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Applied Translational Medicine

Preparing for Changing Cardiac Safety Regulations

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Questions?

- Do I still have to assess proarrhythmic potential of my compound in a Thorough QT (TQT) study?
- 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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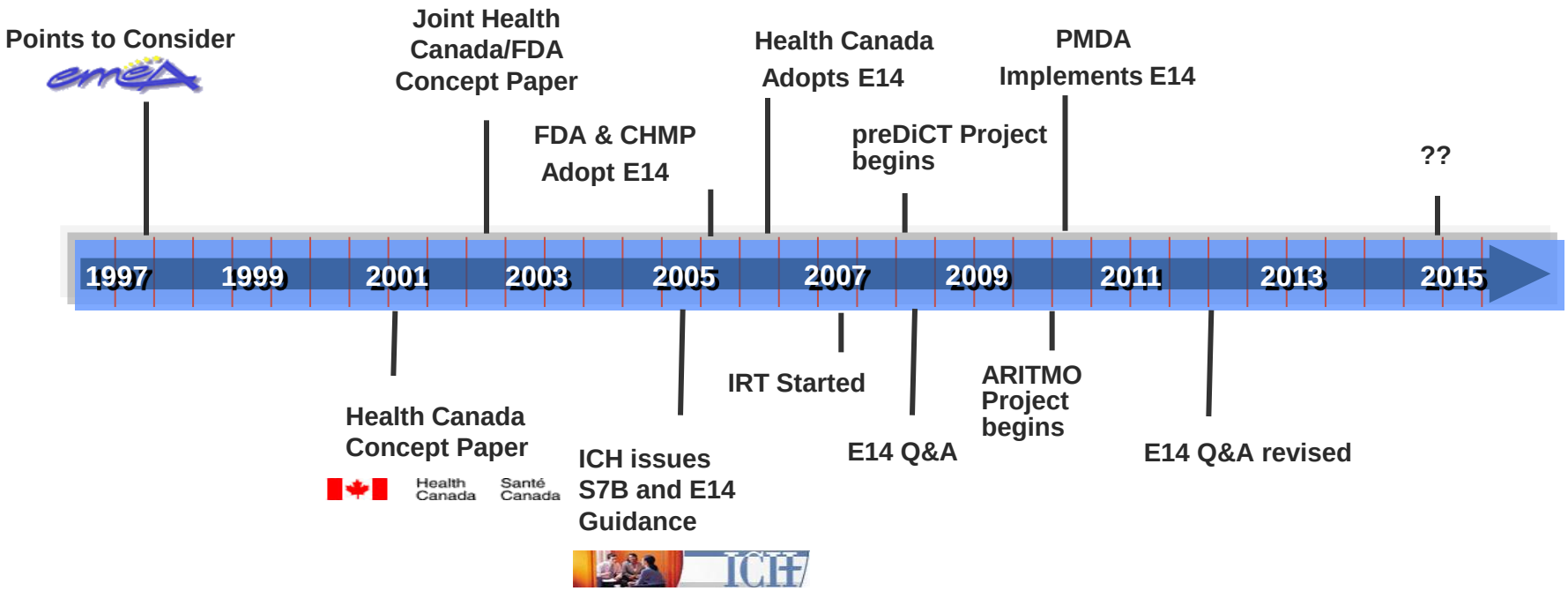
The Evolution of ICH E14



International Conference on Harmonisation E14 Guidance (ICH E14) describes the requirements for a Thorough QT (TQT) study to evaluate proarrhythmic potential of compounds.

