Concentration-QTC Analysis of a Cholinomimetic Agent Integrated into a Phase 1 Japanese Bridging Study Using Intensive ECG Assessments

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Background

The most common cause of dementia is Alzheimer's Disease (AD) [1]. Dementia with Lewy bodies (DLB) is the second most frequent form of dementia in the elderly [2-3]. In people aged 60 to 65 years the prevalence and incidence of dementia is relatively low but there is an exponential increase with age [4], reaching almost 50% in individuals who are 85 years old [5].

It has been shown that there is significant and progressive loss of cholinergic neurons along with their cortically projecting axons in AD [6]. Currently, there is no cure for AD and patients only benefit from drugs targeting symptomatic relief.

A cholinomimetic agent (the IMP) is being developed for the symptomatic treatment of cognitive impairment in AD and other dementia-related disorders, such as DLB. This phase 1 study was conducted to investigate the safety, tolerability and pharmacokinetics (PK) of two doses of the IMP in healthy Caucasian and Japanese men. The aim was to assess if concentration-QTc modelling could be used to predict the effect of the investigational product on QTcF and to use food effect to determine the assay sensitivity.

Methods

Study design:
A randomised, multiple dose, placebo-controlled study with 30 subjects. The study consisted of two treatment periods. The dose given in Treatment Period 2 was higher than that of Treatment Period 1 by a factor of 1.7. The study was conducted to assess the safety and pharmacokinetics of oral doses of the IMP in healthy Japanese and Caucasian subjects.

Double-blind, Placebo Controlled, Multiple Dose

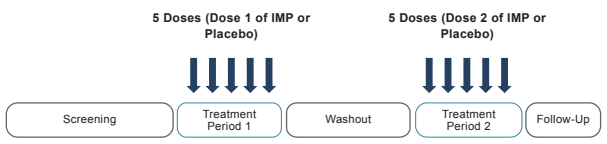

Figure 1: Study Plan schematic.

Meals: The IMP was administered after a light breakfast; breakfast was given at -1 h on dosing days and was consumed within 20 minutes. Standard meals and drinks were given throughout the day at 4, 10 and 23 h after dosing.

ECG Assessment: Triplicate ECGs were performed on every day from Day -1 to Day 6 and at the follow up visit. ECGs were performed at the following time points pre-dose at -2.5, -2, -1.5 h and post-dose at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 12 and at 24 h.

ECGs were recorded after the subjects had been resting in a supine position for at least 10 minutes. ECGs were reviewed by qualified cardiologists in accordance with ICH E14 guidance for industry [7] and ICH E14 implementation working group questions and answers document [8] before they were used for analysis. All ECGs were over read by the same cardiologists who were blinded to the time, date, treatment and any data identifying the subject.

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 the IMP as explanatory variables were used. Based on this model, predictions on the effect of the IMP on QTcF at concentrations seen in the study were made for both races. An additional per timepoint analysis was conducted. The Kenward-Roger approximation was used to determine the placebo corrected change from baseline of QTcF with race and its interaction with treatment and by using a simplified model without race.

Assay sensitivity: The anticipated effect of the meal at -1 h before drug administration was used to show assay sensitivity (Figure 4).

