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Cardiac Safety of Rupatadine in a Single-Ascending-Dose and Multiple-Ascending-Dose Study in Healthy Japanese Subjects, Using Intensive Electrocardiogram Assessments—Comparison With the Previous White Caucasian Thorough QT Study

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Abstract

A thorough QT/QTc study in healthy white Caucasian subjects demonstrated that rupatadine has no proarrhythmic potential and raised no cardiac safety concerns. The present phase I study aimed to confirm the cardiac safety of rupatadine in healthy Japanese subjects. In this randomized, double-blind, placebo-controlled study, 27 healthy Japanese subjects were administered single and multiple escalating rupatadine doses of 10, 20, and 40 mg or placebo. Triplicate electrocardiogram (ECG) recordings were performed on days −1, 1, and 5 at several points, and time-matched pharmacokinetic samples were also collected. Concentration–effect analysis based on the change in the QT interval corrected using Fridericia's formula (QTcF) from average baseline was performed. Data from the formal TQT study in white Caucasian subjects was used for a comparison analysis. The ECG data for rupatadine at doses up to 40 mg did not show an effect on the QTc interval of regulatory concern. The sensitivity of this study to detect small changes in the QTc interval was confirmed by demonstrating a significant shortening of QTcF on days 1 and 5 four hours after a standardized meal. The data from this study exhibited no statistically significant differences in the QTc effect between Japanese and white Caucasian subjects.

Keywords

rupatadine, Japanese, cardiac safety, food effect, assay sensitivity

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline E14 recommends that the QT-prolonging potential of a drug be evaluated primarily by a specific "thorough QT" (TQT) study.[1] In 2005, when the ICH was first adopted, it was not expected that the results of a TQT would be influenced by ethnic factors. However, emerging clinical experience has suggested that interethnic differences can be of particular relevance when assessing the safety of some drugs.[2] Since 2010, when the ICH E14 was fully adopted in Japan, the suitability of foreign data to provide proarrhythmic liability information concerning the Japanese population is still under assessment. Nevertheless, more efficient approaches to reduce the associated costs and alternatives to a conventional TQT study have been extensively discussed to modify the current regulatory requirements now allowing thorough QT assessments in other trials.

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The validity of early QT assessments in phase 1 clinical studies and concentration–effect analysis applied to phase 1 data were proposed as potential alternatives to TQT.[3] The use of a concentration–effect model assumes that the pharmacokinetic (PK)-pharmacodynamic relationship between plasma concentrations of the drug and its effect on QTc is linear, and the response is not delayed by the time course of plasma concentrations.[4] Data-based simulations revealed that concentration–effect models applied to phase 1 studies with a small sample size provided enough power to rule out small drug-induced effects on the QT interval.[5,6] Recent changes to the ICH E14 guideline allow the use of concentration–effect analysis as the primary basis to conclude whether a drug has a QT effect.[7] It is therefore important to avoid false-negative conclusions, especially if exposures exceeding clinically relevant levels are not achieved. Suggestions to include a moxifloxacin arm into single-ascending-dose (SAD) and multiple-ascending-dose (MAD) studies have been made.[8] However, this approach requires significant changes in the study design of a typical phase 1 study, increasing complexity and costs. The ability to detect the effect of a meal on QT interval after the intake of a standardized meal has been demonstrated,[9–12] and this physiological effect on QTc can be readily used as a positive control to verify assay sensitivity in a phase 1 environment as per ICH E14 guideline.[13]

Here we describe the application of a concentration–effect analysis validated by the meal effects on electrocardiograms (ECGs) to a parallel-group phase 1 study. We aimed to investigate the cardiac safety of 10, 20, and 40 mg rupatadine in healthy Japanese subjects.

Rupatadine is a second-generation antihistamine with affinity for H_1-receptor and additional platelet activating factor antagonist activity. Rupatadine was first marketed in 2003 and is now approved and marketed in 62 countries around the world for the treatment of allergic rhinitis and urticaria in adults and adolescents (aged $\geq$ 12 years) and children (aged >2 years).[14] In Europe the principal markets are France, Germany, Italy, and Poland. In Asia, rupatadine is marketed in Singapore, the Philippines, Thailand, and Vietnam and is currently under registration in South Korea and Japan. Recently Rupafin in tablet form and as pediatric oral solution have also been approved by Health Canada. As part of rupatadine's drug development program, its safety has been extensively investigated in several nonclinical and clinical studies.[15–18]

