STATISTICAL ANALYSIS PLAN 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 study

SPONSOR GUERBET B.P. 57400 95943 ROISSY CHARLES DE GAULLE CEDEX - FRANCE Tel.: 33-1-45-91-5000 Fax: 33-1-45-91-5199	**STATISTICAL ANALYSIS PLAN APPROVAL**
BIOSTATISTICIAN [redacted]	**Date and Visa**
BIOSTATISTICIAN [redacted]	**Date and Visa**

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
AV	Atrioventricular
ATC	Anatomical Therapeutic Chemical
AMP	Auxiliary Medicinal Product
BMI	Body Mass Index
BPM	Beats Per Minute
CRF/eCRF	Case Report Form/electronic Case Report Form
CRO	Contract Research Organization
DRM	Data Review Meeting
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
MedDRA	Medical Dictionary For Regulatory Activities
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per Protocol
RBBB	Right Bundle Branch Block
SAE	Serious Adverse event
SD	Standard Deviation
TEAE	Treatment Emergent Adverse Event

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1. SUMMARY OF THE STUDY PROTOCOL

This document presents the statistical analysis plan (SAP) for Guerbet, 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".

This analysis plan is based on the final protocol Version 4.0 including amendment n° 2 dated 27 September 2017.

1.1. Study objectives

The primary objective is to assess the cardiac safety after administration of P03277 by evaluating the QT and QTc intervals in healthy volunteers.

The secondary objective of the trial is to assess the cardiac, clinical and biological safety, plasma concentration, and long term elimination profile of P03277 following its administration in healthy volunteers.

1.2. Study design

GDX-44-006 is a Phase I, single center, randomized, cross-over double-blind placebo-controlled and open-label positive-controlled trial which aims to assess the electrocardiographic safety of a new gadolinium-based contrast agent P03277 in healthy volunteers.

Subjects included in the trial should be administered with three Investigational Medicinal Products (IMPs) and one Auxiliary Medicinal Product (AMP) in a 4*4 cross over sequence according to a William design balanced for first order carry over effect. Twelve subjects will be assigned to each sequence (6 males and 6 females). The volunteers will be enrolled sequentially by cohort of 8 subjects. Sequence and IMP/AMP will be randomly assigned to subjects.

The three 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 AMP will be:
- PC = Positive control (moxifloxacin 400 mg - per os).

Period's duration for moxifloxacin, placebo, P03277 at clinical dose and P03277 at supra-clinical dose will each be 72 hours. The total duration for all periods (confinement) will be 12 days.

After all eligibility requirements satisfied, subject will be randomized to a sequence of IMP/AMP administration. Each subject 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: [-1 hour, 30 min, 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: [-1 hour, 5 min, 10 min, 20 min, 30 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours].

ECG measurements will be compared with ECG parameters collected after administration of placebo (Nacl 0.9%). The test sensitivity will be assessed using a positive control (moxifloxacin 400 mg per os) known to induce delays in QT intervals.

All subjects will undergo 12-leads ECGs to assess subject' safety 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.

Blood samples will be taken to implement a concentration-response approach and to assess the effect of P03277 on QT/QTc intervals according to plasma concentration of the product. Sampling will match with the extracted ECGs timepoints.

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.

2. EVALUATION CRITERIA

2.1. Demographic and other baseline characteristics

Demographic parameters are age, sex, race, ethnicity, childbearing potential, body weight, height, and body mass index (BMI). These parameters will be collected during the screening visit.
Baseline characteristics are:

- the medical history
- prior contrast agents
- prior medications
- the physical examination
- vital signs (systolic and diastolic blood pressure, pulse rate)
- blood samples collection

The laboratory data analysis will be performed by the site laboratory.
The following parameters will be 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, chloride, glucose, blood urea nitrogen (BUN) / urea, creatinine, creatinine clearance estimated by Cockcroft-Gault, eGFR (CKD-EPI), total protein, calcium, magnesium, phosphorus, total bilirubin, unconjugated and conjugated bilirubin, aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase, lactate dehydrogenase (LDH), triglycerides (TG).

- cardiac status from ECG exam (QT, QTcF, QTcB, QRS, PR, RR, heart rate, sinus rhythm).

2.2. Cardiac safety criteria

For each subject, all ECG parameters extracted from the 12-lead Holter ECG in triplicates and read centrally by a core lab will be analysed in the section cardiac safety. The mean of the triplicate ECG recordings will be assessed 1 hour before each administration and up to 24 hours post-administration:

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

The safety 12-lead ECG assessments measured on-site will be available on real-time and used for monitoring (and withdrawn if needed) the subject during the course of the study. Those ECGs will be done as triplicate within 1 hour before administration, 10 minutes and 3 hours post-administration and read by a core lab. These assessments will be presented along with other safety criteria in the safety evaluation section.

2.2.1. Primary cardiac safety criterion

The primary criterion of the study is the QT interval expressed as QTc according to Fridericia's formula (QTcF) change from baseline (in ms).

2.2.2. Secondary cardiac safety criteria

Secondary cardiac safety criteria included to support the primary endpoint are the followings:

- Parameters measured at any timepoints:
  - QT (ms)
  - QTcPOP (ms), Qtc according to population specific correction formula
  - QTcB (ms), QTc according to Bazett's formula
  - RR (ms)
  - QRS (ms)
  - PR (ms)
  - Heart rate (bpm)
  - Interpretation
  - Sinus rhythm (yes/no)
- Morphological analysis:
  - Changes in T and U wave morphologies will be described through the description of morphological abnormalities (Q or QS pattern, axis and voltage, hypertrophy, ST depression and elevation, T/U wave abnormalities, AV conduction, intraventricular conduction defects, rhythm, technical quality). Changes from baseline that represent the appearance or worsening of the morphological abnormality will be analysed.

QTcPOP will be obtained using a linear mixed modelling of QT interval (ms) vs RR interval (ms) on all available extracted Holter ECG from placebo period data.

SAS Procedure:

```
proc mixed data = dataset method = REML;
        class subj ;
        model log(QT) = log(RR) / SOLUTION ddfm = kr;
        random subj / type = cs;
run;
```

The slope will determine the correction formula of QTcPOP: $QT/RR^{\propto}$ where RR interval is in seconds. The correction derived from placebo period will be applied to all trial products data.

2.3. Other safety criteria

2.3.1. Clinical and biological safety

2.3.1.1 Adverse events

Adverse events 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/AMP administration). During follow-up period only related AEs and AESI will be recorded.

