Protocol No. GDX-44-006

Thorough QT/QTc study to assess the electrocardiographic safety of a new gadolinium-based contrast agent P03277 in healthy volunteers

Phase I Clinical Trial

Design

Phase I Clinical Trial, Single center, Randomized, Cross-over Double-blind Placebo-controlled and Open-label Positive-controlled (moxifloxacin) in healthy volunteers

EudraCT No.: **2017-000963-34**

IND No.: 123673

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TRIAL SYNOPSIS

Trial Title: Thorough QT/QTc study to assess the electrocardiographic safety of a new gadolinium-based contrast agent P03277 in healthy volunteers Phase I Clinical Trial	
Trial Product(s): G03277	**Active Ingredient(s):** P03277
EudraCT No.: 2017-000963-34	**IND No.:** 123673
Participating countries (Number of sites): Belgium (1 site)	

Trial objectives

Primary objective:

To assess the cardiac safety after administration of P03277 by evaluating the QT and QTc intervals in healthy volunteers.

Secondary objectives:

To assess the cardiac, clinical, biological safety, plasma concentration, and long term elimination profile of P03277 following its administration in healthy volunteers.

Trial design and methodology

Phase I Clinical Trial, single center, randomized, cross-over double-blind placebo-controlled and open-label positive-controlled (moxifloxacin) in healthy volunteers.

The three Investigational Medicinal Products (IMPs) will be:
- P = Placebo (Nacl 0.9%)
- CD = P03277 tested at anticipated clinical dose (0.1mmol/kg)
- SD = P03277 tested at supra-clinical dose (0.3mmol/kg).

The positive control, moxifloxacin, will be an Auxiliary Medicinal Product (AMP).
- PC = Positive control (moxifloxacin 400 mg – *per os*).

Subjects who have provided written informed consent and satisfied all eligibility requirements will be included in the trial and randomized to receive one of 4 sequences, according to a Williams design for a 4*4 cross over which is balanced for first order carry over effect.

The sequences of administration could be for instance:

- Sequence #1: P/CD/PC/SD
- Sequence #2: CD/SD/P/PC
- Sequence #3: SD/PC/CD/P
- Sequence #4: PC/P/SD/CD

12 subjects will be assigned to each sequence (6 males and 6 females).

Sequence and IMP/AMP will be randomly assigned to subjects.

All subjects will be monitored with a 12-lead Holter electrocardiogram (ECG) from 1 hour before any product administration until 24 hours post-administration.
ECGs parameters will be measured as triplicate based on the following timepoints from the 12-lead

Holter ECG monitoring:
- moxifloxacin: pre-dose up to 24 hours post-dose:
  [-1hour, 30min, 1 hour,1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours]
- P03277 and Placebo: pre-dose up to 24 hours post-dose:
  [-1hour, 5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours].

Regarding ECG measurements, there will be one baseline per administration period. The baseline is defined as the mean of 3 triplicates ECGs timepoint measurements within one hour before each administration.

Blood will be drawn for all subjects for:
- Blood samples based on the same timepoints than triplicate ECGs, to implement a concentration-response approach and to assess the effect of P03277 on QT/QTc intervals according to plasma concentration of the product
- Blood sample to assess biochemistry and hematological parameters at screening and 2 days after each IMP administrations.

All subject will undergo 12-leads ECGs to assess subject' safety to monitor subject and trial stopping rules related to the QTcF values. Those ECGs will be done as triplicate within 1 hour before administration and 10 minutes and 3 hours post-administration.

All subjects will be asked to come back at the phase I clinical trial unit at 1 and 3 months after last IMP administration. Blood sample and urine collection will be performed to assess long term elimination of P03277.

Time windows allowance have been defined for each procedures as described in the relevant study plans listed in section 18.2

Number of subjects:

A total of 48 subjects will be randomized in the trial. The recruitment could be stopped before 48 subjects, from the time the number of fully evaluable subjects for the primary criterion is 40. That is to say having taken part to the study, till the last scheduled ECG Holter recording.

Eligibility criteria

Inclusion criteria:

1. Adult healthy volunteers at least 18 years old and below 60 (exclusive)
2. Subject having read the information and provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial-related procedure being conducted
3. Subject assessed as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination)
4. Subject with a Body Mass Index (BMI) > 19 kg/m^2 and < 28 kg/m^2 and a weight at least of 40 kg for female and 50 kg for male and at maximum of 100 kg.
5. Subject able and willing to participate in the trial

To be included in the trial, the subject must meet all these inclusion criteria.

Non-inclusion criteria:

1. Subject with any history or family history of inherited or acquired Long QT syndrome (LQTS)
2. Subject with any history or family history of risk factors for Torsade de Pointe (TdP), unexplained loss of consciousness or convulsion
3. Subject with any history of clinically significant bradycardia

4. Subject with any history of clinically significant cardiac impairment by decreasing of left ventricular ejection fraction (LVEF)
5. Subject with any history of clinically significant arrhythmia (including Wolf-Parkinson-White syndrome)
6. Subject with presence of cardiac pacemaker
7. Subject with frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month)
8. Subject with abnormal 12-lead ECG: PR < 120 ms or PR > 200 ms, QRS > 100 ms, QTc > 450 ms, flat T-waves at screening visit (results provided by the independent ECGs Core Laboratory)
9. Subject with following abnormal vital signs after 10 minutes resting in supine position at screening visit:
    - systolic blood pressure < 90 mmHg or > 160 mmHg
    - diastolic blood pressure < 45 mmHg or > 90 mmHg
    - resting heart rate < 45 bpm or > 80 bpm
10. Subject with any history or presence of relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, hematological, psychiatric, systemic, ocular, or infectious disease; any acute infection or signs of acute illness
11. Subject with abnormal biological, hematological or coagulation tests considered as clinically significant by the investigator and with the following abnormal laboratory parameters (out of normal ranges) (results have to be available at the latest at Day 1) :
    - Low potassium blood level (K^+ < 3.5 mmol/L)
    - Low magnesium blood level (Mg^{++} < 0.66 mmol/L)
    - Estimated creatinine clearance rate (eCCr) < 90 mL/min (Cockcroft-Gault formula)
    - Impaired liver function and transaminases > 2 fold ULN
12. Subject carrier of: HBs antigen, anti-HCV antibodies, anti-HIV1 antibodies, anti-HIV2 antibodies at screening
13. Subject with any history of severe allergic or anaphylactic reactions to any allergen including drugs and contrast agents, or allergic disease diagnosed and treated by a physician
14. Subject with any history of tendinopathy following a fluoroquinolone treatment
15. Subject with any history of allergy to moxifloxacin or one of its compounds or other moxifloxacin contra-indications according to the SmPC description
16. Subject with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to drugs from a similar pharmaceutical class
17. Subject treated with any concomitant medications which could induce a QT prolongation
18. Subject with presence of narcotics or alcohol abuse (alcohol consumption > 40 grams/Day) at screening
19. Subject smoking more than 10 cigarettes or equivalent /Day, unable to stop smoking during the confinement period
20. Subject having an excessive consumption of beverages with xanthine bases (tea, coffee, chocolate) (>6 cups or glasses /Day) and not able to refrain from consuming grapefruit (fresh fruit, juice, ice...) the day before inclusion and during the confinement period
21. Subject having done a blood donation within 3 months before first trial product administration
22. Subject having received any medication within 21 days prior to inclusion, or within 5 times the elimination half-life of that drug, whichever the longest, with the exception of hormonal contraception for female and of Hormonal Replacement Therapy (HRT) in case of menopausal volunteers and paracetamol
23. Subject having received an administration of any contrast agent within 2 weeks before inclusion, or scheduled to receive any contrast agent within 3 months after the last IMP administration
24. Subject having participated to a clinical trial involving an investigational drug or device within 21 days prior to screening, or within 5 times the elimination half-life of that drug whichever the

longest.

25. Subject having a planned simultaneous participation to another clinical trial involving an investigational drug or device
26. Subject having an inability or unwillingness to cooperate with the requirements of this trial
27. Subject having a planned interventions (surgery, radiotherapy, chemotherapy or others) during the course of the trial
28. Subject with any condition which, based on the investigator's clinical judgment, would prevent the subject from participating in all trial assessments and visits (for example: mental or physical incapacity, language comprehension, geographical localization, etc.)
29. Female subject being pregnant or breast-feeding (a female subject of childbearing potential or with amenorrhea for less than 12 months must have a negative pregnancy test at inclusion and must be using a medically approved contraception method)

Subjects presenting with one or more of these non-inclusion criteria must not be included in the trial.

Investigational Medicinal Products administration

Trial product 1: P03277 (0.1 and 0.3 mmol/kg) has to be administered as an IV bolus at 2 mL/sec.

Trial product 2: Placebo (Nacl 0.9%) has to be administered like P03277 as an IV bolus at 2 mL/sec.

Auxiliary Medicinal Product administration

Positive control (moxifloxacin 400 mg) has to be administered per os in open label.

Trial duration for subjects

Minimum trial duration for subjects: 95 days

Maximum trial duration for subjects: 122 days (in case the subject signs the informed consent form within 28 days before inclusion).

Within 4-weeks up to 1 day run-in period, subjects will be screened for the trial. Inclusion in the trial will occur the day the subject will be admitted to the phase I clinical trial unit for the first administration period of the allocated sequence (subjects may be admitted in the phase I clinical trial unit at Day -1 to ensure availability of all results prior to administration). Each subject will have 4 administration periods. Period's duration for moxifloxacin, placebo period, P03277 at clinical dose and P03277 at supra-clinical dose will each be 72 hours. The total duration for all periods will be 12 days.

During the 12 days of assessment and monitoring, the subject will have to stay in the phase I clinical trial unit. Healthy volunteers will be discharged on Day 12 after that all trial procedures have been performed and that all safety results have been reviewed by the investigator who will determine that it is safe to discharge the subject.

1 month and 3 months following the last IMP administration on Day 10, subjects will be asked to come back at the phase I clinical trial unit to assess the P03277 long term elimination (in plasma and urine).

The trial will be considered as completed once all the ECGs collected for all the subjects are reviewed by a core lab and all P03277 plasma concentration and elimination data are available.

Evaluation criteria

For each subject, all ECG parameters will be extracted from the 12-lead Holter ECG in triplicates and read centrally by a core lab. The mean of the triplicate ECG recordings will be considered for each timepoint.

P03277 plasma and urine concentrations samples will be analyzed for each subject by an analytical center. All other drawn samples will be kept by the analytical center for the trial duration.

Primary criterion:

Cardiovascular safety assessment is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of P03277 (at 0.1 and 0.3 mmol/kg) of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF) (in ms). No significant QTc Prolongation will be considered if the upper limit of the 90 % confidence interval of the maximum ΔΔQTcF is < 10%.

Secondary criteria:

Secondary criteria will consist of cardiac, clinical and biological safety evaluations as follow:

- Cardiac safety:
  - Assay sensitivity assessment is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of moxifloxacin of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF) (in ms)
  - Time-matched placebo-corrected, change-from-baseline mean effect, measured at any timepoints of the 12-lead Holter ECG recording :
    - QT (ms)
    - QTc(ms) according to population specific correction formula (QTc_{POP})
    - QTc (ms) according to Bazett's formula (QTcB)
  - Parameters measured at any timepoints:
    - QT
    - QTcF
    - QTc_{POP}
    - QTcB
    - RR (ms)
    - QRS (ms)
    - PR (ms)
    - Heart rate (bpm)
  - T wave morphology changes (yes/no) and U wave occurrence
  - Sinus rhythm (yes/no)
  - Bradycardia and arrhythmia

The following assessments will be done during the subject participation:

- Adverse Events:
  Adverse event will be recorded throughout the start of subject participation up to the end of confinement period except pregnancy (subject's or subject's partner) that will be recorded up to day 17 (7 days after the last IMP administration). During follow-up period, only related AEs and AESI will be recorded.

- Biology:

- Clinical laboratory parameters at screening visit, Day 1 and 2 days after each administration
  Parameters at selection visit and two days after each administration:
  Hematology: Red Blood Cells (RBCs), White Blood Cells (WBCs), neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, Mean red blood Cells Volume (MCV)

  Biochemistry: sodium, potassium, magnesium, chloride, glucose, urea, creatinine, eGFR , total protein, calcium, phosphorus, total bilirubin, unconjugated and conjugated bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH). triglycerides (TG)

- Vital Signs:

Vital signs (blood pressure, pulse rate) will be assessed at screening visit, before each trial product administration and at the same timepoints as the ECGs. Body weight will be assessed at screening visit, inclusion visit and after each trial product administration.

- Tolerance at the injection site:

Tolerance at the injection site will be recorded during injection of P03277 or Placebo, up to 30 min and 1 Day post-injection

- Safety 12-leads ECGs:

Those ECGs will be done as triplicate within 1 hour before administration and 10 minutes and 3 hours post-administration.

- P03277 plasma concentration and long term elimination:

Plasma concentration of P03277 based on the same timepoints of ECGs and plasma and urine concentration of P03277 for long term elimination assessment analysis will be subcontracted to an analytical center.

Statistical methods

- Primary analysis:

In order to be “negative” (successful), the trial must show that both 0.1 and 0.3 mmol/kg doses of P03277 do not increase the QT interval corrected by Fridericia formula (QTcF).
The null hypothesis is that the difference between each of the two doses of P03277 and placebo for the largest mean change from baseline for the QTcF is greater than the non-inferiority margin set to 10 ms according to regulatory guidance. This test is performed at a one-sided at the 5% significance level, which is equivalent to compare the upper limit of the two-sided 90% confidence intervals of the difference with the non-inferiority margin of 10 ms. To conclude that P03277 is non-inferior to placebo, the null hypothesis has to be rejected for both doses simultaneously.
The primary analysis is performed using an analysis of covariance (ANCOVA) model for crossover data with the baseline data and sex as covariate.

- Secondary analyses:

  - In order to validate the assay sensitivity, the trial must show that the positive control increases the QTcF by at least 5 ms.
    The null hypothesis is that the difference between the positive control and placebo for mean change from baseline for the QTcF is less than 5 ms according to regulatory guidance. This test is performed one-sided at the 5% significance level. To conclude that positive control is superior to placebo, the null hypothesis has to be rejected.

As multiple timepoints are examined separately, the overall Type I error rate needs to be adjusted. To address this issue, the method described by Hochberg and Tamhane will be used. To minimize the correction and because the positive control effect is well known, only five timepoint around the peak effect (1h, 1h30, 2h, 3h and 4h) will be used.

- Same analysis as for primary end-point will be repeated for QT, QTc_{POP} and QTcB
- Descriptive statistics at any time from administration up to 24h post dose of Time-matched change from baseline, placebo controlled, of the QT, QTcF, QTc_{POP} and the QTcB will be provided
- Number and percentage of subjects showing values above predefined threshold for QT, QTcB and QTcF (under placebo and two doses of P03277)
- Descriptive statistics at any time of QT, QTcF, $QTc_{POP,}$ QTcB, RR (ms), QRS (ms), PR (ms), Heart rate (bpm)
- QT/QTc values according to plasma concentrations of P03277
- Descriptive statistics on T wave morphology changes, U wave occurrence and sinus rhythm will be presented
- Descriptive statistics on bradycardia and arrhythmia will be presented
- Descriptive statistics will summarize safety data:
  - Biochemistry and hematology
  - Tolerance at the injection site
  - Adverse events
  - Vital signs
  - Safety ECGs
- P03277 plasma concentration description and data will be presented
- Long term (1 and 3 months post-administration) P03277 elimination (blood and urine) data will be descriptively presented.