Rupatadine is almost completely metabolized when administered orally, with very little of the drug being recovered unmetabolized. The main biotransformation pathways of rupatadine include different oxidative processes, namely, oxidation of the pyridine methyl group to the carboxylic acid, hydroxylation in the 3, 5, and 6 positions in the tricyclic ring system, and N-dealkylation of the piperidine nitrogen. Two of its main metabolites, desloratadine and 3-hydroxylated desloratadine, retain antihistaminic properties that may contribute to the overall efficacy of the drug.[18] In vitro metabolism studies in human liver microsomes indicate that rupatadine is mainly metabolized by cytochrome P450 (CYP) 3A4, and a genetic polymorphism in its biotransformation is unlikely.[18] The concomitant administration of rupatadine with potent CYP3A4 inhibitors (like ketoconazole and erythromycin) should be avoided, and comedication with moderate CYP3A4 inhibitors should be used with caution.[19] On the other side, no clinically relevant modifications in mean pharmacokinetic parameters of rupatadine and active metabolites were observed when azithromycin at therapeutic doses was coadministered.[20] Finally, rupatadine 10 mg did not appear to increase the depressant effect of alcohol (0.8 g/kg) after a single dose, both on subjective and objective measurements of psychomotor performance, including quantitative electroencephalography.[21]

The inhibition by rupatadine and its main metabolites of human ether-a-go-go related gene (*HERG*) current in KEK293 cells transfected with the human *HERG* channel was evaluated. Rupatadine inhibited outward current at concentrations higher than the therapeutic concentration by 3 orders of magnitude. Overall, the potential of rupatadine for QT prolongation because of *HERG* channel blockade seems to be very low.[17] A formal TQT study designed in accordance with the ICH E14 guidance has shown that rupatadine has no proarrhythmic potential at 10 times the therapeutic dose of 10 mg after single and repeated doses in white Caucasian subjects.[17] The pharmacokinetics, safety, and cognitive function profile of rupatadine in Japanese subjects has recently been described.[22] Intensive cardiac assessments have been conducted as part of the objectives of this study and now are being reported in this article. This analysis aimed to confirm the results from the previous TQT study following single and multiple doses in Japanese subjects using the well-characterized effect of a meal on QTc to prove assay sensitivity.

Methods

Study Subjects

Eligible were healthy male or female Japanese subjects aged 20–45 years inclusive with a body mass index (BMI) between 18 and 25 kg/m^2. Subjects with ECG abnormalities (PR interval < 120 or > 200 ms; QRS complex > 120 ms; QTc interval > 430 ms for men and > 450 ms for women) were excluded from the study. A

written and signed informed consent form was obtained from each subject before taking part in the study.

The study protocol (EudraCT: 2012-004900-37) was reviewed and approved by a National Health Service Research Ethics Committee (South Central-Berkshire B, United Kingdom) and the Medicines and Healthcare products Regulatory Authority (MHRA). The study was conducted according to the ethical principles of UK law, the Declaration of Helsinki, and Good Clinical Practice guidelines.

Study Design

The present study was a single-center, randomized, placebo-controlled study conducted at Richmond Pharmacology, Ltd, London, United Kingdom. The study comprised a screening period within 21 days before the first administration of rupatadine or placebo (days −21 to −2), an in-house period of 10 days and 9 nights (days −2 to 8) combining a SAD and MAD treatment, followed by 2 outpatient visits (days 9 and 10) and a follow-up visit (day 11). Twenty-one subjects were planned to be randomized to receive single daily oral doses of rupatadine 10, 20, and 40 mg (7 per dose level) and 6 subjects to receive matching placebo (2 per dose level). All planned subjects received placebo on day −1 and a single dose of rupatadine or placebo on day 1 followed by once-daily doses on days 2–5.

Subjects fasted for at least 8 hours prior to the study drug administration on day −1 and on days 1–5. On dosing days standardized meals were served at the following times: breakfast 2 hours postdose, lunch 6 hours postdose, and dinner 12 hours postdose. Each meal was consumed within 25 minutes. The reference meal for the assessment of assay sensitivity was breakfast served after the 2-hour postdose assessments. This meal consisted of cornflakes cereal, semiskimmed milk, fresh mango, white grapes, and peach juice. Breakfast contained 574 kcal, with a percentage ratio between carbohydrates, protein, and fat of 82:9:9, respectively. The same breakfast was given on days 1 and 5.

