CONFIRMATION OF THE CARDIAC SAFETY OF RUPATADINE IN A SAD AND MAD STUDY IN JAPANESE HEALTHY SUBJECTS USING INTENSIVE ECG ASSESSMENTS

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Introduction

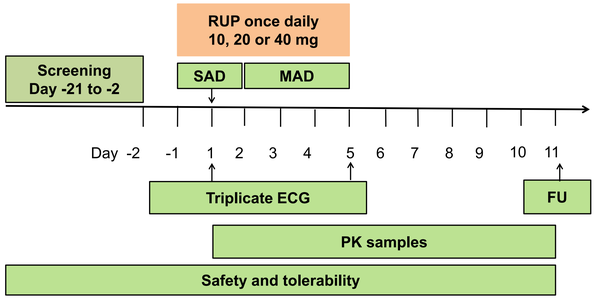
Thorough QTc (TQT) studies are a well-established method for testing the pro-arrhythmic propensity of drugs [1]. However, Phase I studies have been shown to be the ideal candidates for incorporation of early QT assessments with sufficient power to assess the cardiac safety of novel drugs [2]. The analysis of ECG obtained 1-4 hours after the intake of a carbohydrate rich meal has also been proposed as a robust method to demonstrate assay sensitivity in TQT studies [3-4]
The effects of 10 and 100 mg Rupatadine (RUP) on the QT/QTc interval in healthy Caucasian subjects have been demonstrated. This TQT study demonstrated that RUP had no proarrhytmic potential and raised no concerns regarding its cardiac safety [3].

Aim

- This escalating Phase I study aims to confirm the cardiac safety of RUP in Japanese subjects.
- Compare the findings from the TQT study in Caucasians [3]
- Use the effects of food on QTc to confirm assay sensitivity

Methods

Study Design: Randomised, double-blind, placebo-controlled study with 27 Japanese subjects.



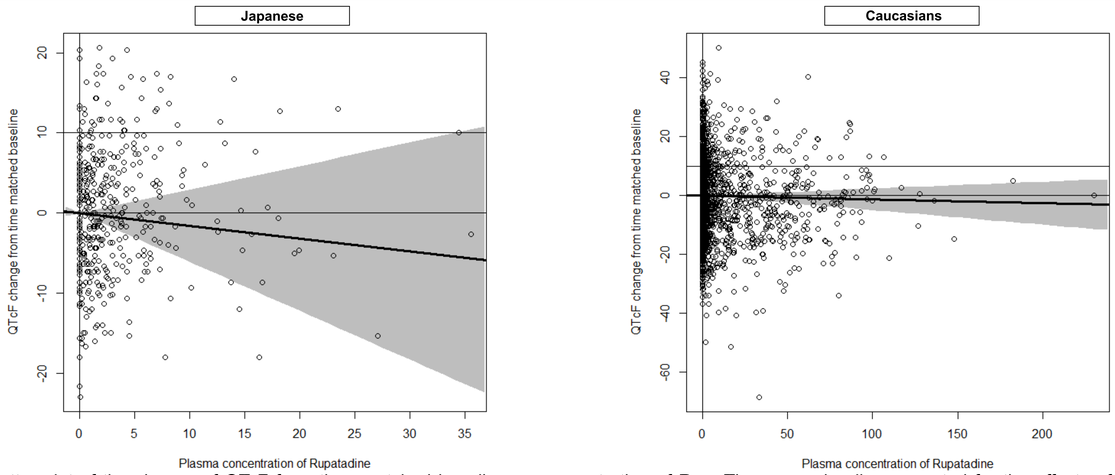
ECG Assessment: Triplicate ECG recordings were performed on Days -1, 1 and 5 at the following time points: pre-dose, and at 0.33, 0.66, 1, 1.5, 2, 3, 4, 5, 6, 8 and 12 h post-dose after the subjects have been resting in a supine position for at least 10 min. Only ECGs recorded electronically at a stable heart rate were valid for QT interval measurements. All ECGs were over-read by the same cardiologist who was blinded to the treatment and the timing of recording being evaluated. Details of procedure have been described in [2].

Meals: On dosing days standardised meals were served as follows: breakfast (2 h post-dose), lunch (6 h post-dose), and dinner (12 h post-dose). The average daily intake was of approximately 2400 kcal with an approximate carbohydrate:protein:fat ratio of 71:11:18.

Statistical Analysis: Individual ECG parameters were listed per time-point and summarised at each time-point by dose level. QT correction by Fridericia's formula was used to estimate the QTc interval. A linear concentration-response model with change from baseline of QTcF as dependent variable and plasma concentration of Rup and the 2 metabolites as explanatory variables was used. Assay sensitivity for the ECG analyses was assessed by calculating the food effect in a time course effect analysis.

Results

Concentration-response analysis



Scatter plot of the change of QTcF from time matched baseline vs concentration of Rup. The regression line corrected for the effects of the 2 metabolites and the spontaneous time course, while the scatter plot represents uncorrected values.

