

Effects on Exposure Estimation with Auto-Inhibition Modeling

Higher estimated exposure at steady-state with auto-inhibition
($AUC_{ss} + 15\%$ and $C_{max,ss} + 11\%$)

Modeling of the Pharmacokinetics of the Selective Orexin-1 Receptor Antagonist ACT-539313 with Auto-Inhibition

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Binge Eating Disorder (BED) is characterized by recurrent episodes of excessive food intake and loss of control of eating behavior. It is associated with significant impairment of psychological and social functioning and can lead to metabolic dysfunction, and cardiovascular disease [1]. Treatment includes cognitive-behavioral therapy, pharmacotherapy, and weight management interventions [2]. SORAs have emerged as a promising pharmacological approach to treating BED [3]. Berger et al. (2020) reported that treatment with ACT-539313 elicited CYP3A enzyme inhibition (i.e., auto-inhibition) [4].

Objective: Develop a population pharmacokinetic (popPK) model for ACT-539313 describing auto-inhibition.

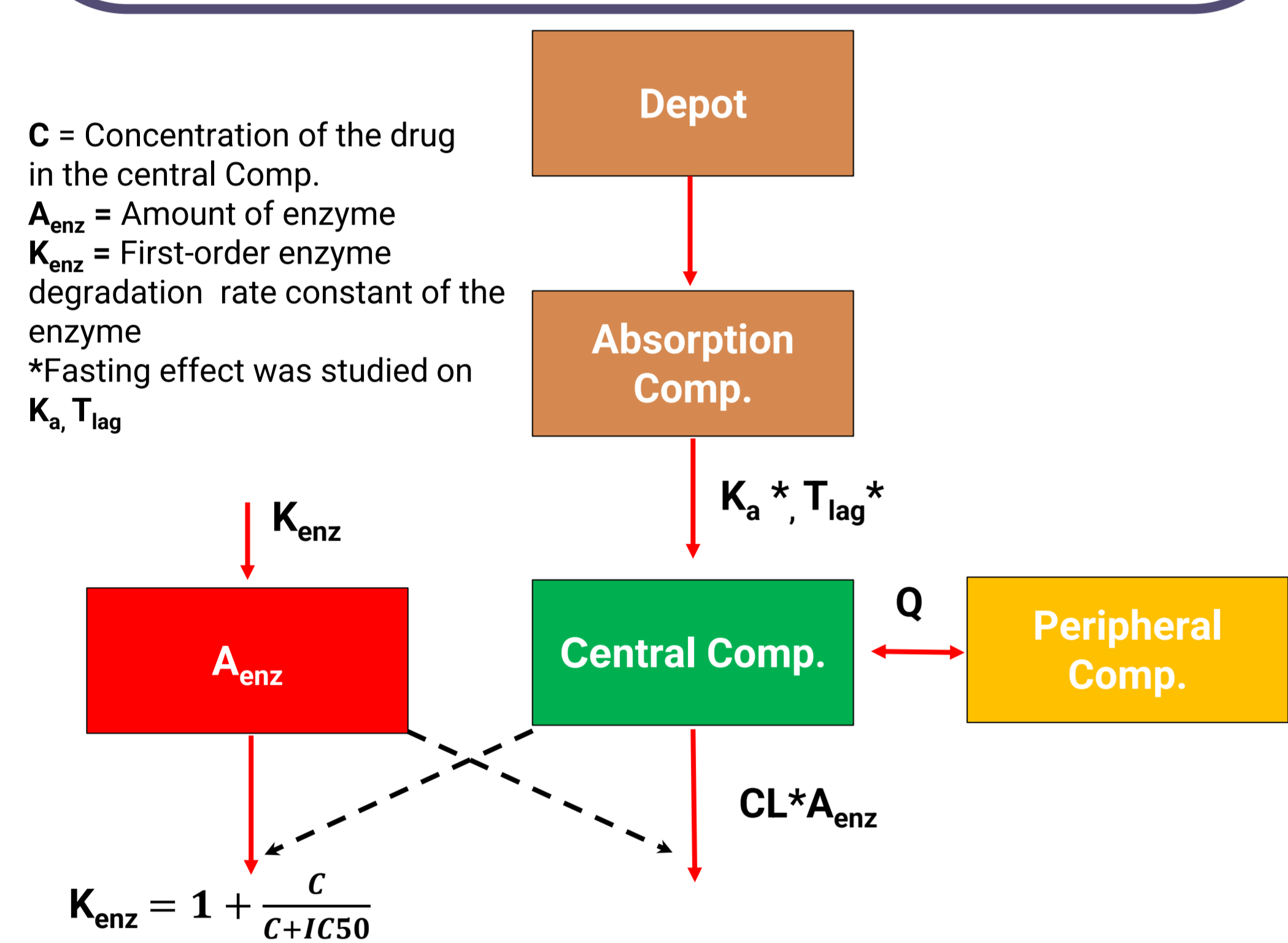


Figure 1: Structural Model

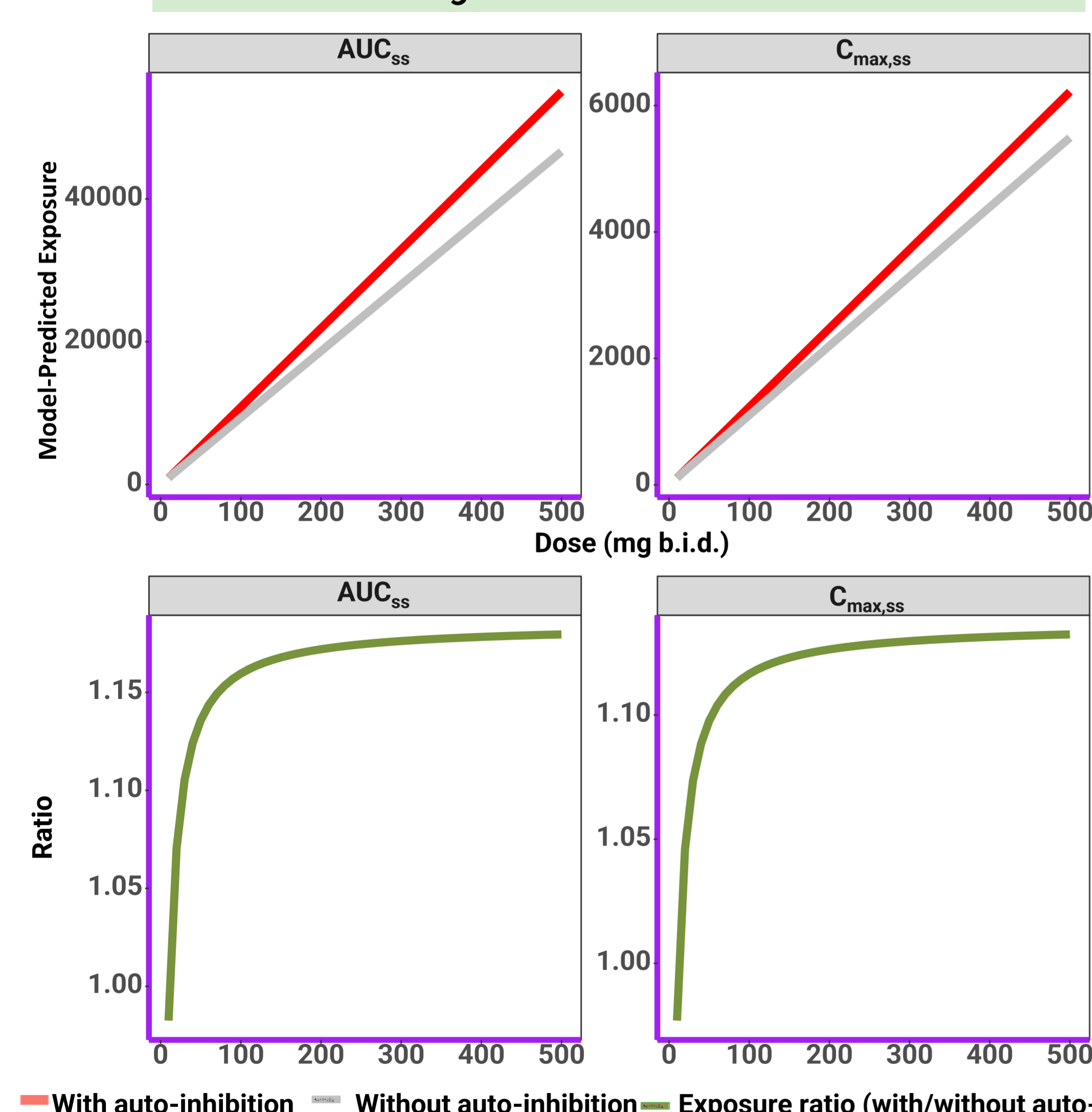


Figure 3: Exposure and Ratio Vs. Dose for Model With and Without Auto-inhibition

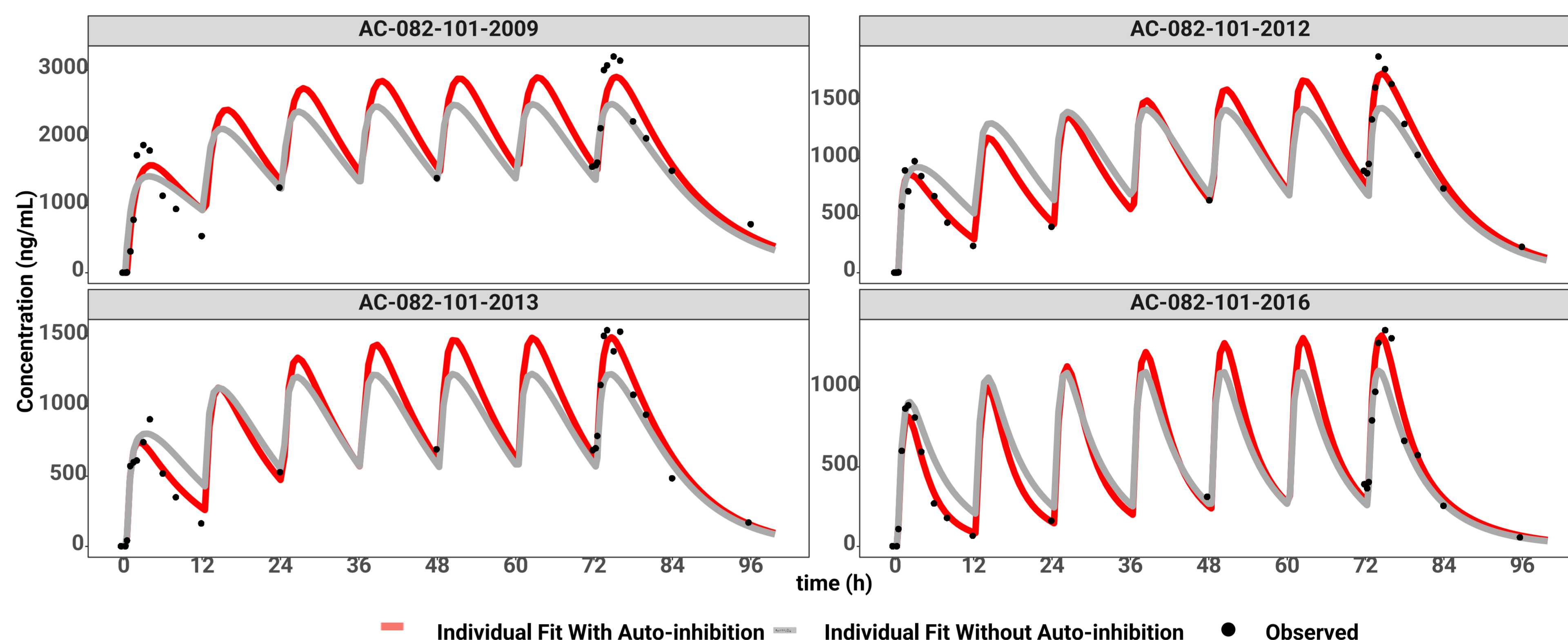


Figure 2: Four Individual Fits (With and Without Auto-inhibition) and Observed Concentration After Multiple Oral Administration of 200 mg ACT-539313

Better fit of the observed data with the auto-inhibition model especially during the elimination phase