ECG Assessments and QTc Evaluation

Twelve-lead ECGs were recorded using a GE Marquette MAC1200 and stored electronically on the Medical MUSE information system (GE Healthcare). Only ECGs recorded electronically at a stable heart rate (HR) were valid for QT interval measurements. ECG recordings were collected on days −1, 1, and 5 predose and 0.33, 0.66, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours postdose. All ECGs were recorded after the subjects had been resting in a supine position for at least 10 minutes. To obtain consistent ECG recordings, the clinical staff ensured that the subjects were awake and avoided any postural changes. At each time, the ECGs were recorded in triplicate to confirm the accuracy and precision of the measurements. Each ECG lasted 10 seconds. The triplicates were performed at 1-minute intervals over 3 minutes.

Each electronic ECG data file contained the ECG data as well as the result of the automated ECG analysis performed by the Marquette 12 SL ECG Analysis Program. All ECGs and their associated automated interval measurements were subsequently blinded and reviewed by qualified cardiologists in accordance with the ICH E14 Guidance for Industry document and ICH E14 Implementation Working Group Questions and Answers document before any of the ECGs were used for the thorough ECG analysis. The uncorrected QT interval, RR interval from which HR was derived according to the formula HR = 60000/RR, PR interval and QRS duration, the presence or absence of U wave, and quantitative and qualitative ECG variations were assessed by cardiologists with extensive experience with manual onscreen overreading using electronic calipers in MUSE for correction of any implausible readings presented by the automated process. All ECGs were overread by the same cardiologist who was blinded to the treatment and the timing of the recording being evaluated. If manual adjustments of the automated measurement became necessary, a second cardiologist confirmed the assessment. Any disagreement between first and second readers was adjudicated by a third and most senior cardiologist. QT correction by Fridericia's formula (QTcF) was used to estimate the QTc interval.

Pharmacokinetic and Safety Assessments

Pharmacokinetic blood samples were taken and used to determine the relationship between rupatadine concentration and QTc interval. PK blood samples were collected on days 1 and 5 just after the ECG assessments at correspondent times. Adverse events were recorded from the signing of the informed consent until the end of the study, on day 11.

Analytical Methods

Venous blood samples for the determination of rupatadine and its metabolites desloratadine and 3-hydroxydesloratadine plasma concentrations were collected using a 7.5-mL lithium heparin Monovette. The blood samples were centrifuged (10 minutes at 3100 rpm) at 4°C to obtain plasma. All plasma samples were stored at -20°C until transferred to a bioanalytical facility.

Samples for determination of rupatadine and its metabolite concentrations were analyzed by Laboratorio Echevarne (Barcelona, Spain). A validated liquid chromatography–tandem mass spectrometry method with liquid–liquid extraction has been used, developed, and satisfactorily validated for the measurement of the analytes in human plasma over the calibration range

0.1–10 ng·mL^{-1}, with a lower limit of quantification of 0.1 ng·mL^{-1}. Plasma concentrations of rupatadine and the metabolites were determined with rupatadine, metabolites and clomipramine hydrochloride as internal standard.

Chromatographic separation was performed through a Columbus C18 (5 μm, 4.6 × 50 mm; Phenomenex, Torrance, California) analytical column, with a mobile phase consisting of 200 mM ammonium acetate and acetonitrile. The flow rate was 1 mL·min^{-1}, and the total run time was 8 minutes. Detection and quantification were performed by mass spectrometry using an API4000 mass spectrometer (AB SCIEX, Concord, Ontario, Canada). Ions were monitored at m/z 416.17–282.05, 311.17–259.10, 327.22–275.27, and 315.25–86.18 for rupatadine, desloratadine, 3-hydroxydesloratadine, and clomipramine hydrochloride, respectively.

The precision and accuracy (expressed as the coefficient of variation [% CV] and as the relative error [% RE], respectively) of the method were found to be within the target limits of ±15% (±20% for the lower limit of quantitation). The selectivity of the method was found to be satisfactory, with no endogenous interference that may adversely affect the analysis. The mean plasma PK parameters and safety assessments for rupatadine in Japanese and white Caucasian subjects are comprehensively described elsewhere.[17,22]

Statistical Methods

The analysis was based on QTcF and on all data from days 1 and 5. All subjects randomized who received study medication and who had valid ECG data for the times during days 1 and 5 were included in the QTcF analysis set.

