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PHARMACODYNAMICS

Absence of QTc prolongation in a thorough QT study with imeglimin, a first in class oral agent for type 2 diabetes mellitus

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Abstract

Purpose Imeglimin is the first in a new class of oral antidiabetic agents, the glimins, currently in development to improve glycemic control in patients with type 2 diabetes mellitus. A thorough QT study was conducted to establish electrophysiological effects of therapeutic and supratherapeutic doses of imeglimin on cardiac repolarization.

Methods In this randomized, double-blind, four-period, placebo and active controlled crossover study, healthy subjects were administered a single dose of imeglimin 2250 mg, imeglimin 6000 mg, moxifloxacin 400 mg, and placebo. 12-Lead Holter ECGs were recorded from 1 h before dosing until at least 24 h after each dose. This study was performed at a single-center inpatient clinical pharmacology unit.

Results The upper bound of the two-sided 90% confidence interval for time-matched, placebo-subtracted, baseline-adjusted QTc intervals (ΔΔQTcF) did not exceed the regulatory threshold of 10 ms in any of the imeglimin dose groups. There were no QTcF values above 500 ms nor changes from pre-dose in QTcF above 60 ms in the imeglimin groups. Imeglimin did not exert a relevant effect on heart rate and PR or QRS intervals. Assay sensitivity was demonstrated by the effect of moxifloxacin 400 mg, with a lower bound two-sided 90% confidence interval for ΔΔQTcF of 10.6 ms.

Conclusion This thorough QT study demonstrated that therapeutic and supratherapeutic exposures of imeglimin did not induce a QT/QTc prolongation with a strong confidence as evidenced by the assay sensitivity.

Trial registration number/date NCT02924337/ October 5, 2016

Keywords Imeglimin · QT interval · Thorough QT study · Type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by beta-cell dysfunction and peripheral insulin resistance leading to hyperglycemia [1, 2]. Chronic hyperglycemia has been associated with the development of both macrovascular and microvascular complications [3]. Recent estimates indicate that there were 422 million adults in the world with T2DM in 2014 [4]. This chronic and progressive disease requires long-term lifestyle modifications and pharmacologic management to maintain effective glycemic control [5]. Unfortunately, although combination therapies improve glycemic control, they also cause side effects, particularly in the elderly population. New drugs with sustained efficacy and a good tolerability profile are still required.

Imeglimin is a novel oral antidiabetic drug to treat T2DM [6]. Imeglimin targets mitochondrial bioenergetics. It improves mitochondrial function by modulating mitochondrial

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respiratory chain complex activities while decreasing reactive oxygen species production [7]. Imeglimin has been shown to induce glucose-stimulated insulin secretion by improving β-cell glucose sensitivity in patients with T2DM [8] and to improve insulin sensitivity in a rodent diabetic model, allowing normalization of glucose tolerance [7]. More recent data suggest that imeglimin prevents the death of human endothelial cells by inhibiting mitochondrial permeability without inhibiting mitochondrial respiration, which may improve cardiovascular risk profile in patients with T2DM [9]. Imeglimin is rapidly absorbed after oral administration, is weakly bound to plasma proteins, and is mainly eliminated unchanged in the urine, with a terminal half-life ranging between 10 and 20 h.

Single doses up to 6000 mg in healthy subjects and repeated doses of up 2000 mg (4000 mg/day) imeglimin have been well tolerated in healthy subjects [10]. Imeglimin has demonstrated favorable efficacy and safety/tolerability profile both in Caucasian and Asian subjects [11, 12]. Imeglimin has recently completed its phase 3 program in Japan with a glycosylated hemoglobin (HbA1c) reduction of 0.87% versus placebo after 6 months of treatment [13].

The potential effect of imeglimin on ventricular repolarization (QT/QTc) was previously investigated in nonclinical assays. Imeglimin (50, 150, and 500 μM) had no inhibitory effect on human Ether-a-go-go-related gene (hERG) tail currently recorded from the human embryonic kidney (HEK) 293 cells and stably transfected with hERG complementary deoxyribonucleic acid (cDNA). In Beagle dogs, slight reduction (up to 37 %) in heart rate was observed in 3 of 6 dogs at the highest single dose of 500 mg/kg. However, no other electrocardiogram (ECG) parameters such as PQ and QRS and QT interval (including QT-correction according to Van de Water) were affected by imeglimin [14].