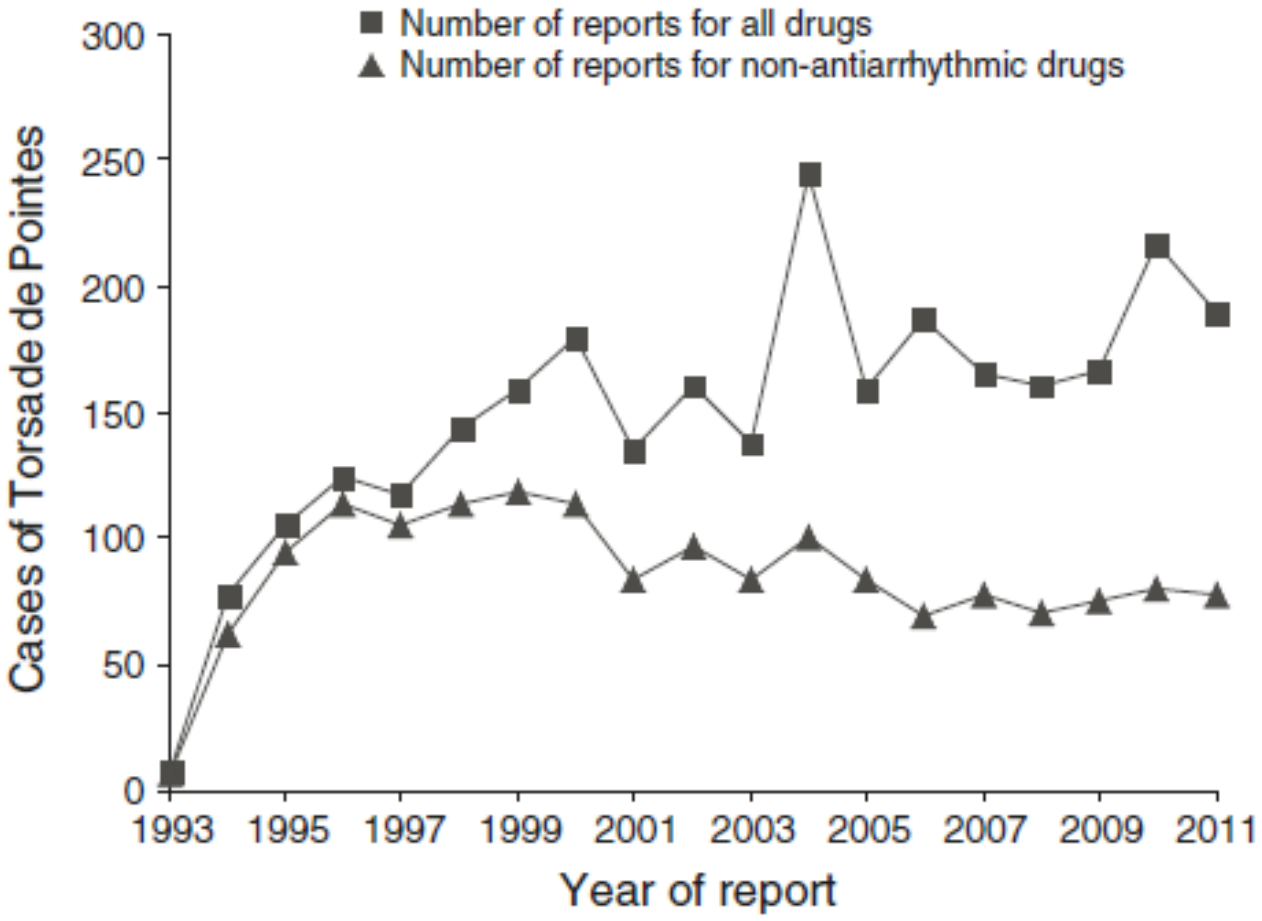
ICH S7B describes preclinical cardiac safety testing requirements for new compounds.

FDA Interdisciplinary Review Team (IRT)

Current Discussion

- **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 how we evaluate proarrhythmia potential?
  - Change proarrhythmia evaluation pre-clinically 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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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 how we evaluate proarrhythmia potential?
  - Change proarrhythmia evaluation pre-clinically 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?
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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

- What has been the impact of ICH E14 and S7B on drug development? Is it worth the cost?

