Bos2 Topic I:

Dose–Exposure-Response relationship

Regulatory perspective

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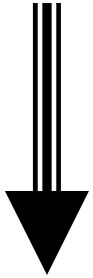
ICH-4 Dose-finding guideline (1994)

- “Agencies should also be open to the use of various statistical and pharmacometric techniques such as Bayesian and population methods, modeling, and pharmacokinetic-pharmacodynamic approaches.

- However, these approaches should not subvert the requirement for dose-response data from prospective, randomized, multi-dose-level clinical trials.”

How much confirmation (e.g. by multidose RCT) needed for regulatory decision?

- Changes in the formulation of a registered drug
- Special populations
- Orphan drugs
- New drugs



Changes in formulation of registered drug

- Minor changes in formulation/dosing schedule

- Examples:

-shortening of lock-out period of an inhaler containing opioids (allowing a more frequent dose)

-Regulatory request for PK-simulations new regimen: accumulation rate was below level of normal titration step.

-No further clinical studies requested

Changes in formulation of registered drug (2)

- Line extension (different application form (e.g IV/SC,IV/patch, IR/SR)

- high level of prior knowledge PK-PD relationships
- PK-PD modeling essential tool in development

- To what extent confirmatory trials are needed depends on
  (a) differences in PK profile between 2 forms
  (b) PK-PD relationship (biomarkers, safety parameters)

- Confirmatory trial probably needed in case of large PK differences, but may be limited to single dose based on PK-PD model

Example line extension

- Biological in RA, from IV to SC
- Healthy volunteers single dose Pk study: Cmax after SC 8o% lower, bioavailability 80%
- Concerns regarding drug-antibody formation

- Step 1: determining target level from earlier IV studies

=>Cmin driving force efficacy (DAS28) & drug-antibody formation

- Step 2: modeling to the target (IV monthly, SC weekly)
- Step 3: small-scaled PK_PD study patients
- Step 4: single-dose confirmatory trial: non-inferiority established ACR20 (20% improvement of 3 out of 6 domains), antibody more reduced SC than IV

Special populations

- Dose finding may be based on PK alone, targeting to therapeutic window of the general population
- Provided that disorder or tolerability in special population are similar to general target population (e.g. elderly more sensitive)

- PK or PK-PD modeling essential in establishing dose adjustments
- Conditions and examples will be discussed second part of this session

Orphan indications

- PK-PD model essential for dose finding
- Limited possibility of confirmative trials at different dose levels
- Solved in SPC and post-marketing studies

- Example: systemic JIA (next presentation)
- Example tafamidis (EPAR):
- Dose completely based on PD effect healthy volunteers (dosing till plateau phase PD effect)
- One single dose applied in pivotal randomised study in patients, stabilisation confirmed in patients

New drugs

- Challenges in the use M&S in dose-finding:

- Lack of suitable biomarker
- Unclear PK-PD relationships (e.g. major depression)
- Non-sensitive endpoints (e.g. composite endpoints rheumatology/SLE, responder rates)
- Variable disease (epilepsy, MS)
- No clear dose-relationship adverse events (idiosyncratic)

- These problems also relevant if you would not apply M&S...

