Novel ECG Biomarkers Proposed for CiPA Early Phase Studies – ECG Core Lab Implementation

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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

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The Case for Novel ECG Biomarkers

- Real concern – avoiding drug induced TdP
- CiPA : examine basic mechanisms of drug induced proarrhythmia – repolarization changes due to effects on cardiac ion channels
- We still want to look at clinical data – will still measure QTc, but want alternative biomarkers to complement QTc in order to further examine the electrophysiologic effects of drugs (e.g., effects on late INa, Ica)
  - QTc has known shortcomings as a biomarker
  - Novel biomarker use to confirm/contradict concordance between clinical and preclinical data
  - Multichannel block one of main concerns, but not the only one

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Novel Biomarkers – When Do We Need Them?

- Assessments of cardiac safety in clinical trials still required:

  TdP is only one of many cardiac safety issues

- Will still collect ECGs in Phase I trials
  - Evaluate IDMs, ECG morphology/rhythm, PK-PD
  - If CiPA assessment LOW RISK and ECG data demonstrates no QTc effects – no need for novel biomarkers
  - If CiPA assessment and ECG data both "high risk" or are discordant (or perhaps equivocal):
    - *(recheck CiPA assessments and ECG data)*
    - Use novel ECG biomarkers to help understand

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Speculation

- CiPA assessment low risk:
  - Phase I QTc UCI < 10 ms: no need for novel ECG biomarkers
  - Phase I QTc UCI ≥ 10 ms: novel ECG biomarkers required
- CiPA assessment intermediate or high TdP risk:
  - Phase I QTc UCI < 10 ms: novel ECG biomarkers probably not useful; reexamine all data
  - Phase I QTc UCI ≥ 10 ms: novel ECG biomarkers - understand magnitude of risk
- Sponsors will decide when to request novel ECG biomarkers – not for every drug
- May also be valuable if data suggest threshold effect – understand magnitude of risk
- May help inform go/no go decisions

My guess – novel ECG biomarkers will be needed occasionally

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Implementation – Operational Points

- Generally no need to run in real time
  - Exception could be for a high risk compound, in order to inform dose escalation decisions
- Generally, will run as a batch after study completion
- Most methods appear to be automated:
  - Is human adjudication possible?
  - If so, is human adjudication desirable?

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Core Lab Implementation

- Difficulty of implementation depends on which specific biomarker chosen
- Some proposed biomarkers are proprietary (? widespread availability)
  - Quantitative T wave morphology analysis
  - Gaussian mesa function
  - ERD and LRD; αL and αR
- Some proposed biomarkers are not proprietary - but different methods of performing measurements are possible
  - J-Tpeak, Tpeak-Tend
    - FDA will provide open source code – how to implement?
    - Measurements can be performed with standard methods, but will the results be equivalent?
    - Is there a need to use a single agreed-upon method?

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J-Tpeak and Tpeak-Tend: Many Methods

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

Is there any reason to think that the results will be the same?

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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?
- Did we actually ever agree on how to measure the end of the T wave?
- Metrics for assessing these new biomarkers?
- Some core labs may be unable to add certain biomarkers

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Problems 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
  - Such labs might feel pressure to adapt their methods to perform measurements in a nonstandard fashion
  - Even if their software is updated by manufacturer, will it use the exact methods described by the FDA open source release?
  - Will platform updates be properly validated, regulatory compliant?

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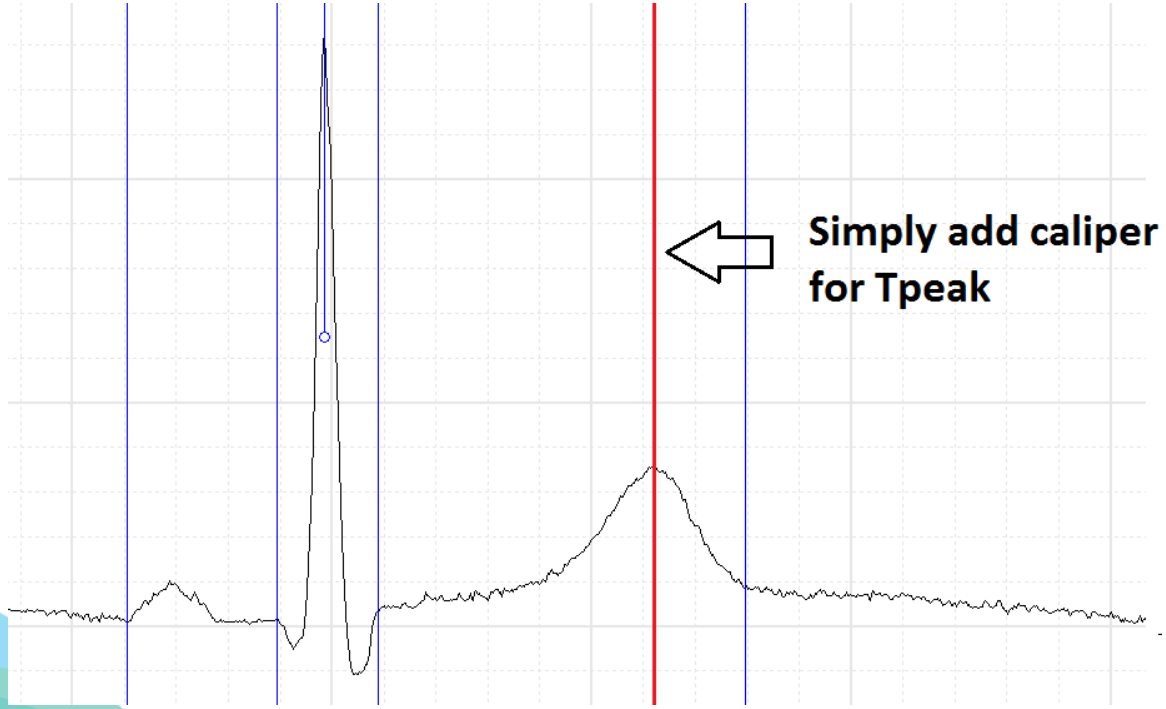
Example: Single Lead Measurement



