

Population Pharmacokinetic Model of Apovincaminic Acid (AVA) — an Exposure Proxy of Vinpocetine

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1. INTRODUCTION

Vinpocetine holds a dual status as both a prescription drug in the EU and an ingredient in dietary supplements. Its pharmacological properties span from neuroprotection, antioxidant and anticonvulsive properties to multifaceted anti-inflammatory effects. Despite renewed scientific interest in vinpocetine, debates persist regarding its pharmacological attributes, since understanding of the pharmacokinetic-pharmacodynamic (PKPD) context is not clear. Due to safety concerns, some countries have banned the inclusion of vinpocetine in dietary supplements. Apovincaminic acid (AVA) is an active metabolite of vinpocetine which is commonly used as a surrogate of vinpocetine exposure [1,2]. Evidence indicates that AVA also serves as the primary mediator enhancing neuronal excitability, a property harnessed by individuals who self-identify as “biohackers” or “neurohackers”.

2. METHODS and OBJECTIVE

PK data for AVA concentration measurements was obtained in a relative bioavailability study (open-crossover design, 12 healthy male subjects, single 20 mg dose of vinpocetine). Population (pop) PK analysis of AVA was performed with Monolix Suite software (v. 2021R2, Lixoft SAS, a Simulations Plus company, USA) [3].

The objective was to develop a popPK model for AVA from the immediate-release formulation of vinpocetine registered as a drug in the EU.

3. RESULTS

- A popPK model of AVA can be characterized by a two-compartment model. This model incorporates zero-order input, a Tlag, and linear elimination.
- PopPK model parameters are provided in Table 1.
- OBS vs. PRED plots are shown in Fig. 1.
- Visual predictive check (VPC) plot is shown in Fig. 2.

	Fixed Effects	S.E.	R.S.E (%)
Tlag_pop; h	0.2	0.0058	2.88
Tk0_pop; h	0.91	0.065	7.18
Cl/F_pop; L/h	53.37	2.78	5.22
V1/F_pop; L	57.06	2.24	3.92
Q/F_pop; L	17.67	2.76	15.6
V2/F_pop; L	103.07	22.11	21.4
Standard Deviation of the Random Effects (ω)			
ω_Tlag	0.088	0.022	25.2
ω_Tk0	0.22	0.052	23.8
ω_Cl/F	0.16	0.037	23.5
ω_Q/F	0.47	0.11	24.3
ω_V2/F	0.33	0.16	48.1
Correlations			
Q/F_Cl/F	0.72	0.2	27.5
Error Model Parameters			
b	0.13	0.011	8.69

