CLINICAL STUDY PROTOCOL

A pilot study on Edoxaban for the resolution of left atrial thrombosis in patients with non-valvular atrial fibrillation

Study code:	**EDO-SP-01-2015**
EudraCT Number:	**2015-004847-37**
Promoter:	**Fondazione Gabriele d'Annunzio** Via dei Vestini, 31 66100 Chieti
Coordinating investigator :	**Prof. Raffaele De Caterina** Università degli Studi G. d'Annunzio Via dei Vestini 66013 Chieti E-mail: rdecater@unich.it
Version and date:	**Ver. 4.0 (18 Sept 2017)**

PROTOCOL SIGNATURE PAGE

Version 4.0 – 18 Sept 2017

Promoter's approval

Name (Block letters)	Qualification
Signature	Date

Investigator's agreement

I have discussed the objectives of this trial and the contents of this protocol with the Promoter's representative. I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution of the ethical review of the study, without written authorisation from Fondazione Gabriele d'Annunzio di Chieti. It is, however, permissible to provide information to a subject in order to obtain consent.

I agree to conduct the trial according to this protocol and to comply with its requirements, subject to ethical and safety requirements and guidelines, and to conduct the trial according to ICH guidelines on GCP and with the applicable regulatory requirements.

I understand that the Promoter may decide to suspend or prematurely terminate the trial at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the trial I will communicate my intention immediately in writing to the Promoter.

Principal Investigator name (Block letters)	Qualification
Signature	Date

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1.1. SYNOPSYS

Name of Sponsor:	***Fondazione Gabriele d'Annunzio - Chieti***	
Name of Finished Product:	Lixiana	
Name of Active Substance:	Edoxaban	
Title of the Study: **Abbreviated Title:**	A pilot study on Edoxaban for the resolution of left atrial thrombosis in patients with non-valvular atrial fibrillation Edoxaban in AF	
Study Coordinating Investigator:	Prof. Raffaele De Caterina	
Study Centres:	A total of 6-8 Italian sites will be involved.	
Background	Current guidelines indicate a ≥3 weeks therapy with VKAs to allow the resolution of LA or LAA thrombus in patients with atrial fibrillation before cardioversion.	
Rationale:	Isolated reports have indicated that complete LA or LAA thrombus resolution may be achieved also with use of oral Factor Xa inhibitors, which have demonstrated the same efficacy but a better safety profile compared to warfarin. The aim of this open-label pilot study is to investigate the percentage of LA/LAA thrombus resolution with edoxaban therapy in patients with non-valvular atrial fibrillation. The subordinated aim is the design a larger and longer study to compare edoxaban and warfarin in the same patient population.	
Planned Study Period:	Start of enrolment: November 2017 End of enrolment: February 2019	**Clinical Phase:** Phase 2
Objectives:	The primary objective of the study will be the definition of the percentage of patients who, after 4 weeks of edoxaban treatment, will experience complete thrombus resolution by TEE. Secondary objectives will be the assessment of bleeding events after 4 weeks of treatment with edoxaban and, after the same period, the incidence of any stroke or peripheral embolism and the time, when applicable, to electrical cardio-version.	
Methodology:	Non-controlled, open-label, 4 weeks pilot study.	
Number of patients:	A total of 25 patients will be included in the study.	
Diagnosis and Criteria for Inclusion:	**Inclusion criteria** Patients with all the following criteria will be eligible for inclusion in the study protocol: 1. Signed written informed consent. 2. Males and females ≥ 18 years of age. 3. Female subjects must be post-menopausal (for at least 2 years), surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and, for those of	

	childbearing potential, have a negative serum β-hCG pregnancy test at screening. 4. Atrial fibrillation (AF) must be documented by ECG evidence (e.g., 12-lead ECG, rhythm strip, Holter, pacemaker interrogation) within 30 days before enrolment. 5. Subjects with newly diagnosed atrial fibrillation are eligible provided that: • -there is evidence that the atrial fibrillation is non-valvular: • -there is ECG evidence on 2 occasions 24 hours apart demonstrating atrial fibrillation. 6. LA or LAA thrombosis documented by trans-esophageal echocardiography (TEE) 7. CHA_2DS_2-VAS_C score >1. **Exclusion criteria** Patients with all the following criteria will not be eligible for inclusion in the study protocol: 1. Hemodynamically significant mitral valve stenosis. 2. Prosthetic heart mechanical or biological valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted). 3. Transient atrial fibrillation caused by a reversible disorder (e.g., thyrotoxicosis, pulmonary embolism, recent surgery or myocardial infarction). 4. Known presence of atrial myxoma. 5. Left ventricular thrombus. 6. Active endocarditis. 7. Active internal bleeding. 8. History of condition associated with increased bleeding risk including, but not limited to: • major surgical procedure or trauma within 30 days; • clinically significant gastrointestinal bleeding within 6 months; • previous intracranial, intraocular, spinal, atraumatic intra-articular bleeding; • chronic haemorrhagic disorder; • Any neoplasm, including intracranial neoplasm, • arteriovenous malformation or aneurysm. 9. Platelet count <90,000/μL at the screening visit. 10. Sustained uncontrolled hypertension: SBP ≥180 mmHg or DBP ≥100 mmHg. 11. Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive within 3 months or any stroke < 14 days). 12. Transient ischemic attack within 3 days. 13. Any oral anticoagulant therapy at the time of the baseline visit. 14. Treatment with: • aspirin >160 mg daily; • aspirin plus a thienopyridine within 5 days; • intravenous antiplatelets within 5 days; • fibrinolytics within 10 days. 15. Anticipated need for therapy with a non-steroidal anti-inflammatory drug in the next 4 weeks. 16. Treatment with a strong inducer of cytochrome P450 and P glycoprotein, such as ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, lopinavir,

