Dose-Response and Exposure-Response Analyses in Dose Selection

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Dose Response *versus* Exposure Response?

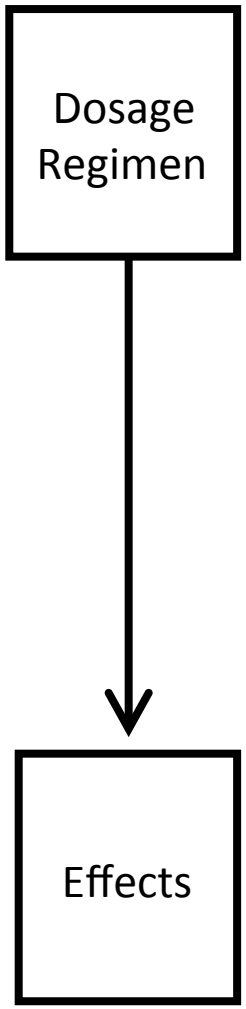
- What is the hardest problem in drug development? Getting statisticians and pharmacometricians to speak productively with each other about the best method to inform dose selection
- DR and ER are complementary methods yet posed as 'competing' methods …. Why?
- Cultural gap
  - Statisticians don't typically understand pharmacokinetic exposure and related underlying physiology and therefore presume these aren't relevant to the questions being asked
  - Pharmacometricians don't typically understand core statistical issues such as bias and operating characteristics of the statistical methods they use and therefore presume these aren't relevant to the questions being asked
- The Truth is that we are asking different questions
  - Goal of this talk is to learn a bit about both sides in the context of dose selection

Dose Selection Regarded As the Most Critical Decision in Drug Development

- In the good old days, dose selection was "easy"…. But today?
- EMA review of 135 Marketing Authorizations between 2010-2014 showed:
  - 9% (12/135) had Major Objections caused by "not established or justified dosing regimens"
  - 10% (13/135) required post-authorization changes in dose in special populations (e.g. hepatic or renal impairment, or due to DDI)
- FDA review of 302 NDAs from 2000-2012:
  - 16% (24/151) first-cycle review failures involved issues of uncertainty/inadequacy of dose selection
- Precision medicine changing how we should think about "dose"
  - The more you understand about the impact of individual characteristics on determinants of response, including drug exposure, the better able you are to determine the patient(s) most likely to benefit
  - Precision medicine, per Lisa LaVange's talk

