An adaptive dose-finding study in postoperative dental pain. MCP-Mod

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Acknowledgements:

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Outline

- MCP-Mod
  - Adaptive Dose-Finding
- Adaptive dose-finding study in postoperative dental pain

What is MCP-Mod?

Multiple Comparison Procedures – Modelling: Overview

- A method for model-based dose-response testing and estimation
  - MCP-step
    - Establish a dose-response signal (the dose-response curve is not flat) using multiple comparison procedures
  - Mod-step
    - Estimate the dose-response curve and target doses of interest (ED_{50}, ED_{90}, MED, etc) using modelling techniques
- What is special about the approach?
  - Modelling pre-specified at design stage as primary analysis
    - Design (doses & sample size) tailored to needs of analysis method
  - Model uncertainty at design stage is addressed by using
    - a candidate set of models (for MCP and Mod step):
    - & a procedure on how to perform model selection (or model averaging)

What is MCP-Mod?

Multiple Comparison Procedures – Modelling

- Method developed Novartis internally in ~ 2004
  - Since then used in a number of completed studies with df element
  - Qualification opinion by EMA in 2014

Drug	Phase	Condition studied	Treatment g
1	Phase IIb	Gout	5 doses, AC
2	Phase IIb	Diabetes	PBO, 4 dose
3	Phase III	Prevention of cardiovascular events	PBO, 3 dose
4	Phase IIb	Psoriasis	PBO, 3 od a
5	Phase IIb	Multiple Sclerosis	PBO, 5 dose
6	Phase IIa/b	Epilepsy	PBO, 2 dose
7	Phase II	Hypertension	PBO, 3 od d
8	Phase IIb	Diabetes	PBO, 5 dose
9	Phase III	Familial Chylomicronemia Syndrome	PBO, 2 dose
10	Phase II	Hypertriglyceridemia	PBO, 3 dose
11	Phase IIb	Hypertension	PBO, 3 dose
12	Phase IIb	Diabetes	PBO, 7 dose
13	Phase IIb	COPD	PBO, 4 od d
14	Phase IIb	COPD	PBO, 3 bid d
15	Phase IIb	Asthma	PBO, 9 od d
16	Phase II	COPD	PBO, 4 dose
17	Phase IIa	Dental pain	PBO, 6 dose
18	Phase II	Generalized anxiety disorder	PBO, 4 dose

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Qualification Opinion of MCP-Mod as an efficient statistical methodology for model-based design and analysis of Phase II dose finding studies under model uncertainty

Draft agreed by Scientific Advice Working Party	5 September 2013
Adopted by CHMP for release for consultation	19 September 2013[1]
Start of public consultation	15 October 2013[2]
End of consultation (deadline for comments)	24 November 2013[3]
Adoption by CHMP	23 January 2014

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MCP-Mod: Dose-response modelling under model uncertainty

*see **Bretz et al (2005)**, Biometrics, 61, 738-748 & **Pinheiro et al (2014)**, Statistics in Medicine, 33, 1646-1661*

Trial Design Stage

General design considerations

Determination of suitable study population, endpoints, etc.

Set of candidate models

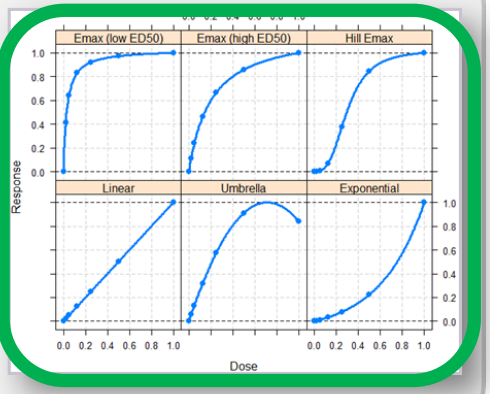
Pre-specification of candidate dose-response models based on available information (similar compounds, mode of action)

Optimal statistical tests

Optimized for candidate dose-response shapes

Design evaluations

Dose determination and sample size calculation to achieve targeted performance characteristics



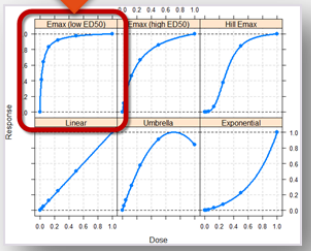
Trial conduct

$p < \alpha$?