	telaprevir, indinavir, conivaptan, claritromycin or planned treatment during the study. 17. Other indication for anticoagulant therapy. 18. Hypersensitivity or intolerance to the study drug, including excipients. 19. Women of childbearing potential who do not want adopt a contraceptive method during the study period and the following 4 weeks. 20. Breast-feeding women during the study period and the following 4 weeks. 21. Anemia (hemoglobin <10 g/dL) at the screening visit. 22. Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT or AST >2 x ULN or total bilirubin >1.5 x ULN. 23. Patients with moderate or severe renal impairment (CrCL <50 mL/min) or patients with end stage renal disease (CrCL < 15 mL/min) or on dialysis.
Test Product, dose and duration of treatment	All patients will receive edoxaban 60 mg once a day, with open-label design, for 4 weeks. Edoxaban daily dose will be reduced to 30 mg/day in case of: body weight ≤60 kg, or concomitant therapy with verapamil/quinidine/dronedarone.
Statistical Methods:	*Sample Size* There are no previous studies conducted with edoxaban on atrial thrombus dissolution and this is a pilot trial. For this reason sample size has been determined empirically, on the basis of case reports with similar products in this clinical conditions (6, 8-10, 15). However, if the proportion of patients with thrombus dissolution after 4 weeks of treatment will be 60%, which is compatible with the above mentioned case reports, a sample size of 25 produces a two-sided 95% confidence interval with range 39-79%. *Primary Analysis* Primary outcome will be the detection of the percentage of patients, after 4 weeks of edoxaban treatment, with complete thrombus resolution by TEE, evaluated with the following Probe angulations: 0°, 45°-to-60°, 90°. As this is a single arm, open-label study, in principle, only a descriptive statistical analysis will be performed for the primary criterion. *Secondary analyses* Secondary endpoints will be: absolute and percent variation of thrombus area at 4 weeks by TEE evaluation (Probe angulations: 0°, 45-to-60°, 90°) and time to electrical cardio-version (when applicable). Only a descriptive statistical analysis will be performed for the secondary criterion. *Safety analysis* Analyses of the safety criteria that will include: percentage of bleeding events at 4 weeks and after 8 weeks (telephone assessment) after the end of the treatment; percentage of any stroke or peripheral embolism at 4 weeks and after 8 weeks (telephone assessment) after the end of the treatment; percentage of any other safety related events (deaths, SAEs and AEs).

Study flow-chart

Timing	**BASELINE**	**FOLLOW-UP**	**PHONE ASSESSMENT**
	Day 0	***Week 4*** *(± 3 days)*	***Week 8*** *(± 3 days)*
Confirmation of consent	■		
Verification of inclusion/exclusion criteria	■		
Demographic data	■		
Medical history	■		
CHA_2DS_2-VAS_C score and HAS-BLED score	■		
Information regarding AF	■	■	
Blood pressure, heart rate	■	■	
EKG	■	■	
Transthoracic echocardiogram	■	■	
Transesophageal echocardiogram	■	■	
Blood count; liver and renal function	■	■	
Concomitant treatments	■	■	
Bleeding events		■	■
Thromboembolic events		■	■
Other adverse events		■	■
Study drug dispensation	■		
Compliance		■	
Study completion form			■

1.2. LIST OF ABBREVIATIONS

ADR	:	Adverse Drug Reaction
AE	:	Adverse Event
AF	:	Atrial Fibrillation
ALT	:	Alanine aminotransferase
AST	:	Aspartate aminotransferase
ATC	:	Anatomical Therapeutic Chemical Classification System
CHA_2DS_2	:	Cardiac failure, Hypertension, Age (x2), Diabetes, Stroke (x 2) risk index
CI	:	Confidence Interval
CRA	:	Clinical Research Associate
CRF	:	Case Report Form
DBP	:	Diastolic Blood Pressure
EC	:	Ethic Committee
ECG	:	Electrocardiogram
FAS	:	Full Analysis Set
GCP	:	Good Clinical Practice
HR	:	Hazard Ratio
ICH	:	International Conference on Harmonisation
LA	:	Left Atrial
LAA	:	Left Atrial Appendage
MedDRA	:	Medical Dictionary for Regulatory Activities
NOAC	:	Non vitamin K oral anticoagulants
OAC	:	Oral Anticoagulant Therapy
PP	:	Per Protocol
SAE	:	Serious Adverse Event
SBP	:	Systolic Blood Pressure
SEE	:	Systemic Embolic Events
SmPC	:	Summary of Product Characteristics
TEE	:	Trans Esophageal Echocardiography
ULN	:	Upper Level of Normal
VKA	:	vitamin K antagonists
WHO	:	World Health Organization

2. INTRODUCTION AND STUDY RATIONALE

2.1. TARGET PATHOLOGY AND THERAPY

It is estimated that atrial fibrillation (AF) affects up to 2% of the general Western World population, and up to 5% of acute stroke patients. The lifetime risk of developing an episode of AF is up to 25% in those who have reached the age of 40 (1).

AF is associated with increased rates of death, stroke and other thromboembolic events. Death rates are doubled by AF, whereas stroke is often severe and results in long-term disability. It is estimated that about 20% of stroke is due to AF (1). Moreover, hospitalizations due to thromboembolic complications and progressive cognitive dysfunction due to asymptomatic embolic events are also ascribed to AF (1).

Current guidelines indicate a ≥3 weeks therapy with vitamin K antagonists (VKAs) to allow the resolution of left atrial (LA) or left atrial appendage (LAA) thrombus in patients with atrial fibrillation (1) before cardioversion.

The presence of LA and LAA thrombi is usually detected by transesophageal echocardiography (TEE). When thrombus is detected, the percentages of thrombus resolution with VKAs vary, in various studies, from 55% to 85% usually in 4 weeks time (2-5). Such range is at least in part related to the level of anticoagulant activity obtained, and resolution likely depends on optimal anticoagulation intensity under VKA treatment, which is sub-optimal in the induction phase of VKA treatment.

Isolated reports (6, 15) have indicated that complete LA or LAA thrombus resolution may be achieved with the use of oral Factor Xa inhibitors, which in randomized trials were non-inferior to warfarin with regard to the incidence of the primary outcome measure (7), including any stroke or peripheral embolism in patients with non-valvular atrial fibrillation, but also ensure immediate and stable anticoagulation. Oral Factor Xa inhibitors have also demonstrated a better safety profile than warfarin.

2.2. TARGET PATHOLOGY DEFINITION

Non-valvular atrial fibrillation in patient with high atrial fibrillation-related thromboembolic risk, and LA or LAA thrombosis.

2.3. INFORMATION ON THE TEST PRODUCT

Edoxaban is an oral direct factor-Xa inhibitor similar to the previously developed molecules rivaroxaban and apixaban.

As reported in the approved SmPC, both animal and Phase I studies have demonstrated that edoxaban is highly effective in factor Xa-inhibition activity and reducing clot formation. In rat and monkey models, edoxaban demonstrated almost complete inhibition of factor-Xa activity and (in particular in monkeys) a rapid onset of inhibitory effect.

Edoxaban quickly reaches peak plasma concentrations in 1.5 hours; its half-life is between 10 and 14 hours. Oral bioavailability is quite high (more than 62%) and factor-Xa inhibition is highly selective, competitive, and concentration-dependent. Plasma concentrations of edoxaban are also closely correlated with the suppression of other coagulation indices and various platelet-activation parameters.

The results for all-cause mortality in the pivotal study ENGAGE AF-TIMI 48 study were 769 (3.99% per year) for subjects taking edoxaban 60 mg as opposed to 836 (4.35% per year) for warfarin [HR (95% CI): 0.91 (0.83 - 1.01)].

