



POPULATION PHARMACOKINETICS OF THE ACTIVE METABOLITE OF LEFLUNOMIDE IN KOREAN POPULATION

Yesong Shin^{1,2}, Dongwoo Chae¹, Kyungsoo Park^{1*}

¹ Department of Pharmacology, Yonsei University College of Medicine, Seoul, Korea
² Brain Korea 21 FOUR Project for Medical Science, Yonsei University, Seoul, Korea

Background

- Leflunomide is an immunosuppressive drug indicated for the treatment of rheumatoid arthritis. While the pharmacokinetics (PK) of its active metabolite A771726 show large interindividual variability influenced by several factors [1,2], no efficient dose individualization strategy is currently in use.
- The goal of this study was to develop a population PK model for leflunomide and propose an optimal dosing strategy in RA patients.

Methods

Details of data

- A771726 blood concentration was used for Pharmacokinetics analysis of Leflunomide
- Data were collected from 50 healthy male volunteers between the age of 19 and 37 with body weight over 55.8kg, 400 observations.
- The subjects were given single doses of Leflunomide 40mg under fasting condition.

Model building

- Based on the collected data, a PK model was built using NONMEM software version 7.4.
- Two-compartment model with first order absorption and enterohepatic recycling, with allometric scaling were chosen for the basic pharmacokinetic structural model.