Results

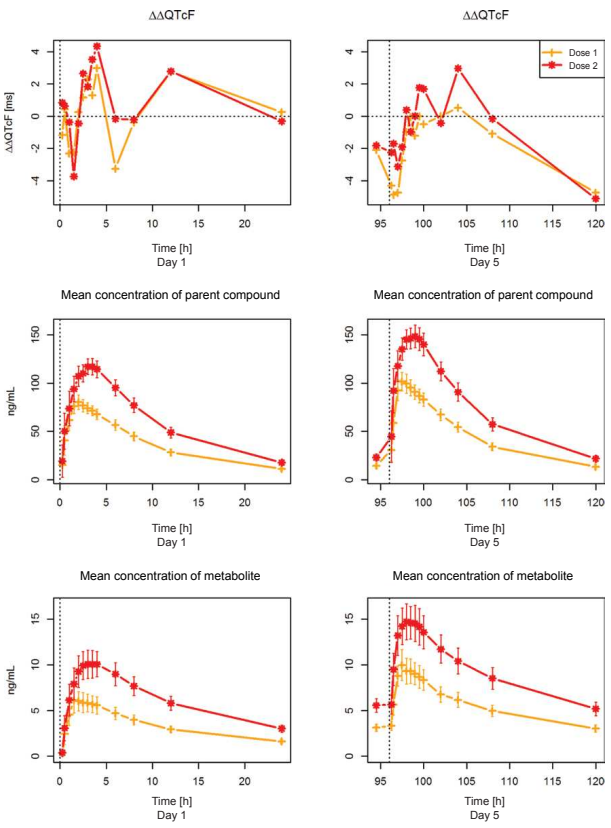

Figure 2. Placebo corrected mean change from baseline of QTcF and arithmetic mean concentrations of the IMP and the metabolite by timepoint and dose group. For mean concentrations including 2-sided 90% confidence intervals. Abbreviation ΔΔQTcF: Placebo corrected change from baseline.

A delay of the peak effect on QTcF by 3 h on Day 1 and by more than 5 h on Day 5. The delay suggests that there is hysteresis between the concentration of each of the moieties and a possible effect on QTc. The significance of this delay is limited because the effect seen is very small and all confidence intervals include zero.

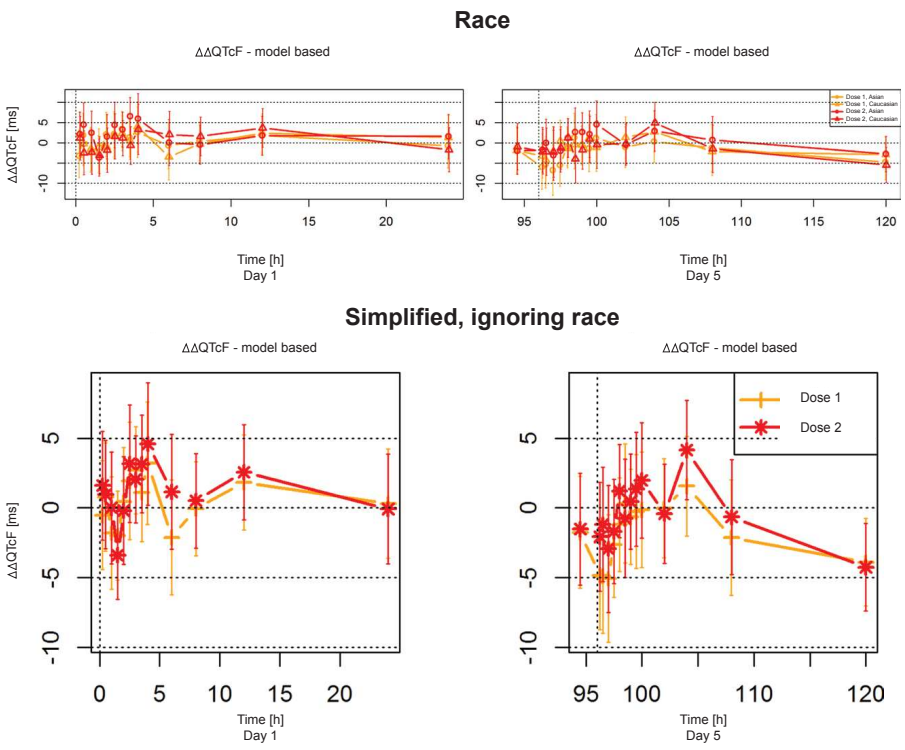

Figure 3. Placebo-corrected change from baseline of QTcF based on separate linear models for each timepoint with 2-sided 90% confidence intervals, by race and ignoring race.

The estimated differences to placebo are below 5 ms in most cases. Only for Japanese receiving the 25 mg dose, values of up to 6.6 ms are seen at 3.5 and 4 h of Day 1. The individual confidence intervals exceed 10 ms at these and a few other points in time. If race is ignored all confidence intervals exclude 10 ms. These models show that there is no significant difference when compared with race. Difference between race are not significant.