Given the small number of subjects per treatment group, a concentration–effect analysis[23] was chosen as the primary analysis, as it allows making joint use of data from all dose groups and all times. Because an influence of the 2 main metabolites on the QT interval cannot be excluded, a linear concentration–effect model with change from average baseline of QTcF as a dependent variable and plasma concentrations of rupatadine as well as the 2 metabolites as explanatory variables was used. In addition, fixed effects for times (where times on day 1 and day 5 were considered separate points) as well as random intercepts for each subject were included.[24] This model allows separation of the effect of the drug and its metabolites from the spontaneous diurnal variation. The former is represented by the regression coefficients for the respective analyte, whereas the diurnal variation that is independent of the concentration is represented by the parameter estimates of the time factor. Based on this model, predictions of the effect at the combined geometric mean of the individual C_{max} values for rupatadine and each of the 2 metabolites were made for each dose group. These predictions were given together with 90% confidence intervals. In addition, concentration values seen in the white Caucasian study were also used to predict the effect ("predefined concentrations").

A number of sensitivity analyses were also performed. These included, among others, separate analyses for day 1 and day 5, subgroup analyses by sex, and separate models for rupatadine and each of the metabolites alone. To better understand any differences between races, data from the TQT study in white Caucasian subjects[17] were used as sensitivity analyses for comparison with the effect seen in this study.

From these analyses, made to compare the results of the present study with those of the TQT study in white Caucasian subjects, 2 models will be briefly reported here. First, a simple model with rupatadine concentration as the only covariate and change from average baseline was also fitted separately to each of the 2 data sets, and scatterplots together with a regression line were produced. Second, a joint model was fitted to the data of both studies. This model used a time-matched baseline, which was also used in the original analysis of the data from white Caucasian subjects. Only times common to both studies were included. A model similar to the primary one, but with study/race and its interactions with the slopes, was fitted.

The analysis of HR effects was performed using a primary model with rupatadine and the 2 metabolites (desloratadine and 3-hydroxylated desloratadine) included.

Assay Sensitivity

Tests for assay sensitivity were performed on the basis of the primary model, using a contrast between the fixed-effects estimators for the spontaneous time course of the change of QTcF from average baseline and the same day's predose value. More specifically, the change from the 2-, 4-, and 6-hour values on each of the days was estimated. Because breakfast was served after the 2-hour point, a significant shortening of QTc at the 2 times, that is, 2 and 4 hours after the start of breakfast, was expected. Relative to the start of a meal that followed an overnight fast, the relevant ECG assessment times were 0.33, 0.66, 1, 1.5, and 2 hours. This effect should have been present on both day 1 and day 5. To account for the multiplicity of the 2 times on each day, 95% confidence intervals were provided instead of 90% confidence intervals. Because we required the effect to be demonstrated on both days, no additional correction for the multiplicity of days was needed. The test for assay sensitivity was added retrospectively, as the methodology used for the analysis was being developed at the

time of planning of this study. It should be noted that the estimate of the spontaneous time course is based on the model and, by construction, is an estimate based on all dose groups.

Results

Subject Disposition and Demographics

Sixty-one subjects were screened in total, of whom 28 subjects did not meet the screening criteria and 6 withdrew consent prior to enrollment. The most common criteria not met by the subjects who failed screening included medical history, abnormal values of BMI, urine, and blood parameters, ECG and Holter parameters, and being on concomitant medication. Twenty-seven subjects fulfilled the eligibility criteria and were randomized to treatment. All 27 subjects enrolled completed the study and were included in all the analysis sets. Demographic data and subject disposition are described elsewhere.[22]

Pharmacokinetics

Rupatadine was absorbed rapidly following administration of single and multiple oral doses in Japanese subjects, with a median time to reach the maximum serum concentrations on days 1 and 5 between 0.67 and 1 hour. After single and multiple doses of rupatadine, the C_{max} and AUC increased proportionally with the dose range (10–40 mg).

Following single and multiple rupatadine 10-mg doses, plasma concentration parameters in the Japanese subjects were found to be within the range of values exhibited by the white Caucasian subjects. The C_{max} in Japanese subjects was found to range between 2.4 and 8.9 ng·mL^{-1} for the 10-mg dose, between 4.5 and 23.45 ng·mL^{-1} for the 20-mg dose, and between 8.06 and 34.5 ng·mL^{-1} for the 40-mg dose.[16] The C_{max} in white Caucasian subjects was found to range between 1.3 and 9.8 ng·mL^{-1} after single and multiple doses of 10 mg rupatadine and between 16 and 230 ng·mL^{-1} after single and multiple doses of 100 mg rupatadine.

