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Christian Funck-Brentano[1], Mathieu Felices[2], Nathalie Le Fur[3], Corinne Dubourdieu[3], Pierre Desché[3], Frédéric Vanhoutte[4], Pascal Voiriot[5]

[1] INSERM, CIC-1901 and UMRS 1166, F-75013 Paris, France; AP-HP, Pitié-Salpêtrière Hospital, Department of Pharmacology and CIC-1901, F-75013 Paris, France; Sorbonne Université Médecine, F-75013 Paris, France; Institute of Cardiometabolism and Nutrition (ICAN), F-75013 Paris, France,

[2] Phinc, 36, rue Victor Basch, 91300 Massy, France

[3] Guerbet, BP57400, 95943 Roissy CDG Cedex, France

[4] SGS Clinical Pharmacology Unit, ZNA Stuivenberg, Antwerp, Belgium

[5] Cardiabase, 78 avenue du XXème Corps, 54000 Nancy, France,

Corresponding author: Christian Funck-Brentano, Service de Pharmacologie Médicale & CIC-1901, Hôpital Pitié-Salpêtrière, F-75013. E-mail: christian.funck-brentano@aphp.fr

PI statement: The authors confirm that the Principal Investigator for this paper is Frédéric Vanhoutte and that he had direct clinical responsibility for the subjects.

Running title: Thorough QT study of gadopiclenol

Keywords: contrast media; electrocardiography; healthy volunteers;

Word count: 3709 **Table count:** 3 **Figure count:** 3

ABSTRACT

AIM

We investigated the effect of gadopiclenol, a new gadolinium-based contrast agent, on the QTc interval at clinical and supra-clinical dose, considering the relative hyperosmolarity of this product.

METHODS

This was a single centre, randomized, double-blind, placebo- and positive-controlled, four-way crossover study. Forty-eight healthy male and female subjects were included to receive single intravenous (i.v.) administrations of gadopiclenol at the clinical dose of 0.1 $mmol \cdot kg^{-1}$, standard for current gadolinium-based contrast agents, the supra-clinical dose of 0.3 $mmol \cdot kg^{-1}$, placebo and a single oral dose of 400 mg moxifloxacin.

RESULTS

The largest time-matched placebo-corrected, mean change from-baseline in QTcF (ΔΔQTcF) was observed 3 h after administration of 0.1 $mmol \cdot kg^{-1}$ gadopiclenol (2.39 ms, 90% confidence interval (CI): 0.35, 4.43 ms) and 5 min after administration of 0.3 $mmol \cdot kg^{-1}$ (4.81 ms, 90%CI: 2.84; 6.78 ms). The upper limit of the 90% CI was under the threshold of 10 ms, demonstrating no significant effect of gadopiclenol on QTc interval. From 1.5 to 4 h post-dose moxifloxacin, the lower limit of the 90% CI of ΔΔQTcF exceeded 5 ms demonstrating assay sensitivity. Although there was a positive slope, the concentration-response analysis estimated that the values of ΔΔQTcF at the maximal concentration of gadopiclenol at 0.1 and 0.3 mmol·kg-1 were 0.41 and 2.23 ms, respectively, with the upper limit of the 90% CI not exceeding 10 ms. No serious or severe adverse events or treatment discontinuations due to adverse events were reported.

CONCLUSION

This thorough QT/QTc study demonstrated that gadopiclenol did not prolong the QT interval at clinical and supra-clinical doses and was well tolerated in healthy volunteers. The positive slope of the QTc prolongation vs. concentration relationship suggests that hyperosmolarity could be associated with QTc prolongation. However, the amplitude of this effects is unlikely to be associated with proarrhythmia.

Key words: Gadopiclenol, Thorough QT study, QTc interval, Osmolarity, healthy subjects.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Gadopiclenol is a gadolinium-based contrast agent in clinical development.
- Hyperosmolarity is associated with a reduction of hERG (KCNH2) current and only one thorough QT study has been reported with gadolinium-based contrast agents.

WHAT THIS STUDY ADDS

- This study demonstrated that intravenous administration of gadopiclenol at clinical and supra-clinical doses does not prolong the QTc interval. There was no difference in the occurrence of adverse events or other safety parameters between gadopiclenol and placebo, supporting the overall good safety profile of gadopiclenol.
- The study supports the view that hyperosmolarity of gadolinium-based contrast agent is not associated with clinically significant prolongation of ventricular repolarization.
- However, since there was a positive relationship between QTc prolongation and gadopiclenol concentration, it cannot be excluded that contrast agents of greater osmolarity could be associated with clinically significant QTc prolongation.

Introduction

Magnetic resonance imaging (MRI) is a widely used technique in the diagnosis of a large number of pathologies but most notably in the field of oncology. It has allowed more accurate tumour detection, characterization and staging [1]. Often contrast agents are used to improve the MRI imaging [1, 2]. These agents most typically contain the paramagnetic gadolinium ion in a chelated form to avoid its potential toxicity. Two types of chelates, linear and macrocyclic, have been approved by regulatory authorities. Linear chelates are less stable than macrocyclic chelates, and thus more prone to release gadolinium within the body.

