EMA EFPIA workshop
Break-out session no. 4

Theme 1
Modelling and simulation to optimize the design of confirmatory trials

Case Studies: Common ground

- Modelling and simulation using supplementary information to underwrite Phase 3 dose selection and Phase 3 design.
  - MKS (Pfizer): Using information from other indications for this compound.
  - VC (Roche): Using literature information for this disease area / endpoint.

Case Studies: Position statement

Understanding the totality of data and how it relates to prior information from Phase 3 (for example, through evidence synthesis of literature data) provides quantitative evidence to support Phase 3 design and dose-selection

Question: Regulatory feedback

- Require ***early*** regulatory feedback and ***agreement*** on the acceptability of these approaches, models, inferences to minimise the probability of EOP3 discussion around the Phase 3 study design, choice of doses.

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Case Study 1: Using totality of data for dose-selection, Phase 3 design, internal and regulatory decision making.

Mike K. Smith
Pfizer

Case study key points

- Dose-selection should be based on quantifying effects across all key endpoints.
- Quantifying the probability of meeting Phase 3 target efficacy and Phase 3 trial success across the dose-range facilitates internal and external decision making.
- Sensitivity analyses for Phase 3 should be performed to examine “What if…?” questions.

Background & Rationale

Current Ulcerative Colitis (UC) treatment paradigm: Steroids, anti-inflammatories, Anti-TNFalphas.

Tofacitinib: Oral treatment, small molecule

- Studied in other inflammatory indications.

M&S ***in addition to*** Statistical Analysis Plan (SAP) / Clinical Study Report (CSR) analyses and clinical interpretation of Phase 2 trial data.

Objectives of the M&S work

- Modelling and simulation carried out to provide additional quantitative evidence for Phase 3 dose-selection and internal decision making.

Available data

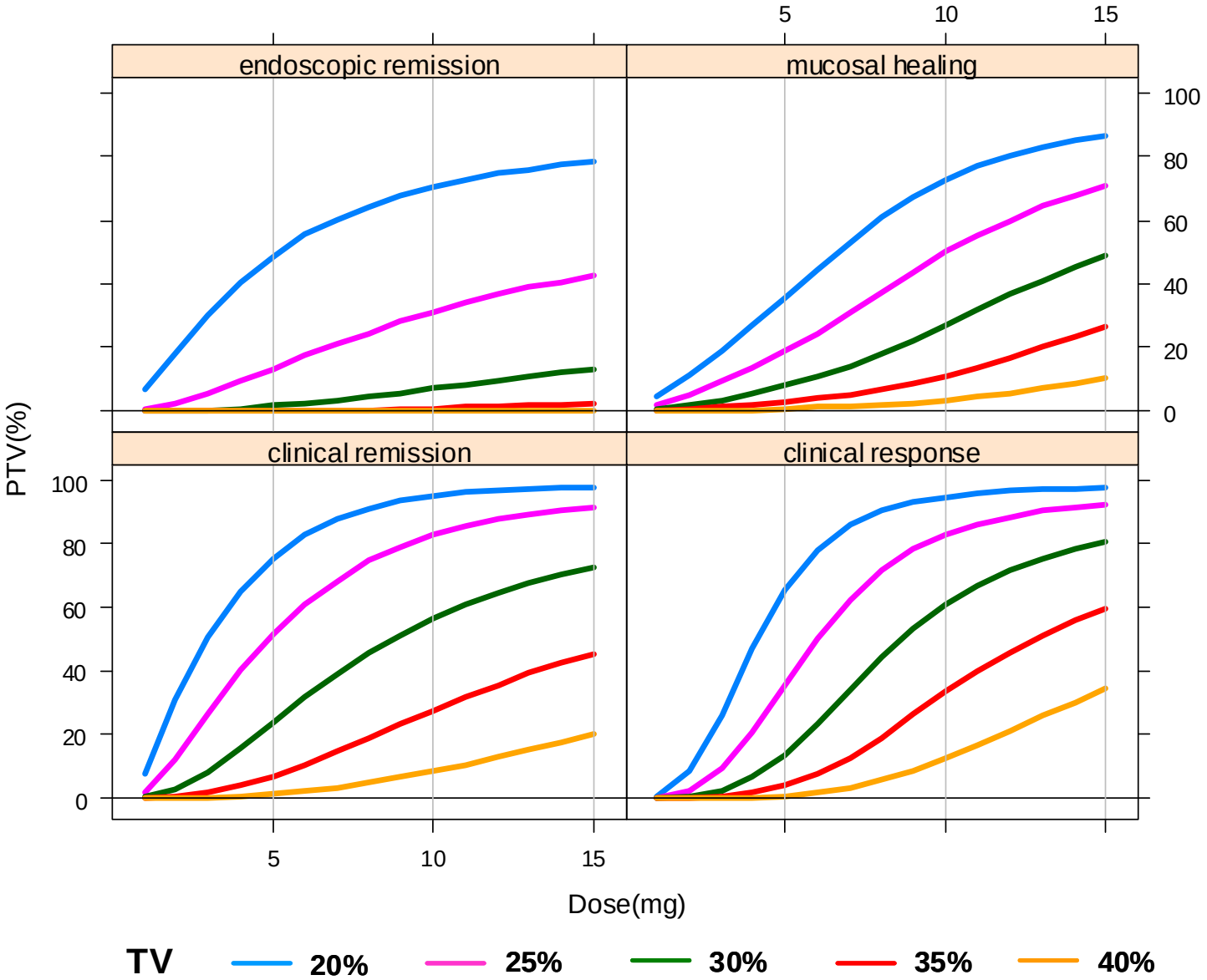
- Tofacitinib study in Ulcerative Colitis (UC) A3921063 (N=146 patients)
- Placebo, 4 active doses tofacitinib.
- 8 week endpoint
- Endpoints: Mayo Score clinical response / remission; endoscopic endpoints (mucosal healing, endoscopic remission)
- CSR Analysis based on Emax dose-response model of efficacy.
  - Good evidence of efficacy vs placebo across efficacy endpoints.

