Novel ECG Biomarkers – Practical Implications, Workflow, and Open Source Code

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Disclosures

• I am a full time employee of ERT
• ERT provides ECG core lab services and other solutions to the pharmaceutical industry
• I provide consulting services to the pharmaceutical industry
• No other disclosures
Why Novel ECG Biomarkers?

• Real concern – avoiding drug induced TdP
• CiPA : ex-vivo evaluation of risk of drug induced TdP
• Clinical ECGs still needed – but alternative biomarkers to complement (rather than replace) QTc are desirable
  – QTc: known shortcomings as a biomarker
  – Novel biomarker use to help confirm/contradict concordance between clinical and preclinical data
  – Multichannel block a main concern, but not the only one

TdP is only one of many cardiac safety issues
Use Case for Novel Biomarkers?

• CiPA assessment low risk:
  • Phase I QTc UCI < 10 ms (very low risk)
  • Phase I QTc UCI ≥ 10 ms: novel ECG biomarkers useful

• CiPA assessment intermediate or high TdP risk:
  • Phase I QTc UCI < 10 ms (reexamine preclinical and clinical data)
  • Phase I QTc UCI ≥ 10 ms (agreement that risk is high)

• Threshold effect – could help understand magnitude of risk
• May help inform go/no go decisions

Speculation: needed only for one scenario as above
Implementation – Operational Points

• Generally no need to assess novel biomarkers in real time
  – Exception could be for a high risk compound, in order to inform dose escalation decisions
• Easiest to run as a batch after study completion
• Digital ECGs only
• **Methodology will be absolutely critical**
Ion channels and ECG: Theory

Courtesy of Jose Vicente
J-Tpeak and Tpeak-Tend: Some Issues

• Definition of J point – less straightforward than QRS onset
• Definition of Tpeak:
  – Visual (point at which amplitude is greatest)
  – Algorithmic
  – What about notched, bifid or biphasic T waves?
• Still need to measure QRS onset and T wave offset
  – QRS onset: relatively simple
  – T wave offset: no universal consensus
• Standardization of HR correction method
J-Tpeak and Tpeak-Tend: Many Methods

- FDA method – open source code – uses vector magnitude lead
- GE QT Guard Plus – proprietary – uses vector magnitude lead
- Measurement in a single lead
- Measurement on a superimposed global median beat

Different methods will likely produce different results
Example: Single Lead Measurement

But – which lead?

Simply add caliper for Tpeak
Single Lead Measurement

10 ms difference between peak of T wave in V3 and V4
Measurement from Superimposed GMB

But - the peak of the T wave varies between leads

Simply add caliper for Tpeak
Superimposed GMB

20 ms difference between peak of T wave in different leads within the superimposed beat
Methods must be standardized!

- Unless methodology is standardized, high risk of flawed data submissions
- How to assess quality?
  - In TQT, positive control insures assay sensitivity
  - How will validity of J-Tpeak and Tpeak-Tend measurements be assessed?
- Best solution: agree on a standardized methodology for new biomarkers
- FDA will make their algorithms available as open source code
- To date, validation has been entirely based on the FDA methodologies
- Proposal: any alternative to FDA methodology should undergo equivalent validation before being accepted for regulatory submission
Concentration Dependence of Quinidine Ion Channel Effects

As concentration changes, relative contribution of inward/outward current block changes

Courtesy of Jose Vicente
Challenges for Core Labs

• Different core labs use different platforms for measurements
  – Some core labs use external proprietary software platforms which may not allow for any code changes
  – Pressure to adapt their methods (single lead or GMB) to perform JTpeak and Tpeak-end measurements in a nonstandard fashion?
  – If external manufacturer updates software, will it use the exact methods described by the FDA open source release?
  – Will platform updates be properly validated, regulatory compliant?
Challenges for Sponsors

• When to request novel ECG biomarker analysis?
• ECGs must be collected digitally – no retrospective analysis of paper ECGs
• Format of collected ECGs must be accepted by the core lab
• ECGs collected by a CRO without any core lab involvement may not be in correct format
• Sponsors must understand methodology issues in order to understand core lab capabilities
Challenges for Regulators

• Regulators will need to understand when novel biomarkers are useful, and when irrelevant
• Regulators must be able to confirm methodology used to measure J-Tpeak and Tpeak-Tend
• Will the ECG Warehouse be able to accept these additional caliper placements?
• Should data measured with alternate methods be rejected?
• Any concerns about wagging the dog? (FDA involved in the research and publication of the software)
Summary

- Some biomarkers (esp. J-Tpeak and Tpeak-Tend) can be measured with different methods
- Consensus required about what to measure, specific methods
- Validation and standardization of methods are necessary
- ECG Core Labs will need to modify methods to allow introduction of new measurements and properly validate
- Sponsors will need to choose when to use novel biomarkers
- Regulators need to be ready for novel biomarker data