

PhRMA Adaptive Dose-Ranging WG and FDA Meeting

May 02, 2007

Adaptive Dose-Ranging Studies WG members

- Alex Dmitrienko, Eli Lilly
- Amit Roy, BMS
- Brenda Gaydos, Eli Lilly
- Frank Bretz, Novartis
- Frank Shen, BMS
- Greg Enas, Eli Lilly
- José Pinheiro, Novartis
- Michael Krams, Wyeth
- Qing Liu, J & J
- Rick Sax, Astra Zeneca
- Tom Parke, Tessella
- Björn Bornkamp, Univ. Dortmund
- Beat Neuenschwander, Novartis
- Chyi-Hung Hsu, Novartis
- Franz König, Med. Univ. Vienna

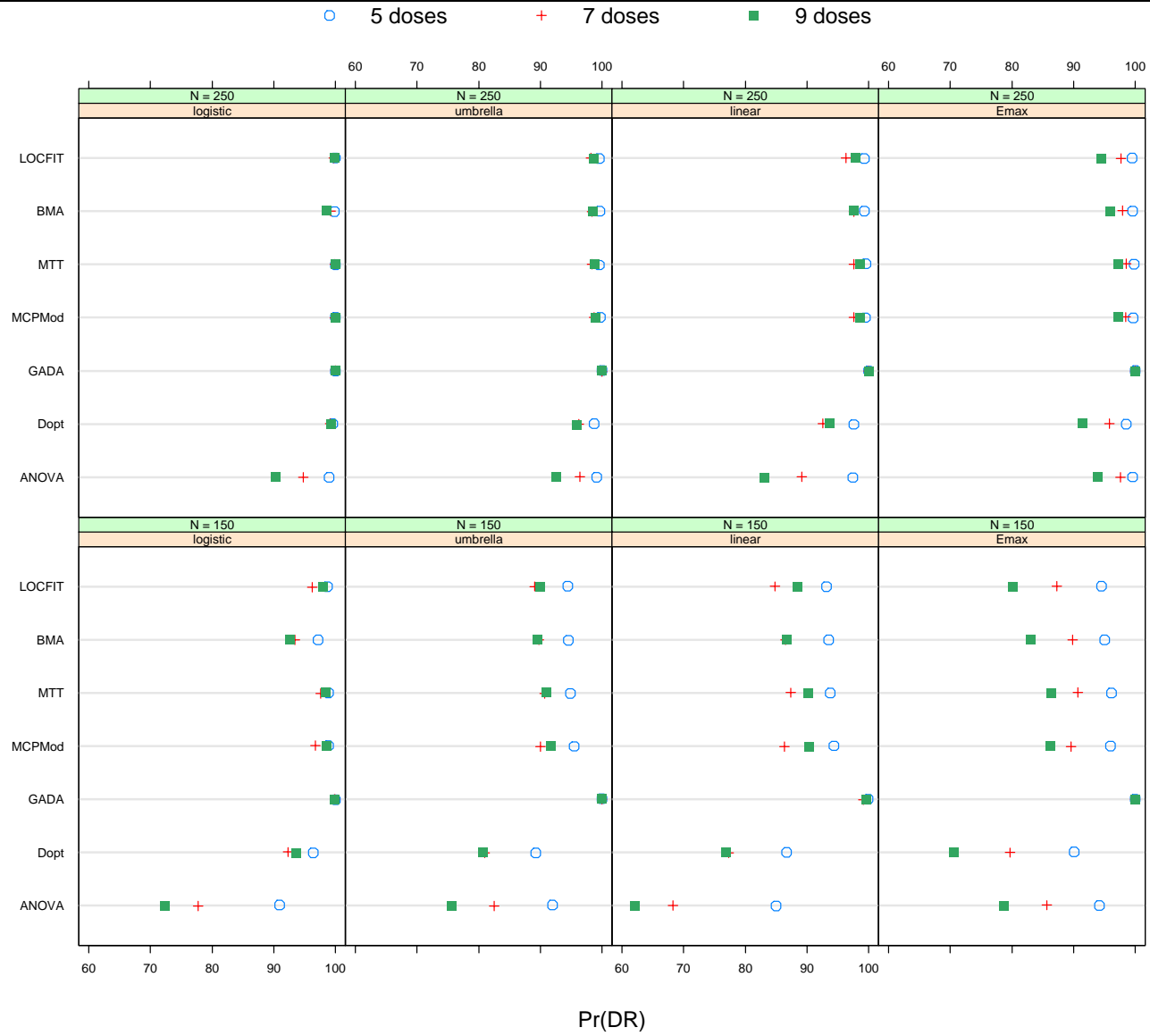
Motivation: need for better dose finding