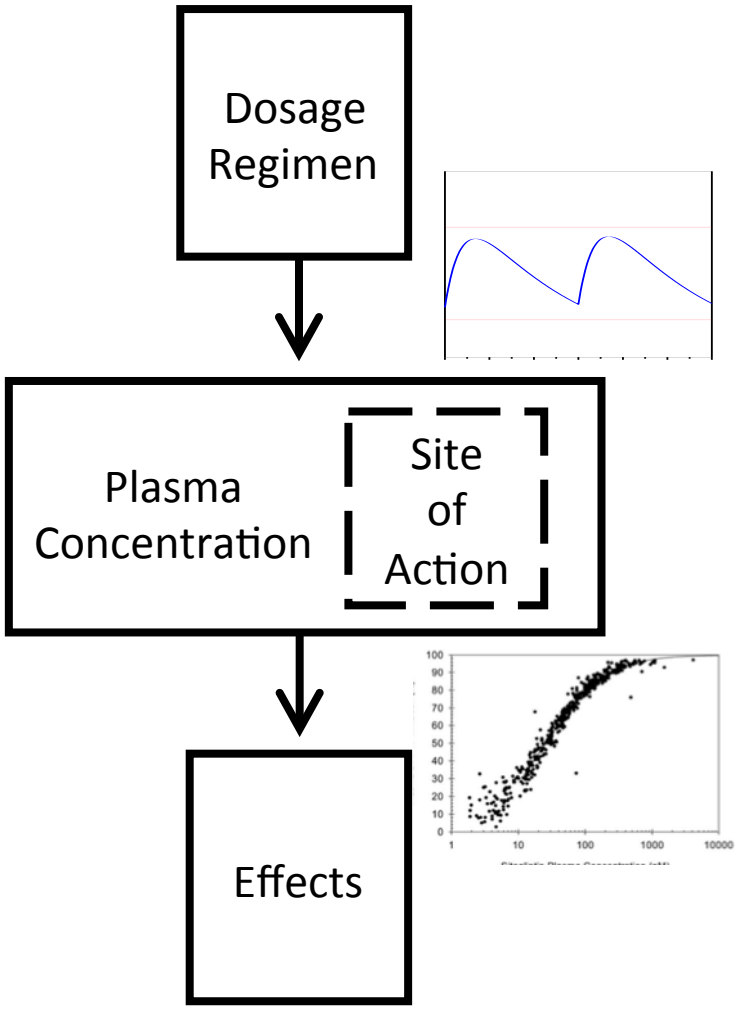
Modeling Dose-Response

- Dose: What a patient is supposed to get when prescribed a drug
- Response: Measure of pharmacological effect of a drug
- Statistical analysis typically straightforward: within-group estimates and pairwise comparisons between dose-groups
  - Trend tests often performed
  - Continuous models for dose-response (e.g. regression line, hill equation / Emax model) less commonly fit
- Baseline patient characteristics are typically assessed, but D-R analyses do not distinguish where in the causal pathways any differences arise
- Dose-response modeling gives a straightforward way to answer what happens when patients get a medication
  - Power of the approach relies on the simplicity, e.g. facilitates ITT assessment



Modeling Dose-Exposure-Response

- Exposure: measures of acute or integrated drug concentration (e.g. average, maximum or minimum concentration)
- Response: Measure of pharmacological effect of a drug
- Modeling typically broken into two steps: modeling of *dose* to *exposure*, then modeling of *exposure* to *response*
  - Patient characteristics can effect either or both relationships
  - Either step involves individual patient variation; modeling the two relationships can drive to an understanding of why a given dose may work differently in different people
  - Allows for a more mechanistic approach to thinking about dose selection
- Statistical analyses often utilize non-linear models that focus on estimating parameters that define the curve, rather than group-level estimates
- Requires more measurements to get the data for the modeling; need to assess exposure in patients in the study
- Also, often exposure-response modeling will utilize biomarkers instead of, or in addition to, the ultimate clinical endpoint – possibly with additional models linking the biomarkers to the clinical endpoint



Dose Response vs Exposure Response General Considerations

Attributes of Dose-Response

- Dosage regimen is "fixed" – assigned by study design – instead of being a measurement
- Agnostic to *why* patient characteristics cause different responses – variability in exposure becomes part of the variability in response
- Easy to implement intention-to-treat analyses, survival analyses – just need dose and outcome
- Easier to utilize 'dose' in adaptive designs than PK

Attributes of Exposure-Response

- Between-subject variability in disposition means that dose really isn't "fixed" when thinking about what drives response
- Drives one more level of understanding in how the drug works – can understand complexities such as
  - Nonlinear relationship between dose and exposure
  - Time lags between dose administration and acute pharmacodynamic effects
  - Differential impact of patient characteristics on D-E vs E-R
- Greater understanding can drive decisions in changing dosing forms or regimen, switching populations

Examples

1. Complementary ER modeling of biomarker with DR assessment of clinical response
2. ER modeling to support pediatric development
3. ER/DR modeling to support formulation change
4. ER and DR modeling in Phase I/II

Example: JANUVIA

Approved DPP-4 inhibitor for treatment of diabetes

Phase I biomarker studies used E-R models to guide dose selection in Phase II. Ultimate Phase III dose selection utilized D-R assessment.