The pharmacokinetics of the marketed gadolinium-based contrast agents (GBCAs), which are administered intravenously (i.v.), is very similar in that they distribute only in the extracellular space, are excreted via the kidneys and have a half-life of 1 to 2 h [3, 4]. In patients with severe renal impairment, administration of GBCAs, mainly if not exclusively the linear chelates, has been associated with the development of nephrogenic systemic fibrosis most likely due to accumulation of dissociated gadolinium in tissues [5, 6]. In recent years, it has become increasingly clear that with linear GBCAs, gadolinium deposits can also be found in bone and other tissues including brain in patients with normal kidney function and an intact blood brain barrier exposed to multiple cumulative doses. Although clinical data on the potential toxicity of these gadolinium deposits is sparse [7-10], linear GBCAs have been suspended in Europe (except from gadobenic acid and gadoxetate disodium restricted to liver MRI) while macrocyclic GBCAs are still fully authorized due to their favourable benefit risk balance. Therefore, safety of new GBCAs must be ascertained.

Gadopiclenol is a new macrocyclic GBCA in clinical development. As part of the development of a compound, cardiac safety needs to be assessed in preclinical models and clinical studies. Gadopiclenol induced a concentration-dependent inhibition of hERG tail current amplitude (data on file) but this effect was considered to be non-specific and due to

the hyperosmolarity of the tested solutions and to the relatively high molecular weight (970.1 g/mol) of gadopiclenol. Hyperosmolarity has been shown to inhibit hERG current [11] and to transiently increase dispersion of refractoriness following intracoronary infusions of contrast agents [12]. Gadopiclenol had no effect on the action potential of rabbit Purkinje fibres nor did it prolong the QTc interval *in vivo* in conscious dogs (Guerbet, data on file). Further, no cardiac events were reported in the first-in man study [13] and in a dose-response phase IIb study [14].

In the present study, the QT/QTc interval prolongation of gadopiclenol was investigated in a dedicated thorough QTc study which was performed according to the ICH E14 guideline [15].

Methods

The study was performed in compliance with the principles of the Declaration of Helsinki and Good Clinical Practice. The study was registered with ClinicalTrials.gov (ref: NCT03657264). The protocol, its amendments, and any other written information provided to subjects were approved by an independent Ethics Committee (ZNA/OCMW Antwerp, Belgium). The study was performed in a single centre (SGS Clinical Pharmacology Unit, Antwerp, Belgium) and only started after approval of the competent national health authority was received. Written informed consent was obtained from all subjects prior to any study-related assessment took place.

Subjects

Eligibility of the 48 subjects who participated in the study was assessed at the screening visit, which took place within 4 weeks prior to first study treatment administration. Subjects were included if they were healthy, male or female between 18 and 60 years of age, with a body mass index between 19 and 28 kg/m² and weighing at least 40 (females) or 50 (males) kg and

no more than 100 kg. Subjects could not participate in case of a history or family history of inherited or acquired Long QT syndrome or risk factors for Torsade de Pointe, unexplained loss of consciousness or convulsion or any history of clinically significant bradycardia, cardiac impairment due to decreasing left ventricular ejection fraction, or arrhythmia (including Wolf-Parkinson-White syndrome). Non-cardiac exclusion criteria included smoking more than 10 cigarettes per day, any history of severe allergy or allergic disease, treatment with any concomitant medications which could induce QT prolongation and administration of any contrast agent within 2 weeks before inclusion or scheduled to receive any contrast agent within 3 months after the last investigational medicinal product administration.

Study design

This single-centre study was conducted according to a randomised, 4-way crossover, double-blind placebo-controlled and open-label positive-controlled (moxifloxacin) design. Each subject was randomised to one of 4 sequences of the 4 study treatments according to a Williams's design [16] which was balanced for first order carry-over effect. The 4 study treatments were: bolus i.v. placebo (0.9% NaCl), bolus i.v. gadopiclenol at the dose of 0.1 $mmol \cdot kg^{-1}$, standard dose for most currently approved GBCAs, bolus i.v. gadopiclenol at the supra-clinical dose of 0.3 $mmol \cdot kg^{-1}$ and oral 400 mg moxifloxacin. The supra-clinical dose was set at 0.3 $mmol \cdot kg^{-1}$, which is a dose still used for some approved GBCAs for limited applications. Starting at time zero, gadopiclenol was administered at a rate of 2 mL/s with a total volume of 11 to 58 mL, i.e. in 5.5 to 29 seconds, depending on volunteer’s body weight and gadopiclenol dose administered.

Each treatment period lasted 72 h resulting in a total study duration of 12 days for each participant during which the subjects remained confined in the clinical trial unit. One and

3 months after last study drug administration, subjects had to return to the clinical trial unit to assess the long-term elimination of gadopiclenol.