In the same study there was a significantly lower rate in favour of the edoxaban 60 mg treatment group compared with the warfarin group of major bleeding (2.75%, and 3.43% per year, respectively) [HR (95% CI): 0.80 (0.71,- 0.91); p = 0.0009], and intracranial hemorrhage (0.39%, and 0.85% per year, respectively) [HR (95% CI): 0.47 (0.34 - 0.63); p < 0.0001].

The lower rates of fatal bleeds were also significant for the edoxaban 60 mg treatment group compared with the warfarin group (0.21%, and 0.38%) [HR (95 % CI): 0. 55 (0.36 - 0.84); p =

0.0059 for superiority], primarily because of the reduction in fatal Intracranial haemorrhage bleeds [HR (95% CI): 0.58 (0.35 - 0.95); p = 0.0312].

2.4. STUDY RATIONALE

The aim of this open-label pilot study is to investigate the extent of LA/LAA thrombus resolution with edoxaban therapy in patients with non-valvular atrial fibrillation.

A subordinated aim of this study is the planning and design of a larger study directly comparing edoxaban vs warfarin in the same patient population. With the exception of few case reports, there are no data in the same patient population referred to antithrombotic treatments other than vitamin K antagonists.

As the main goal of this exploratory study is the estimation of the magnitude of the LA/LAA thrombus resolution with edoxaban, no control group with vitamin K antagonists has been considered, providing that, for the purpose of this study, the magnitude of the response of warfarin is satisfactory defined (1).

2.5. OVERALL RISK AND BENEFIT ASSESSMENT

Anticoagulant therapy is anyway necessary for the population under study

Patients with AF have an increased risk of recurrent embolism, and therefore should receive anticoagulant therapy. In particular, for patients with CHA_2DS_2-VASc score >1 the Guidelines for the management of atrial fibrillation (1) recommend an anticoagulant therapy in any case. Either oral anticoagulant therapy (OAC), including non-vitamin K oral anticoagulants (NOACs), or aspirin 75–325 mg daily are recommended, with preference of OAC to aspirin.

No use of placebo

Placebo is not used in this study, neither as a comparative agent nor as an add-on agent, in the cohort of patients under study.

Edoxaban is safer than warfarin

In the pivotal ENGAGE AF-TIMI 48 study (7) it has been demonstrated that more than half of the lower rates of all-cause deaths with edoxaban as compared to warfarin were directly attributable to fewer fatal bleeding events and non-fatal major bleeding that contributed to a death within 30 days. There were no differences between edoxaban and warfarin in deaths due to non-cardiovascular causes, nor for any of the 3 most common cardiovascular causes of death, sudden cardiac death, heart failure, ischemic stroke. However, warfarin was associated with approximately twice the risk of fatal bleeding as compared to edoxaban

Positive results with other NOACs

There have been few recent case reports about the resolution of LAA thrombus in patients treated with NOACs (6, 8-10), showing disappearance of thrombi after very 5 weeks or less of NOACs treatment, and consistently suggesting that such therapy might be effective the this clinical condition.

Summary of risk and benefit assessment

Taking into account all medical needs, the positive safety data of edoxaban compared to warfarin, and the encouraging efficacy data from drugs belonging to the same class, it can be reasonably concluded that the participation to this study does not expose the patient to unforeseen risks.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

The primary objective of the study will be the definition of the extent of patients who, after 4 weeks of edoxaban treatment, will experience complete thrombus resolution by TEE.

3.2. SECONDARY OBJECTIVE(S)

Secondary objectives will be the assessment of bleeding events after 4 weeks of treatment with edoxaban and, after the same period, the incidence of any stroke or peripheral embolism and the time, when applicable, to electrical cardioversion.

4. ETHICAL CONSIDERATIONS RELATING TO THE STUDY

The trial will be conducted according to Good Clinical Practices (CPMP/ICH/135/95), as well as the Declaration of Helsinki and its subsequent amendments (see Appendix) and national regulations. This protocol and related documents (included the informed consent form) will be submitted for approval to independent local Ethics Committees before the study set up, according to national regulations.

All the protocol amendments or critical events liable to increase the risks incurred by the subjects or to compromise the validity of the study or subjects' rights will be submitted to the Coordinator, the concerned Authorities and the Ethics Committees.

After being informed orally and in writing of all aspects and constraints of the trial, as well as of their freedom to withdraw their participation at any time, patients will sign a consent form. A time for informed reflection on the protocol will be given to each patient before they give written consent and before starting the study procedures.

Patients will be made aware of their rights to decline to participate or to withdraw from the study at any time.

This study does not involve the use of placebo.

5. STUDY DESIGN

5.1. OVERALL DESCRIPTION

This is a pilot, non-controlled, open-label, 4-weeks study.

5.2. DISCUSSION OF THE STUDY DESIGN

5.2.1. Choice of the Study Population

A total of 25 patients with non-valvular atrial fibrillation, high atrial fibrillation-related stroke risk, and documented LA or LAA thrombosis will be included in the study.

5.2.2. Choice of the Study Design

With the exception of some case reports (6, 15), there are no studies conducted with NOACs to assess their efficacy in the resolution of non-valvular atrial thrombi once they are formed in the atria. For this reason, this study was designed to get preliminary clinical indications in order to is plan a larger study directly comparing edoxaban and warfarin in the same patient population.

Due to its exploratory objective, no control group will be considered. Duration of the study is consistent with recommendations given by the guidelines, and with the reported clinical experiences (1, 6, 8-10, 15).

5.2.3. Choice of the Sample Size and the number of centres

There are no previous studies conducted with edoxaban on atrial thrombus dissolution, and this is a pilot trial. For this reason, sample size has been determined empirically, on the basis of case reports with similar products in this clinical conditions (6, 8-10, 15) and better described in section 14.

The involvement of 6-8 sites implies an enrolment of an average of about 4 patient per site to be recruited in about 15 months.

5.3. STUDY PERIOD

The planned start of enrolment is November 2017. The total duration of the enrolment phase is supposed to be 15 months and therefore the completion of the recruitment is expected by February 2019.

The last patient visit is expected by September 2018.

6. STUDY POPULATION

In this pilot study a total of 25 patients with non-valvular atrial fibrillation, high atrial fibrillation-related stroke risk and LA or LAA thrombosis will be recruited.

6.1. INCLUSION CRITERIA

Patients with all the following criteria will be eligible for inclusion in the study protocol:

1. Signed written informed consent
2. Males and females ≥ 18 years of age
3. Female subjects must be postmenopausal (for at least 2 years), surgically sterile, abstinent, or, if sexually active, be practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; and, for those of childbearing potential, have a negative serum β-hCG pregnancy test at screening
4. Atrial fibrillation (AF) must be documented by ECG evidence (e.g., 12-lead ECG, rhythm strip, Holter, pacemaker interrogation) within 30 days before enrolment.
5. Subjects with newly diagnosed atrial fibrillation are eligible provided that:
    a. there is evidence that the atrial fibrillation is non-valvular
    b. there is ECG evidence on 2 occasions 24 hours apart, demonstrating atrial fibrillation
6. LA or LAA thrombosis documented by transesophageal echocardiography (TEE)

7. CHA_2DS_2-VAS_C score >1.

6.2. EXCLUSION CRITERIA

Patients with all the following criteria will not be eligible for inclusion in the study protocol:

Cardiac-related conditions

1. Hemodynamically significant mitral valve stenosis
2. Mechanical or biological prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted)
3. Transient atrial fibrillation caused by a reversible disorder (e.g., thyrotoxicosis, pulmonary embolism, recent surgery or myocardial infarction)
4. Known presence of atrial myxoma
5. Left ventricular thrombus
6. Active endocarditis.

