STUDY PROTOCOL

FRANCE ZIMINO® REGISTRY: A FRENCH REGISTRY EVALUATING THE USE OF ZIMINO®

Short study title:	**France-LEVO**
Study design:	Real-life, multicentre registry study
Coordinating Investigator	**Pr Bernard Cholley, MD, PHD**
CO-Coordinating Investigator:	Pr Alexandre Mebazaa, MD, PhD
Sponsor:	ARCOTHOVA, SAR II – Hôpital Haut-Lévèque Avenue Magellan 33600 Pessac, France
Version:	V1
Date:	08 November 2019

Information

Title	France Zimino® registry: A French registry evaluating the use of Zimino
Protocol version	Final Version - V1_08.11.2019
Date of protocol	08 November 2019
Active substance	Levosimendan
Medicinal product	Zimino
Product reference	Not applicable
Procedure number	2019-A02903-54
Marketing authorisation holder (MAH)	Orion Corporation, Finland
Research question and objectives	To provide real-life follow-up data on patients who have been treated with Zimino® according to local routine clinical practice in France.
Country of study	France
Sponsor	ARCOTHOVA (Anesthésistes-Réanimateurs Cœur Thorax Vaisseaux)

Marketing authorisation holder

MAH	Orion Corporation, Finland

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2. LIST OF ABBREVIATIONS

ANSM	Agence Nationale de Sécurité du Médicaments et des Produits de Santé
CRF/eCRF	Case report form/electronic Case Report Form
EEC	External Electrical Cardioversion
EC	Ethics Committee
EDC	Electronic Data Capture
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practices
IABP	Intra-Aortic Aalloon Pump
ICU/CCU	Intensive Care Unit /Coronary Care Unit
MACE	Major Adverse Cardiovascular Event
SAE	Serious Adverse Event
SAPS	Simplified Acute Physiology Score
SAS®	Statistical Analysis System
SOFA	Sequential Organ Failure Assessment
VA ECMO	Veno-Arterial ExtraCorporeal Membrane Oxygenation
VV ECMO	Veno-Venous ExtraEorporeal Membrane Oxygenation

3. RESPONSIBLE PARTIES

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The sponsor is responsible for the design and conduct of the study. The sponsor will ensure adequate monitoring of the study.

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Pr Jean-Luc Fellahi-Hospices Civils de Lyon
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Sponsor and Scientif committee signatures are provided in Annex 1.

Investigators

In this protocol 'investigator' refers to physician who is responsible for all treatment decisions and the conduct of the study at a study centre.

Signatures of the investigators will be collected in Annex 2.

4. ABSTRACT

Title
France Zimino® registry: A French registry evaluating the use of levosimendan (Zimino®)

Protocol version and date
V1, 08 November 2019

Rationale and background
The French National Authority for Health (Haute Autorité de santé) requested a registry study to obtain post-market surveillance data to describe baseline clinical profiles, management and outcome of patients treated with Zimino®. This study is designed to provide real-life data on the use, safety and clinical outcomes of Zimino® in routine clinical practice in France.

Research question and objectives
Primary objective:

- To provide real-life follow-up data on patients who have been treated with Zimino® according to local routine clinical practice in France.

Secondary objectives:

- To describe the use of concomitant inotropes during hospitalisation.
- To assess re-hospitalisations 30 and 90 days after hospital discharge.
- To evaluate tolerance and serious adverse events (SAEs) during hospitalisation.
- To assess mortality 30 and 90 days after hospital discharge.

Primary endpoints

- Indication for Zimino®.
- Dose and duration of treatment with Zimino®.
- Length of intensive care unit / coronary care unit (ICU/CCU) stay from the start of Zimino®.
- Length of hospital stay from the start of Zimino®.

Secondary endpoints

- Concomitant inotropes during hospitalisation.
- Re-hospitalisations 30 and 90 days after hospital discharge.
- Tolerance, as assessed by hypotension and atrial fibrillation during hospitalisation.
- SAEs, including major cardiovascular events (MACEs), mechanical assistance, dialysis or any other event engaging the vital prognosis during hospitalisation.
- Mortality during hospitalisation 30 and 90 days after hospital discharge.