Trial Analysis Stage

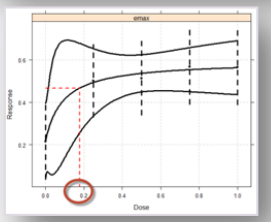
MCP step

- Assessment of dose-response signal using contrast tests
- Model selection (or model averaging) out of the set of significant models



Mod step

Dose-response and target dose estimation based on selected model(s)



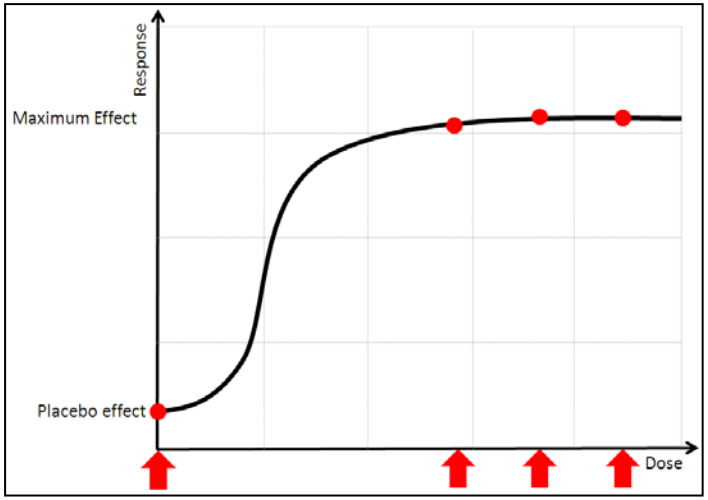
Scope of MCP-Mod

- Development Phase
  - Ph II dose-response studies to support dose selection for Phase III
- Dose-Response
  - Population dose-response (cross-sectional) *usually*
  - Response can be continuous, binary, count, time-to-event
- Number of doses, dose-range
  - Minimum: 2 active doses (for the MCP-step), 3 active doses (Mod step)
  - Recommendations (rules of thumb): 4-7 active doses, >10-fold dose range
- Control
  - MCP-step makes most sense when there is a placebo control in the trial
- Basic MCP-Mod can be extended
  - regimen, random effects, longitudinal, ...

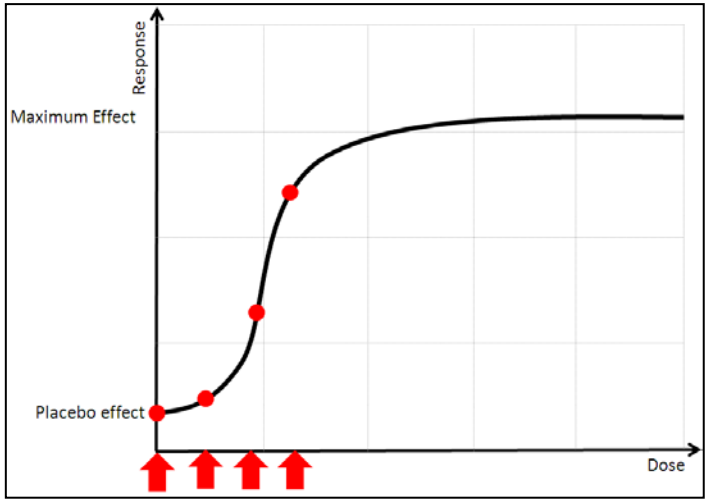
Adaptive Dose-Finding

Why?

- Between development phases
  - e.g. Phase IIa/IIb or Phase II/III
- Or within a dose-finding study (Ph IIb)
  - Uncertainty on doses and dose-range: Avoid situations like



or



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Adaptive Dose-Finding

And how?

