event Recorder, in which the subject’s heart rhythm is recorded. A subject is considered in SR on Day 5 if the remote ECG recording at the intended time shows SR. 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 estimate of the proportion and its associated 95% Clopper-Pearson CI will be derived.

10.2.2 B - Safety analyses

The safety of inhaled flecainide is evaluated by collection of the following measurements performed according to the schedule of study assessments:

- Monitoring of AEs, SAEs, AESIs, and SAESIs;
- Physical examinations;

- Vital signs (heart rate, systolic and diastolic blood pressure, respiratory rate and oxygen saturation);
- Routine ECGs or 10-second printouts of the telemetry rhythm strip performed for safety purposes are printed and reviewed on-site;
- Continuous telemetry;
- Pulmonary function by lung auscultation and oxygen saturation;
- Clinical local laboratory assessment (incl. hematology, comprehensive metabolic and coagulation panel).

Safety analyses will be performed and the results summarized in the safety population. The verbatim terms used in the eCRF by Investigators to identify AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) and Preferred Term. All reported AEs with onset during the treatment phase or that were already present but worsened either in intensity or frequency following the treatment (i.e., TEAEs) are included in the analysis. The incidence and percentage of subjects with at least 1 occurrence of a Preferred Term are included, according to the most severe grade using a 3-point scale (mild, moderate, severe). The number of events per Preferred Term is summarized. Causality (relationship to study treatment) is summarized separately. The incidence and frequency of TEAEs (including TESAEs and AESI) are summarized according to SOC and Preferred Terms. Durations of events are determined and included in listings, along with the action taken and outcome.

10.2.2.1 B - Clinical laboratory evaluation analyses

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 at discharge.

10.2.2.2 B - Vital signs analyses

Vital signs measurements and their change from baseline are summarized for the safety population at each scheduled time point using descriptive statistics. Time course of the changes is summarized in tables and also represented graphically.

10.2.2.3 B - Physical examination analyses

Physical examination findings are summarized at screening and presented in subject listings.

10.2.3 B - Pharmacokinetic / Pharmacodynamic analyses

Table 2 describes the PK parameters to be calculated for plasma flecainide concentrations. The PK analysis is performed in all enrolled subjects who inhaled the full assigned dose (PK population).

Table 2 - Pharmacokinetic parameters to be calculated for plasma flecainide

AUC_{0-10}:	The area under the plasma concentration versus time curve from the start of dosing (time zero, T_0) to 10 minutes after initiation 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 after initiation 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 end of dosing) is obtained. If t_{max} is reached prior to the end of dosing, a negative value will be reported.
$t_{½}$ distribution:	The distributive half-life is calculated by the equation $t_{½} = \ln(2)/k_{dist}$

The effects of inhaled flecainide on the following ECG intervals is measured:

- Heart rate (HR)
- RR interval
- PR interval
- QRS duration
- QTcF duration
- JTc duration (QTc-QRS)

PK and PD data are analyzed in an exploratory manner and summarized descriptively. Time course of the changes is summarized in tables and also graphically represented. Details are given in a PK/PD analysis plan. The results of these analyses are presented in a separate report.

10.3 B - Sample size determination

In Part B, the estimated sample size of 25 mITT subjects for the 120 mg dose cohort is based upon the evaluation of the following statistical hypotheses using an exact binomial test,
H_0: $\rho = 20\%$ versus H_A: $\rho > 20\%$ ($\alpha = 0.05$).

Given the actual conversion rate for the Part A 120 mg dose cohort is 44%, a sample size of 25 subjects has 84% power to reject the null hypothesis (H_0) in favor of the alternative (H_A) with a one-sided significance level of 0.05. The null hypothesis is rejected when at least 9 subjects' AF converts to SR within 60 minutes after initiation of dosing.

If 9 subjects' AF converts to SR, the resulting conversion rate is 36% with a 90% exact binomial confidence interval of [20.24%, 54.39%]. If 9 or more subjects' AF converts to SR, the lower bound of the 90% exact binomial confidence interval will be greater than 20.24%. When the lower bound of the 90% confidence interval for conversion rate is greater than 20%, there is sufficient support for the rejection of the null hypothesis in favor of the alternative.

It is expected approximately 20 subjects will participate in the Handheld Echo Sub-Study in Part B and the Part C Medically-Led Cardioversion Study; however, the Sub-Study does not have a minimum or maximum enrollment target.

XII. Study protocol (Part C - EU only): Medically-Led Cardioversion and Patient-Led Under Medical Supervision Cardioversion Studies

2 C - Study objectives

All Part C objectives are exploratory:

- 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, including resumption of SR
- To explore the feasibility of implementing a portable cardiac ultrasound (HHE) at screening in an emergent setting

3 C - Study design

Part C is conducted in Europe only. Part C comprises two distinct studies, a Medically-Led Cardioversion Study (procedures are identical to those in Part B) and a Patient-Led Under Medical Supervision Cardioversion Study (procedures include the subject self-preparing and self-administering the study drug under medical supervision in the clinic).

Subjects with recent-onset AF who have not been previously treated with flecainide acetate inhalation solution will first be enrolled into the Medically-Led Cardioversion Study to determine eligibility for rollover participation in the Patient-Led Under Medical Supervision Cardioversion Study.

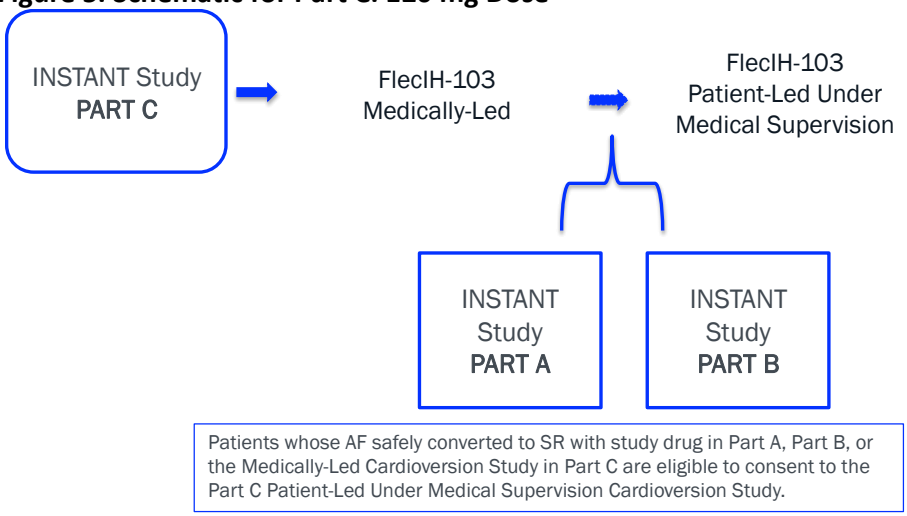
Subjects who first participate in the Medically-Led Cardioversion Study whose AF converts to SR with flecainide acetate inhalation solution and who did not experience any serious AE(s), serious AESIs, or difficulties or issues with inhalation (in the opinion of the investigator) are then eligible for the Patient-Led Under Medical Supervision Cardioversion Study.

Subjects from Part A and Part B who already had a previous AF episode converted to SR with flecainide acetate inhalation solution and who did not experience any serious AE(s), serious AESIs, or difficulties or issues with inhalation (in the opinion of the investigator) are also eligible for the Patient-Led Under Medical Supervision Cardioversion Study. These subjects do not need to participate in the Part C Medically-Led Cardioversion Study prior to proceeding into the Patient-Led Under Medical Supervision Cardioversion Study.

The schematic for subject flow into Part C is described in

Figure 5.

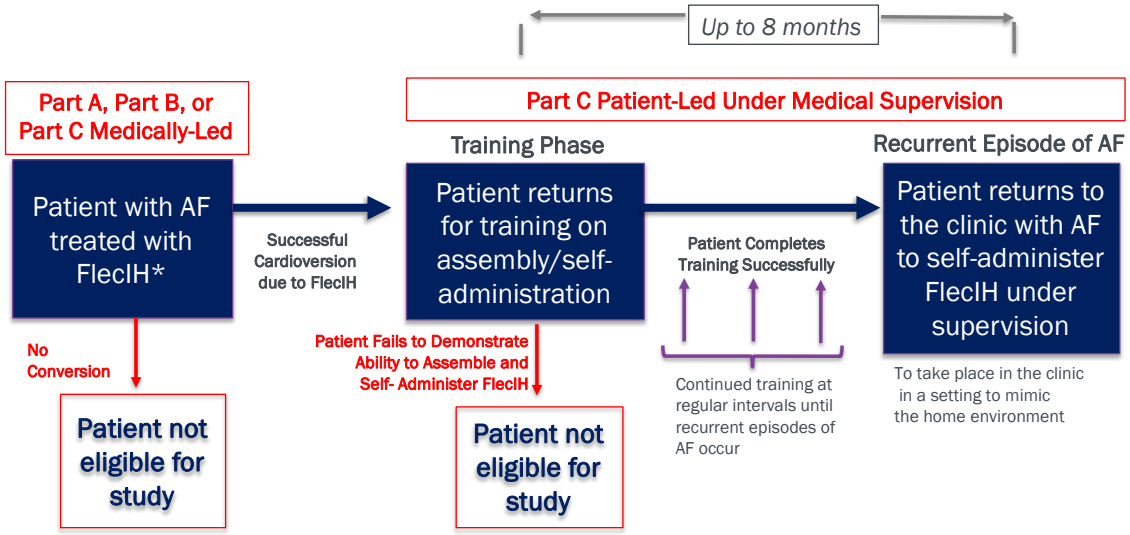
Figure 5. Schematic for Part C: 120 mg Dose



For both studies in Part C, subjects receive a repeat dose regimen of 120 mg eTLD (2 x 60 mg) FlecIH-103 inhalation solution. The dose regimen is described in Section 5.1 B. The study design for Part C is described in **Figure 6**.