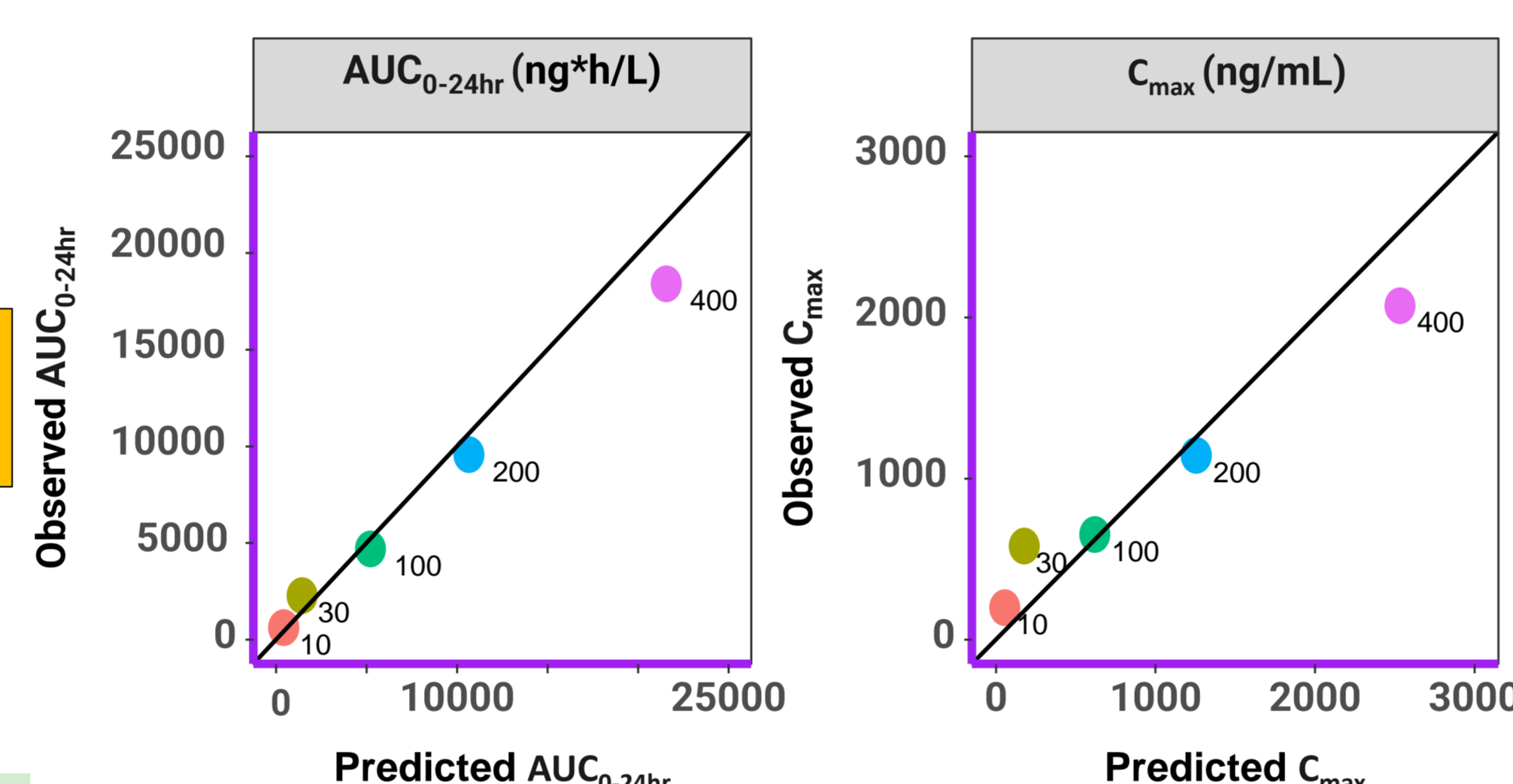


Figure 4: Observed Versus Predicted Exposure Parameters After Single Administration of Doses (10, 30, 100, 200 & 400 mg)

Data:

- Combined data from 3 phase I studies in healthy subjects (single and multiple ascending doses of 10, 30, 100, 200, and 400 mg) and 1 phase II clinical study (multiple doses of 100 mg).

Model development:

- NLME modeling approach.
- SAEM algorithm, and COSSAC for covariate selection.
- Evaluated several models with and without auto-inhibition component.
- Svensson et al. (2018) model was adopted after modification to describe the enzyme turnover [5].

Simulation:

- Based on the final parameter estimates, multiple oral doses twice daily, doses ranging between 10 – 1000 mg.

Table 1. Characteristics of the Participants

Characteristics	187 Total Subjects	124 Healthy Subjects	63 Obese Patients
Age* (Years)	40.1	41.4	37.4
Sex			
Female	75	25	50
Male	112	99	13
Body weight* (Kg)	86.0	78.5	100.8
Height* (cm)	174.4	177.1	169.0
Body Mass Index* (kg/m ²)	28.4	25.0	35.0
Lean Body Mass* (Kg)	57.3	58.1	55.9
Fat Mass* (Kg)	28.7	20.4	44.9

*Mean

Table 2. Parameter Estimates for the Selected Models

Parameter	Phase I data (dense PK)		All Phase I data without auto-inhibition		All Phase I data with auto-inhibition	
	Estimate	RSE (%)	Estimate	RSE (%)	Estimate	RSE (%)
T_{lag} (h)	0.24	0.6	0.24	Fixed	0.24	Fixed
Fasted T_{lag}	-0.19	40.6	-0.19	Fixed	-0.19	Fixed
K_a (1/h)	0.27	10.3	0.27	Fixed	0.27	Fixed
Fasted K_a	-0.37	32.0	-0.37	Fixed	-0.37	Fixed
CL (L/h)	13.18	5.7	10.64	3.4	19.35	3.06
V_1 (L)	13.14	15.0	12.77	8.69	14.98	8.73
V_2 (L)	30.31	13.3	38.12	5.39	33.55	5.54
Q (L/h)	1.32	55.8	7.47	20.3	8.94	11.3
K_{enz} (1/h)					0.61	53.4
IC_{50} (ng/ml)					65.77	21.2

Conclusions

- The auto-inhibition model provided a good fit for the PK of ACT-539313 and could guide future dosage regimen design.
- The model highlighted the relevance of capturing auto-inhibition adequately: steady-state exposure is underestimated without the auto-inhibition components.
- Further research for better understanding of the effect of body size on the PK of ACT-539313 may be helpful to ensure that dosages are appropriate for all patients.
- The APT fellows have successfully achieved the goals of the immersion program [6].

References

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