celerion

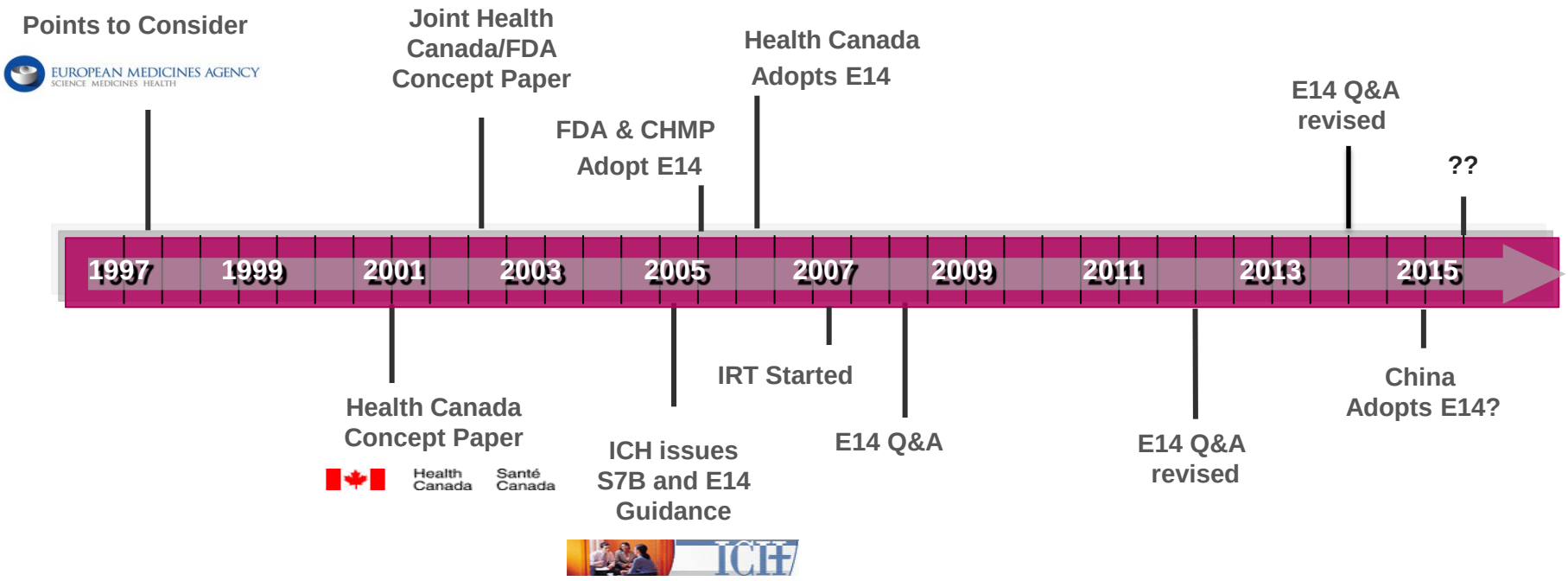
Applied Translational Medicine

Driving Efficiency in Early Cardiac Safety Evaluation Using Highly Automated Systems vs. a Standard Semi-Automated Method

