# Phase 2b dose selection, leveraging comparator data through multidisciplinary modeling & simulation

Thomas Kerbusch

Thomas Kerbusch* (1), Russ Wada (2), Anthe Zandvliet (1), Kuenhi Tsai (6), Jing Su (6), Joanna Zhuoying Peng (4), Yaming Hang (6), Christine Xu (3), Richard Shames (5), Ann Horowitz (3), Diane Neiman (4), Mani Lakshminarayanan (6), Usha Barai (3), Ferdous Gheyas (3), Paul Peloso (4), Devan Mehrotra (6), Nancy Zhang (2), Hanbin Li (2), Jaap Mandema (2), Gary Herman (4), Sandy Allerheiligen (6)

(1) Merck Research Laboratories, Oss, The Netherlands; (2) Quantitative Solutions, Menlo Park, CA, USA; (3) Merck Research Laboratories, Kenilworth, NJ, USA; (4) Merck Research Laboratories, Rahway, NJ, USA; (5) Merck Research Laboratories, Palo Alto, CA, USA; 6 Merck Research Laboratories, Upper Gwynedd, PA, USA.

MERCK

Multi-disciplinary collaboration
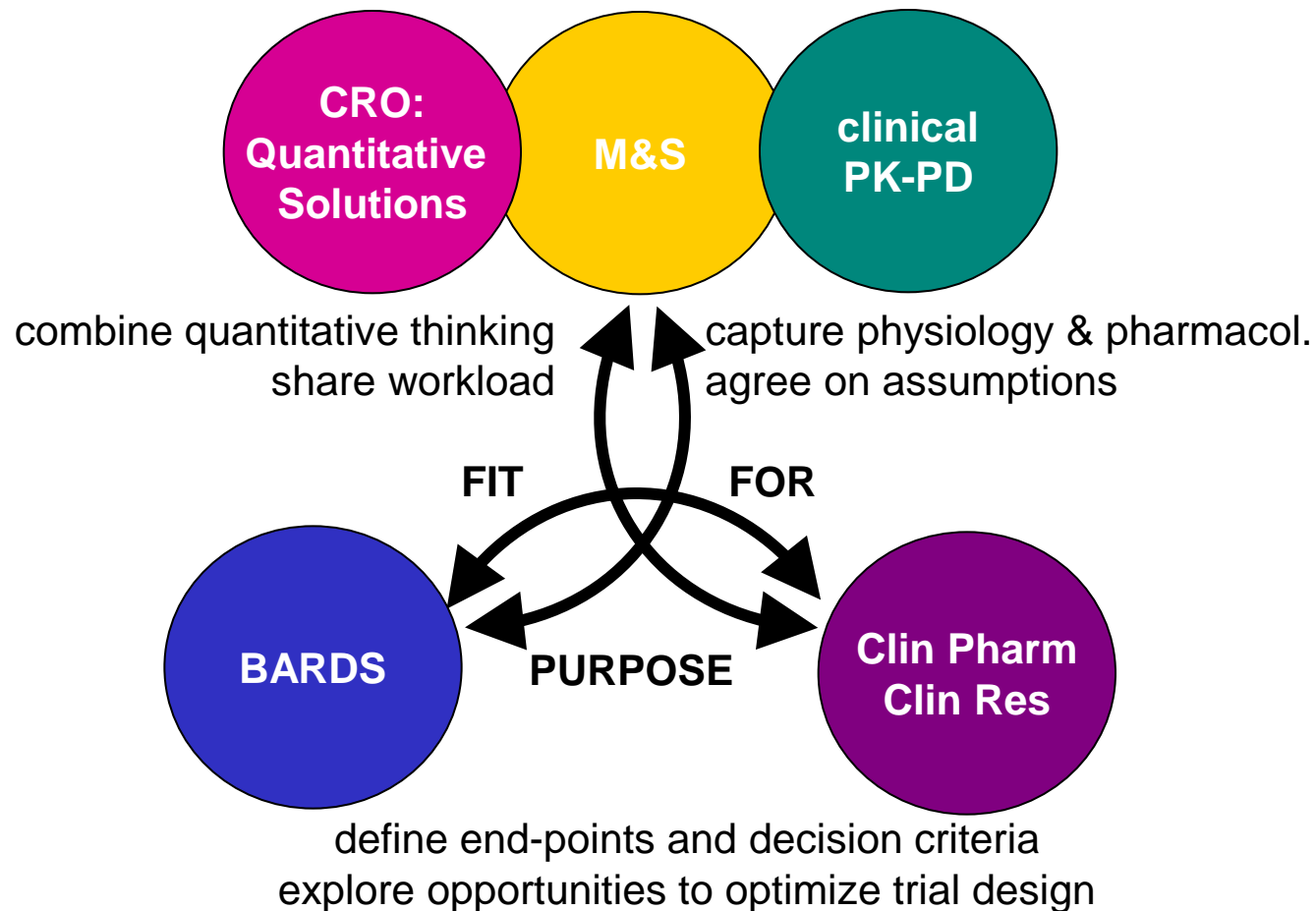
Difficult to establish a dose-response relationship based on Phase 1b data

