

Population pharmacokinetics of the selective S1P₁ receptor modulator ponesimod and its primary metabolites in healthy and organ-impaired subjects

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INTRODUCTION

Background

- Ponesimod (ACT-128800) is a potent, orally active, selective sphingosine-1-phosphate 1 (S1P₁) receptor modulator inducing rapid, dose-dependent, and reversible reduction of circulating lymphocytes¹.
- Ponesimod was shown to be effective in phase II trials in psoriasis and multiple sclerosis^{2,3}.
- Population pharmacokinetic (PK) models that characterize the PK of ponesimod and its metabolites including the influence of hepatic/renal dysfunction may be relevant for safety evaluations in organ-impaired subjects.

Objectives

- Characterization of the PK of ponesimod and its primary metabolites, M12 and M13, in healthy and hepatically and renally impaired subjects.
- Covariate screening to assess the influence of subject characteristics on the PK.

METHODS

Data

- Five phase I studies including healthy (N=112), hepatically (N=3x8 with mild, moderate, and severe hepatic impairment), and renally (N= 2x8 with moderate and severe renal impairment) impaired subjects.
- Data from single and multiple doses and an up-titration regimen, an intravenous (i.v.) and an oral (p.o.) formulation in the dose range from 5 to 100 mg o.d. were pooled. In total, 3618, 3435, and 3314 concentrations from 152 subjects (91 male and 61 female) were available for ponesimod, M12, and M13, respectively.
- The mean age of all subjects was 39 years (range: 20 to 60 years) and the mean body weight was 76 kg (range: 46 to 113 kg).

Modeling

- Non-linear mixed effects modeling, parameter estimation with SAEM.
- Monolix⁴ (version 4.31), R⁵ (version 3.0.2), and Berkeley Madonna^{6,7} (version 8.3.18).