In line with the current recommendations (International Conference on Harmonisation E14 :ICH E14) requiring that all non-antiarrhythmic compounds undergo clinical evaluation of QT/QTc interval prolongation [14], a thorough QT study was performed to test the effect of a therapeutic dose and supratherapeutic dose of imeglimin versus placebo and the positive control moxifloxacin. The optimal doses selected for phase 3 clinical trials are 1000 mg and 1500 mg twice daily in Japan and in Europe/USA, respectively. However, because the accumulation ratio of C_{max} for 1500 mg twice daily doses in healthy subjects is approximately 1.3, the dose of 2250 mg imeglimin as a single oral dose has been proposed to cover the therapeutic exposure at a steady state. The supratherapeutic dose of 6000 mg imeglimin was selected because this is the maximal tolerated dose [10]. Moxifloxacin produces a well-characterized, reproducible, and small effect on the QTc interval at a dose of 400 mg, typically of 5–14 ms [12]. Therefore, a single dose of 400 mg has been used as a positive control to establish that the study has sufficient sensitivity to detect small changes in the QTc interval.

The purpose of this thorough QT study was to assess the effect of a single therapeutic dose (2250 mg) and a single supratherapeutic dose (6000 mg) of imeglimin on the QT/QTc interval.

Methods

This clinical trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [15] and was approved by an Independent Ethics Committee/Institutional Review Board (Office for Research Ethics Committees Northern Ireland - ORECNI). All participants provided written informed consent prior to any trial-related activities. This trial was registered with EudraCT (2016-001821-14) and ClinicalTrials.gov (NCT02924337). This trial was conducted at a single center (Hammersmith Medicines Research – HMR, Cumberland Avenue, London NW10 7EW) between August 2016 and December 2016.

Subjects

Female or male subjects aged 18–45 years with a body mass index (BMI) of 18.5–29.9 kg/m^2 (weighing between 55 and 95 kg) and willing to use reliable contraception were screened and selected according to a complete medical history, including physical examination, vital signs, 12-lead ECG, and clinical laboratory tests.

Study design

This was a randomized, placebo-controlled, four-treatment, four-period balanced crossover study. Subjects who met all eligibility criteria and who agreed to participate in the trial were randomly assigned to one of the following treatment groups:

(a) Single therapeutic imeglimin dose (double-blind), 2250 mg
(b) Single supra-therapeutic imeglimin dose (double-blind), 6000 mg
(c) Single oral moxifloxacin dose (open-label), 400 mg
(d) Placebo (double-blind), matched to imeglimin

All patients received the four different treatments in a random order. The positive control (400 mg moxifloxacin, Avelox®; Bayer Vital, Leverkusen, Germany) was given as one open-label capsule. The inclusion of a moxifloxacin arm within the study was to provide an open-label active control [12].

The four treatments were included in 12 sequences based on three orthogonal Williams's squares, as recommended for thorough QT studies. This design ensured double-blind

conditions for placebo and imeglimin treatments, while allowing for open-label administration of moxifloxacin.

A washout of at least 7 days between subsequent visits was required. Subjects were screened within 21 days prior to the study. All subjects were admitted to the clinical pharmacology unit on day 1 and were kept under medical surveillance for 24 h post-dose (day 2) during each treatment period.

Electrocardiogram assessment

Continuous ECG was recorded using a 12-lead Holter machine (Mortara H12+ Holter recorders, 1000 Hz) for 1 h before and at least 24 h after each dose. 12-Lead 10-s ECGs were extracted at time points that were selected to cover the anticipated peak plasma level of imeglimin and a sufficient number of time points to characterize any potential effect on the QTc interval post dosing of imeglimin: 20, 40, and 60 min prior to the dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post dosing. ECGs were recorded in triplicate at all time points with at least 1 min between recordings and within the 5-min time windows preceding each time point. Extracted ECGs were manually read and interpreted under blind conditions by skilled readers at a central core ECG laboratory using computer-assisted, semi-automatic, on-screen measurement of the extracted digital ECG waveforms according to standardized methodology. All interval measurements (PR, QRS, QT) were based on the global superimposed median beats. Each median beat was mathematically derived from the available 10-s recording of the corresponding lead. The 12 individual median beats were graphically displayed as temporally aligned and overlapped (or superimposed) one on another. Global interval measurements were subsequently defined as the interval from the earliest onset of any viable lead to the latest offset of any viable lead. The final QC assessment was performed by a single senior cardiologist in blind settings.