2.3.1.2 Laboratory data

For each subject, blood samples will be collected before the first trial product administration and 2 days after each administration. The laboratory data analysis will be performed by the site laboratory. The following parameters will be 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, chloride, glucose, blood urea nitrogen (BUN) / urea, creatinine, eGFR (CKD-EPI), 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).

2.3.1.3 Vital signs

Vital signs (Systolic Blood Pressure, Diastolic Blood Pressure, Pulse Rate) will be assessed before each trial product administration, on the same timepoints than cardiac safety parameters and at Day 12.
Body weight will be assessed at inclusion visit and after each trial product administration to determine the volume of IMP to be administered (except at Day 12).

2.3.1.4 Tolerance at injection site

For all subjects, injection-site tolerance (burning, pain, eruption, extravasation, inflammation, or other) will be assessed over the day following each injection (during the injection, up to 30 min ± 5 min and one 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) from 0 (no pain) to 10 (maximal pain).

2.3.1.5 Safety 12-leads ECGs

12-leads ECGs to assess subjects' safety and to monitor subject and trial stopping rules related to the QTcF values will be collected as triplicates within 1 hour before administration, 10 minutes, 3 hours after administration and at Day 12.
In addition to the real-time on-site reading, all safety ECGs (QT, QTcF, QTcB, QRS, PR, RR, heart rate, sinus rhythm) will be independently reviewed by a ECGs Core Laboratory (independent reviewer).
The safety analyses will be based on the ECGs Core Laboratory data.

2.3.1.6 Concomitant medications

Concomitant medications will be recorded at the time of informed consent form signature until end of the study.

2.3.2. Plasma concentration and long term elimination parameters

2.3.2.1 Plasma concentration parameters

Blood samples will be drawn from period 1 to period 4, for every subject, to evaluate plasma concentration of P03277.
Specific timepoints are defined for pre-dose up to 24 hours post dose: [-1 hour, 5 min, 10 min, 20 min, 30 min, 1 hour, 1.5 hours, 2 hours, 3 hours, 4 hours, 8 hours, 24 hours].

2.3.2.2 Long-term elimination parameters

One blood sample and one urine sample will be collected at Day 38 and Day 94 for each subject who received at least one dose of IMP in order to assess the potential long term/delayed elimination of P03277.
Presence and concentration of P03277 in those samples will be measured.

3. STATISTICAL METHODS

3.1. General considerations

After the database lock, the statistical analysis will be performed [redacted] under the supervision of GUERBET Biostatistician on the basis of the present document.

A quality control of the statistical analysis will be performed both by GUERBET and the CRO to ensure the reliability of the results.

The GUERBET validation strategy will be described in the Statistical Analysis Validation Plan which will be based on this present document.

Thorough description of all parameters reported will be presented separately by trial product or sequence group. Summary tabulated results will be provided by group and assessment time, if relevant or they will be replaced by the corresponding individual data listings if too few subjects are concerned.

Tabulations of quantitative parameters will include the following summary statistics: Number of Subjects, Mean, Standard Deviation, Minimum, Median and Maximum. If for a given parameter, the raw value has been collected with x decimal places, the mean, median and standard deviation will be rounded to x+1 decimal places, while the minimum and maximum values will be tabulated as reported with x decimal places.

Tabulations of frequencies for categorical data will include all possible categories and will display the number of observations in a category as well as the percentage (%) relative to the respective group. Percentages will be rounded to one decimal place. The category missing will be displayed only if there are actually missing values. Percentages will be calculated on the total of non-missing recorded categories.

All statistical tests will be performed at the significant threshold of 5% one sided.

SAS® Version 9.2 will be used for all descriptive summaries and [redacted] analyses.

3.2. Null and alternative hypothesis

Per ICH E14 [2], 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.

<u>Primary Analysis</u>

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 or equal 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:

- μ_{ij} 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)
- μ_{ij0} is the expected average of QTcF for corresponding placebo

Null hypothesis:
$Hi: \mu_{ij} - \mu_{ij0} \geq 10, i = 1 \dots 11, j = 1,2$
Alternative hypothesis:
$Ki: \mu_{ij} - \mu_{ij0} < 10, i = 1 \dots 11, j = 1,2.$

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 (in ms).
In order to validate the assay sensitivity of the trial, the positive control must 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 lower limit of the two-sided 90% confidence intervals of the difference with 5 ms:

- μ_i is the expected average of QTcF for positive control at each timepoint (where i is corresponding to one timepoint)
- μ_{i0} is the expected average of QTcF for corresponding placebo

Null hypothesis
$Hi: \mu_i - \mu_{i0} < 5, i = 1 \dots 5$
Alternative hypothesis
$Ki: \mu_i - \mu_{i0} \geq 5, i = 1 \dots 5$

To conclude that positive control is superior to placebo, the null hypothesis has to be rejected for 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 [3] will be used.
To minimize the correction and because the positive control effect is well known, only five timepoints around the peak effect will be used: 1h, 1h30, 2h, 3h and 4h.

3.3. Determination of 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 [4].

N can be estimated by $N = 2 * \left[t_\alpha(\gamma) + t_{\beta'}(\gamma)\right]^2 [\sigma/(\delta - 10)]^2$
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 σ = 9 ms and an expected difference of δ = 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 - β = 85% and a Type I error of α = 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 σ = 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, until 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.

3.4. Adjustment for covariates

For the primary analysis and the assay sensitivity, QTcF at baseline and sex are considered as covariates taken into account in the models used for the analyses.

3.5. Handling of dropouts or missing data

No imputation will be performed in this trial.

3.6. Interim analyses and data monitoring

Safety analysis will be performed for data monitoring committee (DMC) during the trial.

3.7. Multicenter studies

Not Applicable.

3.8. Multiple comparisons/multiplicity

The multiplicity is handled by considering a study "negative" (i.e. successful) if both P03277 doses reject simultaneously the null hypothesis for all timepoints and if for the assay sensitivity, the null hypothesis is rejected for at least one timepoint, using the method described by Hochberg and Tamhane to deal with multiple timepoints.

3.9. Use of a subset of subjects for cardiac safety analysis

The primary analysis will be done using the Per Protocol Set and will be repeated using the Full Analysis Set.
The assay sensitivity analysis will be done using the Full Analysis Set and repeated using the Per Protocol Set.

3.10. Active control studies intended to show equivalence

Not Applicable.