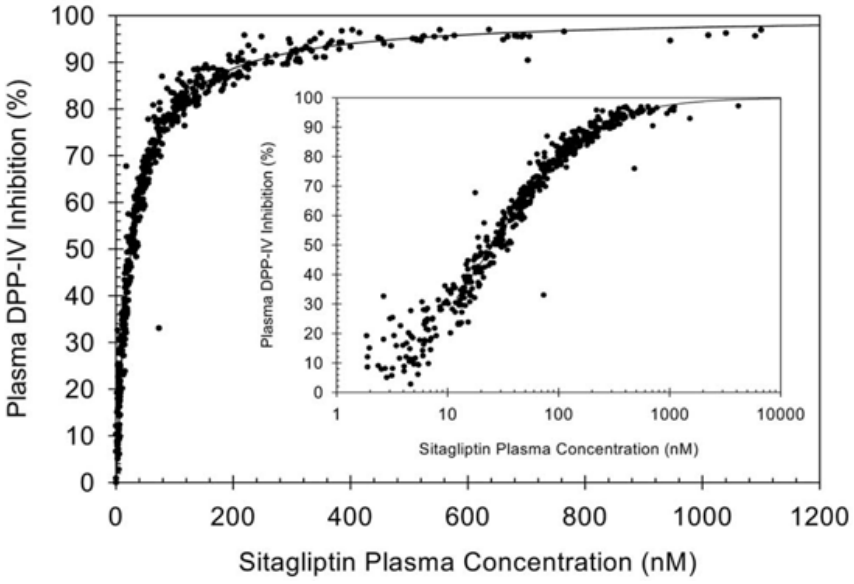
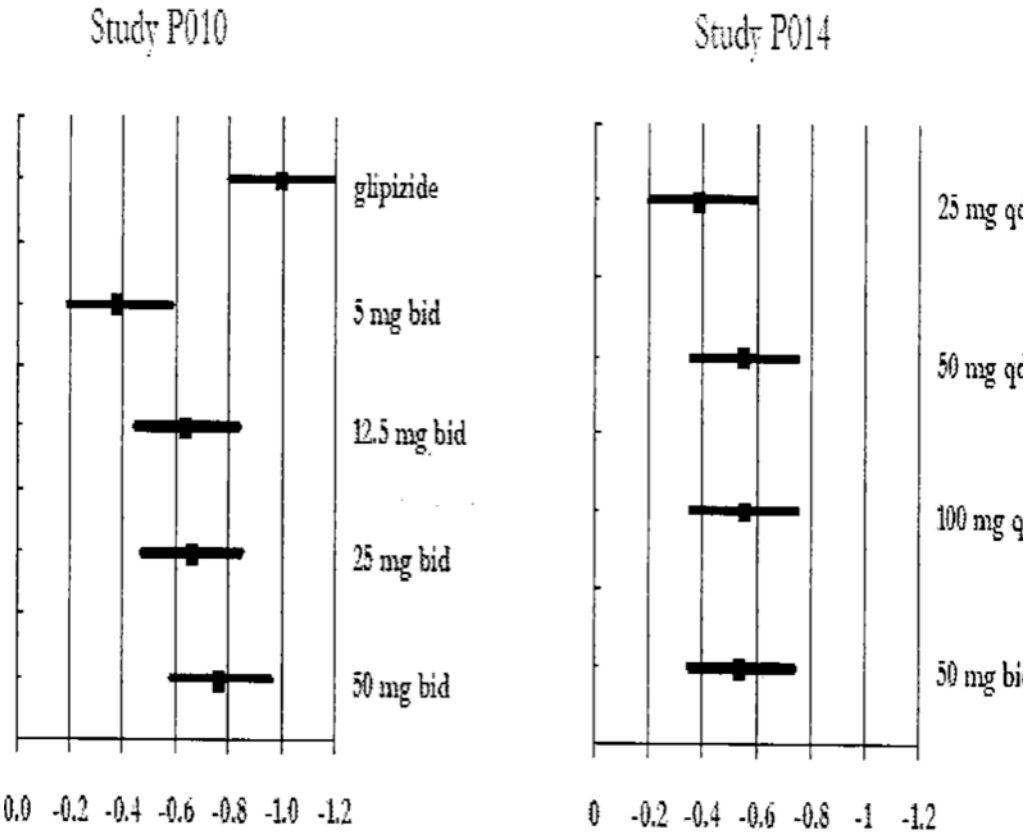