ECG recordings

During each treatment period, 12-lead Holter ECG monitoring using a Mortara H12+® (Milwaukee, WI, USA) was performed from 1 h before each administration (baseline) and up to 24 h post-administration. Triplicate ECGs were extracted from the recordings using a dedicated software (Antares®, AMPS, Montichiari, Italy) at the following time points for gadopiclenol and placebo: predose and then 5 min, 10 min, 20 min, 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h, 8 h, and 24 h postdose. For moxifloxacin, the time points were: predose and then 30 min, 1 h, 1.5 h, 2 h, 3 h, 4 h postdose.

Using a computerized measurement system, calipers were placed on the recording based upon the global waveforms from all 12-leads. A qualified cardiologist not otherwise involved in the study and blinded to treatment then adjudicated the placement of the calipers on the ECG tracing and performed adjustments if warranted. He/she also noted any significant morphological abnormality on the tracing. All tracing from a given subjects were measured by the same observer.

QT values were corrected for heart rate using Fridericia's and Bazett's formulae and plots were created of QTc versus RR intervals of baseline and placebo data. The correction according to Fridericia showed a horizontal regression line for the relationship between QTc and RR whereas that for Bazett’s correction (QTcB) deviated significantly from horizontal. This indicated that the Fridericia formulae was the appropriate correction for QT in the current study.

Statistical analysis of ECG data

The primary endpoint was defined as the largest time-matched placebo-corrected, mean change-from-baseline QTcF (ΔΔQTcF) in ms of the two gadopiclenol doses. The null hypothesis was that the mean change from baseline in QTcF difference between each of the two doses of gadopiclenol and placebo was greater or equal to the non-inferiority margin for at least one time point. An Intersection-Union test was performed at a one-sided 5% significance level. This is equivalent to compare the upper limit of the two-sided 90% CI of the difference between each of the two doses of gadopiclenol and placebo with the non-inferiority margin of 10 ms at each time point. The primary analysis was performed using an analysis of covariance model for crossover data with baseline data as covariate, sequence, period, trial drug and sex as fixed effect and subject as a random effect. Differences with placebo between means were tested through the model for each time point and for the two doses of gadopiclenol using the Student's t-test. For each time point, the two-sided 90% CI of the difference between each of the two doses of gadopiclenol and placebo were calculated for testing the hypotheses. The primary analysis was conducted on subjects who had no major protocol deviations, defined as having an impact on the primary endpoint (per protocol set). As a supportive analysis, the primary analysis was repeated including all randomized subjects who received at least one study product (safety set).

Assay sensitivity assessment was defined as the largest time-matched placebo-corrected, change from-baseline mean effect of moxifloxacin on QTcF. In order to validate the assay sensitivity of the trial, the positive control had to increase the ΔΔQTcF by at least 5 ms for at least one time point. To account for multiple time points, the overall Type I error rate was adjusted according to Hochberg and Tamhane [17].

Considering an expected intra-variability for ΔQTcF of 9 ms and an expected difference of 2 ms between gadopiclenol and placebo, a sample size of 40 subjects was

sufficient to demonstrate non-inferiority with a non-inferiority margin of 10 ms, a power of 85% and a one-sided Type I error of 5%. This sample size was also sufficient to detect a difference of 5 ms (with an expected difference of 12 ms for at least one time point and an expected intra-variability for ΔQTcF of 9 ms) between moxifloxacin and placebo with a power of 85%. To account for potential dropouts and/or unevaluable data points, 48 subjects were included in the study.

Categorical analyses were performed to determine the number of subjects for each treatment who had values for QTcF >450 ms, >480 ms and >500 ms and/or changes from baseline in QTcF >30 ms and >60 ms.

Plasma Gadopiclenol Concentrations

Blood samples for the measurement of gadopiclenol concentration were drawn from predose to 24 h postdose in each period except in the period in which moxifloxacin was administered. The time points of blood samplings coincided with those at which ECGs were extracted from the Holter recording.

The concentrations of gadopiclenol in plasma were determined using liquid chromatography methods with tandem mass spectrometry detection. The analytical methods were validated as per FDA and EMA guidance documents [18, 19]. The assays were linear in the concentration range 5–2500 $\mu g \cdot ml^{-1}$ and the limit of quantification was 5.0 $\mu g \cdot ml^{-1}$. The performance of the method was monitored using quality control samples at concentrations of 15, 1250 and 2000 $\mu g \cdot ml^{-1}$. At these concentrations, precision (%CV) was ≤ 4.28% whereas bias varied from 1.44 to 2.59% in plasma.

The plasma concentration data of gadopiclenol were subjected to descriptive statistics and were graphically displayed. No pharmacokinetic analysis was performed.

Concentration-response analysis

A concentration-response relationship was investigated between ΔΔQTcF and gadopiclenol concentrations using a mixed linear model with baseline-corrected QTcF as the dependent variable [20]. Placebo data were included in the analysis with concentration values set to 0 and gadopiclenol concentrations below the limit of quantification were also set to 0. The fixed effect parameters of the pre-specified model were intercept, slope for gadopiclenol concentrations, influence of baseline on intercept, study treatment (gadopiclenol or placebo) specific intercept, and theoretical time points post-administration. Subject specific random effects were added on intercept and slope parameters with an unstructured covariance matrix.

