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Applied Translational Medicine

# Celerion's Symposia Series: Bridging the Gap from Phase I to Proof-of-Concept

San Francisco, CA

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Applied Translational Medicine

# Are You Ready for the Changing Cardiac Safety Regulations?

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Senior Director, Cardiac Safety Services

# Questions?

- Do I have to do a Thorough QT (TQT) study for my compound?
- If I have a TQT to conduct, what does that look like?
- If I don't have a TQT to conduct, what does that look like?
- What approach to evaluating cardiac safety is the most cost effective for my compound?
- What approach does Celerion advocate for evaluating cardiac safety?
- Are ICHE14 and S7B changing?
- What other cardiac safety related regulatory changes are coming?



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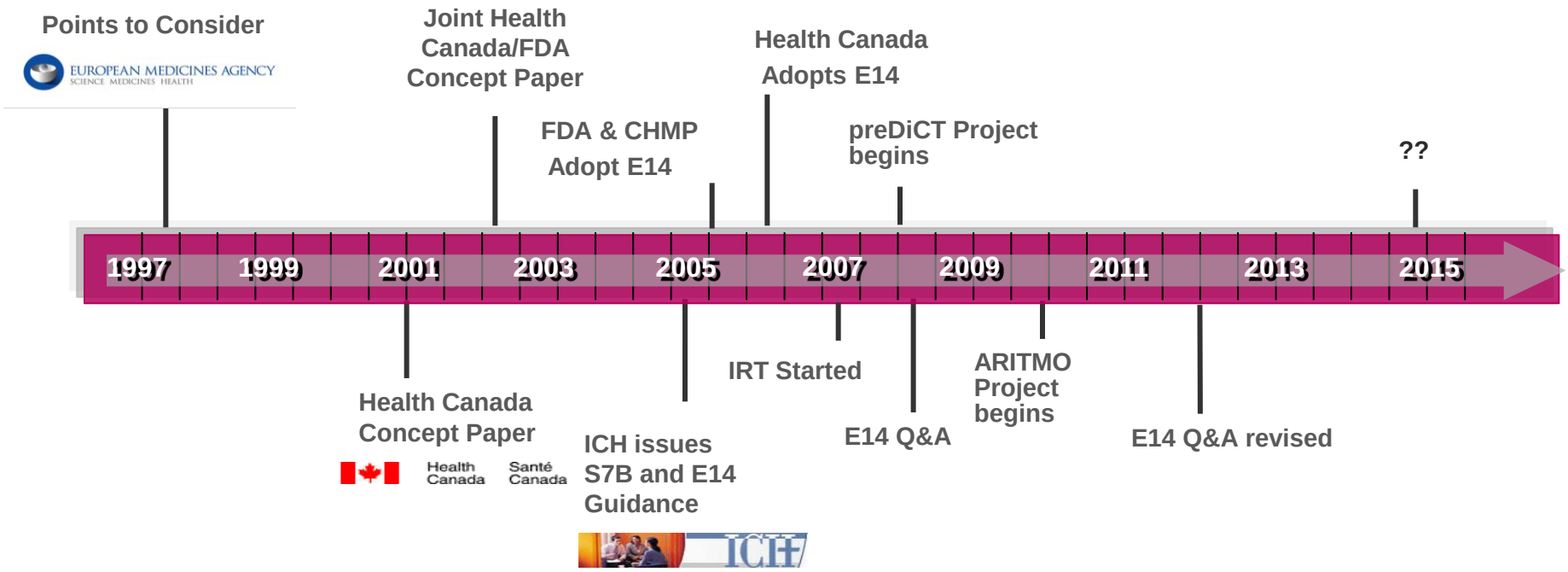
# The Evolution of ICH E14