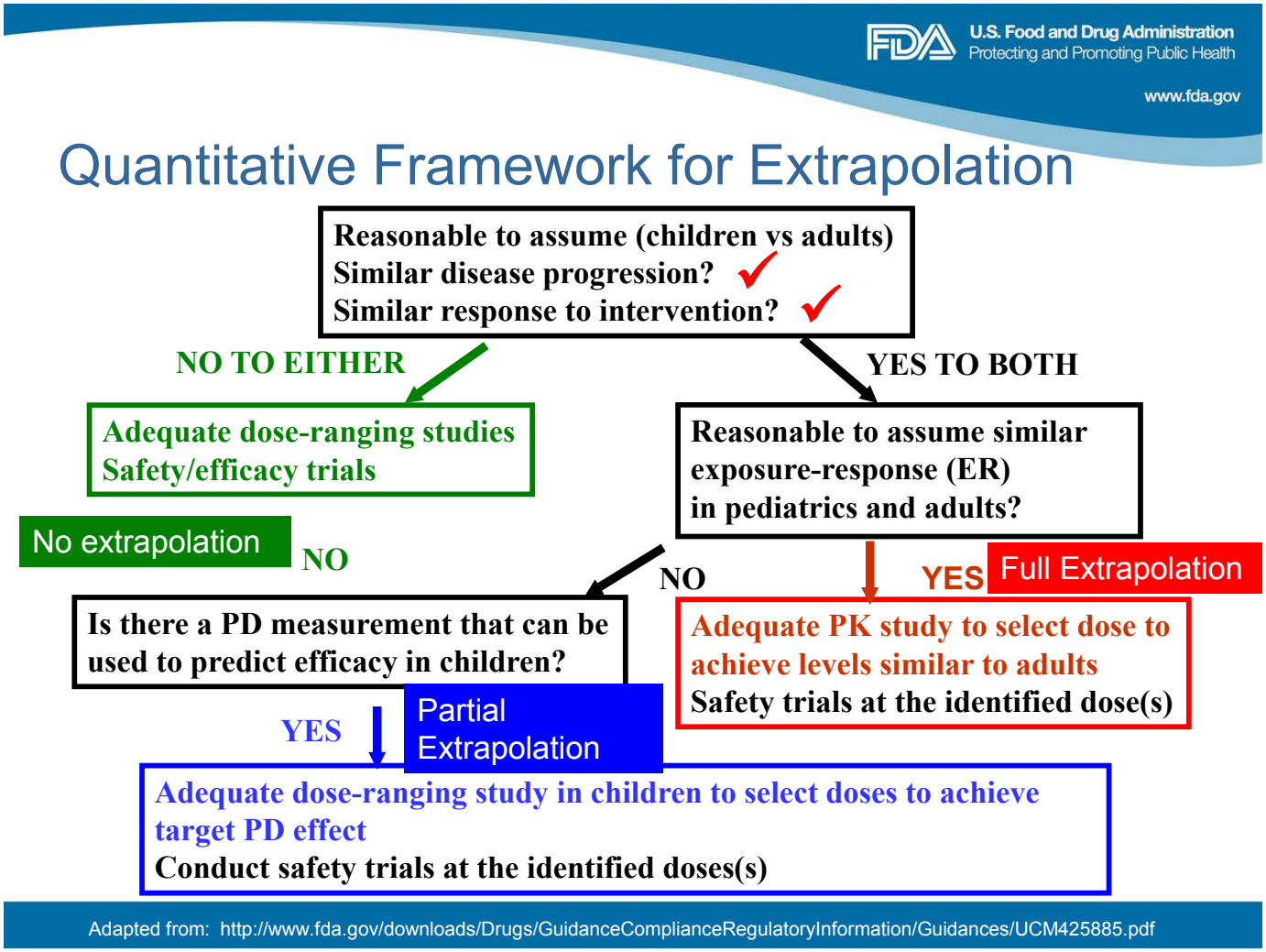


