Relationship between the Dose of Urate Lowering Therapies and Serum Uric Acid in Healthy Volunteers and Gout Patients: A Model Based Meta-Analysis (MBMA)

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Objectives:

The purpose of this model-based meta-analysis was to characterize the steady-state dose-response (DR) relationship for the reduction of sUA across compounds with different mechanism of action (Xanthine Oxidase Inhibitors (XOi), Urate transport (URAT1) inhibitors, and Purine nucleoside phosphorylase (PNP) inhibitor).

Methods:

Data: A comprehensive literature search was conducted for PNP inhibitor, XOi and URAT1 inhibitors administered alone or in combination to healthy volunteers (HV) or gout patients. Serum uric acid (sUA) data, demographic, and other trial information were extracted. Summary level data of sUA CFB was summarized in Table 1 and Figure 1. There were 4 Febuxsotat trials in Japanese and 1 in Chinese. Dose response relationship for sUA change from baseline (CFB) was analyzed using NONMEM v7.2.

Table 1. Summary of Serum Uric Acid Data

	Compound	No. Trials	No. Arms	No. Patients/HVs
XOi inhibitor	Febuxostat	15	46	2645/302
	Allopurinol	7	35	2250/0
URAT1i inhibitor	Lesinurad	7	19	263/72
	Benzbromarone	5	16	516/0
	Arhalofenate	2	5	495/0
PNP inhibitor	BCX4208	3	21	354/0
Placebo		11	11	423/21
Total		39	153	6946/395

Modeling assumption:

1) Steady state response reached after one week treatments

2) Common maximal effect (E_{max}) for each mechanism of action, but different potency ($logED_{50}$) for each compound.

3) A scaling factor of E_{max} accounting different responses between the populations.

4) Response was not impacted by prophylaxis treatment.

5) sUA level could not be reduced below a certain value (floor effect). This value was fixed to 1 and sensitivity analysis was performed by fixing different floor values (0.01, 0.1, 0.5 and 1).

Modelling: The following equations (1-6) were used to characterize the dose response relationship of sUA CFB:

$$E_{ij} = E_{placebo,ij} + E_{drug,kij} + \frac{\varepsilon_{ij}}{sqrt(N_{ij})}$$

$$E_{placebo,ij} = PCB + \eta_{1i}$$

$$E_{drugk,ij} = \frac{E_{max,kij} * (Floor - BASE_{ij}) * DOSE_{ij}}{DOSE_{ij} + \exp(\log(ED_{50,k}))}$$

$$E_{max,kij} = E_{max,k} * e^{\eta_{2i}} + \theta * (BASE_{ij} - 9.2)$$

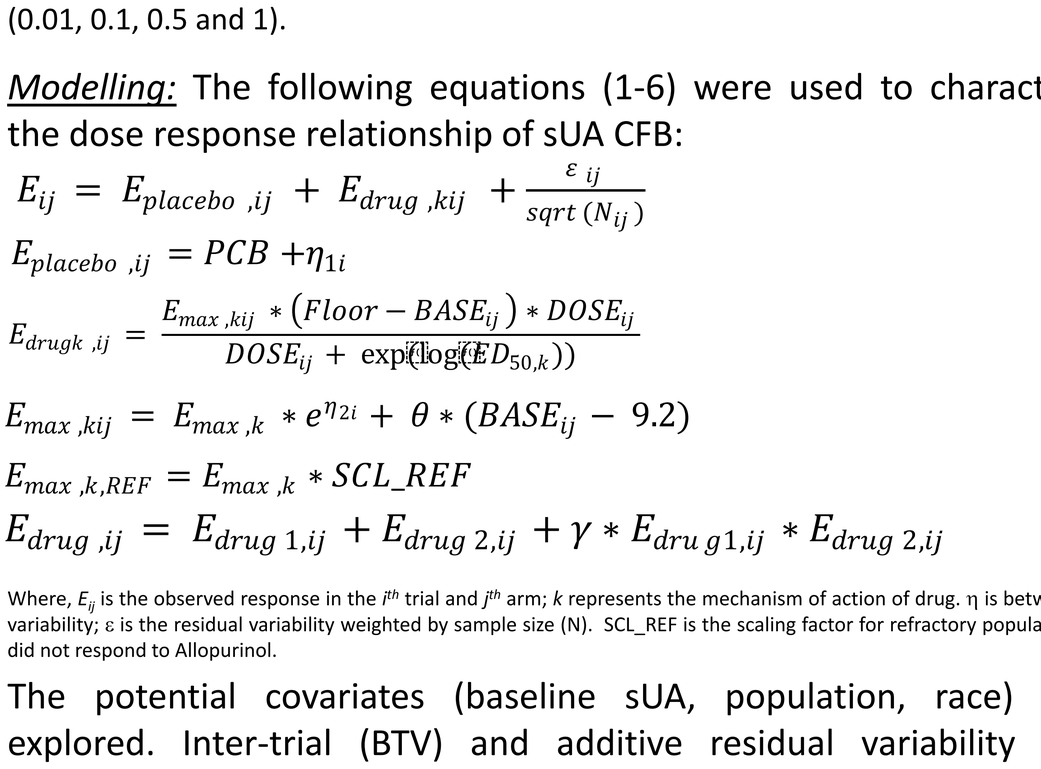
$$E_{max,k,REF} = E_{max,k} * SCL\_REF$$

