# Potential Labeling Implications of Proposed Preclinical Proarrhythmia Testing Paradigm


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# Disclosures and Disclaimers



- Currently an employee of Genentech; prior employee of AZ and Amgen
- Views expressed here are my own, and not necessarily the official views of the companies I work for or have worked for
- ….which is OK because I have more questions than views

# Background and Context



- Why we put info in product label (prescribing information)
  - Communication of risk and strategies to mitigate risk
  - Medicolegal (duty to warn)
- Problems
  - Information fatigue (more important risks de-prioritized or overlooked)
  - Inconsistency in language (complicates planning, marketing, clinical use)
  - Uncertain clinical implications (clinicians may not know what to do with info)
- Nevertheless, labels often contain preclinical (or clinical!) safety data despite uncertain clinical significance
  - e.g., mutagenicity/carcinogenicity; or FQs and arthropathy
  - Almost by definition, most QT info in labels falls in this category: biomarker with uncertain clinical significance (unless arrhythmia identified post-market)
  - Proposed new paradigm unlikely to profoundly affect this labeling approach
    - Merely substituting one biomarker (TQT) for another (CIPA)

# Labeling Implications of Preclinical Proarrhythmia Assessment Will Depend On



- Performance characteristics of integrated assessment (predictiveness) and how comfortable people feel with it
- Whether assessment can is purely related to TdP or does it detect/exclude other types of arrhythmia
  - Will Na or Ca channel effects be cause for new label language?
- Whether the risk is binary (yes/no) or multi-level (e.g., 1-5 scale)
- Whether additional pre-clinical and clinical ECG would still be expected or could they be applied strategically
- Risk:benefit for intended population

# Implications for New Molecular Entities: Possible Scenarios

# New Molecular Entities – Negative Assay



- No drug effects on ion currents:
  - And presuming basic ECGs for safety in Ph1/2 are negative, and TQT (and Ph3 ECGs) not necessary (based on proposed paradigm)
  - Two potential labeling options to consider:
    - No language

      vs.
    - Language in label noting that a preclinical proarrhythmia assessment was performed and results were negative
  - The former assumes that assessment has low false negative rate
  - The latter is similar to how mutagenicity/carcinogenicity data and some clin pharm and QT data are already handled in labels
    - Nonclinical Toxicology section (section 13)
    - Clinical Pharmacology section (section 12)
    - Warnings and Precautions (section 5)

# New Molecular Entities – Negative Assay



- No drug effects on ion currents *but* large positive QT signals from routine Ph1/2 ECG monitoring emerge in clinical trials:
  - Additional work would be likely be required to assess risk (e.g., preclinical, clinical) to determine which is most relevant
  - Labeling would depend on results of that additional work
    - Likely clinical data would trump preclinical data until comfort and validity of integrated preclinical assessment known

# New Molecular Entities – Positive Assay



- + drug effects on cardiac ionic currents *and* likely proarrhythmia risk based on integrated in silico assessment:
  - Sponsor performs risk-benefit assessment
    - Life threatening indication with no alternative therapies:
      - Continue development with additional risk characterization and risk mitigation strategies (e.g., additional clinical ECG assessments)
      - Labeling would likely include results of preclinical proarrhythmia assessment supplemented with information from additional clinical risk assessment work
        - ? Warnings and Precautions (vs other sections)
    - Other indications:
      - Sponsors unlikely to continue development

# New Molecular Entities – Positive Assay



- + drug effects on cardiac ionic currents but *low* proarrhythmia risk based on integrated in silico assessment:
  - TQT study would presumably not be necessary according to proposed paradigm
    - But would sponsors be willing to rely on in silico model and continue development? Some may not want to take risk
  - Label implications depend on confidence in modeling; possible options include:
    - No language
    - Language describing ion channel effects but clarifying that in silico modeling suggests low proarrhythmic potential
  - Unclear what implications of Na or Ca current effects would be
    - Does in silico model accurately predict not-TdP arrhythmias?
    - Would intensive ECGs be required to assess QRS or PR?
    - Labels might need to contain language on Na/Ca channels

# Implications for Approved Products: Possible Scenarios

# Approved Drugs – Possible Scenarios



- Approved drug with established TdP risk:
  - Nonclinical proarrhythmia risk assessment unlikely to add value
- Approved drug with QT effects but TdP risk not established
  - Most such drugs have language in label around QT (e.g., Warnings and Precautions and/or Clinical Pharmacology sections)
  - Sponsors may choose to conduct nonclinical proarrhythmia assessment and labeling implications would depend on results:
    - Low risk based on integrated assessment:
      - Two possibilities, again depending on confidence in assessment:
        - Removal of existing QT language (especially if known clinical QT effect is small)
        - Update existing language in label to put QT effects in context (would large clinical QT effects need to stay in label?)
    - High risk based on integrated assessment:
      - Language in label would likely need to be modified to reflect risk

# Questions? Comments?