A Comparison of Proposed Pharmacokinetic Modified Dose-Controlled (PKMD) versus Traditional Fixed Dose-Controlled (FD) Clinical Study Designs

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Introduction

Traditional study designs

Fixed dose-controlled
- All subjects in a study/cohort receive same dose
- Pro: Easy to conduct
- Con: Some patients may be under- or over-dosed

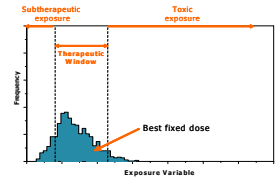
Concentration-controlled
- Subject doses titrated to desired concentration range, subsequent doses based upon concentration measurements
- Pro: Maximize number of patients receiving target exposure
- Con: Difficult and costly to conduct

Objective

To examine a proposed study design that combines the ease of a fixed dose with the benefits of a concentration-controlled study

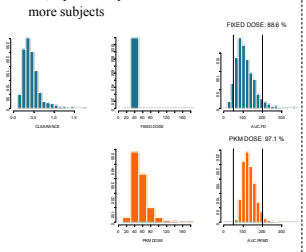
Fixed Dose-Controlled Study Design

Goal of a clinical study: maximize the number of patients receiving a therapeutic benefit without toxicity
- "Best fixed dose" (FD) maximizes number of patients in the therapeutic window
  - Some patients will still be subtherapeutic or toxic at that dose



Proposed Solution: Pharmacokinetic Modified Dose-Controlled (PKMD) Study Design

Subject doses based upon individual pharmacokinetic (PK) parameters such as clearance (CL)
- PK parameters may be dependent upon subject covariates (such as age, weight, smoking, etc.)
- By adjusting dose to account for differences in PK, optimal exposure should be reached for more subjects



Frequency distributions of clearance, dose, and AUC, a measure of drug exposure, shown for a FD and PKMD design for a specific patient population. By adjusting the doses to compensate for differences in clearance, the variability in the AUC (D/CL), is substantially reduced. The vertical bars in the AUC histograms indicate the target therapeutic window.

What information is needed before a PKMD design can be implemented?

- Population PK analysis
  - PK parameters expressed as a function of covariates and unexplained random variability
- Exposure-response analysis
  - Exposure metric selected (e.g., AUC, Cmax, Cavg)
  - Average subtherapeutic and toxic exposure levels should be established in order to determine the therapeutic window
- Available dosage strengths

Methods

Comparing FD with PKMD study design

Calculate fixed dose for all subjects:
- Target exposure = geometric mean of the cutoff values for the window
  - $AUC_{target} = \sqrt{AUC_{tox} \cdot AUC_{eff}}$
  - $FD = AUC_{target} \cdot CL_{pop}$
    - Round (up or down) to nearest available dosage strength

Calculate PKM dose for each subject:
- $CL_{pred,i}$ = predicted CL of each individual based on their covariates
- $PKMD_i = AUC_{target} \cdot CL_{pred,i}$
  - Round (up or down) to nearest available dosage strength

Calculate exposure for each subject:
- $AUC = D/CL_i$
  - CL_i = true individual clearance
  - D = FD or PKMD
- Count number of subjects falling within the therapeutic window in the FD and PKMD groups
- Calculate the extent of improvement

Simulation study:

- Population (n=1000):
  - Age: 41 ± 9 y (18-64 y)
  - Weight: 75 ± 10 kg (50-100 kg)
- $CL_{pred,i} = CL_{pop} \cdot (WT/75)^{1.75} \cdot (AGE/41)^{-1.5}$
- $CL_i = CL_{pred,i} \cdot e^{\eta}$
  - $CL_{pop} = 0.385$ L/h
- Exposure metric: AUC
  - $AUC_{target} = 100$ mg·h/L (fixed)

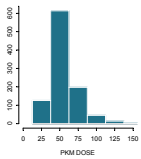
Simulation scenarios

Variables	Default values	Other scenarios
Width of therapeutic window	4-fold	2 – 10 fold*
Minimum available dosage form	25 mg	20 mg
Dose Rounding	Up	Down, closest
Unexplained variability in CL (ω)	0.4	0.2 – 1.0

* Window width = $WW = AUC_{tox} / AUC_{eff}$

WW	AUC_{eff}	AUC_{tox}
2	70.71	141.42
3	57.74	173.21
4	50.00	200.00
5	44.72	223.61
6	40.82	244.95
7	37.80	264.58
8	35.36	282.84
9	33.33	300.00
10	31.62	316.23

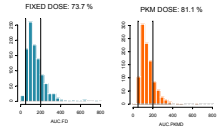
Example with default values
- Window width = $WW = AUC_{tox} / AUC_{eff} = 4$
  - $AUC_{eff} = 50$ mg·h/L
  - $AUC_{tox} = 200$ mg·h/L
- $FD = AUC_{target} \cdot CL_{pop} = 100 \cdot 0.385 = 38.5$ mg
- $PKMD_i = AUC_{target} \cdot CL_{pred,i}$
  - Min $CL_{pred,i} = 0.136$ L/h → $PKMD_i = 13.5$ mg
    - age=58 y, weight=55.6 kg
  - Max $CL_{pred,i} = 1.48$ L/h → $PKMD_i = 147.6$ mg
    - age=21 y, weight=91.1 kg
- Rounding: up
  - FD = 50 mg
  - PKMD range: 25 – 150 mg



