

Tailor-made dissolution profile comparisons using in vitro-in vivo correlation models.

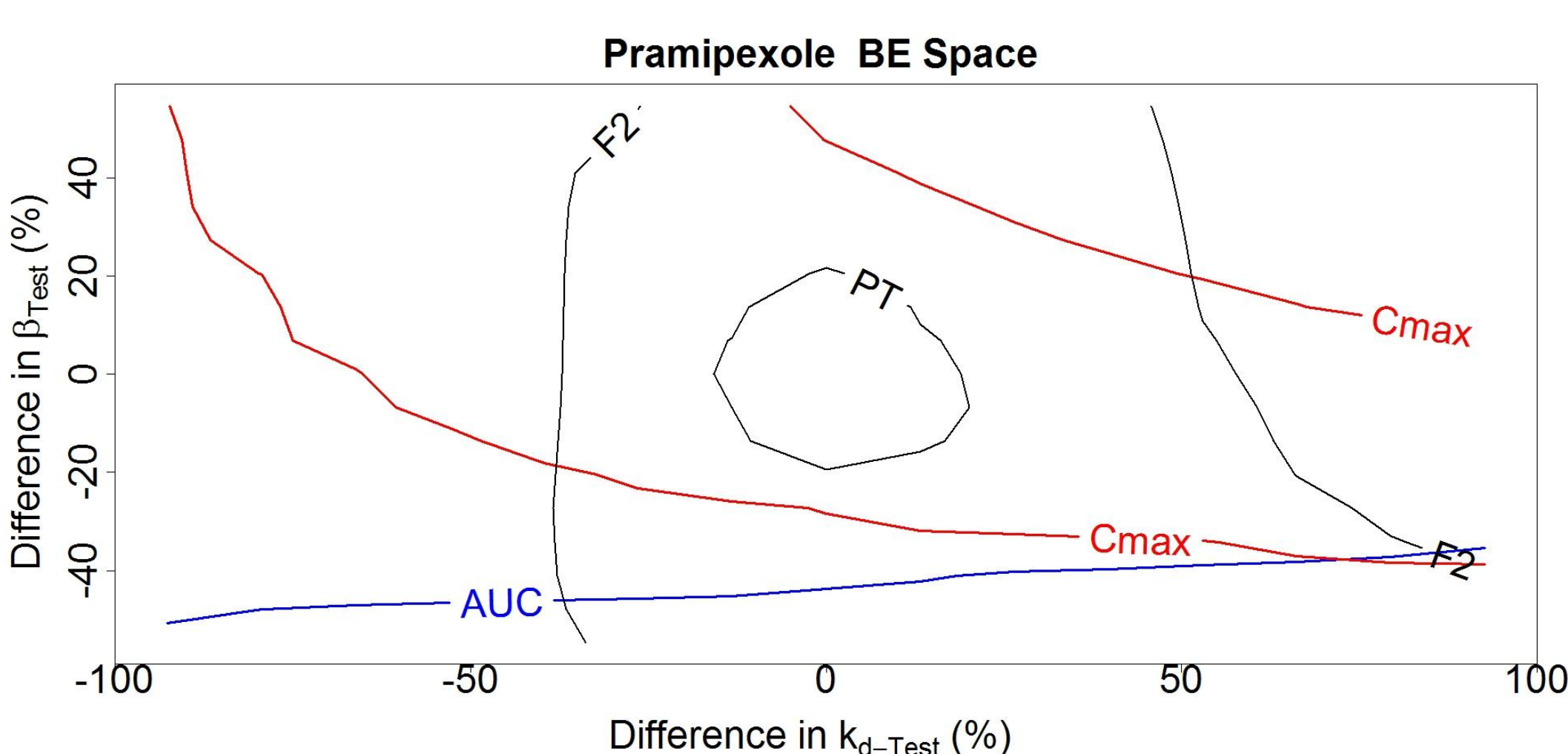
José David Gómez-Mantilla¹,
Vicente Casabó², Ulrich Schäfer¹,
Thorsten Lehr³, Claus-Michael Lehr^{1,4}.