3.11. Examinations 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.

4. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

Primary analysis will test each timepoint: 11 instead of 9 mentioned in the protocol.
A model will be performed for each timepoint, the time will no more be included in the model. There is no change on the statistical analysis as Intersection-Union test was planned.

In secondary analysis, same analysis as for primary endpoint will be repeated for HR in addition of QT, QTcPOP and QTcB.
Descriptive analysis on number and percentage of subjects showing values above predefined threshold will be presented for PR and QRS.

5. STATISTICAL AND ANALYTICAL PLANS

5.1. Disposition of subjects

Subject disposition will be based on all subjects who have signed their informed consent form and tabulated by sequence and overall for the following categories:

- Total number of subjects included;
- Total number of subjects exposed to each trial product;
- Number (percentage) of subjects completing the study;
- Number (percentage) of subjects prematurely discontinuing from study.

Reason of screen-failure and premature discontinuation will be presented.

5.2. Data sets analysed and protocol deviations

Data sets analysed
There will be four subject sets defined for this study: 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 who signed their informed consent form. This set will be used for subject disposition summaries and individual listings.
All subjects who failed the screening visit (not selected) or withdrawn from the study before the randomization are screen-failed subjects and will be presented in the all enrolled data set. Those subjects have different data collected depending on the selection status i.e. complete screening visit and inclusion visit data collected for volunteers who have been selected at screening visit while only screening visit data were collected for subjects who did not comply with the eligibility criteria.

The Safety Set will include all subjects receiving at least one administration of IMP, 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.

The number of subjects by analysis set will be tabulated by sequence group and overall.

The following table describes how the above defined subjects sets will be used in the different analyses conducted.

Analyses Sets	Safety Set	Full Analysis Set (FAS)	Per protocol (PP) Set
Demographic data and baseline characteristics	✓	✓	✓ *
Exposure	✓		
Cardiac safety assessment		✓	✓
Safety assessment	✓		

*: If the difference between FAS and PP set is greater than 10%

Protocol deviations

As per ICH E3 guideline, a protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol, with or without impact to the patient safety or the efficacy assessments. Protocol deviations are displayed in the Clinical Study Report (CSR) as a metric of the feasibility and reliability of the study. The list of protocol deviations are presented in the table below and can be updated if necessary before breaking the blind. Protocol deviations will be gathered from monitoring files, clinical database and external vendors of off-site data (Laboratory data, ECG…)
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 categorisation is done in this document, then categorisation will be done before breaking the blind during the statistical data review meeting. The decision will be duly described in the meeting minutes.

The deviations are listed in the table below:

Category	Description	Source	Status
Inclusion criteria not met	Adult healthy volunteers not aged at least 18 years old	Clinical database (prior amendment 2)	Non major
	Adult healthy volunteers not aged at least 18 years old and below 60 (exclusive)	Clinical database (after amendment 2)	Non major
	Subject not having read the information and not provided his/her consent to participate in writing by dating and signing the informed consent prior to any trial-related procedure being conducted	Monitoring	Major
	Subject not assessed as healthy by a comprehensive clinical assessment (detailed medical history and complete physical examination)	Clinical database	Non major
	Subject without a Body Mass Index (BMI) > 19 kg/m² and < 28 kg/m² or a weight at least of 40 kg for female and 50 kg for male and at maximum of 100 kg	Clinical database	Non major

	Subject not able or not willing to participate in the trial	Clinical database	Non major
Non-Inclusion criteria met	Subject with any history or family history of inherited or acquired Long QT syndrome (LQTS)	Clinical database	Major
	Subject with any history or family history of risk factors for Torsade de Pointe (TdP), unexplained loss of consciousness or convulsion	Clinical database	Major
	Subject with any history of clinically significant bradycardia	Clinical database	Major
	Subject with any history of clinically significant cardiac impairment by decreasing of left ventricular ejection fraction (LVEF)	Clinical database	Major
	Subject with any history of clinically significant arrhythmia (including Wolf-Parkinson-White syndrome)	Clinical database	Major
	Subject with presence of cardiac pacemaker	Clinical database	Major
	Subject with frequent headaches and/or migraine, recurrent nausea and/or vomiting (more than twice a month)	Clinical database	Non major
	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)	Clinical database	Major
	Subject with following abnormal vital signs after 10 minutes resting in supine position at screening visit: <90 SBP >160mmHg, <45 DBP >90mmHg, <50 HR >80bpm	Clinical database (prior amendment 2)	Non major
	Subject with following abnormal vital signs after 10 minutes resting in supine position at screening visit: <90 SBP >160mmHg, <45 DBP >90mmHg, <45 HR >80bpm	Clinical database (after amendment 2)	Non major
	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	Clinical database	Non major
	At Day-1: K+ < 3.6 mmol/L, Mg++ < 0.8 mmol/L, eCCr < 90 mL/min, impaired liver f./ALT-AST > 2xULN	Clinical database / Monitoring (prior amendment 2)	Non major

	At Day-1: K+ < 3.5 mmol/L, Mg++ < 0.66 mmol/L, eCCr < 90 mL/min, impaired liver f./ALT-AST > 2xULN	Clinical database (after amendment 2)	Non major
	Subject carrier of: HBs antigen, anti-HCV antibodies, anti-HIV1 antibodies, anti-HIV2 antibodies at screening	Clinical database	Non major
	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	Clinical database	Non major
	Subject with any history of tendinopathy following a fluoroquinolone treatment	Clinical database	Non major
	Subject with any history of allergy to moxifloxacin or one of its compounds or other moxifloxacin contra-indications according to the SmPC description	Clinical database	Non major
	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	Clinical database	Non major
	Subject treated with any concomitant medications which could induce a QT prolongation	Clinical database	Major
	Subject with presence of narcotics or alcohol abuse (alcohol consumption > 40 grams/Day) at screening	Clinical database	Non major
	Subject smoking more than 10 cigarettes or equivalent /Day, unable to stop smoking during the confinement period	Clinical database	Non major
	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	Clinical database	Non major
	Subject having done a blood donation within 3 months before first trial product administration	Clinical database	Non major
	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	Clinical database	Non major

	female and of Hormonal Replacement Therapy (HRT) in case of menopausal volunteers and paracetamol		
	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	Clinical database	Non major
	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	Clinical database	Non major
	Subject having a planned simultaneous participation to another clinical trial involving an investigational drug or device	Clinical database	Non major
	Subject having an inability or unwillingness to cooperate with the requirements of this trial	Clinical database	Non major
	Subject having a planned interventions (surgery, radiotherapy, chemotherapy or others) during the course of the trial	Clinical database	Non major
	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.)	Clinical database	Non major
	Pregnant or breast-feeding (a childbearing potential woman or amenorrhea less than 12 months must have a negative pregnancy test at inclusion and be using a medically approved contraception method)	Clinical database / Monitoring	Non major
Subject not withdrawal as per protocol	Stopping rules detected on laboratory measurements and subject not withdrawn: increase in serum creatinine by more than 25% or 0.5 mg/dL (44 umol/L) compared to the baseline value	Laboratory database	Non major
	Stopping rules detected on ECG measurements and subject not withdrawn: QTc Friderica > 500 ms or an increase of > 60 ms over the baseline	ECG database	Non major