Pharmacokinetics assessment

Blood samples for assay of imeglimin and moxifloxacin were taken before and frequently up to 24 h (at times that correspond with the ECG matches) after each dose of imeglimin, moxifloxacin, and placebo. Plasma concentrations of imeglimin and moxifloxacin were determined using validated high-performance liquid chromatography coupled with mass spectrometry (HPLCMS/MS) analytical method by AmatsiAvogadro (France) and Atlanbio (France), respectively. The lower limit of quantification (LLQ) for the imeglimin assay was 10 ng/mL and 40 ng/mL for moxifloxacin assay. Any values below the LLQ were reported as below the limit of quantification (BLQ). Pharmacokinetic parameters were derived from plasma concentration data by PhinC Development, using Phoenix 4. For calculation of all PK parameters, and for individual concentration–time plots, plasma concentrations BLQ were treated as follows: values that occurred before the first measurable concentration were taken as zero; all other values were taken as missing. For calculation of plasma concentration summary statistics, BLQ values were taken as 0, unless they fell between two quantifiable concentrations, in which case they were treated as missing. The following parameters were derived: maximum (peak) plasma concentration (C_{max}), time to reach maximum (peak) plasma concentration (t_{max}), area under the plasma concentration–time curve from time 0 to the time of last measurable concentration ($AUC_{0\text{-}t}$), area under the plasma drug concentration–time curve from time zero to infinity ($AUC_{0\text{-}\infty}$), and apparent terminal elimination half-life ($t_{1/2}$).

Safety profile evaluation

Safety was assessed by recording adverse events (AE), vital signs, and laboratory assessments.

Study endpoints and statistical methods

A sample size of 44 evaluable subjects was considered necessary to demonstrate that imeglimin does not prolong QTcF above the regulatory threshold and to obtain assay sensitivity with a power of at least 80%.

According to ICH E14 [14], a negative thorough QT/QTc study is one in which the upper bound of the one-sided 95% confidence interval for the largest time-matched mean of the drug on the QTc interval excludes 10 ms.

Considering a non-inferiority approach for the primary endpoint, the primary hypothesis to be tested was:

- H_0: $\Delta\Delta QTcF_{max} \geq 10$ ms
- H_A: $\Delta\Delta QTcF_{max} < 10$ ms

The null hypothesis was to be rejected if the upper bound of the one-sided 95% confidence interval (equivalent to the upper bound of the two-sided 90% confidence interval) of the largest mean ΔΔQTcF excluded 10 ms.

The primary test of the hypothesis was equivalent to translating into a set of individual tests of hypotheses by time points, known as intersection union tests. The individual intersection-union test hypotheses at a time point *i* can be formalized as:

- $H_{0,i}$: $\Delta\Delta QTcF_i = \mu_{\Delta QTcF,\ imeglimin,\ i} - \mu_{\Delta QTcF,\ placebo,\ i} \geq 10$ ms
- $H_{A,i}$: $\Delta\Delta QTcF_i = \mu_{\Delta QTcF,\ imeglimin,\ i} - \mu_{\Delta QTcF,\ placebo,\ i} < 10$ ms

The primary objective would be achieved if the upper bounds of the one-sided 95% confidence interval of the mean

ΔΔQTcF excluded 10 ms at each time point of ECG extraction.