The Patient-Led Under Medical Supervision Cardioversion Study 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 6. 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.

4 C - Study population

Part C does not have an enrollment target; enrollment will continue in the Part C Medically-Led Cardioversion Study at the discretion of the Sponsor to support rollover participation in the Part C Patient-Led Under Medical Supervision Cardioversion Study.

Subjects to be included in the Patient-Led Under Medical Supervision Cardioversion Study must be re-checked for eligibility according to the same criteria in Part B (Section 4.1 B and 4.2 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 return again if the future for a different recurrent episode of AF.

4.1 C - Inclusion criteria

Subjects to be included in Part C must meet the same inclusion criteria as described in Section 4.1 B.

4.2 C - Exclusion criteria

Subjects are NOT eligible to participate in Part C if they meet ANY of the exclusion criteria described in Section 4.2 B.

4.3 C - Screen failures

Refer to Section 4.3 B.

5 C - Treatment

5.1 C - Study treatments

Refer to Section 5.1 B.

5.2 C - Treatment assignment

After the consent form has been signed, the investigational site enters the eCRF to obtain a unique subject identification number (SID) for that subject (if not previously obtained). Subjects may be enrolled provided they meet all the inclusion criteria and none of the exclusion criteria.

Subjects are assigned to a 120 mg eTLD (2 x 60 mg) FlecIH-103 repeat dose regimen in both studies in Part C.

5.3 C - Identity of study drug(s)

Refer to Section 5.3 B.

5.4 C - Non-study therapy

Refer to Section 5.4 B.

5.5 C - Discontinuation criteria

Refer to Section 5.5 B.

6 C - Study procedures

For the Part C Medically-Led Cardioversion Study, the study procedures are identical to Part B. Refer to Section 6 B for more information.

The Part C Patient-Led Under Medical Supervision Cardioversion Study is divided into consenting, training, treatment, and follow-up periods, as described in the following sections.

Windows for PK blood draws and vital signs assessments

Where PK blood draws and vital signs assessments coincide at scheduled time points, PK blood draws are prioritized and must occur at the protocol-specified time point (with the exception of the 60 minutes post dose time point, which may be collected within a ± 5-minute window, and the 90 minutes post dose time point, which may be collected within a ± 10-minute window). Vital signs should be collected as close as possible to the scheduled time point after PK blood

draw is completed. As vital sign assessments coincide with PK blood draws, any deviations from the protocol-required time points for vital signs will not be recorded as protocol deviations. Any missed vital signs assessments will be recorded as protocol deviations.

Discharge window

Discharge is left to the discretion of the Investigator, but may not occur before 90 minutes post dose, with a -10-minute window allowed. Because discharge may occur, at the earliest, at 80 minutes post dose due to the window, all 90-minute post dose study assessments also have a ±10-minute window (may be performed between 80 and 100 minutes post dose, inclusive).

For the Schedule of Assessments please refer to Appendix 4.

6.1 C - Patient-Led Under Medical Supervision Cardioversion Study: consenting

Consent for the Part C Patient-Led Under Medical Supervision Cardioversion Study may occur in the following ways:

- Potentially eligible subjects from Part A will need to return to the clinic to provide consent and train on the assembly of the device and self-administration of study drug as soon as possible.
- Potentially eligible subjects from Part B may consent to the Part C Patient-Led Under Medical Supervision Cardioversion Study prior to or after discharge and complete the training on the assembly of the device and self-administration of study drug as soon as possible.
- Potentially eligible subjects from the Part C Medically-Led Cardioversion Study may consent to the Patient-Led Under Medical Supervision Cardioversion Study prior to discharge (or return to the clinic within approximately two weeks) and complete the training on the assembly of the device and on self-administration of study drug.

6.2 C - Patient-Led Under Medical Supervision Cardioversion Study: training

Once consented to the Patient-Led Under Medical Supervision Cardioversion Study, a training visit will be conducted by study personnel in accordance with the Patient-Led Training Procedure (site-facing document only), which describes step-by-step what the subject will be responsible for performing. The subject will be provided a Patient IFU document to follow during training and the self-administration procedure.

Subjects who successfully complete the training as determined by their ability to complete the procedures with minimal assistance, will be 'certified' and considered eligible to continue participation. A subject who does not successfully complete the procedures may be eligible

with additional training unless deemed unable or unfit to participate by the study personnel. Subject will continue to be re-trained on a regular basis (approximately monthly).

During the training visit, the following procedures will be performed:

- Study personnel will demonstrate all applicable steps to the subject, in accordance with the Patient-Led Training Procedure.
- The subject will practice all applicable steps and ask questions as needed. Note: study drug may NOT be used during inhalation practice/training.
- Study personnel will answer all of the subject's questions, ensuring the subject has a clear understanding of all applicable steps.
- The subject will perform the required steps unassisted in order to become 'certified' for self-administration. If the subject has difficulty in understanding or performing the required steps, they may receive further assistance from the study personnel, and try once again to repeat the required steps unassisted. Certification should be noted in the subject's source records. No formal certificate will be provided to the subject.
- The subject may be deemed unable or unfit to participate by the study personnel if certification is not possible after up to 3 attempts. If this is the case, the subject will be early terminated from Part C.
- Once certified, the subject is given a nebulizer to take home to independently practice with the device to learn to assemble it and inhale.
- Study personnel informs the subject that they must return to the clinic for refresher training at least every 3 months, to avoid early termination from the study. The refresher training may also be completed by telemedicine visit or video conference (e.g., Facetime, Skype), if the site and subject have the capability. Study personnel should schedule a return training visit prior to the subject leaving the clinic.
- Study personnel provides the subject with a training video and instructs the subject to watch the video approximately monthly as a refresher. Subjects without access to a computer may return to the site monthly to view the training video if necessary, or do so via a telemedicine visit or video conference, if the site and subject have the capability.
- The study personnel instruct the subject to contact the clinic for return instructions as soon as they feel symptoms of a recurrence of paroxysmal AF. Subjects must return to the clinic and self-administer study drug within 48 hours of the onset of symptoms. If the subject cannot reach the study personnel, they should take the steps to care for themselves as they would normally if they were not participating in this study (e.g., proceed to emergency care or their regular doctor).

Study personnel will contact the subject approximately monthly to check for adverse events and concomitant medications and confirm if subject has viewed the training video.

6.3 C - Patient-Led Under Medical Supervision Cardioversion Study: treatment

After completion of training and becoming certified for patient-led self-administration of study drug, all eligible subjects may return to the clinic for a recurrence of symptomatic paroxysmal AF within 48 hours of the onset of symptoms. Subjects will independently dispense the dose into the nebulizer, reassemble the nebulizer, and self-administer the study drug in the clinic under observation of study personnel. For additional details refer to the IFU. Subjects will self-administer 120 mg eTLD (2 x 60 mg) FlecIH-103 according to the same dosing regimen in Part B (Section 5.1 B).

Subjects return for patient-led self-administration of study drug for a single recurrent episode(s) of paroxysmal AF within 8 months of signing consent. End of study coincides with Day 5 after the subject's treatment visit, or 8 months after signing consent, whichever comes first.

Before dosing

The following procedures will be performed prior to dosing:

- The eligibility criteria for Part C are identical to Part B and must be checked and confirmed prior to dosing.
- Blood samples are to be drawn per Investigator discretion to confirm the subject's eligibility at approximately 30 minutes prior dosing, in accordance with the requirements in Section 9.2 C.
- A standard 12-lead ECG (using site's own equipment) is recorded to confirm that the subject's heart rhythm is AF and remains in AF for at least 30 minutes prior to dosing. Once the recording of the ECG is completed and the presence of AF is confirmed, this 12-lead ECG may be disconnected.
- A baseline PK blood sample is drawn prior to dosing.
- A symptom-driven physical exam is performed prior to dosing, if deemed necessary by the Investigator.
- The subject is connected to the telemetry system and to the AECG (Holter) approximately 30 minutes prior to dosing (after being disconnected from the standard 12-lead ECG).
- A single source for the time of all assessments shall be utilized for each patient. For example, if telemetry is used, all assessments for that patient must be recorded from the same telemetry unit. All times shall be reported in a 24-hour format. **NOTE:** The date and time displayed on study Holter monitor AECG must be set to match the date and time of the device used for capturing the time of all assessments, for each subject.
- An IV catheter/cannula is placed for blood sample draws.
- Pre-dose vital signs (heart rate, systolic/diastolic blood pressure, respiratory rate [breaths/min], oxygen saturation, and body temperature) are recorded. approximately 30 minutes prior to dosing.

NOTE: When time points for drawing blood samples and recording of vital signs coincide, assessments should be performed in said order.

- The subject's weight is recorded (for calculation of creatinine clearance)
- Pre-dose vital signs (excluding body temperature) are recorded again within 10 minutes prior to dosing.
- The subject's AF-related symptoms are recorded prior to dosing.
- The subject is offered the opportunity to review once again the steps for dispensing the study drug, assembly of the nebulizer, and the instructions for self-administration of study drug. This review of the steps will be done along with the study personnel; any remaining questions prior to the start of the inhalation can be addressed by the study nurse.