The parameters estimated from the selected model are presented with their standard error and 95% confidence interval (CI). The predicted placebo- and baseline-corrected QTcF for each dose level is presented with its 2-sided 90% CI and the model is graphically presented by a regression line over the concentration range collected during the study together with its 90% confidence region. The appropriateness of the chosen linear model was checked by inspecting the standard goodness-of-fit plots.

Safety assessments

The safety and tolerability of gadopiclenol, as compared to baseline and placebo, was assessed by recording of adverse events (AEs), vital signs (blood pressure and pulse rate) measurements, ECG recording, clinical laboratory assessments and monitoring of injection site tolerance. Adverse events were recorded throughout the study, vital signs were recorded at screening and predose up to 24 hours postdose at the same time points as Holter ECGs, 12-lead safety ECGs were done in triplicate within 1 hour before each study treatment administration and 10 min and 3 h post administration and blood samples for clinical laboratory assessments were drawn at screening and on Day 1 and 2 of each treatment period.

Injection-site tolerance (burning, pain, eruption, extravasation, inflammation, or other) was 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 became aware of any related adverse event. In case of injection-site pain, the subject was asked to specify the level of pain using a visual analogic scale.

Results

Subject disposition and demographics

In this study, 48 subjects were randomised, all received the 4 study treatments and completed the study. Due to the occurrence of extravasation during the injection of placebo, one subject was excluded from the per protocol set. Therefore, 48 and 47 subjects were included in the safety and per protocol sets, respectively.

Half of the enrolled subjects were male and half female and except one Asian subject all were Caucasian. A summary of the demographics of the safety set is provided in Table 1.

Effect of gadopiclenol on QTcF and HR, assay sensitivity and categorical analysis

Baseline QTc of each study period was not significantly different and there was no period effect. Baseline-corrected least-square mean differences between gadopiclenol and placebo and between moxifloxacin and placebo versus time after administration are shown in Figure 1. Following i.v. injection of 0.1 mmol·kg^{-1} of gadopiclenol, at none of the tested time points the upper limit of the 90% CI of ΔΔQTcF exceeded 10 ms indicating the absence of an effect of gadopiclenol on QTcF. The largest time-matched placebo-corrected change from baseline was recorded 3 h postdose and was 2.39 ms (90% CI: 0.35, 4.43). A similar result was obtained with the supra-clinical dose of 0.3 mmol·kg^{-1} with a maximum observed ΔΔQTcF of

4.81 ms (90% CI: 2.84, 6.78) occurring at 5 min after i.v. injection. This increase in ΔΔQTcF was short-lasting and had disappeared 20 min after administration (ΔΔQTcF = 0.20 ms (90% CI: -1.71, 2.12)).

Figure 1 also shows a plot of ΔΔQTcF versus time following administration of 400 mg moxifloxacin. A relevant (90% CI lower limit > regulatory threshold of 5 ms) increase in ΔΔQTcF was first observed 1.5 h after moxifloxacin administration and lasted up to 4 h after administration, with a maximum of 10.83 ms (90% CI: 8.21; 13.46) 4 h post administration. This result demonstrates adequate assay sensitivity of the study.

In this study, no QTcF values exceeding 450 ms and no increases from baseline > 30 ms were recorded. No effect on heart rate was observed for any of the study treatments. The mean maximal placebo-corrected changes from baseline for gadopiclenol- and moxifloxacin-treated subjects were 1.63 bpm (90% CI: -0.14, 3.41) for the 0.1 mmol·kg^{-1} group, 2.55 bpm (90% CI: 0.77, 4.34) for the 0.3 mmol·kg^{-1} group and 1.71 bpm (90% CI: 0.43, 2.98) in the moxifloxacin group. There was also no significant change in systolic or diastolic blood pressure.

Plasma gadopiclenol concentrations

Following i.v. administration gadopiclenol, concentrations rapidly declined (Figure 2) and at time point 24h all gadopiclenol concentrations were below the limit of quantification. At 1 and 3 months after last study drug administration, the gadopiclenol plasma concentrations were below the limit of quantification in all subjects.

Concentration-response analysis

The concentration-response analysis indicated that there was a relationship between ΔΔQTcF and gadopiclenol plasma concentration in that with increasing concentration there was an

increase in ΔQTcF. The final model parameters are summarized in Table 2. A graphical illustration of the model-predicted linear relationship between gadopiclenol concentration and ΔΔQTcF is provided in Figure 3. At the geometric mean C_{max} of gadopiclenol, the model-predicted effect on ΔΔQTcF was 0.41 ms (90% CI: -0.08, 0.90) at a dose of 0.1 mmol·kg^{-1} and 2.23 ms (90% CI: 1.19, 3.26) at the supra-clinical dose of 0.3 mmol·kg^{-1}.