Joy Olbertz PharmD, PhD

Senior Director, Cardiac Safety Services

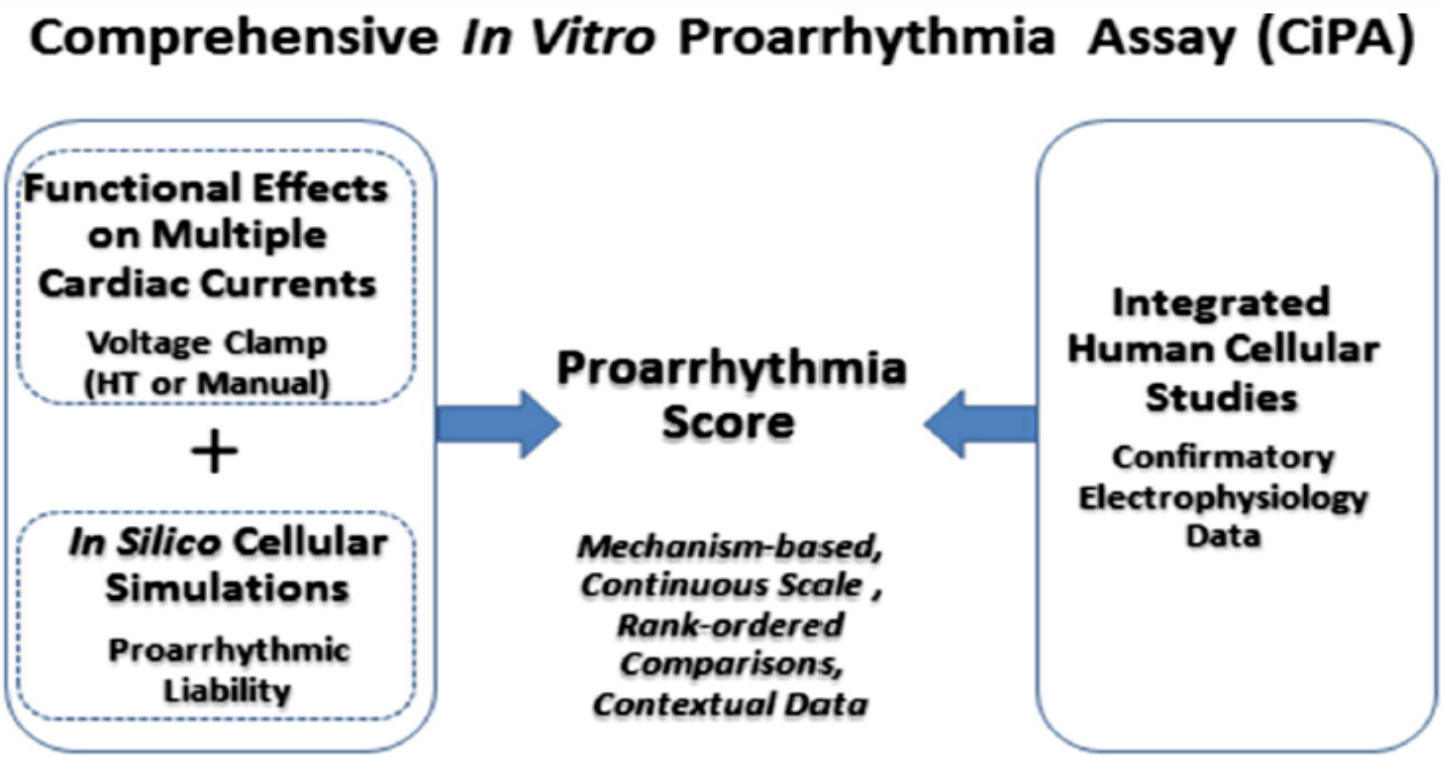
The evolution of ICH E14



celerion

CiPA: Shifting Pre-clinical Paradigm

WILL NOT REPLACE CLINIC ECG EVALUATION



Philip T. Sager , Gary Gintant , J. Rick Turner , Syril Pettit , Norman Stockbridge. **Rechanneling the cardiac proarrhythmia safety paradigm: A meeting report from the Cardiac Safety Research Consortium.** American Heart Journal null 2013 null. http://dx.doi.org/10.1016/j.ahj.2013.11.004