- Cohorts Phase 1b study:
  - ●1x mg/kg (n=4) IV
  - ▲5x mg/kg (n=4) IV
  - ◆30x mg/kg (n=8) IV
  - ▼100x mg/kg (n=8) IV
  - ■ placebo ratio 3:1

- Strong PoC response: All active treatments resulted in maximal effect at W28

- Need to select Phase 2b dose-range using Phase 1b data

- Problem:
  - Limited Phase 1b data, with n=3-6 patients per dose group.
  - No robust PKPD model could be established.

IV doses at 0, 8, and 12 weeks
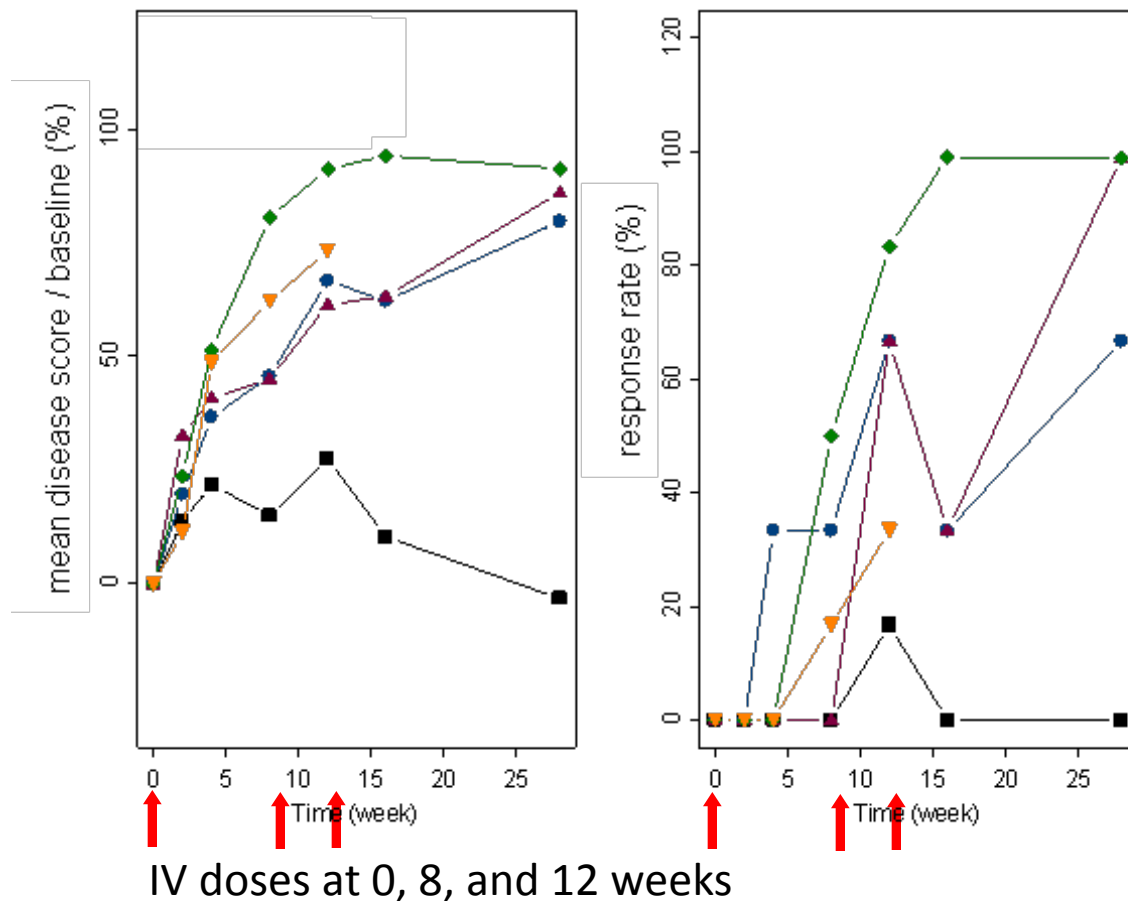
Dose selection for Phase 2b study using limited Phase 1b data