Safety and tolerability

There were no serious AEs, AEs of severe intensity or AEs that led to premature study withdrawals. A total of 116 treatment emergent AEs were reported in 41 subjects (85.4%): 25 subjects (52.1%) with gadopiclenol 0.1 mmol·kg^{-1}, 22 subjects (45.8%) with gadopiclenol 0.3 mmol·kg^{-1}, 16 subjects (33.3%) with moxifloxacin and 22 subjects (45.8%) with placebo. A summary of all AEs including those considered not related to study treatments is provided in Table 3. Most AEs (108) were of mild intensity and 8 were moderate (1 with gadopiclenol 0.1 mmol·kg^{-1}, 3 with gadopiclenol 0.3 mmol·kg^{-1}, 2 with positive control and 2 with placebo).

Overall, fewer AEs were reported by fewer subjects following moxifloxacin administration when compared to i.v. administration of study treatments including placebo. There was no obvious difference in AE reporting between gadopiclenol and placebo.

No safety concern was observed regarding hematology and biochemistry parameters, vital signs remained stable during the study and no clinically significant findings on safety ECG and Holter ECG were observed.

Discussion

The results of this thorough QT/QTc study show that administration of gadopiclenol, a new macrocyclic GBCA, at standard clinical and supra-clinical doses did not result in a prolongation of the QTc interval in healthy volunteers. At all time points, the upper bound of the 90% CI of ΔΔQTcF was less than 10 ms and, therefore, from a regulatory and clinical relevance standpoint this study can be considered negative. The observed increase in QTcF following oral moxifloxacin administration demonstrated that the present study had adequate sensitivity to detect an increase in QTcF.

There are only a limited number of studies published on the effects of GBCAs on the QTc interval. Only one thorough QT/QTc study was reported with gadobutrol which showed an ΔΔQTc increase of 9.91 ms (90% CI 8.01–11.81) at a dose of 0.5 mmol·kg^{-1}. This marginally positive QT-prolonging effect decreased to 7.62 ms (90% CI: 6.37, 8.87), i.e., a negative thorough QT study, after QT/RR hysteresis correction [21], Hysteresis correction was justified by a 13.1 bpm increase in heart rate which did not occur in our study. A randomized, double-blind, placebo-controlled, crossover clinical trial in patients requiring contrast-enhanced magnetic resonance imaging did not show any significant QTc prolongation with gadoterate meglumine [22]. In a 2-way crossover study comparing gadobenate at a dose of 0.2 mmol·kg^{-1} to placebo an increase of 3.1 ms in ΔΔQTcB was observed with no difference between healthy volunteers and patients with coronary artery disease [23]. It is interesting to note that both gadobutrol and gadobenate have a higher osmolarity at marketed concentrations (1603 and 1970 mOsm·l^{-1}, respectively) than gadopiclenol (843 mOsm·l^{-1}) [13]. In a comparative study of the high-osmolarity iodinated contrast agent diatrizoate (osmolarity: 1515 mOsm·l^{-1} [24]) and the low-osmolarity iodinated contrast agents ioxaglate, iopamidol and iohexol, diatrizoate had the largest effect on QTc [25]. It is thus likely that the small effects on QTc observed in this and other studies with

GBCAs are related to the high osmolarity of the compounds rather than to their chemical structure and this is supported by *in vitro* data [11, 22]. The concentration-response analysis confirmed the absence of clinically significant QTc prolongation with gadopiclenol. However, since there was a positive relationship between gadopiclenol concentration and QTc response, it cannot be excluded that contrast agents of greater osmolarity could be associated with clinically significant QTc prolongation.

Another hypothesis to explain small and transient QTc prolongation with hyperosmolar compounds could be linked to abrupt changes in ventricular loading associated with increased blood pressure [26, 27]. However, such an effect was not documented in this and other studies of GBCAs and there was no significant change in blood pressure in the present study.

The pharmacokinetic and safety profile observed in the present study are in line with previously published results [13] and confirm the good safety profile of gadopiclenol. AEs were mainly related to the mode of administration and their frequency did not differ from placebo.

A limitation of the present study is that it was performed in healthy volunteers who did not have electrolyte abnormalities that could possibly affect cardiac conduction, with ECGs devoid of any clinically relevant abnormality and who were not treated with concomitant medications that could possibly affect cardiac repolarisation. Patients who are scheduled to undergo an MRI may have any of the above.

In conclusion, results from this thorough QT/QTc study show that both anticipated clinical and supra-clinical doses i.v. gadopiclenol do not prolong the QTc interval and confirm the previously observed favourable safety and pharmacokinetic profiles. In addition, the study supports the view that hyperosmolarity of gadolinium-based contrast agent could be associated with minimal and clinically insignificant prolongation of ventricular repolarization.

Authors contribution

All authors were involved in the study design, data interpretation, reviewed the results and approved the final manuscript.

