Clinical trial simulations to design a crossover study assessing the equivalence on the pharmacodynamic surrogate marker between an immediate and a modified release formulations

Anne Dubois, Marylène Gaignet, Jacques Thuet and Marylore Chenel

Department of Clinical Pharmacokinetics, Institut de Recherches Internationales Servier, Courbevoie, France

Introduction

- Formulation of drug X with marketing authorisation
  - Immediate release (IR)
  - Administration twice a day (b.i.d.)
- 3 new formulations to improve patient compliance
  - Modified release (MR1, MR2, MR3)
  - Administration once a day (o.d.)

Objectives

To design a crossover study comparing the pharmacodynamic (PD) surrogate marker (SM) between the IR and one of the MR formulations on 24 healty volunteers at steady state

1. Choice of the equivalence interval to perform an equivalence test on the SM: ±2, ±3, ±5 SM units (SMu)
2. Choice of the MR: MR1, MR2, MR3
3. Choice of the MR dose: D1, D2, D3

Methods

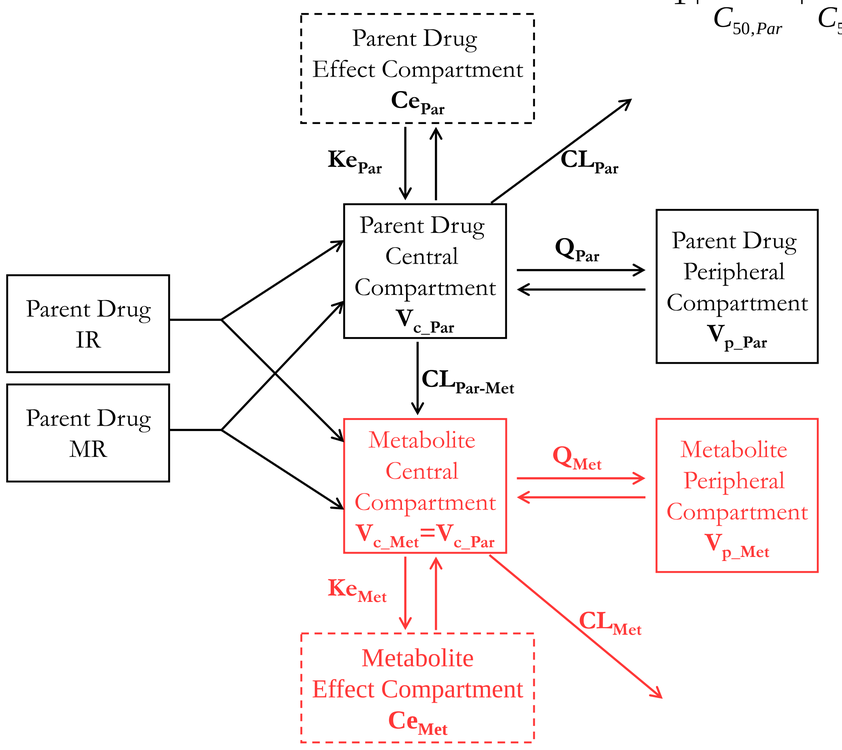
1. Population pharmacokinetic (PK) modelling

- Data from a single dose four-period crossover trial
  - 14 healthy volunteers
  - 4 formulations: IR, MR1, MR2 and MR3
  - Data available for the parent drug (Par) X and its metabolite (Met)
- Joint modelling of the Par and Met concentrations for the IR and each of the 3 MR (⇒ 3 population PK models)
- PK structural model
  - Two compartment model for Par and Met
    - Same disposition for the IR and the MR formulations
    - $V_{c\_Met}=V_{c\_Par}$
  - IR: first order absorption
    - Fraction of absorption (F): $F_{IR,Par}+F_{IR,Met}=1$
    - Same lag time (Lag_{IR}) but different absorption constants for Par and Met ($Ka_{IR,Par}$ and $Ka_{IR,Met}$)
  - Each MR: sequential zero and first order absorption
    - Fraction of absorption: $F_{MR,Par,0}+F_{MR,Par,1}+F_{MR,Met,0}+F_{MR,Met,1}=1$
    - Same duration of the zero order for Par and Met ($Tk0_{MR}$)
    - Same lag time (Lag_{MR}) and same first absorption constant(s) for Par and Met
      - MR1: 1 first order constant (Ka_{MR})
      - MR2, MR3: 2 first order constants ($Ka_{MR,1}$ until T_{Ka} then $Ka_{MR,2}$)