	Stopping rules detected on ECG measurements and subject not withdrawn: Torsade de pointes event / Ventricular tachycardia / Ventricular fibrillation flutter / Seizures	ECG database	Non major
	Subject received a contrast agent within two weeks before the inclusion up to the end of confinement period and subject not withdrawn	Clinical database	Major
	Any exam performed after a withdrawal of consent	Clinical database, Laboratoty database, ECG database	Non major
Unblinding	The blind was not maintained on-site	Monitoring	Non major
	The blind was not maintained off-site	Monitoring	Major
	The code was broken	Clinical database	Major
Forbidden concomitant medication	Concomitant medication taken during the confinement period having an impact on the primary criteria	Monitoring	Major
Trial product deviation	Subject randomisation not followed the sequential list of sequences	Clinical database	Non major
	IMP/AMP administered is not the IMP/AMP allocated by randomisation	Randomisation database	Major
	The volume actually administered is different from 10% to 20% than the calculated one	Clinical database	Non major
	The volume actually administered is different of more than 20% than the calculated one	Clinical database	Major
	Power injector not used	Clinical database	Non major
	The actual injection rate is different than 2mL/s	Clinical database	Non major
	Saline flush volume administered not at minimum of 10 mL	Clinical database	Non major
	Location of injection site is not adequate	Clinical database	Non major
	The dose of AMP actually administered is different from 400 mg	Clinical database	Non major
	Temperature excursion for trial product	Monitoring	Non major
	Extravasation	Clinical database	Major

Missing data	Age is missing	Clinical database	Non major
	Sex is missing	Clinical database	Non major
	Weight is missing at screening visit	Clinical database	Non major
	Height is missing	Clinical database	Non major
	Race is missing	Clinical database	Non major
	Physical examination not performed	Clinical database	Non major
	Vital signs not measured	Clinical database	Non major
	Other contrast agent administration not completed	Clinical database	Non major
	Urine sample not done or missing at screening visit	Clinical database	Non major
	Pregnancy test is missing	Clinical database	Non major
	12-lead safety ECG not performed in triplicates	Clinical database	Non major
	12-lead safety ECG results missing	ECG database	Non major
	12-lead safety ECG from paper instead of digital analysis	ECG database	Non major
	12-lead Holter ECG not performed	Clinical database	Major
	12-lead extracted QTCF from Holter ECG with more than 3 measurements of triplicates at baseline missing	ECG database	Major
	12-lead extracted Holter ECG not performed in triplicates	ECG database	Non major
	Blood sample for central laboratory assessment not performed	Clinical database	Non major
	Laboratory biochemistry results missing	Laboratory database	Non major
	Laboratory hematology results missing	Laboratory database	Non major
	Urine sample for long term elimination not performed	Clinical database	Non major
	Urinary result for long term elimination missing	PK database	Non major
	Blood sample for long term elimination not performed	Clinical database	Non major

	Blood sample results for long term elimination missing	PK database	Non major
	Blood sample for plasma concentration not performed	Clinical database	Non major
	Results for plasma concentration missing	PK database	Non major
	Tolerance at injection site not performed	Clinical database	Non major
	VAS questionnaire not completed while subject reported pain	Clinical database	Non major
	Visit not done	Clinical database	Non major
Non respect of study's schedule and procedures	Urine sample for drug screening not performed at latest the day before first administration	Clinical database	Non major
	Blood samples collection for P03277 plasma concentration assessment not performed after vital signs	Clinical database	Non major
	Blood samples collection for laboratory data not performed before IMP /AMP administration of first period	Clinical database	Non major
	Vitals signs not performed at scheduled time	Clinical database	Non major
	Blood samples collection for P03277 plasma concentration not performed at scheduled timepoint	Clinical database	Non major
	12-lead Holter ECG not performed at scheduled time	ECG database	Non major
	12-lead safety ECG not performed at scheduled time	ECG database	Non major
	Initiation of Holter not performed 1 hour before administration	Clinical database	Non major
	12-lead Holter ECG not performed according to procedures	Monitoring	Non major
	12-lead safety ECG not performed according to procedures	Monitoring	Non major
	Blood sample collection not performed at scheduled time	Clinical database	Non major
	Not allowed retest	Monitoring	Non major
	VAS questionnaire not correctly printed	Monitoring	Non major

Subjects presenting at least one major protocol deviation will be excluded from the Per Protocol Set.

Frequency and percentages of subjects with protocol deviations will be presented by sequence group and overall breaking down by status (major/non major). A listing of all protocol deviations will also be provided in CSR appendix 16.2.2 and major protocol deviations will be flagged.

5.3. Measurements of study drug compliance

Study drug in this study refers to the injection of the contrast media. Number of subjects with theoretical volume to be administered not equal to the one actually administered will be presented and the difference for those subjects will be tabulated in mL and percentage:

$$Compliance = (1 - \frac{theoretical\ volume - \ actual\ volume}{theoretical\ volume}) \times 100$$

5.4. Demographic and other baseline characteristics

5.4.1. Demographic data

Demographic parameters are age, sex, childbearing potential, body weight in kilograms (kg), height in centimetres (cm), BMI (kg/m²) and ethnic origin (self-reported race/ethnicity).
Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for age, body weight, height and BMI. Frequency and percentages will be calculated for sex.

BMI will be derived for each collection of body weight using the formula:

$$BMI = \frac{Body\ Weight\ (kg)}{Height\ (m)^2}$$

5.4.2. Study disease

Not Applicable.

5.4.3. Risk factors

Not Applicable.

