CiPA, Pre-clinical Testing
& ICH S7B

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Expressing an opinion

What is not covered?

*Analysis/critique of the components – too little time to try for ourselves.*
The issue was drug-induced TdP
• Focus shifted quickly to the surrogate of QTc prolongation
• CiPA is shifting the focus back towards TdP
• Improved QTc measurement and concentration-QTc modeling have enabled assessment in early clinical studies
ICH S7B and E14

- They work – no unanticipated cases of drug-induced TdP with molecules approved after 2005
- If it ain’t broke why fix it?
  - Nonclinical assessment had little impact on clinical development
  - The scheme lacks specificity overall, leading to a lost opportunity cost for everyone
  - Companies generally doing more any way
  - Focusing on FIH study entry was the point of lowest overall value

Figure 5. hERG Assay Accuracy of QTc Prolongation

<table>
<thead>
<tr>
<th>Prediction</th>
<th>QTc</th>
<th>In Vivo Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>QTc</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

Accuracy: 0.77
Sensitivity: 0.43
Specificity: 0.86
Pos Pred Value: 0.43
Neg Pred Value: 0.86

<table>
<thead>
<tr>
<th>Prediction</th>
<th>QTc</th>
<th>In Vivo Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTc</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>QTc</td>
<td>4</td>
<td>17</td>
</tr>
</tbody>
</table>

Accuracy: 0.54
Sensitivity: 0.33
Specificity: 0.59
Pos Pred Value: 0.14
Neg Pred Value: 0.81

Abernathy & Leishman, SPS Mtg Berlin 2017
How Has CiPA Already Changed SP & S7B?

- CiPA has injected science into a topic susceptible to becoming a check list of assays to conduct.
- CiPA has brought ’new’ technology to proarrhythmia assessment – Too new? Too different?
- CiPA has signaled an era of model-informed drug development – Along with PBPK modeling it was the first example of PBPD modeling highlighted in a March 2017 FDA Advisory Committee Meeting.

Softer Value Of CIPA

- A recent survey suggests many companies do additional assays rather than just GLP ICH S7B assessments
- CIPA creates a common framework of assays and a consistent basis for regulatory discussions
- Greater control and standardization of assay protocols under CIPA
- Appreciation of the value of earlier screening

**Nonclinical approaches used to address proarrhythmia issues.**

<table>
<thead>
<tr>
<th>Answer options</th>
<th>Response percent</th>
<th>Response count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conduct a battery of in vitro (i.e., binding studies, ion channel studies, etc.), and in vivo CV safety pharmacology assays to screen drug candidates and establish risk during drug discovery</td>
<td>75%</td>
<td>58</td>
</tr>
<tr>
<td>Conduct “fit-for-purpose” nonclinical safety pharmacology tests based on an integration of observations derived from chemistry (SAR), toxicology findings and other scientific considerations (e.g., drug indication, drug class, pharmacology, PK/PD etc.)</td>
<td>31%</td>
<td>24</td>
</tr>
<tr>
<td>Perform safety testing based on GLP findings from safety pharmacology and toxicology studies only</td>
<td>20%</td>
<td>15</td>
</tr>
<tr>
<td>I do not know</td>
<td>4%</td>
<td>3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>My Opinion</th>
</tr>
</thead>
<tbody>
<tr>
<td>These are my opinions and not those of Eli Lilly and Company or the ICH E14/S7B discussion group</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ion Channel</th>
<th>it is a positive to have effective standardized assays, I worry about the burden of the hERG assay required to get the kinetic information, but believe it may not always be necessary</th>
</tr>
</thead>
<tbody>
<tr>
<td>In Silico</td>
<td>this is a nice robust validation of modifications to a mature model, I worry about there being few ion channel neutral compounds in the training set</td>
</tr>
<tr>
<td>Myocytes</td>
<td>a complex package with many moving parts, I worry about there being two methods each of which will give distinct concentration-response relationships and, more than one supplier of cells which will also gives distinct concentration-response relationships. I also worry about an assay to be used to identify mechanistic gaps but validated as a classification tool.</td>
</tr>
<tr>
<td>Clinical ECGs</td>
<td>a nice set of prospective mechanistic studies. I worry that these have been designed and tested to give mechanistic insight but may be used as classification tools. I also worry that they may not be sensitive enough when QTc changes are around 10ms.</td>
</tr>
<tr>
<td>Decision-Making</td>
<td>risk is a continuum but decisions usually become binary, will the practical cut-offs advance the scheme from where it is now?</td>
</tr>
</tbody>
</table>
Scenarios