- Key Phase 3 endpoints: Induction of remission (8 weeks), maintenance of remission (1 year)

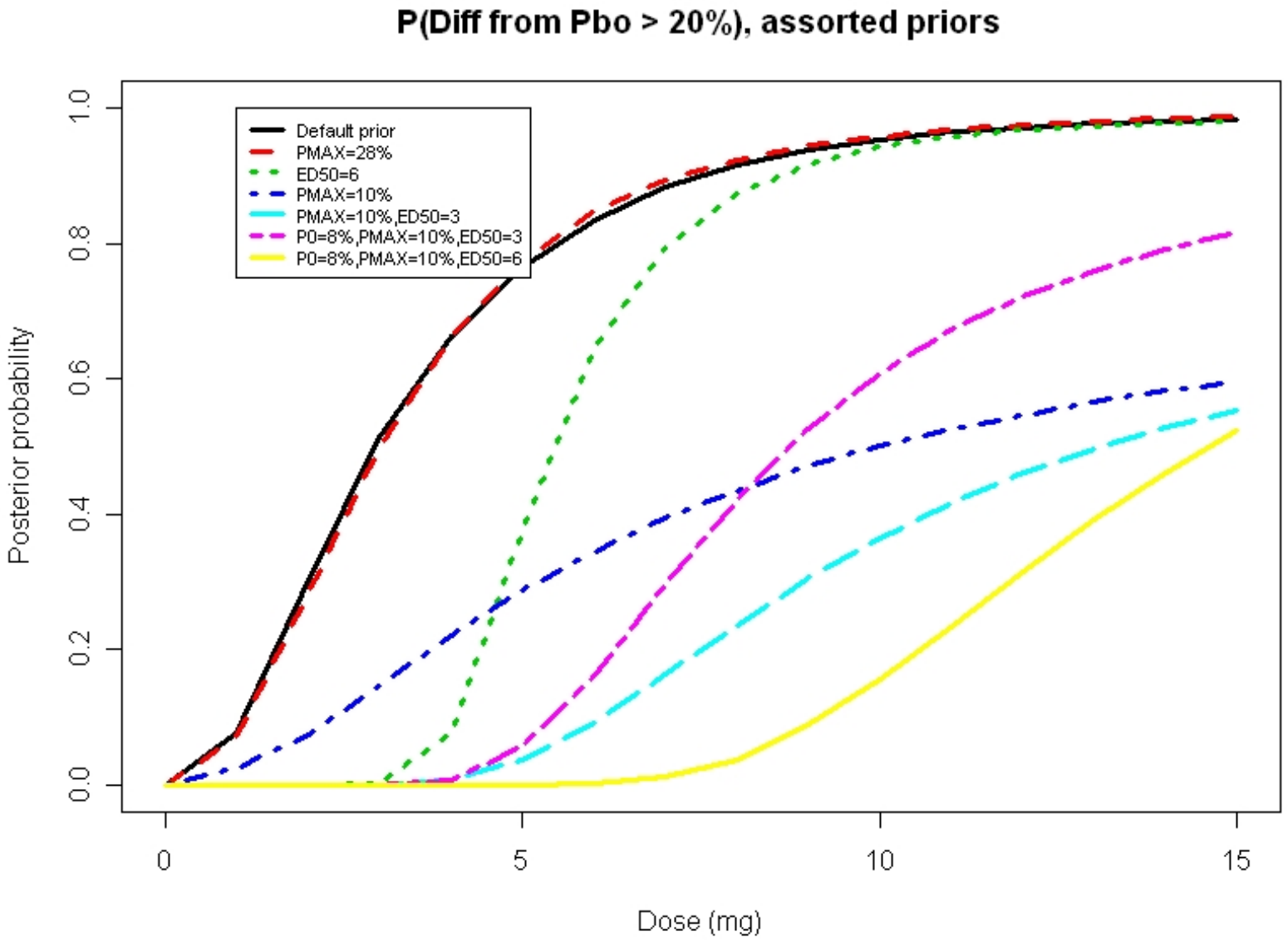
- Literature data (anti-TNFalpha):
  - 2 studies (ACT1 & ACT2) using Remicade (infliximab); 1 study using Humira (adalimumab).
  - ACT1 and ACT2 are the only reported studies with induction and maintenance data.

