Can the Thorough QT Study Be Replaced?

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Can the TQT study be replaced?

Yes.

Thank you. Any questions?
Four genre of replacement efforts

• Retrospective assessment of hERG assays
  – Doomed for lack of standard hERG

• IQPharma – good quality ECGs in early studies
  – Highly likely to succeed, but marginally beneficial
Cardiac ionic currents

ECG

Action potential

Inward currents

Outward currents

hERG →

Roden et al. 2002
QT interval tracks cardiac action potential duration
What’s wrong with hERG phobia?

• Not all proarrhythmic risk attributes to hERG blockade (false negatives).
  – For example, anti-epileptic drugs are mostly sodium channel blockers
    • Felbamate- SVT, TdP, AF
    • Pregabalin- VF
What’s wrong with hERG phobia?

• Not all proarrhythmic risk attributes to hERG blockade (false negatives).

• Not all QT prolongation represents effects on hERG (false positives, part 1).
  – QRS prolongation from blocking Na, Ca (inward) currents
  – True repolarization effects can represent minor potassium currents (we see negative hERG and then a plateau effect on QT of 10 ms or so)
What’s wrong with hERG phobia?

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives).
- Some true hERG blockers are *anti*-arrhythmic, because of effects on inward currents, too (worse false positives).
  - Verapamil
  - Ranolazine
  - Amiodarone
What’s wrong with hERG phobia?

- Not all proarrhythmic risk attributes to hERG blockade (false negatives).
- Not all QT prolongation represents effects on hERG (false positives).
- Some true hERG blockers are anti-arrhythmic, because of effects on inward currents, too (worse false positives).
- Optimizing against hERG reduces selectivity for target receptor and against other off-target receptors (bad bargain).
  - Maybe no candidate
Four genre of replacement efforts

• Retrospective assessment of hERG assays
  – Doomed for lack of standard hERG

• IQPharma – good quality ECGs in early studies
  – Highly likely to succeed, but marginally beneficial

• Two approaches to proarrhythmia risk
  – ECG morphology changes to tell you about underlying channel effects
  – Comprehensive proarrhythmia assay
Working towards rational approach to assess arrhythmia

- Darell Abernethy/FDA
- Arthur Brown/Chantest
- Thomas Colatsky/FDA
- Gary Gintant/Abbott
- Christine Garnett/Pharsight
- Craig January/U Wisconsin
- Lars Johannesen/FDA
- John Koerner/FDA
- Naomi Kruhlak/FDA
- Derek Leishman/Lilly
- Marek Malek/U London
- Sebastian Polak/Simcyp
- Philip Sager/consultant
- Mary Ross Southworth/FDA
- David Strauss/FDA
- Robert Temple/FDA
- Nick Thomas/GE
- Douglas Throckmorton/FDA
- Jiwen Zhang/GE
Candidate Comprehensive Proarrhythmia Assay

- Screening for all ion channels
  - Structure-activity relationship modeling
  - Receptor affinity assays

- Characterization of all ion channel activities
  - Whole-cell patch clamp of isolated cardiac myocytes
  - High throughput methods

- Interpretation (integrated view)
  - Computer models of myocytes and the heart

- Verification
  - Human ECG

- Adaptation to new data
  - Post-market data → assay revision
Summary

Drug development has entered an era in which the decision to advance a compound into development is based upon a narrow assessment of proarrhythmic risk. This decision process is likely to exclude potentially safe and effective drugs.

We need a more comprehensive assessment of ion channel effects of potential new drugs to make informed decisions about risks, and we probably need to accept more uncertainty at the time of approval about what risk we have excluded.
Can the TQT study be replaced?

Yes. Actually, we must.

Thank you. Any questions?