Continuous Learning From Confirmatory Trials

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Modeling & Simulation for Medical Products Workshop

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

• Pharmacometrics scope at FDA
• Motivation for learning while confirming
• Case studies
• Summary
Pharmacometrics Scope at FDA

Tasks

• NDA/BLA reviews
• IND reviews
  – Dose-Finding trials
  – Registration trials
• QT Reviews
  – Central QT team
• Model-based drug development tool evaluation
• Research
  – Disease Models
  – Pediatrics
  – PBPK
• Knowledge Management

Decisions Influenced

• Evidence of Effectiveness
• Labeling
• Quantify benefit/risk
  – Dose optimization
  – Dose adjustments
• Trial design
Learn While Confirming

• The understandable focus of commercial drug development on confirmation, as this immediately precedes and justifies regulatory approval, has led, in my view, to a parallel intellectual focus that slight learning. The predictable result … is that clinical drug development is often inefficient and inadequate.

• Phase 3/4. Although learning is not the primary goal of this phase, it is a most important subsidiary one. Because confirming, the primary purpose of this phase, must not be compromised, one must learn while confirming, not instead of confirming.

• The most obvious reason is that at no earlier stage is it possible to study as large a number and as wide a variety of patients as in phase 3/4. …Thus, important “learning” about the response surface for purposes of appropriate labeling will either take place at this stage or will not occur at all.

• The most important reason to learn while confirming … is because confirmation sometimes fails. …What is needed at this point to plan future action is a diagnosis: why did the confirmation fail? Only if there are learning-oriented features to the study can this question be answered.

Learning versus confirming in clinical drug development, Lewis B Sheiner, CPT, 1997
Comments from FDA Officials

• “Pharmacometrics brings much-needed quantitative, mechanistic reasoning to the clinical review process. Use of modeling and simulation can fill in the huge gaps left by even the most comprehensive development program, and can save less informative programs. As we continue to synthesize clinical data using pharmacometric techniques, we will advance the science of drug development in ways we have not anticipated. I will continue to support pharmacometrics in CDER”--Janet Woodcock, Director, CDER

• “One of the most important benefits of pharmacometric analyses is providing insight into dose-response/concentration-response by using blood levels collected (population PK), together with patient effects to relate blood level to response, providing potentially richer data than the D/R data from the fixed dose D/R studies (where patients, despite the dose assignment, experience a range of drug concentrations)”--Robert Temple, Deputy Director for Science, CDER

• “At NDA review, exploration of exposure response relationships can complement planned analyses, providing supportive evidence of effectiveness, and helping with decisions relating to choice of dosing regimens to approve”--Norman Stockbridge, Director, Division of Cardiovascular and Renal Products
Case Studies

• Ticagrelor
  – Approved with failed subgroup analysis
  – Evidence based on a post hoc analysis

• Paliperidone
  – Approved regimen not studied in phase 3
  – Strategy to handle real life scenarios derived from population PK simulation
Case 1: Ticagrelor

- Indication: reduction of thrombotic events in acute coronary syndrome patients
- Mechanism of action: selective and reversible P2Y12 ADP-receptor antagonist
- Dose: loading dose of 180 mg and maintenance dose of 90 mg BID plus aspirin
- Phase 3 trial: superiority compared to clopidogrel 75 mg QD
- Regulatory dilemma: opposite results in US vs non-US even though overall results positive
Overall Efficacy Results (CV death + MI + Stroke)

Kaplan-Meier Estimated Rate (%)

- Ticagrelor (864 / 9333)
- Clopidogrel (1014 / 9291)

No. at risk
- Ticagrelor: 9333, 8628, 8460, 8219, 6743, 5161, 4147
- Clopidogrel: 9291, 8521, 8362, 8124, 6743, 5096, 4074

Tic vs. Clop
- HR: 0.84
- 95% CI: (0.77, 0.92)
- p-value: <0.001

Days after Randomization: 0, 60, 120, 180, 240, 300, 360

11.67% for Ticagrelor
9.80% for Clopidogrel
Efficacy Across Regions

78% of North America patients are from US

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total Patients</th>
<th>Tic</th>
<th>Clop</th>
<th>HR (95% CI)</th>
<th>Interaction p-value</th>
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<tbody>
<tr>
<td>Asia / Australia</td>
<td>1714</td>
<td>95</td>
<td>116</td>
<td>0.80 (0.61, 1.04)</td>
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<tr>
<td>Cent / Sth America</td>
<td>1237</td>
<td>91</td>
<td>104</td>
<td>0.86 (0.65, 1.13)</td>
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<tr>
<td>Euro / Md E / Afr</td>
<td>13859</td>
<td>576</td>
<td>712</td>
<td>0.80 (0.72, 0.90)</td>
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<tr>
<td>North America</td>
<td>1814</td>
<td>102</td>
<td>82</td>
<td>1.25 (0.93, 1.67)</td>
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</tbody>
</table>