Assay sensitivity was assessed using the comparison between positive control (moxifloxacin) and placebo. The corresponding hypothesis for assay sensitivity was as follows:

- H_0: $\Delta\Delta QTcF_i = \mu_{\Delta QTcF,\ moxifloxacin,\ i} - \mu_{\Delta QTcF,\ placebo,\ i} \leq$ 5 ms for all time points *i*
- H_A: $\Delta\Delta QTcF_i = \mu_{\Delta QTcF,\ moxifloxacin,\ i} - \mu_{\Delta QTcF,\ placebo,\ i} >$ 5 ms for at least one time point

Multiplicity in terms of multiple treatment comparisons was addressed using a sequential testing approach. Multiplicity regarding multiple time points on the primary endpoint does not necessitate any adjustment, as the hypotheses tested rely on the intersection-union test. Multiplicity regarding multiple time points on assay sensitivity was addressed using a Bonferroni adjustment.

The change from baseline in QTcF (ΔQTcF) was analyzed at each time point using a mixed analysis of variance (ANOVA) model including treatment, period, and treatment by period interaction as fixed effects and considering the subject as a random effect. All treatments, including moxifloxacin, were included in the model. For each time point, the least square means (LS means) for the difference between imeglimin doses and placebo (ΔΔQTcFi), and their two-sided 90% confidences interval, were derived. The primary objective was achieved if the upper bound of the one-sided 95% confidence interval of the mean ΔΔQTcF excluded 10 ms at each time point of ECG extraction.

Assay sensitivity was determined using the same ANOVA model as used for the primary analysis. At each time point, two-sided 90% confidence interval (for which the lower bound is equivalent to the lower one-sided 95% confidence interval) of the mean difference between moxifloxacin and placebo was estimated. If at least one lower confidence interval bound excluded 5 ms, the study was to be deemed to have assay sensitivity.

The results of the analyses (estimates of ΔΔQTcF over time and CIs) were summarized and presented graphically by the treatment group. The largest time-matched, placebo-adjusted change from baseline (ΔΔmax) for RR, HR, PR, QRS, QT, and QTcB was derived using the same approach as for the primary endpoint.

Actual values and time-matched changes from baseline (Δ) in QTcF, RR, HR, PR, QRS, QT, and QTcB were summarized using descriptive statistics. Categorical and morphological analyses were performed and summarized using descriptive statistics.

The concentration–response relationship for ΔQTcF with imeglimin and moxifloxacin plasma concentrations was investigated using mixed-effects models. Once the final model was selected, predictions of ΔΔQTcF at C_{max} for supra-therapeutic and therapeutic doses for imeglimin and C_{max} of moxifloxacin were obtained with two-sided 90% confidence intervals.

Results

Subject demographics and disposition

Fifty-five subjects were randomized in the study and 49 subjects completed the study (Fig. 1). Six subjects were withdrawn from the study: 1 owing to a treatment-emergent adverse event (TEAE), 3 because of protocol violations (drug abuse), and 2 because of withdrawal of consent.

The baseline characteristics of the subjects are summarized in Table 1.

Primary ECG endpoint—ΔΔQTcF

Estimates of ΔΔQTcF, with the two-sided 90% confidence intervals for imeglimin, are presented by time point in Table 2 and displayed graphically in Fig. 2.

Overall, the analysis showed that the upper bound of the two-sided 90% confidence interval for ΔΔQTcF did not exceed the regulatory threshold of 10 ms for the supratherapeutic dose (6000 mg imeglimin). The maximum ΔΔQTcF was estimated to be 2.9 ms at 6 h after dosing and the upper bound of its two-sided 90% confidence interval was 5.4 ms.

As no signal was elicited for the supra-therapeutic dose, the 2250 mg dose was also considered not causing a prolongation of the QTc interval. This was confirmed by the pattern of the ΔΔQTcF over time presented in Fig. 2 which was consistent with that of the supra-therapeutic dose.