N.LF., C.D., and P.D. supervised the study conduct

F.V. was responsible for the study conduct

P.V. supervised the central reading of the ECGs

M.F. supervised the statistical analyses

C.F-B. produced the final version of the manuscript

Competing interests

CF-B, PV, FV, and MF had support from Guerbet for the submitted work. NLF, CD and PD are current employees of Guerbet. There are no other relationships or activities that could appear to have influenced the submitted work.

This study was funded by Guerbet. Medical writing support was provided by Paul van Giersbergen, (Van Giersbergen Consulting, Wuenheim, France) and was funded by Guerbet.

Data availability statement:

Data will be available on request from the authors after product registration (product under development)

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Table 1

Summary of demographic characteristics

		All subjects
Age (years)	Mean (SD)	40.5 (11.6)
	Range	19–59
Males / Females (n)		24 / 24
Race (*n*, %)	Asian	1 (2.1%)
	Caucasian	47 (97.9%)
Weight (kg)	Mean (SD)	75.3 (8.5)
	Range	58–97
Height (cm)	Mean (SD)	173.5 (8.5)
	Range	154–190
Body mass index (kg/m^2)	Mean (SD)	25.0 (2.2)
	Range	19.8–28.2

Table 2

Model parameters of final concentration-response model

	Parameter estimate (SE)	**95% CI**
Intercept (placebo) (ms)	-2.88 (1.07)	-5.04 – -0.72
Slope (ms per $\mu g \cdot ml^{-1}$)	0.0011 (0.0003)	0.0005 – 0.0016
Baseline covariate (ms)	-0.40 (0.03)	-0.47 – -0.33
Gadopiclenol specific intercept (ms)	-0.40 (0.35)	-1.09 – 0.30

Table 3

Summary of treatment-emergent AEs that occurred in at least 2 subjects

	Gadopiclenol 0.1 mmol·kg^{-1} (N=48)		**Gadopiclenol 0.3 mmol·kg^{-1} (N=48)**		**Moxifloxacin 400 mg (N=48)**		**Placebo (N=48)**	
	Subjects	**AEs**	**Subjects**	**AEs**	**Subjects**	**AEs**	**Subjects**	**AEs**
At least one AE	25 (52.1%)	33	22 (45.8%)	33	16 (33.3%)	18	22 (45.8%)	32
Application site irritation*	6 (12.5%)	7	7 (14.6%)	8	5 (10.4%)	5	6 (12.5%)	6
Headache	6 (12.5%)	6	5 (10.4%)	6	4 (8.3%)	4	4 (8.3%)	4
Injection site haematoma	4 (8.3%)	4	3 (6.3%)	3	0 (0.0%)	0	1 (2.1%)	1
Injection site pain	2 (4.2%)	2	0 (0.0%)	0	0 (0.0%)	0	4 (8.3%)	4
Diarrhoea	0 (0.0%)	0	1 (2.1%)	1	3 (6.3%)	3	2 (4.2%)	2
Injection site erythema	2 (4.2%)	2	1 (2.1%)	1	0 (0.0%)	0	1 (2.1%)	1
Dysgeusia	1 (2.1%)	1	1 (2.1%)	1	0 (0.0%)	0	2 (4.2%)	2
Dizziness	1 (2.1%)	1	0 (0.0%)	0	2 (4.2%)	2	0 (0.0%)	0
Nausea	0 (0.0%)	0	2 (4.2%)	2	0 (0.0%)	0	1 (2.1%)	1

Abdominal pain	1 (2.1%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.1%)	1
Injection site reaction*	1 (2.1%)	1	0 (0.0%)	0	1 (2.1%)	1	0 (0.0%)	0
Catheter site haematoma	1 (2.1%)	1	1 (2.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Injection site inflammation	1 (2.1%)	1	0 (0.0%)	0	0 (0.0%)	0	1 (2.1%)	1
Injection site rash	1 (2.1%)	1	1 (2.1%)	1	0 (0.0%)	0	0 (0.0%)	0
Oropharyngeal pain	0 (0.0%)	0	1 (2.1%)	1	0 (0.0%)	0	1 (2.1%)	1
Back pain	0 (0.0%)	0	2 (4.2%)	2	0 (0.0%)	0	0 (0.0%)	0

* These adverse events were associated with catheter placement or the electrode patches