TRIAL FLOW CHART

	Screening visit	Inclusion visit	Administration periods												Follow-up period	
			Period 1			Period 2			Period 3			Period 4			D10 + 1 month	D10 + 3 months
	D-28 to D-1	D-1 to D1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D38 +/- 3days	D94 +/- 3days
Informed consent signature	X															
Eligibility criteria[1]	X	X														
Physical examination	X		X			X			X			X		X		
Medical history	X															
Prior contrast agents[1]	X	X														
Concomitant treatments[1]	X	X	←	—	—	—	—	—	—	—	—	—	—	→		
Vital signs[2]	X		←	→		←	→		←	→		←	→	X		
12 lead ECG[3]	X		X			X			X			X		X		
Body weight	X	X[11]			X			X			X			X		
Height	X															
Blood sampling for biology assessment[4][5]	X		X		X			X			X			X		
Drugs screening and Serology[4][5]	X															
Pregnancy test[6]		X														
Blood sampling for Plasmatic Concentration[7]			←	→		←	→		←	→		←	→			

	Screening visit	Inclusion visit	Administration periods												Follow-up period	
			Period 1			Period 2			Period 3			Period 4			D10 + 1 month	D10 + 3 months
	D-28 to D-1	D-1 to D1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D38 +/- 3days	D94 +/- 3days
Blood and urine sampling for long term elimination assessment															X	X
12-lead Holter ECG(8)			←	→		←	→		←	→		←	→			
IMP/AMP administration			X			X			X			X				
Tolerance at injection site(9)			X	X		X	X		X	X		X	X			
Adverse events(10)	←													→	X	X

(1) Eligibility criteria, prior contrast agents and concomitant medication checked at the screening visit must be confirmed at the inclusion visit
(2) Vital signs: systolic blood pressure, diastolic blood pressure and heart rate at screening and pre-dose up to 24 hours post dose : [-1hour, 5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours] (5, 10 and 20 min are not applicable for AMP period).
(3) 12 lead ECG: as triplicate for screening to check inclusion criteria and as triplicate for safety within 1 hour before administration and at 10 minutes and 3 hours post-administration (triplicates is defined by 3 ECGs taken in close succession according to the ECG core lab specifications)
(4) Blood sampling for biology assessment: Hematology: Red Blood Cells (RBCs), White Blood Cells (WBCs), neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, Mean red blood Cells Volume (MCV). Biochemistry: sodium, potassium, magnesium, chloride, glucose, urea, creatinine, eGFR, total protein, calcium, total protein, phosphorus, total bilirubin, unconjugated and conjugated bilirubin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, Lactate DeHydrogenase (LDH). Triglycerides (TG).
(5) For screening blood and urine sampling and serology, results have to be available at the latest at D 1
(6) Only for female subject of childbearing potential or with amenorrhea for less than 12 months
(7) P03277 plasma concentration sample will be drawn at pre-dose up to 24 hours post dose : [-1hour, 5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours] (5, 10 and 20 min are not applicable for AMP period).
(8) 25 hours ongoing from one hour before trial products administration up to 24 hours post-dose
(9) Unless for moxifloxacin which will be administered per os and on open label
(10) Adverse events will be recorded from screening visit to end of confinement except pregnancy (subject's or subject's partner) that will be recorded up to Day 17. During follow-up period, only related AE and AESI will be recorded.
(11) IMP volume to be injected at Day 1 should be based on weight measured at inclusion visit or the day before (Day -1)
Time windows allowance have been defined for each procedures as described in the relevant study plans listed in section 18.2

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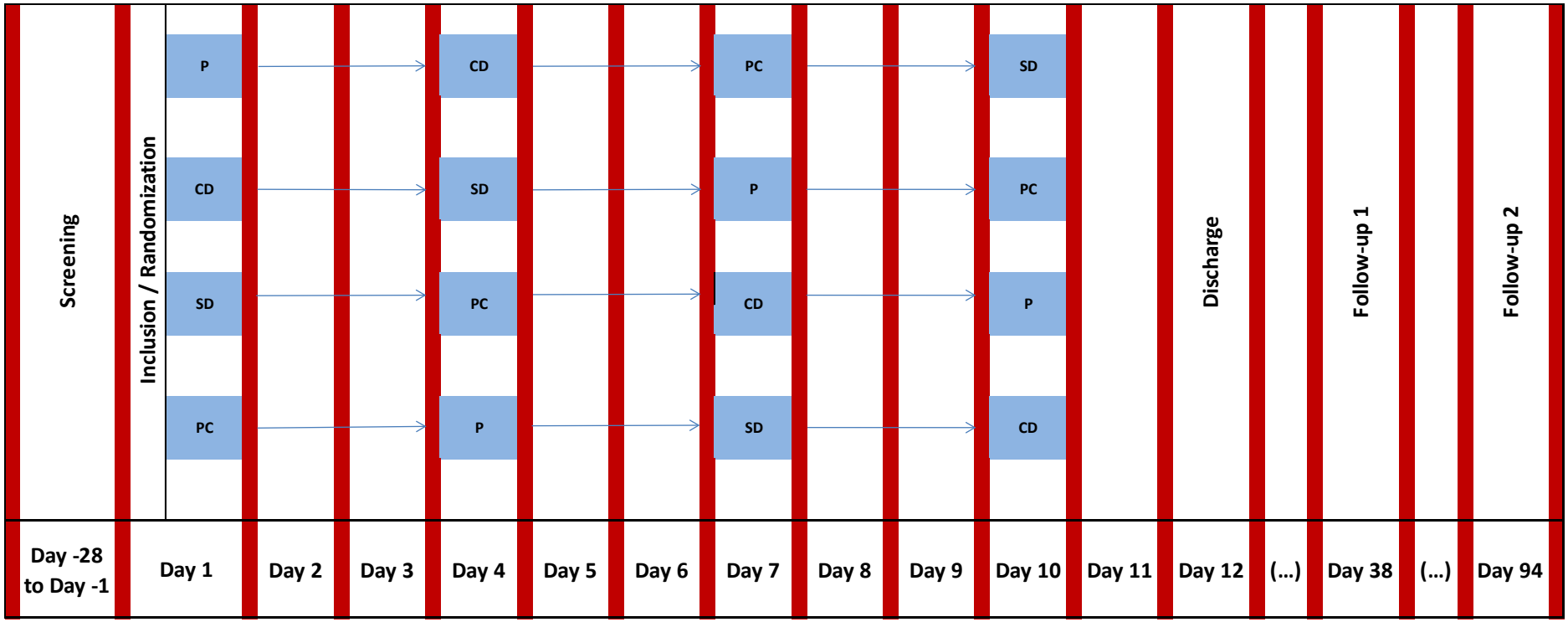
TRIAL DIAGRAM

(example of possible sequences)



PC= Positive Control, P= Placebo, CD= P03277 at anticipated clinical dose, SD= P03277 at supra-clinical dose.
Screening can be done within 28 up to 1 days before inclusion.
Minimum trial duration for subjects: 95 days
Maximum trial duration for subjects: 122 days (In case of ICF is signed 28 days before inclusion).

SIGNATURE PAGE

[redacted]

PRINCIPLE INVESTIGATOR STATEMENT

I agree to conduct the clinical trial in accordance with the present protocol (and its amendments, if applicable) and to comply with the requirements of the Declaration of Helsinki, the Good Clinical Practice (GCP) guidelines of the International Conference on Harmonisation (ICH) and all other laws and regulations in force on the use of investigational medicinal products.

[redacted]

ABBREVIATIONS

AE	Adverse Event
AMP	Auxiliary Medicinal Product
AR	Adverse Reaction
BMI	Body Mass Index
CA	Competent Authority
CRA	Clinical Research Associate (syn. Monitor)
CRF/eCRF	Case Report Form/ electronic Case Report Form
CRO	Contract Research Organization
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EMA	European Medicine Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FSI	First Subject In
GBCA	Gadolinium Based Contrast Agent
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention To Treat
LQTS	Long QT Syndrome
LSO	Last Subject Out
QTc	QT corrected for heart rate
QTcB	QT corrected for heart rate according to Bazett's formula
QTcF	QT corrected for heart rate according to Fridericia's formula
QTc_{POP}	QT corrected for heart rate according a population-derived correction mode
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SPC/SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction

ULN Upper limit normal

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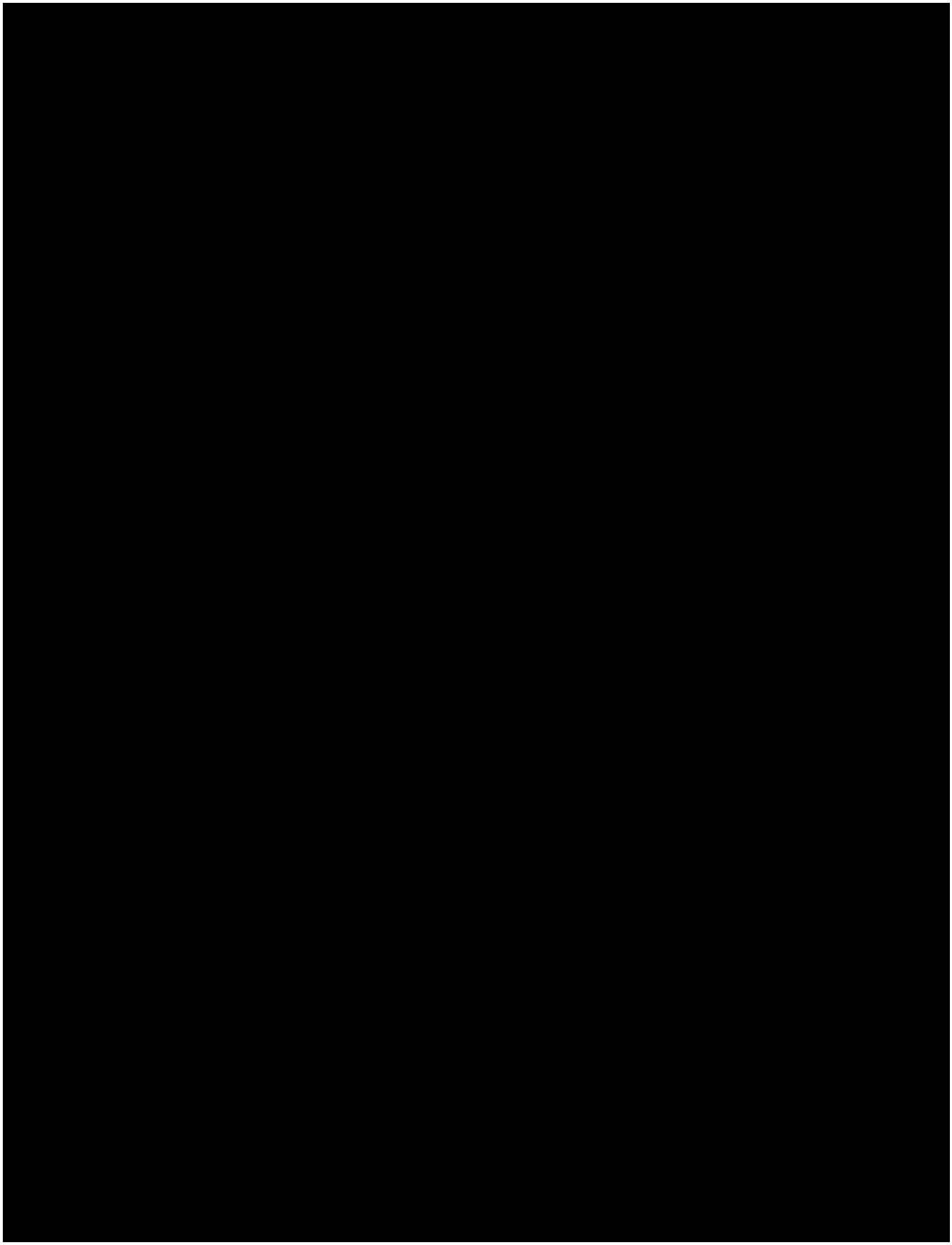

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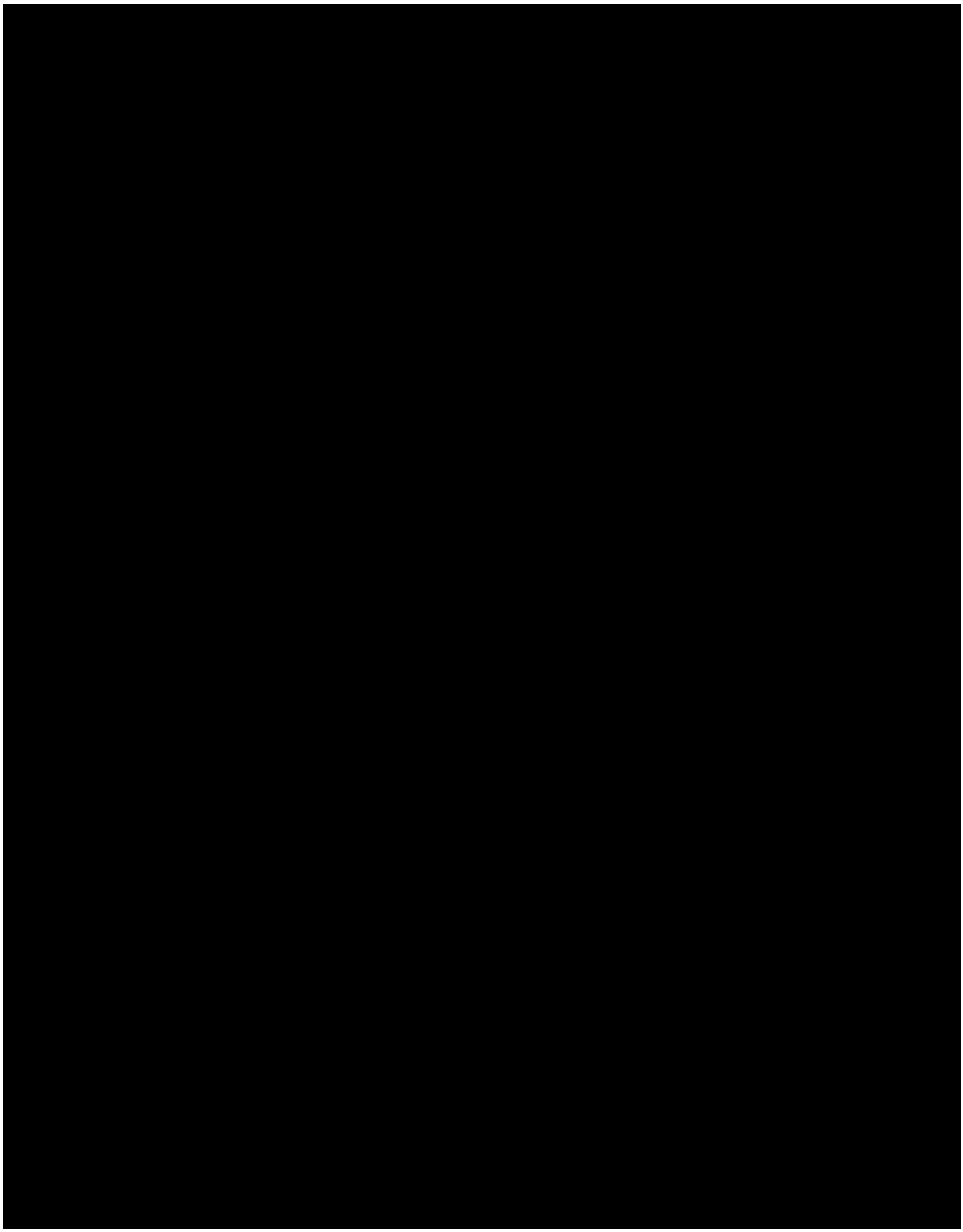


1 INTRODUCTION AND TRIAL RATIONALE

Gadolinium-Based Contrast Agents (GBCAs) have been used extensively in a large range of indications in MRI examinations. GBCAs consist of the active substance gadolinium (Gd) and a chelating agent. They can be categorized by their chemical structures into linear and macrocyclic agents and further subdivided by their charge (ionic or non-ionic). In vitro experiments have shown that the macrocyclic compounds are the most stable, with an undetectable release of Gd3+ ions under physiological conditions.

P03277 is a new chemical entity discovered and developed by Guerbet. It is a non-ionic macrocyclic gadolinium (Gd) complex having a high kinetic stability. It is intended to be used in human, by intravenous bolus injection, as a contrast agent for Magnetic Resonance Imaging (MRI). Potential applications may include but are not limited to imaging of the Central Nervous System (CNS), of "whole body" pathologies and magnetic resonance angiography (MRA), etc.

P03277 has a molecular weight of 970.11 g/mol [redacted]
P03277 is used as an aqueous injectable solution for injection at a concentration of 0.5 M.

