PK-PD IN DRUG DEVELOPMENT

Focus on Clinical Trials

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APPLICATION OF PK-PD IN CLINICAL TRIALS

*Useful for Confirming Predictions*

- **In Vitro & Animal Models**
- **Phase 1 Studies**
- **Phase 2 Studies**
- **Phase 3 Studies**
- **New Drug Application**

Pre-Clinical | Clinical Development

Charles Bonapace, FDA, 16 April 2004

Learn → Confirm → Succeed
CLINICAL DEVELOPMENT PLAN
Implementing a Prospective PK-PD Strategy

- Plan for the use of pre-clinical, early Phase 1 data, and simulation to support dose and schedule selection

- Develop a sparse PK sampling strategy to implement into a Phase 2 study and conduct PK-PD analyses to support dose and schedule selection for Phase 3

- Partner with the FDA throughout the process
PK-PD IN CLINICAL TRIALS

Issues to Understand

• PK and PK-PD is a resource intensive endeavor
  o Sparse PK sample collection ($1,000-5,000 per patient)
  o PK sample shipping ($100-250 per sample)
  o PK sample chemical analysis ($30-75 per sample)
  o Coordinating CRO costs
  o FTE costs around monitoring, data management, verification, quire resolution, etc.

• For the above, it is important to plan for the following:
  o 20-25% above the fully-loaded cost of the clinical trial, plus
  o Mathematical modeling of Phase 1-3 PK and PK-PD data for the entire program (~$1,000,000)
PK-PD IN CLINICAL TRIALS

Return on Investment

• Program risk mitigation
  o Allows for the most optimal dose and schedule to be established

• Can facilitate the understanding of the pharmacology and/or risk-benefit ratio of new drugs

• Can improve the quality of regulatory submissions
  o Facilitate regulatory review
  o Enhance relationship with regulatory authorities
  o Minimize post-submission questions
PK-PD IN CLINICAL TRIALS

Return on Investment

- Can lead to overall time and resources savings
  - Can facilitate the transition to novel dosage forms based on PK studies only, if PK-PD relationships are known
  - Can obviate the need for select clinical trials (e.g., age-gender, renal impairment, etc.)
  - Smaller sample sizes associated with exposure-response vs. dose-response approaches

Table: Sample Size for 90% Power to Reject H0: No exposure-Response relationship

<table>
<thead>
<tr>
<th>S.D. of Response</th>
<th>Dose as &quot;Exposure&quot;</th>
<th>AUC as &quot;Exposure&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>200</td>
<td>140</td>
</tr>
<tr>
<td>1.1</td>
<td>150</td>
<td>120</td>
</tr>
<tr>
<td>1.0</td>
<td>130</td>
<td>90</td>
</tr>
</tbody>
</table>

Based upon Monte Carlo simulation of 1,000 clinical trials.
PK-PD IN CLINICAL TRIALS

Return on Investment

• Allows for the utilization of FDAMA provisions
  o Section 111 provides for “the use of PK bridging studies in pediatric studies of new drugs”
  o Section 115 provides for “new drug approval based upon evidence from a single adequate and well-controlled trial, supported by confirmatory scientific evidence from other studies (e.g., Phase 2 PK-PD studies) in the NDA”

• Allows for the utilization of ICH E5 guidelines for the use of PK bridging studies for submission in Japan, etc.

• Provides a basis for data-driven market differentiation of a product
PK-PD IN CLINICAL TRIALS

Components of a Program

• Laboratory evaluations to understand the PK-PD index and magnitude best associated with efficacy
  ○ *in vitro* time-kill, PAE studies
  ○ *in vitro* PK-PD infection models
  ○ *in vivo* PK-PD infection models

• Phase 1 population PK
  ○ Simulations for Phase 2 dose-selection
  ○ Development of an optimal PK sampling for Phase 2

• Phase 2 population PK and PK-PD

• Phase 3 population PK and PK-PD
PK-PD IN CLINICAL TRIALS

The Development of Gatifloxacin

• In the mid-to-late 1990s, gatifloxacin was under development by Bristol-Myers Squibb for patients with community-acquired respiratory tract infections

• Evaluating and demonstrating gatifloxacin’s activity against *Streptococcus pneumoniae* was considered to be of primary importance

• Pre-clinical and clinical PK-PD evaluations, which focused on *S. pneumoniae*, were integrated in the clinical development plan for gatifloxacin
PRE-CLINICAL PK-PD STUDIES
A Step-Wise Approach