Secondary endpoints

The estimated ΔΔQTcF over time for moxifloxacin was consistent with the expected pattern of moxifloxacin, with a peak of effect between 1.5 and 4 h after administration. The maximum ΔΔQTcF was estimated at 13 m and at 1.5 and 2 h after administration, with the lower bound of the two-sided 90% confidence intervals at 10.6 ms, which is above the value of 5 ms considered to demonstrate assay sensitivity. When

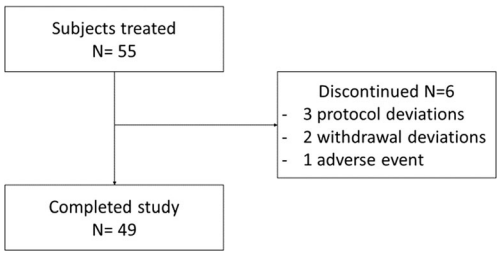

Fig. 1 Flow chart

Table 1 Summary of demographics of subjects

	All subjects ($N = 55$)
Age (years), mean, SD	33.0 (7.26)
Gender, *n* (%)	
Female	21 (38.2)
Male	34 (61.8)
Race, *n* (%)	
White	48 (87.3)
Asian	7 (12.7)
Height (cm), mean (SD)	174.6 (8.64)
Weight (kg), mean (SD)	73.6 (10.2)
BMI (kg/m^2), mean (SD)	24.1 (2.6)

SD, standard deviation

considering the 96.67% confidence intervals (adjusted for multiplicity) at time points 2, 3, and 4 h after administration, each of them was above the threshold of 5 ms. Overall, it can be concluded that imeglimin did not induce a QT/QTc prolongation of regulatory concern with a strong confidence as evidenced by the assay sensitivity.

No particular trend was observed for the PR and QRS intervals. For the QT and QTcB parameters, patterns comparable with those of QTcF were found. No QTcF thresholds above 500 ms or QTc increased by more than 60 ms occurred.

Pharmacokinetics analysis

Descriptive statistics of imeglimin PK parameters are summarized in Table 3.

Imeglimin was rapidly absorbed with a mean C_{max} achieved between 1 and 2 h consistent with historical data. Geometric mean C_{max} was 2.7-fold higher after administration of 6000 mg imeglimin compared with 2250 mg imeglimin. Inter-individual variability, as expressed by CV%, was around 21% and 42% for 2250 mg and 6000 mg imeglimin, respectively.

Exposure (based on geometric mean $AUC_{0-\infty}$) to imeglimin increased by twofold when the dose increased by 2.7-fold. Inter-individual variability, as expressed by CV%, was between 21 and 24% for both doses.

Geometric mean $t_{1/2}$ was about 5.0 h for 2250 mg imeglimin and 5.8 h for 6000 mg imeglimin that reflects mainly the distribution phase occurring from around 2 to 24 h post-dose.

After administration of 400 mg moxifloxacin, mean C_{max} was 2390 ng/mL, with a CV% of 28.5%. The geometric mean AUC_{0-t} and $AUC_{0-\infty}$ were 20700 and 24100 ng*h/mL, respectively, with inter-individual variability around 20%. Geometric mean $t_{1/2}$ was 10.4 h.

Exposure-response relationship analysis

A graphical display of the estimated ΔΔQTcF as a function of imeglimin plasma concentrations, with predicted ΔΔQTcF (and their 90% CI) at C_{max} geometric means for the 2250 mg and 6000 mg doses, is provided in Fig. 3.

The model that provided the best fit was a linear model including a treatment and time point–specific intercept, a linear component for imeglimin plasma concentrations, and a subject-specific random intercept effect. The global intercept, corresponding to mean ΔQTcF under placebo and at time 12 h, was estimated at − 6.9 ms. A shift of 1.15 was estimated for imeglimin, and time-dependent variations around the intercept

Table 2 Placebo-corrected change from time-matched baseline QTcF

Change from baseline and placebo						
Time point (h)	6000 mg imeglimin ($N = 53$)	2250 mg imeglimin ($N = 51$)	400 mg moxifloxacin ($N = 50$)			
	ΔΔEstimate (90% CI)	ΔΔEstimate (90% CI)	ΔΔEstimate (90% CI)	ΔΔEstimate (96.67% CI)*		
Parameter: QTcF interval, aggregate (msec)						
0.5	1.9 (− 0.3; 4.0)	1.7 (− 0.5; 3.8)	4.7 (2.5; 6.8)			
1	1.5 (− 0.9; 3.9)	3.1 (0.8; 5.5)	11.4 (9.1; 13.8)			
1.5	0.4 (− 1.9; 2.7)	1.5 (− 0.8; 3.8)	13.0 (10.6; 15.3)			
2	− 0.2 (− 2.6; 2.2)	0.3 (− 2.1; 2.7)	13.0 (10.6; 15.4)	13.0	(9.8;	16.2)
3	− 1.8 (− 4.0; 0.4)	− 1.6 (− 3.8; 0.7)	12.1 (9.9; 14.4)	12.1	(9.2;	15.0)
4	0.1 (− 2.1; 2.4)	− 0.4 (− 2.7; 1.8)	12.0 (9.7; 14.2)	12.0	(9.0;	14.9)
6	2.9 (0.4; 5.4)	4.0 (1.5; 6.5)	12.4 (9.9; 14.9)			
8	2.5 (0.1; 5.0)	4.8 (2.3; 7.2)	11.7 (9.2; 14.1)			
12	− 0.2 (− 2.4; 1.9)	0.8 (− 1.4; 3.0)	7.4 (5.2; 9.6)			