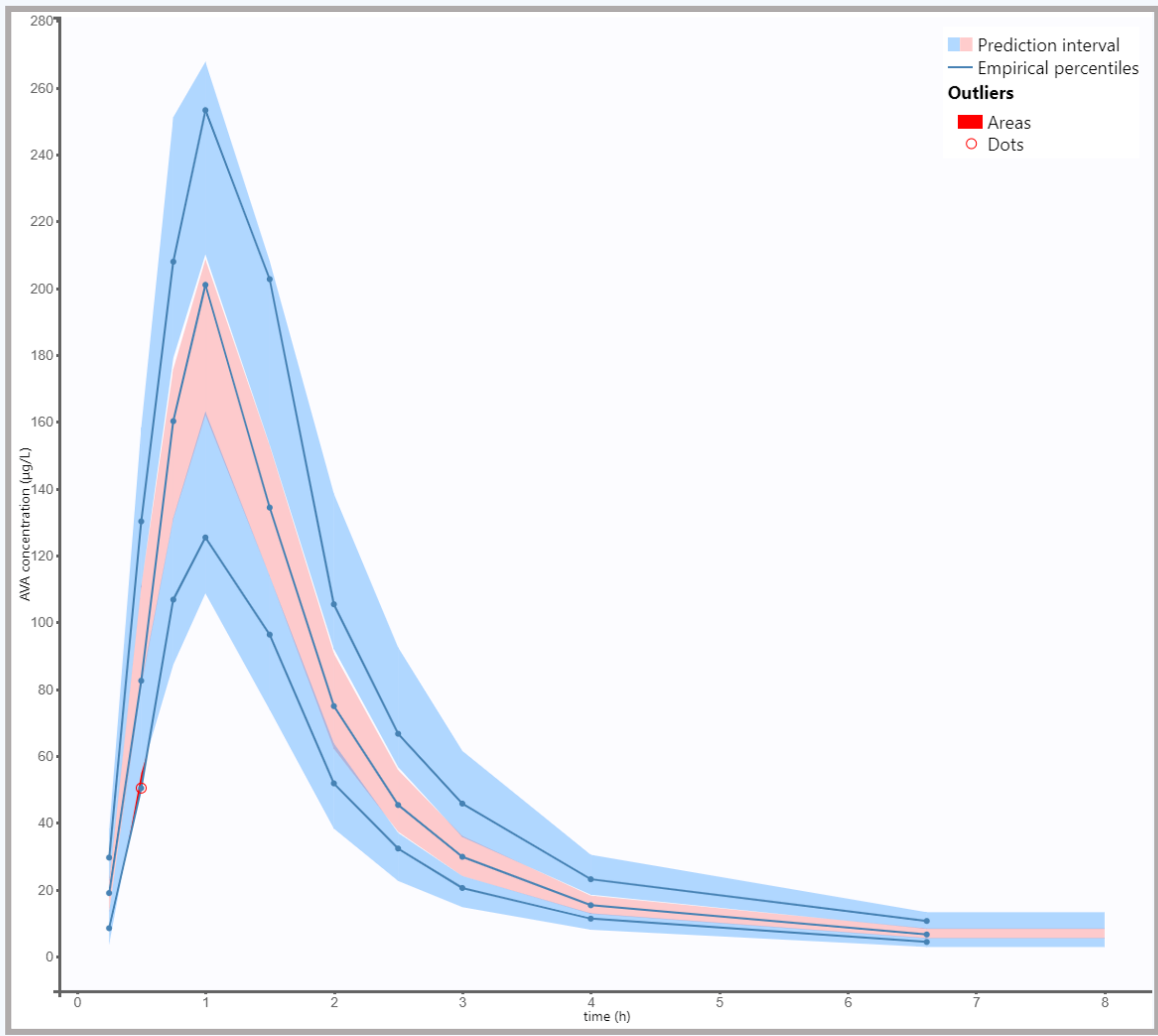
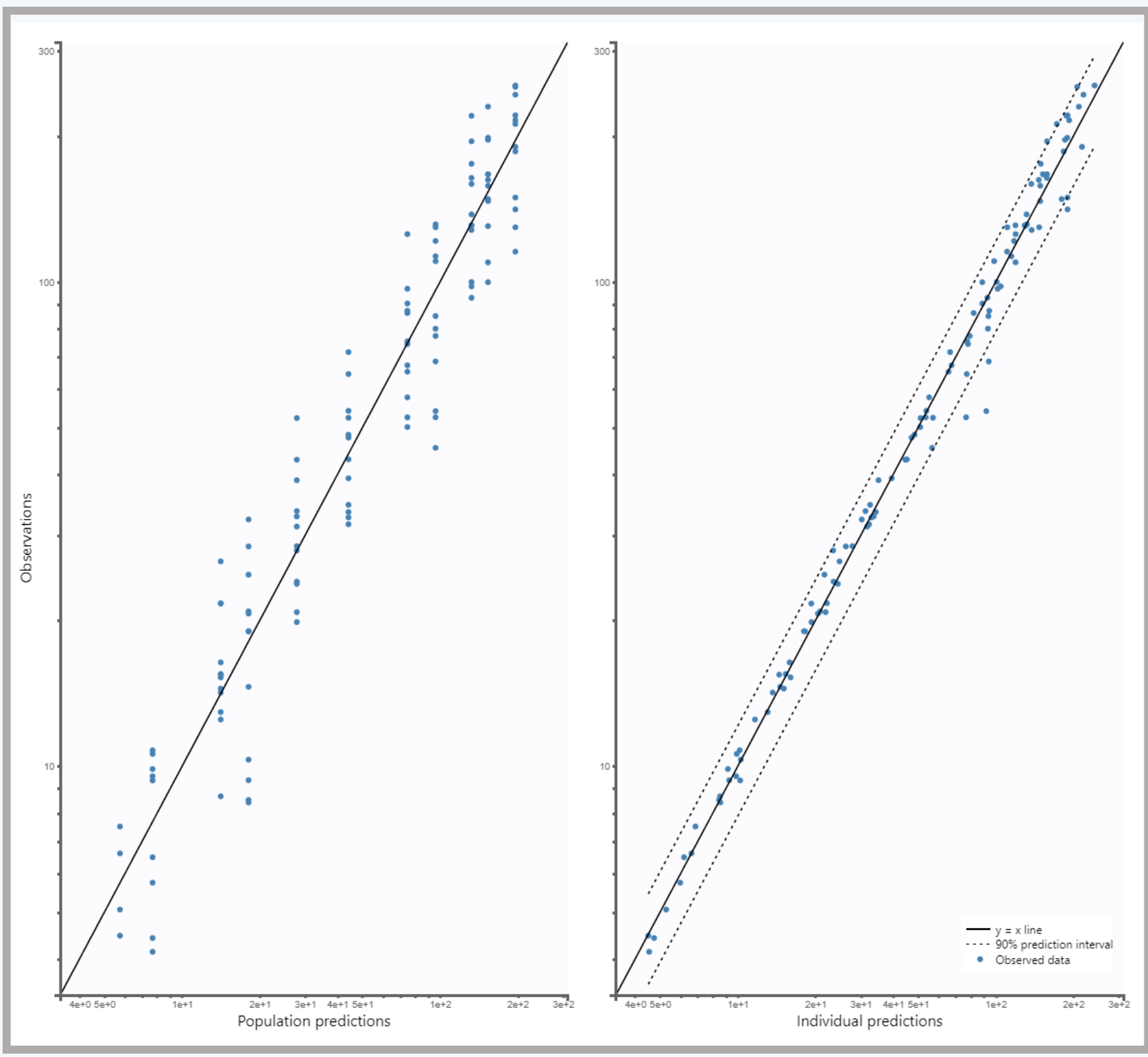


Table 1. PopPK parameters of AVA

Figure 1. OBS. vs. PRED. plot

Figure 2. VPC of AVA

4. CONCLUSION

We propose the first popPK model characterizing AVA (as a vinpocetine exposure proxy) based on the EU-registered formulation of vinpocetine. The proposed popPK model of AVA serves as a crucial tool, enabling exploration of diverse "what-if" dosing scenarios for vinpocetine across various indications, including those subtly suggested.

[1] Petric, Z.; Paixão, P.; Filipe, A.; Guimarães Morais, J. Clinical Pharmacology of Vinpocetine: Properties Revisited and Introduction of a Population Pharmacokinetic Model for Its Metabolite, Apovincaminic Acid (AVA). *Pharmaceutics*, 15, 2502, 2023

[2] Zhang YS, Li JD, Yan C. An update on vinpocetine: New discoveries and clinical implications. *Eur J Pharmacol.* 15;819:30-34, 2018.

[3] Monolix 2021R2, Lixoft SAS, a Simulations Plus company and Simulx 2021R2, Lixoft SAS, a Simulations Plus company, USA, 2022.