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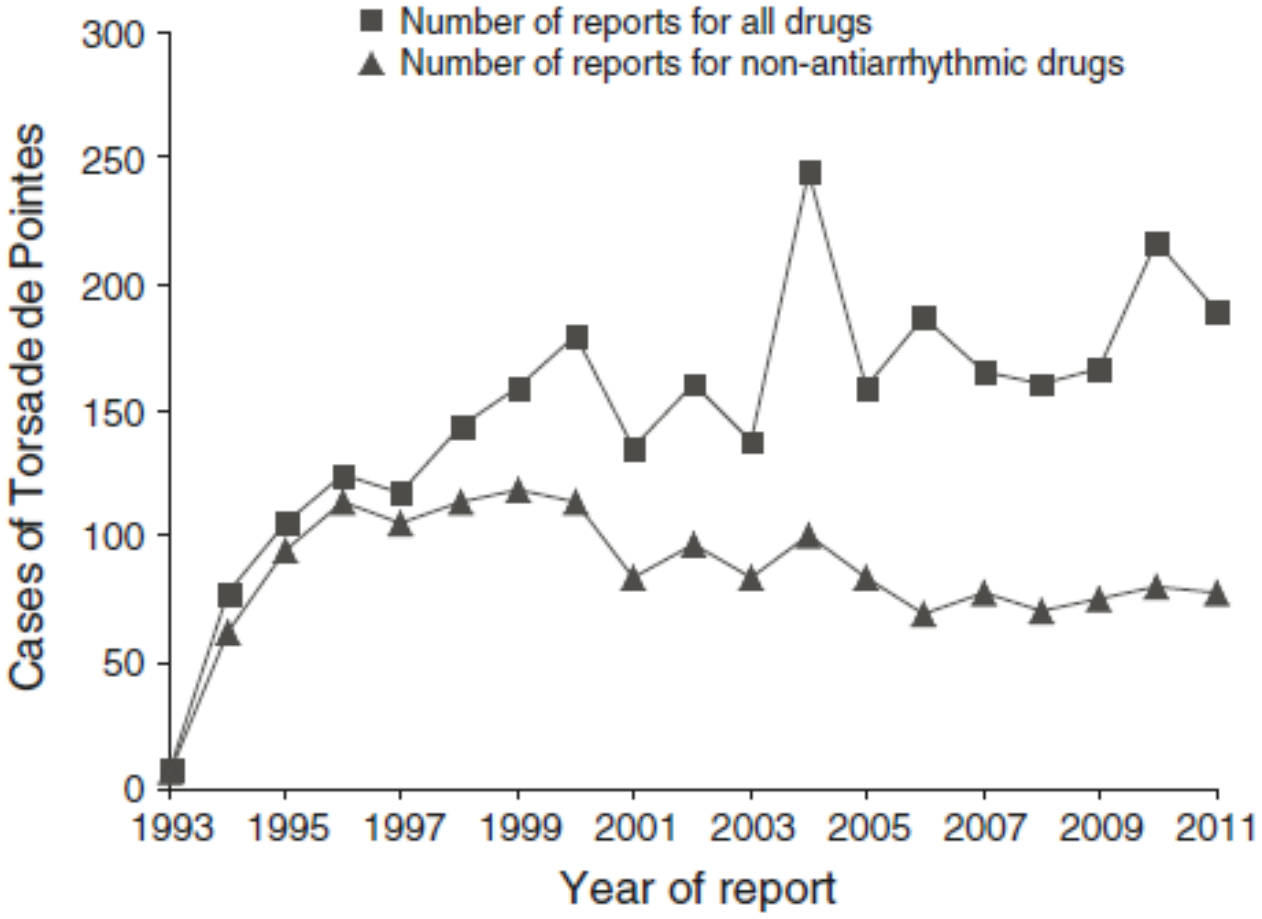
# Current Debate

- **Does the TQT truly predict a compound's proarrhythmia potential?**
- There have been tremendous advancements in both pre-clinical and early clinical monitoring of arrhythmia potential since 2005. How does this:
  - Change proarrhythmia evaluation pre-clinically and/or clinically?
  - Change the need for a TQT?
- What has been the impact of ICH E14 and S7B on drug development? Is it worth the cost?
- What does a positive TQT really mean?