Average Baseline of Change in QTcF and Heart Rate

The mean values in change from average baseline in the QTcF interval for 10-, 20-, and 40-mg doses and placebo confirmed the results obtained from the model-based analysis (Supplementary Information). The values for placebo and the 3 treatment groups tended to be similar on both days 1 and 5. The maximal mean values for 10-, 20-, and 40-mg doses and placebo were observed between 1 and 1.5 hours postdose and the minimal values between 5 and 8 hours postdose, except for the 10-mg treatment group, which on day 5 exhibited the maximal value 12 hours postdose.

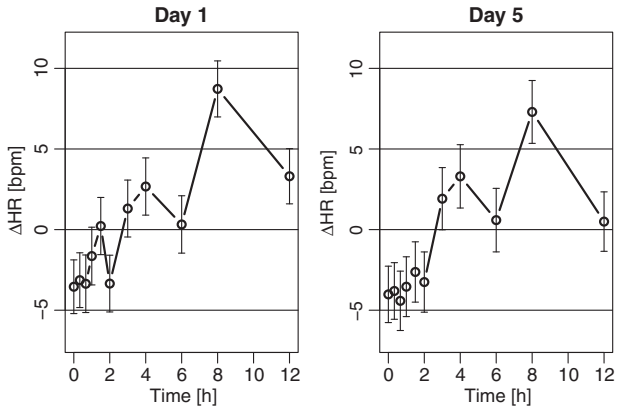

Figure 1. (A) HR effect on days 1 and 5 with a 2-sided 90% confidence interval. Time course analysis estimates based on the primary analysis, that is, a primary model using rupatadine and the 2 metabolites (desloratadine and 3-hydroxylated desloratadine).

HR time course analysis on days 1 and 5 is presented in Figure 1. Note that this is the diurnal variation not attributed to the drug as estimated from the model. Therefore, this estimate is based on data from all dose groups. On days 1 and 5, HR values showed high peaks at 4 and 8 hours. The increases in mean HR correlate with the attributed food effect on HR described by Täubel et al[9] and, by construction, are not related to rupatadine.

Categorical Analyses

There were no subjects with changes in QTcF from time-matched baseline greater than 30 ms. The 20-mg treatment group had an outlier with values of QTcF > 450 ms on day 5. This subject started with high baseline values, and the maximum QTcF value 453.7 ms was observed predose and 1 hour 30 minutes postdose on day 5. There were no uncorrected QT values > 500 ms or QTcF values > 480 ms at any point during the study.

Concentration–Effect Analysis

The main results of the primary concentration–effect analysis are shown in Table 1.

A negative relationship between concentration of rupatadine and change in QTcF was seen, whereas that of the 2 metabolites was positive. However, none of the 2-sided 90% confidence intervals excluded zero, that is, none of the slopes were statistically significantly different from zero.

The predictions derived from the primary model are given in Table 2.

All of them were well below the threshold of 10 ms, indicating no prolongation of QTc of clinical concern. It should be noted that, as the "predefined supratherapeutic" concentrations are well above the maximum concentrations seen in this study, the prediction is an extrapolation in a range in which the validity of

Table 1. Slope Estimates of Rupatadine and Its Metabolites UR-12790 (Desloratadine) and UR-12788 (3-Hydroxylated Desloratadine) Together With 90% Confidence Interval Without Random Slopes Between Japanese and White Caucasian subjects

					90% Confidence Interval		
Parameter	Analyte	Study	Estimate	SE	Lower	Upper	*P*
Slope	Rupatadine	W	−0.01	0.02	−0.05	0.02	.55
		J	−0.16	0.27	−0.61	0.29	.56
	UR−12790	W	0.09	0.07	−0.03	0.21	.23
		J	0.22	0.67	−0.87	1.32	.74
	UR−12788	W	−0.51	0.19	−0.82	−0.19	.01
		J	0.72	0.94	−0.84	2.27	.45

J, Japanese; SE, standard error; W, white Caucasian.
The *P* values of the differences in slope between the 2 ethnic groups for the 3 analytes are presented.