#1 A large pharma new small molecule target team
#2 A large pharma team with a mature project with compound properties in the ‘ion channel space’
#3 Biotech company with the GLP pre-FIH data on a molecule which works at the target but had limited front-loaded safety work
#4 A compound which had unexpected effects in the clinic

Many scenarios are a blend between some of these
Large Pharma – New Project

• This is the scenario familiar to safety pharmacologists for the last 2 decades
• ICH S7B works, therefore.....

Select compounds which have a wide enough separation between concentrations associated with hERG block and predicted efficacious concentrations

Example criteria – >1000-fold separation between target and hERG IC$_{50}$, or a margin between efficacious free plasma concentrations and hERG IC$_{50}$ >30-fold
Scenario #1 - What do we require from CiPA?

- Understand the relationship between conventional screening hERG assay and the CiPA kinetic hERG assay
- **Agreed** definition of ‘no effect at clinically relevant concentrations’
  - Caveats allowed given very early stage e.g. if clinical concentrations increase a re-assessment would be necessary or taking in to account drug-drug interaction
  - Would it be more generous than currently used?
- **Agreed** hERG assay quality at FIH
- Result – Assessment of ‘Low Risk’ of TdP
A kinetic model of drug-channel interaction allows simulation of patch clamp protocols.
Requires more elaborate experimental protocol to capture kinetics.
Can be used to understand differences between assays.
Overall it should provide a more robust assessment of drug-channel interaction.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Cisapride IC50 (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast patch 10s</td>
<td>31</td>
</tr>
<tr>
<td>Ramp 5s</td>
<td>38</td>
</tr>
<tr>
<td>VAP 12s</td>
<td>237</td>
</tr>
<tr>
<td>VAP 1s</td>
<td>38</td>
</tr>
<tr>
<td>Hold @ 0 mV</td>
<td>13</td>
</tr>
<tr>
<td>Hold @ -50 mV</td>
<td>461</td>
</tr>
</tbody>
</table>
Large Pharma –
Mature Project In ‘Suspect’ Space

• The intended target is perhaps another ion channel, or is a CNS target where good brain penetration is essential

• Having tried the conventional screening paradigm (#1) only molecules with modest selectivity or margins have desired efficacy and pharmacokinetic profiles

• Selected compound has a separation between efficacy target and hERG between 100-1000-fold

• Selected compound has good brain penetration
  – Note the if efficacy is CNS and TdP is a peripheral issue the plasma to brain ratio erodes margin
Scenario #2 – What do we require from CiPA?

- The hERG driven concentration-QTc analysis is key
  - Predict from *in vitro* data – (empirical or OHRd Model)
  - Test *in vivo* in safety pharmacology assessments, conduct concentration-QTc analysis
  - Conduct concentration-QTc analysis in early clinical assessments
- Understanding PBPK for molecule likely also critical
- Conduct hERG-driven In Silico CiPA assessment – metric likely to bridge the ‘Low’ to ‘Intermediate’ Risk threshold
  - Additional ion channels may modify the risk metric but QTc prolongation remains possible
- Need to agree on clinical pharmacology and PBPK assessment
- **Question** – “Are the hERG protocols robust enough for this context of use?”
- **Question** – “Is the concentration-response information strong enough in isolated cardiomyocytes to reduce the reliance on the *in vivo* assessment?”
- **Question** – “What might the label look like?”
Predicting QTc

