Adaptive Dose-Ranging Studies:
An Update from the PhRMA WG

José Pinheiro
Novartis Pharmaceuticals

on behalf of the PhRMA ADRS WG

Adaptive Designs WG   KOL series
November 13, 2009
Outline

• Motivation and background
• Recommendations from 1st evaluation round
• 2nd evaluation round: key results & conclusions
• Overall conclusions and recommendations
Motivation

- Pharmaceutical industry **pipeline problem**: fewer approvals, at higher development costs [Bornkamp et al., 2007]
- Stakeholders reaction: FDA’s Critical Path Initiative; PhRMA Pharmaceutical Innovation Steering Committee (PISC) working groups (WG)
- Inadequate dose selection for confirmatory trials identified as **key driver** of poor performance
- Adaptive Dose-Ranging Studies (**ADRS**) WG formed by PISC to evaluate and address the problem
Adaptive Dose Ranging Studies WG

- Main goals: investigate and develop designs and methods for efficient learning about Dose Response (DR) ⇒ better and faster decision making on dose selection and improved labeling

- How: evaluate statistical operational characteristics of alternative designs and methods via comprehensive simulation studies

- Focus: adaptive and model-based dose-ranging designs and methods

- Adaptive Designs WG: another PISC group, focusing on higher level recommendations and advocacy of adaptive designs in general
ADRS WG Membership

Co-Chairs: José Pinheiro, Rick Sax
Current members:

Zoran Antonijevic
Björn Bornkamp
Frank Bretz
Christy Chuang-Stein
Vlad Dragalin
Parvin Fardipour
Bill Gillespie
Chyi-Hung Hsu
Frank Miller
Krishna Padmanabhan

Tom Parke
Nitin Patel
Inna Perevozskaya
Amit Roy
Ashish Sanil
Jonathan Smith
First evaluation round

- Simulation study comparing different dose finding (DF) methods under variety of scenarios (e.g., dose-response models, number of doses)
- Evaluated operational characteristics of methods with regard to:
  - detecting dose-response signal
  - dose selection for Phase III
  - estimation of dose-response profile
- Key conclusions & recommendations published in white paper and presented to Health Auth., with positive feedback
with discussion, including regulators (FDA and CHMP)
Key Conclusions – first round

- Detecting DR is much easier than estimating it
- Sample sizes for DF studies are typically not large enough for accurate dose selection and estimation of DR
- Adaptive dose ranging methods and other innovative DF methods can lead to substantial gains over traditional pairwise testing approaches (especially for estimating DR and selecting dose)
**Recommendations – first round**

- Adaptive, model-based dose ranging methods should be **routinely considered** in Phase II.
- Sample size calculations for DF studies should take into account **precision** of estimated dose.
- When resulting N is not feasible, should consider selecting **more than one** dose for Phase III – preferably coupled with adaptive design.
- PoC and dose selection should, when feasible, be **combined** in one seamless trial.
- Simulations should be used for protocol design.
Second evaluation round

Three work streams (WKS):

- **New Adaptive Methods**: first round evaluation included only 2 ADR approaches – 5 new ones evaluated by WKS (similar simulation design as in first round)
  - Chair: Vlad Dragalin

- **Impact of dose selection** (in Phase II) on likelihood of success of Phase III program and net present value (NPV) for compound in indication
  - Chair: Zoran Antonijevic

- **Value of exposure-response** modeling in dose response characterization and dose selection
  - Chair: Amit Roy
Selected results from WKS simulations
I – New Methods WKS
Simulation models

Change in pain from baseline

Dose

Linear | Umbrella | Sigmoid-Emax

Emax | Emax low | Explicit
Pr(dose right )

<table>
<thead>
<tr>
<th>Number of IA</th>
<th>Linear</th>
<th>9 doses</th>
<th>Umbrella</th>
<th>9 doses</th>
<th>Sigmod Emax</th>
<th>9 doses</th>
<th>Emax</th>
<th>9 doses</th>
<th>Explicit</th>
<th>9 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pr(dose right )

ANOVA
AMCPMod
DCoD
IntR
t-test
MULTOB

Correct target interval probability (%)