After completion of the baseline measurements as described above, the Investigator verifies whether the subject is still in AF. Inhalation of study drug should not start in subjects whose AF has spontaneously converted to SR, or who are in a heart rhythm other than AF.

During dosing

Once the subject confirms they are ready, the subject will dispense the study medication into the nebulizer, reassemble the nebulizer and self-administer the study drug according to the steps outlined in the Patient IFU.

The following procedures will be performed during dosing:

- The study personnel will use a stopwatch to monitor the dosing and will advise the subject when to stop inhaling at the time of completion or when their AF converts to SR, whichever comes first.
- A PK sample will be collected when the subject's AF converts to SR (if applicable).

Notwithstanding any difficulty that the subject experiences with the preparation of the nebulizer or with the self-administration/inhalation of study drug, they should make every attempt to perform the procedure without assistance. If needed, the subject can be referred back to the Patient IFU. If the subject is unable to prepare the device and self-administer the study drug without assistance, the study personnel may assist but this must be documented in the eCRF.

The Investigator may stop the inhalation of the study drug early in the event of a S(AE) such as ventricular arrhythmias (frequent PVCs, non-sustained VT, or sustained VT or VF) or any other life-threatening or serious adverse events.

No other pharmacological or electrical cardioversion may be attempted until at least 90 minutes post dose. Alternate therapy may be given as early 60 minutes pose dose only if deemed medically necessary by the investigator not to wait until 90 minutes post dose;

however, IV flecainide and propafenone may not be administered until at least 90 minutes post dose. Subjects will remain on rhythm monitoring (i.e., cardiac telemetry and study AECG [Holter]) until at least 90 minutes post dose.

After dosing

The following procedures are performed after dosing:

- A PK sample is collected at 3 minutes post dose.
  NOTE: A PK sample must also be collected when conversion of AF to SR occurs (if applicable). If time of conversion is approximately within 1 minute before or after the 3 minutes post dose PK sample, only 1 sample needs to be collected.
- The subject's vital signs are recorded at 1, 3, 10, 30, 60 and 90 minutes post dose.
- The subject's AF-related symptoms are recorded at 30, 60 and 90 minutes post dose.
- The AECG (Holter) is removed at 90 minutes post dose.

The timing of subject's discharge is left to the discretion of the treating physician but may only occur at or after 90 minutes (a -10 minute window is allowed) post dose. At discharge, a plan for follow up study contacts on Days 2 and 5 is made with the subject.

6.4 C - Patient-Led Under Medical Supervision Cardioversion Study: follow-up

Study personnel will contact the subject on Day 2 (+ 1 day) and Day 5 (± 1 day) following self-administration of study drug to assess concomitant medications, adverse events, and subject's AF-related symptoms status.

End of study coincides with Day 5 after the subject's treatment visit, or 8 months after signing consent, whichever comes first.

7 C - Efficacy assessments and endpoints

The efficacy assessments in the Part C Medically-Led Cardioversion Study are identical to those in Part B. Refer to Section 7 B for more information.

The assessments in the Part C Patient-Led Under Medical Supervision Cardioversion Study and the endpoints for Part C are described in the following sections.

7.1 C - Patient-Led Under Medical Supervision Cardioversion Study: rhythm monitoring assessments

Subjects are connected to the AECG (Holter) on Day 1 approximately 30 minutes prior to dosing after the site has confirmed the diagnosis of AF using the standard 12-lead ECG (using site's own equipment). The subject will remain connected to the AECG until at least 90 minutes post dose.

Anonymized AECG recordings are analyzed centrally by a Core Laboratory. Further detail may be found in the separate instructions provided.

7.2 C - Patient-Led Under Medical Supervision Cardioversion Study: AF-related symptoms

Prior to self-administration of the study drug on Day 1, subjects are queried about the presence or absence of each of the following AF-related symptoms:

- Palpitations, i.e. sensation of a racing, uncomfortable, irregular heartbeat or a flip-flopping in your chest
- Lightheadedness or dizziness
- Shortness of breath or dyspnea
- Chest discomfort

At the following time points after dosing, subjects are again queried about each of these symptoms in terms of "no symptoms, improved, unchanged or worsened" as compared to baseline:

- 30, 60 and 90 minutes post dose on Day 1
- On Day 2 (+ 1 day)
- On Day 5 (± 1 day)

7.3 C - Study endpoint(s)

All endpoints in Part C are exploratory:

- 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
- Feasibility of patient-led self-administration of study drug, including:
    - 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
- Proportion of subjects whose AF converted to SR
- 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

8 C - Other assessments

Pharmacokinetic and pharmacodynamic assessments in the Medically-Led Cardioversion Study of Part C are identical to Part B. Refer to Section 8 B for more information.

Other assessments, including PK and PD assessments, in the Part C Patient-Led Under Medical Supervision Cardioversion Study are described in the following sections.

8.1 C - Patient-Led Under Medical Supervision Cardioversion Study: PK assessment(s)

Up to 3 whole blood samples of about 4.0 mL each are collected for measurement of plasma concentration of flecainide acetate: prior to dosing, 3 minutes post dose, and at time of conversion of AF to SR (if applicable). Instructions for the collection, processing and shipping of biological samples are provided in the Laboratory Manual.

Plasma samples are assayed by a validated LC/MS/MS method as in Part B. Samples collected for analysis of flecainide plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

No genetic analyses will be performed on these plasma/whole blood samples.

8.2 C - Patient-Led Under Medical Supervision Cardioversion Study: PD assessment(s)

To evaluate the electrocardiographic effects of inhaled flecainide under oral inhalation dosing regimens in subjects with recent onset of paroxysmal AF, which are detectable on 12-lead ECG recordings mainly by assessing the following PD variables: PR, QRS, and QT intervals.

An independent central review of ECGs is conducted. The ECG recordings will be extracted in triplicate according to the Schedule of Assessments (Section 17.4) 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 -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}
5. After administration of study drug regimen is complete – T_x (1, 3, 10, 30, 60, and 90 minutes post dose)

Details of the Core Laboratory analyses are included in the Core Laboratory analysis plan but at least the following ECG parameters are determined:

- Heart rate (HR)
- RR interval
- PR interval
- QRS duration
- QTcF duration
- JTc duration (QTc-QRS)

ECGs extracted from the 12-lead Holter are provided to Investigators for filing in the subjects' source records. Any original ECG recordings obtained at the site must also be stored in the subject's source records.

9 C - Safety evaluation and reporting

Safety evaluation and reporting in the Part C Medically-Led Cardioversion Study are identical to Part B. Refer to Section 9 B for more information.

Safety evaluation and reporting in the Part C Patient-Led Under Medical Supervision Cardioversion Study are described in the following sections.

9.1 C - Patient-Led Under Medical Supervision Cardioversion Study: adverse events

Adverse events for subjects participating in the study will be captured from time of consent until EOS. End of study coincides with Day 5 after the subject's treatment visit, or 8 months after signing consent, whichever comes first. All AEs, SAEs, and AESIs will be captured and reported in accordance with Section 9.1 B.

Recurrent atrial fibrillation will not be considered as an adverse event as it is an expected event in this patient population. AF recurrence will be captured in a separate eCRF.

9.2 C - Patient-Led Under Medical Supervision Cardioversion Study: clinical local laboratory assessments

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. The following laboratory assessments are required to confirm eligibility:

- serum creatinine
- serum potassium
- serum or urine pregnancy test (only for female subjects of child-bearing potential)

A blood draw for assessment of potassium must always be drawn on Day 1 prior to self-administration of study drug; however, if results are available for any or all other parameters from a blood draw up to 24 hours prior to Day 1, there is no need for a new blood draw for those parameters.

If laboratory values from non-protocol specified laboratory assessments performed at the site's local laboratory are considered clinically significant by the Investigator (e.g., AE or SAE), then the results must be recorded in the eCRF.

9.2.1 C - Patient-Led Under Medical Supervision Cardioversion Study: total blood volume

Blood samples in the Patient-Led Under Medical Supervision Cardioversion Study result in a total maximum estimated blood volume of 15.0 mL per subject:

- PK assessments (up to 3 samples of 4.0 mL each)	12.0 mL
- Clinical local laboratory assessments on Day 1	3.0 mL
Total	15.0 mL

The total blood volume of 15.0 mL corresponds to approximately 1 tablespoon.

9.3 C - Patient-Led Under Medical Supervision Cardioversion Study: vital signs

Weight must be recorded on Day 1 prior to self-administration of the study drug to confirm creatinine clearance eligibility.

Heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min), oxygen saturation and body temperature are recorded on Day 1 approximately 30 minutes prior to self-administration of the study drug. Vital signs (excluding body temperature) are recorded again within 10 minutes prior to dosing. Finally, vital signs are recorded after dosing at 1, 3, 10, 30, 60 and 90 minutes post dose.

9.4 C - Patient-Led Under Medical Supervision Cardioversion Study: physical examination

A symptom-driven physical examination may be performed prior to self-administration of study drug per Investigator discretion to confirm eligibility.

10 C - Statistical methods

10.1 C - Study populations

Refer to Section 0 B.

10.2 C - Statistical analyses

No formal hypothesis testing is planned for Part C. Summary statistics will be generated, including estimates of the endpoints with their associated 90% confidence intervals.