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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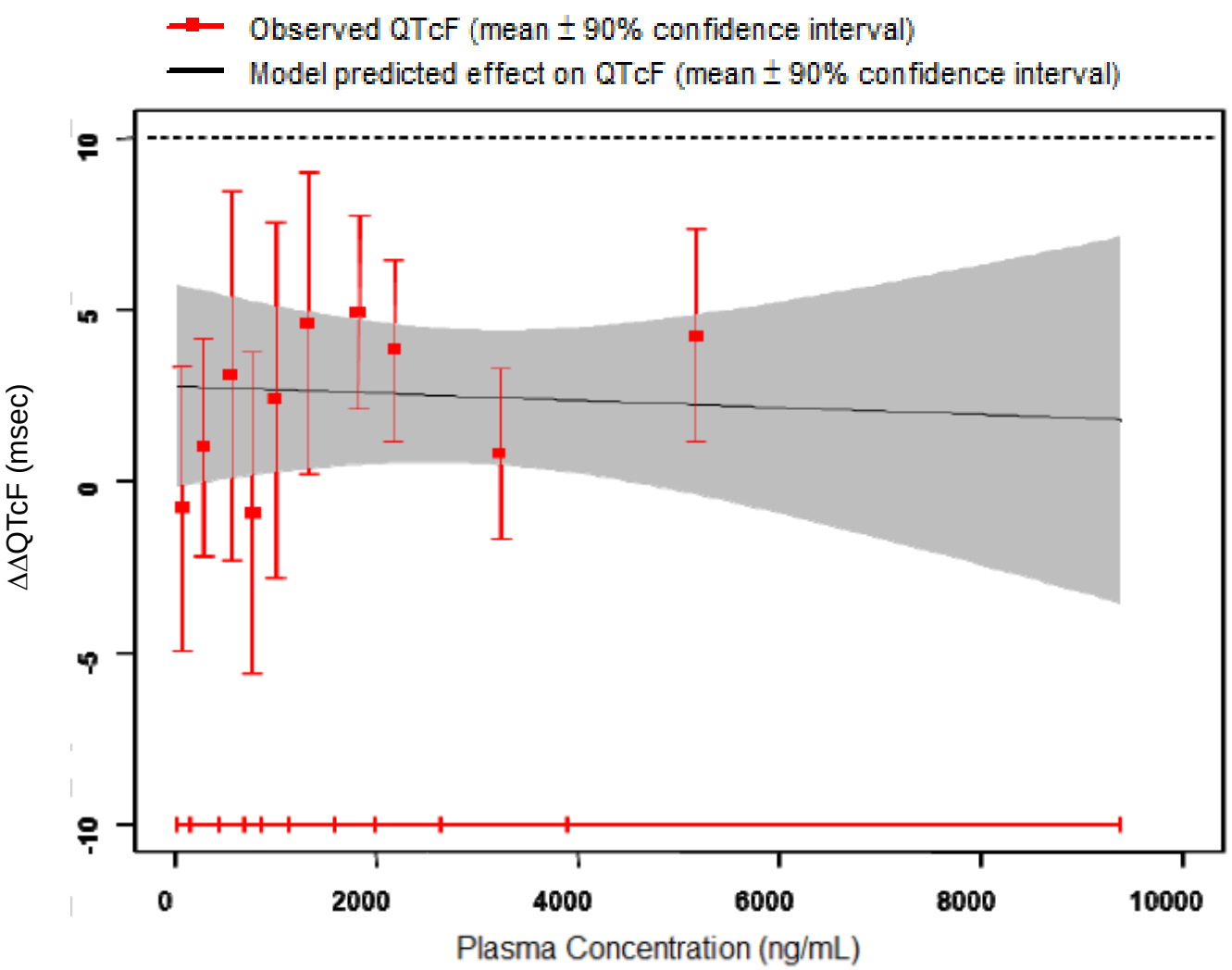
Early Clinical Cardiac Safety Testing

- 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?

