

Population analysis of the *in vivo* pharmacokinetic characteristics of a letrozole sustained delivery formulation in Beagle dogs



Castiñeiras, Adriana^{1,4}; López Ginés, Gema⁴; F Trocóniz, Iñaki^{1,2,3}

(1) Department of Pharmaceutical Sciences, School of Pharmacy and Nutrition, University of Navarra, Spain. (2) IdISNA, Navarra Institute for Health Research, Pamplona, Spain. (3) Institute of Data Science and Artificial Intelligence, DATAI, University of Navarra, Pamplona, Spain. (4) Laboratorios Farmacéuticos Rovi, Spain.

INTRODUCTION AND OBJECTIVES

Letrozole is an aromatase inhibitor that is currently marketed as oral tablets as a first line treatment for hormone-dependent breast cancer in post-menopausal women^{1,2,3}. However, non-adherence and/or premature interruption of treatment are associated to higher mortality risk in these patients⁴. The use of long-acting injectable formulations may help overcome this non-fulfilled necessity, while interindividual variability is reduced and bioavailability is improved⁵. In this sense, Laboratorios Rovi is developing Letrozole ISM[®], a novel polymeric long-acting injectable formulation of letrozole (intramuscular administration, IM).

It is important to control *in vivo* behavior of long-acting formulations to avoid dose dumping due to their higher doses, as well as to ensure adequate plasma levels along the complete dosing period⁶. Over the last decade, the possibility of evaluating and predicting *in vivo* response from *in vitro* data has emerged by the establishment of *in vitro-in vivo* correlations (IVIVCs)^{7,8}. This study was focused on developing a population pharmacokinetic model to characterize the *in vivo* release performance of Letrozole ISM[®] as a step to further establish an IVIVC with both *in vitro* and clinical data.

METHODS

Both the target formulation and 2 additional formulations presenting altered Critical Quality Attributes (and showing a faster and slower release of letrozole *in vitro* when compared to target release) were studied in Beagle dogs (n=5 per formulation). A letrozole solution administered intravenously (IV) was also studied in the same animal model (n=6). Plasma samples were obtained and letrozole was quantified by HPLC-MS/MS (**Figure 1**).

Concentration vs time profiles were processed and analyzed using the non-linear mixed effects approach (nlme) with NONMEM 7.4.

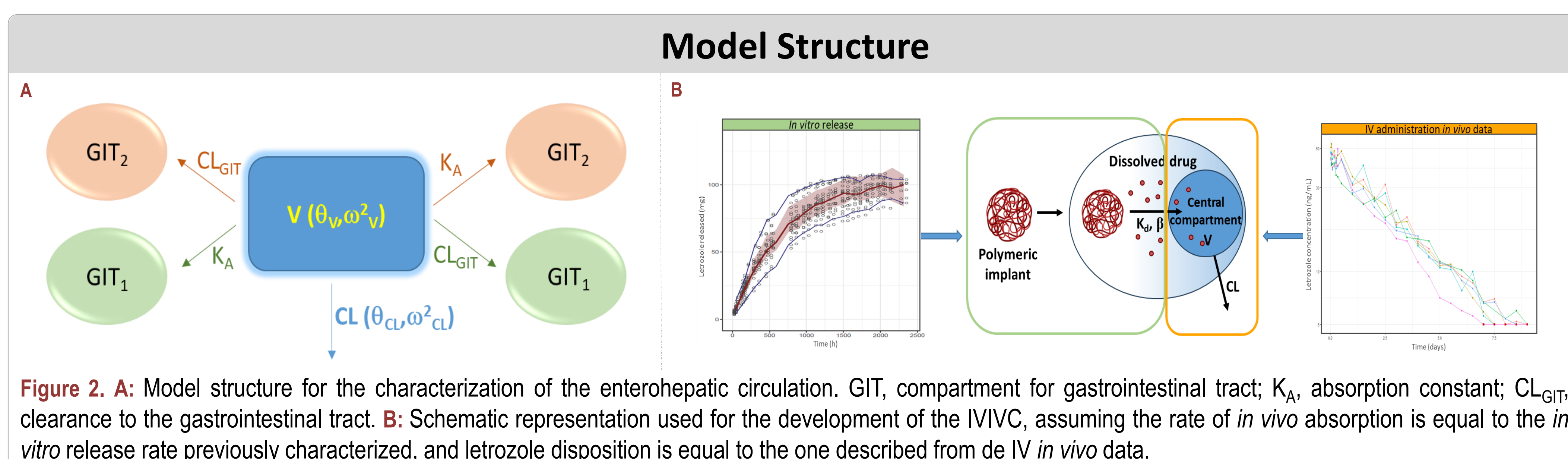


Figure 2. **A:** Model structure for the characterization of the enterohepatic circulation. GIT, compartment for gastrointestinal tract; K_A , absorption constant; CL_{GIT} , clearance to the gastrointestinal tract. **B:** Schematic representation used for the development of the IVIVC, assuming the rate of *in vivo* absorption is equal to the *in vitro* release rate previously characterized, and letrozole disposition is equal to the one described from *de IV in vivo* data.