All statistical analyses performed in the evaluation of the INSTANT Study data are described in the statistical analysis plan (SAP).

10.3 C - Sample size determination

Part C (EU only) does not have an enrollment target; enrollment will continue in the Part C Medically-Led Cardioversion Study at the discretion of the Sponsor to support rollover participation in the Part C Patient-Led Under Medical Supervision Cardioversion Study.

11 Data integrity and quality assurance

The Investigator shall allow study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data/documents. Direct access includes permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of a clinical study.

In accordance with ICH GCP and regulatory requirements, this study may be selected for audit by the Sponsor or by its designated representatives. Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study related records will occur in order to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements. The Investigator will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IRB(s)/IEC(s) are possible. The Investigator shall notify the Sponsor immediately of any such inspection.

The Investigator (and Institution, if applicable) agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the

auditor/inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.1 Monitoring

In accordance with ICH GCP, applicable regulations, and Sponsor/CRO's procedures, monitors provide training of the protocol, the study requirements, and the investigator's and site staff's responsibilities to satisfy regulatory, ethical, and Sponsor's requirements prior to the site being activated for screening. When reviewing data collection procedures, the discussion also includes identification and documentation of source data.

The Monitor performs on-site monitoring visits throughout the study, according to a Monitoring Manual, to verify adherence to the protocol; authenticity, completeness, accuracy, and consistency of the data; that the rights and well-being of human subjects are protected; and adherence to ICH GCP and local regulations on the conduct of clinical research. In certain circumstances (e.g., due to the COVID-19 pandemic), remote monitoring will be performed to the extent possible by local and site regulations.

The Monitor is responsible for inspecting the case report forms and ensuring completeness of the study essential documents by site staff. The Monitor shall have access to subject medical records and other study-related records needed to verify entries on the case report forms. Monitoring visits (including site visit calls), are conducted in accordance with the Monitoring Manual. The Monitor communicates and documents deviations from the protocol, SOPs, ICH GCP and applicable regulations to the Investigator and ensures that appropriate action designed to prevent recurrence of the detected deviations is taken. The Investigator and study site personnel agree to cooperate with the Monitor to ensure that any issues detected in the course of the monitoring visits are documented and addressed.

11.2 Data collection

The data collection tool for this study is a validated electronic data capture (EDC) system, MARVIN. Data required according to this protocol are recorded by Investigator or designee into the internet based EDC, which CRO licenses from XClinical. MARVIN is validated by XClinical and CRO for use in clinical studies. MARVIN allows for the application of software logic to provide data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. CRO applies further logic checks to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from these checks are resolved by the site personnel.

ALL access to MARVIN is regulated through a password-protected security system that is part of the MARVIN software. All relevant study personnel (Sponsor, site, CRO or other) seeking access must complete a MARVIN training before they are granted access to MARVIN. Training records

are maintained. All personnel with access to MARVIN are supported by a Service Desk, which is staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

Electronic CRF completion guidelines are provided to and reviewed with study personnel (including but not limited to Sub-/Co-Investigators, Data Managers and Study Nurses) before the start of the study. Completion of the eCRF is kept up-to-date to enable the Monitor to review the subject's status throughout the study. For this purpose, all eCRF data entry must be completed within the agreed timeframe of the subject's visit/contact. The specific requirements for AE collection and reporting are detailed in Section 9.1 B. The eCRF is completed, reviewed and signed (electronically) by the Investigator. Data entries made in the eCRF are supported by source documents maintained for all subjects enrolled in this study at the site. The site must implement processes to ensure availability of all required source documentation.

Written instructions are provided for collection, preparation, and shipment of plasma samples.

The Investigator or designee must also complete a **subject pre-screening log**, which lists all subjects who were seen to determine eligibility for inclusion in the study including the reason for failure of pre-screening.

Data recorded from screen failures
Data for subjects that have signed IC but were not enrolled into the study (i.e., screen failures) are recorded. At a minimum, the following data shall be recorded in the eCRF:

- Demographic information (SID number; year of birth/age; sex)
- Date/time of IC
- Reason for failure of screening
- Date of last visit/contact

If a subject is deemed a screen failure, all AEs experienced during the screening period are documented and reported as described in Section 9.1 B.

11.3 Data management

Clinical data management is performed according to applicable Sponsor/CRO standards and data cleaning procedures. This applies for data recorded in the eCRF as well as data from other sources (e.g., laboratory, ECG, AECG). For data coding (i.e., AEs and concomitant medications), internationally recognized and accepted dictionaries are used.

11.4 Study documentation and storage

The Investigator maintains an authorized signature log of appropriately qualified personnel to whom he/she has delegated study duties. All personnel authorized to make entries and/or corrections on eCRFs are included on the authorized signature log.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, X-rays, and correspondence.

The Investigator is responsible for maintaining a comprehensive and centralized filing system (Investigator Site File [ISF]) of all study-related (essential) documentation, suitable for inspection at any time by representatives from Sponsor and/or applicable regulatory authorities. Essential documents include:

- Subject files containing ICs and supporting copies of source documentation as used for eCRF completion. In addition, all original source documents supporting entries in the eCRF must be maintained and be readily available.
- Study files containing the protocol with all amendments, the IB (all relevant editions), copies of relevant essential documents required prior to commencing a clinical study, and all correspondence to and from the IRB/IEC and Sponsor.
- Records related to the study drug, including acknowledgment of receipt at site, accountability records with final reconciliation, and applicable correspondence.

Essential clinical trial documents (including case report forms) other than subject's medical files must be kept for at least 15 years after completion or discontinuation of the trial. Subject's medical files shall be retained in accordance with applicable legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice. It is the responsibility of the Sponsor to inform the Investigator as to when the clinical trial documents no longer need to be retained.

No study document may be destroyed without prior written agreement between Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify Sponsor in writing of the new responsible person and/or the new location.

11.5 Archiving

Essential documents are archived in a way that ensures that they can be made readily available upon authorities' request.

Records of subjects, source documents, monitoring visit logs, data correction forms, CRFs, inventory of study product, regulatory documents (e.g., protocol and amendments, IRB/IEC

correspondence and approvals, approved and signed ICs, Investigator's Agreement, clinical supplies receipts, distribution and return records), and other Sponsor correspondence pertaining to the study must be kept in appropriate study files at the site. Source documents include all recordings and observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. These records are retained in a secure file for the period required by the institution or site policy. Prior to transfer or destruction of these records, the Sponsor must be notified in writing and be given the opportunity to further store such records.

12 Financing and insurance

12.1 Financing

Before the initiation of the study, the Investigator and/or Institution signs a clinical study agreement with the Sponsor (or with its authorized representative).

12.2 Reimbursement, Indemnity, and insurance

The Sponsor maintains clinical trial insurance coverage for study subjects in the event of trial-related injuries, in accordance with the applicable laws and regulations of the country in which the study is performed. Also, according to the applicable regulatory requirement(s), the Sponsor provides insurance or indemnity (legal and financial coverage) to the Investigator/Institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

Reimbursement, indemnity and insurance is addressed in a separate agreement according to the terms agreed upon by the parties.

13 Publication policy

The Sponsor fulfils its obligations regarding the public disclosure of study results according to applicable laws and regulations. Furthermore, the Sponsor recognizes the right of the Investigator to publish the results upon completion of the study. The Investigator shall seek to obtain written consent of the Sponsor on any manuscript publication ahead of its submission. For this purpose, the Investigator must send a draft of the manuscript to the Sponsor. The Sponsor will review and provide feedback on the manuscript content to the Investigator in order to reach a mutual final manuscript.

The Sponsor has made information on the study protocol publicly available on the internet at www.clinicaltrials.gov.

14 Ethics and study administrative information

14.1 Compliance statement, Ethics and regulatory compliance

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the Sponsor and Investigator uphold Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. This study will be conducted in compliance with the protocol and in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IRBs/IECs is obtained for all participating sites before start of the study, according to GCP, local laws, regulations and organizations.

Strict adherence to all specifications of this protocol is required for all aspects of study conduct; the Investigator may not modify or alter the procedures described in this protocol. Modifications to the study protocol may not be implemented by either the Sponsor or the investigator without prior approval of a protocol amendment by the IRB/IEC. However, the Investigator or the Sponsor may implement a deviation from or a change of the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB/IEC approval. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment shall be submitted to the IRB/IEC. Any deviations from the protocol must be explained and documented by the Investigator.

14.2 Confidentiality

All records identifying the subject shall be kept confidential and, to the extent permitted by the applicable laws and/or regulations, not be made publicly available. The Investigator must ensure that the subject's anonymity is maintained. Only the subject number is recorded in the eCRF, and if the subject name appears on any other document (e.g., ECG), it must be anonymized before a copy of the document is supplied to the Sponsor or its representatives. Study findings stored on a computer are stored in accordance with local data protection laws. As part of the IC process, subjects are informed in writing that representatives of the Sponsor, IRB/IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection is handled in strictest confidence and in accordance with local data protection laws. If the results of the study are published, the subject's identity remains confidential. The Investigator maintains a list of subjects to enable subject identification if required.