Results

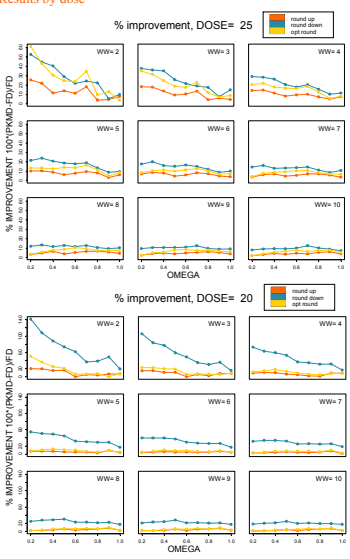
Default scenario results

- Improvement of 11.4%

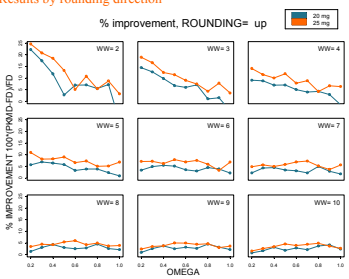


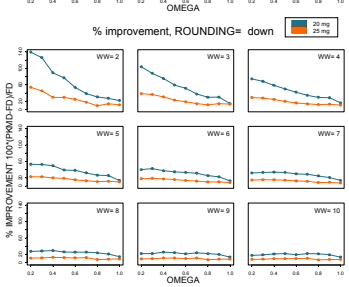
All simulation scenarios

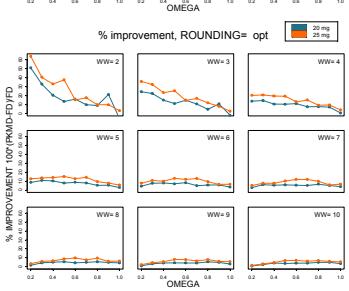
Results by dose



Results by rounding direction







Discussion

Characteristics that affect extent of improvement between FD and PKMD

Unexplained PK variability (ω)

As ω increases, % in therapeutic window decreases for both FD and PKMD designs
- FD: Large ω → wider distribution of true CL → more likely an individual's CL will be far from CL_{pop} → FD may not obtain target exposure
- PKMD: Large ω → inaccurate prediction of an CL_i → calculated PKMD may not obtain target exposure

Extent of improvement for a PKMD versus a FD design decreases with increasing ω
- At very high values of ω, the increase is so minimal that the more complicated PKMD study design may not be worth the effort

Trend is seen for all therapeutic window widths

Width of therapeutic window (ww)

Therapeutic windows greater than 5-6 fold wide are sufficiently large to offset the variability in exposure with FD
- Even for large ω, # of subjects receiving proper therapy is reasonably large in FD → extent of improvement with PKMD is minimal

Dosage strengths and rounding

Rounding down is best option
- 25 mg: down > optimal > up
- 20 mg: down >> optimal > up

20 mg dosage form
- "Best" FD= 37.5 mg → round up to 40 (Δ=2.5 mg) or down to 20 mg (Δ=17.5 mg)
  - FD_{down} close to "best" FD → adequate FD therapy → minimal extent of improvement between FD and PKMD
  - FD_{up} far from "best" FD → inadequate FD therapy → PKMD adjustments would be expected to lead to a significant increase
  - With smaller dosage form, more likely that $PKMD_{administered}$ close to $PKMD_{calculated}$, increasing the benefit of a PKMD compared to a FD study.

25 mg dosage form
- "Best" FD= 37.5 mg → round up to 50 (Δ=12.5 mg) or down to 25 mg (Δ=12.5 mg)
  - FD_{up} and FD_{down} same distance from "best" FD → extent of improvement between FD and PKMD should be similarly large, since the FD is not adequate

PKMD potential limitations

- Calculated doses must be rounded to nearest available dosage strength – may not obtain therapy with the administered dose
  - Solution: Decrease dose increments
  - Consideration: costs involved for manufacturing new formulations
- Pharmacodynamic variability
  - Solution: Individualize target AUC with population PKPD
  - Consideration: significant modeling time and effort

Conclusions

Benefit of PKM versus fixed dosing is (nonlinearly) dependent upon:
- Effect of unexplained PK variability (ω)
- Width of therapeutic window (WW)
- Dosage strengths
- Rounding direction

Examining fixed and PKM dosing schemes with clinical trial simulation can help support rational drug development decision making
- Determining whether PKM dosing is practical for a particular drug development program
  - Extent of improvement may not be sufficient to justify the additional effort of designing and implementing a PKM dose controlled study
- Determining if additional dosage strengths are needed
  - Cost of manufacturing new dosage form versus benefit of increasing subjects receiving therapy must be considered

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