

# K-PD Modeling of a Novel Oral 5-Lipoxygenase Activating Protein Inhibitor for Asthma and its Comparison with a PK-PD Approach



Navin Goyal<sup>1</sup>, Misba Beerah<sup>2</sup>

Clinical Pharmacology Modeling & Simulation, GSK, <sup>1</sup>King of Prussia PA USA, <sup>2</sup> Stevenage UK

## Introduction

➤ During drug development, plasma drug time-concentration profile may not always be available to correlate exposure with the biomarker or clinical endpoints

➤ Kinetic-Pharmacodynamic (K-PD) modeling provides an attractive alternative approach in such situations [1-4]

## Objectives

● To develop a K-PD model to describe the kinetics of effect of a novel 5-Lipoxygenase Activating Protein (FLAP) inhibitor (GSK2190915) on the functional biomarker-cysteinyl leukotriene LTE4, as measured in urine samples

● Compare performance of this K-PD model to the corresponding PK-PD model using data from single and repeat dose escalating study in healthy volunteers.

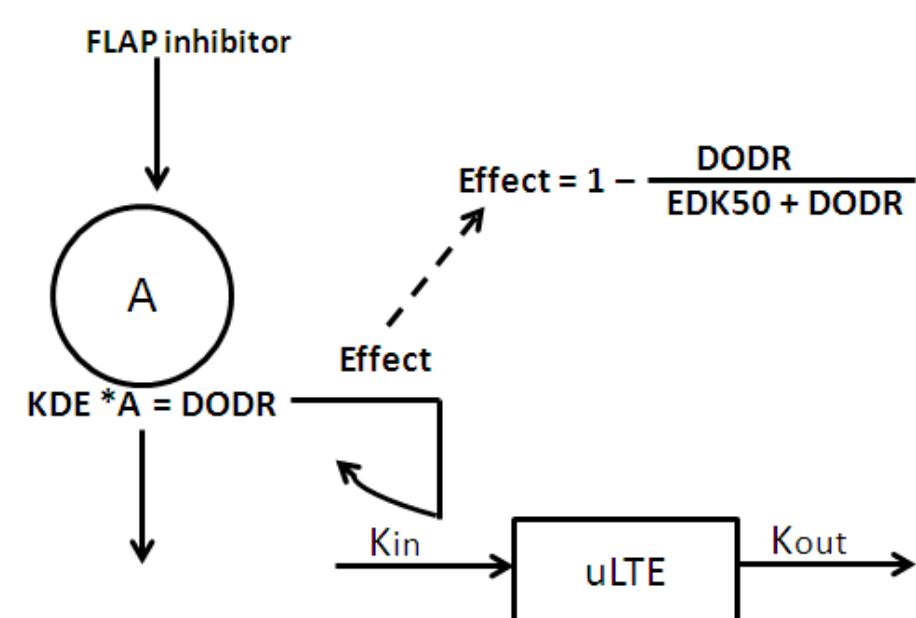
## Methods

➤ Serial drug samples (PK) and urine biomarker samples of LTE4 (PD) available from healthy volunteers receiving 50, 150, 300, 600 or 1000 mg single dose (n=40) and 10,50,150 or 450 mg once daily oral repeat dose (n=32) of GSK2190915 for 11 days were used for modeling [5]

➤ The PK-PD model was a two compartment PK model with first order absorption and an indirect PD response model with inhibition of rate of synthesis of LTE4

➤ The K-PD model completely ignored the PK data and utilized only PD information. The modeling was performed with NONMEM (NMVI). The model setup is displayed in Figure 1

➤ Visual predictive checks (VPCs), goodness-of-fit plots were amongst several criteria used to evaluate the models



**Figure 1: K-PD model setup**

The dose driving rate (DODR) drives the drug pharmacodynamics. The model input profile can be complex if data allows identification of additional parameters

## Results

➤ The K-PD model described the data with similar efficiency as the PK-PD model. The parameter estimates are presented in Table 1

➤ The EDK50 represents the drug's in vivo apparent potency at steady state. This EDK50 estimate when adjusted for the systemic clearance is comparable to the IC50 estimate calculated from the PK-PD model

➤ The EDK50 incorporates the PK and the PD variability in its estimate

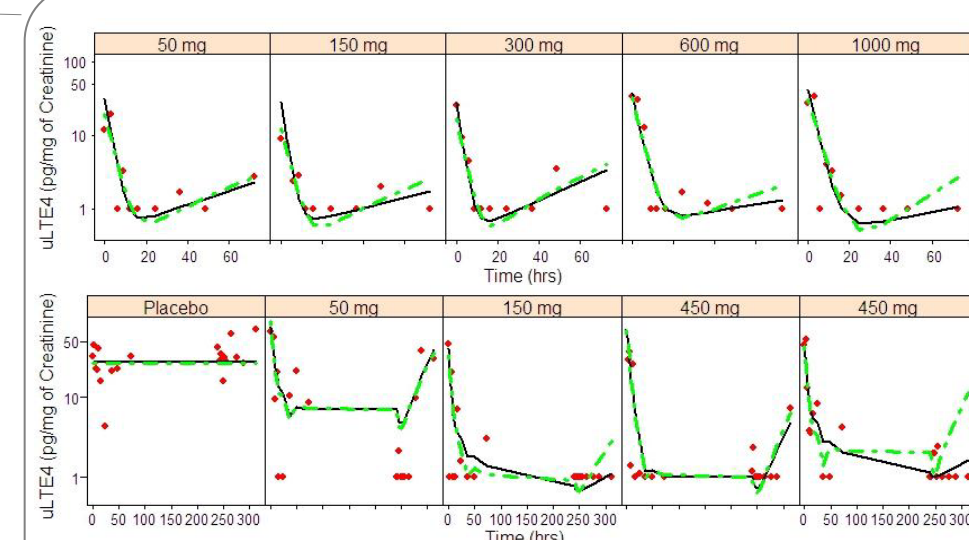
➤ The model predictions from the K-PD and PKPD are overlapping as can be seen from the few representative individual fits in Figure 2 and VPCs in Figure 3

