

External validation of a population pharmacokinetic model of adalimumab in patients with hidradenitis suppurativa

Karine Rodriguez-Fernandez¹, E Gras-Colomer², M Clemente-Martí^{3,4}, V Mangas-Sanjuan^{1,5}, M Merino-Sanjuan^{1,5}

¹ Department of Pharmacy and Pharmaceutical Technology and Parasitology, University of Valencia. Valencia, Spain. ² Department of Pharmacy, Hospital Manises of Valencia, Spain. ³ Department of Pharmacy, University Hospital Doctor Peset of Valencia, Spain. ⁴ Foundation for the Promotion of Healthcare and Biomedical Research in the Valencian Community (FISABIO), Valencia, Spain. ⁵ Interuniversity Research Institute for Molecular Recognition and Technological Development, Polytechnic University of Valencia-University of Valencia. Valencia, Spain.



OBJECTIVES

Hidradenitis suppurativa (HS) is a chronic skin disease characterized by the presence of inflammatory nodules, in intertriginous areas, that can progress to abscesses and fistulas. The medical treatment is based on antibiotics, retinoids, and anti-inflammatory drugs, such as the TNF- α blocker adalimumab (ADA) [1]. The aim of this work is to externally validate a previously developed population pharmacokinetic (PK) model of ADA [2] in patients with HS.

METHODS

A prospective, multicenter (national), observational, post-authorization follow-up study of clinical practice was conducted from November 2017 to April 2021 in two public hospitals in Valencia, Spain: Dr. Peset University Hospital and Manises Hospital. Patients were diagnosed with HS, were following treatment subcutaneous 40/80 mg ADA and were in steady state (Tables 1-2). A summary of the modelling workflow is presented in Figure 1.

ADA schedule (mg/week)	40/7	40/10	40/14	80/10	80/12	80/14	80/21	Total
Subjects	17	2	1	2	1	23	1	39
Observations	25	2	2	2	2	30	2	65
Observations per ID	1/2/4	1	2	1	2	1/2/3	2	

Table 1. Description of the pharmacokinetic experimental data of adalimumab collected in hidradenitis suppurativa disease

Measure	Age (years)	Body weight (kg)	Height (cm)	Albumin [g/dL]	C-reactive protein [mg/L]	Gender [N,%]
Mean	48.25	76.2	170	4.21	7.61	Male [17, 43.5]
Median	46.65	75.5	172	4.3	4.82	
Min	28	41	154	1.2	0.16	Female [22, 56.5]
Max	66	140	185	5	47	

Table 2. Summary of the demographic and biochemical characteristics of the patients

