Implementing exposure (PK) - safety (QT) analysis: a Programmer - Statistician Collaboration

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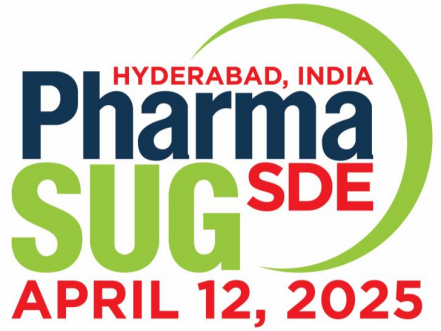


Agenda

- Introduction
- Guidance on Evaluation of QTc Prolongation
- Data aggregation
- Model selection
- Implementation and results
- Overall experience

Today’s Key Focus

- **Building on previous work for consistency and efficiency to support submission**
- **Close collaboration between Programmers and Statisticians**

Introduction

Non-Antiarrhythmic Drugs

Important ↓ identified risk

QT prolongation

Model Informed Drug Development

↓

Exposure - Response

Integrates data and prior knowledge to support drug development and decision-making

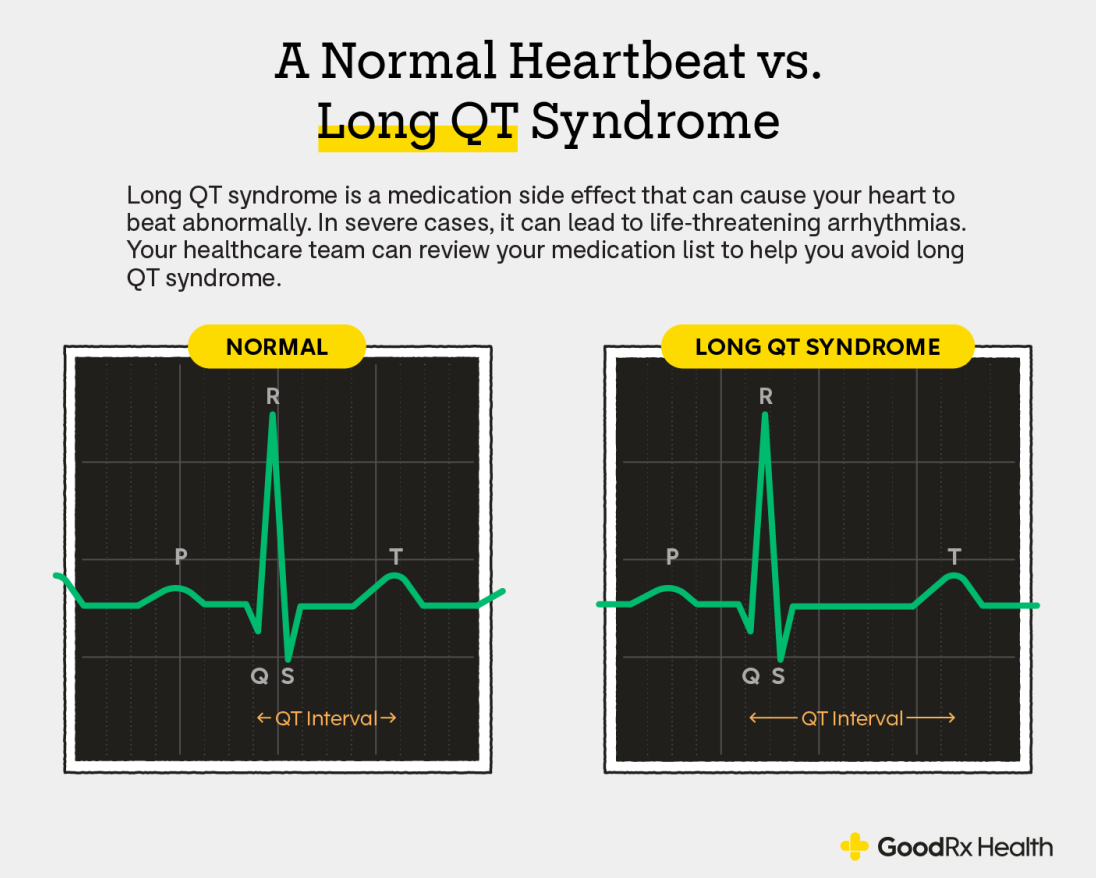
The **PK-QTcF analysis** quantifies the QT prolongation risk as a function of drug exposure