- Poor understanding of dose response (DR) for both efficacy and safety is pervasive in drug development
- Indicated by both FDA and industry as one of root causes of late phase attrition and post-marketing problems with approved drugs
- Current dose finding designs and methods focus on selection of single target dose (e.g., MED) out of fixed, generally small number of dose levels, via pairwise hypothesis testing \implies inefficient and inaccurate
- Adaptive dose-ranging studies WG formed with the goal of investigating ways to improve dose finding

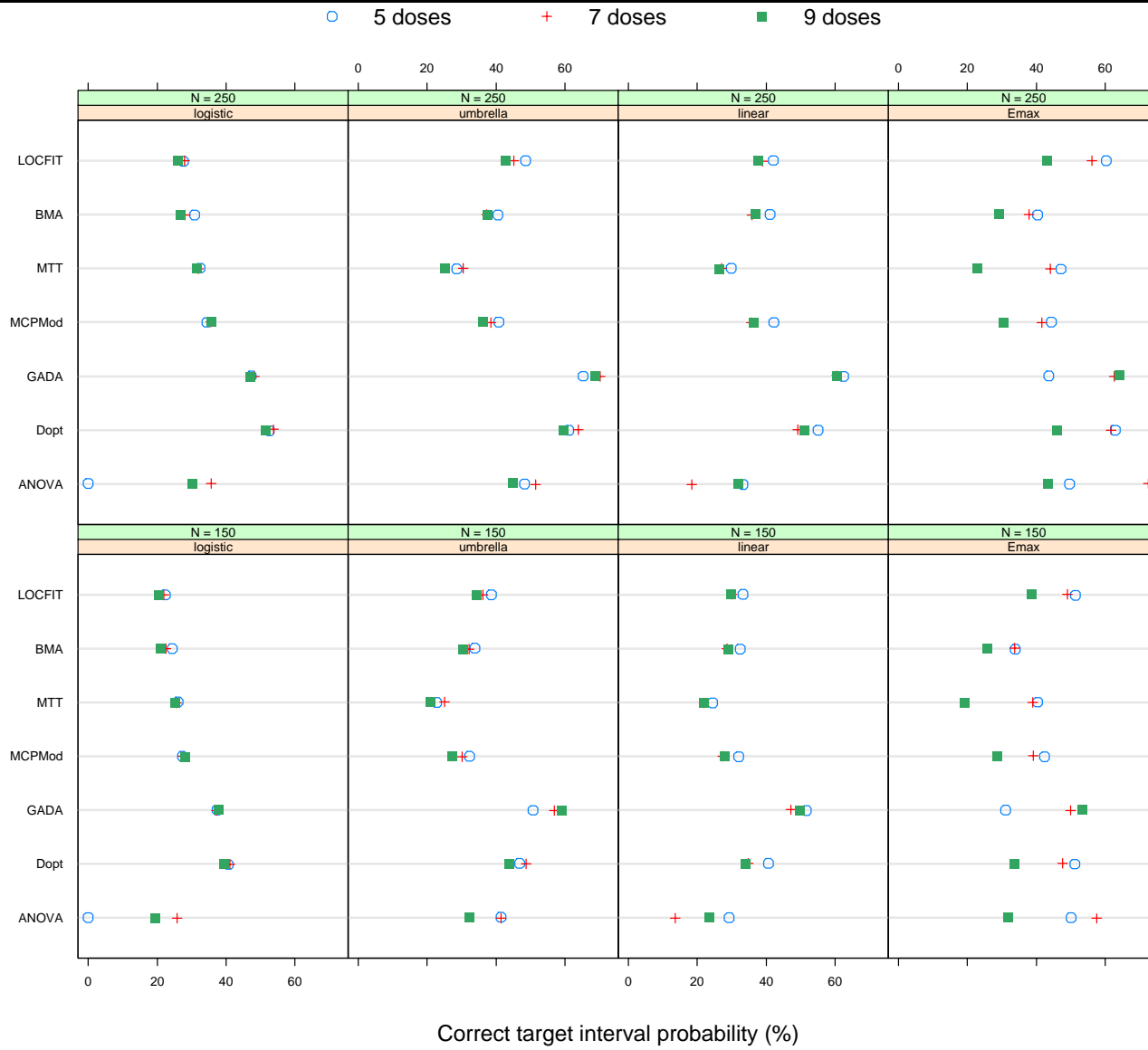
ADRS initiative – Goals

- Investigate and develop designs and methods for efficiently **learning** about safety and efficacy DR profile \implies benefit/risk profile
- Emphasis on modeling/estimation (**learning**) as opposed to hypothesis testing (**confirming**)
- More accurate and faster **decision making** on dose selection and improved labeling
- Evaluate statistical operational characteristics of alternative designs and methods via simulation study to make recommendations on their use in practice

Probability of identifying DR



Prob. of correct interval dose selection



Conclusions

- Adaptive dose-ranging methods lead to gains in **power** to detect DR, **precision** to select target dose, and to estimate DR – greatest potential in the latter two
- **Detecting** DR is considerably easier than **estimating** it
- Sample sizes for DF studies, based on power to detect DR, are typically **inappropriate** for dose selection and DR estimation
- Under assumptions and conventions used in simulations, **none** of methods had good performance in estimating dose in the correct **target interval**: maximum observed percentage of correct interval selection – 60% \implies larger N needed
- **Model-based** methods have superior performance compared to methods based on hypothesis testing

General recommendations

- Adaptive, model-based dose-ranging designs **should be used routinely** in drug development, as they can lead to substantial gains in performance over traditional DF methods