Study design
This is a real-life, non-interventional, observational, multicentre study in all patients (including children) receiving Zimino® in France.
The patients will be evaluated during the index hospitalisation and on follow-up days 30 (±15) and 90 (±15) after hospital discharge. The follow-up can be a phone call or a visit to the hospital. Patients who meet the eligibility criteria will be identified consecutively at each hospital. The participating hospitals will vary in size and medical activities, depending on their location and the population size they serve.
The physician will determine the patient's treatment strategy. Drug prescriptions and the indications to perform diagnostic or therapeutic procedures will be left completely to the discretion of the physicians.
The estimated enrollment period is 12 months (enrollment of the first patient – enrollment of the last patient), or less if the cohort (n=600) is completed earlier, and the maximum total data collection period is 15 months.

Population

Inclusion criteria:

- Patients receiving Zimino® treatment.
- Patients or patient's families not objecting to the patient's participation in the study.

Exclusion criteria: None

Medicinal product, dose and mode of administration

Zimino® 2.5 mg/ml concentrate for solution for infusion. Dose and duration of treatment will be at the discretion of the physicians.

Variables

- Demographic characteristics, including age and sex
- Dates of hospital and ICU/CCU admission and discharge
- Reason for hospitalisation.
- Cardiogenic shock (yes/no; if yes, date of the first symptoms)
- Zimino® prescription, including indication for use, dose and duration (date and hour), bolus (yes/no).
- Concomitant inotropes: drug name, dose, duration (date and hour)
- Chronic atrial fibrillation (yes/no)
- Pre-existing amiodarone before the start of Zimino® (yes/no)
- Pre-existing betablockers before the start of Zimino® (yes/no) and higher dose
- Pre-existing dialysis before the start of Zimino® (yes/no)
    - Start date
    - Date of weaning (or death)
- Pre-existing mechanical assistance before the start of Zimino®
    - Venoarterial extracorporeal membrane oxygenation (VA ECMO) (central or peripheral)
    - Veno-venous ECMO (VV ECMO)
    - Impella® 5.0 or Impella® 2.5 or Impella CP
    - Intra-aortic balloon pump (IABP)
    - Berlin Heart EXCOR

  For all the assistances collect :

    - Start date of mechanical assistance
    - Date of assistance weaning (or death)
- Tolerance information during the levosimendan infusion ncluding:
    - Hypotension
        - Catécholamines (yes/no) if yes : Start date/ stop date
        - Zimino® reduced (yes/no) or Interrupted (yes/no) or Discontinued (yes/no)
    - New atrial fibrillation
        - Need for amiodarone (yes/no)
        - Need for cardioversion (yes/no)
- SAEs after the start of Zimino®:
    - MACEs, defined as death of cardiac origin, stroke, myocardial infarction, heart rhythm disorder requiring cardioversion or cardiogenic pulmonary oedema
    - Death of other cause
    - Mechanical assistance
        - VA ECMO (central or peripheral)
        - VV ECMO

- Impella® 5.0 or Impella® 2.5 or Impella CP
- IABP
- Berlin Heart EXCOR

- Start date of mechanical assistance
- Date of assistance weaning (or death)

- Dialysis
  - Start date
  - Date of weaning (or death)
- Any other event engaging the vital prognosis during hospitalisation, including septic shock and digestive haemorrhage

- Mortality during hospitalisation and up to follow-up days 30 and 90 after hospital discharge.
- Re-hospitalisations up to follow-up days 30 and 90 after discharge, including number and duration of re-hospitalisations, main reason for re-hospitalisation and re-administration of Zimino®

Data sources

Data will be collected from medical records and follow-up interviews and entered into the electronic case report forms (eCRFs).

Data before admission to the hospital and during hospitalisation will be obtained during index hospitalisation. The prospective follow-up data will be obtained on days 30 and 90 after discharge by calling the patient or patient's family or during the patient's visit to the hospital. Follow-up data will also be collected from medical records.

Study size

600 patients will be included in the registry.