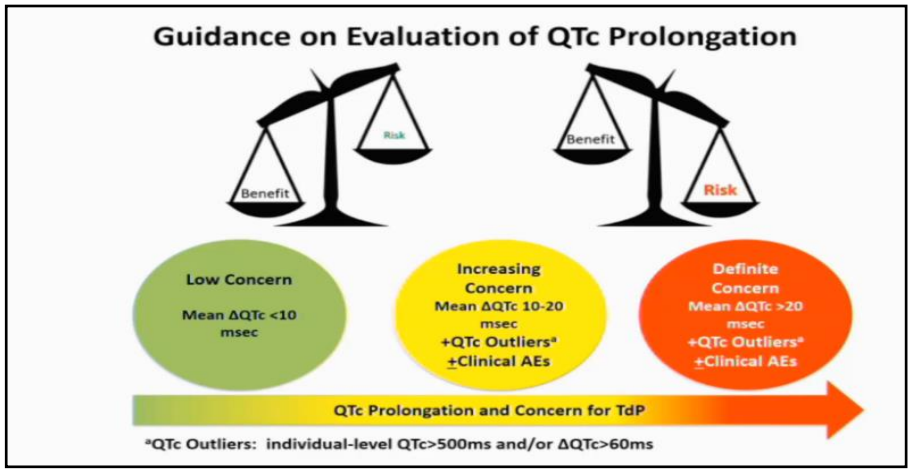
- For early breast cancer (eBC), we've assessed PK, PK-QT relationship, and safety data to support new labeling based on the previously approved for metastatic breast cancer (mBC) data.

eBC populations compared to mBC

- ➢ Better overall health
- ➢ Potentially at lower risk

Guidance on Evaluation of QTc Prolongation





Change from Baseline	Clinical Significance
< 10 ms	Within normal variability; not clinically significant
10-20 ms	May warrant closer monitoring
> 20 ms	Significant
> 60 ms	Highly significant

* FDA Guidance for Industry E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for

Pooling

Objectives:

- ❑ Combining data from multiple studies lead to **more precise estimates** of QT prolongation
- ❑ Understand **the benefit - risk** of the drug for different population and combination partners
- ❑ Demonstrate the **consistency** of results across different studies
- ❑ **Regulatory requirements** to include all relevant data

Original submission	**Subsequent submissions**	**Latest submission**
Healthy Volunteers (HV) + Cancer Studies (mBC + non- BC)	Only Cancer Studies (mBC + non-BC)	Only Cancer Studies (**mBC + non-BC -→ aC** + eBC)

mBC: Metastatic breast cancer non- BC: Non-Breast Cancer eBC: Early-Breast Cancer aC:Advanced Cancer