¹ Biopharmaceutics and Pharmaceutical Technology, Saarland University, Campus A4.1, D-66123 Saarbrücken, Germany.
² Department of Technological Pharmacy, University of Valencia, Burjassot, Spain.
³ Clinical Pharmacy, Saarland University, Saarbrücken, Germany.
⁴ Helmholtz-Institute for Pharmaceutical Research (HIPS), Saarbrücken, Germany.

Limitations of Current Dissolution Profile Comparisons

- Drug unspecific and fixed limits ($f_2 > 50$)
- Limits of similarity are not based on any biopharmaceutical criteria
- Uncertain statistical confidence

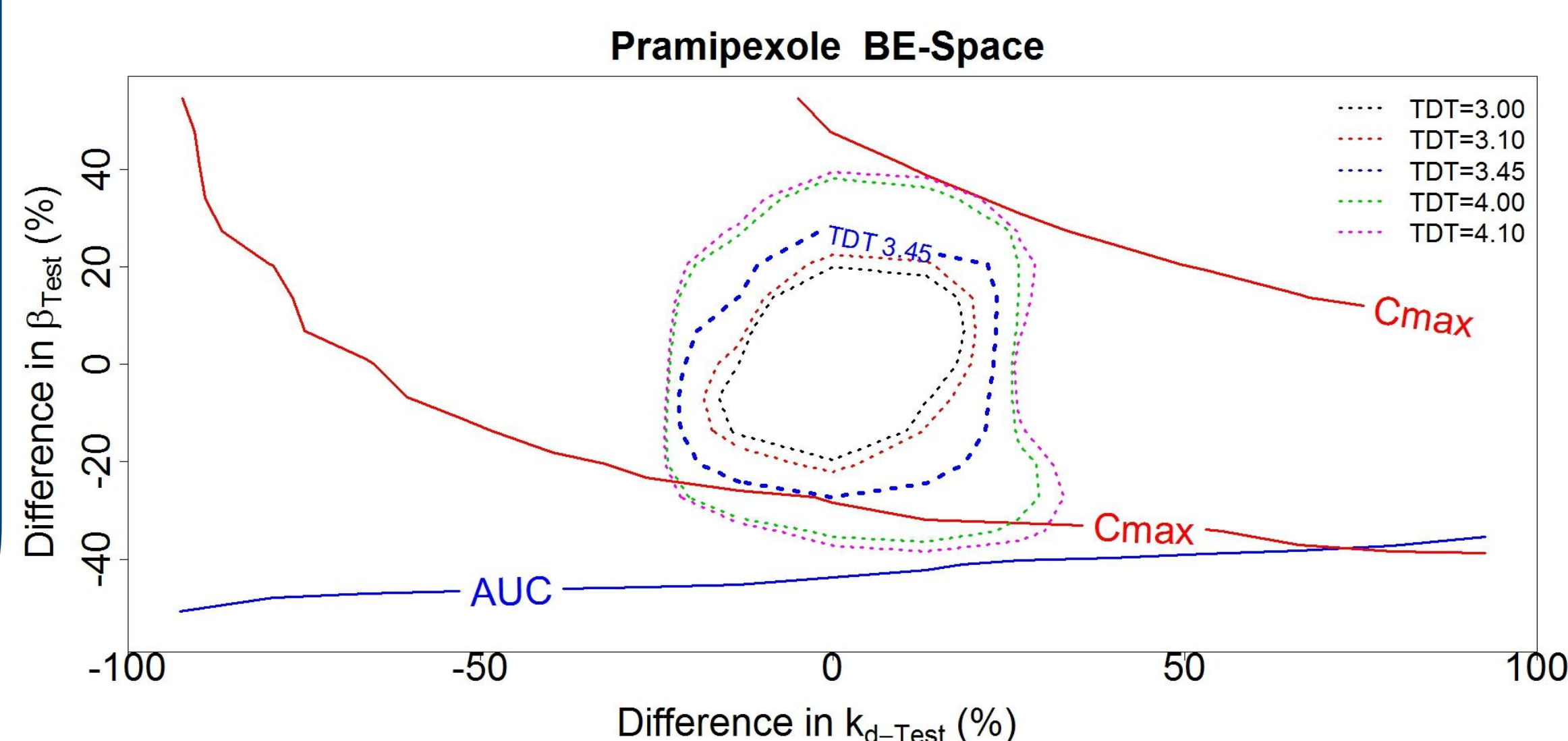
$$f_2 = 50 \times \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\}$$



The overlap between the Bioequivalent Space (BE-space) and the similarity space is not complete. Using traditional dissolution profile comparisons bioequivalent formulations can be categorized as non similar, and non-bioequivalent formulations can be categorized as similar.