P03277 is a Gd chelate with a very high stability, limiting the risk of release of toxic free Gd in the body. The results of preclinical data indicate a good tolerance and a low toxicity profile at dose levels and exposure much higher than the anticipated clinical dose. This satisfactory tolerance has been confirmed in a phase I/IIa trial. In this trial, 36 healthy volunteers and 12 patients were administered with a single dose of P03277 and 18 volunteers with placebo. No serious adverse reaction occurred in any of these volunteers and patients at any of tested dose at 0.025, 0.5, 0.75, 0.1, 0.2, and 0.3 mmol/kg BW. No clinically significant changes in vital signs or laboratory findings were noted.
No ECG findings were reported as AE during the phase I/IIa trial but limited ECG data were available in this first in man trial.

Moreover, a phase IIb dose ranging trial has started in Europe, North America and South Korea where approximately 280 patients will undergo a brain MRI under administration of P03277. During this phase IIb trial ECG monitoring is also performed as 12-leads ECG evaluated at several timepoints until 1 day post-administration.

According the guideline ICH E14 "The clinical evaluation of QT/QTc interval (Figure 2) prolongation and proarrhythmic potential for non-antiarrhythmic drugs" applicable since November 2005, it is recommended to assess the cardiac tolerance (ECG data) of a new product having systemic bioavailability

by conducting a well-controlled trial to assess the potential of a drug to delay cardiac repolarization. This assessment should include testing the effects of new agents on the QT/QTc interval as well as the collection of cardiovascular adverse events.

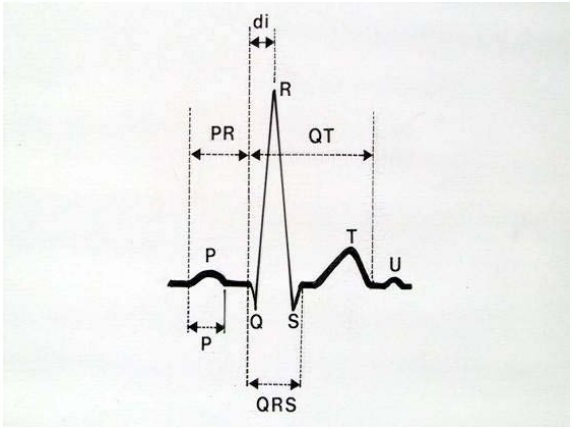


Figure 2: Atrial depolarization (P-wave), ventricular depolarization (QRS complex) and ventricular repolarization (T wave, U wave) [1]

This GDX-44-006 trial will fulfill this regulatory requirement and is part of a clinical development plan to be performed in order to support EMA and FDA approval of P03277.

2 TRIAL OBJECTIVES

2.1 Primary Objective

To assess the cardiac safety after administration of P03277 by evaluating the QT and QTc intervals in healthy volunteers.

2.2 Secondary Objectives

To assess the cardiac, clinical and biological safety, plasma concentration, and long term elimination profile of P03277 following its administration in healthy volunteers.

2.3 Sub-Trial / Ancillary Trial Objectives

Not applicable

3 TRIAL DESCRIPTION

3.1 Protocol Design

Phase I clinical trial, single center, randomized, cross-over double-blind placebo-controlled and open-label positive-controlled (moxifloxacin) **[2]** in healthy volunteers.

This trial will be conducted as 4*4 cross-over design that is more sensitive for detecting QT changes.

According the guideline ICH E14, a "Thorough QT/QTc trial" has to assess the anticipated therapeutic dose and a higher dose than the anticipated therapeutic dose.

The anticipated therapeutic dose for P03277 is 0.1 mmol/kg, which is a standard dose for most GBCAs currently approved. The supra-therapeutic dose of P03277 that will be assessed is 0.3 mmol/kg. Indeed, it is the dose also used with some currently approved GBCAs for limited applications, and it is important in phase I clinical trial to ensure that there is no impact on QT/QTc at this high dose level.

The three Investigational Medicinal Products (IMPs) will be:
- P = Placebo (Nacl 0.9%)
- CD = P03277 tested at anticipated clinical dose (0.1mmol/kg)
- SD = P03277 tested at supra-clinical dose (0.3mmol/kg).

The positive control, moxifloxacin, is an auxiliary medicinal product.
- PC = Positive control (moxifloxacin 400 mg – *per os*)

Subjects who have provided written informed consent and satisfied all eligibility requirements will be included in the trial and randomized, according to a randomization list generated by a statistician not operationally involved in the study, to receive one of 4 sequences according to a Williams design for a 4*4 cross over which is balanced for first order carry over effect.

The sequences of administration could be for instance:

	Period 1	**Period 2**	**Period 3**	**Period 4**
Sequence #1	P	CD	PC	SD
Sequence #2	CD	SD	P	PC
Sequence #3	SD	PC	CD	P
Sequence #4	PC	P	SD	CD

Table 1: Possible assignments of positive control, placebo, P03277 at anticipated clinical dose and P03277 at supra-clinical dose

12 subjects will be assigned to each sequence (6 males and 6 females).

3.2 Trial Duration

The duration of subject's participation could be from 95 days up to 122 days (in case the subject signs the informed consent form (ICF) within 28 days before inclusion).

Within 4-weeks up to 1 day run-in period, subjects will be screened for the trial. Inclusion in the trial will occur the day the subject will be admitted to the phase I clinical trial unit for the first administration period of the allocated sequence (subjects may be admitted in the phase I clinical trial unit at Day -1 to

ensure availability of all results prior to administration). Each subject will have 4 administration periods. Period's duration for moxifloxacin, placebo period, P03277 at clinical dose and P03277 at supra-clinical dose periods will each be 72 hours. The total duration for all periods will be 12 days.

During the 12 days of assessment and monitoring, the subject will have to stay in the phase I clinical trial unit. Healthy volunteers will be discharged on Day 12 after that all trial procedures have been performed and that all safety results have been reviewed by the investigator who will determine that it is safe to discharge the subject.

One month and 3 months following the last IMP/AMP administration on Day 10, subjects will be asked to come back at the phase I clinical trial unit to assess the P03277 long term elimination (in plasma and urine).

For each subject, all ECG parameters will be extracted from the 12-lead Holter ECG in triplicates (3 ECGs taken in close succession according to the ECG core lab specifications) and read centrally by an ECG core lab. The mean of the triplicate ECGs recordings will be considered for each timepoint.

P03277 plasma and urine concentration samples will be analyzed and data reported by an analytical center as described in section 8.4. All other drawn samples will be kept by the analytical center for the trial duration and then will be discarded.

The trial will be considered as completed once all the ECG collected for all the subjects are reviewed by a core lab and all P03277 plasma concentration and elimination data are available.

3.3 Interim Analysis (if applicable)

Not applicable

3.4 Trial Committee(s)

A Data Monitoring Committee (DMC) will be set up for assessing the safety of the Investigational Medicinal Products (IMPs/AMP) during the trial and for monitoring the overall conduct of the clinical trial (see section 12) and will be responsible ensuring the subjects stopping rules for safety reasons are applied (see section 10.2).

The DMC will consist of members of Guerbet team and the principal investigator.

4 SUBJECT SELECTION

4.1 Inclusion Criteria

To be included in the trial, the subject must meet all these inclusion criteria.

1. Adult healthy volunteers at least 18 years old and below 60 (exclusive)

2. Subject having read the information and provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial-related procedure being conducted

3. Subject assessed as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination)

4. Subject with a Body Mass Index (BMI) > 19 kg/m2 and < 28 kg/m2 and a weight at least of 40 kg for female and 50kg for male and at maximum of 100kg

5. Subject able and willing to participate in the trial

4.2 Non Inclusion Criteria

Subjects presenting with one or more of these non-inclusion criteria must not be included in the trial.

1. Subject with any history or family history of inherited or acquired Long QT syndrome (LQTS)
2. Subject with any history or family history of risk factors for Torsade de Pointe (TdP), unexplained loss of consciousness or convulsion
3. Subject with any history of clinically significant bradycardia
4. Subject with any history of clinically significant cardiac impairment by decreasing of left ventricular ejection fraction (LVEF)
5. Subject with any history of clinically significant arrhythmia (including Wolf-Parkinson-White syndrome)
6. Subject with presence of cardiac pacemaker
7. Subject with frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month)
8. Subject with abnormal 12-lead ECG: PR < 120 ms or PR > 200 ms, QRS > 100 ms, QTc > 450 ms, flat T-waves at screening visit (results provided by the independent ECGs Core Laboratory).
9. Subject with following abnormal vital signs after 10 minutes resting in supine position at screening visit:
    - systolic blood pressure < 90 mmHg or > 160 mmHg
    - diastolic blood pressure < 45 mmHg or > 90 mmHg
    - resting heart rate < 45 bpm or > 80 bpm
10. Subject with any history or presence of relevant cardiovascular, pulmonary, gastrointestinal, hepatic, renal, metabolic, haematological, psychiatric, systemic, ocular, or infectious disease; any acute infection or signs of acute illness

11. Subject with abnormal biological, hematological or coagulation tests considered as clinically significant by the investigator and with the following abnormal laboratory parameters (out of normal ranges) (results have to be available at the latest at Day 1)
    - Low potassium blood level ($K^+ < 3.5$ mmol/L)
    - Low magnesium blood level ($Mg^{++} <$ [redacted] 0.66 mmol/L)
    - Estimated creatinine clearance rate (eCCr) < 90 mL/min (Cockroft & Gault formula)
    - Impaired liver function and transaminases > 2 fold ULN
12. Subject carrier of: HBs antigen, anti-HCV antibodies, anti-HIV1 antibodies, anti-HIV2 antibodies at screening
13. Subject with any history of severe allergic or anaphylactic reactions to any allergen including drugs and contrast agents, or allergic disease diagnosed and treated by a physician
14. Subject with any history of tendinopathy following a fluoroquinolone treatment
15. Subject with any history of allergy to moxifloxacin or one of its compounds or other moxifloxacin contra-indications according to the SmPC description
16. Subject with known contra-indication(s) to the use or with known sensitivity to one of the products under investigation or to drugs from a similar pharmaceutical class
17. Subject treated with any concomitant medications which could induce a QT prolongation
18. Subject with presence of narcotics or alcohol abuse (alcohol consumption > 40 grams/Day) at screening
19. Subject smoking more than 10 cigarettes or equivalent /Day, unable to stop smoking during the confinement period
20. Subject having an excessive consumption of beverages with xanthines bases (tea, coffee, chocolate) (>6 cups or glasses /Day) and not able to refrain from consuming grapefruit (fresh fruit, juice, ice...) the day before inclusion and during the confinement period
21. Subject having done a blood donation within 3 months before first trial product administration
22. Subject having received any medication within 21 days prior to inclusion, or within 5 times the elimination half-life of that drug, whichever the longest, with the exception of hormonal contraception for female and of Hormonal Replacement Therapy (HRT) in case of menopausal volunteers and paracetamol
23. Subject having received an administration of any contrast agent within 2 weeks before inclusion, or scheduled to receive any contrast agent within 3 months after the last IMP administration.
24. Subject having participated to a clinical trial involving an investigational drug or device within 21 days prior to screening, or within 5 times the elimination half-life of that drug whichever the longest
25. Subject having a planned simultaneous participation to another clinical trial involving an investigational drug or device
26. Subject having an inability or unwillingness to cooperate with the requirements of this trial
27. Subject having a planned interventions (surgery, radiotherapy, chemotherapy or others) during the course of the trial
28. Subject with any condition which, based on the investigator's clinical judgment, would prevent the subject from participating in all trial assessments and visits (for example: mental or physical incapacity, language comprehension, geographical localization, etc…)

29. Female subject being pregnant or breast-feeding (a female subject of childbearing potential or with amenorrhea for less than 12 months must have a negative pregnancy test at inclusion and must be using a medically approved contraception method)

4.3 Subject Identification

After having obtained the written informed consent, Subjects will be included in the trial and will be allocated a unique Identification Number (Subject ID).

This Subject ID will contain 8 digits: the first three digits corresponding to the country number, the following two digits corresponding to the site number, which are attributed at the beginning of the trial, and the last three digits being chronologically implemented depending on subject enrolment. The lowest enrolment number will correspond to the first subject enrolled at this site and the highest number to the last subject enrolled.

5 INVESTIGATIONAL MEDICINAL PRODUCTS

Investigational Medicinal Product(s) will be manufactured (or commercially available for placebo), labeled, packaged and released in accordance with:

- European Directive 2003/94/EC laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals

In addition, the IMP manufacturing (or commercially available for placebo), packaging, labeling and release will comply with any local applicable regulatory requirement.

Allocation of IMP/AMP to subject will be randomized according to a randomization list generated by a statistician not operationally involved in the study.

Moxifloxacin as positive control is qualified as “Auxiliary Medicinal Product”.

5.1 Investigational and Auxiliary Medicinal Products Description

5.1.1 Investigational Medicinal Product 1: P03277

Name: P03277 [redacted]

Pharmaceutical form: vial of 20 mL, solution for injection

Concentration: 0.5 M

Route and method of administration: by intravenous (IV) bolus injection at 2 mL/s rate without dilution, followed by a saline flush (at least 10 mL) to ensure complete injection of the contrast agent.

Regarding P03277, the IMP will consist of an individually packaged vial in a carton box with a single use detachable label that will allow ensuring accuracy of IMP allocation per subject

P03277 is an aqueous solution. Each vial contains 20 mL of solution presented as a sterile, clear, yellow, ready-to-use solution for injection.

P03277 dose per administration: P03277 will be injected to a pre-specified ordering according to sequence allocated by randomization at 0.1 and 0.3 mmol/kg BW (corresponding to 0.2 and 0.6 mL/kg body weight) via a peripheral vein (the antecubital vein is preferred). The IV injection line will consist of a large bore indwelling catheter (at least 18 gauge).

Sufficient IMP must be allocated to one subject by calculation according to the subject body weight (see section 5.3.1).

The P03277 administration is to be performed by power injector in order to better control injection rate.

Please refer to the ongoing version of Investigator Brochure for more information on P03277.

5.1.2 Investigational Medicinal Product 2: Placebo

Name: NaCl solution

Pharmaceutical form: ampoule of 10 mL, ready to use for injection

Concentration: 0.9 %

Route and method of administration: by intravenous (IV) bolus injection at 2 mL/s rate like P03277 and followed by a saline flush (at least 10 mL) to ensure the blind conditions.

Regarding Placebo, the IMP will consist of two packaged ampoules in a carton box with a single use detachable label that will allow ensuring accuracy of IMP allocation per subject

Placebo administration: NaCl solution 0.9 % will be injected like P03277. The IV injection line will consist of a large bore indwelling catheter (at least 18 gauge).

Volume of placebo to inject for each patient will be equivalent to the volume of P03277 0.3 mmol/kg and determined by calculation according to the subject body weight (see section 5.3.1).

The NaCl solution 0.9 % administration is to be performed by power injector in order to better control injection rate.

Please refer to the ongoing version of summary of product characteristics for more information on NaCl solution.

5.1.3 Auxiliary Medicinal Product 1: Positive control: moxifloxacin

Moxifloxacin is a medicinal product given to the trial subject as a tool to assess the assay sensitivity; it is not being tested or used as a reference in this clinical trial. For this reason, moxifloxacin is called Auxiliary Medicinal Product (AMP) in this trial.

Name: moxifloxacin

Pharmaceutical form: 400 mg film-coated tablets

Dose per administration: 400 mg

Route of administration: *per os*

Regarding moxifloxacin, AMP will consist in a box that contains 1 blister of 1 tablet with a single use detachable label that will allow ensuring accuracy of AMP allocation per subject

All selected subjects will be randomly administered with a single dose of positive control in open condition, as it will be administered orally (as opposed to intravenous injection of P03277 and of Placebo).

Please refer to the ongoing version of summary of product characteristics for more information on moxifloxacin.

5.2 Packaging, Labeling, Storage

Packaging and labeling will be performed in strict accordance with the local regulatory specifications and requirements.

5.2.1 Investigational Medicinal Products

The packaging and labeling of P03277 and Placebo will be performed by Guerbet (or its designee).

In addition to the usual and regulatory labeling for clinical studies, each IMP will have a white detachable sticker indicating the protocol number, IMP number and other locally required information. This label will be stuck on the subject file or trial documentation.

For P03277, IMP will consist in a box that contains one 20 mL vial of P03277.
For Placebo, IMP will consist in a box that contains two 10 mL ampoules of NaCl 0.9%.