5.4.4. Medical history and concomitant diseases

Medical history and concomitant diseases will be coded in System Organ Classes (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or the latest version available at the date of data base lock. Medical histories are the ones flagged as "Not Ongoing" and concomitant diseases are those flagged as "Ongoing" at the screening visit.

Summary tables (number and % of subjects) grouped by SOC and PT will be presented by sequence group and overall for Medical history firstly then for concomitant diseases.

Listing of demographics, study disease characteristics and all diseases will be presented in CSR Appendix 16.2.4 with a flag for ongoing diseases.

5.4.5. Clinical laboratory evaluation at baseline

Laboratory data analysis will be done using the safety set by sequence group and overall. Blood samples will be performed during screening visit. Urinalysis data will be listed only.

Results will be presented in standard international (SI) units and conventional United States units (See Table 1 and Table 2 respectively). Original units will only be listed. Laboratory data will be analyzed quantitatively and qualitatively. Qualitative analyses will be done via comparison of laboratory data to their reference ranges. Quantitative analyses will be done by tabulating raw data.

5.4.6. Vital signs, physical findings and other observations related to safety at baseline

Abnormality detected during physical examination will be listed in section 16.2.9., it will be described in the Adverse Events section.
Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for vital signs (systolic blood pressure, diastolic blood pressure and pulse rate) at screening visit and presented by sequence group and overall. Qualitative analyses of Systolic/Diastolic Blood Pressure (mmHg) and Pulse Rate (beats/min) will be done via comparison of vital signs data to their normal ranges.

5.4.7. Prior medication and procedures

Prior therapies are defined as therapies ended before the first administration.
Prior medications will be coded using the WHODRUG dictionary version September 2016. Prior procedures are therapies not coded as per WHODRUG dictionary.
The number and percent of subjects taking prior medications and procedures will be presented by sequence group and overall.

Summary tables (number and % of subjects) grouped by the first and the fourth level of ATC code will be presented by sequence group and overall for prior medication.

Listing of all prior therapies will be presented in CSR appendix 16.2.4.

5.4.8. 12-lead ECG assessment

Summary statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) will be calculated for cardiac status from the mean of the ECG triplicate examination at screening visit by sequence group and overall (QT, QTcF, QTcB, QRS, PR, RR, heart rate). Frequency and percentages will be calculated for sinus rhythm (yes/no). The number (%) of subjects having at least one “No” for sinus rhythm or having all “Yes” will be summarized.

5.4.9. Other baseline characteristics

Data concerning contrast agent history at screening and inclusion and pregnancy test will be only listed in section 16.2.4.

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

5.5. Cardiac safety evaluation

All cardiac safety analysis will be conducted using the FAS except otherwise specified.
Listing of all cardiac safety data will be presented in CSR appendix 16.2.6. Listing of drug concentration data will be presented in CSR appendix 16.2.5.

5.5.1. Primary analysis of the primary criteria

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.

5.5.1.1 Baseline value

There will be one baseline by administration period.
The baseline is defined as the mean of the 3 triplicates ECGs measured within one hour before each IMP/AMP administration (i.e., first the mean of the 3 triplicates ECGs is done for each timepoint prior IMP/AMP administration: 45, 30 and 15 minutes before administration, then the 3 means are averaged).

5.5.1.2 Primary analysis

The primary analysis is performed using an analysis of covariance (ANCOVA) model for crossover data with baseline data as covariate, sequence, period, trial drug 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.

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 the 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 by looking at normal QQ plots for the residuals and plots of the residuals over predicted values.

The primary analysis will be performed using the Per Protocol Set.

SAS procedure:
proc mixed data = *dataset* method = REML plots=all;
class *Seq Per Trt subj gender*;
model Δ*QTcF* = *Baseline Seq Per Trt gender* / ddfm = kr residual outp=ipred outpm=pred;
random *subj* / type = cs;

lsmeans *Trt*;
Estimate "P03277 0.1 mmol/kg - Placebo 5min after administration" *Trt* 1 0 0 -1 / alpha = 0.1 cl;
run;

5.5.2. Supportive analyses of primary criterion

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, sequence, period, trial drug 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. Only the five following timepoints will be used: 1h, 1h30, 2h, 3h and 4h.

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 hypothesis 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 0.05.

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. CI will be adjusted according to the procedure.

Assay sensitivity will be repeated using the Per Protocol Set.

SAS procedure:
proc mixed data = *dataset* method = REML plots=all;
class *Seq Per Trt subj gender*;
model Δ*QTcF = Baseline Seq Per Trt gender* / ddfm = kr residual outp=ipred outpm=pred;
random *subj* / type = cs;
lsmeans *Trt*;
Estimate "Positive control - Placebo 1hour after administration" *Trt* 0 0 1 -1 / alpha = 0.1 cl;

run;

5.5.3. Additional analyses of primary criterion

Not Applicable.

5.5.4. Analysis of secondary criteria

Analysis of secondary criteria will be done using the Full Analysis Set except otherwise specified.

5.5.4.1 Primary endpoint

Same analysis as for primary end-point will be repeated for QT, QTcPOP, QTcB and HR.

5.5.4.2 Descriptive analysis

- Descriptive statistics (number [n], mean, standard deviation [SD], median, minimum, and maximum) at any time from administration up to 24h post dose of time-matched change from baseline, placebo controlled, of the QT, QTcF, QTcPOP and the QTcB will be provided by trial product group.

- Number and percentage of subjects showing values above predefined threshold for PR, QRS, QT, QTcB, QTcPOP and QTcF:
  - PR interval
    - Value > 220 ms
    - Relative change > 25%
  - QRS interval
    - Value > 120 ms
    - Relative change > 25%
  - 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 (number [n], mean, standard deviation [SD], median, minimum, and maximum) at any time of QT, QTcF, QTcPOP, QTcB, RR (ms), QRS (ms), PR (ms), Heart rate (bpm) will be presented by trial product group. Frequency and percentages will be calculated for interpretation. The worst case of interpretation by triplicates (Abnormal clinically significant > Abnormal non clinically significant > Unable to evaluate/unable to evaluate but measurements provided are correct > Normal ECG) will be presented.

- Frequency and percentages will be calculated for sinus rhythm (yes/no) globally by trial product group. The number (%) of subjects having at least one "No" for sinus rhythm or having all "Yes" after baseline will be summarized.

5.5.4.3 QT/QTc values according to plasma concentrations of P03277

Concentration-response relationship will be investigated between ΔQTc and P03277 concentrations using a mixed model approach.