Our Approach

- This study aims to develop drug-specific dissolution profile comparisons able to detect differences in release profiles between different formulations that can influence the in-vivo performance (bioequivalence) of the formulations.
- Customization of dissolution profiles comparisons was made by adjusting the delta of a recently described Tolerated Difference Test (TDT).
- Bio-relevant limits in release profiles differences were identified for all three formulations.
- Delta values for TDT were tailored for each formulation as follows: 3.8 for metformin, 5.8 for diltiazem and 3.5 for pramipexole, representing the average tolerated difference (in %) between two formulations at any time point to produce bio-equivalent formulations under both criteria, AUC and Cmax.
- All formulations categorized as similar with this tailored TDT are always bioequivalent.



Methods

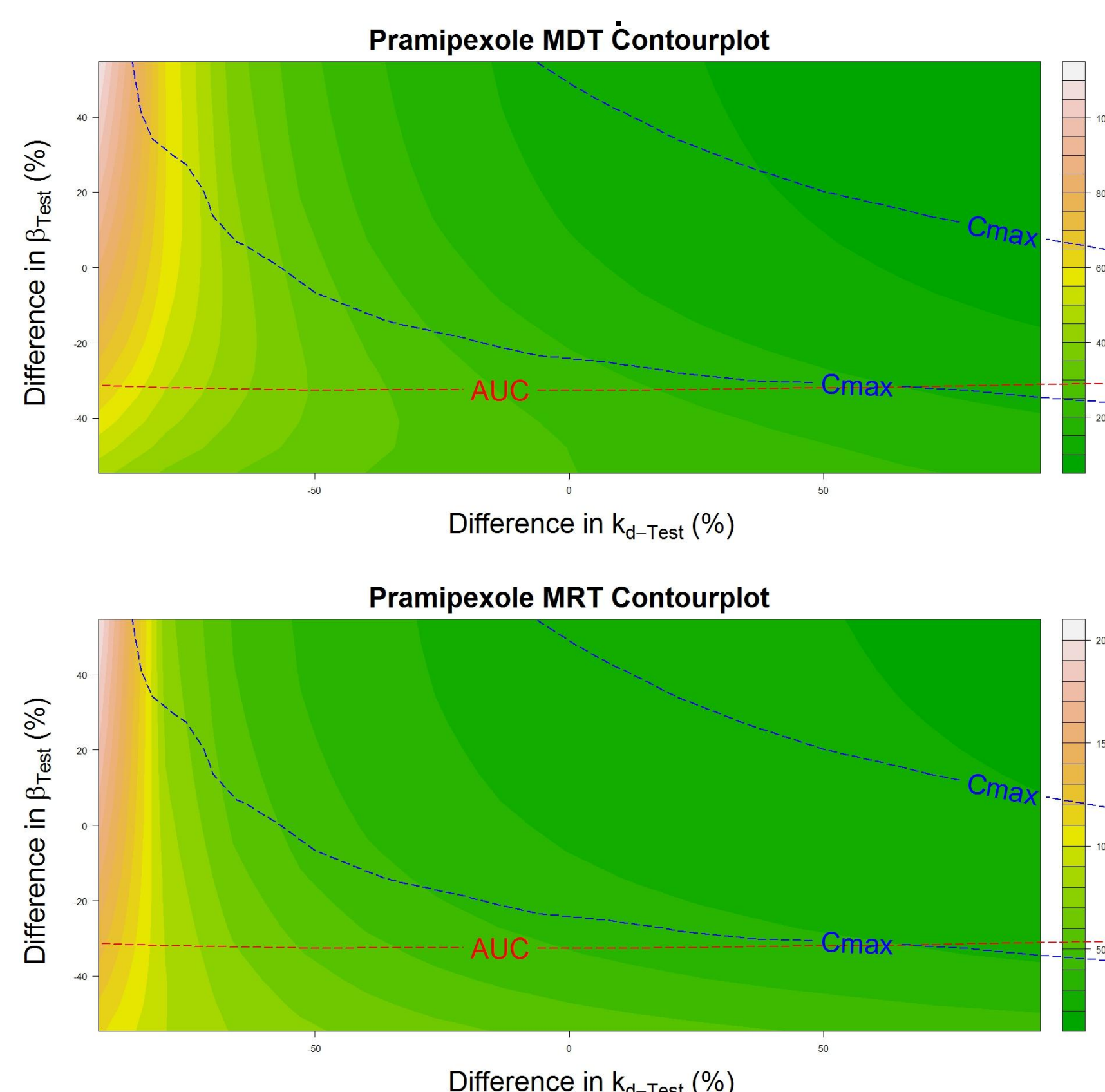
- Published data from Extended release (ER) formulations of metformin, diltiazem and pramipexole.
- Differential equations based IVIVC/PK models with latency time and absorption window.
- Bioequivalence cross over studies simulated with 12 healthy individuals.
- Assessments of bioequivalence following current FDA guidelines.
- Inter Individual Variability (k_a , k_{el} , Cl , V_1 , t_{lag}) was included to fit available population data.
- 1000 repetitions for every bioequivalence study and 5000 repetitions for statistical power explorations.
- Dissolution profiles modelled by Hill equation (metformin, diltiazem) or Weibull equation (pramipexole).
- All simulations and analyses were done using R.