- Initial proposal for Phase 2b dose selection: based on max injectable SC dose
  - 25 mg SC at W0, W4, W16 (n=35)
  - 100 mg SC at W0, W4, W16 (n=70)
  - 200 mg SC at W0, W4, W16 (n=70)
  - 200 mg SC every 4 weeks (n=35)
  - Placebo SC every 4 weeks (n=35)

- Decision required: **Phase 2b dose-selection**
  - Will the initially proposed dose range (25-200 mg) allow for:
    - estimation of dose-response?
    - determination of lowest maximum effective dose?

- Actions: **Conduct a comparator analysis**
  - Model-based dose selection
    - Solution to in-house data limitations: borrow strength from published comparator data
  - Best-in-Class strategy
    - Explore comparator landscape to understand requirements for Phase 3 doses – need for maximum learning in Phase 2b

Critical assumptions comparator analysis

- The maximum efficacy for Merck's compound is similar to other compounds with similar mechanism-of-action (MoA)
- The time-course of the onset of response is similar across compounds
- The efficacy of Phase 1b dose regimen (wk0, wk8, wk12) of Merck's compound is similar to the efficacy of the Phase 2b dose regimen (wk0, wk4, wk16).
- Phase 1b and Phase 2 patient populations are assumed the same.
- Mean study-arm level data were combined for over 10,000 patients.

| Compound		MoA	# Trials	# Study arms incl. plac	# pts
Adalimumab	(Humira)	Type 1	4	9	1658
Etanercept	(Enbrel)	Type 1	9	20	2868
Infliximab	(Remicade)	Type 1	6	15	1695
Ustekinumab	(Stelara)	Type 2	5	13	2868
Briakinumab	(ABT-874)	Type 2	2	6	1585
Merck compound			1	5	24