Time-Kill Studies

Conc. Dep. Killing
- AUC:MIC ratio
- Cmax:MIC ratio

Time Dep. Killing
- PAE
- No PAE
- AUC:MIC ratio
- %T>MIC

In Vitro PK-PD model: Determine PK-PD Target

Animal PK-PD model: Confirm PK-PD Target
IN VITRO PK-PD INFECTION MODELS

Hollow-Fiber Model
Logarithmic phase cultures ($5 \times 10^7$ CFU/mL) of *S. pneumoniae* introduced into peripheral compartment

- Cmax:MIC 2.5; elimination half-life altered to provide AUC:MIC ratios of 10-45

- Samples removed from peripheral compartment at 0, 2, 4, 8, 12, 24, and 30 hrs

- Viable bacterial counts measured by plating serial 10-fold dilutions of each sample into Todd-Hewitt agar and incubating overnight at 37°C in 5%CO₂

- Lowest dilution plated was 0.1mL

PK-PD ANIMAL INFECTION MODELS

Murine-Thigh Infection Model

- 2 Hr
Infect

0 Hr
Begin Therapy

24 Hr
Sacrifice, Harvest, Homogenize Muscle

96 Hr
MURINE PK-PD DATA

Identifying the PK-PD Index Most Associated with Gatifloxacin Efficacy for S. pneumoniae

PRE-CLINICAL PK-PD STUDIES

Summary of Early Findings

• Static *in vitro* time-kill and PAE studies demonstrated the following:
  
  o A concentration-dependent pattern of bactericidal activity for gatifloxacin against *S. pneumoniae*¹
  
  o A PAE of 1.2-4 hours for gatifloxacin against *S. pneumoniae*²

• PK-PD *in vitro* infection and *in vivo* animal models demonstrated and/or confirmed the following:
  
  o AUC:MIC ratio was the PK-PD index most close associated with gatifloxacin bactericidal activity for *S. pneumoniae*³
  
  o The magnitude of the AUC:MIC ratio needed for net bacterial stasis for *S. pneumoniae* was 30-40, which was much lower than 125 (which was commonly believed to associated with efficacy for all organisms at the time)³,⁴

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3. Andes DR and Craig W AAAC 2002:1665-7.;
CLINICAL PK-PD STUDIES
Evaluation of Gatifloxacin in Phase 2 Trials

- Data from 2 double-blind, randomized, multi-center trials of patients with CAP or ABECB with dichotomous endpoints (success/failure) at test-of-cure

- Counts of patients who received study drug:
  - 778 patients with either CAP or ABECB bronchitis
  - 635 patients were clinically evaluable
  - 376 patients were both clinically and microbiologically evaluable
  - 58 patients had infection associated with S. pneumoniae

# Clinical PK-PD Studies

## Logistic Regression Analyses for Gatifloxacin Efficacy

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Significance</th>
<th>Covariate</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.3835</td>
<td>Free-AUC (^1)</td>
<td>0.2165</td>
</tr>
<tr>
<td>Gender</td>
<td>0.5003</td>
<td>MIC (^1)</td>
<td>0.999(^2)</td>
</tr>
<tr>
<td>Clcr(^1)</td>
<td>0.2551</td>
<td>Free-AUC:MIC (^1,3)</td>
<td>0.1596</td>
</tr>
<tr>
<td>Weight</td>
<td>0.3801</td>
<td>Free-AUC:MIC (^1,4)</td>
<td>0.0131</td>
</tr>
</tbody>
</table>

N = 58

1: Clcr = creatinine clearance, AUC = 24-hour area under the serum concentration time curve, MIC = minimum inhibitory concentration.

2. Convergence issue

3. AUC:MIC treated as continuous variable

4. AUC:MIC treated as a categorical variable

CLINICAL PK-PD STUDIES

Univariable Logistic Regression Relationship Between Gatifloxacin Efficacy and AUC:MIC Ratio

MONTE CARLO SIMULATION

Applied to PK-PD

CLINICAL PK-PD STUDIES
Additional Opportunities

- Make PK-PD sampling mandatory
- Select only sites with the required infrastructure
- Attend investigator meetings and train investigators and their staff
- Develop on-line teaching tools for reference
CLINICAL PK-PD STUDIES
Additional Opportunities

- Use process maps to understand risks
- Plan real-time data assembly and feedback to sites
- Define work plan to minimize scope creep, missed timelines and resist/limit last minute exploratory analyses
Subject Participation Rate in Population-Based PK Sampling for Anti-infective Agents