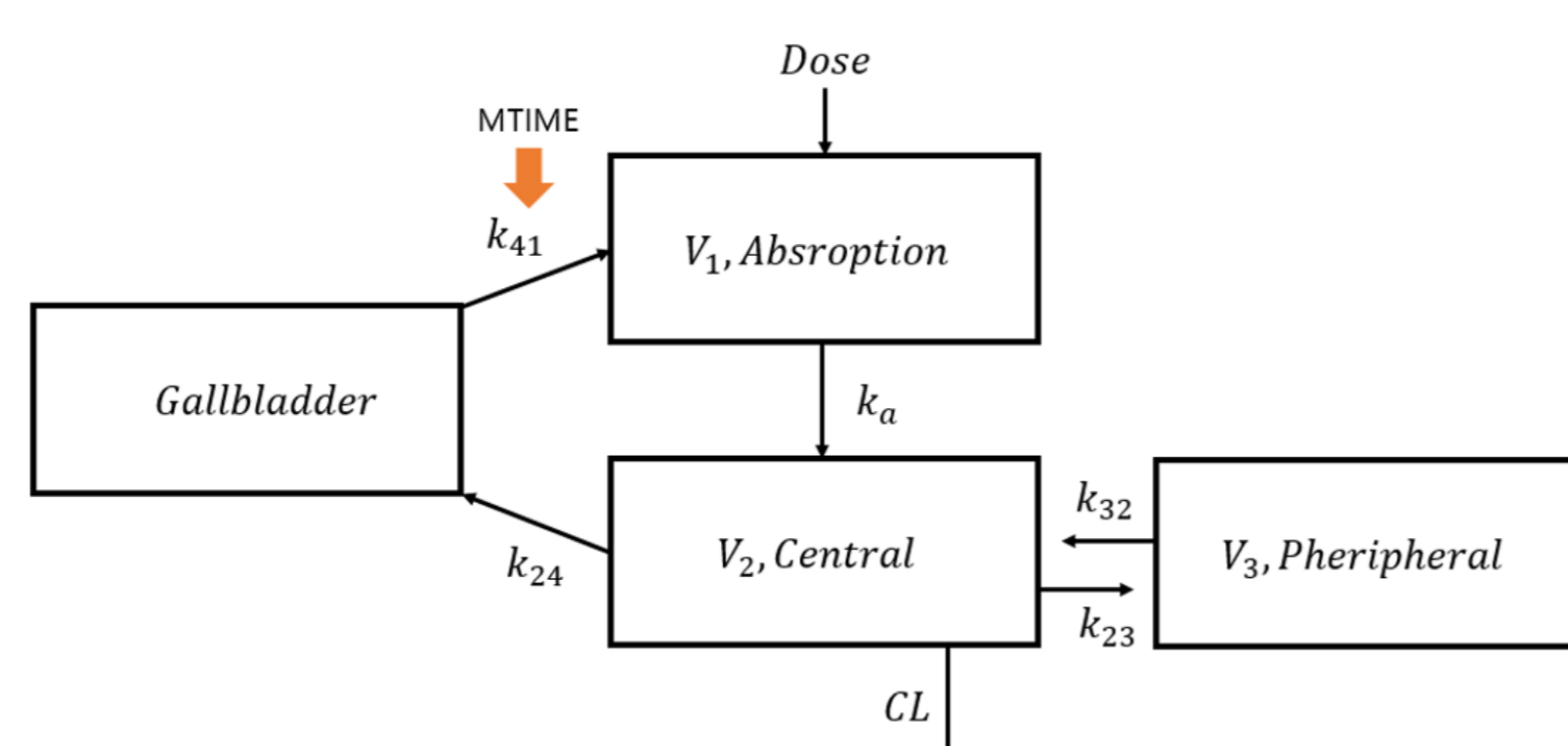


Figure 1. Leflunomide compartmental plot

- No significant covariate was found other than weight included by allometric scaling, which improved the model significantly.
- The minimum value of the objective function (OFV), conditional weighted residual (CWRES) plots were used to choose suitable. Additional and proportional error model was used.
- Multiple dose simulations were performed to determine the optimal dosing regimen.

Results

Parameter	Estimate	RSE%	BSV (CV%)	RSE%
CL (L/h)	0.0273	3.883	27.22	10.26
V2 (L)	6.83	5.534	24.7	17.46
V3 (h)	2.27	4.978		
Q (h ⁻¹)	0.593	19.73		
KA (h ⁻¹)	1.61	15.22	107.2	11.22
DUR (h)	4	0.034		
K24 (h ⁻¹)	0.0116	20.6		
$\sigma_{proportional}$ (CV%)	10.91	12.61		
$\sigma_{additional}$ (SD)	50.89	69.88		

Table 1. parameter estimates

- Parameter description

CL : Leflunomide clearance
V2 : Central compartment volume
V3 : Peripheral compartment volume
Q : intercompartmental clearance
KA : Absorption rate
DUR : gallbladder to absorption (enterohepatic recycling) drug release duration
K24 : central to gallbladder drug uptake rate

- The enterohepatic recycling can be identified by multiple peaks in the plot which explain leflunomide's long half-life.
- The final model parameter values were similar to those from Chinese [3].

