

Comparator-Based Dose-Response Model Prediction of Clinical Irrelevance Following Near Miss Bioequivalence Results for C_{max}

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Introduction

The intermediate doses of a fixed-dose combination in development did not meet prespecified bioequivalence criteria (80%-125%) for C_{max}.

Estimated Geometric Mean Ratio (FDC/coadmin) (90% confidence interval)

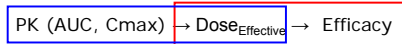
FDC Strength	Compound 1		Compound 2	
	AUC	C _{max}	AUC	C _{max}
Low Dose	0.93 (0.86, 1.01)	0.90 (0.81, 0.99)	1.03 (0.99, 1.07)	1.13 (1.05, 1.22)
Intermediate Dose	0.88 (0.81, 0.97)	0.77 (0.68, 0.87)	0.97 (0.90, 1.04)	1.00 (0.90, 1.10)
Intermediate Dose	0.96 (0.93, 0.99)	0.81 (0.73, 0.90)	0.98 (0.93, 1.03)	1.03 (0.96, 1.10)
High Dose	1.11 (1.06, 1.17)	1.09 (0.99, 1.20)	0.97 (0.93, .02)	0.99 (0.92, 1.06)

Objectives

1. Inform the impact of dosing regimen and formulation to evaluate the relevance of C_{max} and AUC as predictors
2. Characterize the impact of changes in exposure between coadministration and the fixed dose combination on efficacy

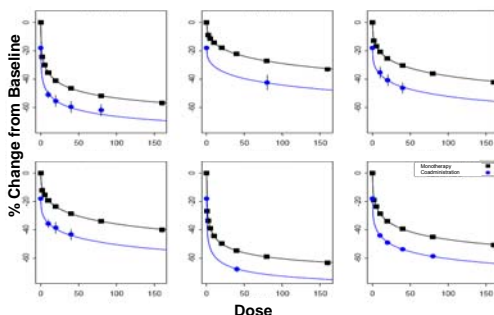
Methods

- In collaboration with Quantitative Solutions, developed a clinical-efficacy (dose-response) model
 - Study-arm level clinical data from 245 trials of 106,808 patients
 - Monotherapy for both classes of compounds
 - Combination therapy
- The impact of dosing regimen and formulation on efficacy was assessed during model building.
 - Assesses the predictability of AUC and C_{max} on efficacy
- Differences in exposure were translated to efficacy (LDL-C reduction) in two steps:

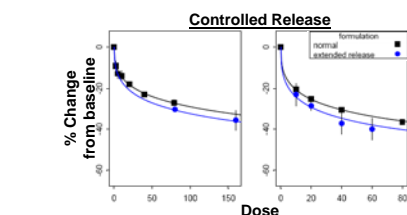
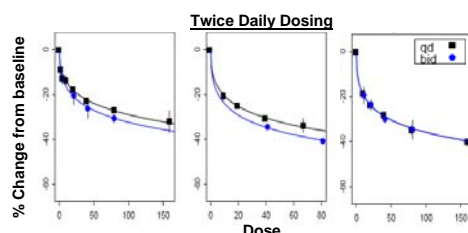


- Dose-Exposure Model
 - Linear regression of log transformed power model
 - Exposure (AUC or C_{max})=A*Dose^N
 - Effective Doses
 - Calculated from individual ratios and power (N)
- Calculated Effective dose distributions
 - 10,000 simulations of Dose-Exposure Model
 - Including bootstrap of population and parameter uncertainty
 - Used as input into the Dose Response Model
- Calculated Difference of LDL-C reduction
 - 10,000 simulations of Dose-Efficacy Model
 - Including parameter uncertainty

Results



Dose response model accurately captures the efficacy for both monotherapy and coadministration

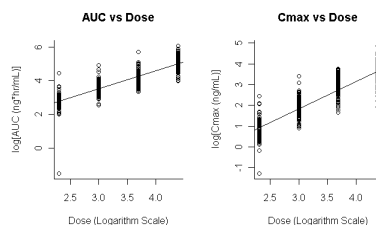


- For the same total daily dose, same or better efficacy for:
 - Twice daily dosing
 - Controlled release formulations

Maintaining exposure at site of action is more important than peak exposure

Compound 1

- AUC_{0-∞} and C_{max}
 - Greater than dose proportional when coadministered with compound 2



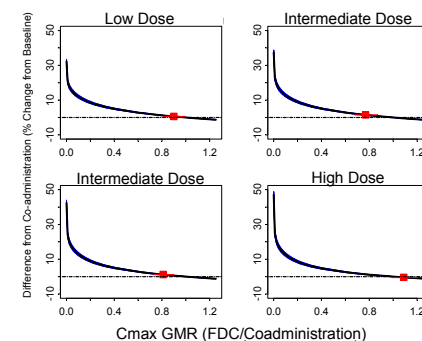
Model	Slope Estimate (95% CI)	P-value
AUC	1.07 (1.01, 1.13)	<.001
C _{max}	1.31 (1.24, 1.37)	<.001

- C_{max} Nonlinearity
 - Small changes in dose → larger C_{max} differences

Mean Predicted Difference in % Change from Baseline in Therapeutic End Point (95% CI)

FDC	AUC Model	Combined AUC-C _{max} Model	C _{max} Model
Low Dose	0.46 (-0.33, 0.95)	0.52 (-0.14, 0.93)	0.53 (-0.15, 1.13)
Intermediate Dose	0.50 (0.21, 0.80)	0.65 (0.34, 0.95)	1.16 (0.58, 1.76)
Intermediate Dose	0.24 (0.00, 0.50)	0.36 (0.09, 0.66)	1.12 (0.46, 1.81)
High Dose	-0.65 (-1.00,-0.29)	-0.58 (-0.98, -0.19)	-0.42 (-1.00, 0.14)

% Changes should be interpreted relative to a 50-65% change across the dose range



Flat response curve for C_{max} and efficacy for coadministration

- Driven by:
 - Observed nonlinearity of C_{max}
 - Relatively flat dose response curve for coadministration

Conclusions

- In the most conservative case, C_{max} is assumed to drive efficacy
 - Differences in C_{max} translate to <1.2% change in efficacy which is not considered clinically relevant
- Using the more clinically relevant metric, AUC is assumed to drive efficacy
 - Differences in AUC translate to <0.65% change in efficacy which is not considered clinically relevant
- Literature data and M&S results predict:
 - The near misses on C_{max} are not clinically relevant to efficacy and do not pose a safety risk