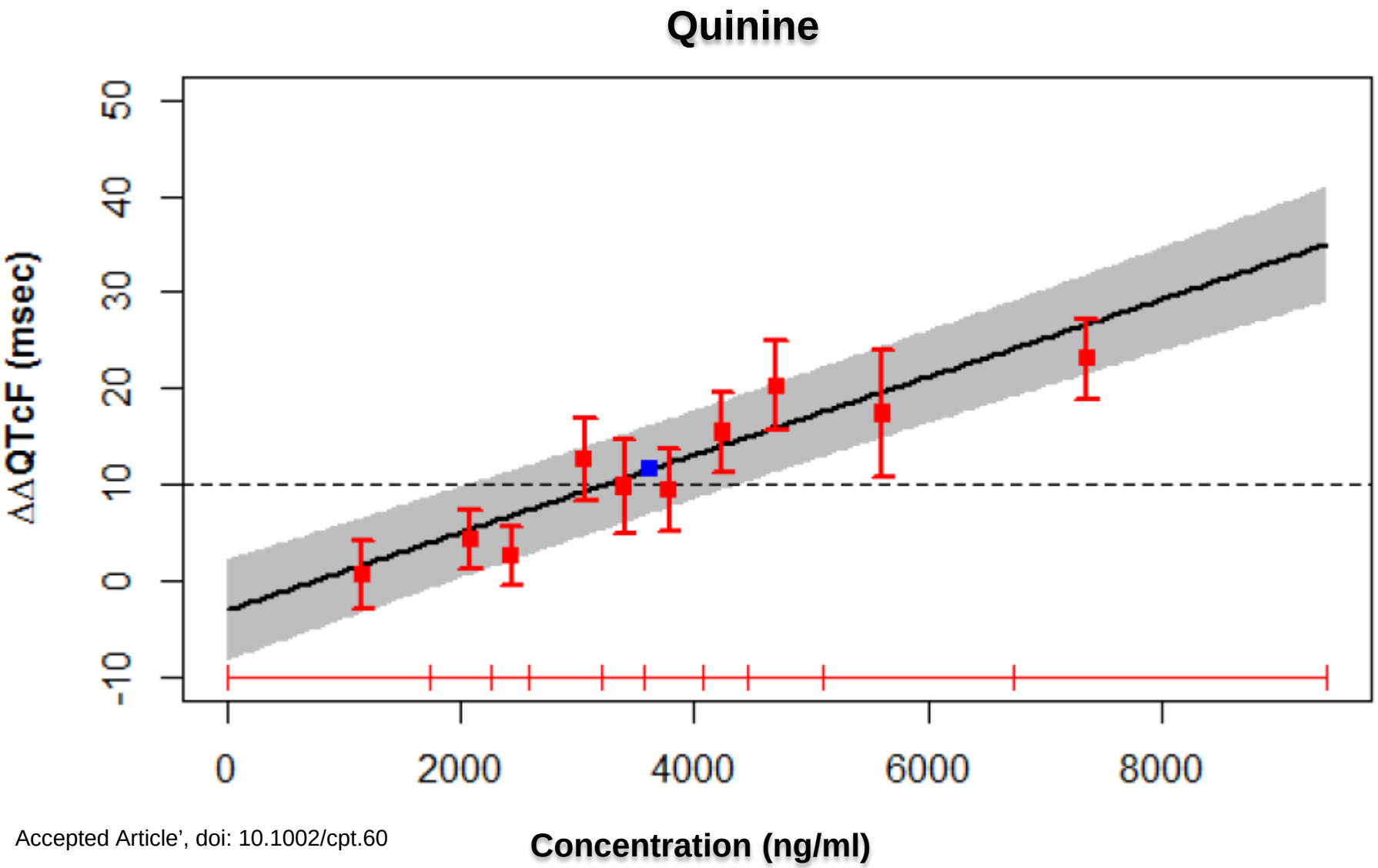
IQ-CSRC Study

- Three period, randomized, placebo-controlled study
- 20 healthy subjects
- Incomplete block design used
  - Each study drug administered to nine subjects and placebo to 6 subjects
- Exposure response analysis performed to evaluate relationship between plasma concentration and placebo corrected, change-from-baseline QTc ($\Delta\Delta$QTc)
- "QT positive" if the UB of the 2-sided 90% CI of the predicted placebo-corrected ΔQTcF is above 10 ms at the observed geometric mean Cmax of the lower dose of the studied drugs