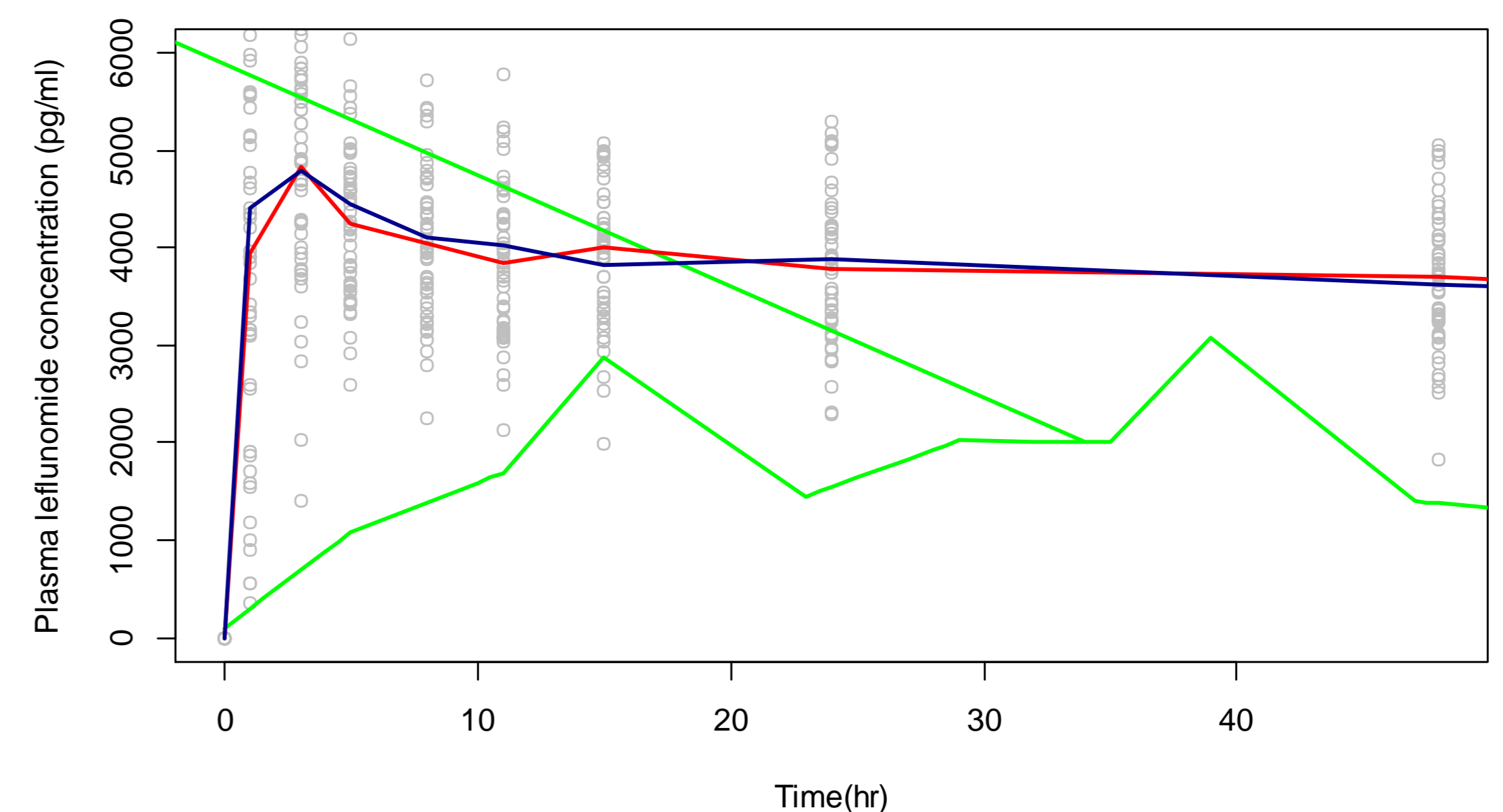


Figure 2. TIME(hr) vs Blood concentration plot (0-48h)