Non-discriminating responder rates new drug

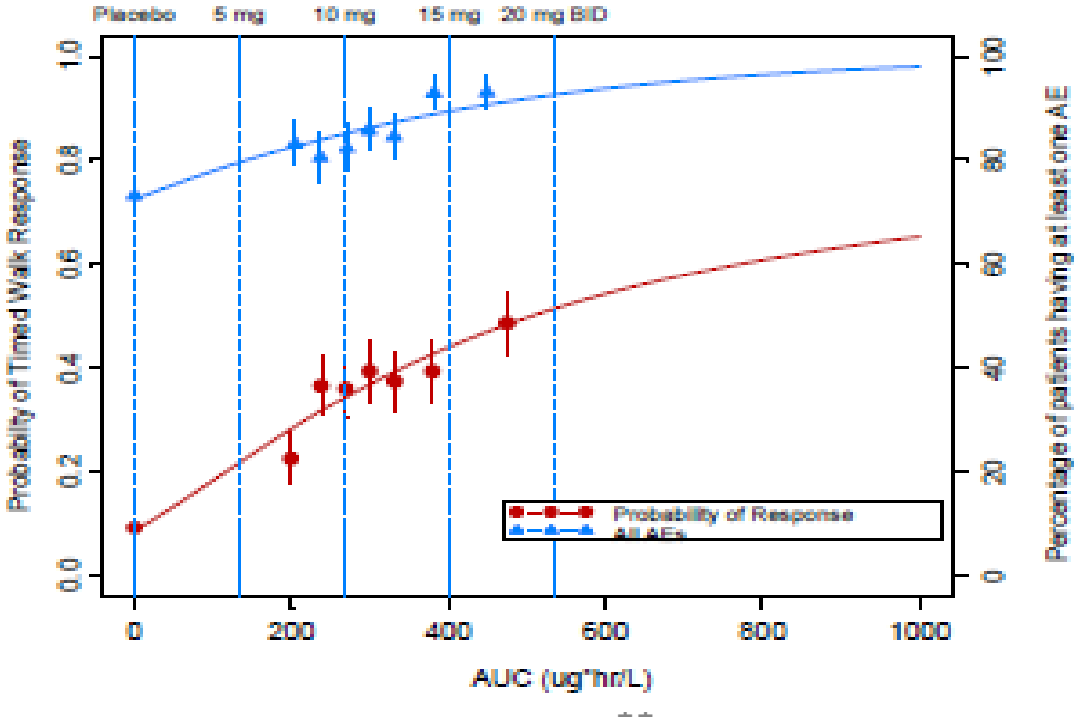
- Often little contrast between responder rates in dosing arms (insensitive upper range)
- Closer look at dose-PK-PD relationships can be helpful for decision making.

- Two examples:

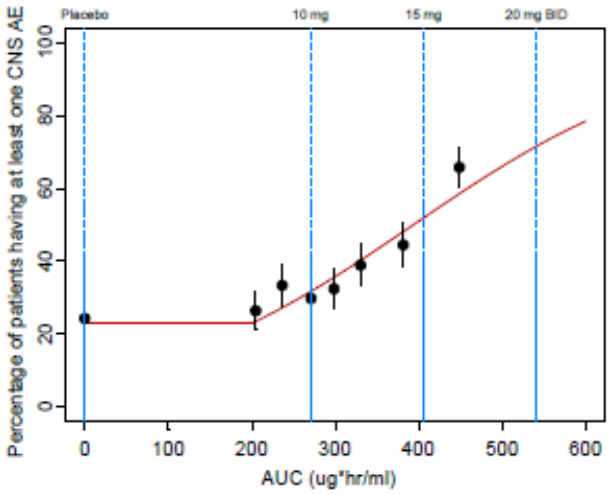
M&S dose finding Example 1

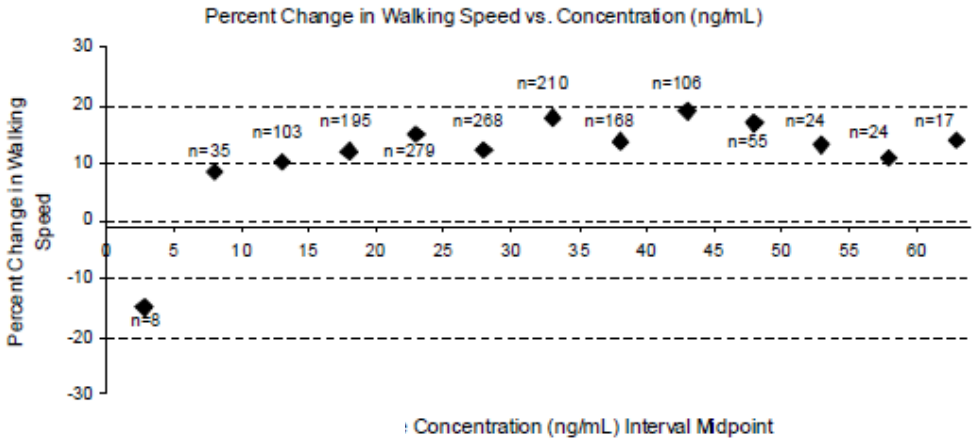
Model appears to indicate that 20 mg or more is most effective