*96.67% confidence interval corresponds to a confidence level adjusted for 3 time points in order to maintain the overall confidence to 90%

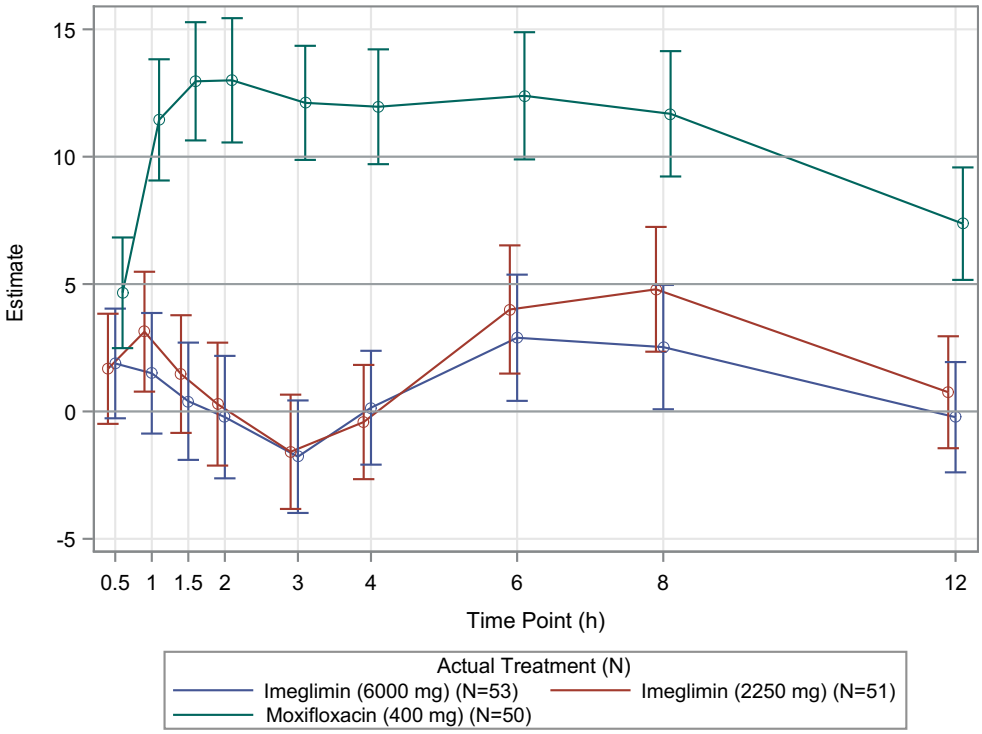

Fig. 2 Placebo-corrected change from time-matched QTcF across treatment groups

varied between − 5.5 and 4.7 ms. No drug component was found affecting significantly ΔQTcF. However, as no evidence was found suggesting a nonlinear relationship, a linear slope component was estimated at − 0.0002 ms per ng/mL (p = 0.9115, 90% CI = − 0.00024; 0.00209).

The exposure–response analysis confirmed that imeglimin did not induce QT/QTc prolongation, as evidenced by the upper bound of the two-sided 90% confidence interval for the supratherapeutic dose below the threshold of 10 ms. The slope between imeglimin concentration and the placebo-corrected time-matched QTcF was close to 0 and the two-sided 90 % confidence interval of the predicted value of this parameter at the geometric mean maximum plasma concentration (C_{max}) associated with each dose was below 2 ms. So, the results of the exposure–response analysis were in full agreement with the primary endpoint and there was no concentration-exposure dependency on QTc intervals by imeglimin.