But – which lead?

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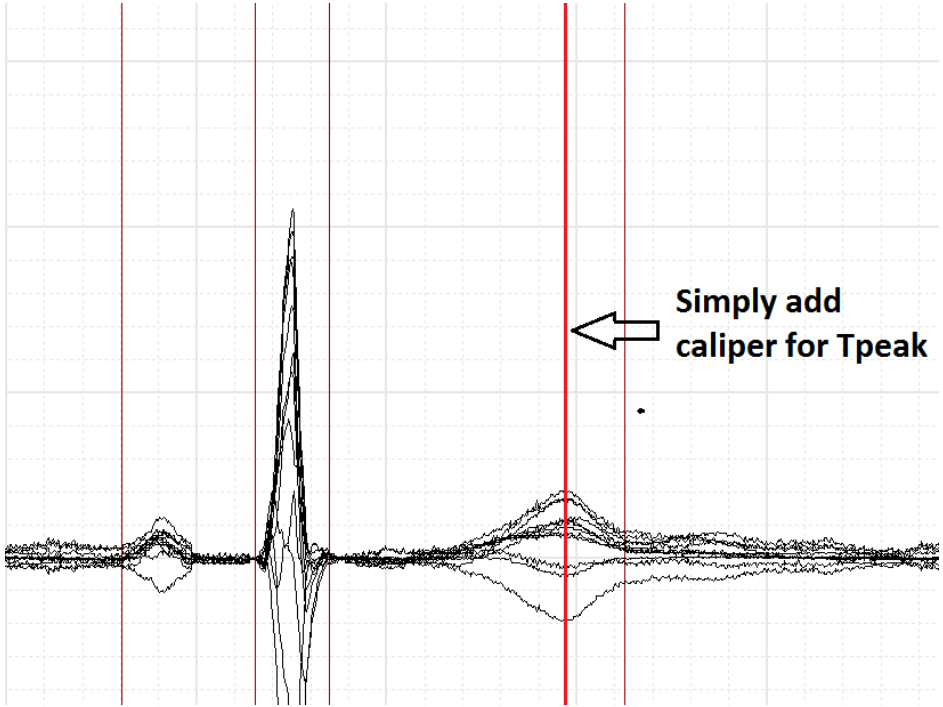
Example: Measurement from Superimposed GMB



But - the peak of the T wave varies between leads

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Issues for Core Labs

- Proprietary analyses might not be widely available
- Core labs using commercially available measurement tools may not have the ability to alter the code
  - 1 lead, GMB, principle component, vector magnitude lead?
  - Do additional calipers need to be placed?
  - How does the new output fit into the database structure?
- Will different sponsors request different analyses?
- Will sponsors understand the differences between methods?
- Standardized method, or will each lab select the method(s) to offer?

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Issues for Sponsors

- Sponsors must understand the paradigm in order to decide when to request novel ECG biomarker analysis
- ECGs must be collected digitally – cannot analyze paper ECGs
- Sponsors must understand methodology issues in order to understand core lab capabilities
- ECG format must be accepted by the core lab
- ECGs collected by a CRO without any core lab involvement may not be in correct format

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Summary

- Several novel ECG biomarkers under consideration
- Some biomarkers are proprietary
- Some biomarkers can be measured with different methods
- Consensus required about what to measure, specific methods
- Validation and standardization of methods are necessary
- Sponsors will choose when to use novel biomarkers
- ECG Core Labs will need to modify methods to allow introduction of new measurements and properly validate

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