Race	Dose	Concentration (ng/ml)			Prediction				
		C_{max} of	Parent compound	Metabolite	Estimate	SE	df	t-value	90% CI
Japanese	1	Parent Compound	118	9.4	-0.1	1.83	36.6	-0.03	-3.2, 3.0
		Metabolite	114	11.0	-0.2	1.90	36.2	-0.12	-3.4, 3.0
	2	Parent Compound	173	17.1	-0.7	2.20	38.2	-0.32	-4.4, 3.0
		Metabolite	168	17.4	-0.7	2.23	36.2	-0.33	-4.5, 3.0
Caucasian	1	Parent Compound	110	10.7	0.2	1.92	36.7	0.10	-3.0, 3.4
		Metabolite	105	9.1	-0.1	1.84	35.8	-0.04	-3.2, 3.0
	2	Parent Compound	173	15.4	1.1	2.14	44.8	0.50	-2.5, 4.7
		Metabolite	165	13.8	0.8	2.06	45.2	0.39	-2.6, 4.3

Table 1. Predictions at various combinations of concentrations of the two moieties based on the primary linear model. Abbreviations: CI, confidence interval; Cmax, maximal plasma concentration; df, degrees of freedom; SE, standard error

Virtually no change was predicted compared to placebo.

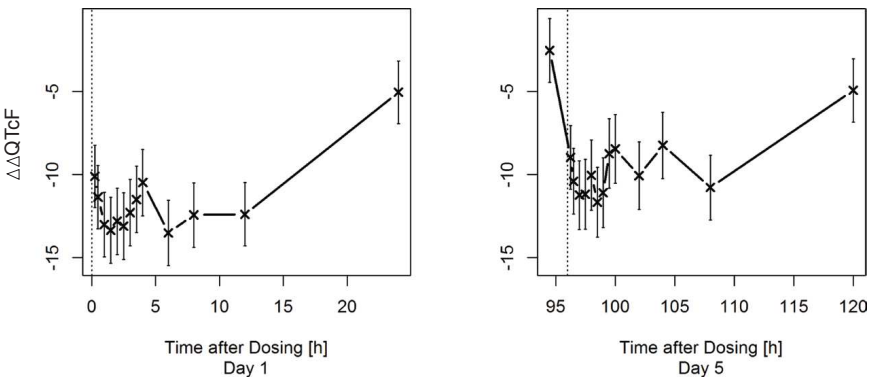

Figure 4. Parameter estimates for Assay Sensitivity based on the simplified linear model

Assay sensitivity was assessed by means of the effect of the meal given 1 h before drug administration on Days 1 and 5. The simplified model was used. This meal is expected to produce a shortening of QTcF between 5 and 10 ms in the time window between 2 and 4 h after its start. This was tested by looking at the change from baseline of the time effect estimator at 1, 2 and 3 h after drug administration, i.e., 2, 3 and 4 h after start of the meal. These estimators are expected to indicate a shortening of between 5 and 10 ms and to be significantly negative on the one-sided 5 % level, i.e. the two sided 90 % confidence interval is completely below zero. All are significantly negative.

Conclusions

- The study met the criteria for a negative QT study, with the upper boundary of a 2-sided 90% CI falling below 10 ms with respect to the doses tested.
- Concentration-QTc analysis showed the absence of any relevant effect of the parent compound or the metabolite on QTc.
- The sensitivity of the study to detect small changes in the QTc interval was confirmed by demonstrating a significant shortening of QTc after a standardized meal.

References

1. Riedel WJ.Curr Opin Pharmacol. 2014;14:18-22.
2. Zaccai, J, C McCracken, C Brayne. Age Ageing. 2005;34: 561–6.
3. McKeith IG, DW Dickson, J Lowe, Emre M, O'Brien JT, Feldman H, et al. Neurology. 2005;65:1863–72.
4. Jorm AF, Jolley D. 1998;51(3):728-733.
5. Fitzpatrick AL, Kuller LH, Ives D, et al. Incidence and prevalence of dementia in the cardiovascular health study. J Am Geriatr Soc. 2004;52(2):195-204.
6. Potter PE, Rauschkolb PK, Pandya Y, Sue LI, Sabbagh MN, Walker DG, Beach TG. Acta Neuropathol. 2011;122:49-60.
7. ICH Harmonized Tripartite Guideline E14. International Conference of Harmonization, Step Guideline, EMEA, CHMP/ICH/2/04, 2005.
8. ICH Harmonized Tripartite Guideline. E14. International conference on harmonisation, E14 Implementation and working group, Question and Answers; 2012.

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