Model Selection Process

Programming checks

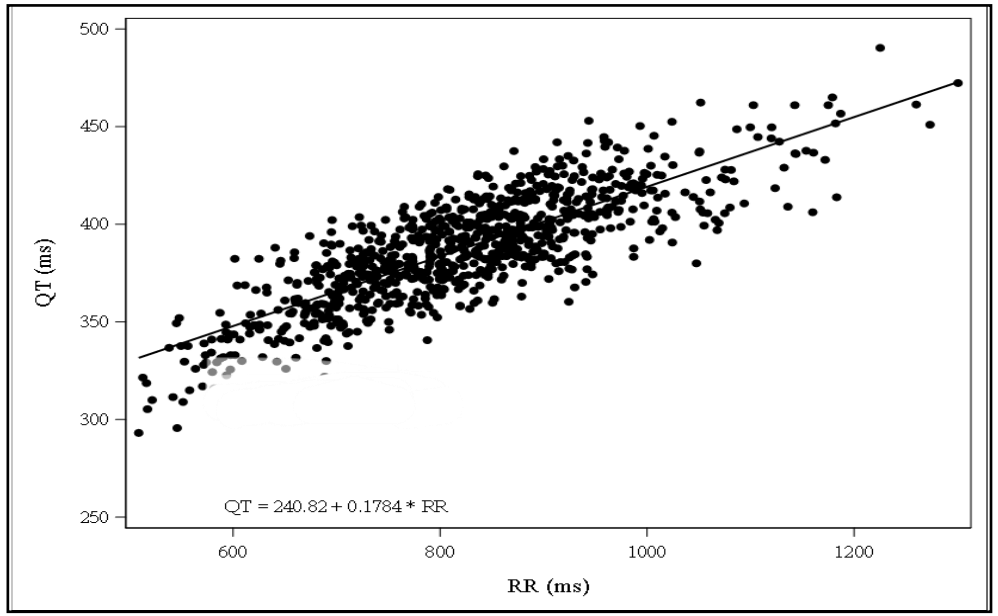
Statistician's evaluation

- Developed the output with all the co-variates using SAS
- 32 candidate models were considered
- As per SAP, statistically insignificant covariates were removed
- Developed the final PK-QT model after model selection
- Model checks (residual plots) for the final model

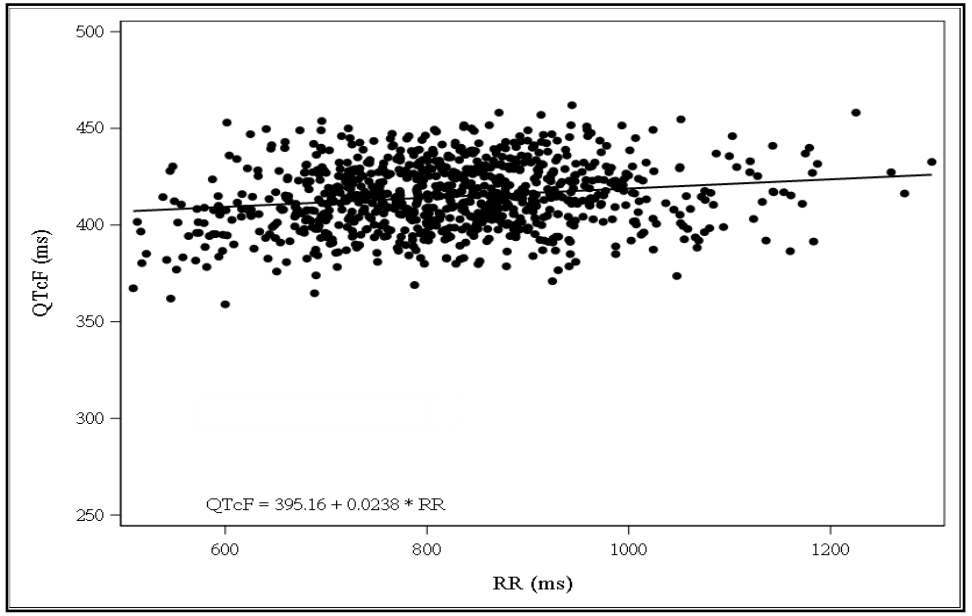
Significant	Not Significant	Default
• combination partner (combination 2 vs. combination 1 vs. no combination) • population (eBC vs. aC)	• age group(< 40, ≥ 40 to < 65, ≥ 65) • sex (male, female) • race (Asian vs. non-Asian)	• log transformed concentration • centered baseline QTcF

Correction Methods:

Before modeling the PK-QTcF relationship, QT and QTcF at baseline were plotted against RR at baseline to assess the appropriateness of the **Fridericia correction**, also suggested in the **ICH E14 guidance**.



$$QTcF = QT / \sqrt[3]{RR}$$



There is no obvious correlation between QTcF and RR, and hence QTcF provided adequate correction for RR.

