

# Effect of Levofloxacin on QT/QTc Assessed in Healthy Japanese and Caucasian Subjects

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- Description of studies and methods
- Presentation of our research results
- Discussion of results and literature
- Conclusions

- Little is known about racial differences of medication induced QTc changes
- Genetic factors relating to inter-individual variations in the length of the QT interval are well recognized
- It is thus perceivable that different human populations may respond differently to medicines

- The results of two published studies using Levofloxacin in Japanese<sup>1</sup> and Caucasian<sup>2</sup> subjects were pooled in a post hoc analysis to investigate the similarity of dose-effect responses in Japanese and Caucasian healthy volunteers

<sup>1</sup> **Sugiyama A** et al. Effect of single 500 mg iv. levofloxacin dose on QT interval in healthy subjects. Japanese Journal of Chemotherapy. 2009 57(2)106-14

<sup>2</sup> **Taubel J**, Naseem A, Harada T, Wang D, Arezina R, Lorch U, Camm AJ. Levofloxacin can be used effectively as a positive control in thorough QT/QTc studies in healthy volunteers. British Journal of Clinical Pharmacology, 2010, 69(4): 391-400.

- Levofloxacin is a fluoroquinolone antibiotic
- Fluoroquinolones inhibit HERG K<sup>+</sup> channels
- Levofloxacin is a less potent inhibitor than Moxifloxacin in-vitro<sup>1</sup>
- In the case of Levofloxacin inhibition occurs at levels much greater than those observed clinically<sup>1</sup>

<sup>1</sup> Kang J et al. Interactions of a series of fluoroquinolone antibacterial drugs with the human cardiac K<sup>+</sup> channel HERG. Mol Pharmacol 2001; 59:122-6

# Study Designs and Results



	Sugiyama et al.	Taubel et al.
Site:	Kitasato University, Tokyo	St George's University, London
Design:	2-way cross-over trial	4-way cross over trial
IMP:	Levofloxacin 500mg i.v.	Levofloxacin 1g and 1.5g p.o.
Controls:	Placebo	Placebo Moxifloxacin 400mg oral s.d.
Subjects:	48 24 young (20-45), 12M/12F 24 elderly (65-79, 12M/12F)	64 mean age 29 years 34M/30F
Baseline Correction:	Single ECG baseline for both periods	time matched ECG baseline day preceding each of the periods

- Triplicate 12-lead bed-side ECG were recorded
- ECG were analysed automatically and manually over-read (manual adjudication) using a threshold method in different sites
- Intervals were extracted and QTcF calculated
- The Caucasian study established a new baseline for each period of the crossover, whereas the Japanese study used a common baseline for both periods. Therefore the baseline was not used in this analysis.

# “E14” Analysis Results (dose response)



	Sugiyama et al.	Taubel et al.
$\Delta\Delta QTcF$ (CI*) [ms]	3.4 (5.2) following 500mg i.v.	4.7 (7.0) following 1000mg p.o. 7.1 (9.1) following 1500mg p.o. (dose proportional response)





\* upper bound of one-sided 95% confidence interval



Assuming a bioavailability of 100%, a linear dose response in Japanese comparable to Caucasians (same slope) would lead to a 6.8 and 10.2 ms prolongation of QTc at 1000mg and 1500mg doses respectively.

- the Levofloxacin pk data from both trials and the numerical ECG data from the Japanese dataset were transferred to London for a pooled analysis
- to make the two datasets comparable a concentration-response model was fitted
- the predicted effect on QTcF at the geometric mean  $C_{max}$  of the two oral doses was calculated based on the primary model for each race together with a two-sided 95 % confidence interval. The same was done for the difference of these effects between races.