In case of damaged IMP, a new IMP will be allocated to the subject.

All IMPs will be stored in a secure place, under the responsibility of the Investigator or other authorized individual and under the conditions described in the SmPC or Investigator's Brochure. The IMPs should be stored at a temperature between 15°C and 25°C in the original package, protected from light and not frozen.

At the time of the trial completion, all used (including empty vials) and unused IMPs should have been returned to the Sponsor or to the predefined location for storage before destruction.

5.2.2 Auxiliary Medicinal Product: moxifloxacin

The positive control will be commercially purchased and used with its primary packaging.
The secondary packaging and labeling of positive control will be performed by Guerbet (or its designee).
In addition to the usual and regulatory labeling for clinical studies, each AMP will have a white detachable sticker indicating the protocol number, AMP number and other locally required information. This label will be stuck on the subject file or trial documentation.
For positive control, AMP will consist in a box that contains 1 blister of 1 tablet.

In case of damaged AMP, a new AMP will be allocated to the subject by chronological order.

All AMPs will be stored in a secure place, under the responsibility of the Investigator or other authorized individual and under the conditions described in the SmPC. The AMPs should be stored at a temperature between 15°C and 25°C in the original package and not frozen.

At the time of the trial completion, all used (including empty box) and unused AMPs should have been returned to the Sponsor or to the predefined location for storage before destruction.

5.3 Condition of IMP and AMP Allocation

5.3.1 Investigational Product(s) Allocation / Randomization

Subjects who have provided written informed consent and satisfied all eligibility requirements will be included in the trial and randomized to receive one of 4 sequences described in section 3.1.

IMP will be randomly assigned to subjects according to a randomization list generated by a statistician not operationally involved in the study.

The volume (mL) of P03277 or placebo having to be injected to the subjects will be determined by calculation according to the subject body weight before each administration (see Table 2: Volume of P03277/Placebo injection by dose and body weight).
The weight to be used to determine the dose to be administered will be the rounded weight below the subject's measured weight. The standard volume for Placebo will correspond to the P03277 volume given at the high dose 0.3 mmol/kg, i.e. 0.6 mL/kg.

Volume of P03277/Placebo injection by dose and body weight			
Adults	**P03277 - CD**	**P03277 - SD**	**P**
	Dose (mmol/kg) 0.1	**Dose (mmol/kg) 0,3**	**Placebo**
	Dose (mL/kg) 0.2	**Dose (mL/kg) 0,6**	
Body Weight Kilograms (kg)	**Volume (mL)**	**Volume (mL)**	**Volume (mL)**
40	8	24	24
41	8	24	24
42	8	25	25
43	8	25	25
44	8	26	26
45	9	27	27
46	9	27	27
47	9	28	28
48	9	28	28
49	9	29	29
50	10	30	30
51	10	30	30
52	10	31	31
53	10	31	31
54	10	32	32
55	11	33	33
56	11	33	33
57	11	34	34
58	11	34	34
59	11	35	35
60	12	36	36
61	12	36	36
62	12	37	37
63	12	37	37
64	12	38	38
65	13	39	39
66	13	39	39
67	13	40	40
68	13	40	40

69	13	41	41
70	14	42	42
71	14	42	42
72	14	43	43
73	14	43	43
74	14	44	44
75	15	45	45
76	15	45	45
77	15	46	46
78	15	46	46
79	15	47	47
80	16	48	48
81	16	48	48
82	16	49	49
83	16	49	49
84	16	50	50
85	17	51	51
86	17	51	51
87	17	52	52
88	17	52	52
89	17	53	53
90	18	54	54
91	18	54	54
92	18	55	55
93	18	55	55
94	18	56	56
95	19	57	57
96	19	57	57
97	19	58	58
98	19	58	58
99	19	59	59
100	20	60	60

Table 2: Volume of P03277/Placebo injection by dose and body weight

The administration has to be performed by power injector in order to better control the injection rate.

In case of problem of IMP allocation (e.g. wrong IMP administered to a subject), the site must immediately report the incident to Guerbet unblinded staff in order to ensure that all corrective actions are

taken. Corrective actions may include transferring the IMP to quarantine to prevent further IMP allocation by the site until the situation is under control again.

5.3.2 Auxiliary Product Allocation

AMP will be randomly assigned to subjects according to a randomization list generated by a statistician not operationally involved in the study.

In case of problem of AMP allocation (e.g. wrong AMP administered to a subject), the site must immediately report the incident to Guerbet in order to ensure that all corrective actions are taken. Corrective actions may include transferring the AMP to quarantine to prevent further AMP allocation by the site until the situation is under control again.

5.3.3 Double-Blind Conditions

To ensure that administrations of the P03277 and placebo are carried out under double-blind conditions, third party (nurse, technician, pharmacist and/or physician) will be responsible for preparing and administrating the IMP(s) according to the randomization list prepared by the statistician. This (these) person(s) will ensure non-disclosure of information. He/she will stick the detachable label of the box into the Subject's records or appropriate form. He/she will also write his/her name, date and signature and the subject number on the box, and after use, he/she will close the box with a seal.

The phase I clinical trial unit must ensure that the subject and investigator remain blind about the administered product.

Any disclosure relating to the nature of the IMP injected by the person responsible for IMP allocation will be considered a protocol deviation.

12-lead Holter ECG reading of all patients will be evaluated in blinded conditions regarding subject, product, date and time-point identifier as described in section 8.3.3.5

5.3.4 Individual Trial Treatment Unblinding

The blinding system will be made of two sets of envelopes.

One sealed envelopes set is kept at the phase I clinical trial unit, the other at the Guerbet pharmacovigilance Representatives (Sérénité 24/24h).
The sets of envelopes should be kept in a safe place and accessible to any person authorised to unblind.

In case of an adverse event occurring for a subject and which nature would require immediate knowledge of the allocated IMP, the individual trial treatment may be unblinded, if absolutely necessary for the safety of the subjects and if unblinding impacts the management of medical care (see section 9.5).

Conditions and procedure for breaking the code will be reviewed with the investigator and his/her team during the initiation visit.

The persons authorized to unblind trial product during the trial usually are: the principal investigator and the Sponsor Pharmacovigilance physician/officer.

If a Guerbet representative receives an external request for unblinding (Authorities, health care professionals taking care of the subject, etc.), he/she must inform the Sponsor Pharmacovigilance Physician/Officer.

If the investigator and the Sponsor Pharmacovigilance physician/officer unblind the trial product, he/she must inform the Clinical Project Manager as soon as possible by letter, fax or e-mail but shall not reveal the nature of the trial product in order to protect as much as possible the double-blind design of the trial.

Unblinding must be documented on the opened envelope by indicating the subject's identification number, age and gender, the date, time and the reason for unblinding, the identity of the person who performed the unblinding.

Please refer to section 9.5 for detailed information on subject safety monitoring.

5.4 IMP and AMP Management

The investigator, the pharmacist, or other personnel allowed to store and dispense Investigational Medicinal Product(s) and Auxiliary Medicinal Product(s) are responsible for ensuring that the IMP and AMP used in the clinical trial is securely maintained as specified by the sponsor and in accordance with the applicable regulatory requirements.

The clinical unit has to ensure that an IMP/AMP storage temperature monitoring will be done 24 hours a day and 7 days a week.

Any quality issue noticed with the receipt or use of an IMP or AMP (deficient IMP/AMP in condition, appearance, pertaining documentation, labeling, expiry date, etc.) or temperature excursion should be promptly notified to Guerbet, who will initiate a complaint procedure.

Under no circumstances shall the investigator supply IMP or AMP to a third party, allow the IMP or AMP to be used other than as directed by this clinical trial protocol, or dispose of IMP or AMP in any other manner.

If during the administration of IMP/AMP, the subject experiences a Serious Adverse Event (SAE), the IMP administration must be discontinued and the subject rendered emergency medical care and monitored until the event is resolved (see section 9.2)

5.5 Trial Product(s) Compliance and Accountability

The investigator, the pharmacist, or other allowed personnel will keep accurate records of Investigational Medicinal Products and Auxiliary Medicinal Products accountability at site level as well as accurate records of the batch numbers and quantities of the IMP/AMP given to each subject.

The dosing information will be recorded in individual subject's records or appropriate form. When protocol required IMP/AMP administration conditions are not followed, reason(s) will be given and recorded by the investigator.

6 CONCOMITANT MEDICATIONS / PROCEDURES

6.1 Concomitant Medications

Subject having received any medication within 21 days prior to inclusion or within 5 times the elimination half-life of that drug, whichever the longest (with the exception of hormonal contraception for female and of HRT in case of menopaused volunteers and paracetamol, which will be collected as concomitant medication) cannot take part to the trial GDX-44-006 (refer to non-inclusion criteria).

6.1.1 Concomitant Treatments of Special Attention

In case of a subject has to be administered with any other GBCAs between discharge and Follow-up 1 and 2 for any unscheduled reason, this information will be recorded.

6.1.2 Prohibited Concomitant Treatments

Use of any prescription drugs (except for contraceptive pills, paracetamol and AE countermedication), herbal supplements medication, dietary supplements, and/or over the-counter (OTC) within 3 weeks prior to inclusion until the end of the confinement period will be prohibited.

6.2 Procedures

Not applicable

7 EVALUATION CRITERIA

For each subject, all ECG parameters (except stopping rules ECG parameters) will be extracted from the 12-lead Holter ECG in triplicates **[3]** and read centrally by a core lab. The mean of the triplicate ECG recordings will be considered for each timepoint.

P03277 plasma and urine concentration samples will be analyzed for each subjects by an analytical center as described in section 8.4.

Details about ECG reading process and samples to assess P03277 concentration handling will be described in separate documents.

Hematology and biochemistry parameters will be assessed ongoing by the phase I clinical trial unit staff.

7.1 Primary Criterion

Primary criterion of cardiovascular safety assessment of P03277 is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of the two P03277 doses of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF)(in ms). No significant QTc prolongation will be considered if the upper limit of the 90 % confidence interval of the maximum ΔΔQTcF is < 10%.

To determine the ΔΔQTcF, the Heart Rate (RR) value and QT value (ms) will be assessed on triplicates 12-lead Holter ECG:

- moxifloxacin: pre-dose up to 24 hours post dose:
  [-1hour, 30min, 1 hour,1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours]
- P03277 and Placebo: pre-dose up to 24 hours post dose:
  [-1hour, 5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours].

7.2 Secondary Criteria

Secondary criteria will consist of cardiac, clinical and biological safety evaluations as follow:

7.2.1 Cardiac Safety

- Assay sensitivity assessment is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of moxifloxacin of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF) (in ms)

- Time-matched placebo-corrected, change-from-baseline mean effect, measured at any timepoints for all IMPs/AMP (Cf. IMPs/AMP related to ECG timepoints listed in section 7.1:
  - QT (ms)
  - QTc(ms) according to population specific correction formula (QTc_{POP})
  - QTc (ms) according to Bazett's formula (QTcB)

- Parameters measured at any timepoints assessed through a 25 hour 12-lead Holter ECG recording :
  - QT
  - QTcF
  - QTc_{POP}
  - QTcB
  - RR (ms)
  - QRS (ms)

- PR (ms)
- Heart rate (bpm)

- T wave morphology changes (yes/no) and U wave occurrence

- Sinus rhythm (yes/no)

- Bradycardia and arrhythmia

7.2.2 Clinical and Biological safety

7.2.2.1 Adverse Events

Adverse event will be recorded throughout the subject participation up to end of confinement for all AEs except pregnancy (subject's or subject's partner) that will be recorded throughout the subject participation up to 7 days after the last IMP/AMP administration (day 17). During follow-up period only related AEs and AESI will be recorded.

7.2.2.2 Biology

For each subject, blood samples will be performed at screening visit, at Day 1 and 2 days after each administration. The blood analysis will be performed by the site laboratory (except P03277 plasma and urine concentration assessment which will be managed by an analytical center)

The following parameters will be obtained and assessed:

- Hematology: Red Blood Cells (RBCs), White Blood Cells (WBCs), neutrophils, eosinophils, basophils, lymphocytes and monocytes, platelet count, hemoglobin, hematocrit, Mean red blood Cells Volume (MCV).
- Biochemistry: sodium, potassium, magnesium, chloride, glucose, urea, creatinine, eGFR, total protein, calcium, phosphorus, total bilirubin, unconjugated and conjugated bilirubin, Aspartate Amino Transferase (AST), Alanine Amino Transferase (ALT), alkaline phosphatase, Lactate DeHydrogenase (LDH). Triglycerides (TG).

  Blood Urea Nitrogen (BUN) will be calculated on the basis of serum Urea values.

For all laboratory assessments, the site laboratory will flag laboratory values falling outside of the normal ranges on the site laboratory report (which the investigator should review and sign off) and the investigator will report any values considered clinically significant as an AE.

7.2.2.3 Vital signs

Vital signs (blood pressure, pulse rate) will be assessed at screening visit, before each trial product administration and on the same timepoints of ECG.

Body weight will be assessed at screening visit, inclusion visit and after each trial product administration.

7.2.2.4 Tolerance at injection site

For all subjects, injection-site tolerance (burning, pain, eruption, extravasation, inflammation, or other) will be assessed over 1 day following each injection (during the injection, up to 30 min ± 5 min and the day after injection) and over a longer period if the investigator becomes aware of any related AE. In case

of injection-site pain, the subject will be asked to specify the level of pain using a visual analogic scale (VAS, [redacted]) from 0 (no pain) to 10 (maximal pain).

7.2.2.5 Safety 12-leads ECGs

12-leads ECGs to assess subject' safety and to monitor subject and trial stopping rules (see section 10.2) related to the QTcF values will be done as triplicate within 1 hour before administration and 10 minutes and 3 hours post-administration.

In addition of the real-time on-site reading, all Safety ECGs will be independently reviewed by a ECGs Core Laboratory (independent reviewer).

The data to be used for safety analyses (section 11.3.9) will be the ECGs Core Laboratory data.

7.2.3 P03277 plasma concentration and long term elimination parameters

P03277 plasma concentration and long term elimination analysis will be subcontracted to a analytical center and will be supervised by Guerbet.

Specific analytical protocols will be established for analysis of P03277. All parameters description and data will be reported in a separate report. All analytical methods used in this trial will be validated prior to any sample analysis.

7.2.3.1 Plasma concentration parameters

Plasma concentration of P03277: blood samples will be drawn from period 1 to period 4, to every subject. Specifics timepoints are defined:

Pre-dose up to 24 hours post dose:
[-1hour, 5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3hours, 4 hours, 8 hours, 24 hours].

P03277 concentrations in plasma will be analyzed using a validated LC-MS-MS method.

7.2.3.2 Long term elimination parameters

To assess potential long term/delayed elimination of P03277, one blood and one urine sample will be collected for each subject (having received at least one dose of IMP) on Day 38 and Day 94.
Only the presence and concentration of P03277 in those samples will be assessed by measuring P03277 concentrations using a validated LC-MS-MS method.

8 TRIAL SCHEDULE AND PROCEDURES

8.1 Trial Schedule

This paragraph describes in detail how the visits are carried out, in their chronological order and according to the flowchart. Time windows allowance have been defined for each study procedures as described in the relevant study plans listed in section 18.2**.**

8.1.1 Screening Visit – (Day -28) to (Day -1)

During this visit, the following tasks or assessments will be performed:

- Written informed consent will be obtained from the subject as described in section 13.3;
- The subject will be attributed an Identification Number as described in section 4.3;
- Demographic data (such as sex, age, race and ethnicity) will be recorded;
- Verification of all eligibility criteria will be done by the Investigator;
- A physical examination will be performed and Vital Signs (systolic and diastolic Blood Pressure in supine position, Pulse Rate), body weight and height will be measured;
- Medical history will be obtained. The Investigator will question on any possible previous contrast agents injection (name of contrast agent injected and tolerance will be recorded);
- Medications and treatments on-going at the time of signing informed consent will be documented;
- 12-lead ECG assessment (Triplicate ECG);
- Blood samples collection for biological assessment and serology;
- Urine samples collection for drugs screening;

All results have to be available at the latest at Day 1.

If all selection requirements are fulfilled, an inclusion appointment will be scheduled to check biological and serology results and to proceed at the subject inclusion.