Figure legends

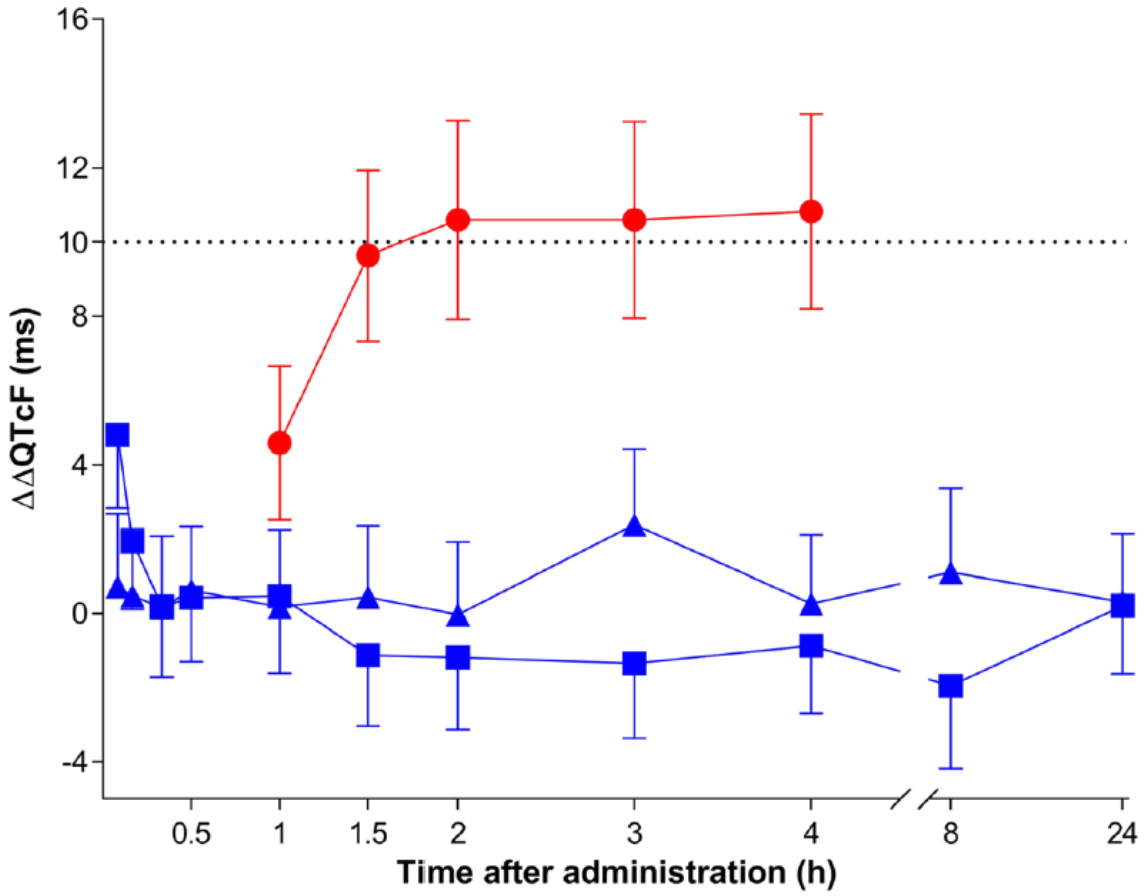

Figure 1

Time-matched, placebo-corrected change from baseline in QTcF (ΔΔQTcF). Data are presented as time-matched least square differences between study drugs and placebo and their corresponding 90% CI. ▲–▲, 0.1 mmol·kg^{-1} i.v. gadopiclenol, ■–■, 0.3 mmol·kg^{-1} i.v. gadopiclenol, ●–●, 400 mg oral moxifloxacin. The threshold of 10 ms is shown as a dotted horizontal line.