Figure 34 LSM Difference from Placebo (95% CI) – Phase 2 Studies



Pairwise Differences	Difference in LS Means	95% CI for Difference in LS Means
MK-0431 50 mg b.i.d. versus Placebo	-0.77	(-0.96, -0.58)
MK-0431 25 mg b.i.d. versus Placebo	-0.66	(-0.85, -0.47)
MK-0431 12.5 mg b.i.d. versus Placebo	-0.64	(-0.84, -0.45)
MK-0431 5 mg b.i.d. versus Placebo	-0.38	(-0.58, -0.19)

Example: Pediatric Dose Selection



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Example: Pediatric Dose Selection

Case Study #1

Derivation of darunavir doses in HIV-infected treatment experienced pediatric patients ages 6 to 17 years

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm129567.pdf

Example: Pediatric Dose Selection

Study Design (Part 1)

- 44 pediatric patients randomized to two dose arms for 2 weeks

Weight (kg)	Darunavir Dose (Group A)	Darunavir Dose (Group B)
20-30	300 mg	375 mg
30-40	375 mg	450 mg
40-50	450 mg	600 mg

* Adult dose is 600 mg

$$\text{Dose}_{\text{child}} = \text{Dose}_{\text{adult}} * \frac{(\text{Body Weight}_{\text{child}})^{0.75}}{70}$$

Example: Pediatric Dose Selection

U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Study Design (Part 2)

- Week 2 interim PK data were analyzed
- Dose group B was chosen for Part 2
  - 22 patients in dose group A were switched to higher dose
  - 24 additional subjects were enrolled
- Safety and activity (viral load) measured through 48 weeks

Example: Pediatric Dose Selection

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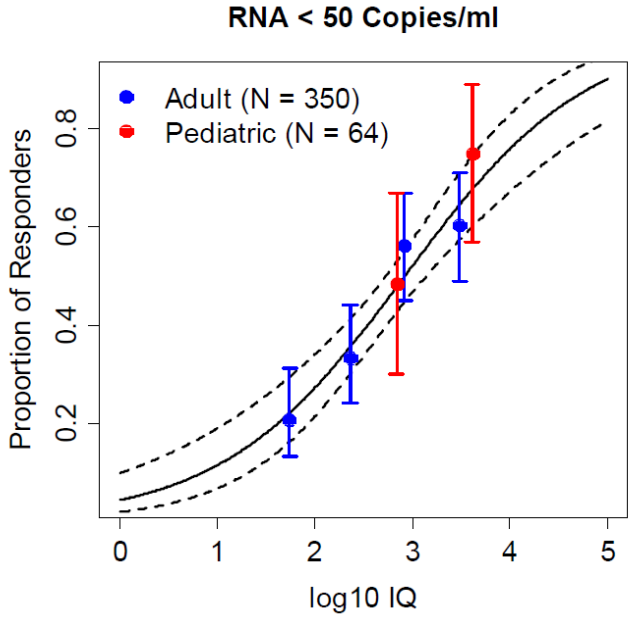
Is it reasonable to assume similar exposure-response relationship in adults and children?