# Cases of Torsades de Pointes




Annual number of spontaneous reports of Torsade de Pointes received by the US FDA Adverse Event Reporting System, Stockbridge et al. Drug Safety 2013;36:167-182



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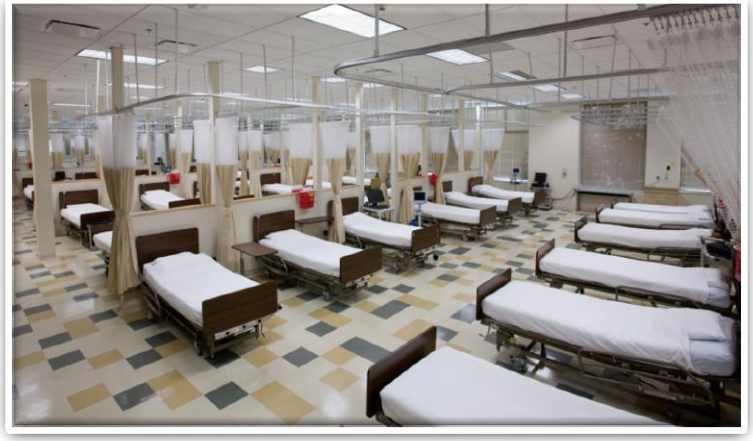
# Pre-clinical: CiPA

- Comprehensive In vitro Proarrhythmia Assay (CiPA) Initiative
  - Ion Channels
  - Stem Cell Myocytes
  - In Silico modeling
- Targeting S7B update in 2016

# Early Clinical Cardiac Safety Evaluation

- Add intense ECG monitoring to early Single Ascending Dose (SAD) and Multi Ascending Dose (MAD) studies.
  - Pool data from different dose levels to evaluate concentration response relationship
  - Typically during SAD and MAD studies the highest doses are given allowing for better concentration response modeling





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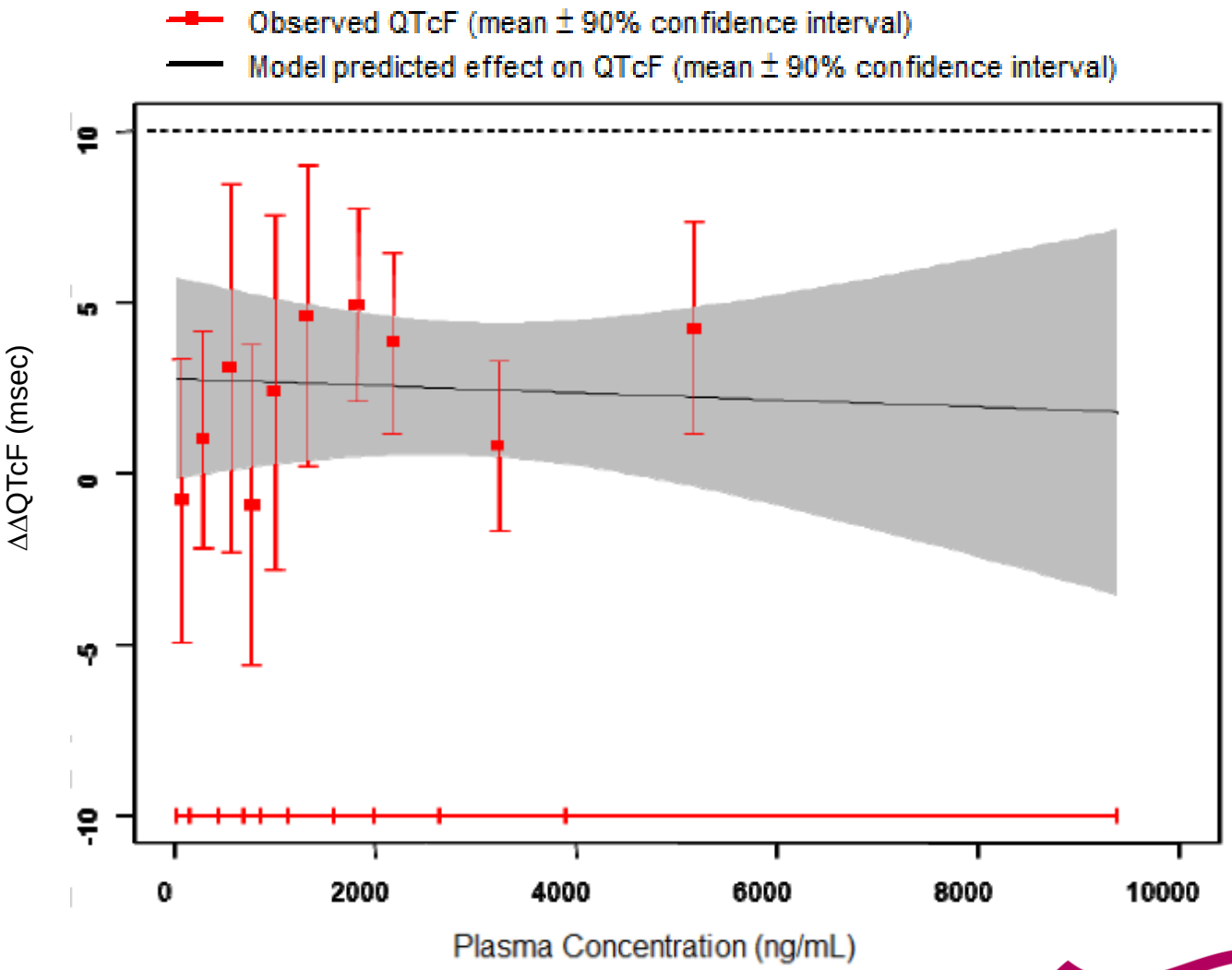
# Early Clinical ECG monitoring