Number of IA
## Average prediction error

<table>
<thead>
<tr>
<th></th>
<th>9 doses</th>
<th>9 doses</th>
<th>9 doses</th>
<th>9 doses</th>
<th>9 doses</th>
<th>9 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
<td><img src="image5.png" alt="Graph" /></td>
<td><img src="image6.png" alt="Graph" /></td>
</tr>
<tr>
<td>Umbrella</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
<td><img src="image9.png" alt="Graph" /></td>
<td><img src="image10.png" alt="Graph" /></td>
<td><img src="image11.png" alt="Graph" /></td>
<td><img src="image12.png" alt="Graph" /></td>
</tr>
<tr>
<td>Sigmoid Emax</td>
<td><img src="image13.png" alt="Graph" /></td>
<td><img src="image14.png" alt="Graph" /></td>
<td><img src="image15.png" alt="Graph" /></td>
<td><img src="image16.png" alt="Graph" /></td>
<td><img src="image17.png" alt="Graph" /></td>
<td><img src="image18.png" alt="Graph" /></td>
</tr>
<tr>
<td>Emax</td>
<td><img src="image19.png" alt="Graph" /></td>
<td><img src="image20.png" alt="Graph" /></td>
<td><img src="image21.png" alt="Graph" /></td>
<td><img src="image22.png" alt="Graph" /></td>
<td><img src="image23.png" alt="Graph" /></td>
<td><img src="image24.png" alt="Graph" /></td>
</tr>
<tr>
<td>Explicit</td>
<td><img src="image25.png" alt="Graph" /></td>
<td><img src="image26.png" alt="Graph" /></td>
<td><img src="image27.png" alt="Graph" /></td>
<td><img src="image28.png" alt="Graph" /></td>
<td><img src="image29.png" alt="Graph" /></td>
<td><img src="image30.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

### 5 doses

<table>
<thead>
<tr>
<th></th>
<th>5 doses</th>
<th>5 doses</th>
<th>5 doses</th>
<th>5 doses</th>
<th>5 doses</th>
<th>5 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td><img src="image31.png" alt="Graph" /></td>
<td><img src="image32.png" alt="Graph" /></td>
<td><img src="image33.png" alt="Graph" /></td>
<td><img src="image34.png" alt="Graph" /></td>
<td><img src="image35.png" alt="Graph" /></td>
<td><img src="image36.png" alt="Graph" /></td>
</tr>
<tr>
<td>Umbrella</td>
<td><img src="image37.png" alt="Graph" /></td>
<td><img src="image38.png" alt="Graph" /></td>
<td><img src="image39.png" alt="Graph" /></td>
<td><img src="image40.png" alt="Graph" /></td>
<td><img src="image41.png" alt="Graph" /></td>
<td><img src="image42.png" alt="Graph" /></td>
</tr>
<tr>
<td>Sigmoid Emax</td>
<td><img src="image43.png" alt="Graph" /></td>
<td><img src="image44.png" alt="Graph" /></td>
<td><img src="image45.png" alt="Graph" /></td>
<td><img src="image46.png" alt="Graph" /></td>
<td><img src="image47.png" alt="Graph" /></td>
<td><img src="image48.png" alt="Graph" /></td>
</tr>
<tr>
<td>Emax</td>
<td><img src="image49.png" alt="Graph" /></td>
<td><img src="image50.png" alt="Graph" /></td>
<td><img src="image51.png" alt="Graph" /></td>
<td><img src="image52.png" alt="Graph" /></td>
<td><img src="image53.png" alt="Graph" /></td>
<td><img src="image54.png" alt="Graph" /></td>
</tr>
<tr>
<td>Explicit</td>
<td><img src="image55.png" alt="Graph" /></td>
<td><img src="image56.png" alt="Graph" /></td>
<td><img src="image57.png" alt="Graph" /></td>
<td><img src="image58.png" alt="Graph" /></td>
<td><img src="image59.png" alt="Graph" /></td>
<td><img src="image60.png" alt="Graph" /></td>
</tr>
</tbody>
</table>

### ANOVA

- Linear
- Umbrella
- Sigmoid Emax
- Emax
- Explicit

### AMCP Mod

- DCoD
- IntR
- t-test
- MULTOB
Selected results from WKS simulations
II – Exposure Response WKS
Simulation models

![Graph showing simulation models for different scenarios: Emax base, Emax steep, Emax grad, Sig-Emax base, Sig-Emax no-effect, Sig-Emax steep. The graphs illustrate changes in response (y-axis) across different concentrations of Css [ng/mL] (x-axis).]
MED Precision

17 ADRS WG results and recommendations
Average prediction error

<table>
<thead>
<tr>
<th>σ_{CI}</th>
<th>Emax base</th>
<th>Emax steep</th>
<th>Emax grad</th>
<th>Sig-Emax base</th>
<th>Sig-Emax no-effect</th>
<th>Sig-Emax steep</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**σ_{CI}**, σ_{ER} = 0.75

- DR, σ_{ER} = 0.75
- ER, σ_{ER} = 0.75

σ_{CI} = 30%, σ_{CI} = 30%, σ_{CI} = 30%, σ_{CI} = 30%, σ_{CI} = 30%, σ_{CI} = 30%

σ_{CI} = 50%, σ_{CI} = 50%, σ_{CI} = 50%, σ_{CI} = 50%, σ_{CI} = 50%, σ_{CI} = 50%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%

σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%, σ_{CI} = 70%
Selected results from WKS simulations
III – Impact on Phase 3 WKS
### Pr(Success Ph III)

**Average Phase III program success probability (%)**

<table>
<thead>
<tr>
<th>Method</th>
<th>Doses</th>
<th>Model</th>
<th>1 dose Ph. III</th>
<th>2 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCFIT</td>
<td>9</td>
<td>logistic</td>
<td><img src="image1" alt="Graph" /></td>
<td><img src="image2" alt="Graph" /></td>
</tr>
<tr>
<td>BMA</td>
<td>9</td>
<td>umbrella</td>
<td><img src="image3" alt="Graph" /></td>
<td><img src="image4" alt="Graph" /></td>
</tr>
<tr>
<td>MTT</td>
<td>9</td>
<td>linear</td>
<td><img src="image5" alt="Graph" /></td>
<td><img src="image6" alt="Graph" /></td>
</tr>
<tr>
<td>MCPMod</td>
<td>9</td>
<td>Emax</td>
<td><img src="image7" alt="Graph" /></td>
<td><img src="image8" alt="Graph" /></td>
</tr>
<tr>
<td>GADA</td>
<td>5</td>
<td>logistic</td>
<td><img src="image9" alt="Graph" /></td>
<td><img src="image10" alt="Graph" /></td>
</tr>
<tr>
<td>Dopt</td>
<td>5</td>
<td>umbrella</td>
<td><img src="image11" alt="Graph" /></td>
<td><img src="image12" alt="Graph" /></td>
</tr>
<tr>
<td>ANOVA</td>
<td>5</td>
<td>linear</td>
<td><img src="image13" alt="Graph" /></td>
<td><img src="image14" alt="Graph" /></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Dopt</td>
<td><img src="image15" alt="Graph" /></td>
<td><img src="image16" alt="Graph" /></td>
</tr>
</tbody>
</table>

**Average Phase III program success probability (%)**

20 ADRS WG results and recommendations
## Expected Net Present Value (NPV)

### 1 dose

- **LOCFIT**
- **BMA**
- **MTT**
- **MCPMod**
- **GADA**
- **Dopt**
- **ANOVA**

### 2 doses, accel.

- **LOCFIT**
- **BMA**
- **MTT**
- **MCPMod**
- **GADA**
- **Dopt**
- **ANOVA**

### 2 doses, normal

- **LOCFIT**
- **BMA**
- **MTT**
- **MCPMod**
- **GADA**
- **Dopt**
- **ANOVA**

### Parameters

- **N = 250**
- **N = 150**

### Models

- **logistic**
- **quadratic**
- **linear**
- **emax**

### Average expected NPV (millions)

<table>
<thead>
<tr>
<th>Model</th>
<th>N = 250</th>
<th>N = 250</th>
<th>N = 250</th>
<th>N = 250</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCFIT</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>BMA</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>MTT</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>MCPMod</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>GADA</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>Dopt</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>ANOVA</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

### N = 150

<table>
<thead>
<tr>
<th>Model</th>
<th>N = 150</th>
<th>N = 150</th>
<th>N = 150</th>
<th>N = 150</th>
</tr>
</thead>
<tbody>
<tr>
<td>LOCFIT</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>BMA</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>MTT</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>MCPMod</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>GADA</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>Dopt</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>ANOVA</td>
<td>400</td>
<td>600</td>
<td>800</td>
<td>1000</td>
</tr>
</tbody>
</table>

### 21 ADRS WG results and recommendations
Key conclusions: second round

- No **silver bullet** approach to DF conundrum
- No design/method uniformly best: relative performance **depends** on scenario, assumptions
- Approaches are **multifaceted**: e.g., adaptive, model-based, Bayesian, optimal design, etc
- **Factored view** of individual components: e.g., frequent adaptations not always add value
- Learning priorities in trial lead to different operational characteristics: e.g., dose selection vs. DR characterization
- Better DR learning approaches exist and can **produce substantial knowledge gains**
Recommendations: 2\textsuperscript{nd} round

- Recommendations from 1\textsuperscript{st} round remain valid

- Toolbox approach: comprehensive set of useful, practical designs and methods, such as:
  - response-adaptive allocation
  - model-based estimation
  - optimal designs
  - Bayesian methods
  - Exposure-response modeling

- Revisit resource allocation balance between DR learning and confirmatory phases, to optimize likelihood of program success and E(NPV)
Recommendations: 2nd round (cont.)

- Toolbox should be implemented in software, with good simulation and reporting capabilities; open-source strategy would be most efficient.
- Comprehensive, simulation-based evaluations to guide modern protocol design.
- **Reinforce** 1st round recomm. to bring 2 or 3 doses into Ph. 3, when uncertain at end of Ph. 2.
- More program-level planning should be used, instead of focusing on individual trials.