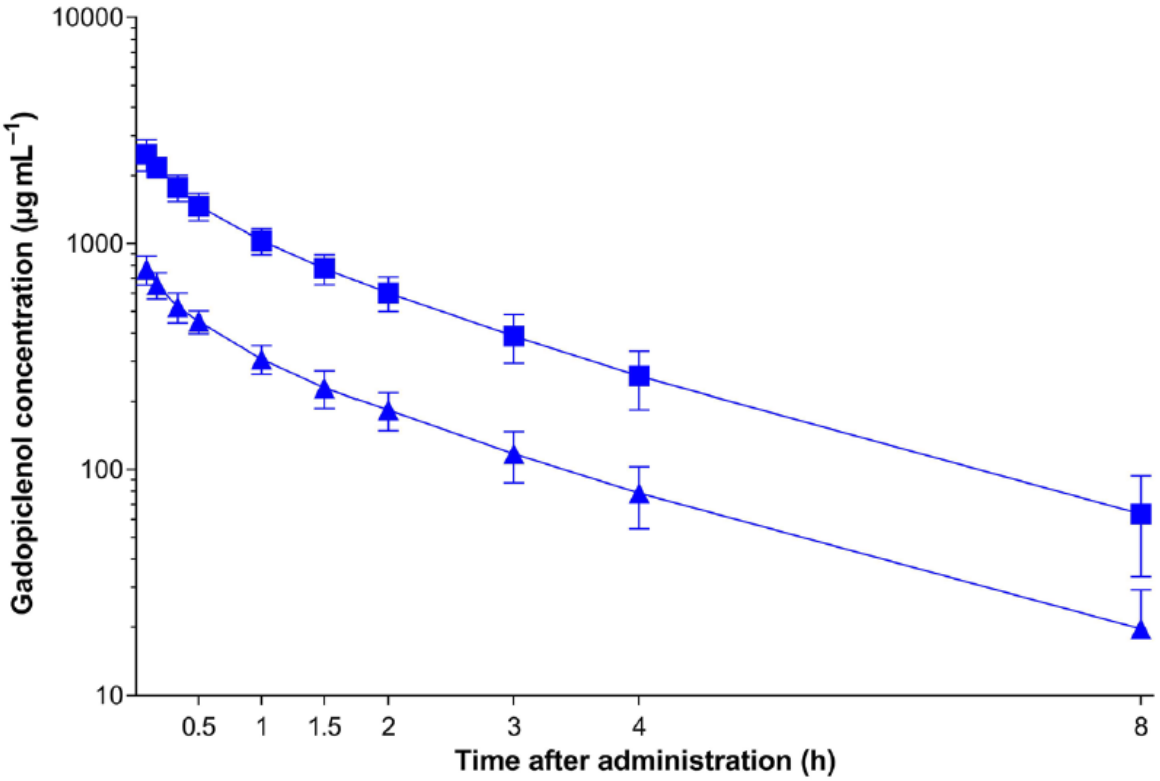

Figure 2

Plasma concentration-time profiles of gadopiclenol. Data are presented as arithmetic mean ± SD. ▲–▲, 0.1 mmol·kg^{-1} i.v. gadopiclenol, ■–■, 0.3 mmol·kg^{-1} i.v. gadopiclenol.

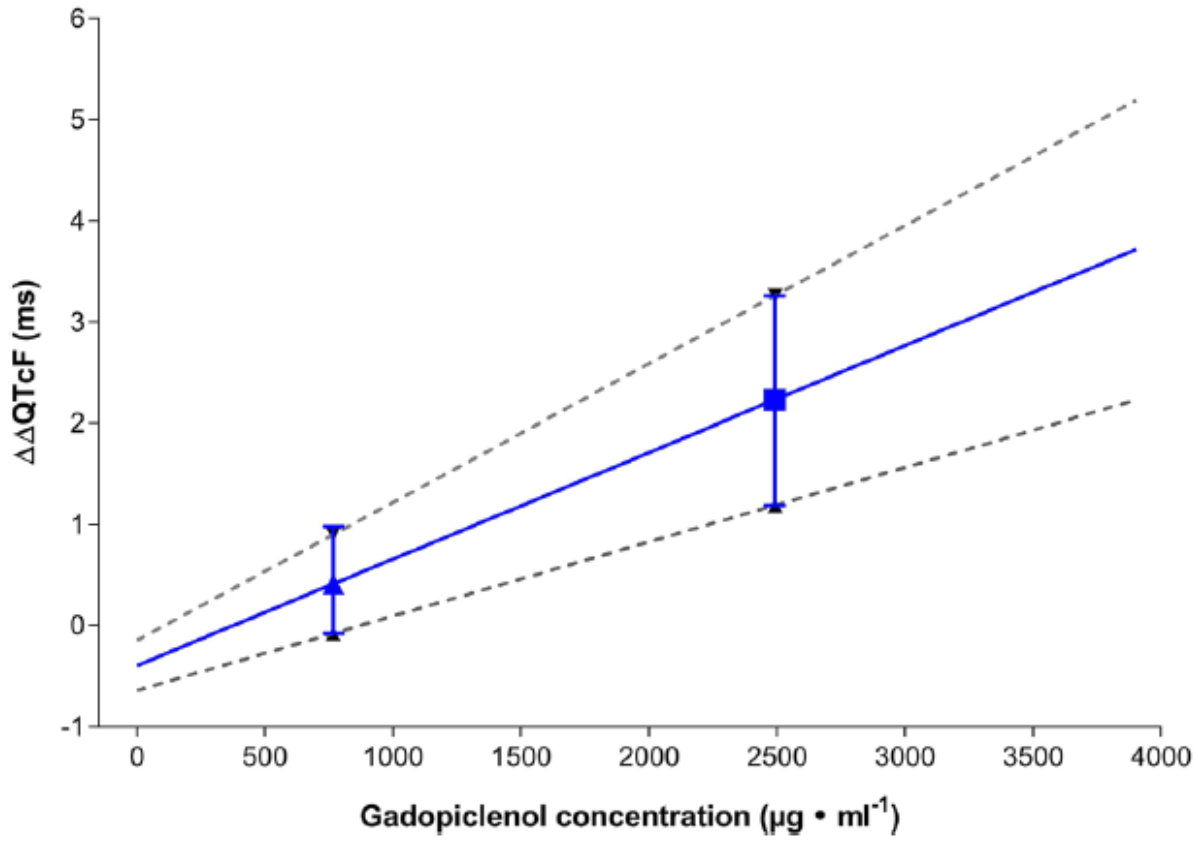

Figure 3

Model-predicted effect of gadopiclenol on baseline- and placebo-corrected QTcF (ΔΔQTcF) over a concentration range of 0 to 4000 µg·ml^{-1}. The ΔΔQTcF at the doses of 0.1 mmol·kg^{-1} (▲) and 0.3 mmol·kg^{-1} (■) are shown with their respective 90% CI. The lines represent the model-predicted linear relationship between concentration and effect on ΔΔQTcF and the lower and upper 90% CI.