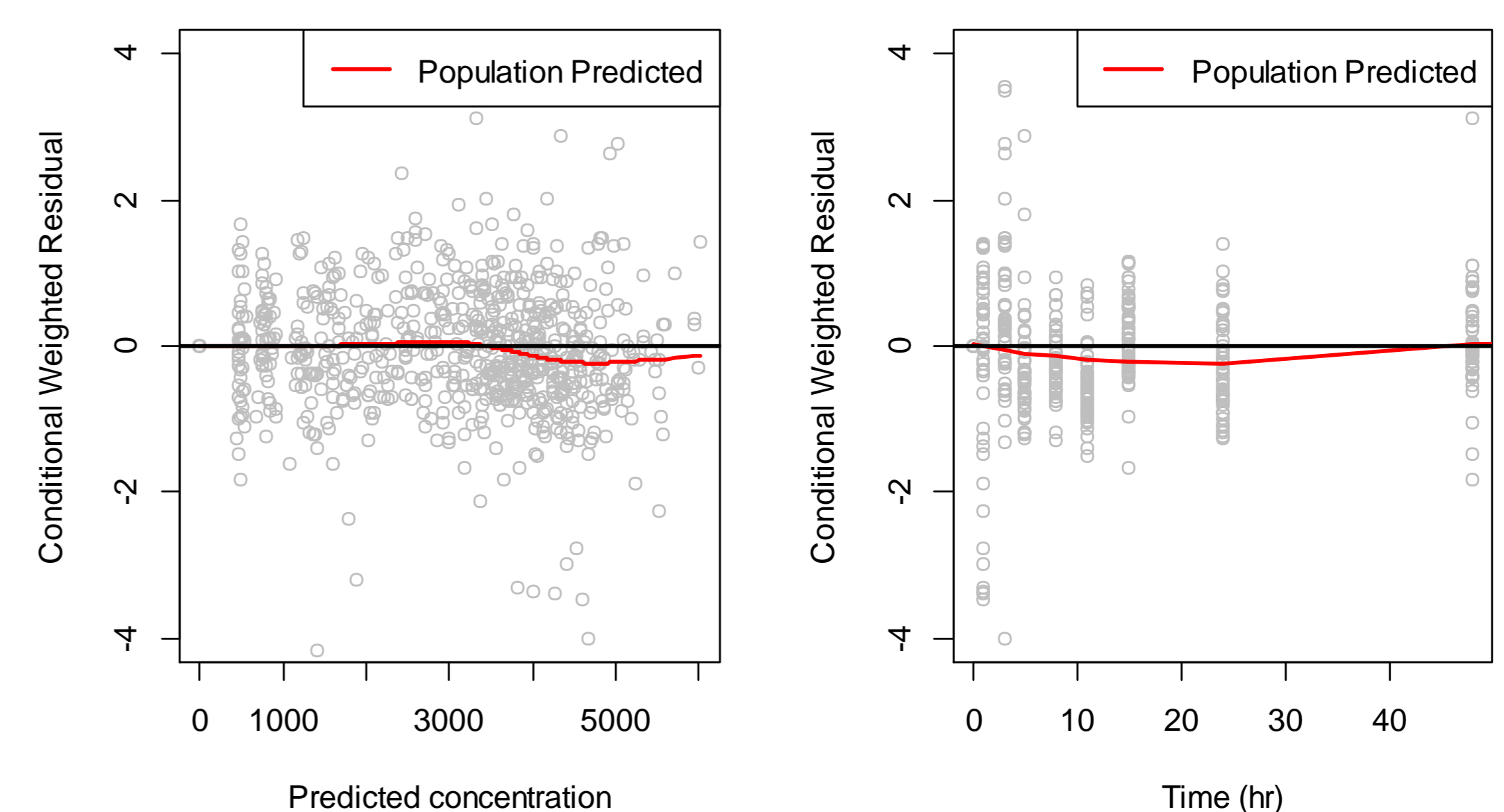


Figure 3. PRED vs CWRES & TIME vs CWRES

- Multiple dose simulations based on the final model suggested that to attain target concentration, the loading dose should be increased by 15 mg for every 10 kg increase in body weight.

Parameter	Loading Dose (mg)	Maintenance Dose (mg)
50KG	70 QD	15 QD
60KG	85 QD	20 QD
70KG	100 QD	20 QD
80KG	115 QD	20 QD
90KG	130 QD	25 QD

Table 2. The propose of the loading and maintenance doses recommendation of leflunomide in each weight subgroups

Conclusions

- The population PK model incorporating EHC well described the pharmacokinetic profile of A771726.
- Based on extensive model simulations, we propose a personalized dosing scheme for RA patients based on body weight.
- The large inter-individual variability of KA could be due to pharmacogenetic differences, such as that related to ABCG2, or could be due to our use of a common KA for both initial drug absorption and EHC-mediated reabsorption.
- The use of Physiologically Based Finite Time Pharmacokinetic (PBFTP) model might be a possible solution in this case.

References

- [1] AM Hopkins, MD Wiese, SM Proudman, CE O'Doherty, DJR Foster, and RN Upton. Semiphysiologically Based Pharmacokinetic Model of Leflunomide Disposition in Rheumatoid Arthritis Patients. CPT Pharmacometrics Syst Pharmacol. 2015 Jun; 4(6): 362-371.
- [2] Bohanec Grabar P, Investigation of the influence of CYP1A2 and CYP2C19 genetic polymorphism on 2-Cyano-3-hydroxy-N-[4-(trifluoromethyl)phenyl]-2-butenamide (A 77 1726) pharmacokinetics in leflunomide-treated patients with rheumatoid arthritis. Drug Metab Dispos. 2009 Oct;37(10):2061-8. doi: 10.1124/dmd.109.027482. Epub 2009 Jul 6.
- [3] W. Weber, L.H. The population approach: Measuring and managing variability in response, concentration and dose; COST B1 medicine: European cooperation in the field of scientific and technical research, Brussels: European Commission: 1997; pp 238-244.
- [4] W. Weber, L.H. Use of a population approach to the development of leflunomide: A new disease-modifying drug in the treatment of rheumatoid arthritis; Hoechst Marion Roussel. COST B1 medicine, Geneva: 1997; pp 239-244
- [5] Chryssafidis P, Tsekouras AA, Macheras P. Re-writing oral pharmacokinetics using physiologically based finite time pharmacokinetic (PBFTP) models. Pharm. Res. 2022; 39