14.3 Informed consent

Before any study-specific procedures take place, it is the Investigator's responsibility to obtain voluntarily-given informed consent, in writing, from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential risks of the study. Subjects must have

the opportunity to ask questions, receive satisfactory answers to their inquiries, and have adequate time to decide whether or not to participate in the study. The Investigator shall explain that written approval of the IRB/IEC has been obtained to conduct the study. The written IC will be prepared in the local language(s) of the potential subject population. Each subject shall be provided a copy of their signed and dated IC.

14.4 Supply of new information affecting study conduct

The Sponsor will inform all Investigators involved in the clinical study, IRBs/IECs, and regulatory authorities of any new information that may adversely impact the safety of subjects or the conduct of the study, and when needed, amends the protocol and/or subject IC. The Investigator shall immediately inform the subject whenever new information becomes available that may be relevant to the subject's consent or that may influence the subject's willingness to continue participation in the study. The communication will be documented in the subject's medical records, including whether the subject is willing to remain in the study or not.

If the subject IC is revised, it must be re-approved by the IRB/IEC. The Investigator shall obtain written IC from the subject to continue participation with the approved revised IC, even if the subjects is already informed of any changes verbally. The Investigator or designee and the subject shall sign and date the approved revised IC, and a copy of the signed and dated IC shall be provided to the subject.

14.5 Regulatory compliance

The study protocol, IB, subject information and subject consent form, subject card or written instructions to be given to the subject, available safety information, subject recruitment procedures, and information about payments and compensation available to the subject shall be submitted to the IRB/IEC for ethical review and approval according to local regulations, prior to site activation for screening. The written approval should identify all documents reviewed by name and version.
Changes in the conduct of the study or planned analysis are documented in a protocol amendment and/or the SAP.

All subsequent substantial protocol amendments and changes to the IC are submitted to the IRB/IEC for approval. The Investigator shall notify the IRB/IEC of deviations from the protocol, SAEs occurring at the site, and other AE reports received from Sponsor/CRO, in accordance with local requirements.

As required by local regulations, the Sponsor or designee ensures all legal aspects are covered, and approval of the appropriate regulatory bodies obtained, prior to site activation for screening, and that implementation of changes to the initial protocol and other relevant study

documents happen only after the appropriate notification of or approval by the relevant regulatory bodies.

14.6 Protocol Amendments

Any amendments to the study protocol as the study progresses are communicated to the Investigator by the Sponsor. All protocol amendments must be submitted to the site IRB/IEC for review and approval prior to implementation at the site, unless immediate implementation of the change is necessary for subject safety.

14.7 Study termination

The Sponsor has the right to terminate this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to if the benefit-risk ratio becomes unacceptable owing to, for example,

- Safety findings from this study (e.g., SAEs)
- The DSMB has the responsibility for recommending early termination of the study to the Executive Committee and the Sponsor, which has ultimate authority/responsibility for making the decision. The criteria that the DSMB follows to determine whether/when to recommend termination of the study is detailed in DSMB charter (separate document).

The Investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g., IRB(s)/IEC(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the Sponsor. The Investigator retains all other documents until notification is given by the Sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in any post-study follow-up, must be taken care of in an ethical manner.

Details for individual subject's premature termination and withdrawals from the study are found in Sections 5.5 A, 5.5 B, and 5.5 C.

15 References

1. Fridericia LS. The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease. *Acta Medica Scandinavica*. 1920;53:469-486.
2. Jensen PN, Gronroos NN, Chen LY, Folsom AR, deFilippi C, Heckbert SR and Alonso A. Incidence of and risk factors for sick sinus syndrome in the general population. *J Am Coll Cardiol*. 2014;64:531-8.
3. Markey GC, Salter N and Ryan J. Intravenous Flecainide for Emergency Department Management of Acute Atrial Fibrillation. *J Emerg Med*. 2018;54:320-327.
4. Camm AJ, Capucci A, Hohnloser SH, Torp-Pedersen C, Van Gelder IC, Mangal B, Beatch G and Investigators A. A randomized active-controlled study comparing the efficacy and safety of vernakalant to amiodarone in recent-onset atrial fibrillation. *J Am Coll Cardiol*. 2011;57:313-21.
5. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, Gillum RF, Kim YH, McAnulty JH, Jr., Zheng ZJ, Forouzanfar MH, Naghavi M, Mensah GA, Ezzati M and Murray CJ. Worldwide epidemiology of atrial fibrillation: a Global Burden of Disease 2010 Study. *Circulation*. 2014;129:837-47.
6. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV and Singer DE. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285:2370-5.
7. Shen MJ, Choi EK, Tan AY, Lin SF, Fishbein MC, Chen LS and Chen PS. Neural mechanisms of atrial arrhythmias. *Nat Rev Cardiol*. 2011;9:30-9.
8. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC, Jr., Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW and American College of Cardiology/American Heart Association Task Force on Practice G. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol*. 2014;64:e1-76.
9. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, Castella M, Diener HC, Heidbuchel H, Hendriks J, Hindricks G, Manolis AS, Oldgren J, Popescu BA, Schotten U, Van Putte B, Vardas P, Agewall S, Camm J, Baron Esquivias G, Budts W, Carerj S, Casselman F, Coca A, De Caterina R, Deftereos S, Dobrev D, Ferro JM, Filippatos G, Fitzsimons D, Gorenek B, Guenoun M, Hohnloser SH, Kolh P, Lip GY, Manolis A, McMurray J, Ponikowski P, Rosenhek R, Ruschitzka F, Savelieva I, Sharma S, Suwalski P, Tamargo JL, Taylor CJ, Van Gelder IC, Voors AA, Windecker S, Zamorano JL and Zeppenfeld K. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37:2893-2962.

10. Aliot E, Capucci A, Crijns HJ, Goette A and Tamargo J. Twenty-five years in the making: flecainide is safe and effective for the management of atrial fibrillation. *Europace*. 2011;13:161-73.
11. Andrikopoulos GK, Pastromas S and Tzeis S. Flecainide: Current status and perspectives in arrhythmia management. *World J Cardiol*. 2015;7:76-85.
12. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P, Guidelines-CPG ESCCfP and Document R. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace*. 2012;14:1385-413.
13. Kowey PR, Marinchak RA, Rials SJ and Filart RA. Acute treatment of atrial fibrillation. *Am J Cardiol*. 1998;81:16C-22C.
14. Wakai A and O'Neill JO. Emergency management of atrial fibrillation. *Postgrad Med J*. 2003;79:313-9.
15. Martinez-Marcos FJ, Garcia-Garmendia JL, Ortega-Carpio A, Fernandez-Gomez JM, Santos JM and Camacho C. Comparison of intravenous flecainide, propafenone, and amiodarone for conversion of acute atrial fibrillation to sinus rhythm. *Am J Cardiol*. 2000;86:950-3.
16. Coll-Vinent B, Fuenzalida C, Garcia A, Martin A and Miro O. Management of acute atrial fibrillation in the emergency department: a systematic review of recent studies. *Eur J Emerg Med*. 2013;20:151-9.
17. Chen S, Dong Y, Fan J and Yin Y. Rate vs. rhythm control in patients with atrial fibrillation--an updated meta-analysis of 10 randomized controlled trials. *Int J Cardiol*. 2011;153:96-8.
18. Li H, Easley A, Barrington W and Windle J. Evaluation and management of atrial fibrillation in the emergency department. *Emerg Med Clin North Am*. 1998;16:389-403.
19. Hohnloser SH, Dorian P, Straub M, Beckmann K and Kowey P. Safety and efficacy of intravenously administered tedisamil for rapid conversion of recent-onset atrial fibrillation or atrial flutter. *J Am Coll Cardiol*. 2004;44:99-104.
20. Kochiadakis GE, Igoumenidis NE, Hamilos ME, Marketou ME, Chlouverakis GI and Vardas PE. A comparative study of the efficacy and safety of procainamide versus propafenone versus amiodarone for the conversion of recent-onset atrial fibrillation. *Am J Cardiol*. 2007;99:1721-5.
21. Rozen G, Hosseini SM, Kaadan MI, Biton Y, Heist EK, Vangel M, Mansour MC and Ruskin JN. Emergency Department Visits for Atrial Fibrillation in the United States: Trends in Admission Rates and Economic Burden From 2007 to 2014. *J Am Heart Assoc*. 2018;7.
22. Savelieva I, Graydon R and Camm AJ. Pharmacological cardioversion of atrial fibrillation with vernakalant: evidence in support of the ESC Guidelines. *Europace*. 2014;16:162-73.
23. Holmes B and Heel RC. Flecainide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 1985;29:1-33.
24. Roden DM and Woosley RL. Drug therapy. Flecainide. *N Engl J Med*. 1986;315:36-41.