This analysis will be performed on the Per Protocol Set including all time points for which a pair of ΔQTc and P03277 concentrations is available.

Graphical exploration:

In order to assess quality of QTcF correction before and after dosing the following figures will be provided:

- Scatter plot of QTcF (y-axis) versus RR (x-axis) for baseline and placebo data with a regression line
- Scatter plot of ΔQTcF (y-axis) versus ΔRR (x-axis) for values collected during P03277 treatment periods with a regression line.

In both cases, the regression lines should tend toward an horizontal line, otherwise, a dependency still exist between QTcF and RR and QTcPOP may be considered as preferred dependent variable.

The following exploratory plots will also be performed before starting the modelling:

- Scatter plot of individual ΔQTc values *vs.* time-matched concentrations including a nonparametric trend curve will be provided to assess the pattern of the relationship
- Scatter plot of individual ΔHR values *vs.* time-matched concentrations including a nonparametric trend curve will be provided to detect impact of the treatment on HR
- Time course of ΔΔQTc by dose level as calculated during the primary criteria analysis
- Time course of ΔΔHR (or ΔΔRR) by dose level as calculated during the secondary criteria analysis

The SAS syntax corresponding to the scatter plot of change in QTc vs. concentrations including a trend curve is:

```
proc sgplot data = dataset ;
    scatter x=Concentrations y=CHG/  transparency=0.6 group=TRT name="p1"
    legendlabel="Individual Delta QTc-Concentration pairs";
```

```
    loess x= Concentrations y=CHG/ nomarkers  smooth=0.3 name="p2"
    legendlabel="Trend line" lineattrs=(color=green);
    refline 0/axis=y;
    label TRT="Actual treatment";
    xaxis grid label="Concentration Unit";
    yaxis grid label="ms";
    keylegend "p1" "p2";
run;
```

Model development:

The model development will start with the pre-specified mixed linear model as detailed in Garnett et al. [1] considering ΔQTcF as dependent variable. In case of the graphical exploration suggests that Fridericia correction does not account for all RR variation, ΔQTcPOP will be used instead.

Placebo data will be considered for the analysis with concentration values set to 0. Moreover, concentrations below the limit of quantification will also be set to 0.

The fixed effect parameters of the pre-specified model will be intercept, slope for P03277 concentrations, influence of baseline (centered on mean) on intercept, treatment specific intercept (0=P03277, 1=Placebo), and theoretical timepoints post-administration. Subject specific random effects will be added on intercept and slope parameters with an unstructured covariance matrix. In case of the unstructured covariance matrix is not supported by the data, other simplified or reduced structures will be investigated (ex. variance components).

$$\Delta QTc_{ijk} = (\theta_0 + \eta_{0,i}) + TRT_j + (\theta_1 + \eta_{1,i})C_{ijk} + TIME_k + \theta_2(QTc_{ijk=0} - \overline{QTc_0}) + \varepsilon_{ijk} \quad (1)$$

Where *i* is the subject, *j* the treatment and *k* the time.

The ΔΔQTc and their 2-sided 90% confidence intervals will be calculated at P03277 0.1 mmol/kg and 0.3 mmol/kg C_{max} geometric means as follows:

$$\Delta\Delta QTc_i = (TRT_0\text{-}TRT_1) + \theta_1 Cmax_i$$

The SAS syntax corresponding to Equation 1 and ΔΔQTc estimation is:

```
proc mixed data = dataset method = REML plots=all;
ods output estimates=EST solutions=SOL CovParms=COV;
      class Trt Time subj;
      model ΔQTc = Baseline Trt Concentration Time / ddfm = kr solution alphap=.05
      residual outp=ipred outpm=pred;
      random  INT Concentration/ subject = subj  type = un;
```

Estimate "ΔΔQTc P03277 0.1 mmol/kg" *Trt* 1 -1 *Concentration* $Cmax_1$ / alpha = 0.1 cl;
Estimate "ΔΔQTc P03277 0.3 mmol/kg" *Trt* 1 -1 *Concentration* $Cmax_2$ / alpha = 0.1 cl;
run;

No additional covariate investigation will be performed and in order to avoid unnecessary model-building steps, non-significant fixed parameters will not be removed from the model, unless they cause problem of convergence or estimability issues. Random effects not supported by the model will be remove as they may result in non-convergence problems.

Model evaluation:

Goodness of fit plots will be provided, consisting on:

- QQ plot of residuals
- Concentrations versus residuals
- Time, baseline and treatment versus residuals

Any marked bias in residual plots may suggest model misspecification. Moreover, a large and significant treatment specific intercept (TRT term in the model) may also indicate model misspecification (i.e. lack of linearity).

In addition, structural model hypothesis will be checked from graphical exploratory plots:

- The absence of effect on HR will be investigated from time course of ΔΔQTc by dose level
- The hypothesis of direct relationship will be evaluated from the time course of ΔΔQTc by dose level. If the primary analysis allow to reject the hypothesis of QT/QTc prolongation, hysteresis phenomenon will not be considered, otherwise, hysteresis will be investigated by visual inspection comparing time of peaks in QT response and concentrations
- The hypothesis of linear relationship between ΔQTc and concentrations will be evaluated from exploratory scatter plot and the goodness of fit plots.

In case of the linear relationship between ΔQTc and P03277 concentrations cannot be accepted, an alternative model such as saturable model will be considered.

$$\Delta QTc_{ijk} = \left(\theta_0 + \eta_{0,i}\right) + TRT_j + \frac{(\theta_1+\eta_{1,i})c_{ijk}^{\gamma}}{(\theta_2+\eta_{2,i})^{\gamma}+c_{ijk}^{\gamma}} + TIME_k + \theta_3\left(QTc_{ijk=0} - \overline{QTc_0}\right) + \varepsilon_{ijk} \quad (2)$$

In Equation 2, the parameter θ_1 is the maximum asymptotic effect due to treatment, and the parameter θ_2 is the concentration at which the effect is half θ_1.

In case of a hysteresis phenomenon cannot be discarded, an effect compartment model combining a population PK model on P03277 and a PKPD model will be envisaged.

Display of results

Parameters estimated from the selected model will be presented with their standard error and 95% confidence interval.
ΔΔQTc predicted for each dose level will be presented with their 2-sided 90% confidence interval and a graphical display of predicted ΔΔQTc over the concentration range collected during the study will also be provided.