In contrast, the exposure–response analysis confirmed that moxifloxacin induced QT/QTc prolongation of the expected

Table 3 Summary statistics for imeglimin pharmacokinetic parameters

Treatment		C_{max} (ng/mL)	t_{max}* (h)	$t_{1/2}$ (h)	$AUC_{0\text{-}t}$ (h*ng/mL)	$AUC_{0\text{-}\infty}$ (h*ng/mL)
2250 mg imeglimin	***N***	52	52	52	52	52
	Mean	2430	2.00	4.97	18400	19,000
	CV%	20.5	0.50–4.05	14.0	21.1	21.1
	CI 95% mean	2290 - 2570		4.78–5.16	17,300–19,400	17,900–20,100
	GM	2380		4.92	17,900	18,600
	CI 95% GM	2260–2520		4.73–5.12	16,900–19,100	17500 –19700
6000 mg imeglimin	***N***	53	53	53	53	53
	Mean	7020	1.00	5.78	37100	38,900
	CV%	42.2	0.50–1.52	21.5	24.2	23.8
	CI 95% mean	6200–7830		5.44–6.13	34700–39600	36,400–41,500
	GM	6500		5.65	36100	37,900
	CI 95% GM	5840–7230		5.32–6.00	33,800–38,600	35,500–40,400

*Median. range: *CV*, coefficient of variation; *GM*, geometric mean

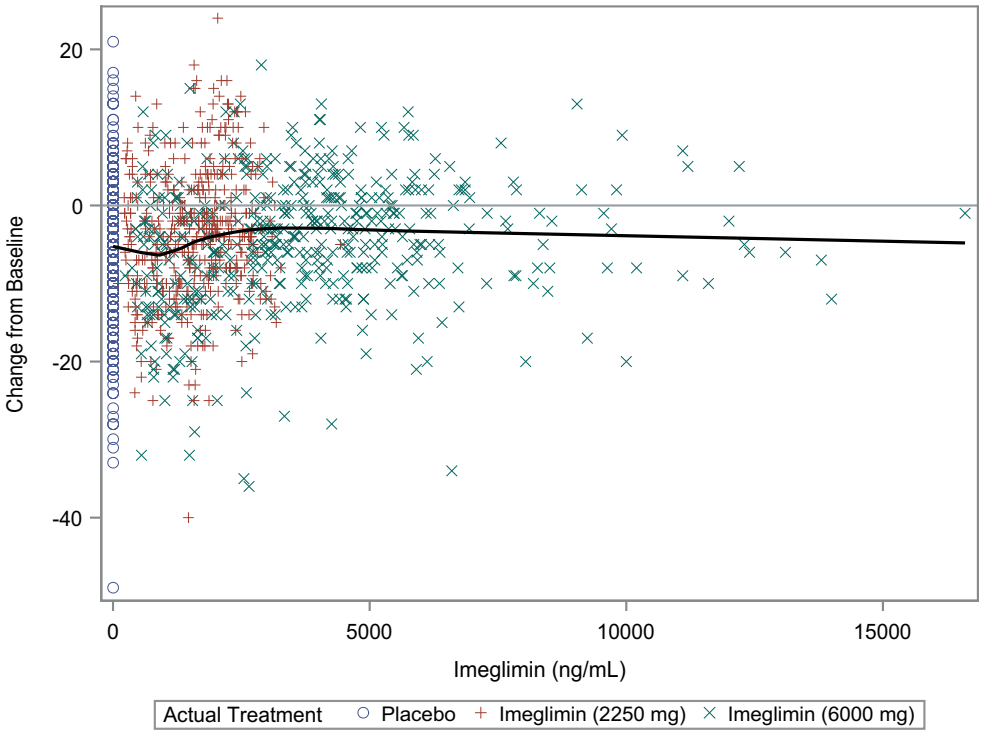

Fig. 3 Exposure-response relationship of imeglimin—change from baseline in QTcF

magnitude to demonstrate assay sensitivity, as evidenced by the lower bound of the two-sided 90% confidence interval above 5 ms.