YES



Exposure = IQ = C_{0h}/IC_{50}

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Example: Pediatric Dose Selection

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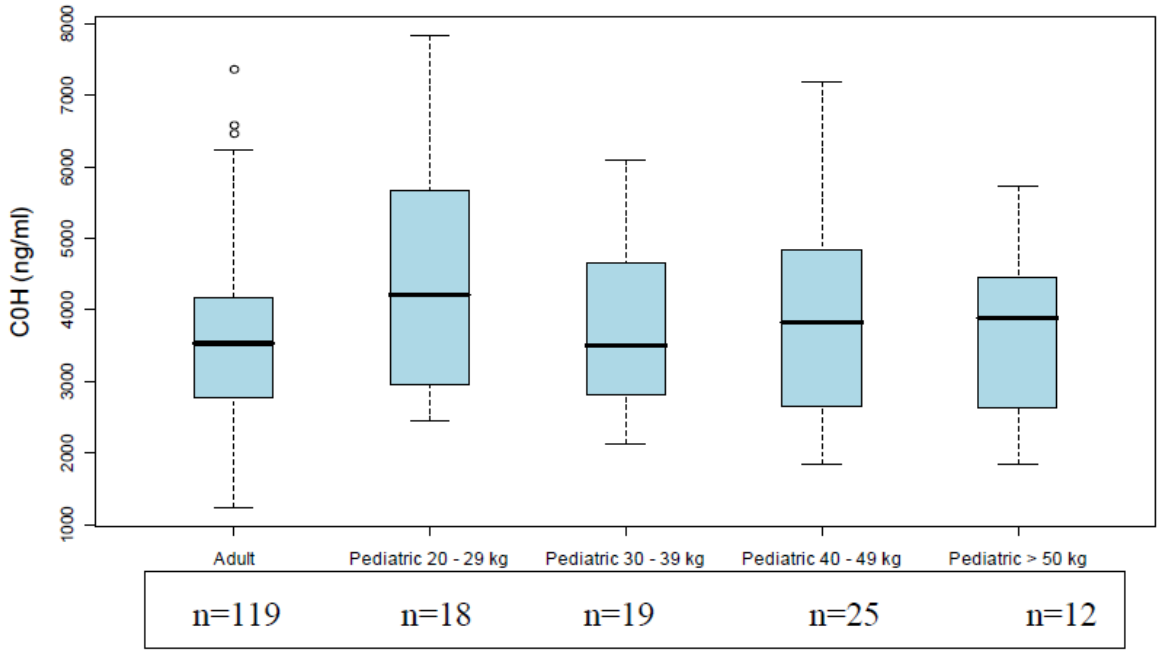
Similar Exposure in Pediatric and Adult Patients



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Example: ISENTRESS® BID vs QD

Situation: dose selection for QD formulation of ISENTRESS
400 mg BID marketed dose; desire to switch to QD dosing

- Initial effort: 800 MG QD had similar AUC, higher Cmax but lower Ctrough
- 800 mg QD study failed to show non-inf

TABLE 1 Summary pharmacokinetic parameters

Parameter	Value for group[d]				
	Raltegravir QD group		Raltegravir BID group		
	No. of patients	GM (% CV‡)	No. of patients	GM (% CV‡)	GM ratio, QD/BID (90% CI)
Intensive pharmacokinetic profiles					
AUC[a] (μM · h)	22	30.87 (70)	20	13.14 (99)	1.17 (0.80, 1.72)
C_{max} (μM)	22	13.46 (69)	20	3.38 (135)	3.98 (2.58, 6.16)
C_{trough}[b] (nM)	22	40 (111)	20	257 (167)	0.15 (0.09, 0.26)