Data analysis

The objective of the study is to provide real-life follow-up data in patients who received Zimino®. There is no formal hypothesis to be tested. All enrolled patients who have received Zimino® will be included in the analysis. All variables will be summarised overall and by indication for the use. For categorical variables proportions and 2-sided 95% confidence intervals will be presented. If applicable, the potential differences between indications of Zimino® will be tested. Additional subgroup analyses may be performed based on the observed data.

Milestones

Data collection for the main study is expected to start by January, 2020 and to be completed before December 31th, 2020.

5. AMENDMENTS AND UPDATES

A pilot e-CRF study may be conducted before the main study to evaluate the feasibility of the methods to establish a Zimino® registry. A protocol amendment may be prepared accordingly.

6. MILESTONES

Milestone	Planned date
First Patient In	January, 2020
Last Patient In	January, 2021
Last Patient Out	April, 2021
Interim report	NA
Final Data base lock	July, 2021
Final report of study results	October, 2021

7. RATIONALE AND BACKGROUND

7.1 Background

The French National Authority for Health (Haute Autorité de Santé) requested a registry study to obtain post-market surveillance data to describe baseline clinical profiles, management and hospital outcome of patients treated with Zimino®.

7.2 Rationale

There is an increased interest in the use of real-life data to observe how new medicines are used in clinical practice. A properly designed registry can provide real-life view of clinical practice, patient outcomes, safety and effectiveness.

This study is designed to provide real-life data on the use, safety and clinical outcomes of Zimino® in clinical practice in France.

8. RESEARCH QUESTION AND OBJECTIVES

In this real-life, multicentre study, patients treated with Zimino® will be followed for 90 days after discharge from the hospital

The primary objective is to provide real-life follow-up data on patients who have been treated with Zimino® in France.

The secondary objectives are:

- To describe the use of concomitant inotropes during hospitalisation.
- To assess re-hospitalisations at 90 days after discharge.
- To evaluate tolerance and serious adverse events (SAEs) during hospitalisation
- To assess mortality during hospitalisation and at 30 and 90 days after discharge.

9. RESEARCH METHODS

9.1 Study design

This is a real-life, multicentre study in patients treated with Zimino® in a real-life setting.

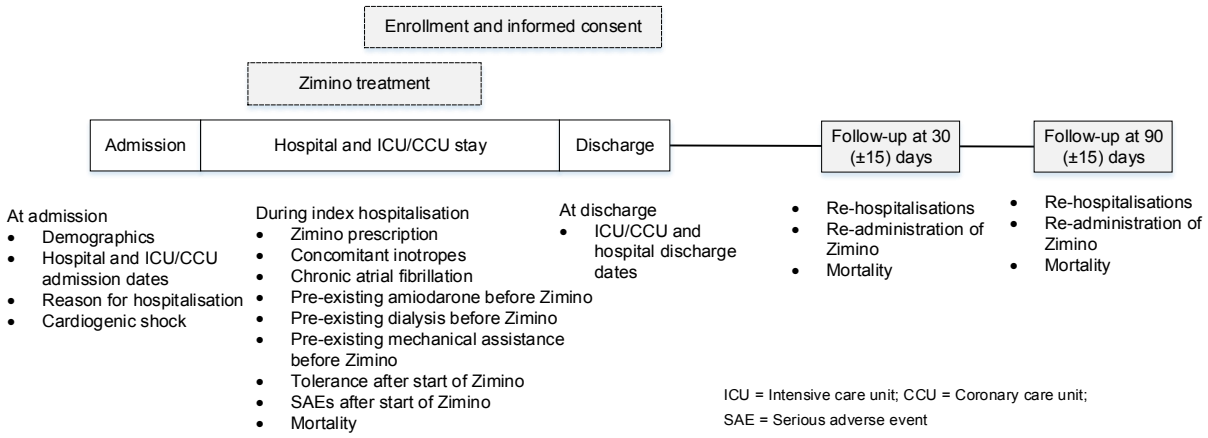
Each patient will be treated as decided by the physician according to current local clinical practice. The decision to prescribe Zimino® to the patient is made by the physician in charge, regardless of the possibility to include the patient in the study. The informed consent may be obtained at any time during hospital stay, before or after the start of Zimino® .