$$E_{drug,ij} = E_{drug\,1,ij} + E_{drug\,2,ij} + \gamma * E_{drug\,1,ij} * E_{drug\,2,ij}$$

Where, E_{ij} is the observed response in the i^{th} trial and j^{th} arm; k represents the mechanism of action of drug. η is between trial variability; ε is the residual variability weighted by sample size (N). SCL_REF is the scaling factor for refractory population who did not respond to Allopurinol.

The potential covariates (baseline sUA, population, race) were explored. Inter-trial (BTV) and additive residual variability were estimated and the latter was weighted by sample size. The inter-arm variability (IAV) and correlation among repeated measurements was investigated using L2 option.

Figure 1. Observed sUA CFB at steady-state



*Employees and shareholders of Pfizer Inc

Results:

Observed steady-state absolute sUA CFB are presented in Figure 1. There is limited data for refractory population.

The final E_{max} DR model (eq 1-6) described data well (Figure 2) and parameters were well estimated (Table 2). It was found that:

1) Different response between HV and patients could be accounted by baseline effect.
2) There was no clinical significant race effect on the response.
   i) Japanese patients' response was not statistically significant from western
   ii) Chinese E_{max} was about 10% less than other populations.
3) Maximum effect of Lesinurad reduced by 33% in the non-responder population to Allopurinol.
4) The combination effect was less than additive among all the co-medication situations, suggesting it was less than the sum of their separate effect
5) IAV and correlation among multiple measurements were not significant. The correlation was low (7%).