- Safety database from Phase 2 & Phase 3 studies of tofacitinib in other indications.

M&S Results – P(Target Value)



Sensitivity to prior choice



M&S Assumptions

- We assume that the Emax model adequately describes the dose-response relationship across clinical endpoints.
  - Simple dose-response relationship of proportion of patients achieving response / remission / endoscopic remission / mucosal healing.
  - Longitudinal modelling not performed since endoscope only taken at baseline, week 8.
- Assume that Phase 2 and Phase 3 populations are comparable, Phase 2 data is predictive of Phase 3.
  - Sensitivity analysis quantifies the effect of departures from this assumption.
- Little information in literature about extrapolation from week 8 induction to 1 year maintenance in UC.
  - 8 week induction to 1 year maintenance ***not*** modelled.
  - Phase 3 maintenance study includes > 1 active dose.

Regulatory Feedback on Case Study 1

- M&S presented as supportive evidence for Phase 3 program design and dose-selection at EOP2 regulatory interactions with FDA, EMA, PMDA.

- Dose-selection rationale was accepted in pre-meeting feedback, with no additional discussion of dose-selection necessary.
  - No specific feedback on M&S methods, results.
  - Sponsor interprets this as acceptance of the methods, results and application of M&S derived information.

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Case Study 2: PPARγ phase 3 dose selection using a general PPAR drug-disease model based on a meta analysis of over 40 PPAR clinical trials.

Valérie Cosson
F. Hoffmann–La Roche Ltd

Case study key points

Optimization of dose and Phase III design selection using a robust HbA1c kinetic model to describe the PPAR pharmacotherapeutic 'landscape'

- By understanding the dose response for each of the three compounds developed previously (Rezulin, Actos and Avandia), and by combining this information with Phase II data on Roche PPAR, critical decisions around the Phase III program design can be made.

- The selection of doses for Phase III, the choice of competitor, and the level of efficacy required to demonstrate clinical benefit are of particular importance.

Data Source / Available Data

- Aggregation of the clinical study data for studies on Actos, Avandia and Rezulin from numerous sources of information:
  - FDA documentation
  - EMA documentation
  - Literature search engines
  - Internet searches

- A total of 42 studies in Type 2 diabetes patients treated with PPAR:
  - 139 treatment arms:
  - 298 longitudinal profiles
  - N > 16000 patients

- For each treatment arm, often (but not always) data available for both HbA1c and FPG.

A joint FPG/HbA1c model

FPG Model

Disease/Placebo effect

$$plac\_eff = intercept \times (1 + fr \times slope1 \cdot time + (1 - fr) \times oad\_eff \cdot time\_delay))$$

where $time\_delay = 1 - exp(-k1 \cdot time_2)$

fr = fraction of patients in 'drug naive' group

Drug/Delay

$$drug\_eff = \frac{E_{max} \cdot Dose^{\gamma}}{ED_{50\,j}^{\gamma} + Dose^{\gamma}} \times (1 - exp(-k2 \cdot time))$$

where

$k2$, the delay in reaching full PD effect

γ. the hill coefficient

$Emax$, the maximal effect

ED_{50}, the dose which gives 50% of $Emax$

$j = 1,2,3,4,5,6$ (tro, pio, ros od, ros bid, 570, rag)