Borje Darpo and Christine Garnett. "Early QT assessment–how can our confidence in the data be improved?." British journal of clinical pharmacology (2012).

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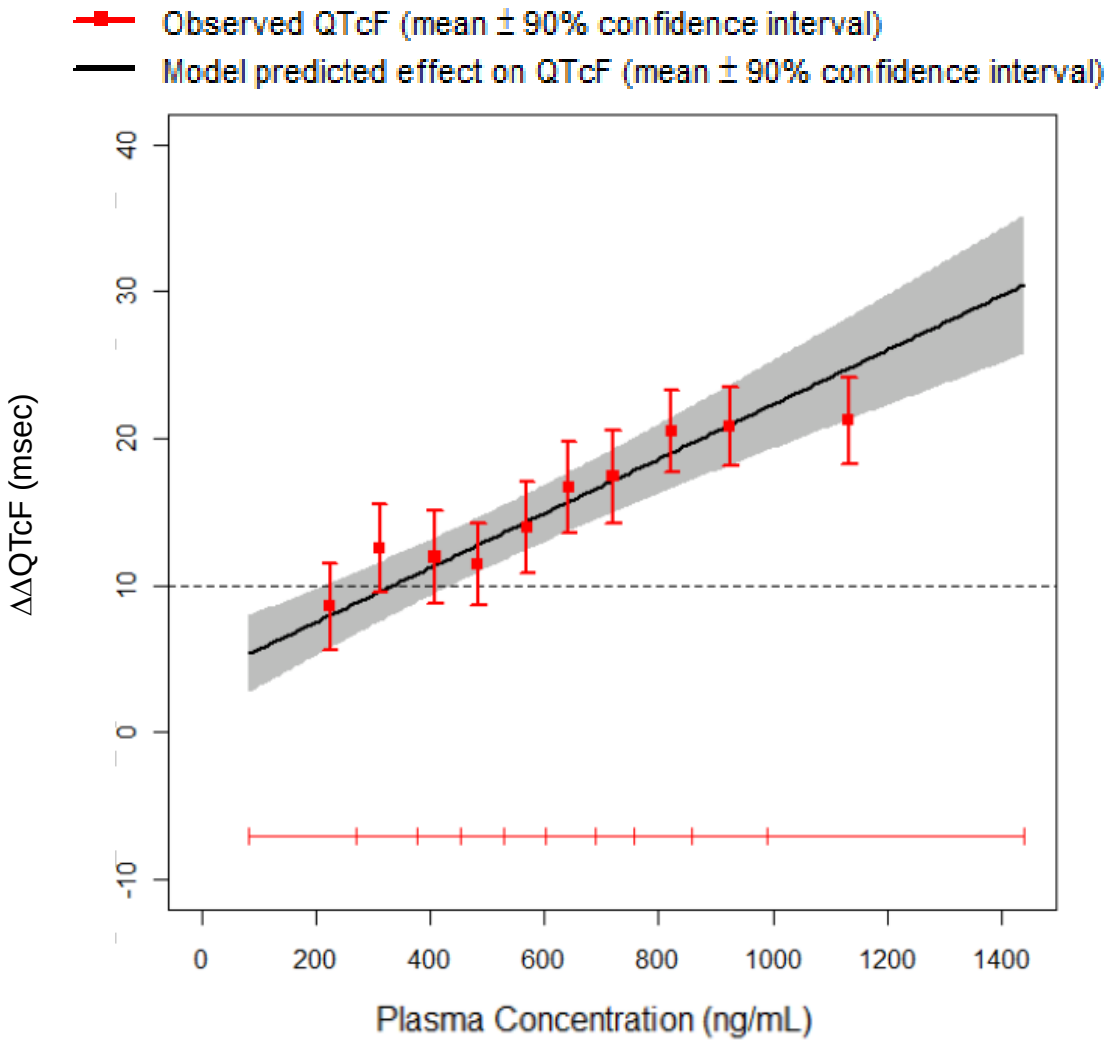
# Early Clinical ECG monitoring