Dissolution Models

$$f_{dis}(t) = \frac{t^n}{t_{50}^n + t^n} \quad (\text{Hill})$$

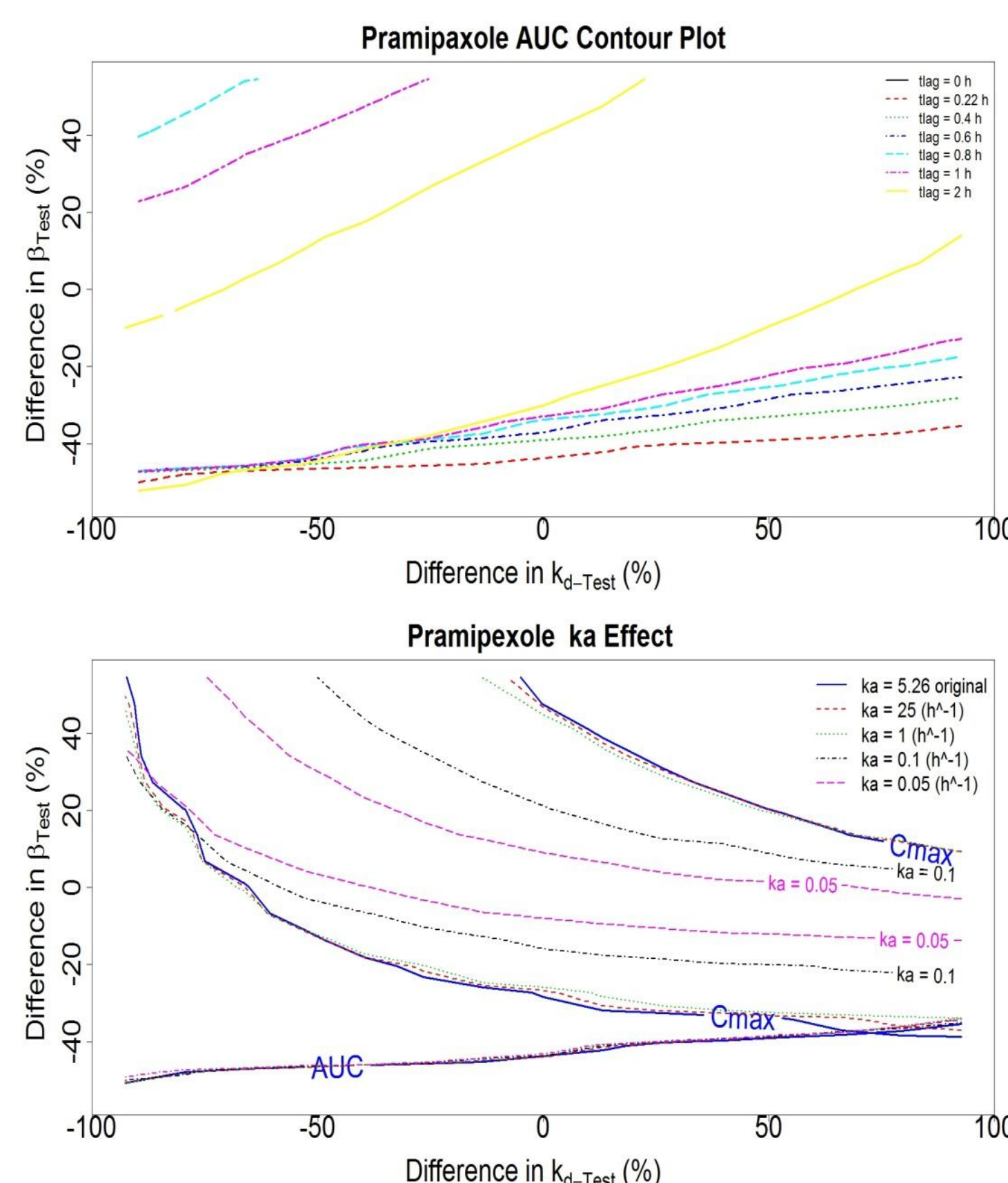
$$\frac{Q_t}{Q_\infty} = \left(1 - e^{-(at)^B} \right) \quad (\text{Weibull})$$