**Table 1** Pharmacokinetic parameters of levofloxacin in Caucasian subjects [Mean  $\pm$  standard deviation]

Dose	C <sub>max</sub> [ $\mu\text{g}/\text{mL}$ ] (arithmetic mean)	C <sub>max</sub> [ $\mu\text{g}/\text{mL}$ ] (geometric mean)	AUC <sub>24</sub> [ $\mu\text{g}\cdot\text{h}/\text{mL}$ ]
500mg i.v.	10.2 $\pm$ 2.3 	10.0 $\pm$ 1.3	66.3 $\pm$ 14.8 
1000mg p.o.	9.6 $\pm$ 2.1 	9.3 $\pm$ 1.2	99 $\pm$ 17 
1500mg p.o.	13 $\pm$ 2.1	12.5 $\pm$ 1.2	150 $\pm$ 26

- The absolute bioavailability of oral Levofloxacin has been reported as  $>99\%$ <sup>1</sup>

<sup>1</sup> Chien SC, Chow AT, Natarajan J, Williams RR, Wong FA, Rogge MC, Nayak RK. Absence of age and gender effects on the pharmacokinetics of a single 500-milligram oral dose of levofloxacin in healthy subjects. Antimicrob Agents Chemother. 1997 Jul;41(7):1562-65

# Japanese and Caucasian pk after 500mg iv



	Sugiyama	Taubel	Chien
C <sub>max</sub> [μg/ml]	10.2 ± 2.3 (+180%)		5.7 ± 0.8
AUC <sub>inf</sub> [μg·h/ml]	66.3 ± 14.8 (+155%)		44.0 ± 7.3
Weight	<b>57.8 ± 7.6</b>	<b>71.1 ± 9.9</b>	<b>77.1 ± 8.2</b>
Dose/kg	8.7mg/kg (+135%)	14.1mg/kg (1g p.o.)	6.5mg/kg

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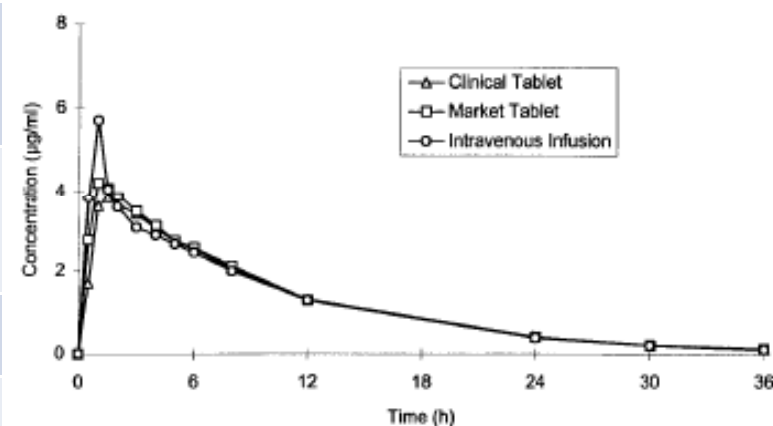
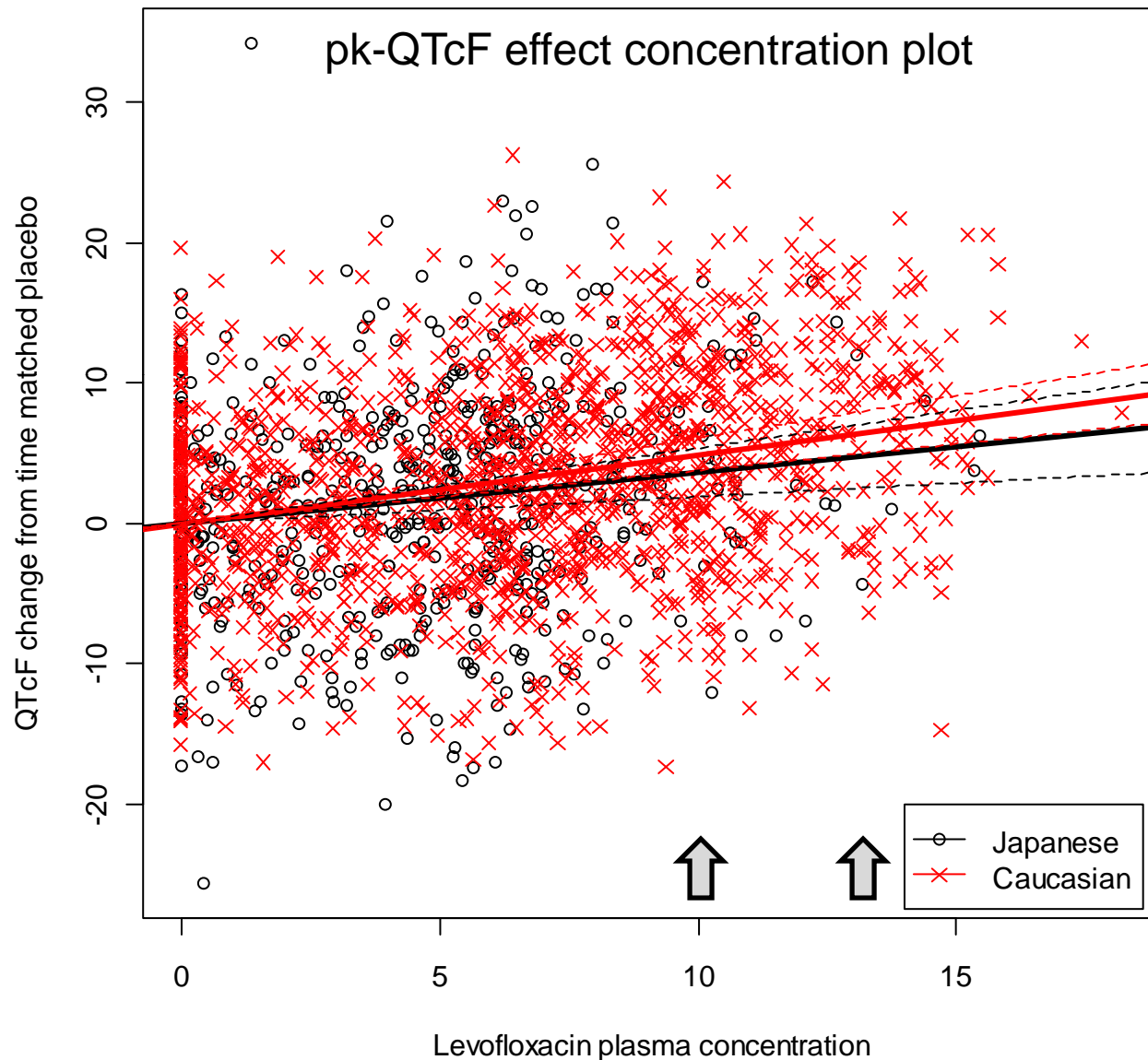