➤ The K-PD model run time was 4 times faster than the PK-PD model

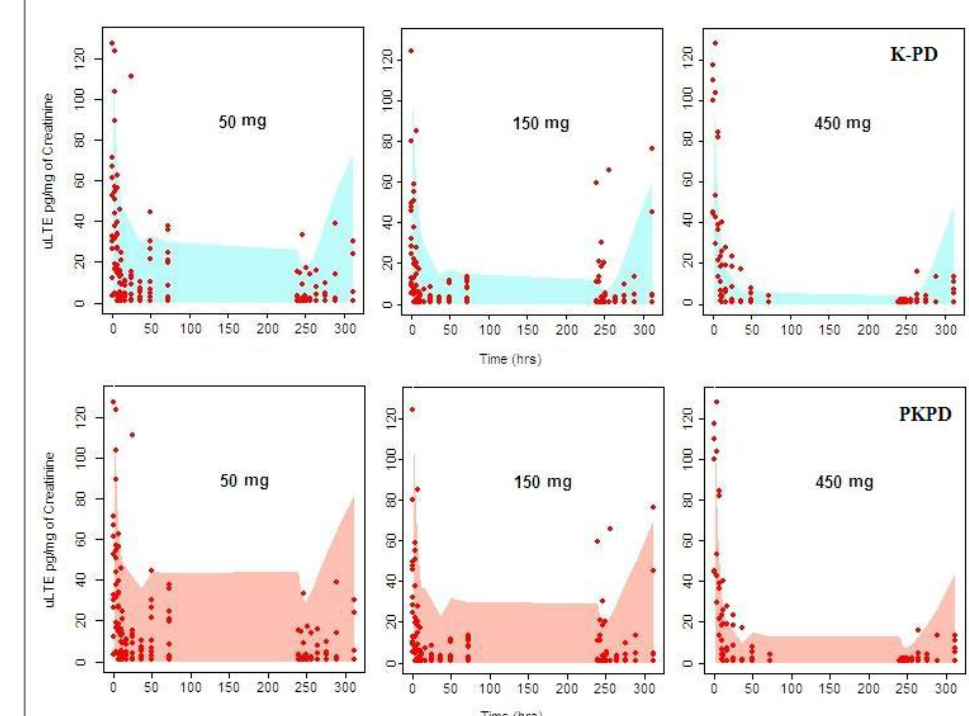
Parameter	PK-PD Mean (90 % CI)	K-PD Mean (90 % CI)
CL/F (L/hr)	7.79 (6.65 – 8.93)	
BSV CL/F (%CV)	38 (30 – 45)	
V2/F (L)	83.32 (67.31 – 99.33)	
IC50 (ng/ml)	32.96 (19.67 – 46.27)	
BSV IC50 (BSV %CV)	144 (93 – 185)	
Kin (pg/mg Cr/hr)	7.92 (5.98 – 9.85)	12.37 (9.92 – 14.82)
Kout (1/hr)	0.21 (0.19 – 0.24)	0.30 (0.25 – 0.36)
KDE (1/hr)		0.03 (0.02 – 0.04)
EDK50 (mg/hr)		0.19 (0.14 – 0.25)
BSV EDK50 (%CV)		96 (79 – 138)
NM Run Time (min)	58	14

**Table 1: Parameter Estimates from the PKPD and K-PD models**

The mean and 90% CI of population parameter estimates and between subject variability (BSV) for the two models. The estimates were obtained by bootstrapping the models (n=500 runs each)



**Figure 2: Individual fits with observed data**  
Observed data (●) with K-PD (—) & PKPD (—) model predictions for few subjects at various doses with single doses (upper) and repeated doses (lower)



**Figure 3: K-PD and PKPD VPCs**  
Trial simulations with the K-PD (upper) and PKPD (lower) models. The shaded regions are 90% prediction intervals with observed data (●)

## Conclusions

➤ This work demonstrates the value of K-PD modeling in providing a good description of kinetics of drug effect even in absence of systemic drug concentrations

➤ The K-PD model for GSK2190915 provides a valuable tool to support its clinical drug development; e.g. paediatric studies where plasma samples may not be available

➤ Certain limitations exist with generalizing the K-PD approach across untested dosing routes or regimens

➤ Diligent use of K-PD methodology may obviate requiring systemic concentrations in clinical studies where appropriate

## References

- Verotta D and Sheiner L, Semiparametric analysis J Pharmacokinet Biopharm, 1991. 19(6): p. 691
- Fisher D & Wright P, Are plasma concentration values necessary for pharmacodynamic modeling of muscle relaxants? Anesth, 1997. 86(3): p. 567
- Gabrielsson J, Jusko W, and Alari L, Modeling of dose-response-time data: Biopharm Drug Dispos, 2000. 21(2): p. 41-52
- Jacqmin P, et al., Modeling response time profiles in absence of drug conc.: JPKPD, 2007. 34(1): p. 57-85.
- Bain G et al; PK, PD and safety of GSK2190915, a novel oral anti-inflammatory 5-lipoxygenase-activating protein inhibitor, British Journal of Clinical Pharmacology, 2012: p. In Press.
- Beal, S., Sheiner, L.B., Boeckmann, A., & Bauer, R.J., NONMEM User's Guides. (1989-2009), Icon Development Solutions, Ellicott City, MD, USA, 2009