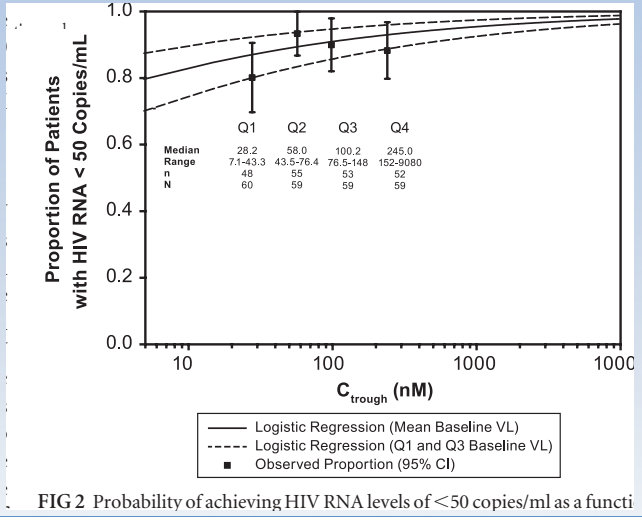
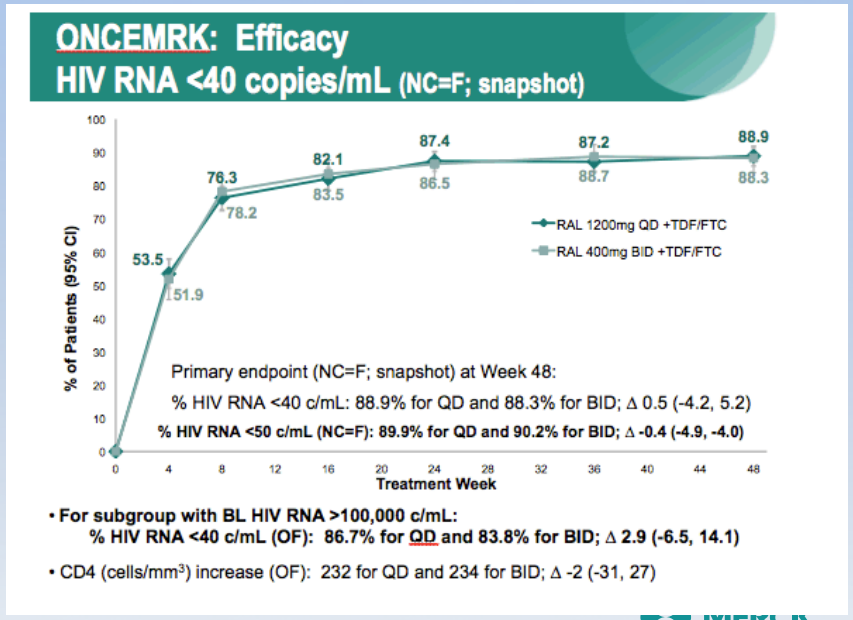


FIG 2 Probability of achieving HIV RNA levels of <50 copies/ml as a functi

- PK/PD modeling suggested 90% POS that 1200 mg QD would meet clinical non-inferiority
- Non-inferiority achieved at 1200 mg



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Example: MK-0557

- NPY-Y5 receptor antagonist considered for treatment of obesity
- E-R modeling of PET imaging study used to guide dose selection for Phase II
- D-R assessment of Phase II used to assess doses for later phase studies
  - Exposure measured as trough concentrations
  - Low variability in PK for any given dose, and a wide dose range led to similar conclusions between D-R and E-R

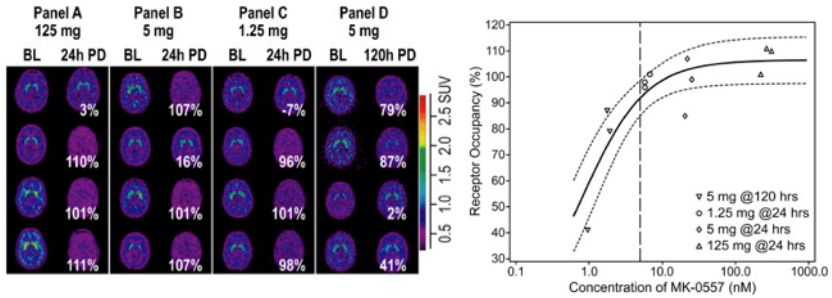
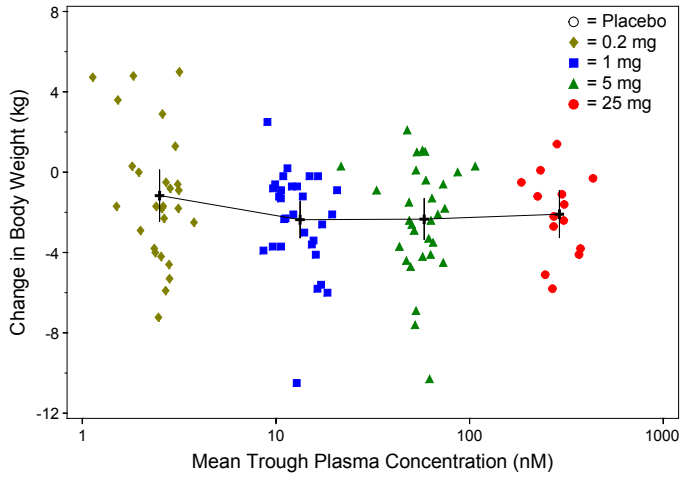