- How to adapt at an interim analysis?
  - „optimal design“
    - try to optimize a mathematical measure of information
      - e.g. determinant of Fisher information
    - fit models at interim, obtain parameter estimates and calculate doses/allocations to be used for the rest (usually: pick the best design based on a list of „feasible“ candidate designs)
  - „scenario-based design“
    - Specify scenarios on how the observed dose-response curve might look like at interim
    - For each scenario decide based on clinical considerations which design to use in the second stage
    - At interim: Select the design corresponding to the scenario, to which the observed data correlate best

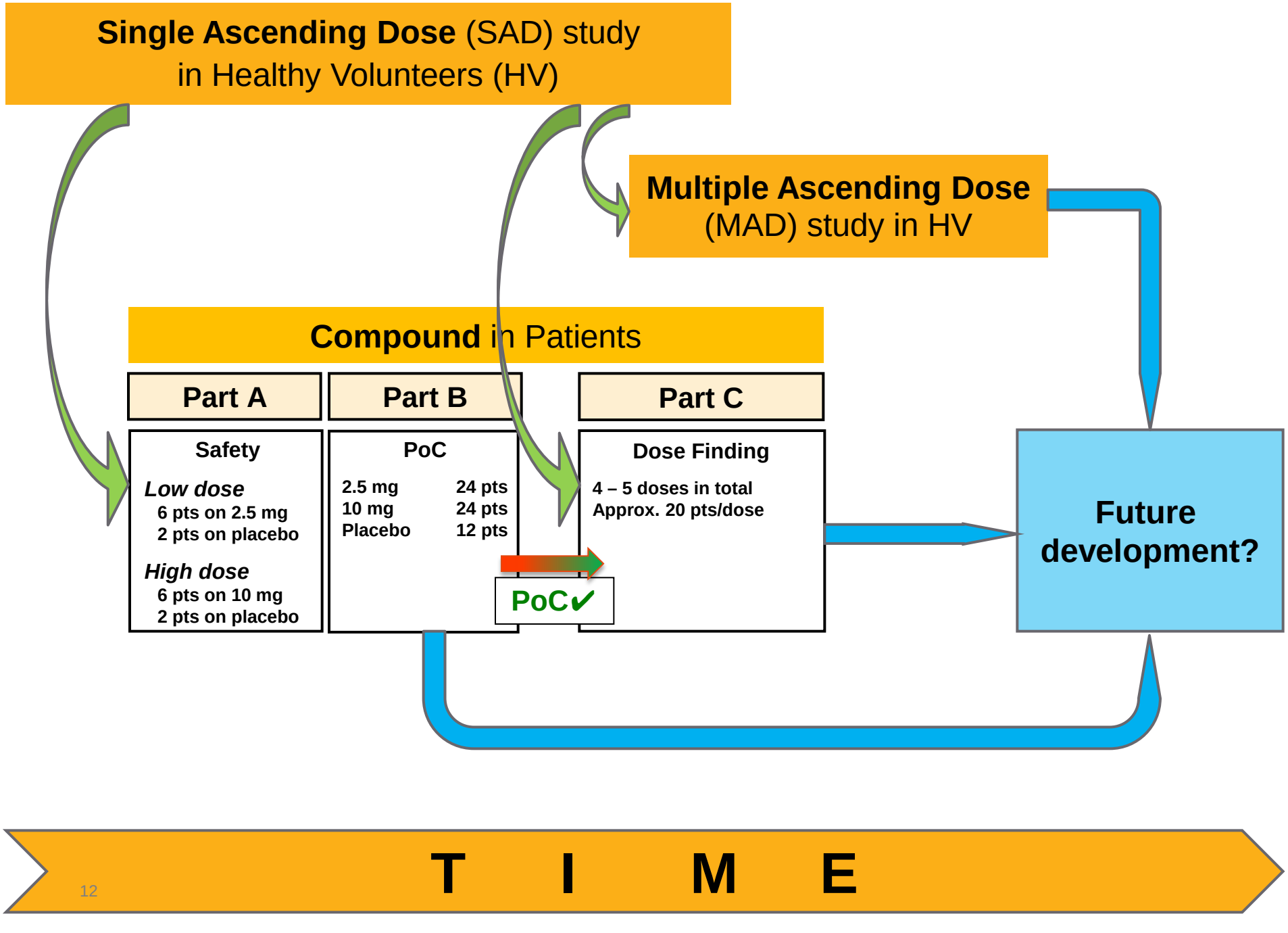
Adaptive dose-finding study in postoperative dental pain