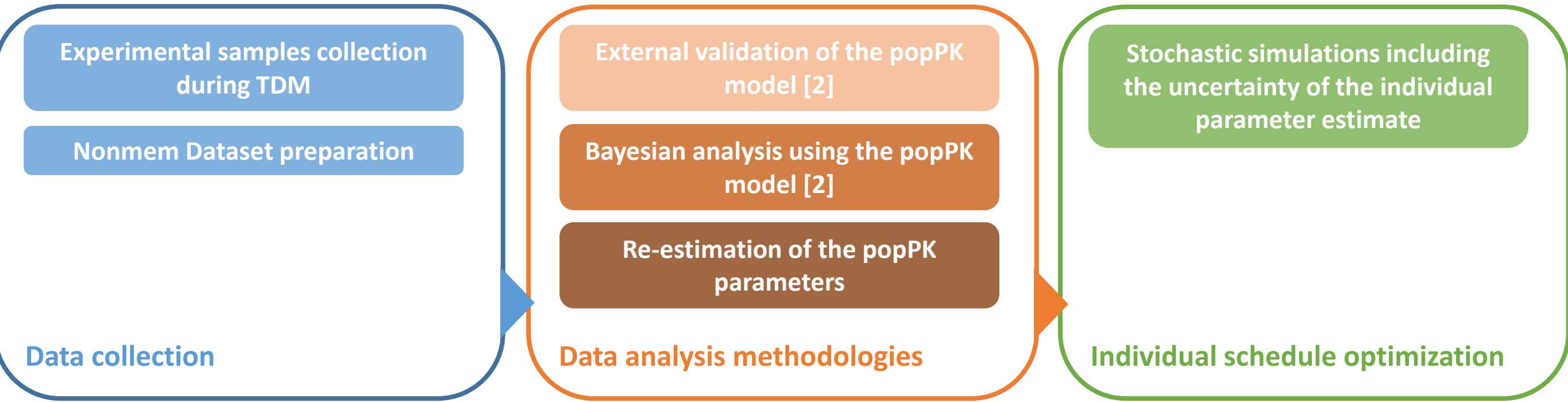
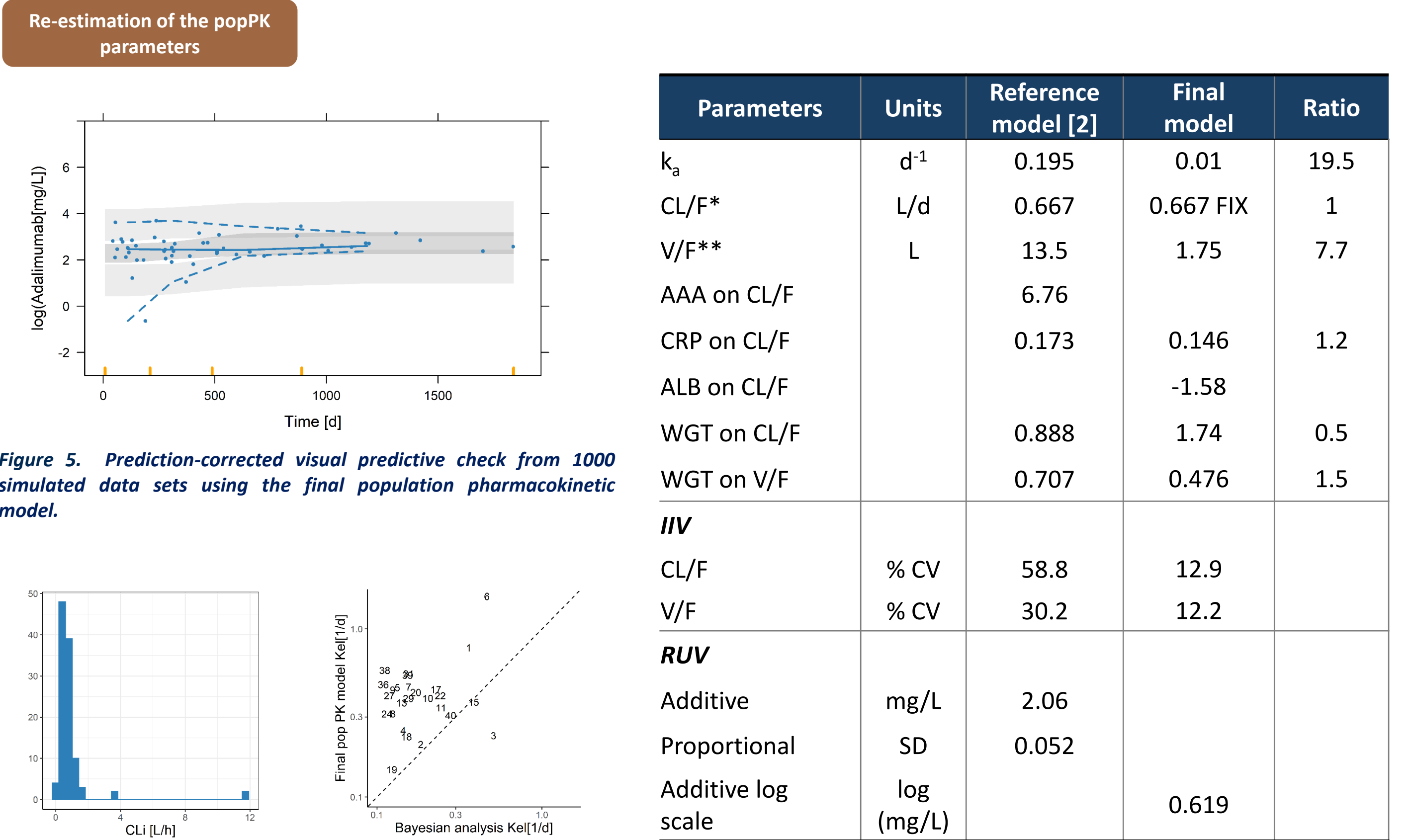