Effect

$$effect = plac\_eff \times (1 - drug\_eff)$$

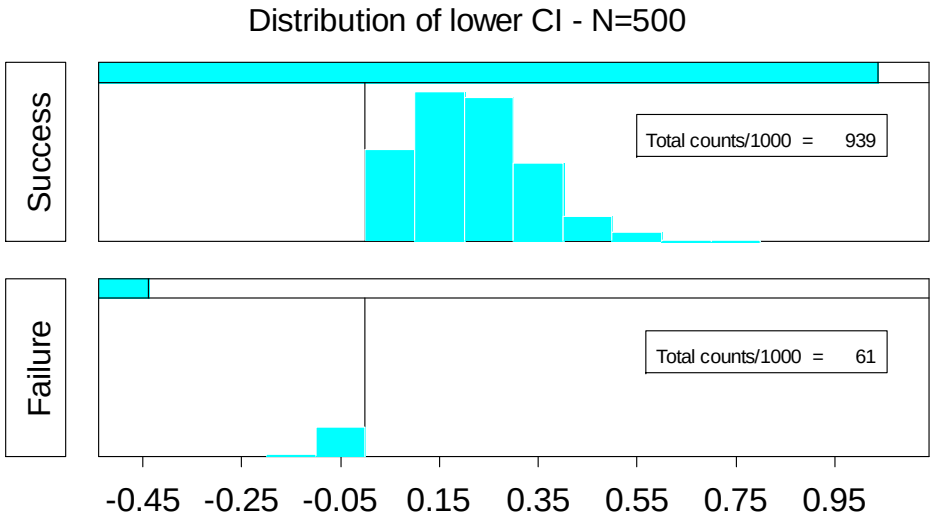
HbA1c Model

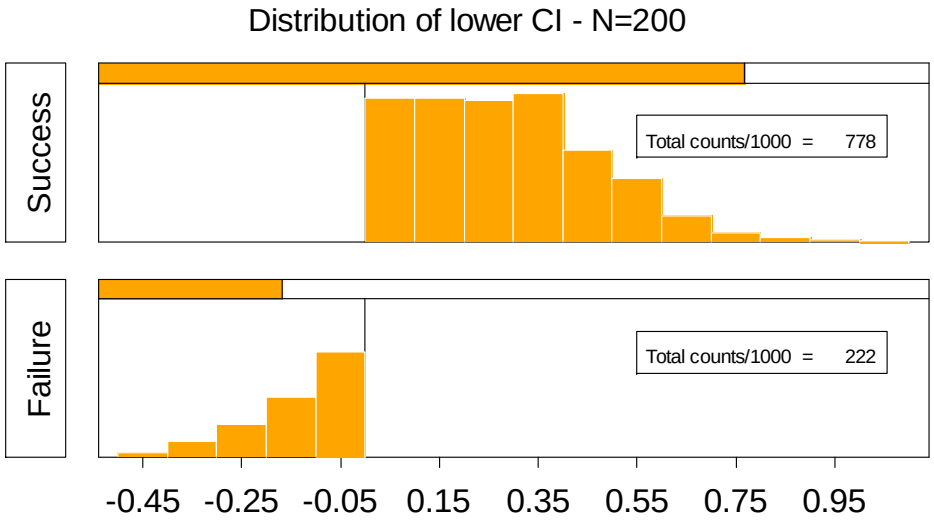
- A similar structure for HbA1c:
  - Shared Emax and ED_{50}
  - Different equation for drug/delay (HbA1c changing more slowly)

Joint FPG/HbA1c Model

- Model had 38 parameters, including 6 random effects

M&S Results: The likelihood of success was determined for different sample sizes in Phase III