Before start of Phase IIa trial

- Candidate compound as analgesic
  - Different pain indications of interest
- First and only clinical study: SAD FiM in HVs, slowly ongoing
  - At 10 mg at time of protocol design (later stopped at 40mg)
- Idea of the study: Quick assessment of drug efficacy (PoC)
  - Dental pain after removal of molar teeth
  - Single dose, single day, easy recruitment (one center), fast endpoint (pain reduction over 6h post operation)
  - Common first check on pain indications
    - later: potentially branching out to other indications

Before start of Phase IIa trial

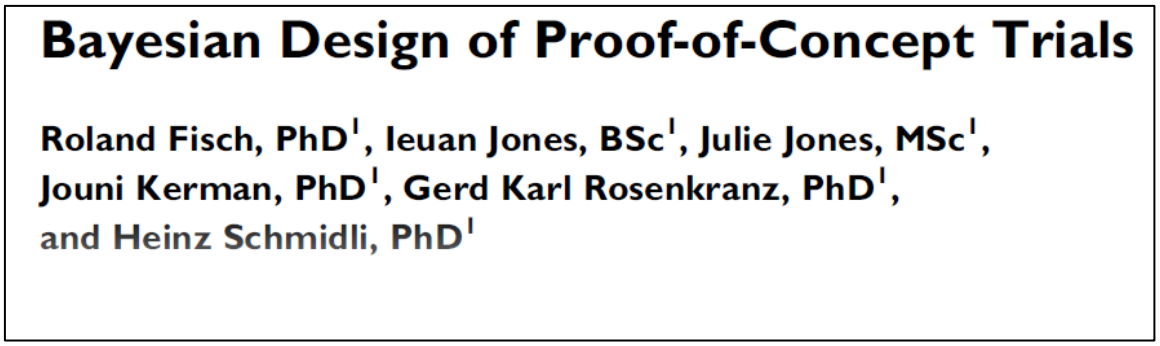
- Additional Interest: Determine dose-response curve if basic level of efficacy can be determined for a high dose
  - Advantage combination of ongoing safety studies will provide dose-response information for safety but als efficacy early on
  - Might suggest dose(s) for further study (in this or other indication, when extrapolation is possible)


Single Ascending Dose (SAD) study in Healthy Volunteers (HV)
Multiple Ascending Dose (MAD) study in HV
Compound in Patients
Part A
Part B
Part C
Safety
Low dose
6 pts on 2.5 mg
2 pts on placebo
High dose
6 pts on 10 mg
2 pts on placebo
PoC
2.5 mg 24 pts
10 mg 24 pts
Placebo 12 pts
PoC✔
Dose Finding
4 – 5 doses in total
Approx. 20 pts/dose
Future development?
T I M E

Statistical methods used

At interim

- Bayesian decision criterion used to declare PoC
  - Essentially comparing active doses to placebo and to target threshold (with different levels of proof required)
  - Using information on historical placebo controls
  - See Fisch et al. (2014) for an overview of the methodology