25. Wang Z, Page P and Nattel S. Mechanism of flecainide's antiarrhythmic action in experimental atrial fibrillation. *Circ Res*. 1992;71:271-87.
26. Wijffels MC, Dorland R, Mast F and Allessie MA. Widening of the excitable gap during pharmacological cardioversion of atrial fibrillation in the goat: effects of cibenzoline, hydroquinidine, flecainide, and d-sotalol. *Circulation*. 2000;102:260-7.
27. Shinagawa K, Mitamura H, Takeshita A, Sato T, Kanki H, Takatsuki S and Ogawa S. Determination of refractory periods and conduction velocity during atrial fibrillation using atrial capture in dogs: direct assessment of the wavelength and its modulation by a sodium channel blocker, pilsicainide. *J Am Coll Cardiol*. 2000;35:246-53.
28. Kirchhof P, Engelen M, Franz MR, Ribbing M, Wasmer K, Breithardt G, Haverkamp W and Eckardt L. Electrophysiological effects of flecainide and sotalol in the human atrium during persistent atrial fibrillation. *Basic Res Cardiol*. 2005;100:112-21.
29. Arnsdorf MF and Sawicki GJ. Flecainide and the electrophysiologic matrix: the effects of flecainide acetate on the determinants of cardiac excitability in sheep Purkinje fibers. *J Cardiovasc Electrophysiol*. 1996;7:1172-82.
30. Varro A, Bodi I, Jednakovits A and Rabloczky G. Frequency-dependent effects of class I, III and IV antiarrhythmic drugs on the conduction and excitability in rabbit ventricular muscle. *Arch Int Pharmacodyn Ther*. 1988;292:157-65.
31. Wang ZG, Pelletier LC, Talajic M and Nattel S. Effects of flecainide and quinidine on human atrial action potentials. Role of rate-dependence and comparison with guinea pig, rabbit, and dog tissues. *Circulation*. 1990;82:274-83.
32. O'Hara G, Villemaire C, Talajic M and Nattel S. Effects of flecainide on the rate dependence of atrial refractoriness, atrial repolarization and atrioventricular node conduction in anesthetized dogs. *J Am Coll Cardiol*. 1992;19:1335-42.
33. Voigt N, Heijman J, Wang Q, Chiang DY, Li N, Karck M, Wehrens XHT, Nattel S and Dobrev D. Cellular and molecular mechanisms of atrial arrhythmogenesis in patients with paroxysmal atrial fibrillation. *Circulation*. 2014;129:145-156.
34. Echt DS, Liebson PR, Mitchell LB, Peters RW, Obias-Manno D, Barker AH, Arensberg D, Baker A, Friedman L, Greene HL and et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. *N Engl J Med*. 1991;324:781-8.
35. Conard GJ and Ober RE. Metabolism of flecainide. *Am J Cardiol*. 1984;53:41B-51B.
36. Funck-Brentano C, Becquemont L, Kroemer HK, Buhl K, Knebel NG, Eichelbaum M and Jaillon P. Variable disposition kinetics and electrocardiographic effects of flecainide during repeated dosing in humans: contribution of genetic factors, dose-dependent clearance, and interaction with amiodarone. *Clin Pharmacol Ther*. 1994;55:256-69.
37. McQuinn RL, Quarfoth GJ, Johnson JD, Banitt EH, Pathre SV, Chang SF, Ober RE and Conard GJ. Biotransformation and elimination of 14C-flecainide acetate in humans. *Drug Metab Dispos*. 1984;12:414-20.

38. Conard GJ, Carlson GL, Frost JW, Ober RE, Leon AS and Hunninghake DB. Plasma concentrations of flecainide acetate, a new antiarrhythmic agent, in humans. *Clin Ther*. 1984;6:643-52.
39. Duff HJ, Roden DM, Maffucci RJ, Vesper BS, Conard GJ, Higgins SB, Oates JA, Smith RF and Woosley RL. Suppression of resistant ventricular arrhythmias by twice daily dosing with flecainide. *Am J Cardiol*. 1981;48:1133-40.
40. Sallstrom J, Al-Saffar A and Pehrson R. Pharmacokinetic-pharmacodynamic modeling of QRS-prolongation by flecainide: heart rate-dependent effects during sinus rhythm in conscious telemetered dogs. *J Pharmacol Toxicol Methods*. 2014;69:24-9.
41. InCardaTherapeutics. Investigators Brochure. Flecainide acetate inhalation solution (a Class ic antiarrhythmic agent) and the aeroeclipse II breath actuated nebulizer (BAN). Draft version, 29 Sep 2017. 2017;draft version.
42. Crijns HJ, van Wijk LM, van Gilst WH, Kingma JH, van Gelder IC and Lie KI. Acute conversion of atrial fibrillation to sinus rhythm: clinical efficacy of flecainide acetate. Comparison of two regimens. *Eur Heart J*. 1988;9:634-8.
43. Suttorp MJ, Kingma JH, Jessurun ER, Lie AHL, van Hemel NM and Lie KI. The value of class IC antiarrhythmic drugs for acute conversion of paroxysmal atrial fibrillation or flutter to sinus rhythm. *J Am Coll Cardiol*. 1990;16:1722-7.
44. Donovan KD, Power BM, Hockings BE, Dobb GJ and Lee KY. Intravenous flecainide versus amiodarone for recent-onset atrial fibrillation. *Am J Cardiol*. 1995;75:693-7.
45. McNamara RL, Tamariz LJ, Segal JB and Bass EB. Management of atrial fibrillation: review of the evidence for the role of pharmacologic therapy, electrical cardioversion, and echocardiography. *Ann Intern Med*. 2003;139:1018-33.
46. de Paola AA, Horowitz LN, Morganroth J, Senior S, Spielman SR, Greenspan AM and Kay HR. Influence of left ventricular dysfunction on flecainide therapy. *J Am Coll Cardiol*. 1987;9:163-8.
47. Josephson MA, Kaul S, Hopkins J, Kvam D and Singh BN. Hemodynamic effects of intravenous flecainide relative to the level of ventricular function in patients with coronary artery disease. *Am Heart J*. 1985;109:41-5.
48. US Prescribing Information , Flecainide Acetate Tablets: 50, 100 and 150 mg. Aurobindo Pharma Ltd, East Windsor, NJ, USA; December 2017. https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=14e89448-3a18-42e3-8537-2589be1ef94e.
49. Nabar A, Rodriguez LM, Timmermans C, Smeets JL and Wellens HJ. Radiofrequency ablation of "class IC atrial flutter" in patients with resistant atrial fibrillation. *Am J Cardiol*. 1999;83:785-7, A10.
50. Falk RH. Proarrhythmia in patients treated for atrial fibrillation or flutter. *Ann Intern Med*. 1992;117:141-50.
51. Van Gelder IC, Tuinenburg AE, Schoonderwoerd BS, Tieleman RG and Crijns HJ. Pharmacologic versus direct-current electrical cardioversion of atrial flutter and fibrillation. *Am J Cardiol*. 1999;84:147R-151R.

52. Fresco C and Proclemer A. Clinical challenge. II. Management of recent onset atrial fibrillation. PAFIT-2 Investigators. *Eur Heart J*. 1996;17 Suppl C:41-7.
53. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM, 3rd, Thomas JD and American College of Cardiology/American Heart Association Task Force on Practice G. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2438-88.
54. Dolgin M FA, Gorlin R, Levin RI. New York Heart Association. Criteria Committee. . Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. . 9th ed. Boston, MA: Lippincott Williams and Wilkins. March 1, 1994.

16 Protocol Amendments

Refer to separate Summary of Changes document.

17 Appendices

17.1 Appendix 1: Definition of terms

Abnormal liver function is defined as chronic hepatic disease (e.g., cirrhosis) or biochemical evidence of significant hepatic derangement (e.g., bilirubin > 2 times the ULN, in association with aspartate aminotransferase/alanine transferase/alkaline phosphatase > 3 times the upper limit of normal, and so forth).

Abnormal renal function is defined as chronic dialysis, renal transplantation, or serum creatinine ≥ 200 μmol/L (≥ 2.26 mg/dL).

Aortic or mitral stenosis typically refers to a narrowing, stiffening or obstruction of flow at the level of the native aortic or mitral valve. The earlier released AHA/ACC heart disease guidelines[53] define the stages for stenosis.

*Body mass index (*BMI) is defined as the body mass divided by the square of the body height, and is expressed in units of kg/m^2.

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 for ≥ 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies. All individuals with an estimated GFR < 30 mL/min/1.73 m^2 are classified as having severe renal impairment.

Heart failure (HF) classification according to the New York Heart Association (NYHA) Functional Classification places subjects in one of four categories based on how much they are limited during physical activity.[54]

Class	Subject Symptoms
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortness of breath).
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea (shortness of breath).
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Paroxysmal AF (PAF), also termed intermittent AF, is defined as an episode of AF that terminates spontaneously or with intervention in less than seven days[8, 9].

The *QT interval corrected for heart rate (QTc)* is estimated according to the Fridericia's formula[1],

$$QTc_F = \frac{QT}{\sqrt[3]{RR_{\text{interval in sec}}}}$$

, and where the RR interval is equal to (60 / HR) and HR is the heart rate in beats per minute.

Sick sinus syndrome is an ECG diagnosis suggesting sinus node disease. It may be manifested by sinus bradycardia, sinus tachycardia, ectopic atrial rhythm, or sinus pauses, alone or in combination.

17.2 Appendix 2: Adverse Events: Definitions and classifications of AE assessment

17.2.1 Definitions

17.2.1.1 Adverse Events

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

For the purposes of this study, a recurrence of AF will not be considered as an AE. Atrial fibrillation recurrence will be collected in a specific, designated eCRF.

17.2.1.2 Serious adverse event

An SAE (experience) or reaction is any untoward medical occurrence that, at any dose:

a) results in death.
b) is life-threatening.
   NOTE: The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
c) requires inpatient hospitalization or prolongation of existing hospitalization.
   NOTE: A hospitalization or prolongation of hospitalization is not regarded as an SAE if at least one of the following exceptions is met:
   - The admission results in a hospital stay of less than 24 hours
   - The admission is not associated with an AE (e.g., social hospitalization for purposes of respite care).