The patients will be evaluated during the index hospitalisation and at day-30 and day-90 after discharge. The follow-up can be done via a phone call, or a visit to the hospital. The study design is presented in .

Figure 1.

The estimated enrollment period is 12 months (enrollment of the first patient – enrollment of the last patient), or less if the cohort (n=600) is completed earlier, and the maximum total data collection period is 15 months.

Figure 1. Study design



9.2 Setting

9.2.1 Hospitals

France-Levo will enroll 600 consecutive patients receiving levosimendan at all French sites where Zimino® is prescribed.

9.2.2 Study population

The study will enrol 600 patients in France.

To ensure that patients are captured in a representative way and to avoid selection bias issues, study participation will be proposed to all consecutive patients who have received Zimino® during the recruitment period. The hospitals will stop recruitment once data from 600 patients have been collected.

All available information regarding patients receiving Zimino® but not entered into the registry will be collected.

9.2.2.1 Inclusion criteria

Patients are eligible to be included in the study if all of the following criteria apply:

1. Patients receiving Zimino®.
2. Patients or patient's families not objecting to the patient's participation in the study.

9.2.2.2 Exclusion criteria

None.

9.2.2.3 Removal of patients from assessments

Patients are free to discontinue the study at any time without providing a reason. However, the investigator should try to identify the reason and document it in the case report form (CRF).

The study monitor should be notified about premature discontinuations. If the discontinuation is due to an SAE, the study monitor should be notified by investigator within 24 hours.

9.2.3 Medicinal product

Current clinical practice use.

9.2.4 Study procedures

The prospective follow-up data will be obtained on days 30 and 90 after discharge by calling the patient or a patient's family member, or during a visit to the hospital if the patient is hospitalized or comes for a scheduled consultation. Follow-up data may also be obtained by review of medical records.

For patients who have been transferred to another hospital, follow-up data will be collected by contacting the respective hospital according to local practice. For patients who have been discharged home or to another care facility, follow-up data will be collected by contacting the patient or the patient's family. Every effort will be made according to local practice to ensure that the patient is alive before contacting the patient's family.

Table 1 lists study procedures and indicates with an 'x' during which visit a particular procedure is performed.

Table 1. Schedule of study procedures

	During index hospitalisation	During follow-up	
		30 (±15) days after discharge	90 (±15) days after discharge
Patient identification	x		
Informed consent	x		
Inclusion criteria	x		
Demographic characteristics	x		
Hospital and ICU/CCU admission dates	x		
Reason for hospitalisation	x		
Cardiogenic shock	x		
Zimino® treatment	x		
Concomitant inotropes	x		
Chronic atrial fibrillation	x		
Pre-existing amiodarone	x		
Pre-existing dialysis	x		
Pre-existing mechanical assistance	x		
Tolerance	x		
SAEs	x	x	x
Mortality	x	x	x
ICU/CCU and hospital discharge dates	x		
Re-hospitalisations		x	x

ICU = Intensive care unit; CCU = Coronary care unit; SAE = Serious adverse event

9.3 Variables to be collected

Data will be collected for all patients and recorded on the CRFs as follows:

9.3.1 Demographic and baseline characteristics

- Age,
- Sex
- Date of admission to the hospital

- Date of ICU/CCU admission
- SAPS II score (= IGS2)
- SOFA score on ICU admission
- Reason for hospital admission (pop-up menu) [1) medical HF decompensation, 2)surgical cardiac procedure, 3)other ICU admission (text)]
- Did the patient have cardiogenic shock (yes/no)?
    - If yes, date of the first symptoms of the cardiogenic shock