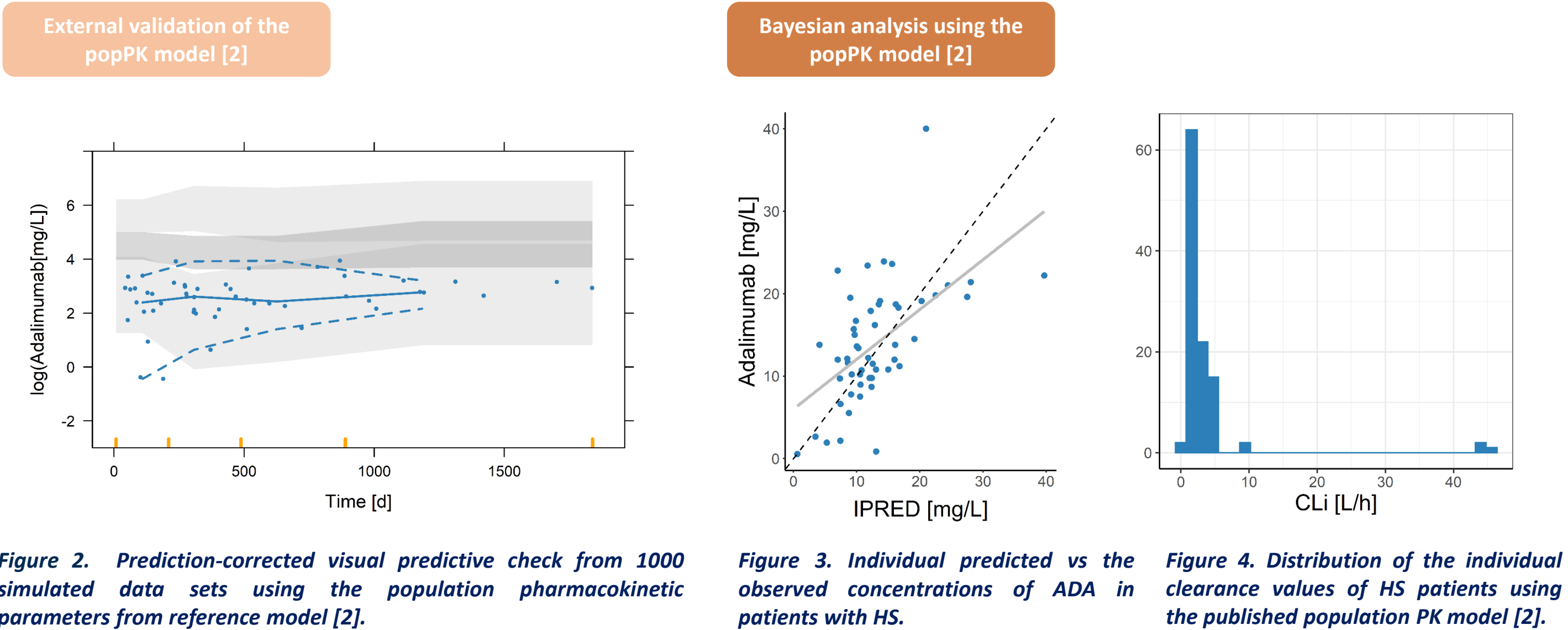