From SAP to SAS

As per the Statistical Analysis Plan (SAP):

The model is a linear mixed model with subject as a random effect and the mean function in the form of:

ΔQTcF = log(concentration/median concentration + 1) + (baseline QTcF - median baseline QTcF) + combination + population + combination* log(concentration/median concentration + 1)

Implementation using SAS:

PROC MIXED was specifically designed to fit mixed effect models

```
proc mixed data= pceg0;
   class usubjid popcat(ref="Early breast cancer") combo(ref = "NSAI (letrozole or anastrozole)");
   model chg = laval sbase combo popcat combo*laval/ solution residual alpha=0.05 alphap = 0.1 outpm = estMu;
   random usubjid;
   ods output solutionF = est_ds;
 run;
```

- Method = default (REML)
- DDFM = default (CONTAIN)

Results from Final PK-QT model

From code and results to actionable insights

Parameter	Estimate (95% CI)	Standard error	Pr > |t|
Intercept	1.76 (-0.70, 4.21)	1.25	0.160
.....	.....	.....	.....
Combination 1	-0.60 (-2.86, 1.66)	1.15	0.603
Combination 2	.		
No combination	-7.84 (-10.25, -5.42)	1.23	<.001
Early breast cancer	.		
Non-early breast cancer	5.37 (2.85, 7.90)	1.29	<.001

- Combination partners, and populations significantly influenced ΔQTcF. The final PK-QT model showed a lower mean QTcF increase in early breast cancer patients compared to advanced patients

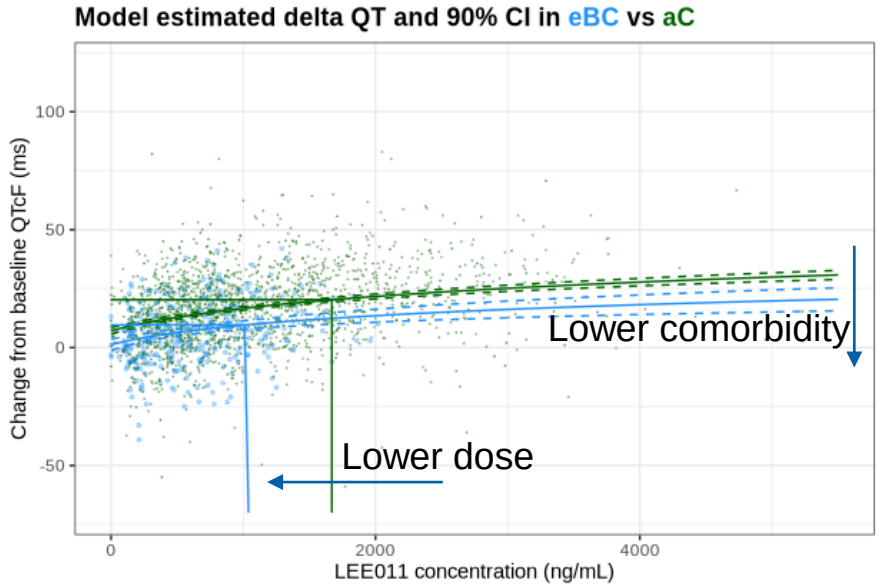
Concentration level	Concentration (ng/mL)	Baseline QTcF (ms)	Estimated mean QTcF change from baseline (ms) (90% CI)
Early breast cancer patients			
400 mg Cmax combo		419.0	
Geo-mean	1010		10.0 (8.02, 11.91)
Metastatic breast cancer patients			
600 mg Cmax combo		411.0	
Geo-mean	1670		20.7 (19.76, 21.63)

- The lower dose in early/adjuvant settings, and combined with lower disease burden, is expected to have fewer dose-dependent cardiac toxicities

Reinforce the Robustness of PK-QT modelling in Early Breast Cancer

- Aligned with approved USPI for mBC (metastatic breast cancer) 20.7 ms for mBC in new model vs. 22.0 ms in USPI

- Aligned with observed QTcF safety data from eBC (early breast cancer) 10.0ms in new model vs. 9.4ms at 2 hours / 11.4ms at 4 hours post-dose in eBC



- The updated model's mean ΔQTcF estimates demonstrate model consistency with both historical and current data

USPI : United States Prescribing Information

1 Garnett C, et al. Scientific white paper on concentration-QTc modeling. J Pharmacokinet Pharmacodyn. 2018

Takeaway Messages

- **Cross functional collaboration and discussion with subject matter experts**
- **Early breast cancer patients enable more favorable label claims for safety compared to metastatic breast cancer patients**
- **Data-driven methods identified a more tolerable QT safety profile in early breast cancer, supporting drug approval and label extension**

PK-QT model results included in the USPI, TGA, Swissmedic label

USPI : United States Prescribing Information TGA: Therapeutic Goods Administration

Thank you

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