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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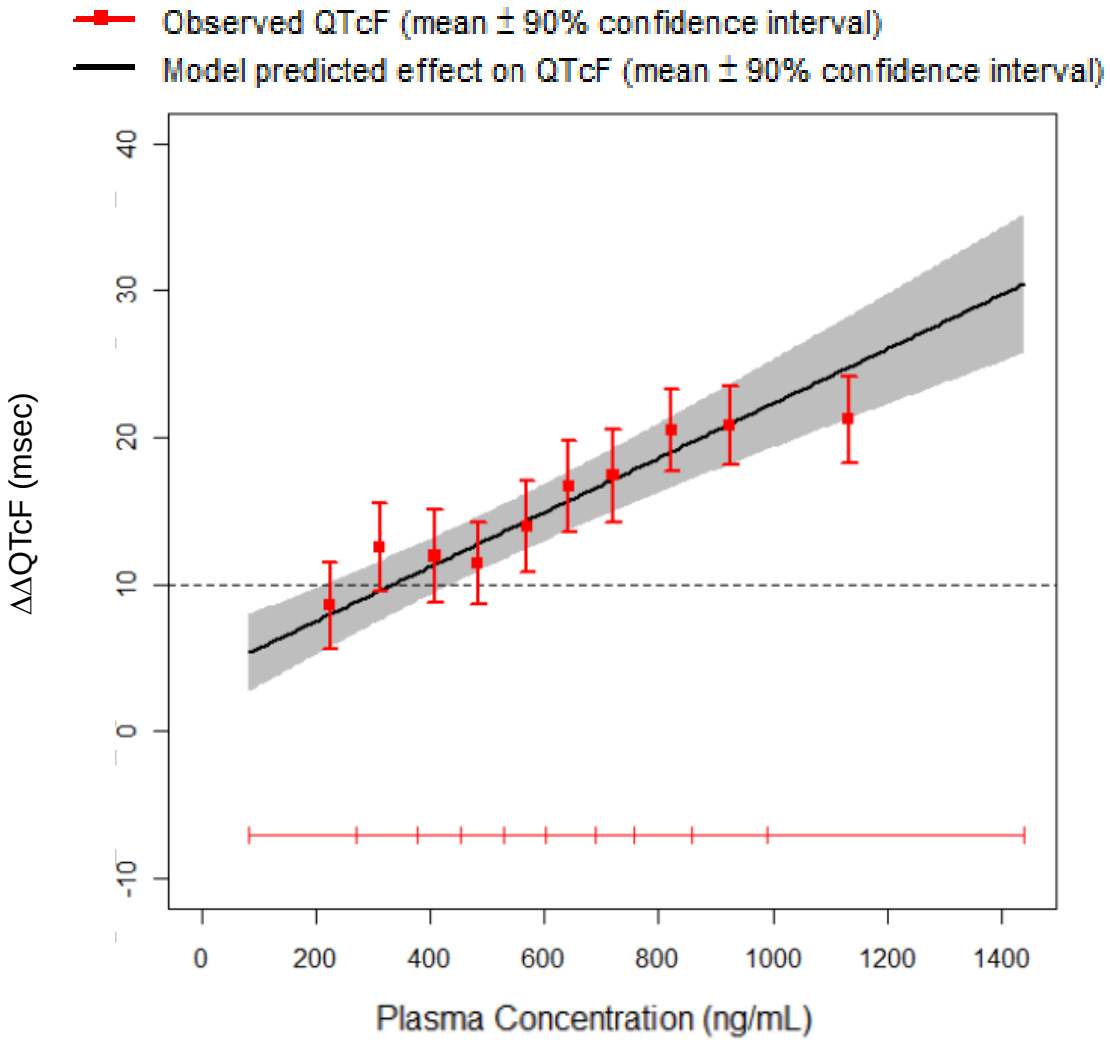
Early Clinical ECG monitoring



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Early 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

What does the TQT look like now?