Confidence in estimating efficacy response can be enhanced by co-modeling through correlation
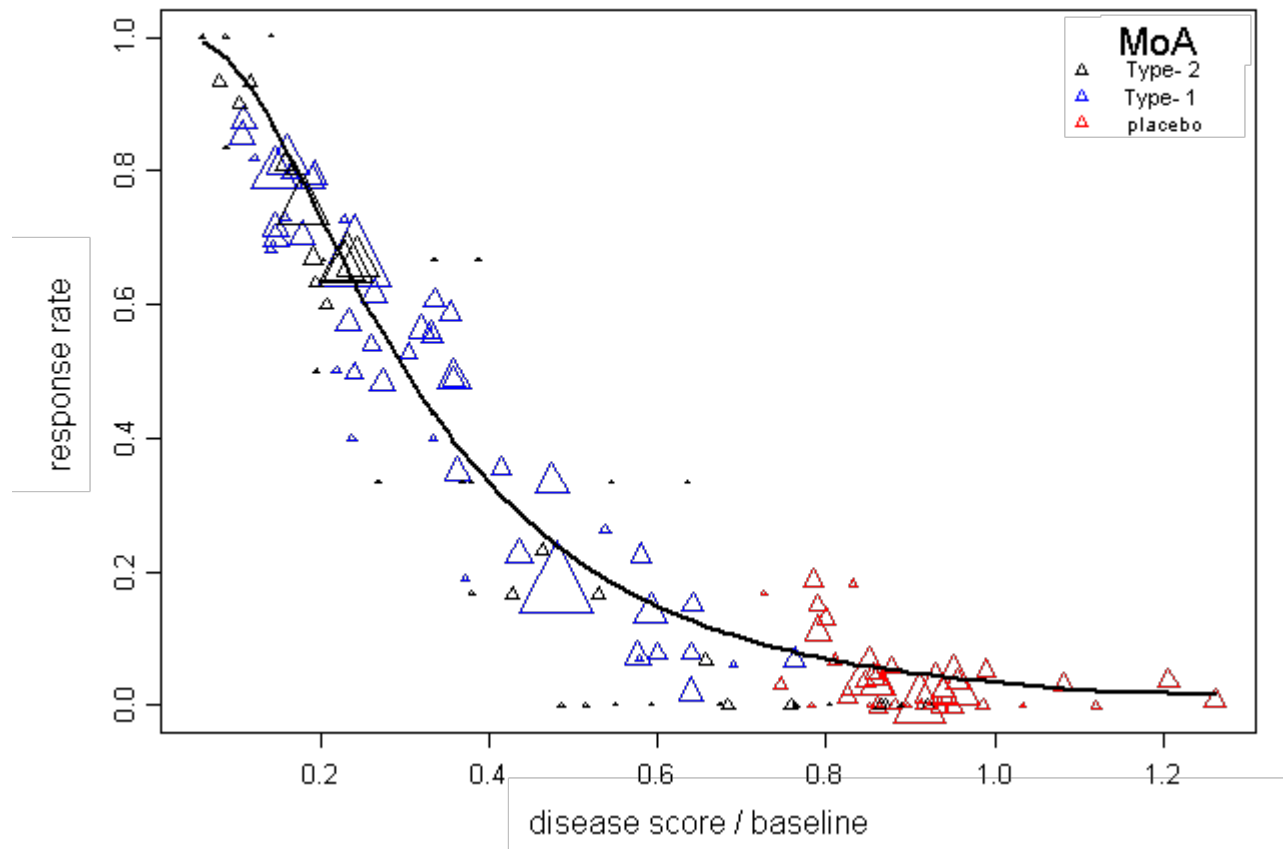

Data are plotted across all arms and time points in the database. Symbol size is proportional to the square root of the arm size. The fitted line is the cumulative normal distribution with mean of log (disease score / baseline), standard deviation of 0.66, and cutoff at -1.2.