9.3.2 Zimino® treatment

- Indication for the use of Zimino® pop-up menu: 1) cardiogenic shock (medical setting or post cardiac surgery), 2) Heart failure decompensation (medical, setting), 3) Low cardiac output syndrome (post cardiac surgery), 4) heart failure decompensation in a patient receiving beta-blockers, 5) ECMO weaning, 6) repetitive use in a patient with end-stage heart failure, 7) other (text)
- SOFA score on the day of ZIMINO® initiation
- Start of Zimino® treatment (start date and hour)
- Dose (μg/kg/min) and total dose (mg) of Zimino®
- Was bolus injection of Zimino® administered (yes/no)?
- End of Zimino® treatment (stop date and hour)

9.3.3 Concomitant inotropes

- Use of other inotropes (yes/no)
    - Dobutamine,
    - Start of dobutamine (date and hour)
    - Maximal dose of dobutamine
    - End of dobutamine (stop date and hour)
    - Noradrenaline
    - Start of noradrenaline (date and hour)
    - Maximal dose of noradrenaline
    - End of noradrenaline (stop date and hour)
    - Adrenaline
    - Start of adrenaline (date and hour)

- Maximal dose of adrenaline
- End of adrenaline (stop date and hour)
- Milrinone
- Start of milrinone (date and hour)
- Maximal dose of milrinone
- End of milrinone (stop date and hour)

9.3.4 Chronic atrial fibrillation

- Chronic atrial fibrillation (yes/no)
- Pre-existing treatment with amiodarone before the start of Zimino® (yes/no)

9.3.5 Pre-existing dialysis

- Pre-existing dialysis before the start of Zimino® (yes/no). If yes,
  - Date of weaning (or death)

9.3.6 Pre-existing mechanical assistance

- Pre-existing mechanical assistance before the start of Zimino® (yes/no). If yes,
  - Date of insertion
  - Type of mechanical assistance
    - Venoarterial extracorporeal membrane oxygenation (VA ECMO) (central or peripheral)
    - Veno-venous ECMO (VV ECMO)
    - Impella® 5.0, Impella® 2.5) or Impella CP
    - Intra-aortic balloon pump (IABP)
    - Berlin Heart EXCOR
  - Date of weaning (or death)

9.3.7 Tolerance

- Hypotension during and after the start of Zimino® (yes/no).
  - If yes, was noradrenaline started or its dose increased? (yes/no).
  - Duration of hypotension (minutes, hours)

- New atrial fibrillation after the start of Zimino® (yes/no)? If yes,
    - Was amiodarone given? (yes/no).
    - Was beta-blocker given ? (yes/no)
    - Was cardioversion performed?
    - Persistent AF? (yes or no)
    - If transient, duration of AF (min, hours, days)

9.3.8 Serious adverse events during and after the start of Zimino® (regardless of causal relationship to Zimino)

SAEs will be collected regardless of causal relationship of the event to Zimino® treatment:

- MACE defined as death of cardiac origin, stroke, myocardial infarction, heart rhythm disorder requiring external electrical cardioversion (EEC) or cardiogenic pulmonary oedema
- Death of non cardiac origin
- Mechanical assistance : Start date and date of weaning
- Dialysis : Start date and date of weaning
- Any other event engaging the vital prognosis, including septic shock and digestive haemorrhage
- Date of start event, end of event or ongoing

For all the variables above, duration of the event will also be recorded.

9.3.9 Mortality

Time of death and cause of death will be recorded up to follow-up day 90.

9.3.10 Length of ICU/CCU and hospital stay

- Date of ICU/CCU discharge.
- Hospital-free days at day-30 and day-90
- Date of hospital discharge

The length and clinical aspects of the hospital and CCU/ICU stay before starting Zimino® are expected to vary widely among patients. Therefore, all length of stay endpoints are primarily measured from the time of starting Zimino® treatment.

9.3.11 Re-hospitalisations up to 30 (±15) and 90 (±15) days after hospital discharge

- Was the patient re-admitted to the hospital (yes or no)
- If yes: date of admission
- If yes: date of discharge
- Main reason for re-hospitalisation
- Re-administration of Zimino® (yes/no)

9.4 Data sources

Data will be collected from medical records and follow-up interviews and entered into the eCRFs.

9.5 Study size

The study will enrol 600 patients in France.