2. PK/PD model

- Agonist Emax model with compartment effect for Par (Ce_{Par}) and Met (Ce_{Met})

$$SM = Base - (Base - 35) \times EFF_{ParMet} \text{ with } EFF_{ParMet} = \frac{\frac{Ce_{Par}}{C_{50,Par}} + \frac{Ce_{Met}}{C_{50,Met}}}{1 + \frac{Ce_{Par}}{C_{50,Par}} + \frac{Ce_{Met}}{C_{50,Met}}}$$



3. Clinical trial simulations plan

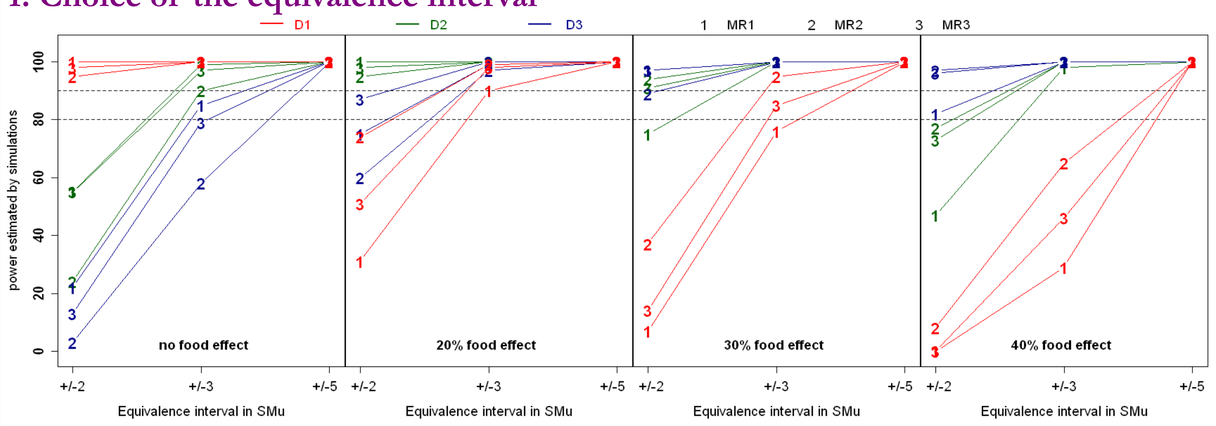
- Equivalence test on the daily mean of SM (μ)
  - For one subject, $\delta=\mu_{MR}-\mu_{IR}$. Δ is the mean of δ for the 24 healthy volunteers
  - H_0: $\Delta \in [\alpha ; +\alpha]$ (α =2, 3, 5 SMu) is rejected if $CI_{90\%}(\Delta) \in [\alpha ; +\alpha]$
- For each equivalence interval, each MR formulation and each MR dose (27 simulation settings): simulation of 100 two-period crossover trials on 24 healthy volunteers assuming
  - Multiple dose administration (Par and Met concentrations + SM at steady state)
    - IR at a fixed b.i.d. dose
    - MRi (i=1, 2, 3) at o.d. dose Dj (j=1, 2, 3)
  - Measurement time design: 28 SM measurements over 24 hours
  - Food effect on the IR
    - 0, 20, 30 or 40% of increase on the bioavailability ⇒ $Dj \times E_{food}$ (E_{food}=1, 1.2, 1.3, 1.4)

⇒ The equivalence test is performed on the data of each simulated trial and for each simulation setting, P_{eq} is estimated by the number of trials where H_0 is rejected

- For the chosen equivalence interval, MR formulation and MR dose: evaluation of the SM measurement time design (from 12 to 28 measurements)