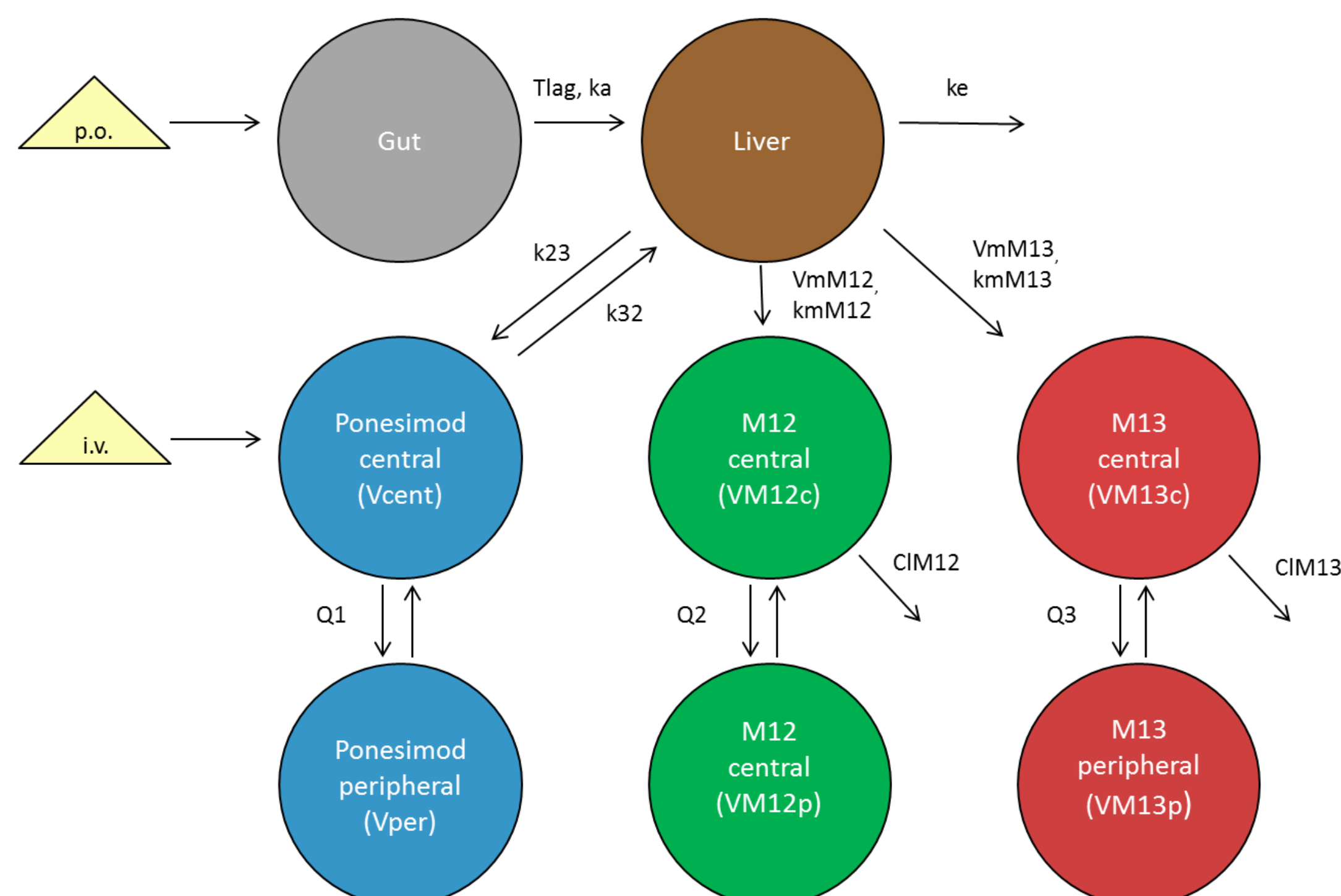


Figure 1. Structural model for ponesimod and its metabolites

Modeling steps

- The PK model was developed sequentially. After determination of the number of compartments for ponesimod, the absorption model was developed.
- Metabolites were added stepwise. A liver compartment that connects the central compartments of the three analytes was added to capture a potential first-pass metabolism and rapid occurrence of the metabolites.
- The volume of distribution of the central compartment of the metabolites was fixed to 1 as they could not be properly estimated.

Table 1. PK parameter estimates from Monolix

Parameter	Estimate	r.s.e. (%)	IIV** (%CV)	r.s.e. (%)
Tlag (h)	0.36	6	57	9
ka (1/h)	0.85	7	69	7
k23 (1/h)	1.4	2	16	11
k32 (1/h)	1.7	3	25	10
Vcent (L)	32	2	9	13
Body weight on Vcent	0.51	22	-	-
Vper (L)	136	4	37	7
Body weight on Vper	0.83	26	-	-
Q1 (L/h)	82	9	86	8
ke (1/h)	0.14, 0.11, 0.08, 0.03*	3, 12, 10, 11	24	8
VmM12 (ng/L*h)	0.19	2	17	13
kmM12 (ng/L)	82, 108, 82, 170*	4, 15, 14, 16	35	8
VM12c (L)	1***	-	-	-
VM12p (L)	9.7	32	240	17
Q2 (L/h)	0.27	9	55	21
CIM12 (L/h)	0.88, 0.67, 0.37, 0.16*	4, 18, 15, 18	35	9
VmM13 (ng/L*h)	0.15	3	26	9
kmM13 (ng/L)	104, 206, 314, 480*	4, 16, 15, 16	33	10
VM13c (L)	1***	-	-	-
VM13p (L)	2.3	8	63	10
Q3 (L/h)	0.69	9	60	17
CIM13 (L/h)	0.18, 0.14, 0.08, 0.06*	4, 18, 16, 15	36	10

* Model parameters for healthy subjects and subjects with mild, moderate, and severe hepatic impairment

** Inter-Individual Variability (random effect)

*** Parameters were fixed

- A covariate analysis was carried out using a forward inclusion and backward elimination process ($p < 0.01$). Covariates tested included demographic variables, i.e., age, sex, body weight as well as hepatic and renal function.
- The adequacy of the model was evaluated based on goodness-of-fit plots, visual predictive checks, and parameter variability.