Table 2. Predictions at Geometric Mean C_{max} at 3 Concentrations Performed for Japanese and for the Predefined Therapeutic and Supratherapeutic Concentrations Derived From the Primary Model

				Change in QTcF			
	Plasma Concentrations					90% Confidence Interval	
Scenario	Rupatadine	UR-12788	UR-12790	Estimate	SE	Lower	Upper
Geometric mean C_{max} at 10 mg	5.27	2.08	2.56	0.5	0.69	−0.7	1.61
Geometric mean C_{max} at 20 mg	9.66	3.06	4.88	0.9	0.99	−0.7	2.52
Geometric mean C_{max} at 40 mg	18.45	6.54	11.46	2.4	1.94	−0.8	5.63
Predefined therapeutic	4.49	1.58	2.46	0.5	0.49	−0.3	1.29
Predefined supratherapeutic	81.08	12.27	35.52	5.3	5.82	−4.3	14.86

SE, standard error.

the model is not given. This is reflected in the wide confidence interval for this prediction, which spans a range of nearly 20 ms. This prediction must be rejected as unreliable. Sensitivity analyses confirm the findings of the primary analysis.

A simple comparison of the results in the 2 studies is displayed in Figure 2, in which, for each of the studies, the observed ΔQTcF values are displayed as scatterplots over the concentration of rupatadine. In addition, the regression line from a simple mixed-effects model with rupatadine as the only predictor is displayed. It shows a nonsignificant, slightly positive slope for the Japanese study (Figure 2A) and a negative slope for the white Caucasian study (Figure 2B) that is just significant on the 2-sided 10% level and confidence ranges that exclude an effect of regulatory concern for the whole range of concentrations covered.

The key results of the joint model are shown in Table 3. Essentially, the results of the model agree with those obtained from the Japanese data only. The only difference is seen in the effect of 3-hydroxylated desloratadine, where a significantly negative relationship was assessed for white Caucasian subjects, whereas a nonsignificantly positive one was seen in Japanese subjects, in agreement with what was observed using the Japanese data only. It should be noted that the range of plasma concentrations in the white Caucasian study was much larger than in the Japanese study because of administration of higher doses.

Assay Sensitivity

The time course analysis of the food effect on QTc was estimated from change from average baseline and change from predose baseline (Figure 3). After the reference meal, given at the 2-hour point postdose, QTc dropped 2 to 4 hours after the meal on both days (points 4 and 6 hours). The estimated changes based on the primary model using change from average baseline are shown in Table 4. All 95% confidence intervals for these estimators are well below zero, and therefore assay sensitivity can be considered to be shown. Analysis based on a change from predose values produced similar results.

Discussion

Limited data are available to address the question of whether specific ethnic studies are required to assess cardiac safety in Japanese subjects. The present phase 1 study in healthy Japanese evaluated the effect of single and multiple doses of rupatadine on the QTcF

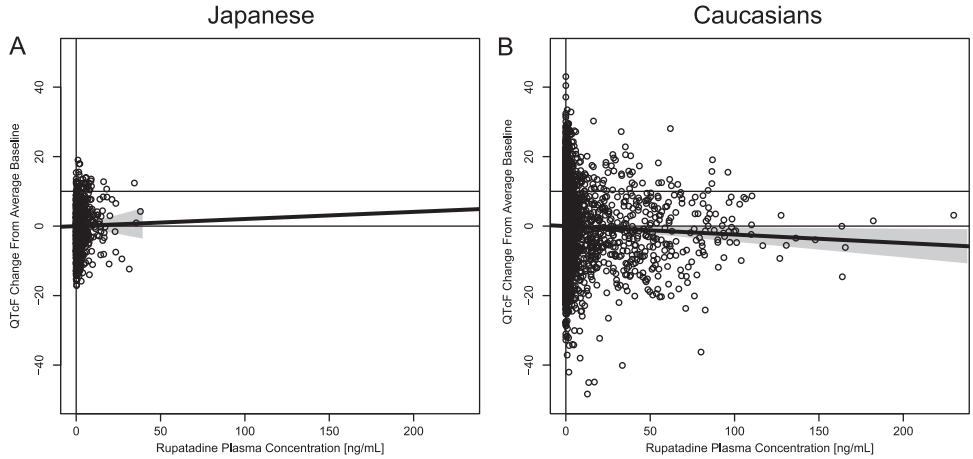

Figure 2. Concentration–effect relationship. Scatterplots of the change of QTcF from average baseline versus plasma concentrations of rupatadine following administration of 10, 20, and 40 mg rupatadine in Japanese subjects (A) and, 10 and 100 mg rupatadine in white Caucasian subjects (B) on days 1 and 5. The scatterplot values are corrected for the spontaneous time course as estimated from the model, that is, for each observation, the predicted value, had the subject received placebo it is subtracted from the observed one. A 2-sided 90% confidence interval is given to the maximum concentration seen. Generalized r^2 values defined as 1 - var(residuals)/var(dependent variable) for each of the mixed models are 0.30 for white Caucasian subjects and 0.54 for Japanese subjects.