TDT against MDT and MRT



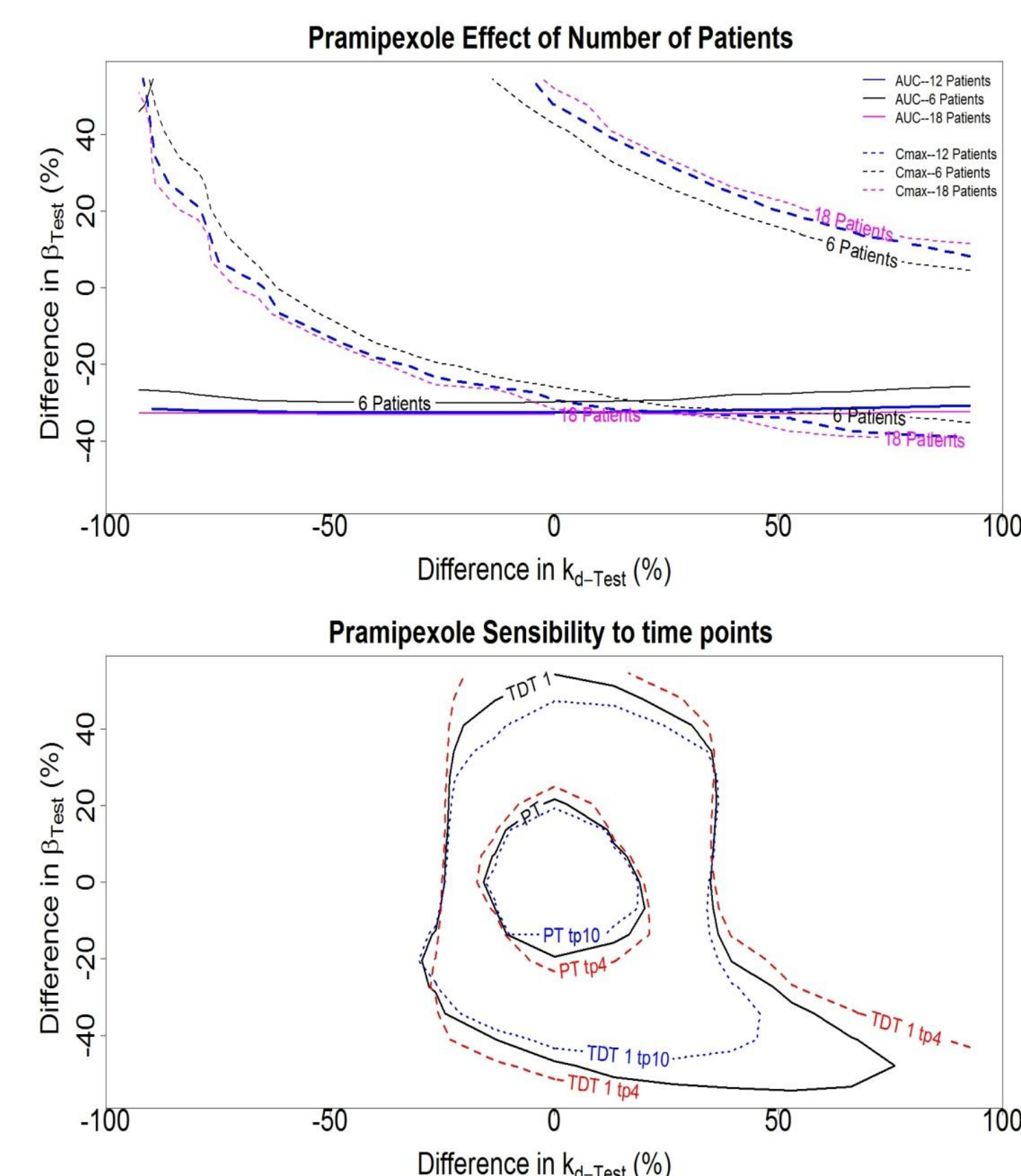
Surface response of Mean Dissolution time (MDT) or Mean Residence Time (MRT) do not match the BE-space. Formulations with the same MDT or MRT could be non-bioequivalent.

