RETROSPECTIVE VALIDATION USING PK- PD MODELLING OF ECG DATA DERIVED FROM A SINGLE ASCENDING DOSE STUDY IN ACCORDANCE WITH THE PRINCIPLES OF THE ICH E14 GUIDELINE UTILISING THE EFFECTS OF A MEAL TO ESTABLISH ASSAY SENSITIVITY

J Taubel[1], U Lorch[1], M Sust[2], G Ferber[1] and AJ Camm[3]

[1]Richmond Pharmacology Ltd., St George's University of London, Cranmer Terrace, London, United Kingdom

[2]Esteve Av. Mare de Déu de Montserrat, 221, 08041 Barcelona

[3]Department of Cardiological Sciences, St George's University of London, Cranmer Terrace, London, United Kingdom

2-41-1710307

Introduction

Thorough QTc (TQT) studies are a well established method for testing the pro-arrhythmogenic propensity of drugs. Since the E14 guideline of the International Conference on Harmonisation (ICH) was adopted by the EU and the US in 2005 a TQT study has become a staple part of nearly every drug development program. Although the planning, conduct and analysis of TQT studies have become routine, they still represent a burden not only with respect to costs but also because they are usually performed in healthy volunteers who do not benefit from the treatment. Thus in recent years the impetus has shifted for alternatives to a TQT study.

A vast proportion of TQT studies use moxifloxacin (400 mg), an anti-bacterial fluoroquinolone as a positive treatment arm to assure assay sensitivity as per ICH E14 guidelines. However, moxifloxacin produces a QTc change greater than the 5 ms threshold proposed by the guidelines. We have shown that food is a good candidate for a positive control because it produces a QTc shortening effect[1] that is correlated closely with the release of C peptide and blood glucose concentrations[2].

Concentration-response analysis has been proposed as a more powerful alternative for the assessment of QTc-prolonging properties of a drug[3]. Its premise requires that the PK-PD relationship between plasma-concentrations of the drug and its effect on QTc be linear and does not show hysteresis. Until recently, its application to parallel group studies was hampered by the fact that a double difference of QTc cannot be calculated on a per subject basis in these trials. Recently, a model based on change from baseline with fixed time and concentration effects has been proposed which overcomes this limitation. In addition to allow for a placebo-corrected prediction of the drug effect at a given plasma concentration with an unbiased standard error, the estimate of a time effect can be used to show assay sensitivity, if the effect of food is accepted to provide such an assay sensitivity. This second point makes the use of a model with time effect attractive also for a cross-over study.

Aim

The aim of this study was to apply both models of concentration response analysis to a four-way cross-over Phase I study to investigate the PK, PD and safety of escalating single doses of a sigma-1 receptor antagonist (S1RA) E-52862, and demonstrate the use of the time effect attributable to food to show assay sensitivity.

Methods

Study Design

32 healthy Caucasian subjects aged between 18-35 years (inclusive) were randomised to receive the following treatments over four treatment periods (1-4):

Period 1			Period 2			Period 3			Period 4	
Day - 1	Day 1	Washout*	Day - 1	Day 1	Washout*	Day - 1	Day 1	Washout*	Day - 1	Day 1
Placebo	Placebo		Placebo	500 mg		Placebo	600 mg		Placebo	800 mg
Placebo	500 mg		Placebo	Placebo		Placebo	600 mg		Placebo	800 mg
Placebo	500 mg		Placebo	600 mg		Placebo	Placebo		Placebo	800 mg
Placebo	500 mg		Placebo	600 mg		Placebo	800 mg		Placebo	Placebo

E-52862 or Matching Placebo Capsule taken as a single oral dose in a sitting position with 240mL of water.

*Washout period will last for 7 days between doses (168 hours)

Statistical Analysis

Measurements of QT intervals were performed automatically with subsequent manual adjudication in accordance with ICH E14. An individual correction as well as Fridericia's formula was used to calculate QTc. Only results on based on the individual correction (QTcI) are presented here. For the plasma concentrations of E-52862, a linear mixed effects concentration-response model was fitted. One used the time matched difference to placebo of QTcI as dependent variable and the respective concentration as covariate. The other used change of QTcI from average baseline as dependent variable, time as factor and the respective plasma concentrations as covariate. Both series of models further included sex, period and sequence as fixed effects and allowed for random intercept and slope per subject. The first model also allowed for a fixed intercept.

Results

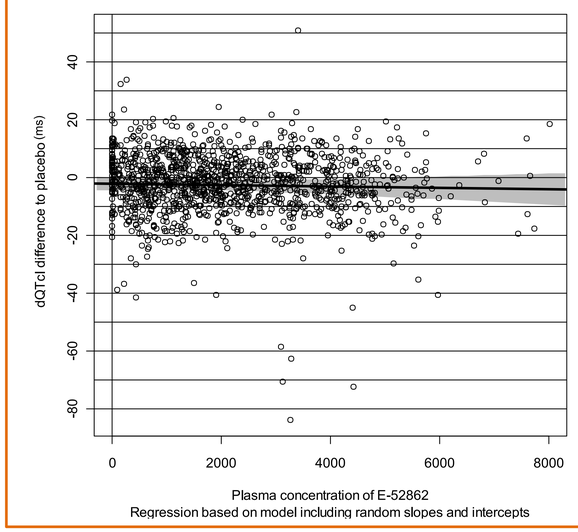
The results for unchanged E-52862 using the two models are given in Table 1 (panel A). Consistently, both models predict a slight shortening of QTcI with increasing concentration of E-52862.