If any of the selection requirements is not fulfilled (out of biological results if results not available on screening visit), the subject will not perform the inclusion in the phase I clinical trial unit and will be considered as a screening failure.

8.1.2 Inclusion visit – (Day 1 or the day before (Day-1)

At the Inclusion visit the following tasks or assessments will be performed at first:

- Eligibility criteria, concomitant medication and prior contrast agents checked at the screening visit must be confirmed at the inclusion visit and updated if applicable;
- Biology results, drug testings and serology results from screening visit will be checked by the Investigator;
- Urinary collection for pregnancy test, only for female subject of childbearing potential or with amenorrhea for less than 12 months;

- Body weight (IMP volume to be injected at Day 1 should be based on weight measured at inclusion visit

If all selection requirements are fulfilled, the subject will be considered as included;

- Subject inclusion in the phase I clinical trial unit confirmation: start of confinement period;
- Subject randomization and sequence allocation.

If any of the selection requirements is not fulfilled, the subject will not perform the inclusion in the phase I clinical trial unit and will be considered as a screening failure.

8.1.3 (Day 1) to (Day 3), (Day 4) to (Day 6), (Day 7) to (Day 9) and (Day 10) to (Day 12) – Periods 1, 2, 3 and 4:

During these periods the subject has to stay at the phase I clinical trial unit and will be continuously monitored by the phase I clinical trial unit staff especially for adverse event and concomitant medication if applicable.

8.1.3.1 Before IMP/AMP administration

- Day 1:
  - Physical examination
  - Blood sample collection for baseline values of biological assessment
  - IMP/AMP allocation
- Day 4, Day 7 and Day 10:
  - Physical examination
  - Biochemistry results has to be reviewed in order to check subject stopping rules (see section 10.2): Creatinine results should be available before to proceed at the IMP/AMP allocation and administration
  - IMP/AMP allocation
  - IMP/AMP number have to be entered in the subject's record and/or appropriate form

8.1.3.2 Within 1 hour before administration

- Day 1, Day 4, Day 7 and Day 10, T-1h:
  - Vital Signs (systolic and diastolic Blood Pressure in supine position after 10 minutes of rest, Pulse Rate)
  - 12-lead Holter ECG monitoring initiation for the next 25 hours and the Holter start date and time information have to be entered in the subject's record and/or appropriate form
  - 12-lead ECG as triplicate for safety (within the 1 hour pre-dose in supine position and after 10 minutes of rest)
  - Blood samples collection for P03277 plasma concentration assessments

8.1.3.3 Administration of the allocated IMP/AMP

- Day 1, Day 4, Day 7 and Day 10, T0 (for IMP it is the end time of injection):
  - Administration of the allocated IMP/AMP date and time information have to be entered in the subject's record and/or appropriate form

- Only for IMPs administration
  - have to be done on Double-Blind Conditions (AMP will be administered on open label as the Route of administration is *per os)*
  - The appropriate volume of IMP will be administered by the unblinded site staff as IV bolus at the rate of 2 mL/second following a saline flush at the same rate.
  - The following information have to be entered in the subject's record and/or appropriate form: subject weight, calculated volume to be administered, volume actually administered and actual rate of the injection, volume of saline flush, any reason for different rate than 2mL/s or different volumes of more than 10% than the calculated one
  - Tolerance at injection site will be followed during injection (except for AMP): burning, pain, eruption, extravasation, inflammation, or other. In case of injection-site pain, the subject will be asked to specify the level of pain using a visual analogic scale (VAS, [redacted]) from 0 (no pain) to 10 (maximal pain).

8.1.3.4 After administration

- Day 1, Day 4, Day 7 and Day 10:
  - T[5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours] **(5, 10 and 20 min are not applicable for AMP)**
    - Vital Signs (systolic and diastolic Blood Pressure in supine position after 10 minutes of rest, Pulse Rate).
    - Blood samples collection for P03277 plasma concentration assessment (always after vital signs) as close as possible of defined time point. Real time collection have to be entered in the subject's record and appropriate form
  - T[10 min, 3 hours]
    - 12-lead ECG as triplicate for safety (in supine position and after 10 minutes of rest)
  - T[30 min]
    - Tolerance at injection site will be followed (except for AMP): burning, pain, eruption, extravasation, inflammation, or other. In case of injection-site pain, the subject will be asked to specify the level of pain using a visual analogic scale (VAS, [redacted]) from 0 (no pain) to 10 (maximal pain).

In addition, the following information have to be entered in the subject's record and appropriate form:

- Meal start and end time during the Holter recording

Safety ECGs have to be transferred to the ECG core laboratory.

8.1.3.5 Days following administration

- Day 2, Day 5, Day 7 and Day11, T[24 hours]:
  - Vital Signs (systolic and diastolic Blood Pressure in supine position after 10 minutes of rest, Pulse Rate).
  - Blood samples collection for P03277 plasma concentration assessment (always after vital signs) as close as possible of defined time point. Real time collection have to be entered in the subject's record and appropriate form

In addition, the following information have to be entered in the subject's record and appropriate form:

- Meal start and end time during the Holter recording
- Holter end date and time information

Tolerance at injection site (except for AMP): burning, pain, eruption, extravasation, inflammation, or other. In case of injection-site pain, the subject will be asked to specify the level of pain using a visual analogic scale (VAS, [redacted]) from 0 (no pain) to 10 (maximal pain).

- Day 3, Day 6, Day 9:
  - Body weight
  - Blood sample collection for biological safety assessment.

8.1.4 (Day 12) - Discharge

On Day 12, the healthy subjects will be discharged after that all trial procedures had been performed and after an appropriate clinical examination including:

- Physical examination
- Body weight
- Vital signs
- 12 lead ECG
- Blood sample collection for biological safety assessment

and based on which investigator has determined that it is safe to discharge the subject.

In case of abnormal findings, the subject will be asked to stay at the clinical unit for appropriate follow-up.

8.1.5 (Day 38) and (Day 94) – Follow-up Period

Healthy subjects will be asked to come back in the phase I clinical trial unit at Day10 + 1 month and Day10 + 3 months.

- The Investigator will question on any possible GBCAs injection since the discharge day (name of contrast agent injected and tolerance will be recorded);
- Only AEs related to the IMP or moxifloxacin, whether serious or not and AESI should be reported and documented in the medical file and the appropriate section of the CRF.
- Blood samples and urine collection for long term P03277 elimination assessments.

8.1.6 Confinement period

The healthy subjects will be confined in the phase I clinical unit from Day 1 to Day 12 (2 day post last dosing) in order to perform investigational procedure and safety follow-up.

During the confinement period, no grapefruit (and grapefruit derivated products), alcohol, tobacco and beverages with xanthine bases (tea, coffee, chocolate) will be permitted for healthy subjects. Correct hydration of the subjects should be ensured during the confinement period. The clinical staff will ensure that subjects drink at least 1.5 liters of water per day. The healthy subjects will be discharged on Day 12. All subjects will be asked to come back to perform safety follow-up visits on Day 10+ 1 month and on Day 10 + 3 months.

If newly-emergent changes in safety profile occur, further examination can be performed for as long as necessary, to assure that the changes have resolved, and/or that the subject is stable.

8.2 Imaging Protocol

Not applicable.

8.3 ECGs records and readings

8.3.1 On site-ECG Recording

8.3.1.1 ECGs equipment and consumables

12-lead ECG machine and 12-lead ECG Holter recorder equipment and consumables will be supplied (and re-supplied if applicable) by Guerbet (or its ECGs Core Laboratory).

All materiel description, technical specification, specific requirements and user procedures will be provided to the site as part of the Site ECGs Manual.

Guerbet (or its ECGs Core Laboratory) will document the ECGs tasks and obligations of the investigational site in the Site ECGs Manual.

8.3.1.2 Safety 12-leads ECGs

12-leads ECGs to assess subject' safety and to monitor subject and trial stopping rules (see section 10.2) related to the QTcF values will be done as triplicate within 1 hour before administration and 10 minutes and 3 hours post-administration.

The subject will be at rest for at least 10 minutes prior to any ECG recording.

8.3.1.3 12-leads ECG Holter

All subjects will be monitored with a 12-lead ECG Holter recorder from 1 hour before any product administration until 24 hours post-administration.

8.3.2 On site-Reading of 12-leads ECGs

12-leads ECGs to assess subject' safety and to monitor subject and trial stopping rules (see section 10.2) related to the QTcF values will be read in real-time on-site.

The investigator or a designee trained to the ECG reading would have to give an overall interpretation of the ECG at each timepoint on the following parameters:

- heart rate (RR interval),
- PR interval,
- QRS duration,
- QT
- QTc Fridericia.

All clinically significant abnormal changes will be recorded as AEs. Any clinically significant abnormal changes from baseline must be followed until the abnormality is resolved or is adequately explained.

8.3.3 Off Site Reading of ECGs

In addition to the real-time on-site reading, all Safety ECGs will be independently reviewed by a ECGs Core Laboratory (independent reviewer) and data will be available within 48 hours.

The data used for safety analysis (see section 10.2) will be the ECGs Core Laboratory data.

The data to be retained for study and/or subject stopping rules (see section 10.2) application will be the ECGs Core Laboratory data.

As far as the 12-lead Holter ECG monitoring is concerned ECGs parameters will be measured as triplicate and the mean of the triplicate will be considered for each following timepoints:

- moxifloxacin: pre-dose up to 24 hours post-dose:
  [-1hour, 30min, 1 hour,1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours]
- P03277 and Placebo: pre-dose up to 24 hours post-dose:
  [-1hour, 5min, 10 min, 20 min, 30min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours].

The baseline is defined as the mean of 3 triplicates ECGs timepoint measurements within one hour before each administration.

8.3.3.1 Site Qualification

ECGs Core Laboratory will perform site training. These contacts will ensure that the protocol-stipulated ECGs can be performed by the site, might be programmed and prepared prior to enrollment of the first subject and that the Site ECG Manual will be accurately followed by the investigator.

8.3.3.2 Receipt and Tracking of ECGs

ECGs Core Laboratory will request that the investigational site submit anonymous Safety and Holter ECGs data to the ECGs Core Laboratory in a format that will be agreed prior to trial start and by electronic way.

Safety ECGs and ECGs extracted from Holter recording will be tracked in database of the ECGs Core Laboratory.

Investigational site has to keep a copy of all safety ECGs and Holter data as back-up if there is any problem of transmission and for archiving of the source data.

8.3.3.3 ECG Processing and Quality Check

Safety ECGs and Holter data received by the ECGs Core Laboratory will be translated to a readable and analyzable ECG format, according the ECGs Core Laboratory procedure.

The ECGs Core Laboratory will ensure that all Site ECGs Manual requirements have been followed. In the event that a problem with Safety ECGs or Holter data is identified (e.g.: inappropriate length, inconsistency of with the ECGs protocol, inappropriate demographic identifier, poor quality data), the investigational site will be notified concerning the nature of the problems and the steps required for corrective action. The ECGs Core Laboratory will follow-up on all cases requiring remedial action by the investigational sites. Guerbet (or the ECGs Core Laboratory) may conduct site training for the investigator site in case of recurring data quality issues.

8.3.3.4 Expert ECG Reader(s) Training

ECGs Core Laboratory will train expert off-site readers to the trial ECG reading specifications.

8.3.3.5 Blinded Assessment of ECGs

ECGs from Holter recorder database including all evaluable ECGs will be assessed by one or more expert reader(s), with expertise in the interpretation of ECGs for QT and arrhythmia assessment, who will not participate in the trial, and does not have affiliation with the institution where the trial will be conducted. The reading will be performed in a strictly fully blinded manner.

ECGs Core laboratory has to ensure that all ECGs (except safety ECGs) of a given patient have to be read on the same day by the same reader and the reader has to be blind about subject, product, date and time-point identifier **[2]**

8.3.3.6 Inter and Intra-Reader Variability Assessment

The assessments of inter and intra-reader variability will be done by the ECGs Core Laboratory and according their internal quality system.

8.3.3.7 ECG Warehouse and Final Deliverables

Guerbet (or its ECGs Core Laboratory) will submit all ECGs extracted from Holter data to the required competent authority's warehouse as requested format.

Safety ECGs, all Holter data and original ECGs copies extracted from Holter data will be maintained in a secure environment. The ECGs Core Laboratory will maintain a centralized ECGs archive that will contain every data received from the clinical investigators for the trial and original ECGs copies extracted from Holter. Measurements will also be stored so that these data may be audited if necessary. The resulting database will be transferred to Guerbet after database lock for archiving.

8.4 Other Centralized Trial Procedures

8.4.1 P03277 plasma concentration and long term elimination samples

Details on samples handling for plasma concentration and long term elimination assessment, will be provided to the investigational site in a separate document.

Blood samples

A peripheral catheter will be placed until the 8 hour timepoint for blood collection in the forearm (controlateral to the injection site).

For the collection at 24h, 1 and 3 months after the last IMP/AMP administration, blood samples will be collected by direct venipuncture.
For P03277 analysis, blood will be collected into requested tubes. Plasma will be obtained after blood collection by centrifugation and aliquots stored at -20ºC [-18 to -36°] for analysis. Plasma will be divided into two different aliquots P03277 analysis.

In case of remaining blood collected, it will be discarded.

One aliquot for P03277 determination will be sent on frozen condition to the analytical center. One aliquot collected will be kept in the clinical center for the trial duration and will be sent to the analytical center only if necessary. At the end of the trial as described in section 3.2, non-sent aliquots will be discarded.

Urine samples

Urine fraction will be collected at 1 and 3 months after the last IMP administration.

One aliquot will be sent to the analytical center. One aliquot collected will be kept in the clinical center and will be sent on frozen condition to the analytical center only if necessary. Aliquots will be placed into polypropylene tubes, will be tightly capped and stored at -20ºC [-18 to -36°] until shipment for analysis.

After having aliquoted the samples, the remaining urine will be destroyed.

8.4.2 Sample management

The samples will be stored at -20°C [-18 to -36°] before being sent in frozen condition to the qualified analytical center in order to be kept frozen during the shipment.

The schedule of the sample shipments to the analytical center will be discussed with the sponsor during the trial. A few days before the shipment, a fax or email will be sent to the analytical center with at least the following information:
- Date and time of shipment,
- Name and address of the carrier.

The exact content of the shipment should be sent to the analytical center.

The determination of P03277 in plasma and urine will be performed using a validated LC-MS/MS method.
Specific analytical protocols will be established for analysis of P03277. Data will be reported in a separate report. All analytical methods used in this trial will be validated prior to any sample analysis.

9 SAFETY REPORTING

The Investigator will report to the sponsor any adverse event whether related or not to the investigational medicinal product, serious or not, that occurred during the confinement period of a trial subject and only IMP or moxifloxacin related adverse events or AESI (related or not) during follow-up period. Special situations such as treatment errors, suspicion of transmission of an infectious agent via an IMP or moxifloxacin, unusual failure in efficacy, overdose (symptomatic or not), misused, drug exposure during pregnancy or breastfeeding even if uneventful, suspected drug-drug interaction with another product (symptomatic or not) will also be reported to the sponsor.

The definition, modalities of collection and reporting are provided below.

9.1 Adverse Event

9.1.1 Definition of Adverse Event

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product (ICH E2A).

9.1.2 Collection and Recording of Adverse Events

The Investigator or his/her designee will invite the subject to report any experienced abnormality as part of the usual clinical follow-up. In addition, any biological value assessed as significant by the Investigator should be considered as AE.

In order to ensure complete safety data collection, all Adverse Events occurring from the screening visit (ICF signature) until the end of the confinement period, must be reported and followed even if no IMP or moxifloxacin were administered. Only related Adverse Events (serious or not) or AESI (related or not) will be recorded during follow-up visits.

AE should be reported and documented in the medical file and the appropriate section of the CRF

As reminder the subject's participation is defined as the period from the screening visit (ICF signature) to the last trial visit in the general case and defined in section 10 in case of premature discontinuation.

Reported AE is followed up from onset to recovery or stabilization of sequelae. If no follow-up is performed, the investigator must provide a justification in the medical file.