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# Early Clinical Cardiac Safety Testing

- Consortium for Innovation and Quality in Pharmaceutical Development/Cardiac Safety Research Consortium (IQ/CSRC)
  - Looking at five marketed drugs with a positive QT signal - one with a negative signal
    - Ondansetron, dofetilide, quinine, dolasetron, moxifloxacin
    - Levocetirizine
  - SAD-like study
- QT assessment criteria: The upper bound of the two-sided 90% confidence interval (CI) of the projected placebo-corrected delta QTcF is above 10 ms at the observed peak plasma level of the drug
- Positive control?
- Concern over potential false negatives (regulators) and false positives (sponsor)

# Early Cardiac Safety Evaluation

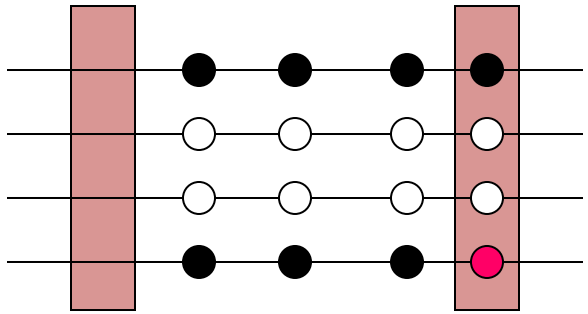
- ECG data collection
  - Is data collection the same as a TQT?
  - Data acquisition and protocol requirements are very similar to TQT
  - Time-points
    - Do we really need 10-12 time-points? Does this increase risk of false positive?
    - Typically response is seen around Tmax and 3-4 subsequent time-points

# Early Cardiac Safety Evaluation

- What are the cost implications of adding extensive cardiac safety monitoring to SAD and MAD studies?
- If 6 dose levels analyzed estimated ~ $125k
  - Do all ECGs have to be analyzed?
  - Have the clinic assume 10-12 time-points but only analyze data from 5-6 time-points initially
  - If only top 3 doses are analyzed, additional ECG monitoring estimated ~ $95k

# What does the TQT look like now?

## Traditional Design




- Placebo
- Study drug
- Moxifloxacin dosing
- Intense ECG collection



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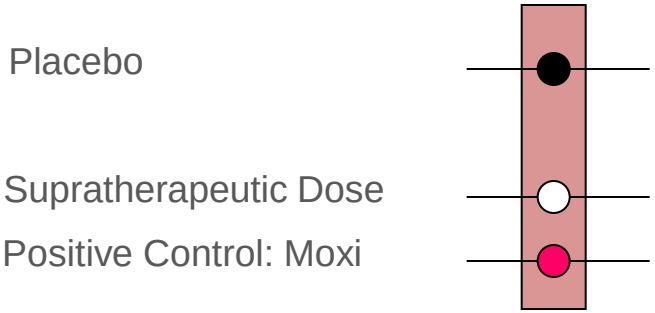
# What does the TQT look like now?