Bleeding risk-related criteria

7. Active internal bleeding.
8. History of condition associated with increased bleeding risk including, but not limited to:
    a. major surgical procedure or trauma within 30 days
    b. clinically significant gastrointestinal bleeding within 6 months
    c. previous intracranial, intraocular, spinal, atraumatic intra-articular bleeding
    d. chronic hemorrhagic disorders
    e. Any neoplasm, including intracranial neoplasm
    f. Arterio-venous malformation or aneurysm.
9. Platelet count <90,000/µL at the screening visit
10. Sustained uncontrolled hypertension: SBP ≥180 mmHg or DBP ≥100 mmHg
11. Severe, disabling stroke (modified Rankin score of 4 to 5, inclusive within 3 months or any stroke < 14 days)
12. Transient ischemic attack within 3 days.

Concomitant or intercurrent therapies

13. Any oral anticoagulant therapy at the time of the baseline visit
14. Treatment with:
    a. aspirin >160 mg daily
    b. aspirin plus a thienopyridine within 5 days
    c. intravenous antiplatelets within 5 days
    d. fibrinolytics within 10 days.
15. Anticipated need for therapy with a non-steroidal anti-inflammatory drug in the next 4 weeks
16. Treatment with a strong inducer of cytochrome P450 and P glycoprotein, such as ketoconazole, itraconazole, voriconazole, posaconazole, ritonavir, lopinavir, telaprevir, indinavir, conivaptan, claritromycin or planned treatment during the study
17. Other indications for anticoagulant therapy
18. Hypersensitivity or intolerance to the study drug, including excipients.

Other concomitant or intercurrent conditions

19. Women of childbearing potential who do not want adopt a contraceptive method during the study period and the following 4 weeks
20. Breast-feeding women during the study period and the following 4 weeks
21. Anemia (hemoglobin <10 g/dL) at the screening visit
22. Known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT or AST >2 x ULN or total bilirubin >1.5 x ULN
23. Patients with moderate or severe renal impairment (CrCL <50 mL/min) or patients with end stage renal disease (CrCL < 15 mL/min) or on dialysis.

6.3. WITHDRAWAL AND /EARLY DISCONTINUATION CRITERIA

In addition to screening failure, the reasons for a patient's premature withdrawal or early discontinuation from the study may be the following:

- The patient's or legal representative's decision that can occur for any reason and at any time

- The Investigator's decision in the patient's interest. Particularly, if a serious adverse event occurs and is considered by the Investigator liable to threaten the health of the patient
- An erroneous inclusionaccording to the protocol. The decision to maintain the patient or not in the study will be taken jointly by the Investigator and the Promoter
- Promoter's or Competent Authorities' motivated decision
- Other reasons, to be specified, such as: death, adverse events, lack of efficacy, major protocol violation, non-compliance, pregnancy, loss at follow-up.

The Investigator should attempt to collect, as soon as possible, the following information for a final assessment:

  - reason(s) for withdrawal to be reported in the case report form
  - evaluation of the patient's clinical condition
  - if necessary, take appropriate therapeutic measures: management of an adverse effect or concomitant disease, prescription of another treatment
  - recover the investigational product previously given to the patient.

In all cases, available data will be kept for the safety analysis.

7. STUDY TREATMENT

All patients will receive edoxaban 60 mg once a day, with an open-label design, for 4 weeks. Edoxaban daily dose will be reduced to 30 mg/day in case of: body weight ≤60 kg, or concomitant therapy with verapamil/quinidine/dronedarone.

7.1. PACKAGING AND LABELLING

The treatment units will be the commercial product manufactured by Daiichi Sankyo. It is dispensed in form of film-coated tablets and packed in blisters.

The commercial outer boxes will be labelled according to European Directives and local requirements.

At the baseline visit, the Investigator will provide the patients with the medications necessary to complete treatment until the next follow-up visit.

7.2. DRUG ADMINISTRATION

One tablet daily to be taken as a whole with some water, with or without food, for a period of 28 days.

7.3. ACCOUNTABILITY ON SITE AND RETURN/DESTRUCTION OF INVESTIGATIONAL PRODUCT(S)

The Investigator should maintain accurate written records of drugs received, dispensed, returned and any remaining treatment units, on the drug accountability form. The packaging of the medication should remain intact until just before the dispensation.

At the end of the study, all used and unused treatments including packaging should be noted, and local destruction or return is organised by the appointed CRA. A copy of the drug accountability form should be provided by the Investigator to the CRA.

8. CONCOMITANT TREATMENTS

Any existing concomitant treatment, any new concomitant treatment or change in the dosage of an existing concomitant treatment during the course of the study must be noted on the CRF.

For all concomitant treatments taken during the study, the following information must be noted in the relevant section(s) of the CRF:

- The name of the treatment and its form
- The reason for prescription
- The route of administration
- The daily dose
- The duration.

9. EVALUATION CRITERIA

9.1. EFFICACY ASSESSMENT

9.1.1. Primary endpoint

Primary outcome will be the detection of the percentage of patients after 4 weeks of edoxaban treatment with complete thrombus resolution by TEE, evaluated with the following Probe angulations: 0°, 45°-to-60°, 90°.

9.1.2. Secondary endpoint

Secondary endpoints will be:

- Absolute and percent variation of thrombus area at 4 weeks by TEE evaluation (Probe angulations: 0°, 45-to-60°, 90°)
- Time to electrical cardioversion (when applicable).

9.2. SAFETY ASSESSMENT

- Incidence of bleeding events at 4 weeks and after 8 weeks (telephone assessment) after the end of treatment
- Incidence of any stroke or peripheral embolism at 4 weeks and after 8 weeks (telephone assessment) after the end of the treatment.

9.2.1. Definition of major bleeding

Major bleeding will be defined as follows (11) and reported as SAEs or AEs as described in Section 11:

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or
3. Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

9.2.2. Non-major bleeding

Clinically relevant non-major bleeding (12) will be defined as bleeding that did not fall under the category of major bleeding, but corresponded to any of the following:

1. hematoma of 5 cm in longest diameter
2. epistaxis or gingival bleeding that occurred in the absence of external factors and lasts ≥5 minutes
3. GI bleeding
4. gross hematuria that is persistent after 24 hours of onset, and
5. other bleeding that was assessed to be clinically significant by the investigator or sub-investigator.