Results

1. Choice of the equivalence interval

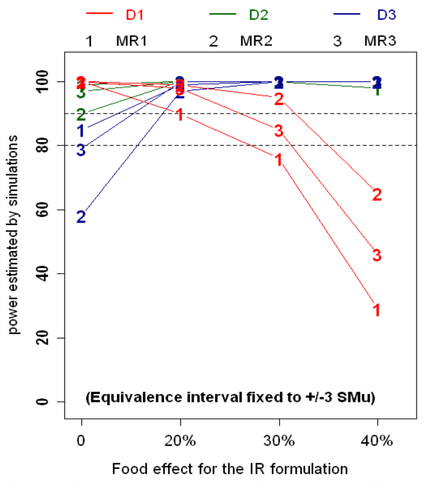


Plot1: P_{eq} *estimated for the 3 potential equivalence intervals taking into account the different simulated food effect for the IR formulation*

- ±5 SMu: P_{eq}=100% for the 3 MR and the 3 MR doses
  ⇒ Equivalence interval too large to discrimate
- ±2 SMu: too small interval considering the variability of measurement
- ±3 SMu: discriminant and clinically meaningful equivalence interval

⇒ Chosen equivalence interval: ±3 SMu

2. Choice of the MR formulation

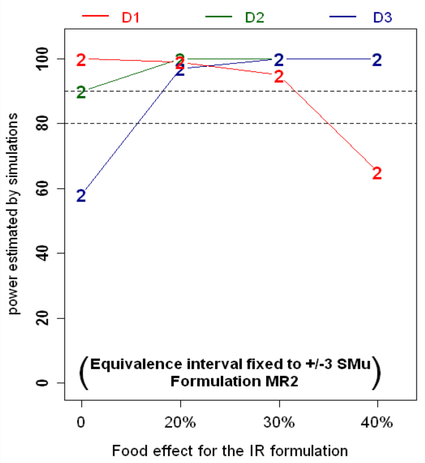


Plot2: P_{eq} *estimated for the 3 potential MR formulations*

For a simulated food effect of the IR formulation at 20% or 30% (more likely), P_{eq} is above 90% for MR2 but not for MR1 and/or MR3

⇒ Chosen MR formulation: MR2

3. Choice of the MR dose

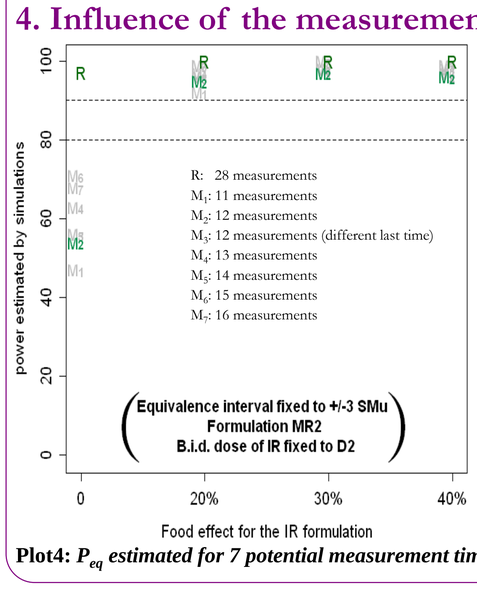


Plot3: P_{eq} *estimated for the 3 potential doses*

For all simulated food effects of the IR formulation, P_{eq} is above 80% for **D2**. For a simulated food effect of the IR formulation at 20% or 30%, P_{eq} is higher for **D2** than for **D1** or **D3**.

⇒ Chosen dose: D2

4. Influence of the measurement time design



Plot4: P_{eq} *estimated for 7 potential measurement time design*

For a simulated food effect of the IR formulation from 20% to 40%, P_{eq} is above 90% for the 12-measurement time design M_2. This design also takes into account the clinical constraints better than M_3.

⇒ Chosen measurement time design: M_2

Conclusion

The present clinical trial simulations were determinant to design the PD equivalence crossover study comparing the SM between the IR and a MR formulation for drug X. Indeed, its results allowed to choose the equivalence interval (±3 SMu), the MR formulation (MR2), the MR dose (D2) and the measurement time design (M_2).

Acknowledgements: we want to thank Pr France Mentré for her helpful advice for the PK modelling and the clinical trial simulations plan.