Table 3. Primary Concentration–Effect Analysis of Rupatadine and Its Metabolites UR-12790 (Desloratadine) and UR-12788 (3-Hydroxylated Desloratadine) Together With 90% Confidence Interval

			90% Confidence Interval	
Parameter	Estimate	SE	Lower	Upper
Slope Rupatadine	−0.08	0.10	−0.24	0.08
Slope UR-12788	0.04	0.45	−0.70	0.78
Slope UR-12790	0.32	0.29	−0.16	0.80

interval using concentration–effect modeling and the effect of a standardized meal to prove assay sensitivity. This study also combined rupatadine data from a specifically designed TQT study previously conducted elsewhere in white Caucasian subjects[17] to explore the potential for ethnicity to have an impact on QTc. Original data sets were available from both studies.

The pharmacokinetic profile of rupatadine and its main metabolites in healthy Japanese subjects, also assessed in this clinical trial, has been recently reported by Taubel et al.[22] The PK parameters in Japanese subjects were shown to be in close agreement with the results exhibited by several white Caucasian studies.[18,25,26]

The potential for antihistamines to prolong QTc interval, leading to torsade de pointes, has raised concerns when astemizole and terfenadine were reported as proarrhythmic drugs.[27,28] However, these effects are not related to interaction with H_1 receptors and therefore are not histamine specific.[26] Nevertheless, the cardiovascular effects of rupatadine have been widely assessed in preclinical[19–21,29] and clinical studies in non-Japanese subjects[15,17] as part of its development. At doses 100 times higher than the therapeutic dose, rupatadine had no effect on ECG parameters in rats, guinea pigs, and dogs.[30] Rupatadine was also shown to be safe, with no clinically relevant changes in QT/QTc intervals of healthy volunteers even at doses 10 times higher than the therapeutic dose[17] and when coadministered with CYP3A4 inhibitors such as erythromycin and ketoconazole, increasing the systemic exposure of rupatadine 3 or 7 times, respectively.[15] In addition, the effect of rupatadine concentrations on a cloned *HERG* potassium channel revealed that the channel was blocked at a concentration 1685 times greater than the C_{max} value reached following administration of 10 mg rupatadine.[14,15,31] In canine Purkinje fibers, no effect on the cardiac action potential was observed with concentrations of rupatadine and 3-hydroxydesloratadine exceeding 2000-fold the C_{max} value of a 10-mg dose in humans.[25] Only some cases of QT prolongation were reported with rupatadine,[32] and 1 case was referred as torsade de pointes associated with rupatadine in postmarketing surveillance.[33] Nevertheless, in this case causation by rupatadine has not been accurately demonstrated because of the involvement of other factors such as concomitant administration of sertraline and a previous family history of prolonged QTc.[34] A recent review, published by Poluzzi et al, did not identify any additional risks associated with rupatadine. Nevertheless, increasing use in the recent years should be followed up carefully.[35]