Figure 2. Basic Goodness of Fit for the Final Model

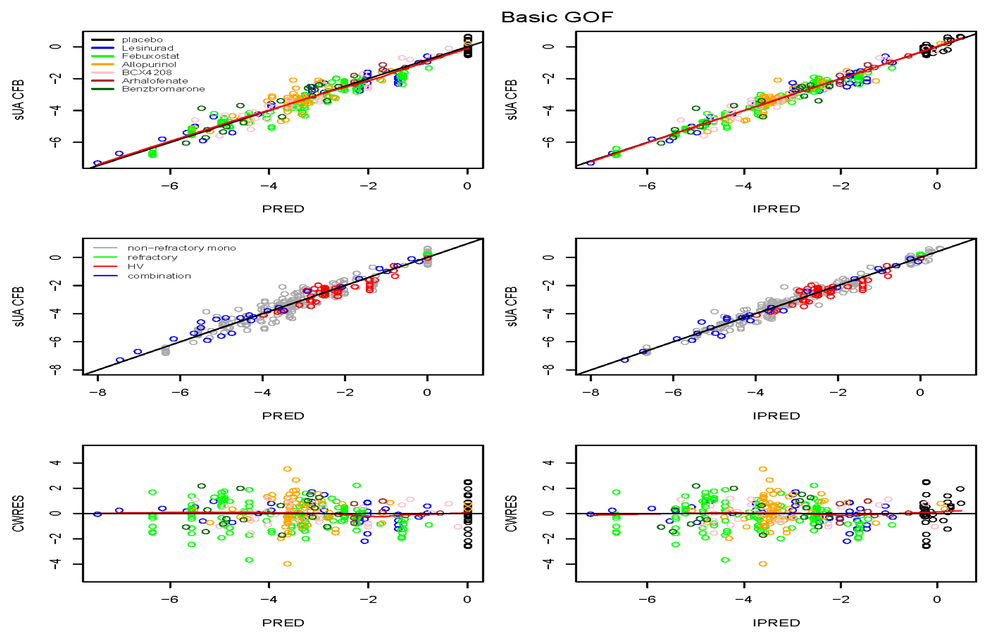


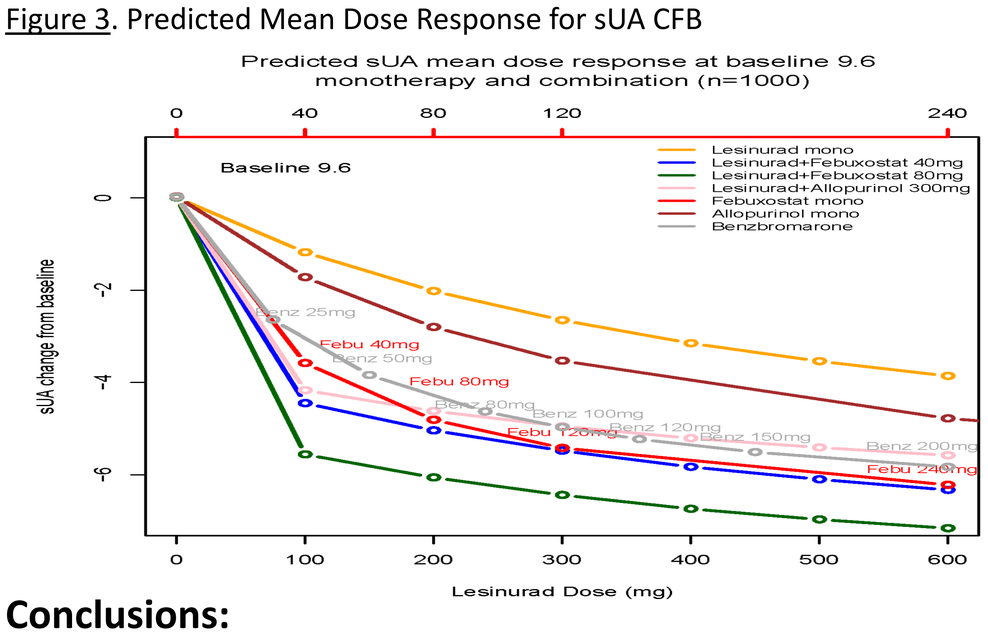
Table 2. Parameter Estimates from the Final Model

Parameter	Estimates (RSE%)	Derived Estimate*	BTV (RSE%)
Placebo (mg/dL)	0.0167 (399)		0.277 (32.38)
E_{max}_XOi (mg/dL)	0.868 (3.23)	-7.12	5.67% (98.76)
E_{max}_XOi_Chinese (mg/dL)	0.773 (4.01)	-6.34	5.67% (98.76)
Log(ED_{50}_Febu) (mg)	3.72 (2.69)	41.3	
Log(ED_{50}_Allop) (mg)	5.77 (1.41)	320.5	
E_{max}_BCX4208 (mg/dL)	0.665 (3.80)	-5.45	
Log(ED_{50}_BCX4208) (mg)	4.22 (3.20)	68	
E_{max}_URAT1i (mg/dL)	0.834 (10.28)	-6.84	
Log(ED_{50}_Les) (mg)	6.2 (3.23)	492.7	
Log(ED_{50}_Arh) (mg)	7.11 (2.29)	1224	
Log(ED_{50}_Benz) (mg)	3.72 (8.49)	41.3	
Baseline_E_{max} (θ)	-0.0356 (27.95)		
SCL_REF	0.658 (9.77)		
Floor	1 fix		
γ1: Les + Febu	0.0825 (8.73)		
γ2: Les + Allop	0.133 (15.94)		
γ1: BCX4208 + Allop	0.112 (10.63)		
Residual	1.58 (22.51)		

Allop: Allopurinol; Arh: Arhalofenate; Benz: Benzbromarone; Febu: Febuxostat; Les: Lesinurad
* Derived E_{max} = $E_{max,estimate}$ *(floor-9.2) = E_{max}*(-8.2)
Derived ED_{50} = exp(log(ED_{50}))

The final model (including parameter uncertainty) was used to simulate sUA CFB DR at different doses for each compounds. Predicted DR profiles are shown in Figure 3.

Figure 3. Predicted Mean Dose Response for sUA CFB



Conclusions:

This model-based meta-analysis provided a broad overview and understanding of effect size of different classes of urate-lowering drugs in order to develop comparative product profiles, aid translation between different populations and predict potential combination effects in the drug development of novel Urate lowering agents.