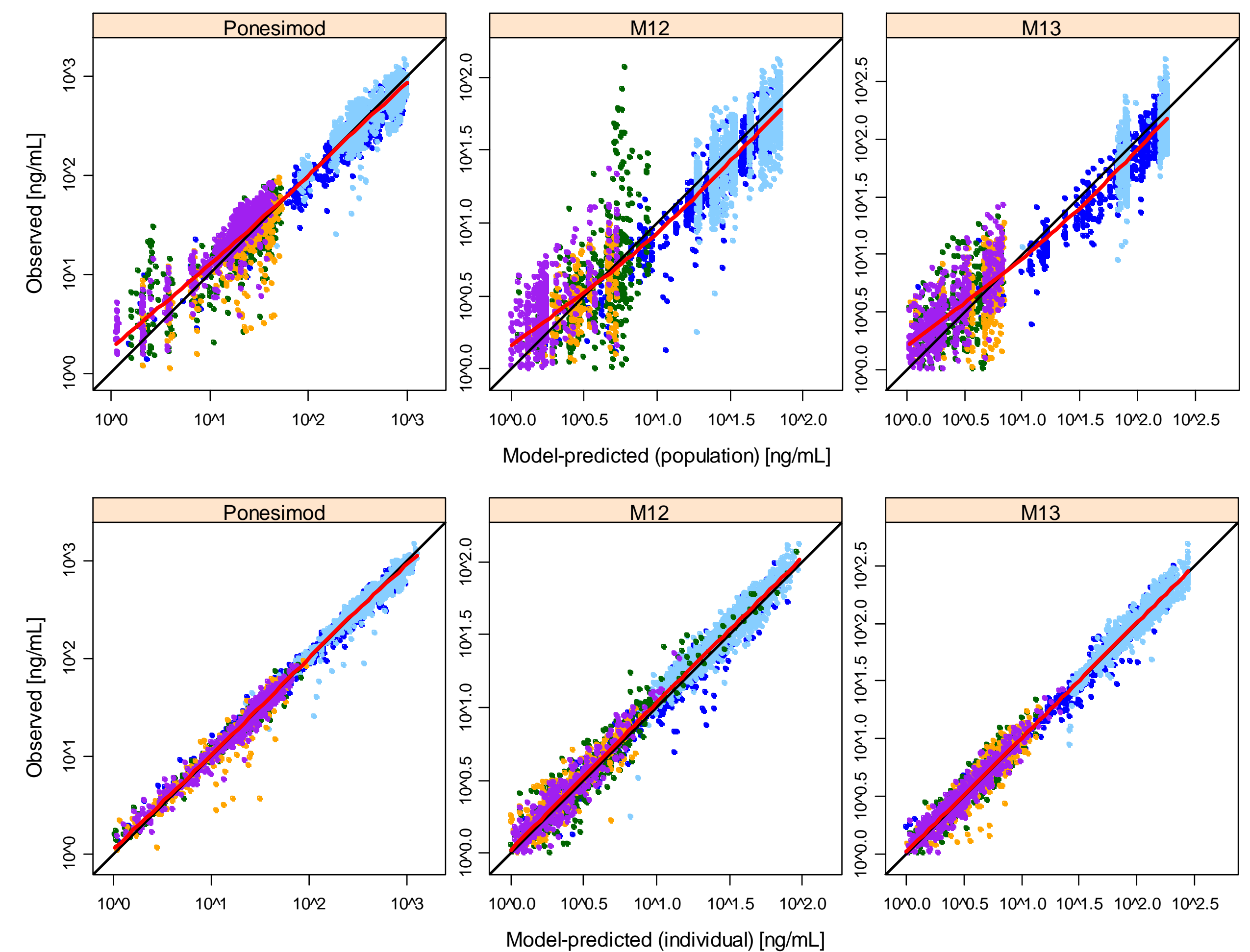


Figure 2. Observed and population-predicted concentrations for ponesimod, M12 and M13 (top) and individual-predicted concentrations (bottom). Colors indicate different studies

RESULTS

- The PK of ponesimod and its metabolites are characterized by two-compartment models for each of the analytes with 1st order absorption including lag time connected via a liver compartment. Elimination was best described by a 1st order process, whereas drug metabolism was saturable (Figure 1).
- Body weight was found to have a significant effect on both volumes of distribution for ponesimod. Hepatic function significantly affected ponesimod metabolism as well as the elimination of all three analytes (Table 1). Renal impairment showed no significant effect.
- Overall, the observed concentrations show a good correspondence with the model-predicted concentrations (Figure 2).
- Figure 3 illustrates the population-typical concentration-time profiles of ponesimod and its metabolites following repeated dosing of 10 mg for 30 days in healthy and severe hepatically impaired subjects. Exposure in a severe hepatically impaired compared to a healthy subject at steady state is 3.6x, 8.4x, and 2.7x higher for ponesimod, M12, and M13, respectively.