- Concentration-QTc relationship can be predicted from in vitro data using an empirically derived PKPD model or a quantitative systems pharmacology model.
- The latter allows unique combinations of ion channel properties.
- The range of predictions in these figures is based on the range of hERG IC\(_{50}\)'s and the range of plasma protein binding values.
- Focus on the hERG assay and other sources of variability will allow distributions to be used rather than ranges.
Biotech Company –
Molecule has positive findings in S7B assays

• Limited front-loading of safety assessment
  – The GLP hERG assay has a potency close enough to predicted efficacious range to suggest QTc prolongation likely in the clinic
  – The a GLP in vivo study demonstrated no QTc prolongation in a low sensitivity assessment (power to detect 20ms change)
  – Elements of this scenario resemble taking forward compounds in oncology

• Overall package of information is limited to required studies

• Question – what is the torsadogenic risk?
Scenario #3 – What do we require from CiPA?

• Based on current practice this compound may be discarded
• Conduct ion channel and *in silico* assessment – need the additional ion channel data
  – Make an *in silico* prediction of TdP risk
  – Scan across multiples of predicted efficacious concentrations to see how risk metric changes
• Consider PBPK and likelihood of variability in exposure levels through drug-drug interactions etc
• Need consensus on likely risk level
• Need consensus on the overall risk benefit
Useful Space Heatmap

- Heat map illustrates that QTc prolongation is likely whenever there is appreciable hERG block, despite calcium channel block.
- The ‘useful’ space can be restricted:
  - Below the white dashed lines are properties likely to be torsadogenic.
  - Jonker et al (2005) suggests focusing on less than 30% hERG block.
  - Consideration of the reduction in the calcium transient AUC would restrict levels of calcium block which could be considered.

Heat Maps are a work in progress.
Learn and Confirm Scenario #4

• A compound believed to be in scenarios #1, 2 or 3 when tested *in vivo* or in man shows unexpected effects, for example….
  – A concentration QTc effect larger than expected
  – A JTc effect larger than anticipated for a low or intermediate risk

• This is a situation where what was learned nonclinically was not confirmed in the clinic

• Need to reassess where the potential gap is based on what is observed
Causes of Discrepancy

- Solubility issues with compounds – more potent \textit{in vivo}
- A metabolite appearing in animals or man which hadn’t been accounted for
- A metabolite unique to man
- An indirect effect on QTc e.g. hypokalemia, hypoglycemia or hypothermia
  - In this scenario, where ion channel and in vitro data has a ‘low risk’ of TdP metric what are the implications
  - What if the QTc and JTc are both prolonged? Does it change the risk assessment?
  - How important is concentration-QTc assessment? How important are other biomarkers?
Can Q&As Based on CiPA to ICH S7B and E14 Address Scenarios?

• Scenario #1 – Yes, by adding clarity on hERG study quality and defining what is sufficient margin to be considered no–effect
• Scenario #2 – Yes, S7B already includes consideration of pharmacokinetics and drug interactions in the integrated risk assessment
• Scenario #3 – Yes, S7B already suggests follow up assays. The CiPA paradigm is designed to address the question regarding TdP risk for such compounds and offers a structured way to do the integrated risk assessment
• Scenario #4 – CiPA still appears to fall short on indirect effects on QTc but these do fit as a component of the integrated risk assessment in S7B (Gap to be filled)
To Conclude

- ICH S7B was focused solidly on predicting QTc prolongation while leaving unaddressed the question of distinguishing nontorsadogenic from torsadogenic effects.
- There was discussion of additional considerations relevant to proarrhythmia risk.
- CiPA appears to offer a supplemental package for S7B which could clarify some scenarios.
- Gaps? Yes. Indirect effects may still be unresolved. The role and quality of *in vivo* QTc assessment unclear.
Acknowledgements

• Matt Abernathy
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