## Crossover Design

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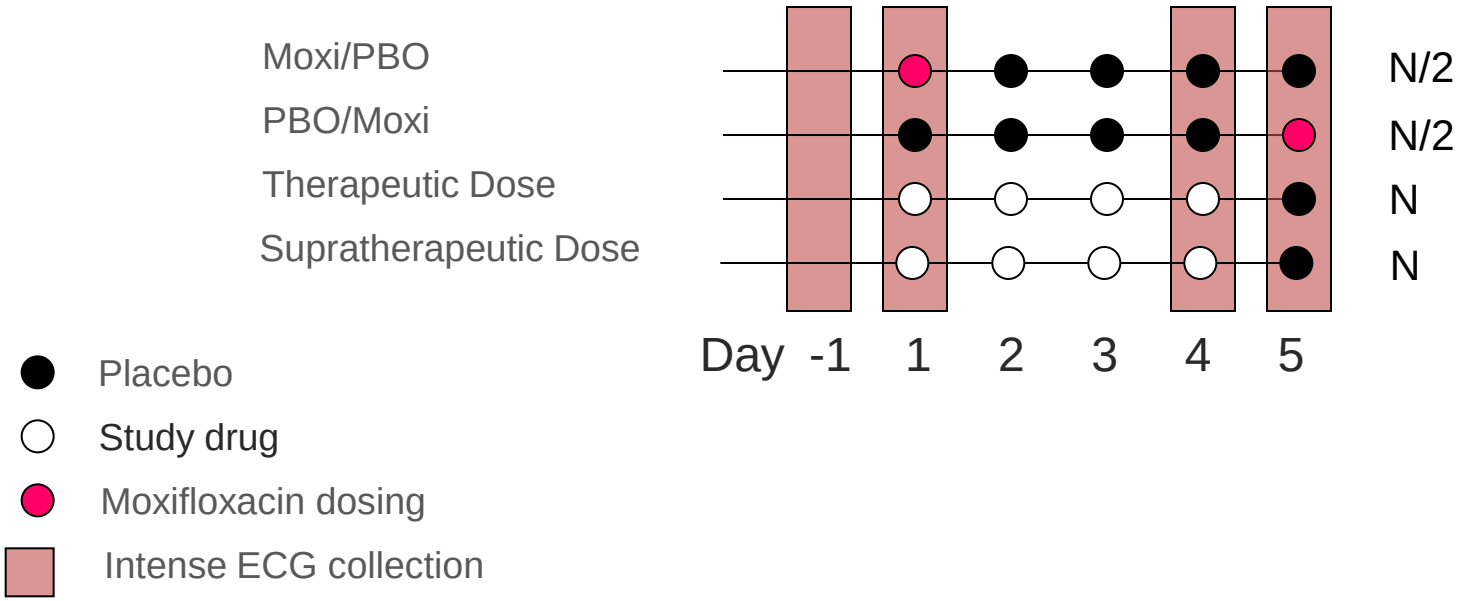
# What does the TQT look like now?

## Parallel with Nested Crossover Design




DDM=average of Moxi/PBO and PBO/Moxi

Moxi/PBO=[$QTc_M(1)$-$QTc_{PB}$ (5)]-[$QTc_{PB}(4)$-$QTc_{PB}$ (-1)]

PBO/Moxi=[$QTc_M(5)$-$QTc_{PB}$ (1)]-[$QTc_{PB}(-1)$-$QTc_{PB}$ (4)]



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# Questions?