FIG. 3. Mean plasma levofloxacin concentration-time profiles for 23 healthy male subjects following the administration of single 500-mg doses of the clinical tablet, the market-image tablet, and the intravenous infusion (study C).

The pk data from the three studies does not fully reconcile; note Sugiyama and Chien are both 500mg i.v. doses given over 60 minutes. Accounting for weight the C<sub>max</sub> results are about 50% out and the AUC data about 20%

# Results



Japanese subjects show the extremes of QTc shortening/lengthening

Caucasians have the highest plasma concentrations

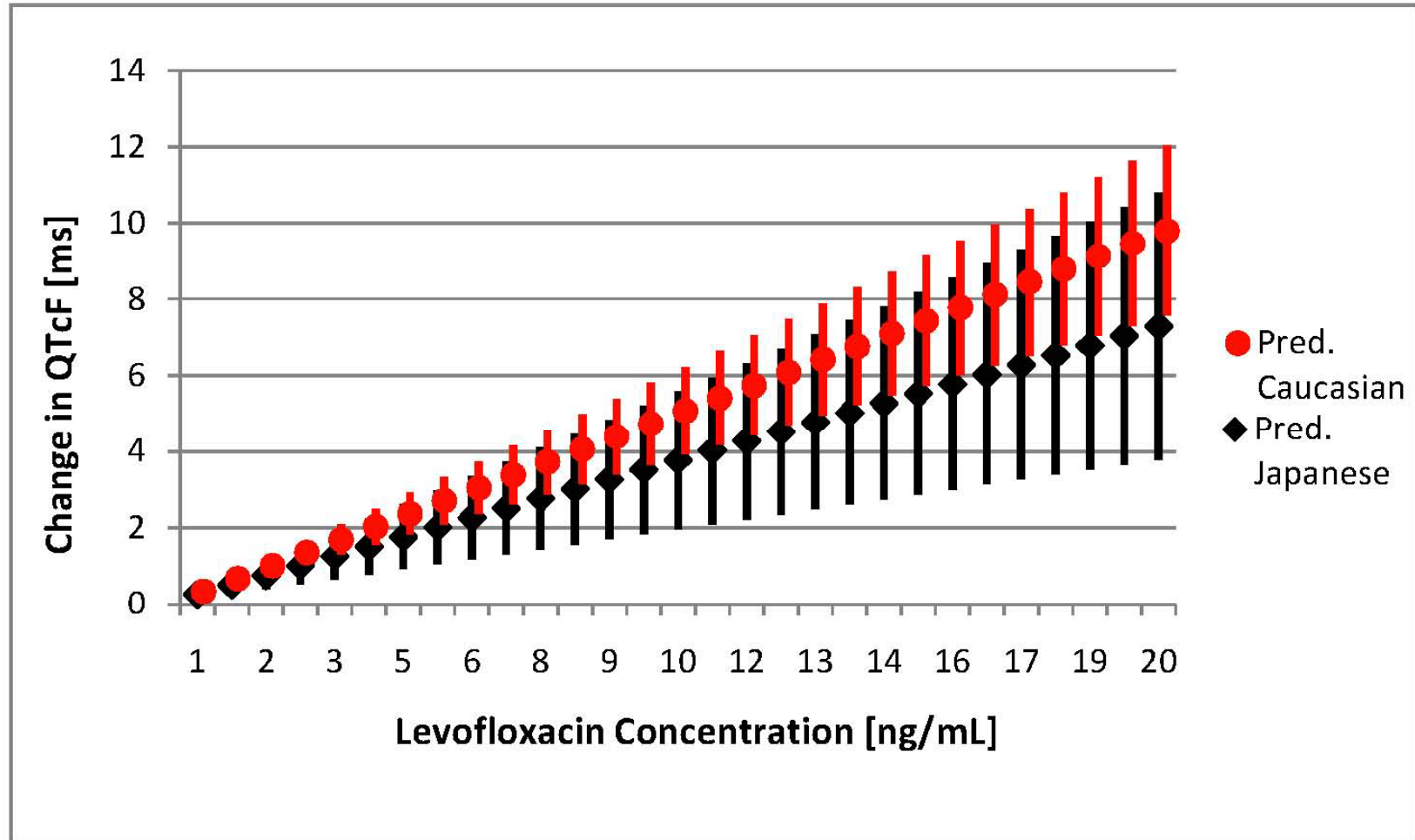
The (linear) slope indicates the QTc prolonging properties of Levofloxacin

The slope for the Japanese subjects is flatter, that of the Caucasians steeper

The confidence intervals overlap

# Results

Predicted QTcF slope and double sided 95% confidence interval



# Results



Model	AIC	BIC	Effect	Estimate	95 % Confidence intervals	
					Lower	Upper
M1	12977.4	13044.6	Offset.Jap.f	-0.462	-2.679	1.755
			Offset.Jap.c	-0.287	-2.501	1.926
			Offset.Cauc.f	-1.286	-4.879	2.306
			Offset.Cauc.m	-1.111	-2.839	0.616
			Slope.J.f	0.392	0.150	0.635
			Slope.J.m	0.367	0.059	0.675
			Slope.Cauc.f	0.404	0.246	0.562
			Slope.Cauc.m	0.594	0.429	0.758
			Slope.diff.Jap	0.025	-0.367	0.417
			Slope.diff.Cauc	-0.190	-0.418	0.038
			Slope.diff.female	-0.012	-0.301	0.278
			Slope.diff.male	-0.227	-0.576	0.123
M2	12979.6	13024.4	Slope.Jap.f	0.373	0.148	0.599
			Slope.Jap.m	0.350	0.071	0.630
			Slope.Cauc.f	0.418	0.262	0.573
			Slope.Cauc.m	0.570	0.410	0.731
			Slope.diff.Jap	-0.023	-0.382	0.336
			Slope.diff.Cauc	0.153	-0.071	0.376
			Slope.diff.female	-0.044	-0.318	0.230
			Slope.diff.male	-0.220	-0.542	0.102

## Concentration-Response Modelling in Japanese and Caucasian Subjects

Effects of plasma concentrations of Levofloxacin on change of QTcF from time matched placebo