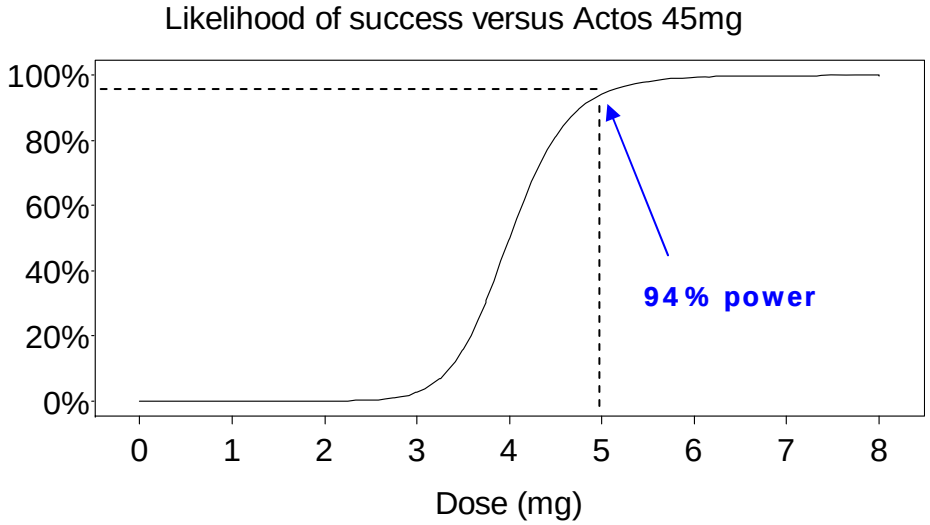
5mg Roche PPAR vs. Actos 45mg

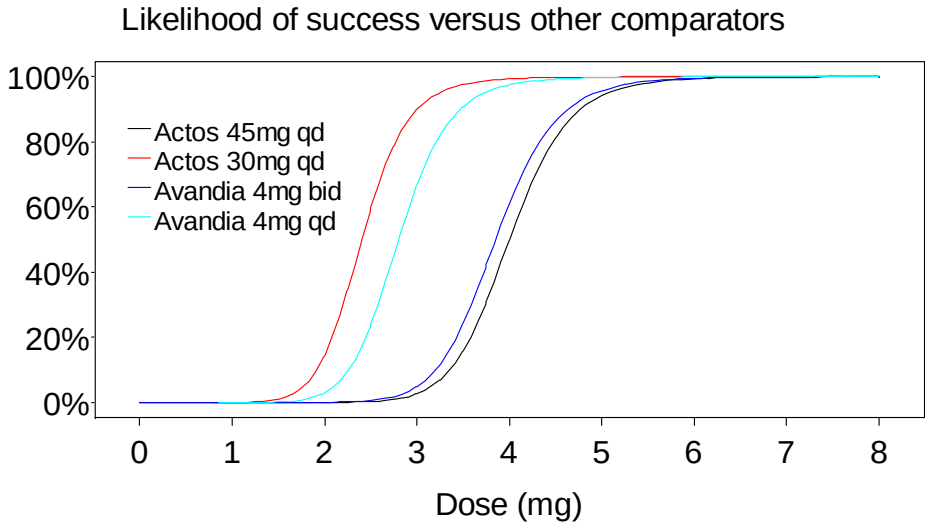
- Variability from using finite sample size "added in"
- 1000 simulated studies

- If lower 95% CI > 0, then have shown superiority (=success).

- Chance of success = 94% for N=500, and 78% for N=200.

M&S Results: The likelihood of success was determined for different comparators over the Roche PPAR dose range





- N=500 per arm
- Y-axis = % of simulations that are successful (lower 95% CI >0 = superiority claim)
- X-axis = Dose of Roche PPAR
- A dose of 5 mg is predicted to have 94% chance to be superior to Actos 45 mg qd

Conclusions on Case Study 2

1. The use of a robust model that described the pharmacotherapeutic area of the PPARγ provided a strong rational for dose and Phase III design selection of the Roche PPAR

2. Planning (1 year) prior to Phase II results enabled model to be in place and evaluated beforehand

Question: Regulatory feedback

- Require ***early*** regulatory feedback and ***agreement*** on the acceptability of these approaches, models, inferences to minimise the probability of EOP3 discussion around the Phase 3 study design, choice of doses.

Context: Regulatory feedback

- Modelling and simulation may have significant impact for Phase 3 planning (design, dose-selection etc.).
- Early technical input from regulators helps ensure inferences, decisions, plans, designs are made on a mutually agreed foundation.
  - Input on: data used in modelling (perhaps including literature data sources), models, assumptions, simulation scenarios.

Question: Regulatory feedback

- Require ***early*** regulatory feedback and ***agreement*** on the acceptability of these approaches, models, inferences to minimise the probability of EOP3 discussion around the Phase 3 study design, choice of doses.

- Advice from EMA for EFPIA:
  - Best timing for seeking this input, feedback?
  - How to ask the right question(s) to get appropriate feedback?

Questions: Extension

- Under what circumstances would using supplementary information (internal or external) be considered acceptable?
  - For dose selection?
  - For Phase 3 design (number of doses, numbers of subjects, comparator arms)?
  - For Phase 3 programme design: 1 study vs 2 studies?
- When should this approach not be considered?