Darpo, Borje, et al. *Annals of Noninvasive Electrocardiology* 19.1 (2014): 70-81.

celerion

IQ-CSRC Study



Accepted Article', doi: 10.1002/cpt.60

Example Single Ascending Dose Study (SAD)

- 5-6 cohorts, 8 subjects per cohort
- Single 24hr Holter monitoring session
  - ECG Extractions
    - 3 triplicate baseline timepoints
    - 6-9 triplicate post-dose timepoints
      - Proactively plan for extended supine periods

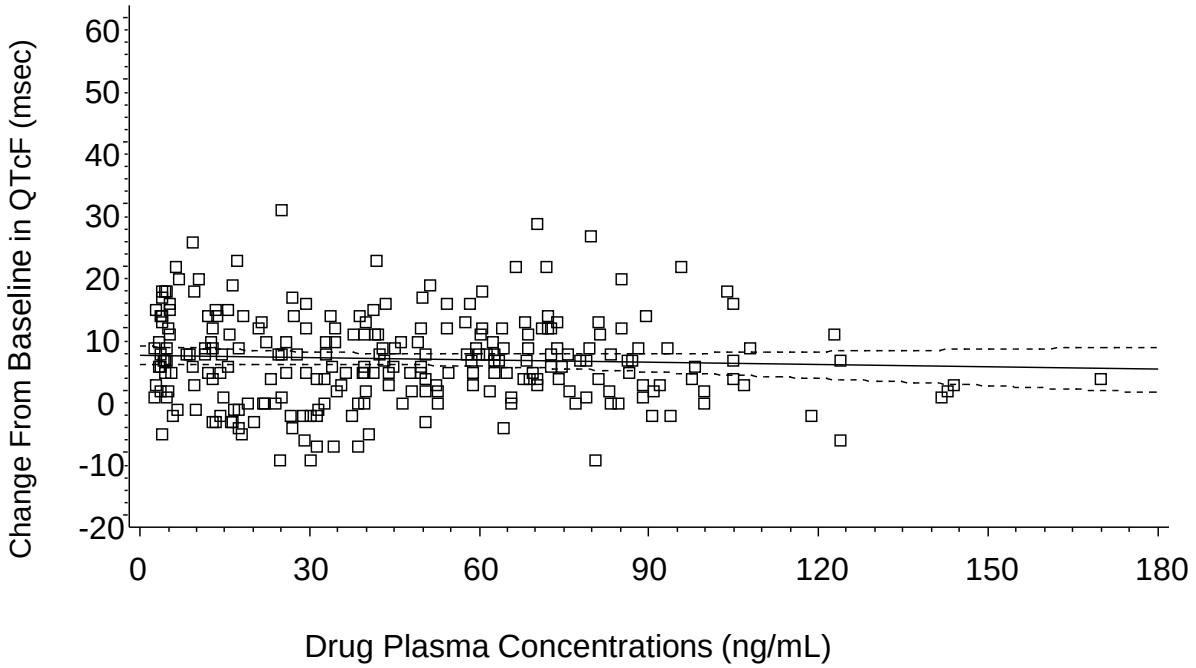
celerion

Case Study: Drug-Drug Interaction

- Drug-Drug Interaction study (N=16)
  - Period 1: Single dose study drug
  - Period 2: Dosing with inhibitor
  - Period 3: Inhibitor + study drug
- ECG extractions: 3 predose timepoints + 7 postdose timepoints in Period 1, 2 & 3

celerion

Case Study #2: Drug-Drug Interaction



Slope = -0.01264 (95% CI: -0.039488, 0.014209)
Intercept= 5.60 (95% CI: 4.07, 7.12)
R^2= 0.0034

celerion

Sounds Promising but…

- When I submit my TQT waiver, what will be required for my preclinical package?
- If there is no positive control in the early clinical study how do I prove it was sensitive enough to identify QTc prolongation, if present?
- How high does the SAD or MAD dose need to be? How does this impact the potential success of my TQT waiver?
- I want to add a patient cohort to the end of my SAD/MAD study. Should I include intense ECG monitoring?
- I am uncertain that early TQT like data collection is the right fit for my program, do I have to do this?