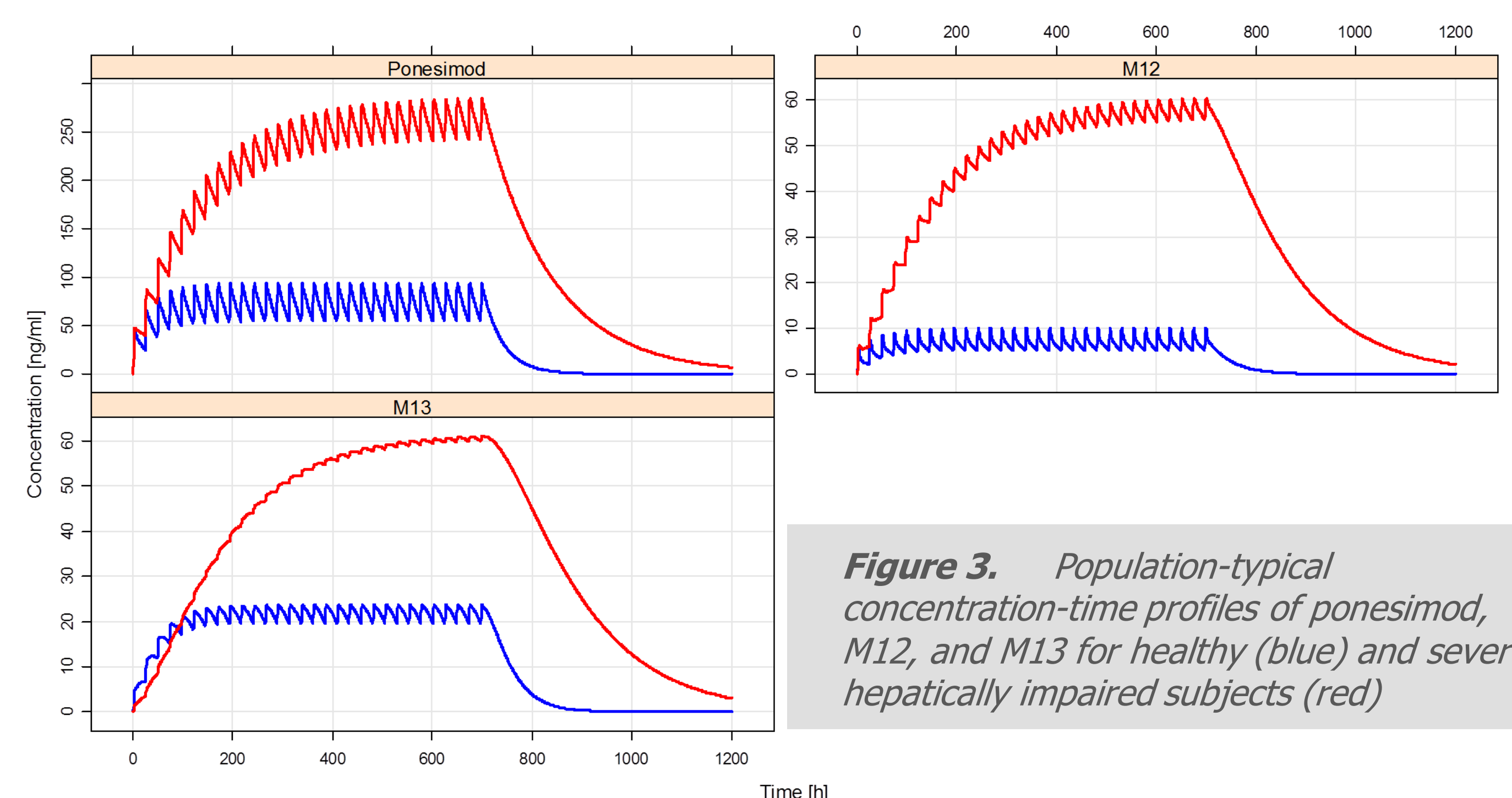


Figure 3. Population-typical concentration-time profiles of ponesimod, M12, and M13 for healthy (blue) and severe hepatically impaired subjects (red)

CONCLUSIONS

- The population PK model developed for ponesimod and its primary metabolites characterized the data well.
- Hepatic function was found to have a strong impact on the clearance of ponesimod and its metabolites.
- The model may serve as a valuable tool for the future drug development process, safety evaluation, and dose adaptation in hepatically impaired subjects.

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