Bayesian Design of Proof-of-Concept Trials

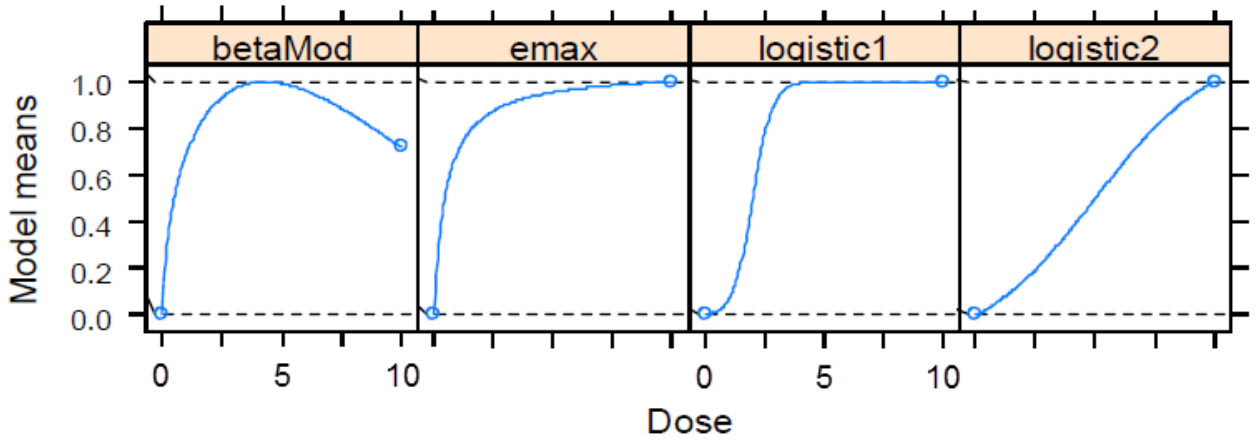
Roland Fisch, PhD[I], Ieuan Jones, BSc[I], Julie Jones, MSc[I], Jouni Kerman, PhD[I], Gerd Karl Rosenkranz, PhD[I], and Heinz Schmidli, PhD[I]

doi: 10.1177/2168479014533970

Statistical methods used

At interim

- Some dose-response information available after PoC part
  - but: only two doses and placebo
- Candidate set of models (before start of trial)
  - At interim updated based on data from 2.5mg and 10mg groups



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Statistical methods used

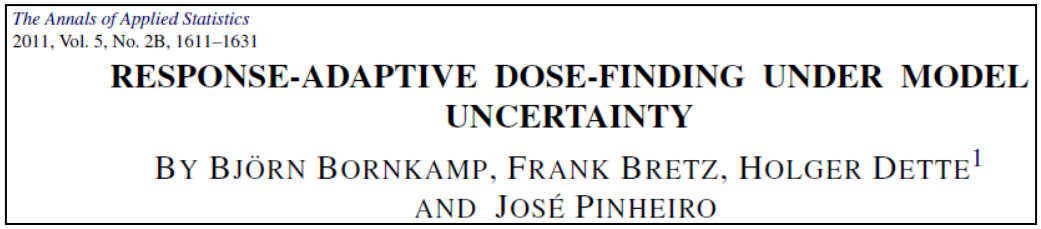
At interim

- Update design using D-optimality: Try to make the averaged determinant of the Fisher information large
  - Minimize max prediction variance around the dose-response curve
  - Input: Parameter estimates for each model and model weights
  - Output: Metric to compare the efficiency of candidate designs
- Dose-range not fixed at trial start
  - Take safety evaluations from single and multiple ascending dose studies, which are ongoing at the same time

Statistical methods used

At interim

- Updated parameters based on Bayesian approach as described in this paper



- Actual implemented design not the exact optimal design
  - a mix based on feasibility and optimality
- Extensive simulations to evaluate the performance of the design
  - see also Vandemeulebroecke et al (2011), Chapter 11, Handbook of Adaptive Designs in Pharmaceutical and Clinical Development, CRC Press

Summary

- Example illustrates a way to integrate PoC and dose-finding in one adaptive exploratory study using MCP-Mod
  - Obtain dose-response information early in development
- Adaptive design in this setting
  - Value of adaptive design often depends on operational constraints (recruitment speed, endpoint duration, time to perform interim analysis, ...)
  - Perfect scenario for an adaptive design (very fast read-out)
- Different types of adaptive designs can be used
  - Here: Guided by D-optimal considerations
  - Alternative: „scenario based designs“