Questions

Driving Efficiency in Early Cardiac Safety Evaluation Using Highly Automated Systems vs. a Standard Semi-Automated Method

Matt Anderson, Ph.D.

Director, Clinical Pharmacology and Experimental Therapeutics

Merck & Co., Inc.

Rationale for Assessment of Vendor HA Methods

- ICH guidance requires a thorough QTc study for all programs by submission, usually conducted at or near entry to Phase 3
- These studies are expensive
- The extraction of ECG intervals from ECG waveforms is tedious and time consuming
- Automated methods for performing this task are known, accessible, and accepted by the FDA

What is Semi-Automated vs. Automated QT Analysis?

SA	HA
Automated Aspect: - Initial, rough QT interval identification **Manual Aspect (major):** - Interval overread and correction by a cardiologist - T- and U-wave analysis	**Automated Aspects:** - Identify periods of minimal QT-RR variability/ noise within time points for ECG selection - QC all beats and perform automated measurements in all "good" beats - Flag "problem" beats **Manual Aspect (minor):** - Adjudicate "problem" beats - Final QC by Cardiologist - T- and U-wave analysis
>45 days to obtain data	48 hours to obtain data
Usually 5 repeated measurements	Flexible number of measurements

Objective of this Comparison

- Automation suggests the potential for data sets with reduced variability and consequently, greater power per subject vs. the SA method
- Can HA methodology improve upon SA methods?

Participants and Methods

- **Five vendors participated, using three algorithms**
- **Vendors were supplied raw data from a study previously analyzed by SA methods**

- **This analysis assessed**
  - ***The scientific validity of the vendor algorithm (alignment with prior SA analysis)***
  - ***The variability of key ECG parameter intervals***
  - ***The overall rank order of vendor performance at these tasks as judged by Clinical Utility Index***

Data Set Analyzed

- Vendors analyzed allocation numbers specified by Merck, for all treatment periods
  - Vendors were blinded to treatments
- All vendors returned > 99% of the analogous SA-extracted Pbo and Moxi data
  - Differences likely reflect the inherent conservatism of each vendor's validation procedures
- Those interval estimates for which data was available from all vendors were used for the final analysis
  - HOWEVER: inclusion of these deleted data points does not significantly alter the conclusions

Assessment Methods

To assess: alignment between SA-derived and HA-derived analyses

- Baseline-adjusted data (e.g., ΔQTcf) used as primary, for all assessments
  - Concordance correlation coefficient (CCC) as tool for comparisons

To assess variability in QTcF, PR, RR, and QRS intervals

- By time analysis, a linear mixed effect model with treatment and period as fixed effects, an unstructured covariance was used to obtain the variance in baseline adjusted QTcf, PR, RR, and QRS intervals for each treatment
- Averaged variance across time points was used for each treatment

A Clinical Utility Index (CUI) weighting these features was used to rank vendors

RESULTS

(SLIDES REDACTED)

Conclusions

- **All automated QTc analysis yield results aligned to the existing standard of semi-automated analysis**
  - **Systematic differences in the absolute value of raw data do not substantially alter outcome across all effect sizes**
    - **Unlikely to have a false positive result for small drug effects**
    - **Unlikely to have a false negative result for marginal moxi effects**
- **SA analysis is analytically competitive with HA analysis**
  - **HA methodology does not necessarily reduce enrollment needs**
  - **However, timelines are longer with SA**
- **Vendor rankings identified by CUI were based on small differences**