Dose-response models of in-house compounds and competitors (week 16 , 95% CI)
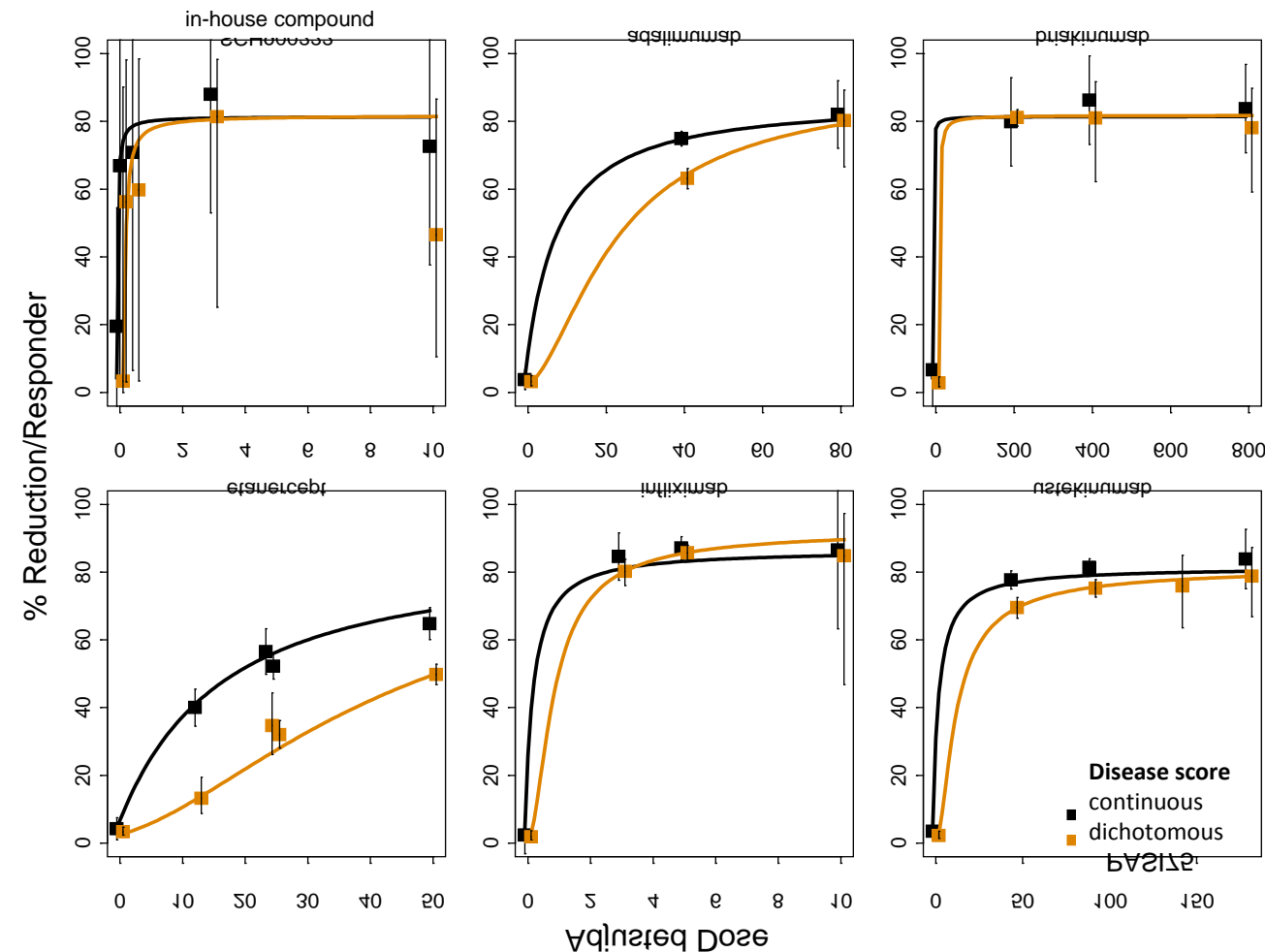
- All compounds were estimated with different potencies