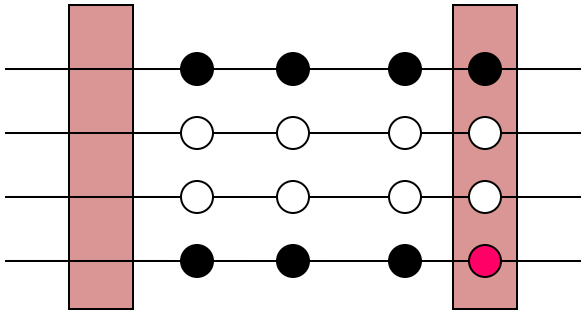
Traditional Design

Placebo

Therapeutic Dose

Supratherapeutic Dose

Positive Control: Moxi



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

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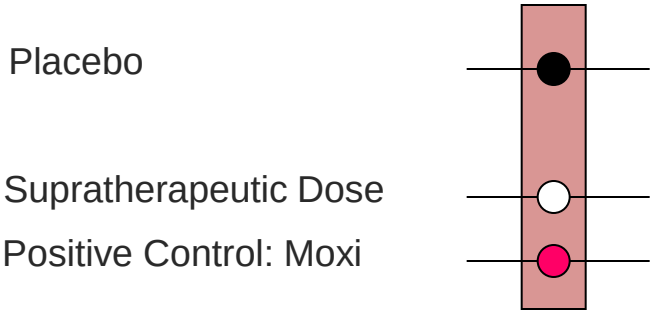
What does the TQT look like now?

Crossover Design



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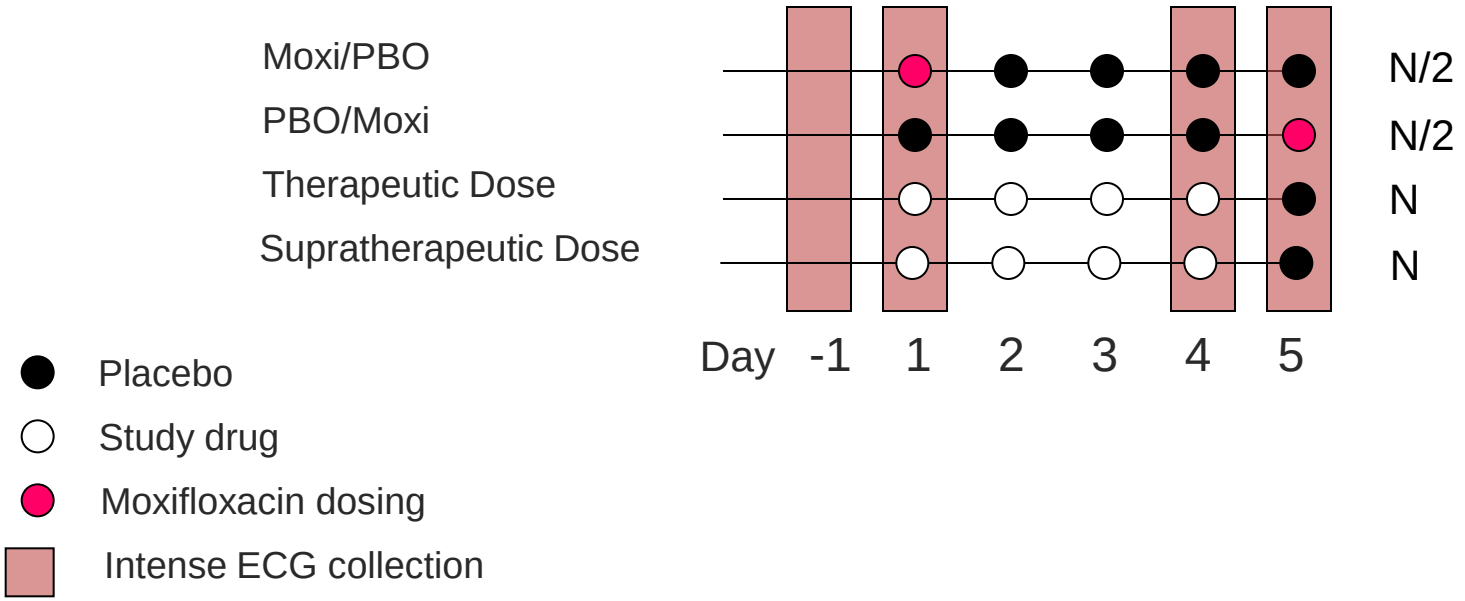
What does the TQT look like now?

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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Q&A