- Early stopping rules, for both efficacy and futility, should be used when feasible to allow **greater efficiency** in adaptive designs – Bayesian methods are particularly well-suited for this purpose
- **Trial simulations** should be used to determine appropriate sample sizes, as well as for estimating operational characteristics of designs/methods under consideration (scenario planning)

Does the FDA agree, in principle, with these?

Specific recommendations

- Sample size calculations for Phase II studies should take into account desired **precision** of estimated target dose and possibly also estimated DR (current methods are not appropriate)
- When resulting sample size is not feasible, should consider **selecting two or three doses** for confirmatory phase to increase likelihood of including “correct” dose – adaptive designs could be used in confirmatory phase for greater efficiency (e.g., dropping less efficient doses earlier)
- Proof-of-concept (PoC) and dose selection should be combined, when feasible, into **one seamless trial**

Does the FDA agree, in principle, with these?

Suggested discussion topics

- Check-list with pre-requisites for successful/acceptable adaptive dose-ranging study (ADRS)
- Evaluation of alternative adaptive dose-ranging approaches
- Guidance documents on ADRS and dose selection
- Further practical questions that need to be addressed with regard to ADRS

Proposal for ADRS check-list

Based on Sue-Jane Wang's adaptive designs checklist

- **Adaptive design plan**
 - Prospectively defined adaptation rules (+ any futility rules)
 - Operating characteristics (e.g., simulation plan and results)
 - Data monitoring committee guidelines (e.g., unexpected safety issues, deviations from planned design and rules)
- **Endpoints requirements:** justification for choice of efficacy and safety endpoints/clinical utility indices/surrogate markers used in adaptation rules (e.g., availability relative to accrual time)
- **Trial integrity:** SOPs for ensuring trial integrity and minimizing operational bias, especially for ADRS included as part of adaptive seamless Ph. II/III trial.