This sample size will allow to describe a proportion of 50% (most conservative hypothesis) with a precision to at least 4.5% with an estimation of non available data fom 10 to 20%.

Hypothesis	Proportion	α	accuracy	N	% Non available data	N total
Scenario 1	50,00%	5%	4,5%	475	10%	523
Scenario 2	50,00%	5%	4,5%	475	15%	547
Scenario 3	50,00%	5%	4,5%	475	20%	570

9.6 Data management

Data to be collected according to the study protocol (and amendments, if any) will be recorded into an electronic data capture (EDC) system using eCRFs at the site.

Investigators and other relevant site personnel will be trained to use the EDC system. After completion of training, they are provided with user names and authorised access to enter and correct data on the eCRFs.

Individual data fields in the EDC system may be locked on an ongoing basis during the study. The fields may be unlocked if further updates are needed. When all data have been entered and all queries resolved, the whole database will be locked.

9.7 Data analysis

Statistical analyses, tables and patient data listings will be performed with SAS® for Windows 9.4 or later (SAS Institute Inc., Cary, NC, USA). Statistical analysis will be performed by or under the supervision of the sponsor.

9.7.1 Statistical hypotheses

No specific statistical hypothesis that would be evaluated in a confirmatory manner is specified in this study or against any historical control. Instead, the emphasis is on estimation and exploratory analyses.

No inferential statistics will be performed.

9.7.2 Analysis populations

All enrolled patients who have received Zimino® will be included in the analysis. All available data will be analysed.

9.7.3 Statistical analyses

The variables will be evaluated by frequency tables and summary statistics, as applicable. Variables will be summarised also by indication for the use, if feasible. For categorical variables, proportions and 2-sided 95% confidence intervals will be presented.

For the primary objective, all clinical and sociodemographic characteristics (age, sex, clinical scores) use of Zinimo treatment (indication, dose, duration, routes) will be described at each available time point.

For secondary objectives, use of concomitant inotropes during the hospitalisation (percentage of patient, duration etc…) will be described, as well as rate of patient rehospitalised at 90 days after discharge.

For safety and tolerance analysis, description of hypothension, new atrial fibrillation will be done as well as all SAEs occurred during and after Zimino® treatment.

Rate of mortality will be calculated and described.

If applicable, the potential differences between indications of Zimino® will be tested in an exploratory way, as no statistical hypothesis have been done. Additional subgroup analyses may be performed based on the observed data.

9.8 Quality control

9.8.1 Training

Training will be arranged for the investigators and other relevant site personnel. This training will include a review of the protocol and completion of the CRFs. The investigators will ensure that appropriate training relevant to the study is given to the medical, nursing and other personnel involved in the study. The investigators will also ensure that any information relevant to the conduct of the study is forwarded to other relevant site personnel.

9.8.2 Investigators

A curriculum vitae must be obtained from all investigators who sign the protocol.

9.8.3 Case report forms

Electronic queries about missing, misleading, incomplete or illogical data will appear in the EDC system. An audit trail within the system will track all changes/corrections made. The investigator has to confirm the content of the eCRFs with an electronic signature.

9.8.4 Monitoring

The study monitor will monitor the study by performing monitoring visits remotely and on-site as agreed by the investigator and the sponsor. The study monitor will ensure that the study is conducted according to the principles of good clinical practice (GCP) and national regulations and that the protocol is followed in all aspects. Each recruiting site will be monitored at least once. It will be verified that the clinical facilities remain appropriate, and that the CRFs correspond with source data.

9.9 Limitations of the research methods

Potential limitations of this study are because of its non-interventional design. However, the non-interventional design of the study is a preferred way to collect real-world data.

One limitation of this study is that there is no control group with which to compare the outcomes. In a severely ill population, serious adverse events are likely to take place, without causal relationship to levosimendan treatment.

Selection bias is avoided by requesting a systematic, consecutive recruitment procedure and using a screening log to collect data on the number of patiens who were not included in the study and the reason for this. Interviewer bias is avoided by using questionnaires similar to routine standard care and training the physicians and nurses before the study start.