Figure 1. Modelling workflow

RESULTS

The ADA PK was described with a one-compartment model with first-order absorption. External validation of the published population PK model is depicted in Figure 3. Then, Bayesian regression using MAXEVAL=0 option with FOCE+I estimation method is shown in Figures 3-4. Using the structural definition of the population PK model, a re-estimation of the parameters was conducted (Figures 5-6). The comparison of both population PK model is summarized in Table 3.



Parameters	Units	Reference model [2]	Final model	Ratio
k_a	d ⁻¹	0.195	0.01	19.5
CL/F*	L/d	0.667	0.667 FIX	1
V/F**	L	13.5	1.75	7.7
AAA on CL/F		6.76		
CRP on CL/F		0.173	0.146	1.2
ALB on CL/F			-1.58	
WGT on CL/F		0.888	1.74	0.5
WGT on V/F		0.707	0.476	1.5
IIV				
CL/F	% CV	58.8	12.9	
V/F	% CV	30.2	12.2	
RUV				
Additive	mg/L	2.06		
Proportional	SD	0.052		
Additive log scale	log (mg/L)		0.619	

Table 3. Population pharmacokinetic estimates of ADA in HS disease patients from reference and final population PK model. k_a : first-order absorption rate constant; CL/F: plasma clearance; V/F: apparent volume of distribution in plasma; AAA: anti-ADA antibodies; CRP: C-reactive protein; ALB: albumin; WGT: weight. IIV: inter-individual variability; RUV: residual unexplained variability

$$*CL = \theta_{CL} * (WGT/75.5)^{\theta_{WGT}} * (CRP/4.82)^{\theta_{CRP}} * (ALB/4.3)^{\theta_{ALB}} * e^{\eta_1}$$

$$**V = \theta_V * (WGT/75.5)^{\theta_{WGT}} * e^{\eta_2}$$

Based on the uncertainty of the individual estimates obtained from the final population PK model, a simulation-based analysis (Figure 8) was conducted to evaluate the probability of having therapeutic ADA concentrations (8.42-12.6 mg/L) [2] for each patient in the next treatment cycle using the most prescribed ADA schedules (40 mg every 7, 10, 12 or 14 days).