   However, invasive treatment during any hospitalization may fulfill the criterion of ‘medically important’ (see below) and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.
d) results in persistent or significant disability/incapacity.
e) is a congenital anomaly/birth defect.
f) is any other medically important condition (see below).

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be

immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

NOTE: A procedure is not an AE or SAE, but the reason for the procedure may be an AE or SAE. Treatment requiring hospitalizations for pre-existing conditions which do not worsen in severity are not SAEs.

17.2.2 Classifications for AE assessment

The following classifications are made by the Investigator, who is a qualified physician, based on all available information at the time of completion of the eCRF.

17.2.2.1 Seriousness

The seriousness of each AE must be determined according to definitions provided under Section 17.2.

17.2.2.2 Intensity

The intensity of an AE is graded as follows:

a) Mild: Discomfort noted, but no disruption of normal daily activity.
b) Moderate: Discomfort sufficient to reduce or affect normal daily activity.
c) Severe: Inability to work or perform normal daily activity.

17.2.2.3 Causal relationship

Causality is assessed separately for each individual AE and detailed in the eCRF. The assessment shall be made based on the available information and can be updated as new information becomes available. The assessment is based on whether there is “reasonable causal relationship” to the medicinal product in question:

a) Related:
   - The AE follows a reasonable temporal sequence from the assigned regimen administration and cannot be reasonably explained by the subject’s clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).
   - The AE follows a reasonable temporal sequence from the assigned regimen administration and is a known reaction to any of the study drug under study or its chemical group or is predicted by known pharmacology.

b) Not Related:
   - The AE does not follow a reasonable sequence from the assigned regimen administration or can be reasonably explained by the subject's clinical state or other factors (e.g., disease under study, concurrent diseases, and concomitant medications).

17.2.2.4 Action taken regarding study drug(s)

Any action taken on study treatment to resolve the AE is documented in the eCRF as follows:

a) Dose Not Changed: No change in study drug dosage is made.
b) Drug Withdrawn: The study drug is permanently stopped.
c) Dose Reduced: The dosage of study drug is reduced.
d) Drug Interrupted: The study drug is temporarily stopped.
e) Dose Increased: The dosage of study drug is increased.
f) Not applicable: Study drug treatment was completed prior to event, or event occurred prior to start of study drug treatment, or subject died.

17.2.2.5 Other action taken for event

If the AE resolution requires any other action, this is captured in the eCRF as follows:

a) None
   - No other treatment was required.

b) Remedial drug therapy required
   - Prescription and/or over-the-counter medication was required to treat the AE.

c) Hospitalization or prolongation of hospitalization required
   - Hospitalization was required or prolonged due to the AE, whether or not medication was required.

d) Other

17.2.2.6 Adverse event outcome

The outcome of each individual AE is documented as follows:

a) Recovered/Resolved
   - The subject fully recovered from the AE with no residual effect observed.

b) Recovered/Resolved with Sequelae
   - The residual effects of the AE are still present and observable.
   - Include sequelae/residual effects.

c) Not Recovered/Not Resolved
   - The AE itself is still present and observable.

d) Recovering/resolving
   - The AE itself is still present and observable, but improving

e) Fatal
f) Unknown

17.3 Appendix 3: Study organization

17.3.1 Data and Safety Monitoring Board (DSMB)

An independent DSMB protects the rights, safety and well-being of subjects participating in this study. The primary role of the DSMB is to examine the open-label safety data for Part A, Part B, Part C (suspected, related SAEs) on an ongoing manner and to alert the Executive Committee in case of any clinically concerning safety issues. The frequency and extent of the data reviews by the DSMB, details about the reviews, and criteria for evaluating need for study protocol modifications are described and specified in the DSMB Charter.

The DSMB can recommend modification of the study protocol, or study, or treatment regimen to the Executive Committee based on pre-specified rules described in the DSMB charter. All activities of the DSMB are documented. This documentation includes data summaries and analyses provided to the DSMB, and all documentation remains confidential within the DSMB until the study is completed.

17.3.2 Executive Committee

The Executive Committee is responsible for the overall design, conduct, and supervision of the study. The Executive Committee also reviews the progress of the study at regular intervals to ensure subject safety and study integrity. The Executive Committee is comprised of designated scientific advisors, CRO, and Sponsor.

17.3.3 Administrative information

17.3.3.1 Sponsor

InCarda Therapeutics, Inc.
Luiz Belardinelli, MD
Chief Medical Officer and US Medical Monitor
39899 Balentine Drive, Suite 185
Newark, CA 94560, USA
Tel.: +1 (650) 704-2805

17.3.3.2 CRO

Cardialysis
Westblaak 98, 3012 KM Rotterdam, The Netherlands
Tel.: +31(0) 206 2828
Fax: +31(0) 206 2844

17.3.3.3 Data Management

Cardialysis
Westblaak 98, 3012 KM Rotterdam, The Netherlands
Tel.: +31(0) 206 2828
Fax: +31(0) 206 2844

17.3.3.4 Safety Management

PrimeVigilance
1 Occam Court
Surrey Research Park
Guildford, Surrey
GU2 7HJ
United Kingdom
Tel.: +44 1483 307920
Tel.: (+) 781-703-5540

17.4 Appendix 4: Schedule of Assessments

17.4.1 PRE-STUDY SCREENING

Table 3 - Pre-Study Screening - Schedule of Assessments

Period	Pre-Study Screening	
Day	Pre-Study Screening [1]	Clinic Visits [2]
Assessment		
Informed consent	X	
Contact eCRF for SID	X	
Demographic information	X	
Medical history	X	
AeroEclipse II BAN (training)	X	X

[1] For subjects who (a) are prescribed a pill-in-the-pocket regimen (flecainide or propafenone) for paroxysmal AF, (b) are within 3 months of undergoing ablation of paroxysmal AF, (c) have experienced an episode of new AF but are not currently experiencing an episode of recent-onset paroxysmal AF, or (d) are known to have paroxysmal AF (or previously diagnosed with paroxysmal AF) and have had one or more previous symptomatic episodes but are not currently experiencing an episode of recent-onset paroxysmal AF.

[2] If the subject returns to clinic for a visit with the Investigator (related or unrelated to the study), repeat training and practice with the inhaler should be performed if possible.

17.4.2 PART A: Schedule of Assessments

Refer to a previous version of the protocol.

17.4.3 PART B and PART C Medically-Led Cardioversion Study: Schedule of Assessments

Table 4 - PART B and PART C Medically-Led Cardioversion Study 120 mg FlecIH-103 (75 mg/mL) REPEAT DOSE REGIMEN - Schedule of Assessments

Period	Screening				Treatment							Extended observation			Follow-up	
	Day 1														Day 2	Day 5 ±1
Phase	Pre-screening	AF-monitoring			1st IH	Break	2nd IH	Post dose						At SR	Visit 1	Visit 2= EOS
Time points (min) [1]	≥ −45	−45	−30	−15	0 – 3.5	3.5 - 4.5	4.5 - 8	1	3	10	30	60	90 [2]	t [3]		
Assessment																
Qualification criteria	X															
Demographic information	X															
Medical history & prior medications	X															
Informed consent		X														
Contact eCRF for SID [4]		X														
Eligibility criteria		X		X												
AF stability		Continuous														
Physical Exam [5]		X														
Handheld echocardiogram [6]		X														
Remote ECG		X											X		X	X
Telemetry		Continuous														
AECG		Continuous														
ECG extracted from AECG [7]		X	X	X	X [8]	X		X	X	X	X	X	X	X		
Vital signs [9]		X	X	X	X [8]	X		X	X	X	X	X	X	X		
PK blood sample		X				X		X	X	X	X	X	X	X		
Enrollment (Allocation) in eCRF		X														
AeroEclipse II BAN (training)		X														
Administer study drug [10]					X		X									
Subject in seated position [11]			Continuous													
Hematology panel [12]		X														
Comprehensive metabolic panel [12]		X											X			
Coagulation panel [12]		X														
Serum or urine pregnancy test [12]		X														
Treatment satisfaction questions [13]													X			
AF symptoms					X [8]						X	X	X		X	X
Concomitant medications & therapies		Continuous														
Adverse events		Continuous														

[1] Time zero is the start of the inhalation. Time points after dosing are based on the end time of the inhalation (e.g., 1 = 1 minute post completion of dosing).
[2] Assessments have a ±10-minute window (i.e., 80-100 minutes)
[3] The actual time of conversion to SR is recorded.
[4] Only if not already done during pre-study screening
[5] Including height, weight and derived-BMI at baseline and auscultation of the heart and the lungs.
[6] A diagnostic echocardiogram using a Sponsor-provided handheld portable ultrasound device (HHE) is performed during screening to evaluate for exclusionary structural heart or functional abnormality for US subjects who do not already have a standard diagnostic echocardiogram (including LVEF) within 6 months prior to screening, or for EU subjects who have specifically consented to the HHE Sub-Study.
[7] Triplicate ECGs are extracted from the AECG by the ECG Core Laboratory after data are transmitted by the site. ECGs are extracted within 5 minutes after the scheduled time point or up to the next scheduled time point, whichever comes first.
[8] Just before starting inhalation (IH) regimen.
[9] Heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min) and SpO2. Body temperature is recorded at screening only. When time-points coincide for blood draws and vital signs, procedures are performed in that order.
[10] Record the start and stop times for each inhalation stage. If a subject's AF converts to SR within the first inhalation stage, then the break and the second inhalation stage will not take place.
[11] The subject shall be seated upright after the –30-minute time point assessments are completed.
[12] Refer to Section 9.2 B.
[13] After 90 minutes post dose and prior to discharge, subjects whose AF is converted to SR by study drug will be asked questions related to their treatment satisfaction (refer to Section 7.4 B).