- Onset of efficacy faster for mean % change than for responder fraction

- Limited Ph 1b data (n=24) resulted in large uncertainty

# Dose-response model of in-house compound: increased response over time (80%CI)
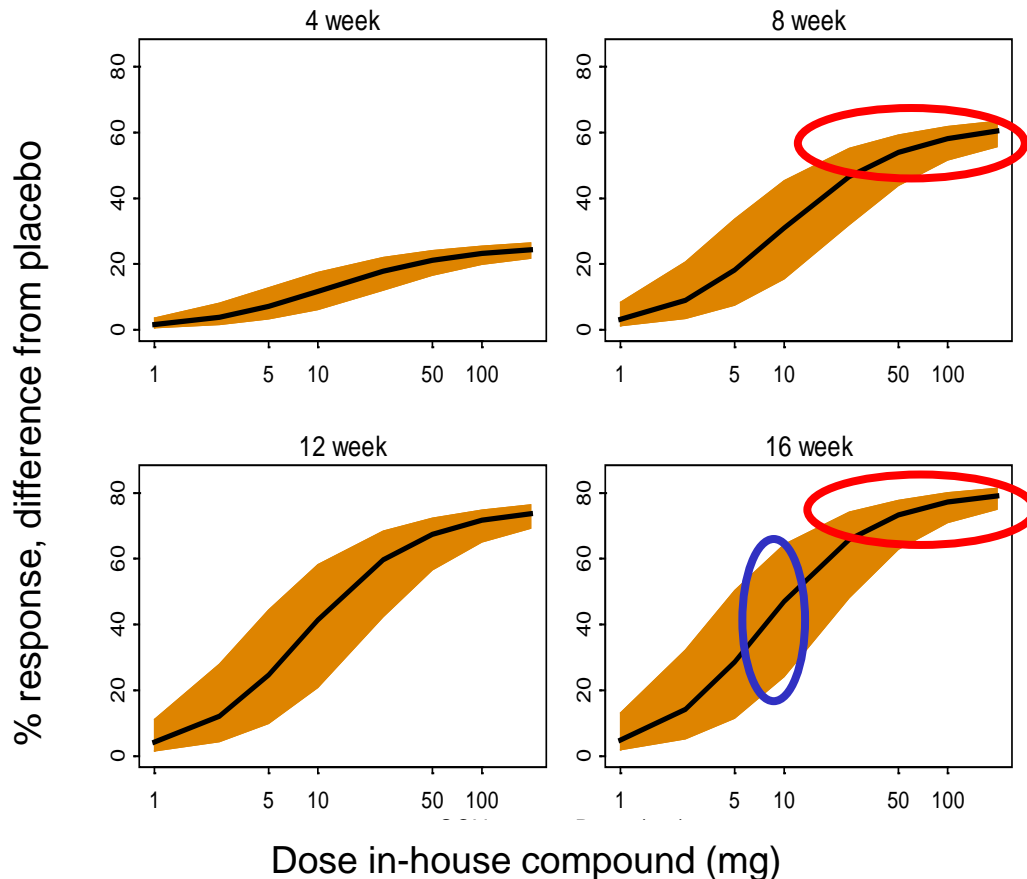
Dose-response

- Near maximum effect is predicted to be achieved ≥50 mg.

- Doses of 50-200 mg are predicted to have little separation in time to reach maximum effect. Therefore, 200 mg is not predicted to have a faster maximum effect.

- 5 mg and 25 mg will allow for doses near ED50 (~8.4 mg) and are predicted to allow for establishing dose-response

Positioning of in-house compound in the competitive landscape: a sneak preview

- Doses > 50 mg (0, 4 16w) predicted to be superior (positive difference in plot) to etanercept, adalimumab and ustekinumab.

