Role of Biomarkers and Quantitative Models in Drug Development

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Disclaimer: My remarks today do not necessarily reflect the official views of the FDA
Outline

• Motivation for using biomarkers and quantitative models in drug development
• Case studies
• Summary
General Dose Selection Strategy

• Safety driven
  – Maximum tolerated dose (MTD)
  – Unnecessarily high dose
  – Even efficacy not always optimal

• Efficacy driven
  – Mechanism based (receptor occupancy, target suppression, pathway biomarker response)
  – Trend for more disease areas
## Biomarkers for Different Diseases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Biomarker</th>
<th>Clinical Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>bone cancer or bone metastases from solid tumors</td>
<td>urinary N-telopeptide normalized to urinary creatinine (UNTx/Cr)</td>
<td>time to first on-study occurrence of a skeletal-related event [SRE], including fractures, radiation to bone, spinal cord compression and surgery to bone</td>
</tr>
<tr>
<td>cardiovascular disease</td>
<td>platelet aggregation inhibition</td>
<td>major adverse cardiovascular events (MACE): CV Death/myocardial infarction/stroke</td>
</tr>
<tr>
<td>lung cancer</td>
<td>tumor size</td>
<td>survival</td>
</tr>
<tr>
<td>osteoporosis</td>
<td>BMD, serum C-telopeptide</td>
<td>fracture</td>
</tr>
<tr>
<td>lupus</td>
<td>anti-dsDNA antibody</td>
<td>renal flare, Systemic Lupus Erythematosus Responder Index</td>
</tr>
</tbody>
</table>
Model-Based Drug Development

“The concept of model-based drug development, in which pharmaco-statistical models of drug efficacy and safety are developed from preclinical and available clinical data, offers an important approach to improving drug development knowledge management and development decision-making”

Case Studies

• Drug X
  – Biomarker, PK-biomarker-surrogate endpoint model, genomics, trial design, clinical trial simulation

• Drug Y
  – Biomarker, potency bridging, exposure-efficacy/safety models, confounding, risk/benefit balance
Case 1: Drug X

- Treatment for a chronic disease
- Polymorphism in metabolic enzyme
  - a/a 20% → Extensive metabolizers (EM’s)
  - a/b 50%  
  - b/b 30% → Poor metabolizers (PM’s)
- ↓ Biomarker (B) & Surrogate (S) levels
- Goal: How to manage a genotypic influence on drug clearance in dose selection for Phase III trial design
Modeling Strategy

• Pharmacokinetics (Drug X)
  – Phase 1 data for population PK model
  – Phase 2 data for model update

• Pharmacodynamics (Biomarker and Surrogate)
  – Model established using clinical trial data available to FDA from drugs in this class & other classes
  – Simultaneous modeling biomarker and surrogate
  – Models updated with Drug X data
\[
\frac{dB}{dt} = K_{in} - K_{out} \left(1 + \frac{E_{\text{max}} \cdot C}{EC_{50} + C}\right) \cdot B
\]

\[
\frac{dS}{dt} = K'_{in} \cdot B - K'_{out} \cdot S
\]
Simulation Strategy & Assumptions

- Population PK model
  - Two-compartment model
  - Clearance dependent on genotype (a/a, a/b and b/b)
- Exposure-response model
  - Drug-Biomarker-Surrogate model
- Trial designs
  - Stratification by genotype
  - Titration by biomarker
- Inclusion criterion
  - Baseline Surrogate > 70 and < 100
- Analysis
  - Response rate at week 26 (Surrogate reduction > 10)
- 100 clinical trial replicates
Stratification by Genotype

(Genotype 1\textsuperscript{st}, Parallel Dose, Placebo Control)

100 Patients = 20 a/a, 50 a/b, 30 b/b

Genotype

400 patients

Dose mg/day

<table>
<thead>
<tr>
<th>Genotype</th>
<th>PM</th>
<th>EM</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>40</td>
<td>120</td>
</tr>
<tr>
<td>200</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>100</td>
<td>10</td>
<td>30</td>
</tr>
<tr>
<td>PBO</td>
<td>PBO</td>
<td>PBO</td>
</tr>
</tbody>
</table>