Any bleeding event that did not meet major or clinically relevant non-major bleeding criteria will be categorized as a minor bleeding event.

9.2.3. Stroke and thrombotic events

Thrombotic events will be defined as and reported as SAEs or AEs, as described in section 11.

1. Ischemic stroke
2. Transient ischemic attack (TIA)
3. Deep vein thrombosis (with or without pulmonary embolism)
4. Any other form of systemic embolism.

9.2.4. Adverse Events

At Inclusion, any concomitant disease will be reported on the CRF. At each further visit, the occurrence of adverse events (AEs) since the last visit will be based on the patient's or patient parents' spontaneous oral reporting, the investigator's non-leading questioning and his/her clinical evaluation. Any AE reported will be re-assessed by the investigator through complementary questioning, and noted in the medical file. All AEs will be reported on the CRF.

9.3. COMPLIANCE

The patient will be reminded to bring back, at each visits, any remaining tablets, boxes (used or unused). At the follow-up visit, the Investigator will record the number of supplied and remaining tablet in the CRF.

Considering the duration of the study, compliance will be judged as:

- Complete if ≥ 100% taken (28 tablets or more)
- Adequate if ≥ 75% and < 100% taken (at test 21 tablets)
- Non adequate if < 75% taken (less than 21 tablets).

10. STUDY PROCEDURES

Each patient considered eligible for selection by the Investigator will be informed of the characteristics and the consequences of the trial both verbally and by reviewing the patient's information sheet and consent form approved by the competent EC. Acceptance to participate

in the study will be subordinated to the signature of the informed consent. A copy will be keep by the patient.

10.1. BASELINE VISIT

A screening assessment can occur on the same day of the baseline visit or up to 7 days before it. The patient will be assessed for the following:

- Collection of the signed informed consent
- Verification of inclusion/exclusion criteria
- Collection of demographic data, including: date of birth (month and year), gender, weight, height (calculated BMI), and race
- Medical history (with evaluation of CHA_2DS_2-VAS_C score and HAS-BLED scores)
- Information regarding AF
- Blood pressure, heart rate
- ECG
- Transthoracic echocardiogram (TTE)
- Transesophageal echocardiogram (TEE)
- Therapy: antithrombotic treatment and concomitant treatments (antihypertensives, heart failure and antiarrhythmic therapies, metabolic and anti-inflammatory, antithrombotic therapies for indications other than AF), and other selected drugs.
- Complete blood count; assessment of liver and renal function.

10.2. FOLLOW-UP (WEEK 4)

After four weeks of treatment, the patient will be visited and assessed for the following:

- Serious adverse events, including hospitalizations, life threatening events and death
- Non-serious adverse events
- Information regarding AF
- Concomitant diseases (current, any change)
- Adherence to the study treatment

- Therapy (current, any change)
- Blood pressure, heart rate
- ECG
- Transthoracic echocardiogram (TTE)
- Transesophageal echocardiogram (TEE)
- Complete blood count; assessment of liver and renal function.

10.3. FINAL TELEPHONE ASSESSMENT (WEEK 8)

- Serious adverse events, including hospitalizations, life threatening events and death
- Non-serious adverse events
- The investigator will also complete the final study form.

10.4. ASSESSMENTS AND PROCEDURES

10.4.1. Stroke risk index

The CHA_2DS_2-VAS_c (Cardiac failure, Hypertension, Age doubled, Diabetes, Stroke doubled, Vascular, Age, Sex) composite stroke risk index is based on a point system in which 2 points are assigned for age ≥75 years and for a history of stroke or TIA and 1 point each is assigned for a history of hypertension, diabetes, recent cardiac failure, vascular diseases, age <75 years, and female gender (13).

10.4.2. Bleeding risk index

HAS-BLED is a scoring system developed to assess the 1-year risk of major bleeding in patients with atrial fibrillation A calculated HAS-BLED score is between 0 and 9, and based on one point assigned to each of the following parameters (14):

1. Hypertension: uncontrolled or >160 mmHg systolic)
2. Abnormal renal function: Dialysis, transplant, Cr >2.6 mg/dL or >200 µmol/L
3. Abnormal liver function: Cirrhosis or Bilirubin >2x ULN or AST/ALT/AP >3 x ULN
4. Stroke: Prior history of stroke
5. Bleeding: Prior Major Bleeding or Predisposition to Bleeding

6. Labile INR: (Unstable/high INRs), Time in Therapeutic Range < 60%
7. Elderly: Age > 65 years
8. Prior Alcohol or Drug Usage History
9. Medication Usage Predisposing to Bleeding: (Antiplatelet agents, NSAIDs).

11. ADVERSE EVENTS: DEFINITION AND REPORTING

11.1. ADVERSE EVENTS

11.1.1. Definition of Adverse Events

An adverse event is any adverse change from the patient's baseline condition, *i.e.* any subjective signs and symptoms, or change in a concomitant disease present at the Inclusion Visit considered related or not related to the treatment.

This includes intercurrent signs, symptoms and illnesses that may occur during the course of the clinical study.

11.1.2. Grading of Adverse Events

Adverse or intercurrent events are graded as follows:

- Mild: awareness of signs or symptoms, but easily tolerated
- Moderate: uncomfortable enough to cause interference with usual activity
- Severe: incapacity with inability to work or do usual activity

11.1.3. Reporting of Adverse Events

The records of adverse events in the CRF describe the nature (diagnosis, signs and symptoms), severity, onset date, stop date, outcome and actions taken, and the relationship to study

treatment (in the Investigator's opinion). It must be specified whether the event is serious or not.

11.2. SERIOUS ADVERSE EVENTS (SAE)

11.2.1. Definition

A serious adverse event (SAE) includes, but is not necessarily restricted to any event which:

- results in death (whatever may be the cause)
- is life-threatening
- results in persistent or significant disability/incapacity
- requires the patient's hospitalisation or prolongation of current hospitalisation. The following ill not be reported as a SAE: a) planned medical/surgical procedures decided or scheduled prior patient's signature of the informed consent; b) preparation for a routine health assessment/procedure; c) administrative or social reasons (e.g., lack of housing, economic inadequacy, care-giver respite, family circumstances)
- Is a congenital anomaly or birth defect.

Other events such as cancer, and any additional adverse experience occurring during the study period, defined by the protocol as serious, or which the Investigator considers significant enough, or that suggest a significant hazard, contra-indications, side effect or precaution, must be handled as serious adverse events.

Any overdosage meeting a seriousness criteria should be reported as a SAE.

11.2.2. Reporting of SAE

All serious adverse events, according to the above-mentioned definitions and regardless of treatment or relationship to study drug, must be recorded by the Investigator as soon as he/she is informed of the event.