Safety: high placebo effect (Multiple sclerosis)



Example 1 (continued)





- Confirmatory trial: Flat PK-response curve (right panel)
- Clear PK-Safety relationship for CNS events (left panel)

- Decision: 10 mg

Example 2

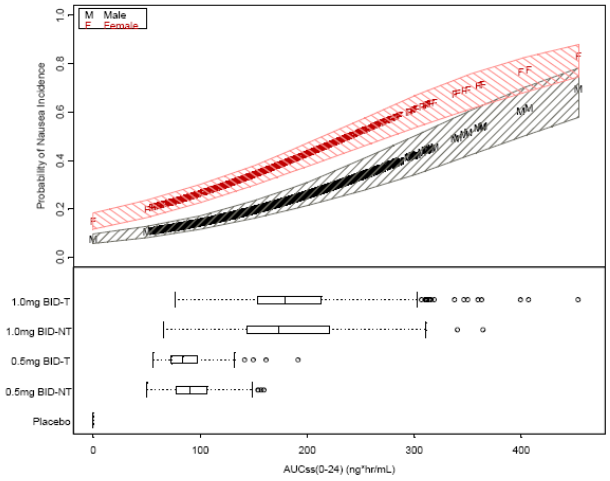
- Phase 2:Placebo:12%

	Low, NT	Low T	*Low pooled*	High NT	High T	*High pooled*
N	124	129	*253*	124	129	*253*
Resp. rates	49.2%	41.1%	*45.1%*	46.0%	55.0%	*50.6%*
OR 95% CI		6.1 3.3-11.1				7.8 4.2-14.3

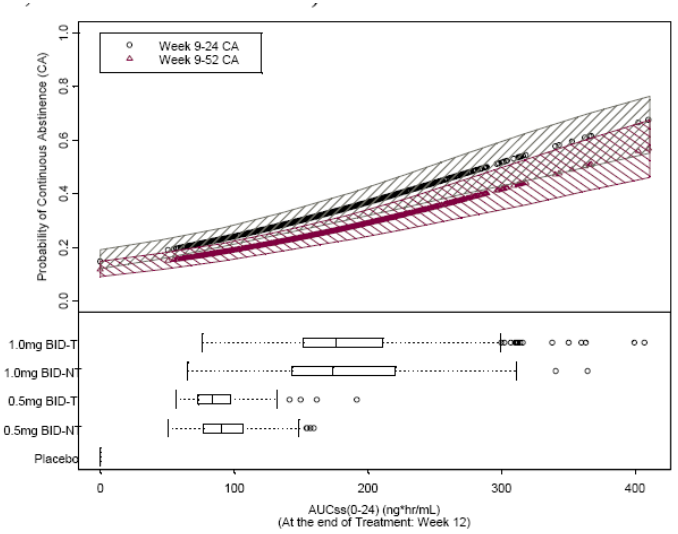
- Phase 3 (692 subject) high dose: 44.2%, placebo:17% (OR:2.7-5.5)

Example 2

PK-safety



Pk-response



Regulatory decision: high dose accepted, but lower dose should become available for intolerant patients

Discussion regulatory view

- Hypothesis: *"Use of M&S with existing information (data, physiological/ mechanistic knowledge) and reasonable assumptions will allow for improvements and efficiency in informed decision making to improve the outcomes for patient safety and efficacy in the clinical pharmacology arena"* appears justified.

- In assessment emphasis on confirmatory trial outcomes. If model assumptions not confirmed, we hardly look back at the models.

- On the other hand: Models often not prominently reported in key reports of the dossier like the Clinical Overview

- Both parties: Do we make optimal use of the possibilities that modeling can offer?

- Sharing expertise in model-building (Scientific Advices)