Safety and tolerability

There was no death, no serious adverse event (SAE), and no severe TEAE. All TEAEs were of mild or moderate intensity. One subject was withdrawn by the investigator following a single dose of placebo, due to a TEAE of pruritic rash.

Imeglimin at a single therapeutic dose of 2250 and moxifloxacin at a single dose of 400 mg were well tolerated. TEAEs were similar to placebo in nature and frequency in these two treatment groups.

After a single supratherapeutic dose of 6000 mg imeglimin, gastrointestinal disorders (diarrhea, vomiting, nausea, abdominal pain) were the most frequently reported TEAEs, with a higher frequency (23 subjects, 43.4%) compared with other treatment groups (3–4 subjects, 5.8–7.8%).

There were no clinically significant changes in laboratory variables, vital signs, or 12-lead digital ECGs, and all physical examinations were normal or not clinically significant.

Discussion

The aim of this thorough QT study was to investigate whether therapeutic and supratherapeutic doses of imeglimin induce prolongation of QT interval. This study was in line with the current recommendations (ICH E14) requiring all non-antiarrhythmic compounds undergo this type of study [14]. This recommendation is based on the fact that drug-induced delays in cardiac repolarization have the potential to increase the probability of fatal cardiac arrhythmia (torsades de pointes). Cardiac repolarization is determined using QT interval corrected for changes in heart rate QT. Thorough QT studies assess the length of QTc prolongation and its relationship to the dose. If the 95% upper confidence limit for the change in the placebo-corrected baseline QTc is less than 10 ms, then the drug is considered to have no clinically relevant effect on QT interval.

The primary endpoint of this study demonstrated an absence of QT prolongation for both doses therapeutic and supratherapeutic of imeglimin (2250 mg and 6000 mg) compared with placebo. The upper limit of the two-sided 90% confidence interval was significantly below the regulatory threshold of 10 ms. There was no concentration-exposure dependency on QTc intervals by imeglimin and no QTcF thresholds above 500 ms or QTc increased more than 60 ms. Furthermore, imeglimin did not exert a relevant effect on heart rate or PR or QRS intervals. Moxifloxacin was used as a positive control for detecting clinically significant increases in QTcF and confirmed assay sensitivity in this study. This study was consistent with previous preclinical data showing no inhibition of hERG tail current with imeglimin.

Imeglimin is a first-in-class oral drug for T2DM. Phase IIb studies in Europe/USA and Japan and phase III in Japan have demonstrated a favorable safety and tolerability profile

[11–13]. Both imeglimin's pharmacokinetic parameters and safety/tolerability profile in this study are consistent with results previously observed in healthy subjects. Previous data of the single ascending dose and multiple ascending doses in healthy Caucasian and Japanese subjects showed a similar safety/tolerability profile [10]. In this study, the most commonly observed adverse events at the highest doses were from the gastrointestinal tract, mainly nausea, abdominal pain, and diarrhea, and the maximal tolerated dose was set up at 6000 mg both in Japanese and Caucasian healthy subjects [10].

A limitation of the study is the inclusion of only healthy subjects, as recommended by the guidance [14]. In that context, results may not equate to potential proarrhythmic liabilities when a drug is used in T2DM patients with a high-risk cardiovascular profile and several concomitant medications.

To conclude, imeglimin is a promising first-in-class oral agent for T2DM and this study demonstrated that imeglimin has no effect on ventricular repolarization. Imeglimin up to 6000 mg was not associated with QT interval prolongation.

Author contribution JD contributed to the interpretation of data and drafted and edited the report. SP, MF, SB, PV, and PF contributed to the study design and interpretation of data and reviewed the report. All authors read the manuscript critically and approved the submitted version.

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Compliance with ethical standards

This clinical trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines [15] and was approved by an Independent Ethics Committee/Institutional Review Board (Office for Research Ethics Committees Northern Ireland - ORECNI). All participants provided written informed consent prior to any trial-related activities.

Conflict of interest JD, SP, SB, and PF are employees of Poxel. MF is an employee of Phinc development. PV is an employee of Banook Group.

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