9.1.3 Description of Adverse Events

The following guidelines and definitions should be used by the investigator for the description of an AE when reporting information in CRF and any specific AE report forms:

- **Nature of AE:** preferably an overall diagnosis or syndrome, rather than individual symptoms or signs. The investigator must report AE using standard medical terminology. The same terms should be used in the source documentation and in the CRF.
- **Date and time of onset:** date and clock time of the AE start
- **Intensity:**

- Mild: the subject is aware of the sign or symptom, but it does not interfere with her/his usual daily activities and/or it is of no clinical consequence
- Moderate: the AE interferes with the usual daily activities of the subject or it is of some clinical consequence
- Severe: the subject is unable to work normally or to carry out his/her usual daily activities, and/or AE is of definite clinical consequence.

- **Date of the event end** (or consolidation): The real date of event end will be entered if the event has come to its end. If the AE is still ongoing by the time of end of trial follow-up for the subject (i.e. last trial visit), the subject should be followed-up until AE resolution or a justification should be provided by the Investigator (i.e. chronic disease) in the medical file.
- **Causal relationship to the Investigational Medicinal Product or moxifloxacin:**
  - Related: the definition of adverse reaction implies a reasonable possibility of a causal relationship between the event and the IMP or moxifloxacin. This means that there are facts (evidence) or arguments to suggest a causal relationship.
  - Not related: Applicable when no IMP or moxifloxacin have been administered (pre-administration period) or when no causal relationship exists between the trial drug and the event, but an obvious alternative cause exists (e.g. the subject's underlying medical condition or concomitant therapy).
- **Causal relationship to a trial procedure:**
  - Related
  - Not related
- **Outcome:**
  - Recovered/Resolved: the AE is no longer present at any intensity or return to baseline values for biological data.
  - Recovered/Resolved with sequelae: the AE is resolved but residual effects are still present.
  - Not recovered/Not Resolved: the AE is still present at the last contact with the subject.
  - Fatal: this AE caused or directly contributed to subject's death.
- **Action taken with regard to administration of the IMP or moxifloxacin:**
  - No Action: for AE occurring during the pre-administration/procedure or post-administration/procedure period, or if the IMP or moxifloxacin administration remained the same in spite of AE being present.
  - IMP or moxifloxacin withdrawn.
- **Other action taken:**
  - IMP unblinding
  - AE-targeted medication: the subject took a medication (either prescription or non-prescription) specifically for this AE. The drug(s) should be reported in the appropriate section of the CRF ("concomitant drug" section)
  - Other AE-targeted action: therapeutic measures other than corrective drug administration (e.g. ice, heating pad, brace, cast…) or subject underwent a procedure (surgery, physiotherapy, additional laboratory test…) for this AE. The therapeutic measure(s) should be reported in the appropriate section of the CRF ("Action other than drug administered for the AE" section)
- **Assessment of the seriousness of the AE**: see Section 9.2 for SAE definition.

9.2 Serious Adverse Event

9.2.1 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose (ICH E2A):

- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability /incapacity
- Is a congenital anomaly / birth defect
- **Is an important medical event**

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as **important medical events** that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. ***These should also usually be considered serious.***
Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Note: Life-threatening in the definition of a serious adverse event refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

In case of a SAE, the investigator is responsible for the measures to be taken to ensure the safety of the trial participants.

Severe / Serious: the term "severe" is used to describe the intensity (severity) of a specific event (within the scale mild, moderate, severe). This is not the same as "serious", which is based on subject/event outcome or action criteria. The event itself may be severe but of relatively minor medical significance.

In this protocol, the following situations will not be considered as SAE, providing that they are clearly documented as such in the subject's source data:

- Any hospitalization that had been planned before the trial and that will take place during the trial, provided there is no aggravation of the disease to which it is related.
- Hospitalizations, which are not associated to an adverse event (such as hospitalization for checkup).

9.2.2 Reporting Serious Adverse Events (SAE)

All SAEs occurring from ICF signature until end of confinement period of each subject **must be reported immediately** by the investigator to the sponsor. Only SAE related to IMP, moxifloxacin or procedure must be reported during the follow-up period. The investigator must immediately forward to Guerbet Pharmacovigilance department a duly completed SAE report form [redacted] provided by Guerbet with trial documents, even if it is obvious that more data will be needed in order to draw any conclusion:

- **By Fax #: + 33 (0)1 45 91 67 70**
- **Or by e-mail to: pharmacovigilance.headquarters@guerbet-group.com**

In case of emergency, Guerbet Pharmacovigilance department may be contacted at: **+ 33 (0)1 45 91 50 00.**

SAEs, as for all adverse events, have to be reported also in medical file and in the appropriate section of the CRF (see section 9.1.2)

In order to allow the assessment and eventual subsequent regulatory reporting of the case, the following minimum information should be filled in:

- Subject's details including age, sex and subject's trial enrollment number
- Subject's medical history relevant to the assessment of the event
- Type of event by reporting a diagnosis or if not available, symptoms
- Date and time to onset of the event
- End date of the event (will be reported in a follow-up report if the event is still ongoing at the time of first notification)
- Date and time of investigational drug or moxifloxacin administration,
- Causal relationship to the investigational drug, moxifloxacin or procedure (mandatory)
- Outcome at the time of reporting

If the investigator is aware of any new relevant information concerning an SAE (e.g.: outcome or any information that can have an impact on the assessment of the seriousness or the causal relationship between the SAE and the IMP or moxifloxacin), he has to send it immediately to Guerbet Pharmacovigilance department on a SAE report form [redacted] as a follow-up report.

The initial and follow up reports shall identify the trial subject by his/her Identification Number assigned for the purpose of the trial.

Additional information (e.g. autopsy results, biological values …) or clarifications may be required by the Sponsor in a timely fashion to ensure accurate follow-up and assessment of each case and should be transmitted, anonymized, with a specific form [redacted] as soon as they are available.

SAEs should be followed up by the investigators until complete recovery of the subject or, if not possible, until stabilization of sequelae. The investigator may be requested by Guerbet to provide follow-up information in order to comply with current regulations as well as for comprehensive assessment purposes.

SAEs associated with trial procedures are to be notified using the same reporting procedure as described above.

In addition, if occurring after the end of the subject's follow-up period defined for this trial, serious adverse and/or unexpected events, that the Investigator thinks may be associated with the trial medication/procedure must be reported to the sponsor regardless of the time between the event and the end of the trial.

According to local requirements, Guerbet or its representatives will communicate relevant safety information to the appropriate agency (ies), IEC and/or all active investigators, as it becomes available.

The transmission of the information to the sponsor does not release the investigator from his responsibility to inform the regulatory authorities, if applicable.

9.3 Special situations

9.3.1 Cases of overdose, lack of efficacy, drug-drug interaction, medication errors or misuses

The safety information regarding the following special situations has to be collected and reported by the investigator with the same procedure as for AE, even if uneventful:

- Unintentional treatment errors (e.g.: wrong route of administration),
- Misuse: where the medicinal product is intentionally and inappropriately used not in accordance with the protocol,
- Occupational exposure to an IMP/AMP
- Suspected drug-drug interaction with another product.
- Overdose: In this protocol, the overdose is defined as more than 0.3 mmol/kg for P03277 and more than 400mg for moxifloxacin. Any overdose, with or without adverse event, will be reported as AE and, in addition, on SAE form if the associated event is serious.

If one of these situations leads to an AE or SAE, the safety information will be managed as for AE or SAE accordingly and will follow the appropriate reporting procedure.

9.3.2 Pregnancy

Any participating subject who becomes pregnant or is aware of a pregnancy (subject's partner) during trial participation should inform immediately the investigational site. The female subject should be immediately withdrawn from IMP or moxifloxacin administration.

Any pregnancy (with or without an Adverse Event) of women participating in the trial or of partners of men participating in the trial, that is discovered after the ICF signature until Day 17, i.e. 7 days after the last IMP/AMP administration, must be reported to Guerbet Pharmacovigilance *via* the SAE Report Form [redacted] (see section 9.2.2).

Pregnancy will be monitored until delivery (health of infant up to 8 weeks of age) or early termination.

Specific forms "history and start of pregnancy" and "course and outcome of pregnancy" will be provided to the investigational sites. These forms will be used to collect information on the medical history of the pregnant woman and any risk factor of pregnancy complication, and on the follow-up and outcome of the pregnancy.

Any complication of pregnancy will be reported as an AE or SAE, as appropriate.

9.3.3 Adverse Events of Special Interest

An Adverse Event of Special Interest (AESI) is an AE designated by Guerbet for transmission to Pharmacovigilance in the same time frame as an SAE.

The list of AESI for this protocol is the following:

- Nephrogenic Systemic Fibrosis (NSF).
- Torsade de pointes
- Sudden death;
- Ventricular tachycardia;
- Ventricular fibrillation and flutter;
- Syncope (excluding vasovagal reaction due to blood sampling);
- Seizures

Also, any suspicion of transmission of an infectious agent via an IMP/AMP should be considered as a serious and processed as an SAE.

In addition, any adverse event resulting from an occupational exposure may be directly reported to Guerbet.

9.3.4 Any suspicion of transmission of an infectious agent via an IMP or moxifloxacin

Any suspicion of transmission of an infectious agent via an IMP or moxifloxacin should be considered as serious and processed as an SAE.

9.4 Other important safety issue /New fact

Any safety issues that may alter the current benefit-risk assessment of an investigational medicinal product, or would be sufficient to consider changes in the trial drug administration or would involve any update of trial documents or in the overall conduct of the trial, should be evaluated by the sponsor. It includes any new event likely to affect the safety of the subjects and that may be related to the conduct of the trial or the development of the trial drug such as:

- A SAE which could lead to the modification of the conduct of the trial
- A significant hazard to the subject population such as lack of efficacy of an IMP used for the treatment of a life-threatening disease (if applicable).
- A new major finding from an animal trial,
- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal products in another country by the same sponsor,
- Recommendations of the DMC, if any, where relevant for the safety of subjects,
- Any serious adverse reaction, expected or not, involving healthy volunteers.

According to local requirements, Guerbet or its representatives will communicate relevant safety information to the appropriate agency (ies), IEC/IRB and/or all active investigators, as it becomes available.

Consequently, this type of important safety issue might lead also to:

- Urgent safety measures and their notification
- Substantial amendments
- Premature discontinuation of the trial
- Premature discontinuation of the subject

9.5 Unblinding Procedures

The blinding system will be made of two sets of envelopes.

One sealed envelopes set is kept at the phase I clinical trial unit, the other at Guerbet pharmacovigilance representatives (Sérénité 24/24h) .The sets of envelopes should be kept in a safe place and accessible to any person authorized to unblind.
The investigator may, under exceptional circumstances unblind the individual trial treatment group (sequence) if he/she considers that this procedure is relevant to the safety of the trial subject. Individual trial treatment unblinding is described in section 5.3.4. Unblinding must be documented on the opened envelope, in the subject medical file, completed in the SAE form sent to Guerbet Pharmacovigilance Department, if applicable.

Suspected Unexpected Serious Adverse Reaction (SUSARs) will be unblinded by Guerbet Pharmacovigilance Department for regulatory reporting purposes; however, these SUSARs will remain blinded to the investigator and to Guerbet personnel responsible for trial management, data analysis, and interpretation of results at the trial's conclusion.

10 PREMATURE DISCONTINUATION OF THE TRIAL

10.1 Premature Discontinuation of the Trial per Guerbet Decision

Guerbet reserves the right to discontinue the trial at any time for medical, administrative or other reasons.

Guerbet will inform the relevant authorities in each country, the ethics committees, the trial site investigators, pharmacists and hospital authorities according to the regulatory texts in force.

10.2 Reasons for Subject's premature discontinuation

Screening Failure: a subject may be discontinued from trial in case of non-fulfillment of eligibility criteria. Subject having been screened and meeting all selection criteria but not included in the 28 days screening period could be re-screened. This implies that the subject will sign a new informed consent form before performing the screening visit and will be allocated with a new trial subject number.

Criteria for premature discontinuation of subjects:

- Adverse Event (according to the investigator's judgement);
- Withdrawal of subject's consent;
- Subject lost to follow-up (date of last contact will be documented in the medical file and the eCRF). Any effort will be undertaken to know the reason for this loss to follow-up and/or to exclude any adverse reaction as this reason. This will be documented in the medical file;
- Discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the trial;
- At the discretion of the investigator if the subject safety or well-being is not compatible with trial continuation;

Specific subjects stopping rules:

If any of the events described below occurs, injection of IMP/AMP should not be done and the subject should be discontinued from the trial:

- Torsade de pointes event;
- Ventricular tachycardia;
- Ventricular fibrillation and flutter;
- Seizures;
- QTc Fridericia >500 ms or an increase of > 60 ms (ECG Core laboratory data) over the baseline (the baseline for safety ECG is defined as the 12-leads triplicate ECGs recorded within 1 hour prior to each administration) measurement before each IMP/AMP administration;
- Renal toxicity characterized by an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 µmol/l) compared to the baseline value;
- Any events which investigator or Guerbet considers raising a significant concern.

Specific trial stopping rules:

If this event described below occurs, enrolment should be suspended and the trial will be on hold:

- Torsade de pointes event in 1 subject;
- Sudden death in 1 subject;
- Ventricular tachycardia in 2 subjects;
- Ventricular fibrillation and flutter in 2 subjects;
- Seizures in 2 subjects;
- QTc Fridericia >500 ms or an increase of > 60 ms (ECG Core laboratory data) over the baseline (the baseline for safety ECG is defined as the 12-leads triplicate ECGs recorded within 1 hour prior to each administration) repeated in 2 subjects;
- Renal toxicity characterized by an increase in serum creatinine by more than 25% or 0.5 mg/dl (44 µmol/l) compared to the baseline value repeated in 2 subjects;

The DMC will review the cases and will decide to stop definitely the trial or not.

Data collected for subjects subsequently discontinuing from the trial (please refer to section 14.3.2):

For subjects prematurely discontinuing the trial, all data available at the time of discontinuation will be reported in the medical file and the eCRF (e.g.: inclusion data, safety data, administration data, P03277 plasma concentration data, ECG data and reason for discontinuation The investigator must make every effort to collect and record all follow-up safety information (i.e., adverse events, injection-site tolerance, as appropriate), unless the subject withdraws consent for further data collection/participation for/in the trial.

11 STATISTICAL ANALYSIS

The following section summarizes the statistical analysis method, which is fully described in the Statistical Analysis Plan.

Continuous variables (e.g., age) will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum, and maximum.

Categorical variables (e.g., sex, race and ethnicity) will be summarized using the number of observations (n) and percentage in each category.

11.1 Statistical Method (null and alternative hypotheses)

Primary analysis
Primary endpoint is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of the two P03277 doses of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF) (in ms).

Primary endpoint is considered as following a standard normal distribution. Normality will be checked by means of plots.

Per ICH E14, a "negative" (successful) 'thorough QT/QTc trial' is one in which the upper bound of the 95% one-sided confidence interval for the largest time-matched placebo-corrected, change-from-baseline mean effect of the drug on the QTc interval excludes 10 ms. Consequently, the trial must show that both 0.1 and 0.3 mmol/kg doses of P03277 do not increase the QT interval corrected by Fridericia formula (QTcF) at all timepoints.

The null hypothesis is that the difference between each of the two doses of P03277 and placebo for the largest mean change from baseline for the QTcF is greater than the non-inferiority margin set to 10 ms according to regulatory guidance. An Intersection-Union test is performed at a one-sided 5% significance level. This is equivalent to compare at each timepoint the upper limit of the two-sided 90% confidence intervals of the difference between each of the two doses of P03277 and placebo with the non-inferiority margin of 10 ms. To conclude that P03277 is non-inferior to placebo, the null hypothesis has to be rejected for all timepoints and both doses simultaneously hence the overall Type I error rate does not need to be adjusted.

Assay sensitivity
Assay sensitivity assessment is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of moxifloxacin of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF)(in ms).

In order to validate the assay sensitivity of the trial, the trial must show that the positive control increase the QTcF by at least 5 ms for at least one timepoint.

The null hypothesis is that the difference between the positive control and placebo for the mean change from baseline for the QTcF is less than 5 ms according to regulatory guidance. This test is performed one-sided at the 5% significance level which is equivalent to compare the upper limit of the two-sided 90% confidence intervals of the difference with 5 ms. To conclude that positive control is superior to placebo, the null hypothesis has to be rejected at, at least, one timepoint.
As multiple timepoints are examined separately, the overall Type I error rate needs to be adjusted. To address this issue, the method described by Hochberg and Tamhane will be used. To minimize the correction and because the positive control effect is well known, only five timepoint around the peak effect (1h, 1h30, 2h, 3h and 4h) will be used.