The Investigator must notify the Promoter about this event by sending, within 24 hours, the "Notification of serious adverse event" form ("first notification") reported in Appendix 17.2 of

the study protocol, with all the available information about the event to the Promoter's pharmacovigilance unit:

Contact	*Number or address*	*Instruction or comment*
e-mail	Farmacia.ortona@asl2abruzzo.it (24 hours coverage)	Please attach PDF scan of the SAE form
Fax	0859172356 (24 hours coverage)	If not possible to send the report by e-mail
Phone	0859172202 (business hours)	Only if it is not possible to send a paper report

11.2.3. Follow-up of SAE

The Investigator must design a specific clinical report and use the "Notification of serious adverse event" form ("follow-up"), and collect the results of the carried-out examinations and the reports of hospitalization.

Serious adverse events must be followed-up until resolution or stabilisation.

11.2.4. SAE Occurring After the Study

Because of the 4 week follow-up after the end of treatment, any SAE occurring after the end of the study last follow-up visit will not be notified to the Promoter.

However, the Promoter must be notified of any event occurring at any time after the end of the study (last follow-up visit) for the patient who may be related to the study treatment in the Investigator's opinion.

12. DATA COLLECTION AND STUDY MONITORING

12.1. DATA COLLECTION

12.1.1. Case Report Form

A paper Case Report Form (CRF) will be used to record all patient data required by the protocol. All the information included into the CRF will be recorded from source documents onto the CRF by an authorized person. A CRF must be completed for each patient who will have a signed informed consent.

12.1.2. Source Documents

A source document is an original record or certified copy of an original record of clinical findings, observations or any other medical or paramedical activities performed during the clinical trial, necessary for the transcription and the verification of the collected data. Documents, such as patients' diaries or similar papers recorded by the patients will also be kept by the Investigator as source documents.

Source documents, along with all other trial-related documents (copies of all "informed consent" forms, drug inventories and any correspondence related to the study) must be kept in the Investigator's file throughout the study, and then, stored for a period of at least 15 years or as per local legal requirements, whatever is the longest.

12.2. STUDY MONITORING

12.2.1. Monitoring visits

On-site visits will be carried out by a CRA appointed by the Promoter at regular intervals throughout the study, according to the monitoring plan schedule. Additional visits and communication by telephone fax or meeting may be performed, if necessary. Any site visit performed by the Promoter's representatives will be recorded in the Investigator's study file.

12.2.2. Direct Access to Source Documents

In accordance to the requirements of the GCP, all Promoter's representatives (Study Manager, CRA and Auditors) have to be given a direct access to all source and study data to perform quality monitoring/audit, thus ensuring accuracy and completeness of data).

Investigators are reminded that all Promoter's representatives keep professional confidentiality with regards to the patient data.

13. DATA MANAGEMENT

All clinical data related to the study will be collected and saved in a computerized database under the supervision of a Data Manager, according to the following procedures:

13.1. DATA ENTRY

All required data will be collected by the Investigator or an authorised designee (duly identified into the delegation task list) on the CRF, and entered in a computerized database.

13.2. DATA CLEANING

The designed Data Manager will define descriptions of both manual and electronic edit checks in the Data Validation Plan for reviewing and querying data.

The designed Data Manager will review the data over the course of the study, in order to identify data inconsistencies. The Investigator will be asked to resolve queries by making changes directly into the CRF.

13.3. DATA CODING

Adverse events, concomitant diseases, medical/surgical histories will be coded using the MedDRA dictionary (latest version in use), whereas concomitant medication will be coded using the WHO-ATC drug dictionary (latest version in use).

13.4. DATABASE LOCK

The validated database will be locked upon request of the designed Data Manager following the completion of all steps required, i.e.: data entry and check of all data, resolution of all queries, validation of the coding, Clinical and Products Safety databases reconciliation and validation Committee.

14. STATISTICAL ANALYSIS

14.1. GENERAL CONSIDERATIONS

The objective of this exploratory study is the estimation of the magnitude of the LA/LAA thrombus resolution after 4 weeks therapy with edoxaban.

14.2. SAMPLE SIZE

There are no previous studies conducted with edoxaban on atrial thrombus dissolution, and this is a pilot trial. For this reason, the sample size has beeen determined empirically, on the basis of case reports with similar products in this clinical conditions (6, 8-10, 15).

However, if the proportion of patients with thrombus dissolution after 4 weeks of treatment will be 60%, which is compatible with the above-mentioned case reports, a sample size of 25 produces a two-sided 95% confidence interval with range 39-79%.

The involvement of 6-8 sites implies an enrolment of an average of about 4 patient per site to be recruited in about 15 months.

14.3. PROTOCOL DEVIATIONS

Prior to the analysis, the Project Manager and Data Manager will review the protocol deviations and will classify them as either minor or major. A protocol deviation will be considered major when it is likely to bias significantly the treatment effect estimate based on the primary efficacy criterion.

Patients with major deviation(s) will be excluded from the Per Protocol data set (see Section 14.4).

A listing of all protocol deviations will be provided for all randomized patients, including the type *(major/minor)* of protocol deviations according to the decisions made by the members of the Validation Committee.

The number and percentage of patients with major protocol deviations will be tabulated by treatment group and type of major protocol deviations on the Full Analysis Set, as defined in Section 14.4.

14.4. DATA SETS ANALYSIS

The following data sets will be analyzed:

- The Full Analysis Set (FAS), composed of all patients having received at least one dose of the study treatment. This data set will be used to perform analyses of Safety and Efficacy.
- The Per Protocol (PP) set, which is the subset of the Full Analysis Set composed of all patients without any major protocol deviation or other source of bias for primary criteria analyses and characterised by a treatment compliance ≥80%.

14.5. HANDLING OF DROPOUTS AND MISSING DATA

14.5.1. Dropouts and Missing Data

The number and percentage of patients who prematurely stopped the study treatment will be provided by treatment group for all treated patients (FAS). Patients who prematurely stopped the study drug will be further described, regarding their time to premature withdrawal and reasons for premature study drug discontinuation.

No replacement of missing data will be performed.

14.6. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Patient's background, medical and surgical history, demographic data, disease characteristics and baseline efficacy criteria will be described on the FAS, by treatment group and overall:

- Quantitative parameters will be described by treatment group and overall using the following: number of patients, number of missing data, mean, standard deviation, minimum, median and maximum values
- Qualitative parameters will be described by treatment group and overall using frequencies.

For each year, concomitant diseases, as well as medical and surgical histories, will be tabulated descriptively by treatment group and overall using the MedDRA codes of System Organ Classes and preferred terms.

14.7. EFFICACY ANALYSIS

14.7.1. Primary Criterion

The primary outcome will be the detection of the percentage of patients, after 4 weeks of edoxaban treatment, with complete thrombus resolution by TEE, evaluated with the following probe angulations: 0°, 45°-to-60°, 90°.