Analysis by Gender

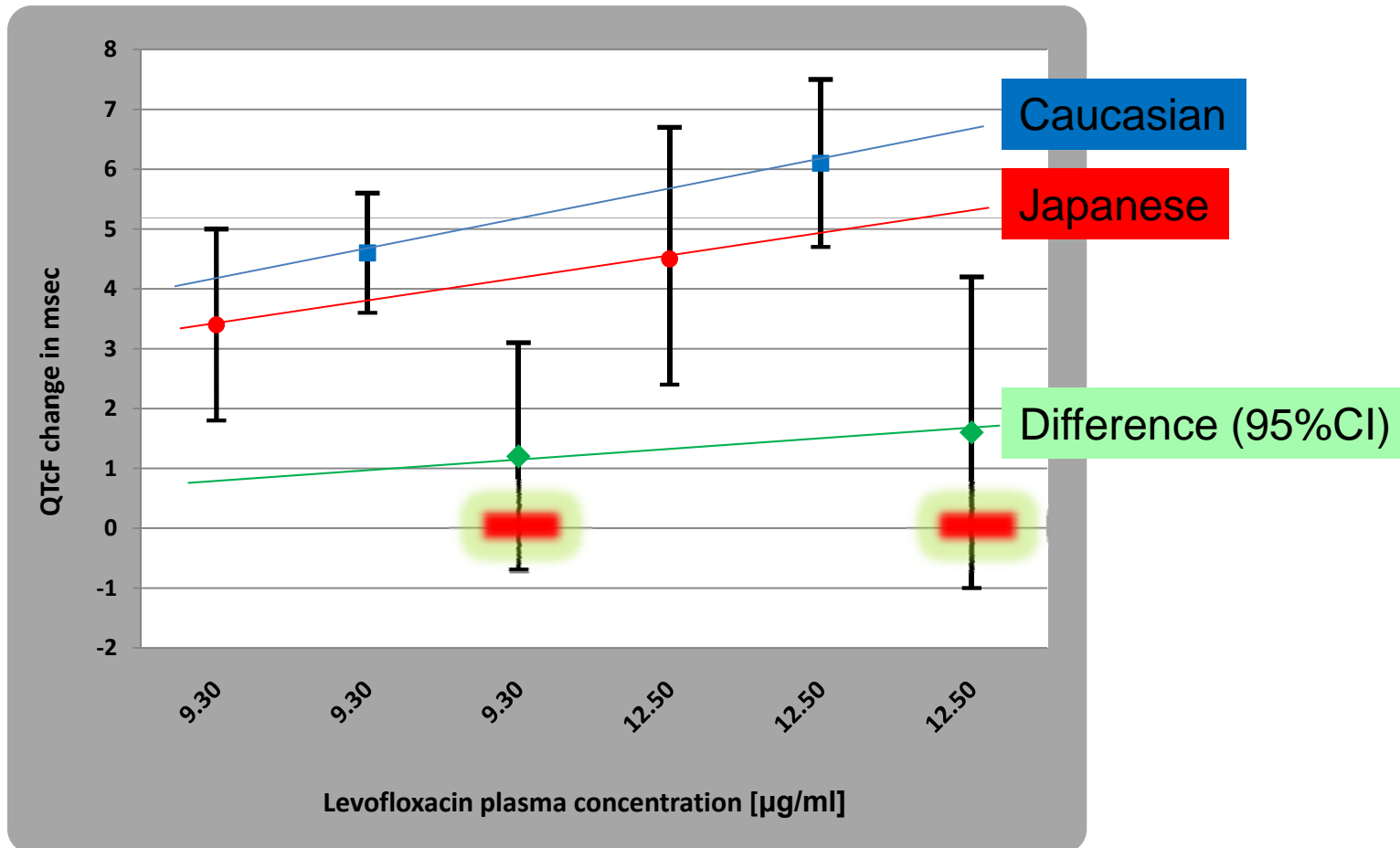
M1: Fixed intercept and slopes, Random: Intercept and slope

M2: No fixed intercept, Random: Intercept and slope

Overall, *inclusion of gender into the analysis does not show any significant effects.*

# Results

Effect of plasma concentrations of Levofloxacin on change of QTcF from time matched placebo.