A Table 1: Performance of various concentration-response models for unchanged E-52862: models based on time matched difference to placebo and change from baseline and time course

Dependent Variable	Slope		
	Estimate	90% Confidence interval	
Difference to Placebo	-0.00024	-0.00101	0.00054
Change from Baseline	-0.00079	-0.00143	-0.00016

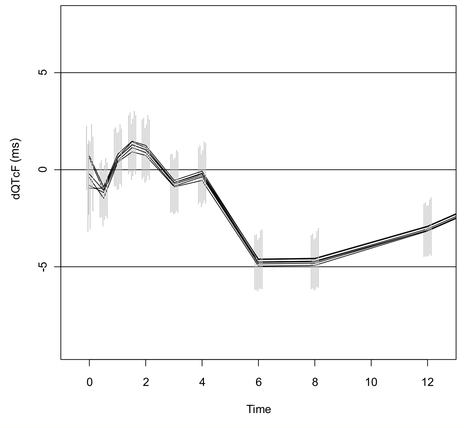
The results for the model based on difference to placebo is illustrated in Figure 1 (Panel B).

B Figure 1: Scatter-plot of difference to time matched placebo of change from average baseline of QTcI against plasma concentration of E-52862. The regression line and corresponding 90% confidence interval are based on the model with random slopes and intercepts.



In the models based on change from baseline, the majority of slopes were significantly negative. The estimated time course corrected for the plasma concentration effect for each of the six best fitting models for QTcI is shown in Figure 2 (Panel C). They show a good consistency of the estimate of the time effect. A test for assay sensitivity can be based on the time course estimates. Based on previous results[1,2], one would require that the difference between the two postprandial time-points 6 and 8 hours to pre-dose would be significantly negative and have a point estimate well below -5 ms. The results of the tests for assay sensitivity are given in Table 2 (Panel D). They confirm that assay sensitivity defined in this way is given.

C Figure 2: Estimates of the time course of change from average baseline corrected for the concentration of each of the 6 analytes. The panel represents the first 12 hour after drug administration. Each line represents the estimates based on the model including random slope for dQTcF and one of the six analytes. Whiskers are two sided 90 % CI



D Table 2: Test of assay sensitivity based on model with time points (ms)

Time-point	Change from pre-dose	95 % Confidence interval		
		Lower	Upper	Significant
6 h	-8.1	-10.4	-5.9	*
8 h	-7	-9.4	-5.0	*

Discussion

The overall aim of this research was to use a concentration response analysis and apply it to a four-way cross-over Phase I study to investigate the PK, PD and safety of escalating single doses of a S1RA E-52862 and demonstrate the use of the time effect attributable to food to show assay sensitivity.

In this study, a shortening of the QTc was observed at 6 and 8 hours as expected. Since this effect was not related to the plasma concentrations of the IMP, it should be visible in the time course estimated from the second series of models. A test for assay sensitivity can be based on this expected effect. It was therefore defined that, for the model of unchanged E-52862, contrasts 6 hour – pre-dose and 8 hour – pre-dose together with two-sided 95 % CIs were to be calculated from the estimates of the time course. If at least one of these CIs was completely below 0, assay sensitivity was deemed to be shown. This was indeed the case and Table 2 showed that for both time-points, the 95 % CIs for the difference to pre-dose were completely below 0.

These analyses further support the premise that if pre-planned, a meal could be used as alternative to moxifloxacin.

This work serves to show that the value of Intensive QT (IQT) studies is significantly enhanced by the analysis of food effects allowing the benchmarking of the ECG data against a well defined and reproducible physiological probe for assay sensitivity.

References

1. Taubel J., Wong A.H., Naseem A., Ferber G., and Camm A. J. Shortening of the QT interval after food can be used to demonstrate assay sensitivity in thorough QT studies. J. Clin. Pharmacol. 52: 1558-1565 (2012).
2. Taubel J., Lorch U., Ferber G., Singh J., Batchvarov V., Savelieva I., Camm A. J. Insulin at normal physiological levels does not prolong QTc interval in thorough QT studies performed in healthy volunteers. Brit. J. Clin. Pharm. 75: 392-403 (2013).
3. Garnett C, Needleman K. Exposure-Response Modelling of QT Prolongation for Clinical Studies. OQT Working Group. (2011)

RICHMOND Pharmacology
www.richmondpharmacology.com

ESTEVE

St George's University of London

ACCP
American College of Clinical Pharmacology
Advancing Clinical Care through Pharmacology