As this is a single arm, open-label study, in principle, only a descriptive statistical analysis will be performed for the primary criterion. The primary analysis will be performed both on the FAS and the PP sets. Whenever appropriate, the statistical significance level will be 5%.

14.7.2. Secondary Criteria

Secondary endpoints will be:

- Absolute and percent variation of thrombus area at 4 weeks by TEE evaluation (probe angulations: 0°, 45-to-60°, 90°).
- Time to electrical cardio-version (when applicable).

Unless otherwise specified in the Statistical Analysis Plan, only a descriptive statistical analysis will be performed for the secondary criterion that will be carried out on the FAS and the PP sets. Whenever appropriate, the statistical significance level will be 5%.

14.8. SAFETY ANALYSIS

The Full Analysis Set will be used to perform all analyses of the safety criteria that will include:

- Percentage of bleeding events at 4 weeks and after 8 weeks (telephone assessment) after the end of the treatment
- Percentage of any stroke or peripheral embolism at 4 weeks and after 8 weeks (telephone assessment) after the end of the treatment
- Percentage of any other safety related events (deaths, SAEs and AEs).

14.8.1. Adverse Events

Any treatment emergent adverse events having been reported, after randomization, during the study for a given patient will be classified by preferred term and corresponding system organ class using the MedDRA terminology.

Numbers and percentages of patient with at least one reported treatment emergency adverse event will be tabulated by treatment group in decreasing order for the arm:

A. By system organ class
B. By system organ class and preferred term
C. By system organ class and preferred term, taking into consideration its most severe intensity
D. By system organ class and preferred term, taking into consideration the most severe relationship to the study treatment.

Recurring adverse events (*i.e.*, adverse events classified with the same preferred term) for a given patient will only be counted once, and only their most severe intensity or most severe relationship to the study treatment will be tabulated.

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

14.8.2. Concomitant treatments

Concomitant treatments will be tabulated by treatment group within a descriptive perspective. They will be classified by therapeutic area according to the WHO-DRUG dictionary using the "anatomical therapeutic chemical" (ATC) classification on the safety data set.

14.9. COMPLIANCE

Compliance will be judged as:

- Complete if ≥ 100% tablets taken (28, or more)
- Adequate if ≥ 75% and <100% tablets taken (at least 21)
- Inadequate if < 75% tablets taken (less than 21).

14.10. INTERIM ANALYSIS AND DATA MONITORING

No formal interim statistical analysis will be performed. Anyway, this is an open label study and just descriptive statistics will be performed on an on-going base through the entire duration of the study.

14.11. ETHICAL CONDITIONS

This study is performed in accordance with the principles stated in the Declaration of Helsinki (2013) and subsequent amendments, and in accordance with the Good Clinical Practice Guidelined (CPMP/ICH/135/95).

14.12. ETHICS COMMITTEE AND LEGAL REQUIREMENTS

This clinical trial was designed and will be conducted in accordance with the Italian Ministerial Decree 17 December 2004 governing the non-profit studies.

All the documents required by National Regulations and any other informative documents that may be requested are submitted for review to an Ethics Committee, whose procedures and operations meet the GCP and National Legal Requirements.

A copy of the formal written approval from the Ethics Committee is provided to the Sponsor (directly by the Ethics Committee or via the Investigator), with a list of names and qualifications of its members.

The request for authorisation by the Competent Authority or its notification if required is carried out by the Sponsor.

The active recruitment of patients will not start before the approval of the Ethics Committee and after the study is authorized by the Competent Authority or notified to the Competent Authority.

14.13. PATIENT'S INFORMATION LEAFLET AND INFORMED CONSENT FORM

An information must be given to the patient before their decision to participate or abstain from participation.

This information is based on the Declaration of Helsinki and the ICH GCP Guidelines. It must also describe the measures taken to safeguard patient's privacy and protection of personal data, according to European Directive 95/46 EC or other local regulation.

Restraints and risks must be explained, as well as the right to discontinue participation in the study at any stage, without affecting their further relationship with the Investigator and/or their future care.

The written information and consent form must be submitted to the patient with an oral explanation. It must be agreed and signed by the patient before any study-related procedure.

One copy of information and consent document is kept by the Investigator, and one copy is given to the patient.

If any information becomes available during the trial that may be relevant to the patient's willingness to participate in the trial, an updated written informed consent must be submitted to the patient to confirm the agreement for continue participating.

14.14. PERSONAL DATA PROTECTION

All information from this study (excluding data from the informed consent) is entered into a computer under the Sponsor's responsibility, in accordance with both the applicable Italian law (Decreto Legislativo 2003-06-30 n. 196 and subsequent amendments) and the European Directive 95/46/CE.

14.15. INSURANCE POLICY

15. THE SPONSOR, BEING RESPONSIBLE FOR THE CLINICAL STUDY, UNDERWRITES AN ADEQUATE INSURANCE POLICY WITH ACE EUROPEAN GROUP LTD, IN FAVOR OF SUBJECTS PARTICIPATING THIS CLINICAL TRIAL. THE INSURANCE CONTRACT WILL BE IN COMPLIANCE WITH THE LOCAL REGULATION AND HEALTH AUTHORITIES REQUIREMENTS. ADMINISTRATIVE PROCEDURES

15.1. PROTOCOL AMENDMENT

Neither the Investigator nor the Sponsor may alter the protocol without the authorization of the other party. All changes to the protocol are subject to an amendment, which must be dated and signed by both parties and must appear as an amendment to the protocol.

Substantial amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities.

Urgent amendments are submitted for approval / authorisation to the Ethics Committees and Competent Authorities, but could be implemented immediately under specific conditions defined with the Sponsor.

15.2. SOURCE DOCUMENTS, INVESTIGATOR'S FILE STORAGE

The Investigators:

- Keeps all trial-related documents in appropriate file folders. Records of patient, original informed consent forms, source documents, CD-ROM with pdf files, drug inventory, Ethics Committees and Sponsor correspondence pertaining to the study must be kept on file
- Retains all documents relating to the screening (consent and investigation results) of all subjects included in the trial or not
- Retains a list of the patient's names, addresses (and/or number of medical file), code numbers to allow checking of data reported on CRFs with those from source documents.

- Authorizes direct access to source documents for monitoring, audits and inspections

- Retains the trial-related documents as strictly confidential at the Investigator's site for at least 15 years or according to local requirements, whatever is the longest, after the completion or discontinuation of the trial (European Directive 2003/63/EC).

15.3. END OF THE STUDY

15.3.1. Definition of the End of Study

The end of study is the date of the last visit of the last patient undergoing the trial. Any change to this definition during the study, for whatever reason, must be notified as a substantial amendment.

