Session 2 summary – Designs & Methods

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- Pairwise comparisons approach
- Dose finding approaches discussed:
  - PK/PD Modeling
  - (Adaptive) MCPMod
  - Model Averaging
  - Bayesian Adaptive Dose Ranging
  - Emax Dose Response Model
- Guiding principles for good dose selection

Pairwise comparisons

- Most widely used approach in Phase 2 studies: dose selection based on hypothesis testing (as opposed to estimation, like in model-based approaches): e.g., select smallest dose significantly different from control
- Motivation: hope that study may be used as one of pivotal trials, if "results look really good" – mini-Phase 3 view of Phase 2B (save time and $$, if successful)
- Need to control multiplicity in pairwise comparisons to ensure "confirmatory grade" control of Type I error - little incentive to consider more than 2 or 3 active doses (increases price of multiplicity adjustment)
- Sample size determination based on power to have at least one pairwise comparison significant – increasing number of doses increases total sample size
- Dose response (or exposure response) estimation is an after thought; # doses and N typically inadequate for DR estimation
- Any type of endpoint (e.g., continuous, binary, etc.), typically focused on one time point (e.g., change from baseline at end of study)

PK/PD modelling

- Focus on exposure-response modeling, using longitudinal data collected on subjects (e.g., time-varying covariates)
- Not just “dose”, but also regimen, steady-state vs. non-steady-state, titration, changes in therapy
- Can leverage data/information across studies
- Not a replacement for more traditional “phamacostatistics” analysis (e.g., dose-response modeling), but supportive of and adding value to it
- Relies on validity of model and underlying assumptions, which may be difficult to verify at study design
- PK data may be collected sparsely, or not at all – to be effective, requires appropriate design with relatively wide range of exposures (possibly more expensive)
- Inferring dose selection from estimated target exposure possibly challenging
- Should be routinely be used in support of dose selection

MCP-Mod

- Combines multiple comparisons and modeling for model-based dose selection (and DR estimation) under model uncertainty
- Can be used to test DR signal (MCP step) and DR estimation (Mod step) via model selection or model averaging
- Intended for Phase 2, but extension available for confirmatory studies (e.g., adaptive Phase 2/3)
- Focus on population dose-response (cross-sectional), but can also leverage longitudinal data
- Can handle most common types of responses: continuous, binary, count, time-to-event, etc.
- Number of doses/dose range:
  - Minimum: 2 active doses (for the MCP-step), 3 active doses (Mod step)
  - Recommendation: 4-7 active doses, >10-fold dose range
- Adaptive version illustrated in talk: requires timely availability of endpoint relative to recruitment speed, to allow adaptations to have an impact

Model Averaging

- Similarly to MCPMod, accounts for model uncertainty by using a set of candidate DR model families
- No model selection used: all candidate models are utilized, with weights accounting for goodness of fit (AIC)
- Focus on model-based dose selection in Phase 2 – not testing of DR signal
- In principle, can be used with any type of endpoint and taking into account longitudinal data – focus on population DR
- Reasonable number of doses (4-7) and dose range (> 10 fold) needed to adequately estimate DR

Bayesian Adaptive Dose Ranging

- Bayesian (statistical) DR model underpins decision making – flexible, allowing for non-monotonic shapes
- Burn-in stage, with no adaptations, followed by response-adaptive randomization (RAR) stage with allocation proportional to posterior prob of dose maximizing effect – evaluated monthly
- Futility and decision to select dose and move to next (confirmatory) stage evaluated at each adaptation point
- Frequentist primary analysis, with pooled data from all stages
- Focus on dose selection to maximize prob of trial success; less emphasis on DR estimation (intended for adaptive Phase 2/3)
- Primary endpoint needs relatively quick availability for frequent adaptations to be effective (could use biomarker, if not the case)
- Information-driven design, with flexible sample size
- Key ideas can be used with any type of endpoint and incorporating longitudinal data

Emax Dose Response Model

- Based on comprehensive meta-analysis, most DR profiles observed in practice follow (hyperbolic) Emax model
- Should Phase 2 studies be planned assuming Emax DR model is appropriate and avoid model uncertainty „penalty“?
- How to balance robustness against model misspecification vs. efficiency by assuming single model family is correct?
- Same meta-analysis indicated that dose range utilized in Phase 2 is typically narrow and should be extended for better characterization of DR
- Testing of DR signal under single model family assumption – relevant? Not an issue?

Guiding Principles

- Selection of dose for Phase 3 is an estimation problem and should not be addressed via hypothesis testing
- Model-based dose finding methods are more efficient than pairwise comparisons approaches
- Proper characterization of dose response for both efficacy and safety should be a requirement in drug development programs (possibly part of label)
- Wider dose/exposure ranges (> 10 fold) and larger number of doses/regimens (> 3) should be routinely used in Phase 2
- Adaptive dose-ranging approaches, when feasible, can lead to substantial efficiency gains (time, number of patients, etc.)
- Having adequate Phase 2 study (with model-based demonstration of efficacy) serve as one of pivotal trials could greatly encourage better dose selection practices

Back up

Hyperbolic Emax Model

What do clinical dose response curves look like?

Most look like hyperbolic Emax curves.

How well were they determined by the studies conducted?

The answer varies due to controllable and uncontrollable reasons.

Dosing ranges are too narrow.

Are there consistent quantitative trends in clinical dose response across unrelated diseases and compounds?

Yes

Distributions of likely parameter values are important in both design and analysis of dose response studies.

Model averaging

Model averaged based dose selection methodology has a potential to increase the accuracy of the dose selections at the end of the Phase IIb clinical studies

PK/PD modelling from Immunology session

Should be always used to support dose selection

Methods not accounting for the time-varying state, such as cross-sectional dose-response analyses, cannot be used for extrapolation and even interpolation purpose. Instead, exposure-response analyses may be more appropriate because it allows to:

- reduce the dimension of the space by naturally accounting for the variation in exposure perhaps supported by appropriate randomized dose changes
- (in case of combination therapy,) provide a larger and more realistic set of models to combine the exposure effect of the different drugs
- use the variability in exposure (of appropriately designed trails) to recover a portion of the 'non observed' dose range corresponding to potentially sub-optimal doses
- include pharmacokinetic interaction information to account for potential differences between indications.

Nevertheless, exposure-response pose challenges that must be accounted for:

- Ensuring the causality of the estimated exposure-response relationship, in case of TDM, but also as a general concern [Nedelman, 2007]
- Ensuring robustness to model misspecification
- In particular: in non-steady state conditions, ensuring that the conclusion (selected dose) is robust wrt potential misspecification of the functional form of the exposure-response relationship in terms of dynamicity of the relationship (e.g., direct vs hysteresis).

Diagnostics for confounding in PK/PD models for oxcarbazepine. Jerry R Nedelman, Donald B Rubin, Lewis B Sheiner, Statistics in Medicine 02/2007; 26(2):290-308

Systems Pharmacology from CNS session

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QSP has been positioned mainly to contribute to target selection, validation and authorisation. However, there is also a role in dose finding

Easier where relationship between pharmacology-biomarker-end Point is well understood

However if this is not understood QSP could provide a better understanding of the MoA and the link between MoA-BM-Efficacy

Downside, models difficult to develop:

Need for systems data coming from in vitro, preclinical in vivo and clinical experiments

Usually need to pool data across several developments