Decision rule

The impact of P03277 on QT/QTc prolongation will be considered as below the threshold of regulatory concern if the upper bound of the 90% confidence interval of ΔΔQTc predicted at supra-clinical dose Cmax is below 10 ms.

5.5.4.4 Morphological analysis

Analysis of morphology will be based on the number of subjects with at least one emergent abnormality. The number (%) of subjects having changes from baseline will be summarized by the finding's conclusion (see Appendices) for each trial product. Localization will be taken into account. The table will exclude reported statement associated to a normal ECG if necessary:

Category	Term includes:
Q or QS pattern	Small Q waves in inferior leads, consider normal variant
Axis and Voltage	Poor Precordial R wave progression, consider normal variant
Axis and Voltage	Abnormal P wave axis, consider normal variant
Hypertrophy	Left ventricular hypertrophy by QRS voltage consider normal variant
ST depression and elevation	ST elevation, consider normal variant
ST depression and elevation	Early repolarization, consider normal variant
T/U wave abnormalities	Normal repolarization pattern
T/U wave abnormalities	U wave, consider normal variant
AV conduction	First degree AV block, consider normal variant
AV conduction	Short PR interval, consider normal variant
Intraventricular conduction defects	Incomplete RBBB, consider normal variant (QRS<=120msec)
Rhythm	Normal sinus rhythm, rate 50-100 bpm
Rhythm	Possible normal sinus rhythm, rate 50-100 bpm
Rhythm	Dominant sinus rhythm
Rhythm	Uncertain supraventricular rhythm, consider normal variant
Rhythm	Respiratory sinus arrhythmia
Rhythm	Respiratory sinus arhythmia, consider normal variant
Rhythm	Sinus tachycardia, rate 100-130 bpm, consider normal variant
Rhythm	Sinus bradycardia, rate 40-49 bpm, consider normal variant
Rhythm	Wandering atrial pacemaker, consider normal variant, unsinusal rhythm
Rhythm	Atrial electronic pacemaker

Rhythm	Atrial electronic pacemaker, intermittent
Rhythm	Ventricular electronic pacemaker, unsinusal rhythm
Rhythm	Ventricular electronic pacemaker, intermittent, unsinusal rhythm
Rhythm	Dual chamber electronic pace maker
Rhythm	Dual chamber electronic pace maker, intermittent

5.6. Safety evaluation

5.6.1. Extent of exposure

Duration between trial products administration and end of period, summary of durations during the study, volume theoretically administered, volume actually administered, dose actually administered, actual rate of administration, volume of saline flush, location of injection site, mode of injection and occurrence of an overdose will be tabulated. Frequency tabulation of actual injection rate will be also displayed per trial product group and overall.
Body weight measured at inclusion visit and after each trial product administration (i.e. before the next administration) will be presented by each trial product group and overall.

The extent of exposure summary will be presented using the Safety Set.

Listing of exposure will be presented in CSR appendix 16.2.5.

5.6.2. 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 events (AEs) will be coded using MedDRA version 21.0.

The time period for the assessment of AEs will be divided into 5 mutually exclusive and exhaustive periods:

- Before IMP/AMP: between informed consent signature and start of the first administration
- Period 1: between start of the first administration and start of the second administration
- Period 2: between start of the second administration and start of the third administration
- Period 3: between start of the third administration and start of the fourth administration
- Period 4: between start of the fourth administration and Day 12 included (date of Day 12 corresponds to date of Day 10 + 2 days not taking into account the time)
- After confinement period: during follow-up periods (> Day 12).

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.

The number (%) of subjects having at least one 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.

A table will be presented showing the total numbers of AEs and SAEs and the distribution of AEs (number [%] of subjects with number of 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 SOC and PT will be presented for all treatment-emergent events and all related treatment-emergent events for each IMP/AMP and overall.
Adverse events during follow-up period will be presented overall by SOC and PT.

Data listings will present all AEs reported, including non-TEAEs. Adverse event listings will be sorted by subject number and will display also the study procedure, body system, and preferred term, time of onset, duration, intensity, seriousness, outcome, relationship to the IMP/AMP, relationship to a study procedure, action taken with IMP/AMP, IMP unblinding, AE-targeted medication, other AE-targeted action, date and time of IMP/AMP administration (presented in CSR appendix 16.2.7).

AE Duration will be computed in days as Date of End of AE - Date of Onset of AE + 1. Date and time of administration displayed will be those of trial product administration preceding the date and time of onset of the AE. If the AE started before Day 1 or after the follow-up period, no date and time of administration will be displayed.

5.6.3. Deaths, serious adverse events and other significant adverse events

All deaths, all serious adverse events and all adverse events of special interest experienced during the treatment period related to the study drug will be separately listed per subject number, presenting: first/last application, treatment phase (Initial or Follow-up), emergence, description, SOC, preferred

term, start and end date, duration, the relationship to study drug, the action taken and the seriousness criteria.

The list of preferred terms of adverse events of special interest is the following:

MedDRA Code	MedDRA Term
10076948	Acute encephalitis with refractory, repetitive partial seizures
10003628	Atonic seizures
10049612	Autonomic seizure
10075606	Change in seizure presentation
10053398	Clonic convulsion
10010920	Convulsions local
10010927	Convulsive threshold lowered
10079424	Focal dyscognitive seizures
10018100	Generalised tonic-clonic seizure
10067467	Nephrogenic systemic fibrosis
10061334	Partial seizures
10056209	Partial seizures with secondary generalisation
10076981	Post stroke seizure
10039906	Seizure
10071350	Seizure cluster
10040703	Simple partial seizures
10042772	Syncope
10043994	Tonic convulsion

5.6.4. Clinical laboratory evaluation

All laboratory values recorded during the study will be individually listed and flagged for values outside reference ranges and clinically significant (presented in CSR appendix 16.2.8).
Laboratory data analysis will be done using the safety set and displayed by trial product group.

The baseline is defined as the last measure before the first trial product administration.
The statistical analysis will present results in standard international (SI) units and conventional United States units (See Table 1 and Table 2 respectively). 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. 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.