Time (weeks)

0 26
## Titration by Biomarker

*(Parallel Dose, Titration at 12 wk, Placebo Control)*

### Dose mg/day

<table>
<thead>
<tr>
<th>All</th>
<th>Titration by Biomarker (Biomarker ↓ &lt;13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>120</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>3X</td>
<td></td>
</tr>
</tbody>
</table>

### Time (weeks)

<table>
<thead>
<tr>
<th>0</th>
<th>12</th>
<th>26</th>
</tr>
</thead>
</table>

400 patients
Summary of Case 1

• At week 26, higher response rates were achieved in stratification by genotype design than titration by biomarker design. But the difference is getting smaller at later weeks.

• BID regimens perform better than QD regimens, especially in EM population.

• High-dose safety data in PM is needed.

• Biomarker-Surrogate relationship can be applied to other drugs with similar mechanism of action.
Case 2: Drug Y

- A new oral anticoagulant under development for the prevention of stroke and systemic embolic (SE) events in patients with non-valvular atrial fibrillation
- Mechanism of action: direct thrombin inhibitor
- Warfarin (Vitamin-K antagonist)
  - Slow onset and offset of action
  - Narrow therapeutic index
  - DDI and food effect
- Reference/bridging drug: ximelagatran
  - Rejected by FDA in 2004, but approved for venous thromboembolism (VTE) following orthopaedic surgery (OS) in EU, but withdrawn by AZ in Feb 2006 due to liver toxicity
Key Issues

• Relative potency (relative to ximelagatran)
  – Less potent
  – 1:2 on anticoagulant effect
  – 1:3 on antithrombotic effect
  – Predictive power of biomarkers

• Exposure-response
  – Exposure-Stroke/SE
    • Confounding
  – Exposure-bleeding
    • Total vs major bleeding

• Risk/benefit balance to guide dose selection
## Efficacy in SPORTIF III and V

### III (open label, non-North America)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Events</th>
<th>Patient years</th>
<th>Event rate (%/year)</th>
<th>95% CI Lower</th>
<th>95% CI Higher</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ximelagatran</td>
<td>40</td>
<td>2446</td>
<td>1.64</td>
<td>1.13</td>
<td>2.14</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>56</td>
<td>2440</td>
<td>2.29</td>
<td>1.69</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Ximelagatran-w</td>
<td>-</td>
<td>-</td>
<td>-0.66</td>
<td>-1.45</td>
<td>0.13</td>
<td>0.100</td>
</tr>
</tbody>
</table>

### V (double blinded, North America)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Events</th>
<th>Patient years</th>
<th>Event rate (%/year)</th>
<th>95% CI Lower</th>
<th>95% CI Higher</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ximelagatran</td>
<td>51</td>
<td>3160</td>
<td>1.61</td>
<td>1.17</td>
<td>2.06</td>
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<tr>
<td>Warfarin</td>
<td>37</td>
<td>3186</td>
<td>1.16</td>
<td>0.79</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Ximelagatran-w</td>
<td>-</td>
<td>-</td>
<td>0.45</td>
<td>-0.13</td>
<td>1.03</td>
<td>0.133</td>
</tr>
</tbody>
</table>
Confounded Exposure-Efficacy
Ximelagatran

Stroke/SE (%/year)

AUC Rank

1. 0
2. 0.5
3. 1
4. 1.5
5. 2
6. 2.5
7. 3
Prevalence of Stroke by Age and Sex

Source: American Heart Association, CDC/NCHS
Exposure-Safety

- Similar confounding issue
- Total bleeding versus major bleeding
- The sponsor and FDA reached consistent conclusions
- Under-prediction for drug Y and model needs to be updated with new data
Summary of Case 2

• Week predictive power of the biomarker for efficacy

• A Bayesian approach was used to address the confounding issue

• Uncertainty related to exposure-efficacy relationship
  – Two doses in phase 3

• Major bleeding should be used to select dose(s)
Conclusion

• Biomarkers play an important role in drug development

• Quantitative models serve as a powerful tool to integrate information from multiple sources

• Clinical trial simulation should be routinely applied to optimize late phase trials
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