<table>
<thead>
<tr>
<th>Program</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic (peds)</td>
<td>35% (76%)</td>
<td>37%</td>
</tr>
<tr>
<td>Antiviral</td>
<td>65%</td>
<td>—</td>
</tr>
<tr>
<td>Antiviral</td>
<td>59%</td>
<td>67%</td>
</tr>
<tr>
<td>Antibiotic</td>
<td>92%</td>
<td>—</td>
</tr>
</tbody>
</table>
CLINICAL PK-PD STUDIES
Post-Approval Evaluations

• Gatifloxacin was approved in December 1999

• Soon thereafter, there were anecdotal reports of rare but serious hyperglycemia in elderly patients receiving standard dosing regimens (400 mg QD)

• One possible reason was believed to be over-exposure due to age-related decreases in renal function
  o AUC values ≥ 60 mg*hr/L in elderly patients predisposed to glycemic alterations were of particular concern

• Available demographics and PK-PD models were used to perform a risk-benefit assessment for alternative dosing strategies
### CLINICAL PK-PD STUDIES

**Gatifloxacin Exposure in Elderly Patients**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>200 mg AUC&lt;sub&gt;0-24&lt;/sub&gt;</th>
<th>400 mg AUC&lt;sub&gt;0-24&lt;/sub&gt;</th>
<th>200 mg AUC&lt;sub&gt;0-24&lt;/sub&gt;</th>
<th>400 mg AUC&lt;sub&gt;0-24&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥65</td>
<td>3.04</td>
<td>50.76</td>
<td>0.92</td>
<td>35.08</td>
</tr>
<tr>
<td>≥70</td>
<td>3.32</td>
<td>56.34</td>
<td>1.22</td>
<td>39.44</td>
</tr>
<tr>
<td>≥75</td>
<td>6.70</td>
<td>61.32</td>
<td>1.96</td>
<td>44.62</td>
</tr>
<tr>
<td>≥80</td>
<td>7.20</td>
<td>66.08</td>
<td>3.22</td>
<td>50.46</td>
</tr>
<tr>
<td>≥85</td>
<td>11.7</td>
<td>73.18</td>
<td>5.48</td>
<td>58.26</td>
</tr>
</tbody>
</table>

Simulation size was 5000 patients.

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### CLINICAL PK-PD STUDIES

**Gatifloxacin PK-PD Target Attainment Probabilities in Elderly Patients**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>AUC$_{0-24}$:MIC $\geq$ 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>200 mg</td>
</tr>
<tr>
<td>$\geq 65$</td>
<td>98.9</td>
</tr>
<tr>
<td>$\geq 70$</td>
<td>99.0</td>
</tr>
<tr>
<td>$\geq 75$</td>
<td>99.1</td>
</tr>
<tr>
<td>$\geq 80$</td>
<td>99.0</td>
</tr>
<tr>
<td>$\geq 85$</td>
<td>99.3</td>
</tr>
</tbody>
</table>

Simulation size was 5000 patients.

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GATIFLOXACIN CLINICAL DEVELOPMENT
A Summary of the Application of PK-PD

• A PK-PD plan implemented early in development
• Pre-clinical PK-PD studies were used to identify the PK-PD measure most closely associated with efficacy and the magnitude required for effect
• Population PK data were used to identify a sparse PK sampling scheme for Phase 2/3
• Phase 2/3 population PK and PK-PD analyses were conducted to confirm early pre-clinical and clinical predications
GATIFLOXACIN CLINICAL PK-PD

*The Gift that Kept on Giving*

- Population PK and PK-PD provided a framework for efficient pediatric development

- PK-PD relationships together with population PK and Monte Carlo simulation models were used to justify susceptibility breakpoints

- The above-described data were also used as a basis for market differentiation

- Population PK and PK-PD were used in risk-benefit analyses that arose in the post-marketing setting
POPULATION PK AND PK-PD

Powerful Tool for Drug Development, with Regulatory and Clinical Applications

Pharmacokinetics
- Animal
- Phase-I
- Phase-II
- Patient Population

Microbiology
- Local Surveillance
- National Surveillance

Mathematical Model
\[ C_{p}^{t} = \left( \frac{A \cdot e^{\alpha t}}{1 + e^{-\alpha t}} + \frac{B \cdot e^{\beta t}}{1 + e^{-\beta t}} + \frac{C \cdot e^{\gamma t}}{1 + e^{-\gamma t}} \right) \cdot fu \]

Pharmacodynamics
- In vitro models
- Animal models
- Human data
THANK YOU FOR YOUR ATTENTION