15.3.2. Early Study Termination

15.3.2.1. Early Study Termination Decided by the Sponsor

The Sponsor Fondazione Gabriele d'Annunzio - Chieti may discontinue the study at any time for any of the following reasons:

- Lack of recruitment
- Deviations from good clinical practice and/or regulations
- Poor product safety/ lack of efficacy
- New information that could jeopardise the patient's safety
- Stopping of the drug development.

15.3.2.2. Early Study Termination Decided by the Competent Authorities

The Competent Authorities may suspend or prohibit a study if they considers that the conditions of authorization are not being met, or has doubts about the safety or scientific validity of the study.

15.4. AUDIT

The Sponsor Fondazione Gabriele d'Annunzio - Chieti is responsible for making sure that both his representatives (Study Manager, CRA, etc.) and the Investigator fulfil the requirements as specified by the GCP Guideline.

An audit can be organized internally by the Sponsor and at the investigational site, where the CRFs are matched against source documents. All study documentation must be directly accessible to auditors.

The practical conditions for the audit are discussed between the Investigator and the Clinical Quality Assurance Department. Oral information about the audit results are given to the Investigator**.**

15.5. INSPECTION

The Health Authorities may inspect any investigation site or the Sponsor in the course of the study or after its completion to verify the conduct of the study and quality of the data. The Investigator must provide the inspectors direct access to study documents.

15.6. CONFIDENTIALITY

The present materials (protocol, CRF, etc.) contain confidential information.

Except if agreed to in writing with the Fondazione Gabriele d'Annunzio - Chieti, the investigators must hold such information confidential, and must not disclose it to others (except where required by Applicable Law).

15.7. STUDY RESULTS PUBLICATION

All the results of this study including data, reports, discoveries and inventions resulting from the study, are the property of the Sponsor Fondazione Gabriele d'Annunzio – Chieti, and have to be considered as confidential.

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17. APPENDICES

17.1. APPENDIX A - DECLARATION OF HELSINKI

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975; 35th WMA General Assembly, Venice, Italy, October 1983; 41st WMA General Assembly, Hong Kong, September 1989; 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996; 52nd WMA General Assembly, Edinburgh, Scotland, October 2000; 53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added); 55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of clarification added); 59th WMA General Assembly, Seoul, Republic of Korea, October 2008; 64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (W MA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data. The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the W MA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act in the patient's best interest when providing medical care."

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continual y through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens. Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed. When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm. All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must

take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formal y documented and witnessed.

    All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legal y authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legal y authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physical y or mental y incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legal y authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legal y authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient- physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

    Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

    Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

    Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers al have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. Al parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

17.2. APPENDIX B - SAE FORM

NOTIFICATION OF SERIOUS ADVERSE EVENT (SAE)

TO BE TRANSMITTED BY FAX WITHIN 24 H TO _____

Site N°: |__|__| Patient N°|__|__| REPORT: INITIAL |__| FOLLOW UP |__| N°_____

PATIENT CHARACTERISTIC

Birth date |__|__| |__|__| |__|__| (dd/mm/yy) Gender M |__| F |__|

Height |__|__|__| cm Weight |__|__|.|__| kg

SERIOUS ADVERSE EVENT:

_____

Onset date: |__|__| |__|__| |__|__| Site staff awareness date: |__|__| |__|__||__|__|
dd/mm/yy dd/mm/yy

NARRATIVE:

……
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SEVERITY CRITERIA:

|__| Resulted in Death on date: |__|__| |__|__| |__|__| (dd/mm/yy)
|__|Life-threatening
|__|Hospitalization / prolongation of hospitalization
|__|Persistent /significant disability/ incapacity
|__| Birth defect or congenital abnormality
|__| Any other serious clinical or laboratory event
In case of death, has an autopsy been conducted? |__| NO |__| YES (please enclose the report)

OUTCOME:

|__|Resolved Date of recovery: |__|__| |__|__| |__|__| (dd/mm/yy)
|__|Resolved with sequelae |__|__| |__|__| |__|__| dd/mm/yy
|__|Improved
|__|Unchanged
|__|Worsened
|__|Death

MEASURES TAKEN FOLLOWING THE SAE:

Study treatment:
|__|None
|__| Temporarily discontinued specify the n° of days: |__|__|
|__| Definitively discontinued (specify end of treatment date |__|__| |__|__| |__|__| dd/mm/yy)
|__| Dose reduced (specify the new dose_____and start date |__|__| |__|__| |__|__|
|__| Not Applicable

The event led to:
|__| Prescription of corrective treatments. Specify names and dosage:
_____

|__| Discontinuation of concomitant treatments. Specify names and dosage:
_____

|__| Other, specify:
_____

FOLLOW – UP:

The SAE is closed after the dosage modification or discontinuation of the study treatment/suspect concomitant?
|__|NO |__|YES |__|NA

The SAE is occurred again after the new dispensing?
|__|NO |__|YES |__|NA

THE SAE IN RELATION TO THE TRIAL:

Study treatment: _____ Treatment number: _____
Date of first study treatment administration: |__|__| |__|__| |__|__| dd/mm/yy
Date of last study treatment administration: |__|__| |__|__| |__|__| dd/mm/yy
Daily dose: _____ Frequency: _____
Formulation: _____ Route of administration: _____

Was the blind open?
|__|NO |__|YES |__|NA

If yes, or if this is an open study, drug administered
|__| _____
|__|Placebo

RELATIONSHIP BETWEEN THE SAE AND THE STUDY TREATMENT

|__|Related
|__|Unrelated
|__|Unknown

Is there a reasonable possibility that the event is related to a concomitant drug ?
|__| NO |__|YES If yes specify:_____

Is there a reasonable possibility that the event is related to a Clinical Trial Procedure?
|__| NO |__|YES If yes specify:_____

CONCOMITANT TREATMENTS (EXCEPT THE TREATMENTS GIVEN FOR THE SAE)

Include drugs taken at the moment of the event onset and in the last two weeks. If more space is need , use additional copies of this page |__| YES

TREATMENT	START DATE	STOP DATE	Ongoing.	ROUTE /DOSE/ FREQ. ADMINISTR.

RELEVANT MEDICAL HISTORY

If more space is need, use additional copies of this page |__| YES

DISEASE	START DATE	STOP DATE	Ongoing.	PERTINENT DETAILS (*)

(*) INCLUDE SURGICAL PROCEDURES AND DATES

OTHER EXAMS |__| NO |__| YES

List only relevant diagnostic and confirmatory tests for event

TEST	DATE	OUTCOME
_____	_____	_____

REPORTER COMMENTS

Report date: |__|__| |__|__| |__|__| dd/mm/yy

The event was reported:

|__| Spontaneously

|__| After request

|__| After source document verification

Reporter:

_____	_____	_____
Print Name	Position	Signature

Investigator's name_____

Investigator's signature_____

Comments:

_____
_____
_____
_____
_____