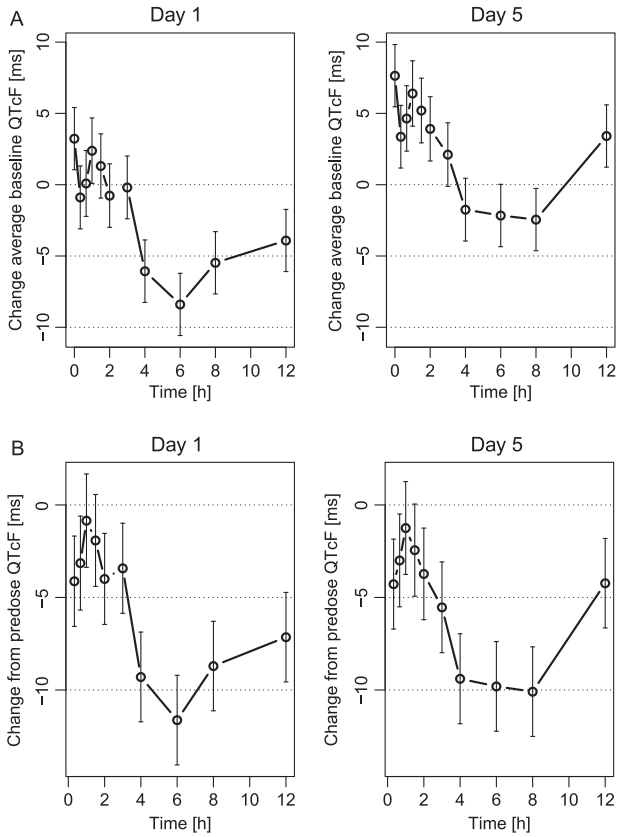

Figure 3. The food effect on days 1 and 5 with a 2-sided 90% confidence interval. Time course analysis based on the primary model: (A) change from average baseline of QTcF; (B) change from the same day's predose value of QTcF.

Table 4. Changes in QTcF From 2-Hour Point (Before Start of Breakfast) to the 4- and 6-Hour Points, Corresponding to 2 and 4 Hours After Start of Breakfast

Time			95% Confidence Interval	
Day	Hour	Estimate	Lower	Upper
1	4	−5.4	−8.3	−2.4
	6	−7.6	−10.5	−4.6
5	4	−6.0	−8.9	−3.1
	6	−6.1	−9.1	−3.1

The estimated change is based on the primary model, that is, it is corrected for any drug effect, and the 95% confidence intervals presented are used to correct for the multiplicity given by the use of 2 times.

The TQT study in white Caucasian subjects had a similarity in study design, as single and multiple doses of rupatadine and placebo were administrated for 5 days.[17] Both studies were parallel-group studies, moxifloxacin was used as an active control in the TQT study, whereas this phase 1 study used the food effect on QT interval to confirm assay sensitivity. In the white Caucasian study, 160 subjects were randomized to either one of the doses of rupatadine (10 and 100 mg) or to placebo. Only common times—1,1.5,2,3,4,6,8, and 12 hours — were used in the analysis of the 2 data sets, and in both studies a meal was given 2 hours postdose. The HR increases at 4 and 8 hours are likely to be correlated with the food effect. The increase in heart rate after food administration is in agreement with the increase in heart rate reported in a TQT study investigating the effects of a meal on the ECG.[9]

The aim of this study was to use a primary concentration–effect analysis to investigate the effect of single and multiple doses of 10, 20, and 40 mg of rupatadine in Japanese subjects. Also, similar models were jointly applied to the data of both studies.

Consistently, the models did not point to any QT-prolonging effect of regulatory concern at any of the doses investigated. The prediction of QTc effects at a 100-mg dose based on white Caucasian data resulted in a wide confidence interval, the upper bound of which exceeded 10 ms. However, this value is an extrapolation and must be interpreted with the utmost reservation because the plasma concentrations observed in the Japanese study, with rupatadine doses up to 40 mg, are much lower than the concentrations in the white Caucasian study, with a maximum dose of 100 mg. In particular, the width of the confidence interval should be seen as a reflection of this being an extrapolation to values 10-fold outside the range investigated. At concentrations measured in this study up to 40 mg, the upper bound of the 2-sided 90%CI was well below the 10-ms threshold of regulatory concern.

The time course effect of a meal on the ECG served as means of testing assay sensitivity and supported a high level of confidence in the results obtained in this phase 1 study. The ability to detect small QTc changes is similar to that of dedicated TQT studies. The decrease in QTcF within 4 hours after food intake is concordant with previous studies[9–12] and further confirms the appropriateness of the use of a standardized meal as a positive control when excluding an effect of regulatory concern in a phase 1 environment. Phase 1 studies do not typically include a positive control, which can constitute a limitation, as systematic errors can occur that cannot be reliably detected without a positive control. The use of a standardized meal and well-controlled food intake offers an effective alternative approach to replace a TQT study by a thorough ECG assessments in phase 1 based on concentration–effect models and the establishment of a substitute for the positive control to show assay sensitivity providing protection against false-negatives.[9,12]

In conclusion, the study confirmed that rupatadine doses have no QTc-prolonging effects in Japanese. These data exhibited no statistically significant

differences in QTc effect between Japanese and white Caucasian ethic groups, allowing the extrapolation of the non-Japanese TQT study data to the Japanese population.

Declaration of Conflicting Interests

E.S. and I.I. are employees of J. Uriach y Compañía, S.A. J.T. and S.F. are employees of Richmond Pharmacology Ltd. G.F. is an employee of Statistik Georg Ferber GmbH, which received funding from Richmond Pharmacology to carry out the statistical analysis of this study.

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