Ticagrelor Better

Clopidogrel Better
Efficacy in US
(CV death+MI+Stroke)

\[ \text{HR} = 1.27 \, (0.92, 1.75) \]
PK and PD Similar

- **Population pharmacokinetics (PK) analysis**
  - Ticagrelor exposure similar between US and non-US

- **Pharmacodynamics (PD): US vs UK**
  - Multiple PD measurements, including ADP-induced platelet aggregation (IPA): similar

- **US efficacy results not explained by regional differences in PK or PD**
Aspirin (ASA) Dose Distribution Differs between Regions

US

Non-US
### Similar Pattern of Effect vs ASA Dose in US and non-US

<table>
<thead>
<tr>
<th>Region</th>
<th>ASA Dose (mg)</th>
<th>Ticagrelor N</th>
<th>Ticagrelor E</th>
<th>Clopidogrel N</th>
<th>Clopidogrel E</th>
<th>HR (95% CI)</th>
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<tr>
<td>US</td>
<td>≥300</td>
<td>324</td>
<td>40</td>
<td>352</td>
<td>27</td>
<td>1.62 (0.99, 2.64)</td>
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<tr>
<td></td>
<td>&gt;100 – &lt;300</td>
<td>22</td>
<td>2</td>
<td>16</td>
<td>2</td>
<td></td>
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<tr>
<td></td>
<td>≤100</td>
<td>284</td>
<td>19</td>
<td>263</td>
<td>24</td>
<td>0.73 (0.40, 1.33)</td>
</tr>
<tr>
<td>Non-US</td>
<td>≥300</td>
<td>140</td>
<td>28</td>
<td>140</td>
<td>23</td>
<td>1.23 (0.71, 2.14)</td>
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<tr>
<td></td>
<td>&gt;100 – &lt;300</td>
<td>503</td>
<td>62</td>
<td>511</td>
<td>63</td>
<td>1.00 (0.71, 1.42)</td>
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<tr>
<td></td>
<td>≤100</td>
<td>7449</td>
<td>546</td>
<td>7443</td>
<td>699</td>
<td>0.78 (0.69, 0.87)</td>
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</tbody>
</table>

Ticagrelor Better 1.0 | Clopidogrel Better 8
Hazard Ratio vs ASA Dose in non-US Patients
Consistency between Non-US and US Patients
Consistency between Non-US and US Patients
Summary for Case 1

- Final approved regimen: 180 mg loading dose and 90 mg BID maintenance dose for ticagrelor + 325 mg loading dose and 75-100 mg maintenance dose for ASA
  - Warning: Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day

- Similar ASA dose-efficacy relationship across regions was established

- Post hoc learning analysis served as the foundation for approval and dose recommendation

- Precedent was set with important implication for future international trials
Case 2: Paliperidone

• Indication: schizophrenia

• Extended-Release tablet is already approved (QD regimen)

• New monthly long acting injection formulation

• Regimens studied in phase 3 trials:
  – 25 mg, 50 mg, 100 mg, 150 mg (day 1, 8, 36, 64)
    25 mg (days 8, 36, and 64)
  – 150 mg (day 1)+
    100 mg (days 8, 36, and 64)
    150 mg (days 8, 36, and 64)

• Proposed regimen:
  – 150 mg (day 1), 100 mg (day 8) and 75 mg (monthly)
Benefit/Risk Assessment

Safety: one death at 150 mg and dose-dependent increase in body weight and serum prolactin levels

- N≥160/arm
- All active arms better than placebo
Additional Support for 75 mg

Dosing Interval at Steady State
(75 mg im. Q 4week)

Median Cmax (6 mg QD ER at steady state)

Median Cmin (6 mg QD ER at steady state)
Real Life Challenges

- Dosing window for the 2nd dose
- Dosing window for the monthly maintenance dose
- What to do after missing a dose
- Switching from ER tablet or other antipsychotics
- Dosing regimen for patients with renal impairment
PK Simulation for Dosing Window
Simulation Based Solutions

• Dosing window for the 2\textsuperscript{nd} dose: ± 4 days
• Dosing window for the monthly maintenance dose: ± 7 days
• What to do after missing a dose
  – 2\textsuperscript{nd} dose: 3 re-initiation regimens
  – maintenance dose: 3 re-initiation regimens
• Switching from ER tablet or other antipsychotics
  – Different maintenance doses and starting times
• Dosing regimen for patients with renal impairment
  – 100 mg (day 1), 75 mg (day 8) and 50 mg (monthly)
Summary for Case 2

• Unstudied regimen was approved
• FDA’s alternative strategy and individualized maintenance dose were accepted by the sponsor
• PK simulation led to recommendations for dosing window, strategy for handling missing dose, switching from prior treatments, dosing regimen for special patients
• All these model based recommendations are included in the product label
Conclusion

• Valuable knowledge can be learned from confirmatory trials

• Rigorous learning analyses and application of integrated knowledge led to
  – Unnecessary trials avoided
  – Faster access of medication for patients
  – Rational dosing regimen
  – Strategy to handle real life issues

• Routine practice in drug development and regulatory review
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