17.4.4 PART C Patient-Led Under Medical Supervision Cardioversion Study: Schedule of Assessments

Table 5 – PART C Patient-Led Under Medical Supervision Cardioversion Study 120 mg FlecIH-103 (75 mg/mL) REPEAT DOSE REGIMEN - Schedule of Assessments

Period	Consenting	Training			Treatment (one recurrent episodes) [1]										Follow-up	
Visit	Before or on Day 1	Training Visit	Phone Calls	Clinic Visits	Day 1										Day 2	Day 5
Phase					Before Dosing		During Dosing	After Dosing								
Visit Window / Time point (min) [2]			Monthly	Q3 months	~ 30	– ≤ 10		1	3	10	30	60	90	At SR [3]	+1 day	±1 day
Assessment																
Informed consent	X															
Train subject on self-administration		X														
Subject performs self-administration evaluation		X														
Site certifies subject in self-administration		X														
AE/CM check		X	X	X	Continuous										X	X
Subject watches training video			X													
Subject completes refresher training (in clinic or by video call)				X												
Changes to medical history					X											
Serum creatinine					X											
Serum potassium					X											
Serum/urine pregnancy test [4]					X											
12-lead ECG [5]					X											
PK blood sample					X				X					X		
Symptom-driven physical examination [6, 7]					X											
Telemetry					Continuous											
AECG (Holter)[10]					Continuous											
Vital signs [8]					X	X		X	X	X	X	X	X			
AF-related symptoms [7]					X						X	X	X		X	X
Self-administration of drug [9]							X									

AE = adverse event; CM = concomitant medication; AECG = ambulatory electrocardiogram; PK = pharmacokinetic

[1] Subjects may return for to self-administer study drug for any recurrent episode of symptomatic paroxysmal AF within 8 months after signing informed consent.

[2] Time zero (T_0) is the start of the inhalation. Time points after dosing are based on the end time of the inhalation (e.g., 1 = 1-minute post dose).

[3] Actual time of conversion to SR is recorded.

[4] For female subjects of child-bearing potential only

[5] To confirm AF diagnosis

[6] Per investigator discretion

[7] Any time prior to dosing

[8] Heart rate, systolic and diastolic blood pressure, respiratory rate (breaths/min), SpO_2, and body temperature. Body temperature is recorded at 30 min pre-dose only. Weight must be recorded any time prior to dosing to confirm creatinine clearance eligibility. When time-points coincide for blood draws and vital signs assessment, procedures are performed in said order.

[9] Record each inhalation's start and stop times, as applicable.

[10] ECGs may be extracted per the timepoints specified in the Part B/Part C Medically-Led Cardioversion Study Schedule of Assessments

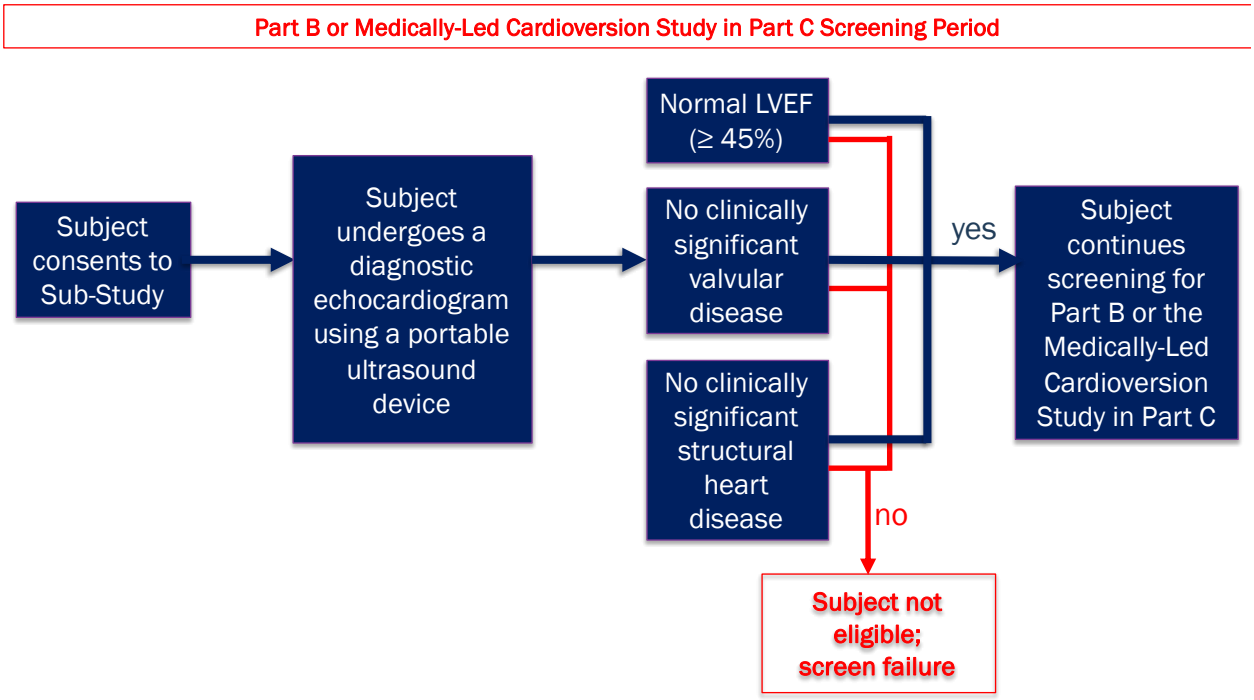
[11] Assessments have a ±10 minute window (i.e. 80-100 minutes)

17.5 Appendix 6: Handheld Echo (HHE) Sub-Study

17.5.1 HHE Sub-Study design

Subjects who consent to participate in Part B or in the Part C Medically-Led Cardioversion Study may also consent to participate in this optional HHE Sub-Study. If they consent, they will undergo a diagnostic echocardiogram (**Figure 7**) using the Sponsor-provided portable ultrasound device. The assessments and measurements to be made from the echocardiogram are described in Section 17.5.4. Only subjects with assessments that are normal, minimal, or absent, will be eligible for the study. If the subject's HHE indicates the subject has a clinically significant enlarged LV and/or reduced EF, or clinically significant structural heart disease (e.g., LV hypertrophy, valvular disease), they will be considered ineligible for enrollment and recorded as a screen failure. The Sub-Study design is shown in **Figure 7**.

Figure 7. HHE Sub-Study Design



17.5.2 HHE Sub-Study population and eligibility criteria

Approximately 20 subjects (only at select EU sites) are expected to participate in this HHE Sub-Study. These 20 subjects will be a subset of those who consent to participate in Part B and the Medically-Led Cardioversion Study in Part C.

17.5.3 HHE Sub-Study procedures

The recording of the echocardiogram must be obtained during the screening period for Part B, as described in **Figure 7** above.

17.5.3.1 HHE Sub-Study Consenting

Subjects who have consented to Part B or the Medically-Led Cardioversion Study in Part C may consent to this Sub-Study during the screening period. Only after signing consent for the Sub-Study may the subject undergo any Sub-Study-related procedures.

17.5.3.2 HHE Sub-Study Evaluation

After providing informed consent for this Sub-Study, subjects will undergo a diagnostic echocardiogram using a Sponsor-provided handheld portable ultrasound device (HHE). The site staff will evaluate the subject's echocardiogram for any structural heart and functional abnormality. Subjects with exclusionary valvular or structural heart disease (as per exclusion criteria, refer to Section 4.2 B) or clinically significant enlarged LV or decreased EF observed on the echocardiogram will be considered ineligible for enrollment and recorded as screen failures.

17.5.4 HHE Sub-Study assessments

17.5.4.1 HHE Sub-Study Portable cardiac ultrasound

Subjects undergo a diagnostic echocardiogram using a Sponsor-provided handheld portable ultrasound device (HHE) on Day 1 during the screening period. The subject may not be enrolled until evaluation of the echocardiogram is completed.

The following data will be recorded from the HHE:

- Date and time HHE administered
- Who performed the HHE (e.g., professional title or study role)
- Date and time HHE report/results became available
- Who analyzed the HHE (e.g., professional title or study role)
- The following assessments will be recorded:
    - LV size
    - LVEF
    - LV hypertrophy
    - Valvular disease
    - Other clinically significant findings

HHE data will 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.

17.5.5 HHE Sub-Study Other assessments

17.5.5.1 HHE Sub-Study Feasibility assessments

The following parameters will be evaluated for feasibility in an exploratory manner:

- Successful capture of the following data:
  - Left ventricular size
  - Left ventricular ejection fraction (LVEF)
  - Left ventricular hypertrophy
  - Valvular disease
- 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

17.5.6 HHE Sub-Study Schedule of Assessments

Table 6 - HHE Sub-Study - Schedule of Assessments

Visit	Day 1
Phase	Screening
Assessment	
Informed consent	X
Diagnostic echocardiogram (HHE) [1]	X
[1] A diagnostic echocardiogram using a Sponsor-provided handheld portable ultrasound device (HHE) will be performed during screening and prior to enrollment to evaluate for exclusionary structural heart or functional abnormality.	