Effect of drug-formulation-patient factors



k_a and t_{lag} are the factors of the drug-formulation that affect the BE-space the most, increasing the t_{lag} reduces the BE-space in both variables (AUC and Cmax). Very small k_a reduces the BE-space in the Cmax space but not in the AUC. Variations in k_{el} , VD , volume of second compartment or inter-compartmental constant had little or no effect in the BE-space.

Effect of comparisons-associated factors



Higher number of patients in the BE trials lead to a bigger BE-space (higher chance be declared bioequivalent). Contrary, increasing the number of time points sampled in the dissolution profiles comparisons, reduces the similarity space.

CONCLUSIONS

- TDT test allows customization of formulation-specific dissolution profile comparisons of extended released formulations with bio-relevant limits.
- Extended release formulations from metformin and pramipexole are more sensitive to changes in release kinetics in term of bioequivalence than formulations with diltiazem.
- Comparisons performed using TDT must be done with at least six time point per release profile.
- k_a and t_{lag} are the factors of the drug-formulation that affect the BE-space the most.
- MDT or MRT should not be used to establish similarity for these formulations.

References

- [1] FDA, 1997. Guidance for industry dissolution testing of immediate release solid..., Rockville, MD.
- [2] P. Buchwald, Direct, differential-equation-based in-vitro-in-vivo correlation (IVIVC) method, J Pharm Pharmacol, 55 (2003) 495-504.
- [3] E. Soto, S. Haertter, M. Koenen-Bergmann, A. Staab, I.F. Troconiz, Population in vitro-in vivo correlation model for pramipexole slow-release oral formulations, Pharm Res, 27 (2010) 340-349.
- [4] J.D. Gomez-Mantilla, V.G. Casabo, U.F. Schaefer, C.M. Lehr, Permutation Test (PT) and Tolerated Difference Test (TDT): Two new, robust and powerful nonparametric tests for statistical comparison of dissolution profiles, Int J Pharm, 441 (2013) 458-467.

Acknowledgments:

Deutscher Akademischer Austauschdienst (DAAD). Saarland University, Germany. Colciencias, Colombia and Helmholtz-Institut für Pharmaceutical Research, for financial support.