Joint analysis

- Slope estimates together with a 90% CI for the primary model without random slopes. p-values for the differences in slope in Caucasians and Japanese for the tree analyses are presented.
- Difference between slopes for the two ethnic groups were not statistically different for the 3 analytes (p>0.2)

Parameter	Analyte	Difference	SE	90 % Confidence interval		
				lower	upper	p-value
Slope	Rupatadine	0.15	0.28	-0.31	0.60	0.60
	Desloratadine	-0.14	0.67	-1.24	0.96	0.84
	Hydroxylate-desloratadine	-1.22	0.96	-2.81	0.36	0.21

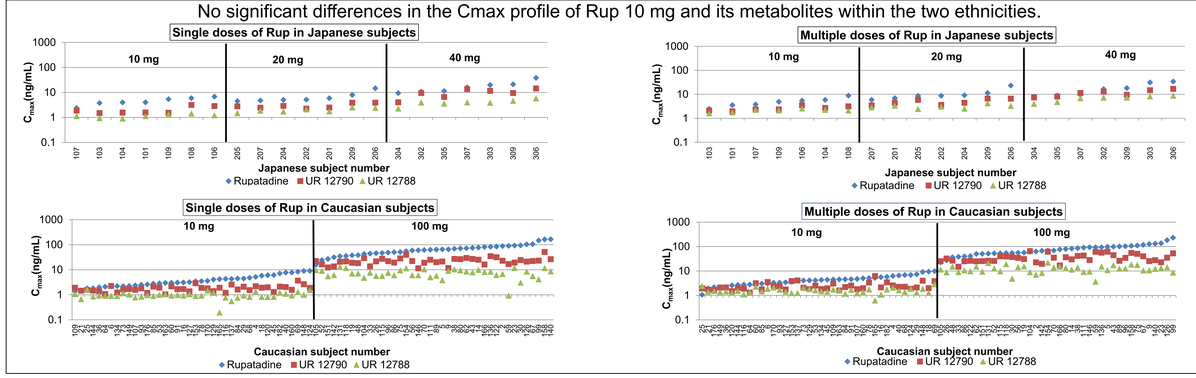
Predictions

Predictions at 3 concentrations performed for Caucasian and Japanese and for the average over the two.

Concentrations				Prediction			
Origin	Rupatadine	Desloratadine	Hydroxi-desloratadine	for	Estimate	90 % Confidence interval	
						lower	upper
Geometric Mean C_{max} at 10 mg (Japanese study)	5.27	2.56	2.08	Caucasians	-0.9	-1.4	-0.4
				Japanese	1.2	-1.2	3.6
				Average	0.2	-1.1	1.4
Geometric Mean C_{max} at 20 mg (Japanese study)	9.66	4.88	3.06	Caucasians	-1.3	-1.9	-0.6
				Japanese	1.8	-1.7	5.3
				Average	0.3	-1.5	2.0
Geometric Mean C_{max} at 40 mg (Japanese study)	18.45	11.46	6.54	Caucasians	-2.6	-3.9	-1.2
				Japanese	4.3	-2.2	10.9
				Average	0.9	-2.5	4.2

Individual C_{max} values for Rup, UR-12790 and UR-12788

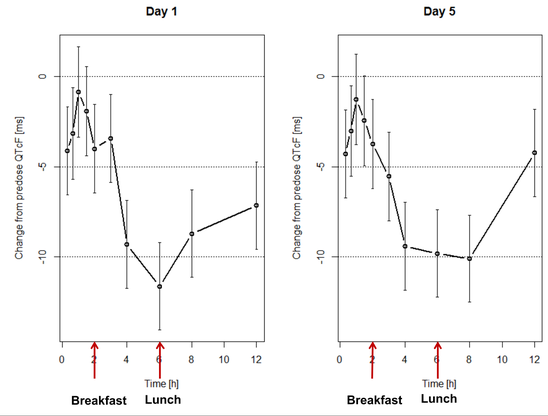
No significant differences in the Cmax profile of Rup 10 mg and its metabolites within the two ethnicities.



Assay sensitivity

Time course analysis of change from the same day's predose value of QTcF showing the food effect on Days 1 and 5 with a two sided 90% CI.

- QTc shortening was observed for 4 h after a first meal.
- On both Days 1 and 5, a slight QTcF prolongation was observed at approximately 1 h which may be correlated with the time when the subjects were disturbed from the supine position to perform the cognitive test.



Conclusions

- In this study the use of a concentration effect analysis showed that an effect of regulatory concern can be excluded for Rup.
- Rup has no QTc prolonging effects in Caucasians and Japanese at the concentrations used in the analysis.
- The data from this study and the TQT study in Caucasians subjects showed no statistically differences between the 2 ethnic groups for the 3 analytes (p>0.2).
- Limitations of this analysis include the difference in the assessment time points between the studies and sample size in this study which contributes to wider CI intervals and reduced power of model based predictions.
- We have demonstrated a consistent physiological response triggered by food on Days 1 and 5 suggesting that a standardised meal may be a good alternative as positive control for the ECG data analysis supporting previous studies [4, 5].

References

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