- Similar potency and onset of action → no major competitive advantage over ustekinumab
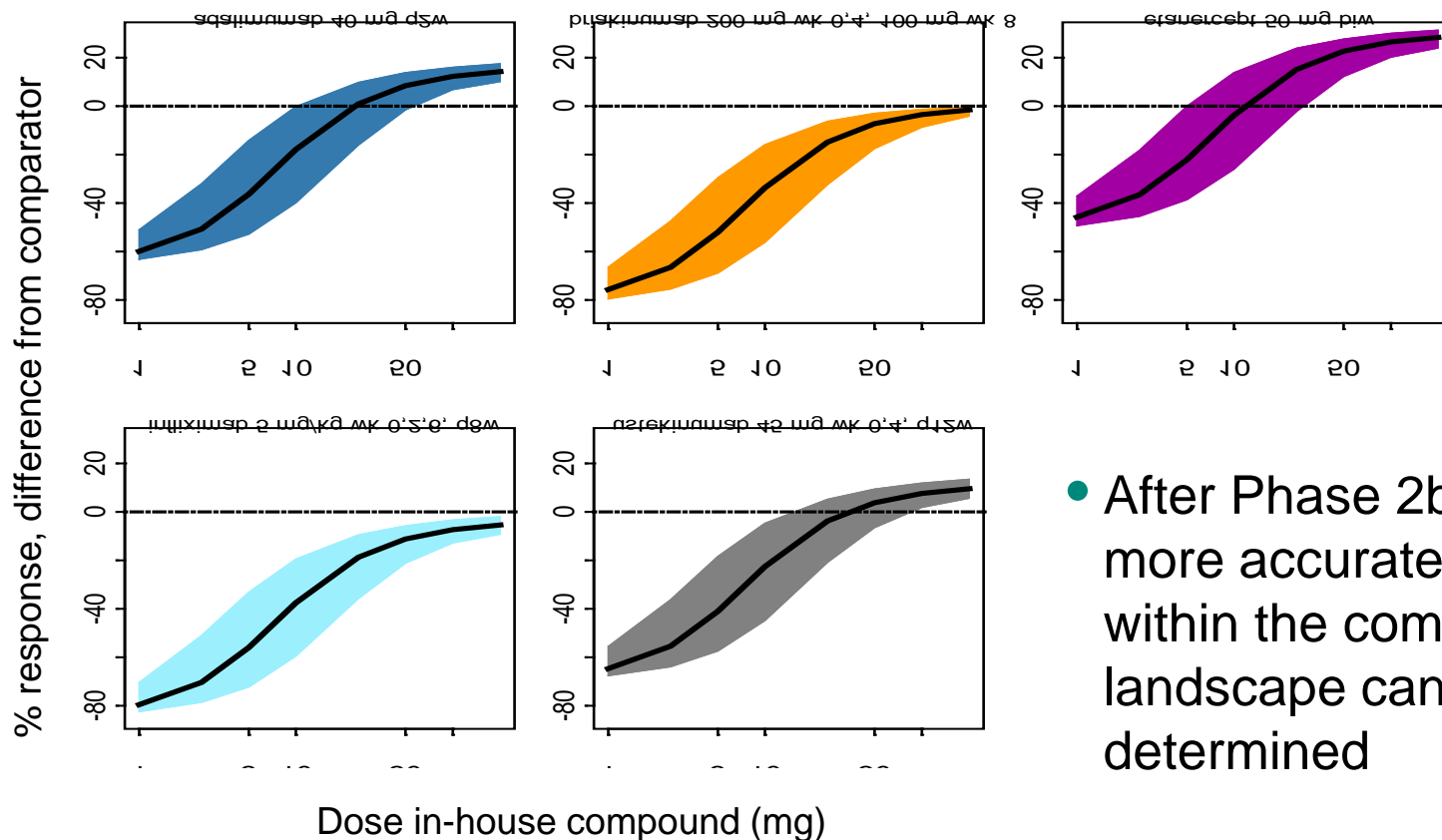
- After Phase 2b a much more accurate positioning within the competitor landscape can be determined

Clinical trial simulations

- Why
  - Including doses around ED50 in the Phase 2b trial will allow for identification of the lowest dose reaching maximum effect ("cusp of Emax"): best dose for Phase 3.

- How
  - Limitations and uncertainty in the available data are a fact.
  - Clinical trial simulations should incorporate these and still allow for a robust dose selection decision for Phase 2b.
  - Dose-range should bracket (predicted) maximum response and ED50.
  - Doses for Phase 2b were evaluated for being "near" placebo, "near" maximum effect or in between (near ED50) by simulating 200,000 Phase 2b trials.