Evaluation of alternative approaches

- Sponsor should evaluate operational characteristics of alternative approaches that could be used in the trial, to justify chosen design/methods (quantification of expected gains) – at a minimum, should include one "traditional" DF approach for comparison
- Simulation plan devised by ADRS WG for comparing alternative methods could serve as template
- Summary of evaluation to be provided to FDA together with programs and datasets used in simulations (for reproducibility of results, if needed)

Guidance documents

- Guidance document with best practices for ADRS and, more generally, dose selection should be promulgated by FDA
- Alternatively, or in addition to, ICH E4 guideline should be updated to reflect current methods and recommendations
- If FDA decides to develop such guidance documents, ADRS WG would like to offer to be involved and help in any way we can

Further practical topics for investigation

- **Sample size** calculations: what would be the required sample sizes to achieve desired accuracy in dose selection – direct quantification of adaptive designs benefit
- Efficacy + safety: joint modeling/decision making, clinical utility indices, appropriate simulation framework
- Selection of more than one dose for Ph. III: investigate/quantify potential benefit, combine with adaptive design for dropping doses

Back-up Slides

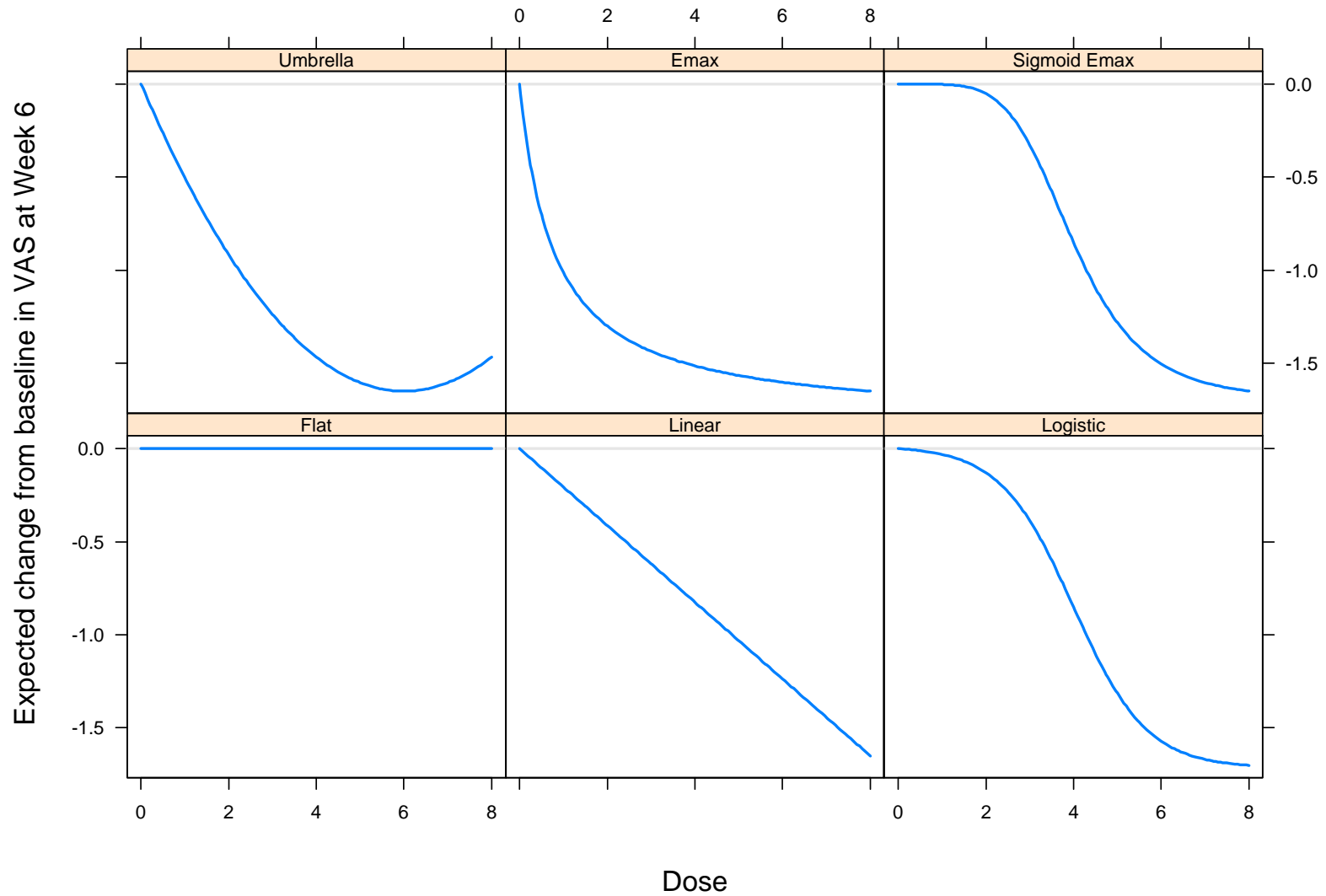
Simulation study: design and assumptions