- This is a post-hoc analysis
- The variable of interest is race
- The results shown may be influenced, masked, distorted or reversed by other variables e.g.:
  - Different sites
  - Different study designs
  - Different doses/drug administration

## Quinidine

- Study in 24 Korean (12M/12F) and 13 Caucasian (7M/6F)
- Caucasian subjects were found to be more sensitive to quinidine induced QTcB prolongation, particularly females
- Two study sites: the authors qualify the findings in their paper stating that they can not rule out various environmental factors

<sup>1</sup> **Shin JG**, Kang WK, Shon JH, Arefayene M, Yoon YR, Kim KA, Kim DI, Kim DS, Cho KH, Woosley RL, **Flockhart DA**. Possible interethnic differences in quinidine-induced QT prolongation between healthy Caucasian and Korean subjects. *British Journal of Clinical Pharmacology*, 2007, 63(2): 206-215.

## Moxifloxacin

- Pooled analysis of 20 TQT studies
- A subset of 60 Asian (Indian, Japanese and Chinese) subjects from 4 studies contributing 3, 9, 20 and 28 subjects each was compared to 788 Caucasian subjects
- C<sub>max</sub> exposure in Asians was +6% compared to Caucasians
- No significant race effects were detected

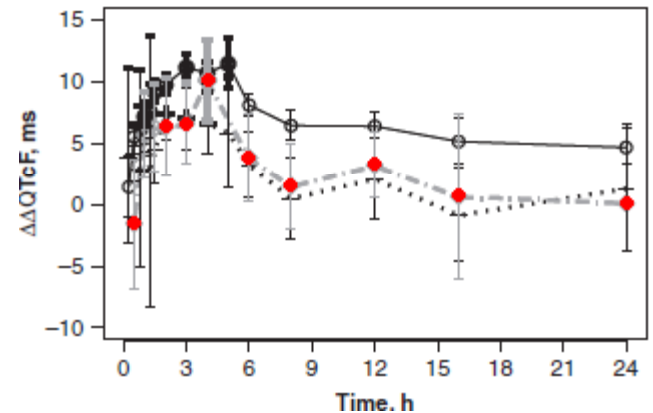


Figure 1. Summary  $\Delta\Delta\text{QTcF}$  versus time plots for the 20 pooled TQT studies divided by ... race category (...Caucasian [ $n = 788$ ], solid, circles; black [ $n = 105$ ], dotted, plus symbols; **Asian [ $n = 72$ ], dash-dot, diamonds**). ... quantile means  $\pm$  90% confidence interval. ...

<sup>1</sup> Florian JA, Tornøe CW, Brundage R, Parekh A, Garnett CE.

Population pharmacokinetic and concentration-QTc models for moxifloxacin: Pooled analysis of 20 thorough QT studies. Journal of Clinical Pharmacology, 2011, Aug;51(8):1152-62. Epub 2011 Jan 12.

However...

- Investigator lead Caucasian and Japanese bridging study where race is the only variable, to assess (amongst others):
  1. racial differences in moxifloxacin response
  2. effects of different types of food on the QTc interval
  3. effects of food on the moxifloxacin response
  4. effect of an euglycaemic insulin clamp on QTc

**Interim results in 11 Caucasian and 13 Japanese only (First 2 Cohorts); not QC checked**

Please note:



The full data will be presented at the upcoming JSCPT, BPS and ASCPT meetings; interested parties can contact the author to discuss specific questions related to our research.

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- Data from our secondary analysis suggests that Japanese and Caucasian healthy volunteers show a similar plasma concentration -- QTcF effect response when administered Levofloxacin 0.5-1g
- A non significant difference in the concentration-effect slope suggests that Japanese would be less sensitive to the HERG channel blocking properties of Levofloxacin

- Data from literature suggests that the same could be true for Moxifloxacin (in a mixed group of Asians) and Quinolone (in Koreans)
- However a recent bridging study (which excluded other variables than race) showed the opposite effect for a 400mg single dose of Moxifloxacin: the data suggests that Japanese could be *more* sensitive to the HERG channel blocking properties of Moxifloxacin

- More work is needed to gather further data
- We recommend a bridging study approach to TQT studies

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- Dr Georg Ferber

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