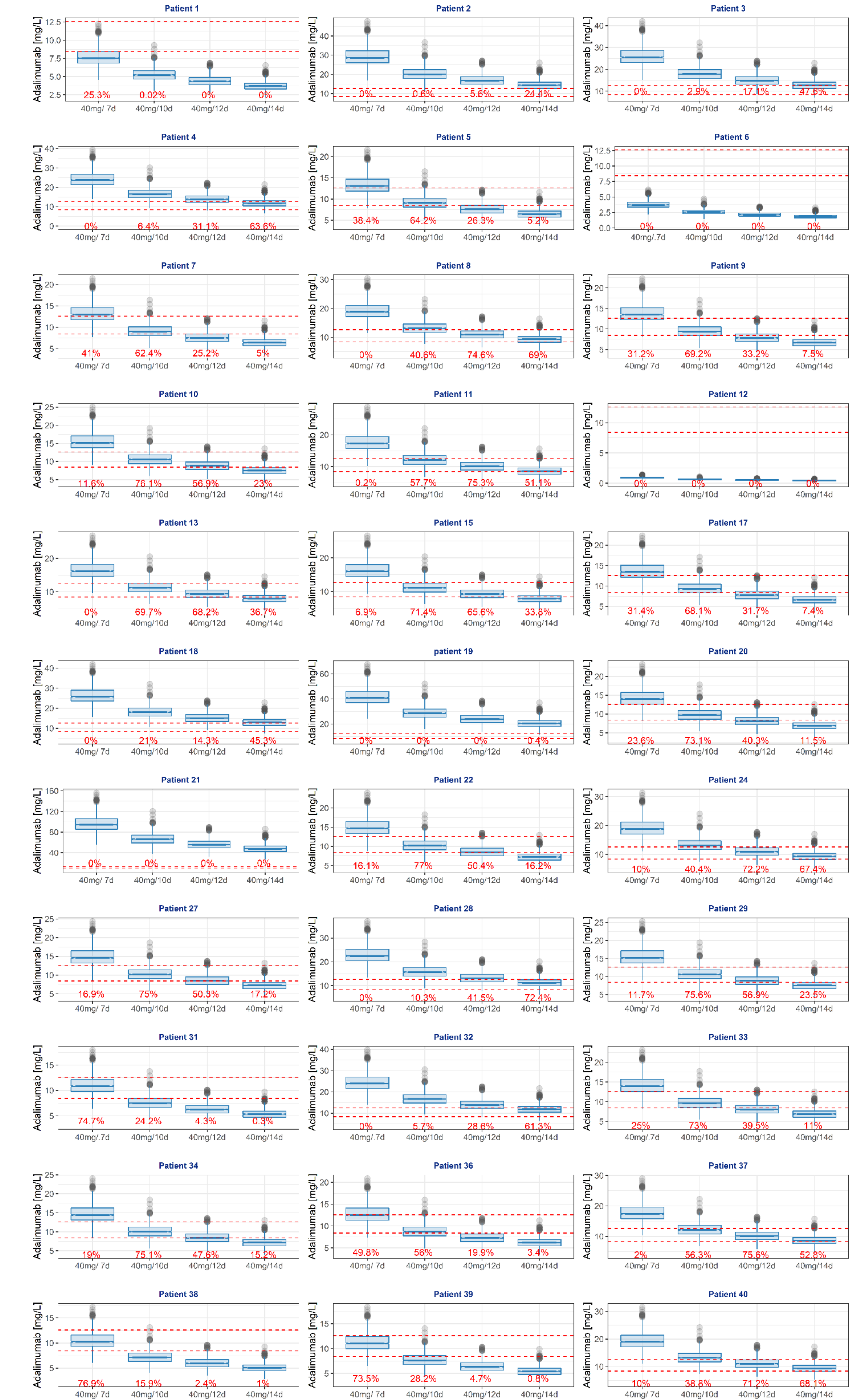


Figure 8. Boxplot of 1000 simulated plasma ADA trough concentration using the final population PK model in patients with HS at steady-state conditions. The red dotted lines represent the therapeutic range of ADA [2]. The red numbers represent the patient's probability of being within the ADA therapeutic range.

The probability of having therapeutic ADA trough levels was greater than 50% in 25 patients, of which 3 (12%), 26 (64%), 11 (44%) and 8 (32%) could be within ADA schedules of 40 mg every 7, 10, 12 or 14 days, respectively. A more exhaustive monitoring is necessary in the rest of the patients to increase the precision in the estimation of their PK parameters.

Individual schedule optimization

DISCUSSION AND CONCLUSION

A previously population pharmacokinetic model has been successfully applied in a real-world HS data set to characterize the absorption and disposition processes of ADA in patients after subcutaneous administration. The re-estimation approach using the structural PK definition as previously published for ADA in HS patients demonstrated successful characterization of the PK time course data. In addition to bodyweight and C-reactive protein as significant covariates, it was concluded the impact of baseline albumin levels on clearance in order to better understand the variability in exposure levels.

The use of the uncertainty in the individual parameter estimates has served as a model-informed tool for optimal schedule selection of ADA in HS patients based on its narrow therapeutic index in clinical practice. According to this analysis, the most selected schedule in our population that would provide therapeutic levels of ADA is 40 mg every 10 days.

References

- [1] Kim, E.S., Garnock-Jones, K.P., Keam, S.J., 2016. Adalimumab: A Review in Hidradenitis Suppurativa. American journal of clinical dermatology, 17: 545-552.
- [2] Nader A, Beck D, Noertersheuser P, Williams D, Mostafa N., 2017. Population Pharmacokinetics and Immunogenicity of Adalimumab in Adult Patients with Moderate-to-Severe Hidradenitis Suppurativa. Clinical pharmacokinetics. 56(9): 1091-102
- [3] Beal SLS, I.B.; Boeckmann A.; Bauer R.J. (2015) NONMEM Users Guides. Icon Development Solutions, Ellicott City, Maryland, USA.
- [4] Lindbom, L., P. Pihlgren, and E.N. Jonsson, PsN-Toolkit--a collection of computer intensive statistical methods for non-linear mixed effect modeling using NONMEM. Comput Methods Programs Biomed, 2005. 79(3): p. 241-57.