Figure 9: Mean Trough Plasma Concentration vs Body Weight Loss At Week 12
Preliminary Data



Mean (95% CI) Change in Body Weight at Week 12 Shown for Subjects with PK data

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Statistical Considerations (Hsu, 2009)

- Hsu, 2009, Pharmaceut. Statist. 2009; 8: 203–215, compared dose-response models and exposure-response models in dose selection
- Simulated a classic parallel group design with 5 dose groups
  - Response simulated as a function of exposure as an Emax model
  - Exposure simulated as a log-normal, based on subject-level clearance simulated, plus inter-day/measurement error added
  - Range of within- and between-subject variability in both exposure and response
  - Trial analyzed using both DR and ER Emax models and minimum effective dose estimated

$$\log(\mathrm{CL}_{ij}) \sim N(\log(\mathrm{TVCL}), \sigma^2_{\mathrm{CL}})$$

$$\log(\mathrm{CL}^*_{ij}) \sim N(\log(\mathrm{CL}_{ij}), \sigma^2_{\mathrm{U}})$$

$$\mathrm{AUCss}_{ij} = d_i/\mathrm{CL}_{ij}$$

$$\mu_{ij} = E_0 + \frac{E_{\max}\,\mathrm{AUCss}^h_{ij}}{\mathrm{EC50}^h + \mathrm{AUCss}^h_{ij}}$$

$$\log(y_{ij}) \sim N(\log(\mu_{ij}), \sigma^2_{\mathrm{Y}})$$

Statistical Considerations (Hsu, 2009)

- ER better when PK variability is minimized (σ^2_U)
  - Result is expected since it matches how the data were simulated
  - When interday/measurement error is more than 40%, DR better than ER, but how likely is this? Modern PK assays have better performance characteristic standards and sample handling errors are learned quickly in early phase studies
- DR better when between-subject variability in clearance (σ^2_{CL}) is low
  - When σ^2_{CL} increases, predictive power of dose decreases
  - When variability is above 50%, DR performance extremely variable
    - This level of variability associated with genetic polymorphisms as well as intrinsic variability in CYP 3A4 systemic and first pass metabolism (often seen in oncology agents REF)
- DR tends to underestimate the dose, while ER tends to overestimate the dose as σ^2_U increases
- If the minimum effective dose is not in the dose range, *neither* method works well – even if $\sigma^2_U = 0$!
  - Due to inability to properly estimate Emax

Trends in Dose Selection

Dose-response

- Adaptive designs
- Model-based dose-response models
  - Movement away from pairwise comparisons to model-based methods and use tools like MCPMod
  - Use of non-linear models
  - See 2014 EMA/EFPIA workshop on importance of dose finding/ selection

Exposure-Response

- Integration with mechanistic models and translational models to leverage preclinical evidence
- Time-series models rather than integrated measures of exposure
- Use of PK/PD for registration endpoints, not just biomarkers pre-POC
- Exploration of impact of PK/ PD on adaptive designs

Closing thoughts

- DR and ER complement each other
  - When used together, can effectively address dose decisions
- But recognize that each answers different questions
- Each performs well, but the circumstances in which they perform well differ

Acknowledgements

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