11.2 Sample Size

A total of 48 subjects will be included in the study trial.

The sample size is determined using published recommendations for a thorough QT trial (Statistical Issues Including Design and Sample Size Calculation in Thorough QT/QTc Studies **[4]**).

N can be estimated by $N = 2*(t\alpha(\gamma) + t\beta'(\gamma))2\ [\sigma/(\delta - 10)]\ 2$

where

- σ^2 is the within subject variability
- $\gamma = N - 2$
- $\beta' = 1-(1- \beta)1/L)$ where β is the Type II error and L the number of measurements
- α is the Type I error
- $t_\alpha(\gamma)$ the critical values for a Student T distribution with γ degrees of freedom at an α level.
- δ is the expected difference between active drug and placebo (0 if no difference excepted, >0 if drug is expected to slightly increase QT)

Considering an expected intra-variability of the primary endpoint of $\sigma = 9$ ms and an expected difference of $\delta = 2$ ms between P03277 (two doses) and placebo, 40 subjects are needed to demonstrate non-inferiority with a non-inferiority margin of 10 ms, a power of $1- \beta = 85\%$ and a Type I error of $\alpha = 5\%$ one-sided on the L = 9 measurements.

This sample size is also sufficient to detect a difference of 5 ms (with an expected difference of 12 ms for at least one timepoint and an expected intra-variability of the primary endpoint of $\sigma = 9$ ms) of the primary endpoint between moxifloxacin and placebo with a power of 85%.

To account for potential dropouts and/or unevaluable data points, 48 subjects will be randomized in the trial. The recruitment could be stopped before 48 subjects from the time the number of fully evaluable subjects for the primary criterion is 40. That is to say having took part to the study, till the last scheduled ECG Holter recording.
A dropout is a subject who is prematurely discontinuing the trial before the end of the last Holter ECG recording.

11.3 Planned Analysis

11.3.1 Disposition of Subjects

Number of completed subjects and number of prematurely discontinued subjects breaking down by reason of prematurely discontinuation including screen-failures will be tabulated.

11.3.2 Data Sets Analyzed

There will be four subject sets defined for this trial: All enrolled subjects set, the Safety Set (SS), the Full Analysis Set (FAS) and the Per-Protocol Set (PPS).

All enrolled Subjects Set will include all subjects having signed their inform consent form. This set will be used for subject disposition summaries and individual listings.

The Safety Set will include all subjects, receiving at least one administration of IMP/AMP, regardless of the quantity. This set will be used for evaluation of safety and description of demographic data and baseline characteristics.

The Full Analysis Set will include all randomized subjects. This set will be used for evaluation of cardiac safety and description of demographic data and baseline characteristics.

The Per Protocol Set will be a subset of the FAS and will include all subjects who have no major protocol deviations throughout their whole trial period. Major deviations will be defined as having an impact on the primary criterion. Primary analysis will be performed on this set.

11.3.3 Protocol deviations

Protocol deviations will be split in major and non-major deviations. A major deviation is defined as a deviation being an impact on the primary criteria. A first categorization will be done in the Statistical Analysis Plan (SAP), then final categorization will be done before the breaking the blind during the Statistical Data Review Meeting.

Frequency and percentages of subjects with protocol deviations will be presented breaking down by status (major/non major).

11.3.4 Demographic and Baseline Characteristics

Demographic parameters are age, sex, race, ethnicity, childbearing potential, body weight, height, and body mass index (BMI). Baseline characteristics are the subject's history (including the medical history), prior contrast agents and concomitant medication, the physical examination and cardiac status from ECG exam at inclusion (QT,QTcF, QTc_{POP}, QTcB and T wave morphology changes and U wave occurrence).

Summary statistics will be calculated for age, body weight, height and BMI and presented overall. Frequency and percentages will be calculated for gender, childbearing potential and ECGs status at inclusion, and presented overall.

Subject's medical history will be coded using the MedDRA dictionary and tabulated by body system, preferred term and status (concomitant or not) and presented overall.

Subject's prior contrast agents and concomitant medication will be coded using the Anatomical Therapeutic Chemical (ATC) Drug dictionary and tabulated by ATC codes and presented overall.

Meal date and start and end time will be listed for each period.

11.3.5 P03277 plasma Concentration and long term elimination

Plasma concentration and long term elimination analysis will be subcontracted to an analytical center and will be supervised by Guerbet.

Specific analytical protocols will be established for analysis of P03277. All parameters description and data will be reported in a separate report. All analytical methods used in this trial will be validated prior to any sample analysis.

- Based on the individual plasma concentration versus time profiles, the plasma concentration will be determined for each subject having received P03277
- Long term P03277 elimination data will be presented in a separate report.

11.3.6 Cardiac safety Data

Cardiac safety data are coming from 12-lead Holter ECG recording read by off-site cardiologists. Triplicate values will be issued for each measurement and the average of the 3 replicates will be used for statistics analyses. Therefore there will be one measure by timepoint by subject.

- **Baseline value**

There will be one baseline by administration period.
The baseline is defined as the mean of 3 triplicates ECGs timepoint measurements within one hour before each IMP/AMP administration.

- **Primary analysis**

Primary analysis will be done using the Per Protocol Set

Primary endpoint is defined as the largest time-matched placebo-corrected, change-from-baseline mean effect of the two P03277 doses of QT interval expressed as QTc according to Fridericia's formula (ΔΔQTcF) (in ms).

The primary analysis is performed using an analysis of covariance (ANCOVA) model for crossover data with baseline data as covariate, sequence, period, time, trial drug, trial drug by time and sex as fixed effect and subject as a random effect.

Test
Differences between means will be tested through the model for each timepoint and for the two doses of P03277 using Student's t-test according to the following items:

- μij is the expected average of QTcF for each dose of P03277 at each timepoint (where i is corresponding to one timepoint and j to the 2 doses)
- μij0 is the expected average of QTcF for corresponding placebo

Null hypothesis
Hi: $\mu ij - \mu ij0 \geq 10$, $i = 1 \ldots 9$, $j=1,2$

Alternative hypothesis
Ki: $\mu i - \mu i0 < 10$, $i = 1 \ldots 9$, $j=1,2$

For each timepoint, the two-sided 90% confidence intervals of the difference between each of the two doses of P03277 and placebo is calculated for testing above hypotheses.

The trial will be considered as successful if, no test is significant that is to say if the upper range of the 90% CI is lower than 10 ms for all tests.

The appropriateness of a linear model will be assured by inspecting the goodness of fit, e.g., by looking at normal QQ-plots for the residuals and plots of the residuals over predicted values. If there is an indication that a linear model is inappropriate, the nonlinearity detected will be taken into account by an appropriate transformation of the concentration values (e.g., log(conc/lloq)) or by the use of an appropriate nonlinear model.

- **Secondary analysis:**

Secondary analysis will be done using the Full Analysis Set except otherwise specified.

- Primary analysis will be repeated using the Full Analysis Set.
- Assay sensitivity analysis:

  The assay sensitivity analysis is performed using an analysis of covariance (ANCOVA) model for crossover data with baseline data as covariate, time, trial drug, trial drug by time and sex as fixed effect and subject as a random effect.

  Test
  Differences between means will be tested through the model for each timepoint using Student's t-test according to the following items:

  - μi is the expected average of QTcF for positive control at each timepoint (where i is corresponding to one timepoint)
  - $\mu i0$ is the expected average of QTcF for corresponding placebo

  Null hypothesis
  Hi: $\mu i - \mu i0 \leq 0$, i = 1…5

  Alternative hypothesis
  Ki: $\mu i - \mu i0 > 0$, i = 1…5

  For each timepoint, the p-value for comparing the doses of positive control with corresponding placebo is calculated for testing above hypotheses.

  Hochberg's step-up procedure:

  Let p1, p2, p3, p4, p5 be the ordered p-values (from the lower to the upper value) and H1, H2, H3, H4, H5 be the corresponding ordered null hypothesis. The testing procedure starts with the less significant comparison and continues as long as tests are not significant (meaning that the alternative statistics is not met). The procedure stops the first time a significant comparison occurs and all remaining hypotheses will be not tested.
  In the first step, H5 is rejected if $p5 \leq \alpha$, in the second step (if any) H4 is rejected if $p4 \leq \alpha/2$, in the third step (if any), H3 is rejected if $p3 \leq \alpha/3$, in the fourth step, H2 is rejected if $p2 \leq \alpha/4$, and in the fifth and last step, H1 is rejected if $p1 \leq \alpha/5$ with α being the 1-sided significance level of 0.025.

  The trial will be considered as positive in terms of assay sensitivity if, at the end of the Hochberg's step-up procedure, at least one test is significant.
- Assay sensitivity will be repeated using the Per Protocol Set.
- Same analysis as for primary end-point will be repeated for QT, QTc_{POP} and QTcB
- Descriptive statistics at any time from administration up to 24h post dose of Time-matched change from baseline, placebo controlled, of the QT, QTcF, QTc_{POP} and the QTcB will be provided.
- Number and percentage of subjects showing values above predefined threshold for QT, QTcB and QTcF (under placebo and two doses of P03277):
  - Absolute QTc interval prolongation:
    - QTc interval > 450 ms
    - QTc interval > 480 ms
    - QTc interval > 500 ms
  - Change from baseline in QTc interval:

- QTc interval increases from baseline > 30 ms
- QTc interval increases from baseline > 60 ms

- Descriptive statistics at any time of QT, QTcF, $QTc_{POP,}$ QTcB, RR (ms), QRS (ms), PR (ms), Heart rate (bpm)

- QT/QTc values according to plasma concentrations of P03277.

- Descriptive statistics on T wave morphology changes, U wave occurrence and sinus rhythm will be presented:

- Descriptive statistics on bradycardia and arrhythmia will be presented

11.3.7 Adverse events

All analyses of AEs will be based on the number of subjects with AEs (and not on the number of AEs) except otherwise specified and using the safety set.

Adverse event will be coded with the MedDRA dictionary.

The time period for the assessment of AEs will be divided into 5 mutually exclusive and exhaustive periods (see Table 3 below):

	Start	**End**
Before IMP/AMP	*Informed consent signature*	*Start of the first administration*
Period 1	*Start of the first administration*	*Start of the second administration*
Period 2	*Start of the second administration*	*Start of the third administration*
Period 3	*Start of the third administration*	*Start of the fourth administration*
Period 4	*Start of the fourth administration*	*Day 12 (except pregnancy cf.9.39.3)*

Table 3: Time periods for the assessment of AEs

Events will be classified by trial products according to time of onset in the corresponding cycle related to trial products.

Events will be classified as treatment-emergent if they have started since the first administration.

Partial start dates/times will be queried. If information is not available to reliably allocate to a session and period, the allocation will be agreed at the data review meeting before database lock. If there is any doubt about treatment emergence, AEs will be classified as treatment emergent.

Overall overview

The number (%) of subjects having at least one AE (AE) as follows will be summarized for each trial product and overall for:

- At least one TEAE
- At least one AE with each of the following classification of intensity

  - Mild
  - Moderate
  - Severe
- At least one adverse reaction (relationship to trial treatment classified as 'Related')
- At least one AE with each of the following classifications of action taken with trial treatment:
  - Dose not changed
  - Trial product withdrawn
- At least one AE with each of the following classifications of outcome:
  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Not recovered/Not resolved
  - Fatal

The table will show the same information for serious AE, defined as AEs with serious classified as 'yes' or missing.

The table will be repeated for all TEAEs.

Distribution of AEs and SAEs

A table will be presented showing the total numbers of AEs and SAEs and the distribution of AEs (number [%] of subjects with 0, 1, 2 etc. AEs) for each IMP/AMP and overall. The table will also show the same information for SAEs defined as TEAEs with serious classified as 'yes' or missing, unless the number of SAEs make this uninformative.

Summaries by System Organ Classes (SOC) and Preferred Term (PT)
Summaries by SOC and PT will be presented for all treatment-emergent events and all related treatment-emergent events for each IMP/AMP and overall.

11.3.8 Laboratory biological data

Laboratory data analysis will be done using the safety set.

The baseline is defined as the last measure before the first trial product administration.

The statistical analysis will present results (see section 7.2) in standard international units and conventional United States units. Original units will be only listed. Laboratory data will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of laboratory data to their reference ranges and according to their clinical significance. Quantitative analyses will be done by tabulating raw data and change from baseline. They will be displayed qualitatively as well by means of shift tables.

11.3.9 Other safety observations

Other safety observation will be presented on the safety set.

Extent of exposure

Duration between IMP/AMP administrations and end of trial, volume/dose theoretically administered, volume/dose actually administered, actual IMP rate of administration, theoretical IMP rate of administration and location of injection site will be tabulated. Frequency tabulation of theoretical volume/dose actually administered and theoretical rate of administration/dose actually performed will be also displayed per trial products groups and overall.

Vital signs

The baseline is defined as the last measure before the first trial product administration.

Vital signs (see section 7.2) will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of vital signs data to their normal ranges and according to their clinical significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

ECG data

The baseline is defined as the last measure before each IMP/AMP administration.

ECG data (see section 7.2) will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of ECG data to their normal ranges and according to their clinical significant changes. Quantitative analyses will be done by tabulating raw data and change from baseline.

Injection site tolerance

Number of subjects experiencing burning, pain, eruption, extravasation and inflammation at site injection will be tabulated per IMPs groups and overall. Pain at injection site will be measured using the Visual Assessment Scale (VAS) and VAS measurements for these subjects will be tabulated.

11.4 Statistical/Analytical issues

11.4.1 Adjustment for covariates

For the primary analysis and the assay sensitivity, covariates (baseline of the primary endpoint and sex) are taken into account in the models used for the analyses.

11.4.2 Handling of Dropouts or Missing Data

No imputation will be performed in this trial.

11.4.3 Interim Analysis

Not applicable

11.4.4 Multicentre Trials

Not applicable

11.4.5 Multiple Comparisons/Multiplicity

As stated in sections 11.1 and 11.3.6, the multiplicity is handled by considering a study "negative" (that is to say successful) if both P03277 doses rejects simultaneously the null hypothesis for all timepoints **and** if for the assay sensitivity, the null hypothesis is rejected at, at least, one timepoint, using the method described by Hochberg and Tamhane to deal with multiple timepoints.

11.4.6 Use of a subset of Subjects for Cardiac Safety Analysis

Because the primary analysis is a non-inferiority analysis, it will be done using the Per Protocol Set and then the analysis will be repeated using the Full Analysis Set. The assay sensitivity analysis will be done using the Full Analysis Set and then repeated using the Per Protocol Set

11.4.7 Active control trials Intended to Show Equivalence

Not applicable

11.4.8 Examination of Subgroups

The trial is stratified by sex which will be taken into account for the primary analysis and the assay sensitivity by putting it in the model. No other examination of subgroups is planned.

12 TRIAL COMMITTEE

The purpose of this phase I trial as per current ICH E14 Guidance, is to satisfy with the regulatory requirement for a new drug in development to conduct a thorough QT/QTc trial in order to demonstrate that P03277 does not prolong the QT and QTc intervals in healthy volunteers.

P03277 is a MRI contrast agent belonging to a well-known product class (GBCA) and there is, a priori, no particular expected safety concerns. In addition, the P03277 has a linear pharmacokinetic profile similar to the other Gd chelates and the preliminary results obtained during the phase I trial with several doses of P03277 showed no clinical and biological alert signal.

Regarding placebo there is no particular expected safety concerns. The positive control is a well-known fluoroquinolone which has been shown to prolong the QTc interval on the electrocardiogram in some patients.

The trial duration per subject is maximum 122 days, P03277 are injected at two different doses in addition of Placebo and Positive Control. The P03277 doses selected for the current trial have been tested as single dose during the phase I trial for which no safety alert was identified.

Trial stopping rules and specific subjects stopping rules have been set up in the trial protocol (see section 10.2) and check points at patient level are done before to proceed to any injection (in order to keep the blind conditions).

For all these reasons, an IDMC (Independent Data Monitoring Committee) has not been established for the trial.