Table 1 Hematology parameters

Hematology parameters		SI Units	US Units
Basophils	BASO	10^9/L	10^3/µL
Basophils/Leukocytes	BASOLE	%	%
Eosinophils	EOS	10^9/L	10^3/µL
Eosinophils/Leukocytes	EOSLE	%	%
Hematocrit	HCT	v/v	%
Hemoglobin	HGB	g/L	g/dL
Lymphocytes	LYM	10^9/L	10^3/µL
Lymphocytes/Leukocytes	LYMLE	%	%
Mean red blood cells volume	MCV	fL	μm^3
Monocytes	MONO	10^9/L	10^3/µL
Monocytes/Leukocytes	MONOLE	%	%
Neutrophils	NEUT	10^9/L	10^3/µL
Neutrophils/Leukocytes	NEUTLE	%	%
Platelet count	PLAT	10^9/L	10^3/µL
Red blood cells = Erythrocytes	RBC	10^{12}/L	10^6/µL
White blood cells = Leukocytes	WBC	10^9/L	10^3/µL

Table 2 Biochemistry parameters

Biochemestry parameters		SI Units	US Units
Magnesium*	MG	mmol/L	mg/dL
Sodium	SODIUM	mmol/L	mEq/L
Potassium	K	mmol/L	mEq/L
Chloride	CL	mmol/L	mEq/L
Glucose Random	GLUC	mmol/L	mg/dL
Urea Nitrogen	UREAN	mmol/L	mg/dL
Urea	UREA	mmol/L	mg/dL
Creatinine	CREAT	µmol/L	mg/dL
Protein	PROT	g/L	g/dL
Calcium	CA	mmol/L	mg/dL
Phosphorus	PHOS	mmol/L	mg/dL
Total bilirubin	BILI	µmol/L	mg/dL
Indirect Bilirubin	BILIND	µmol/L	mg/dL
Conjugated/Direct bilirubin	BILDIR	µmol/L	mg/dL
Aspartate amino transferase	AST	U/L	U/L
Alanine amino transferase	ALT	U/L	U/L
Alkaline phosphatase	ALP	U/L	U/L
Lactate dehydrogenase	LDH	U/L	U/L
Triglycerides	TRIG	mmol/L	mg/dL
eGFR*	GFRE	mL/min/1.73m²	mL/min/1.73m²

* Magnesium and creatinine clearance from Cockcroft-Gault method measured only at screening visit.

5.6.5. Vital signs, physical findings and other observations related to safety

The baseline is defined as the last measure before the first trial product administration.
Vital signs will be analyzed quantitatively and qualitatively by trial product group. Qualitative analyses of Systolic/Diastolic Blood Pressure (mmHg) and Pulse Rate (beats/min) will be done via comparison of vital signs data to their normal ranges. Normal ranges for the shift tables are [90; 160]

mmHg for SBP, [45; 90] mmHg for DBP and [45; 80] for pulse rate. Quantitative analyses of the same parameters will be done by tabulating raw data and change from baseline.

Listings of weight and vital signs will be provided in CSR appendix 16.2.9, including all other parameters recorded in the database [BMI (kg/m2), Systolic/Diastolic Blood Pressure (mmHg), Pulse Rate (beats/min)] and flag for clinically significant.

Holter ECG parameters will only be listed.

The baseline is defined as the mean of the ECGs triplicates measured before each IMP/AMP administration.
12-lead safety ECG will be analyzed quantitatively and qualitatively by trial products group.
Triplicate values will be issued for each measurement and the average of the 3 replicates will be used for statistics analyses. Qualitative analyses will be done via comparison of ECG data to their normal ranges. Quantitative analyses will be done by tabulating raw data and change from baseline. Listings of 12-lead safety ECG with interpretation, morphology analysis and flag for clinically significant will be provided.

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.

Physical examination will only be listed in CSR appendix 16.2.9.

5.6.6. Concomitant medications and procedures

Concomitant medications are those ongoing at or started after the first treatment application. Concomitant medications will be coded using the WHODRUG dictionary version September 2016. Concomitant procedures are therapies not coded as per WHODRUG dictionary.

Incidence of concomitant medications and procedures will be tabulated. The number and percent of subjects taking concomitant medications and concomitant procedures will be presented by trial product group. The denominator will be the number of subjects in the safety set.

Concomitant medications and procedures will be associated to trial product group according to the following rules:

End Period

Start Period	1	2	3	4	5	6
1=Before first administration	-	trial product group 1	trial product groups 1, 2	trial product groups 1, 2, 3	trial product groups 1, 2, 3, 4	trial product groups 1, 2, 3, 4
2=Between first and second administration		trial product group 1	trial product groups 1, 2	trial product groups 1, 2, 3	trial product groups 1, 2, 3, 4	trial product groups 1, 2, 3, 4
3=Between second and third administration			trial product groups 1, 2	trial product groups 1, 2, 3	trial product groups 1, 2, 3, 4	trial product groups 1, 2, 3, 4
4=Between third and fourth administration				trial product groups 1, 2, 3	trial product groups 1, 2, 3, 4	trial product groups 1, 2, 3, 4
5=After fourth administration					-	-
6=Ongoing at the end of the study						-

Summary tables (number and % of subjects) grouped by the first and the fourth level of ATC code will be presented by trial product group and overall for concomitant medications.

Listing of all concomitant medications will be presented in CSR appendix 16.2.4.

5.6.7. PK evaluation

P03277 plasma concentration and long term elimination analysis will be subcontracted to an analytical center and will be supervised by Guerbet.
All parameters description and data will be reported in a separate report.

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7. SHELLS FOR TABLES, FIGURES AND LISTINGS

All outputs will be produced using SAS version 9.2 or a later version.

All data recorded in the Case Report Form (CRF) will be listed. In addition, all derived data used in the analyses will be listed. The listings will include all subjects and will be ordered by subject.

Unless otherwise indicated, in case of continuous or ordinal variables summary statistics are the n, mean, SD, median, minimum and maximum. The mean and median and SD will be reported to 1 decimal more than the data and minimum and maximum to the same number of decimals as the data. In case of nominal variables, summary statistics are the n and the frequency in terms of percentage.

7.1. Clinical study report in-text tables, figures and listings

7.2. Contents of clinical study report section 14

7.3. Contents of clinical study report section 16.2

8. REFERENCES

1. Garnett C & al. Scientific white paper on concentration-QTc modelling. Journal of Pharmacokinetics and Pharmacodynamics 5 Dec 2017
2. ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs
3. Hochberg Y, Tamhane AC Multiple comparison procedures. John Wiley & Sons, Inc. New York, NY, USA ©1987
4. Zhang J, Machado SG Statistical Issues Including Design and Sample Size Calculation in Thorough QT/QTc Studies. Journal of Biopharmaceutical Statistics 2008; 18(3): 451-467

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