Other limitations, such as amount of missing data, are expected to be similar to other multicentre, non-interventional studies.

9.10 Other aspects

9.10.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor and scientific committee.

9.10.2 Insurance and remuneration

Not applicable.

9.10.3 Completion of the study

The sponsor reserves the right to prematurely close the site or terminate the study for valid scientific or administrative reasons.

Sites will be closed upon study completion. A site is considered closed when all required documentation has been collected and closure procedures have been performed.

9.10.4 Retention of records

Recommendations in the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE GPP) will be followed for the retention of records.

10. PROTECTION OF HUMAN SUBJECTS

10.1 Ethical and regulatory compliance

The study protocol, synopsis in French and description of procedure for obtaining a non-opposition statement will be submitted to the applicable ECs for favourable opinion.

The study protocol will be submitted to French National Agency for Medicines and Health Products Safety (ANSM) for information.

The study complies with the MR004 reference methodology and does not require the opinion of the Expert Committee for Research, Studies and Evaluations in the field of Health (CEREES) or specific authorization of the CNIL. Studies in accordance with MR004 are not to be submitted to a Committee for the Protection of Persons (CPP).
In accordance with French law, the documents in this study were registered in the National Register of Reference Methodology Studies of the National Institute of Health Data (INDS) prior to its implementation.

The study will be conducted in accordance with the ethical principles that are consistent with the Declaration of Helsinki, ICH GCP and the applicable legislation on non-interventional studies. The investigators will perform the study in accordance with the local regulations and guidelines governing medical practice and ethics.

The study will be conducted in accordance with the guidelines for the GPP (ISPE GPP) and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (EMA/95098/2010 Rev. 5).

10.2 Patient information and informed consent

Patient information will be given and verbal consent will be obtained in accordance with the French legislation, the Decree No. 2016-1537 of 16 November 2016 on research involving human subjects.

The investigator will ensure that each patient or patient's family is fully informed about the objectives and procedures of the study. The investigator will also explain any possible risks with participating in the study and answer all questions regarding the study. After this, the patient or patient's family will be given sufficient time to make a decision regarding participation in the study.

Patients or their family will be informed of the patients' right to discontinue the study at any time without their medical care or legal rights being affected. They will also be informed that representatives of the sponsor may inspect relevant parts of the patients' medical records and study data.

The investigator must obtain consent before data collection begins. The consent can be given verbally by the patient or the patient's family that they do not object to participating in the study. The investigator should confirm the receipt of verbal consent by entering the date of the consent on the patient's CRF.

10.3 Data protection

Data protection and privacy regulations will be respected for the collection, transmission, processing and storage of patient information.

Information collected during the course of the study will be stored in a database and handled confidentially and according to The General Data Protection Regulation (GDPR) (EU) 2016/679 and local law.

The patients can be identified in the CRFs only by subject number, age and sex.

In compliance with all applicable regulations and laws, it is required that the investigator and institution permit authorised representatives of the study sponsor, regulatory agency(s) and the EC direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analysing and verifying any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the informed consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS / ADVERSE REACTIONS

The sponsor performs safety related reporting according to local national reporting requirements.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered in one of the acceptable registries before the enrolment of the first patient.

The study report will be prepared by or under the supervision of the sponsor. The final report will be approved by the appropriate representatives of the sponsor and the investigators.

The sponsor wishes to collaborate with the investigators to publish the results as timely as possible, without compromising accuracy or industrial property rights of the MAH. The preparation, submission and authorship for publications containing the study results shall be in accordance with a process determined by mutual written agreement between the sponsor and participating investigators and in accordance with International Committee of Medical Journal Editors (ICMJE) recommendations, available at http://www.icmje.org.

13. REFERENCES

EMA/95098/2010 Rev. 5 European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (Revision 5). European Medicines Agency. Accessed April 2018. Retrieved from

http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev5.pdf.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

No.	Document reference no.	Date	Title
1	V_1	08/11/2019	Sponsor and scientific committee signature
2	V_1	08/11/2019	Investigator signature
3	V_1	08/11/2019	Information consent form