However, a Data Monitoring Committee (DMC) will be set up for assessing the safety of P03277 during the trial and for monitoring the overall conduct of the clinical trial as well as ensuring that the trial and subjects stopping rules for safety reasons are applied when required.

The DMC members will be: the principal investigator and Guerbet team (drug safety physician, Medical Expert, clinical project manager and ad-hoc team members). All the members will remain blinded regarding all the trial data. The role and responsibilities of this DMC will be described in a separate document (Data Safety Monitoring Plan).

13 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 References

The trial will be conducted in accordance with the following regulatory / guidance texts:

- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: The Clinical Evaluation Of QT/QTc Interval Prolongation And Proarrhythmic Potential For Non-Antiarrhythmic Drugs E14 Current Step 4 version dated 12 May 2005
- World Medical Association Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, June 1964, and amended in: October 1975 (Tokyo), October 1983 (Venice), September 1989 (Hong Kong), October 1996 (Somerset West), Scotland, October 2000 (Edinburgh), 2002 (Washington), 2004 (Tokyo), October 2008 (Seoul), October 2013 (Fortaleza)
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6 (R2) Current Step 4 version dated 9 November 2016
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A Current Step 4 version dated 27 October 1994
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: General Considerations for Clinical Trials E8 Current Step 4 version dated 17 July 1997
- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
- Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use
- Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products
- International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use: Ethnic Factors in the Acceptability of Foreign Clinical Data E5(R1) Current Step 4 version dated 5 February 1998
- EudraLex, The Rules Governing Medicinal Products in the European Union, Volume 4, EU Guidelines to Good Manufacturing Practice - Medicinal Products for Human and Veterinary Use, Annex 13 Investigational Medicinal Products
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 11 on Electronic Records; Electronic Signatures

- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 211 on Current Good Manufacturing Practice for Finished Pharmaceuticals
- US Food and Drug Administration, Title 21 Code of Federal Regulations Part 54 Financial Disclosure By Clinical Investigators
- Regional / local regulations and other specific populations regulations

13.2 Institutional Review Board/Independent Ethics Committee and Regulatory/Competent Authorities

As per international regulation, the clinical trial may be initiated only after having received the approval by and Institutional Review Board/Independent Ethics Committee (IRB/IEC) and the authorization by the national Regulatory/Competent Authority. The final written approval and authorization must be available for a given investigational site when initiating the trial conduct at this particular site. Amongst all documents required locally, the approval and authorization must be obtained for the protocol, investigator's brochure/SmPC, the subject informed consent form and any other written information or document to be provided to the subjects.

In case of modifications to the trial protocol, subject informed consent form or any other written information provided to the subjects, or to any trial procedure; the modified documents will be submitted to IRB/IEC and Regulatory/Competent Authority opinions. Modifications may be implemented when the final approval and authorization are available.

In case of an emergency situation when the subjects' safety may be at risk, Guerbet may implement emergency safety measures prior to obtaining IRB/IEC approval and Regulatory/Competent Authority opinion. In parallel to implementing these measures, Guerbet will immediately notify the concerned IRB/IEC and Regulatory/Competent Authorities of such implementation.

The documentation related to the approvals and authorizations must be filed in the Trial Master File at Guerbet and at the investigational sites in their respective Investigational Site File (ISF)

Notifications of Serious Adverse Events/Reactions to IRB/IEC and Regulatory/Competent Authority will be made according to the national requirements. Safety reporting is described in section 9 of the present protocol.

Notifications of non-compliances / deviations to IRB/IEC and Regulatory/Competent Authority will be made according to national requirements of participating countries and according to individual IRB/IEC requirements when applicable

13.3 Subject Informed Consent

Prior to participation, all subjects must confirm their free and voluntary willingness to participate in the trial. This confirmation is obtained in writing after having received a full oral and written explanation on the trial:

- Aims, methodology and duration of the trial;
- Potential benefits, foreseeable risks and inconveniencies related to the trial;
- Rights and responsibilities of subjects, with particular emphasis on the right to refuse trial participation or to withdraw consent to participation at any time without consequences or penalties;
- Information on IMP/AMP and its administration;

- Contact details of persons dedicated to the trial at the investigational site.

The language used when informing the subjects and answering their questions must be as understandable as possible and shall not induce any misunderstanding or feeling to be influenced to participate. Subjects must be given ample time to decide whether they agree to participate or not.

Subjects may consent to participate after having received all necessary information and all satisfactory answers to their questions. Their consent must be confirmed in writing by dating and signing the informed consent form(s) approved by the corresponding IRB/IEC.

When the consent may not be directly obtained in writing, a legal representative/impartial witness may be involved in the process and confirm in writing that the subject consented freely and voluntarily.

The information of subjects may only be conducted by qualified investigational site personnel, whose involvement and responsibility for subject information has been fully documented and approved by the Principal Investigator.

The Principal Investigator must ensure that local applicable regulations/requirements are fully observed by the staff under her/his responsibility.

In case of modifications of the subject informed consent or of any other document to be provided to the subjects, the IRB/IEC approval must be obtained prior to implementing the new document(s). Subjects who already consented may be asked to confirm their willingness to continue participating in writing. In any case, the same information and consent process as described above must be followed.

13.4 Trial Records and Archiving

During the course of the clinical trial, investigational sites must ensure completeness and accuracy of the trial records that are to be filed in the Investigator Site File (ISF) provided by Guerbet at the initiation visit. The completeness and accuracy of such files will be checked regularly by Guerbet representative (Clinical Research Associate or Monitor). The final check will occur at the close out visit when investigational site participation is over.

At the end of the trial, investigational sites must ensure the ISF will be archived in an appropriate way that allows timely access and proper retention of documents. Retention period will be of at least 15 years after trial completion. Sites should obtained Guerbet written approval before destroying trial documents.

14 QUALITY CONTROL / QUALITY ASSURANCE

14.1 Direct Access to Source Data/Documents

The investigator will allow Guerbet representatives, the persons responsible for the audit, the representatives of the Ethics Committees and of the Regulatory Authorities to have direct access to source data/documents.

The investigator must guarantee the safety of the trial data in the medical files by implementing security measures to prevent unauthorized access to the data.

The investigator undertakes, in accordance with the regulation in force, to make anonymous any subject data before collection by Guerbet. Especially the name and address of the subjects will be deleted from any medium such as CRF, document for biological results or digital supports.

- If computerized medical files are used, the system must be evaluated by Guerbet (or representative): In case printing of files is not possible, the computerized system must be validated and access should be granted to Guerbet or its representative.

If the computerized system is not validated, the investigator must, at the start of the trial, print, sign and date all the medical files of all subjects and during the trial, print, sign and date in real time each data entry and each data change.

14.2 Clinical Monitoring

Before the trial is conducted at a given investigational site and until the trial is completed/terminated at the same given investigational site, Guerbet will mandate a representative to perform a close monitoring of the trial conduct that will ensure that the investigational site is properly equipped; the staff is adequately experienced and knowledgeable of regulatory and ethical requirements.

The representative will perform regular investigational site visits and report all discussions, subject and IMP/AMP data verification performed with particular attention to subjects' safety and well-being and trial data accuracy and completeness.

14.3 Clinical Data Handling

14.3.1 Data Reported in the eCRF

The eCRF will allow recording of all the data required by the protocol.

The investigator or the designated person from his/her team agrees to complete the eCRF, at each subject visit, and all other documents provided by Guerbet (e.g. documents relating to the IMP management…) and to reply to any data clarifications raised in a timely manner.

The investigator and the appropriate person must attest:

- The authenticity of the data collected in the eCRF;
- The consistence between the data in the eCRF and those in the source documents, with the exception of those data recorded directly in the eCRF and considered as source data.

14.3.2 Data Reported in the eCRF according to Subject Status

For screening failure/non selected subjects, only the date of visit, date of informed consent signature, demographic data, the adverse event, the date and reason for non-selection will be reported.

For included subjects, withdrawn before the first administration of study product, only the selection data, the safety data and the date and reason for discontinuation will be reported.

For subjects withdrawn from the trial after the first administration of study product, all data available at the time of discontinuation will be reported in the medical file and the eCRF (e.g.: inclusion data, safety data, administration data, P03277 plasma concentration data, date and reason for discontinuation …). The investigator must make every effort to collect and record all follow-up safety information (i.e., adverse events, injection-site tolerance, as appropriate), unless the subject withdraws consent for further data collection/participation for/in the trial.

14.3.3 Data Management System

A validated clinical data management system will be used for data process and data storage.

Data processing and control will be closely managed by Guerbet's representative.

14.4 Audits and Inspections

At any time during the trial conduct, Guerbet may mandate a representative to perform an audit of investigational sites in order to assess compliance with the regulatory and ethical requirements, the trial protocol and related instructions and to assess the accuracy and completeness of data generated by the investigational sites.

In parallel, at any time during the trial conduct, Competent/Regulatory Authorities may also carry out an inspection in the facilities of Guerbet and/or the investigational sites. Guerbet will inform all the investigators immediately upon notification of a pending inspection. Likewise, the investigator will inform Guerbet of any pending inspection.

Whether for an audit or for a regulatory inspection, Guerbet and the investigational sites both agree to cooperate in full transparency, confidentiality and professional secrecy.

The investigator must allow the representatives of Guerbet (audit) and/or of the Competent/Regulatory Authorities (inspection):

- To inspect the site, facilities and trial material,
- To meet all members of his/her team involved in the trial,
- To have direct access to trial data and source documents,
- To consult all of the documents relevant to the trial.

15 PUBLICATIONS RULES

16 REFERENCES

Investigator Brochure of the P03277; Please refer to the Investigator Brochure in force.

Moxifloxacin Summary of Product Characteristics; Please refer to the moxifloxacin Summary of Product Characteristics in force.

NaCl 0.9% Summary of Product Characteristics; Please refer to the NaCl 0.9% Summary of Product Characteristics in force.

[1] C. Almange (Rennes), X. André-Fouët (Lyon), M.-C. Aumont (Paris),P. Beaufils (Paris), G. Dérumeaux (Rouen), J.-M. Fauvel (Toulouse), H. Milon (Lyon), J.-C. Quiret (Amiens), G. Roul (Strasbourg), J.E. Wolf (Dijon), Actualisé en 2009 par :M-C. Aumont (Paris), H. Douard (Bordeaux), L. Fauchier (Tours), E. Ferrari (Nice),G. Grollier (Caen), G. Vanzetto (Grenoble), J.E. Wolf (Dijon) : Sémiologie Cardiologique – CNEC.

[2] B. Darpo. Themed Section: QT Safety Review, The thorough QT/QTc trial 4 years after the implementation of the ICH E14 guidance. British Journal of Pharmacology (2010) 159, 49–57.

[3] Scott D Patterson. Investigating Drug-Induced QT and QTc Prolongation in the Clinic: A Review of Statistical Design and Analysis Considerations: Report from the Pharmaceutical Research and Manufacturers of America QT Statistics Expert Team. Drug Infomation Journal. Vd. 39, pp. 243-266,2005 0092-8615/2005

[4] Joanne Zhang & Stella G. Machado (2008) Statistical Issues Including Design and Sample Size Calculation in Thorough QT/QTc Studies , Journal of Biopharmaceutical Statistics, 18:3, 451-467, DOI: 10.1080/10543400802020938, To link to this article: http://dx.doi.org/10.1080/10543400802020938

17 COMPANY LIABILITY INSURANCE

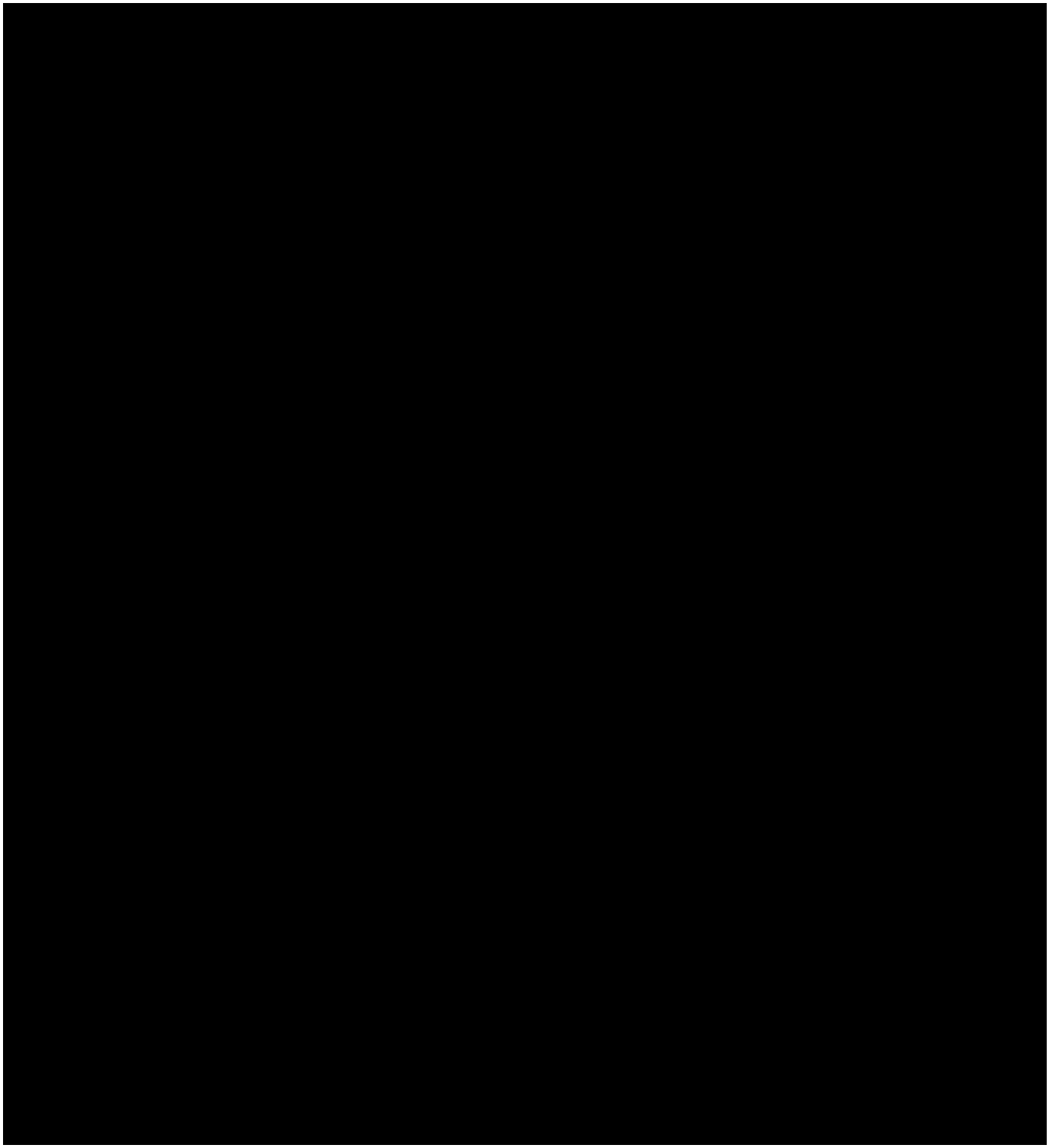
Guerbet's liability, as well as the liability of the investigators participating to this trial, is covered by an insurance policy, a copy of the certificate being submitted to the investigator.

Furthermore, Guerbet and the investigator undertake to comply with the locally applicable legal requirements with respect to insurance.

However, Guerbet and its insurer reject all liability in the following cases, which are merely indicative and not exhaustive:

- An accident due to a cause other than the investigational medicinal product administered,
- An accident occurring during use of the investigational medicinal product differently from the instructions given in the trial protocol,
- An accident occurring for a subject whose consent to participation was not adequately collected.

18 APPENDICES



18.2 List of Study Plans For Study Procedure Time Window Allowance

Procedures performed at Screening Visit

Time windows for the procedures performed at screening visit at the Phase I center are specified in the *Screening Setup Form BE-80-1606627 GDX44-006* document.

Procedures performed during Confinement Period and Follow-up Visits

Time windows for all the procedures performed during the confinement period and follow-up visits at the Phase I center are specified in the *Study Setup Form_BE-80-1606627 GDX44-006* document.

12-Lead Holter ECG Extractions

Time windows for the 12-Lead Holter ECG extractions are defined in the *GDX-44-006_ScopeOfWork* document produced by the ECGs Core Laboratory.