- Proof-of-concept + dose finding trial, motivated by neuropathic pain indication
- Key questions: whether there is evidence of dose response and, if so, which dose level to bring to confirmatory phase and how well dose response (DR) curve is estimated
- Continuous primary endpoint: change from baseline in VAS
- Dose design scenarios:
 - 5 equally spaced doses levels 0, 2, 4, 6, 8
 - 7 unequally spaced dose levels: 0, 2, 3, 4, 5, 6, 8
 - 9 equally spaced dose levels: 0, 1, . . . , 8
- Significance level: one-sided FWER $\alpha = 0.05$
- Sample sizes: 150 and 250 patients (total)

Dose finding methods used in simulation

- Traditional **ANOVA** based on pairwise comparisons and multiplicity adjustment (Dunnett, 1955)
- **MCP-Mod** combination of multiple comparison procedure (MCP) and modeling (Bretz, Pinheiro and Branson, 2005)
- **MTT**: novel method based on Multiple Trend Tests (Capizzi, Survill, Heyse and Malani, 1992)
- Bayesian Model Averaging: **BMA** (Hoeting, Madigan, Raftery and Volinsky, 1999)
- Nonparametric local regression fitting: **LOCFIT**(Loader, 1999)
- **GADA**: Dynamic dose allocation based on Bayesian normal dynamic linear model (Krams, Lees and Berry, 2005)
- **D-opt**: adaptive dose allocation based on D-optimality criterion(Dragalin and Fedorov, 2006)

Dose response profiles



References

- Bretz, F., Pinheiro, J. and Branson, M. (2005). Combining multiple comparisons and modeling techniques in dose-response studies, *Biometrics* **61**(3): 738–748.
- Capizzi, T., Survill, T., Heyse, J. and Malani, H. (1992). An empirical and simulated comparison of some tests for detecting progressive response with increasing doses of a compound, *Biometrical Journal* **34**: 275–289.
- Dragalin, V. and Fedorov, V. (2006). Adaptive model-based designs for dose-finding studies, *Journal of Statistical Planning and Inference* **136**: 1800–1823.

- Dunnett, C. (1955). A multiple comparison procedure for comparing several treatments with a control, *JASA* **50**: 1096–1121.
- Hoeting, J., Madigan, D., Raftery, A. and Volinsky, C. (1999). Bayesian model averaging: A tutorial, *Statistical Science* **14**(4): 382–417.
- Krams, M., Lees, K. R. and Berry, D. A. (2005). The past is the future: Innovative designs in acute stroke therapy trials, *Stroke* **36**(6): 1341–7.
- Loader, C. (1999). *Local Regression and Likelihood*, Springer, New York, NY.