Making the decision
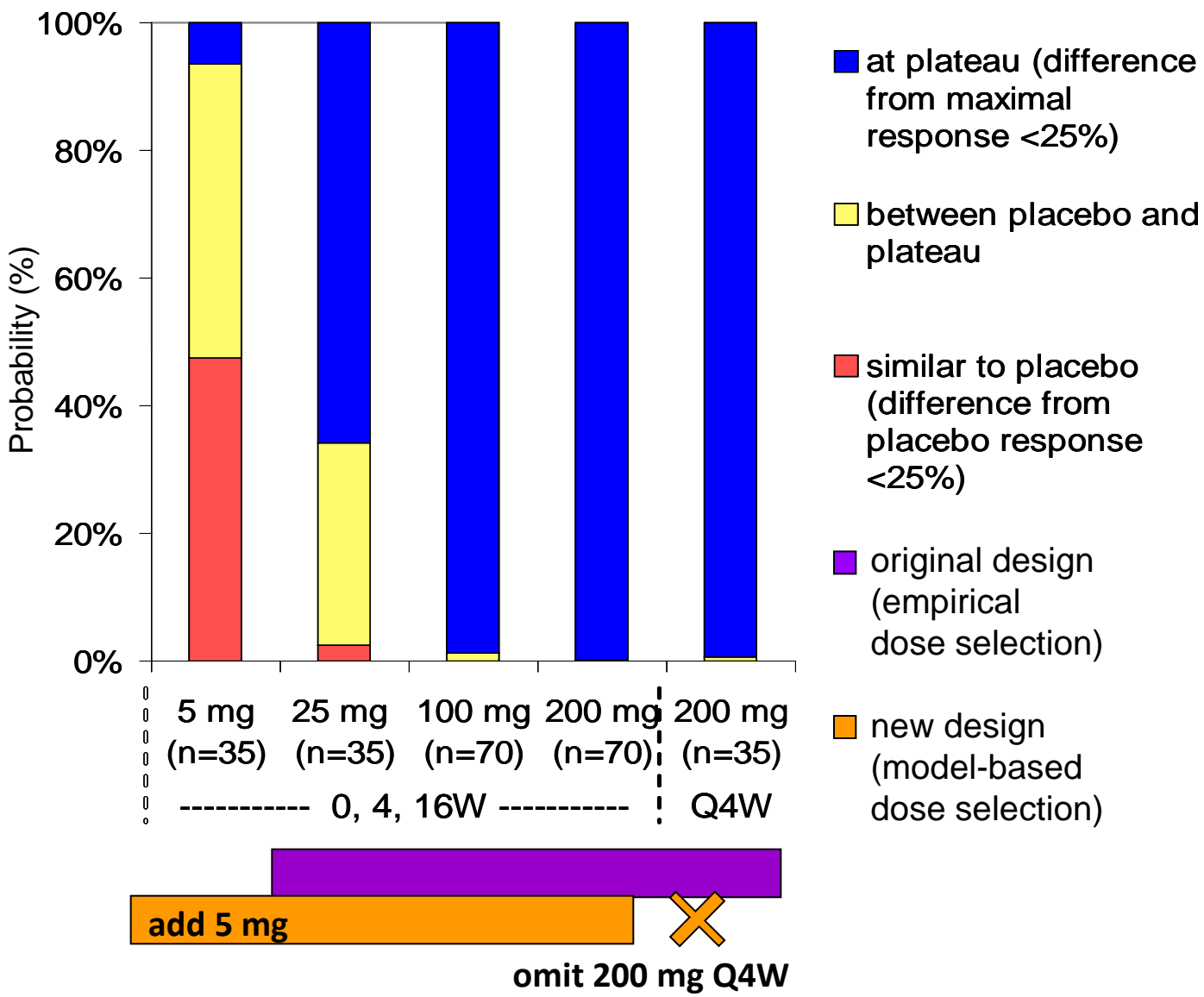
- 100 and 200 mg were predicted to be at the plateau of the dose-response relationship.

- Monthly 200 mg (max. feasible exposure) is not informative: drop arm

- Establishing dose-response requires a dose level between placebo and plateau: reasonable probability of 5 mg not being near plateau or placebo (yellow bar).

Conclusions

25 mg W0, W4, W16 (n=35)
100 mg W0, W4, W16 (n=70)
200 mg W0, W4, W16 (n=70)
200 mg every 4 weeks (n=35)
Placebo every 4 weeks (n=35)

→

5 mg W0, W4, W16 (n=35)
25 mg W0, W4, W16 (n=70)
100 mg W0, W4, W16 (n=70)
200 mg W0, W4, W16 (n=70)
Placebo W0, W4, W16 (n=35)

Value addition of M&S Comparator Data Analysis

- Probability of success of establishing dose-response:
  - was low for the original design:
    - 200 mg arm with monthly injections (max. feasible dose-intensity) is not informative, because 200 mg W0, W4, W16 already predicted above Emax
  - is high for the new design:
    - A 40-fold dose-range 5-200mg brackets the predicted ED50 (8.4 mg) and maximum effect (≥50 mg).

- Model-based dose-response in phase 2b will allow for optimal dose-selection for phase 3.

- Re-evaluating Competitive Landscape will allow for optimal Best-in-Class strategy

BACKUP

Comparative efficacy model

- The model has a maximum effect that gradually increases over time to a steady-state value.
- There is a dose-response relationship at each point in time.
- Key assumptions:
- The maximum efficacy for in-house compound is similar to competitors with same MoA
- The time-course of the onset of response is similar across compounds