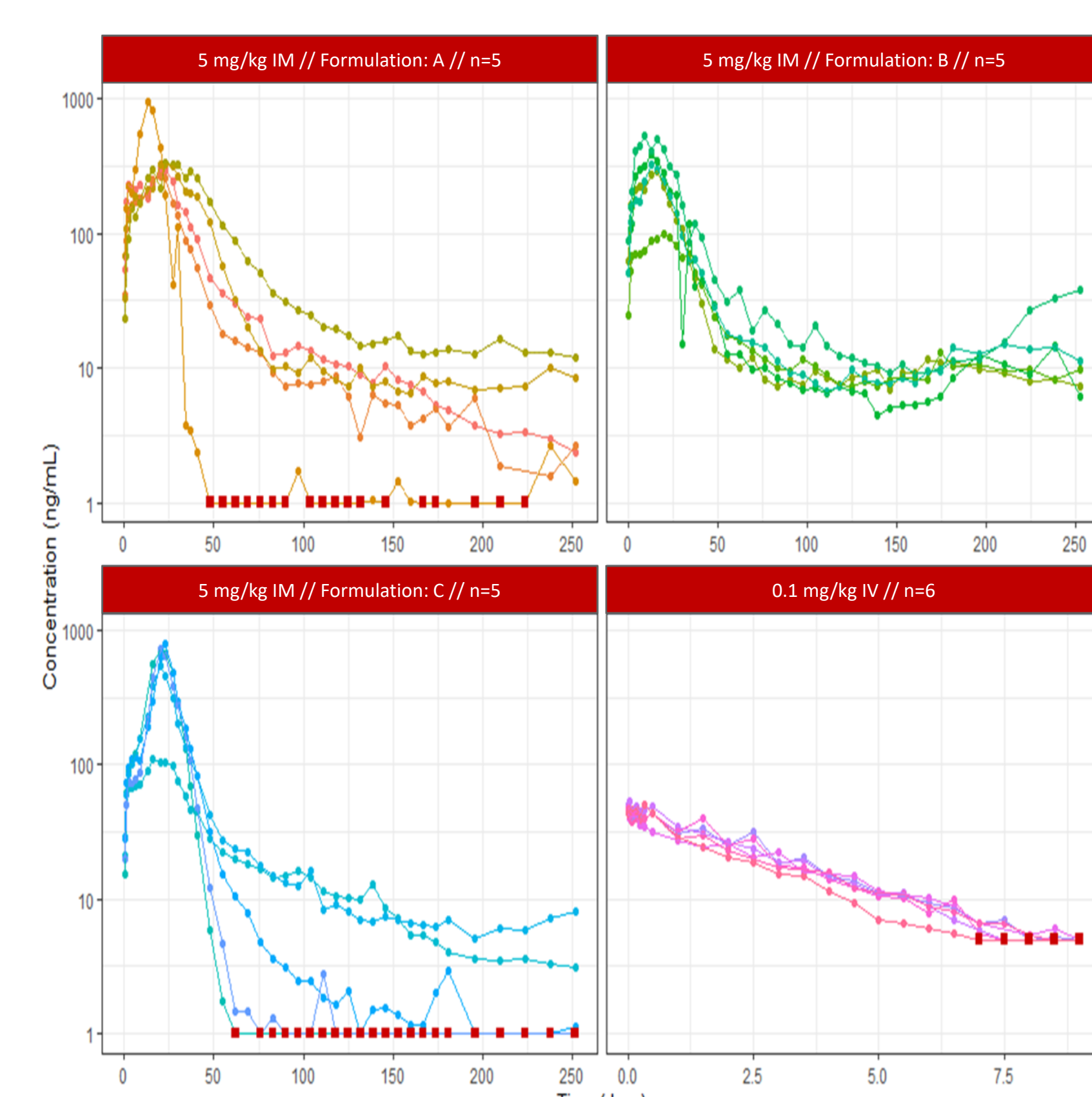


Figure 1. Plasma vs time profiles expressed as ng/mL for 3 intramuscularly administered letrozole long-acting formulations, and one intravenously administered letrozole solution. Data below LOQ are highlighted in red. IM, intramuscular; IV, intravenous.

RESULTS

- Systemic disposition of letrozole was characterized using a one-compartmental model with linear distribution and elimination processes. Complex absorption process after the administration of the long-acting formulation was described considering two depot compartments from which the drug was absorbed into the central compartment following first and zero order processes. Values of 19 L and 0.21 L/h were obtained for the volume of distribution and clearance, respectively, for the dose absorbed following the zero-order process.
- Letrozole enterohepatic recirculation (EHC) was observed and well characterized using a previously described methodology⁹ (**Figure 2A**), although was found not statistically significant (**Figure 3A**).
- Model performance was based on individual fit profiles (**Figure 3B**).
- A comparative between *in vitro* dissolution kinetics and *in vivo* absorption kinetics was performed (**Figure 4**).

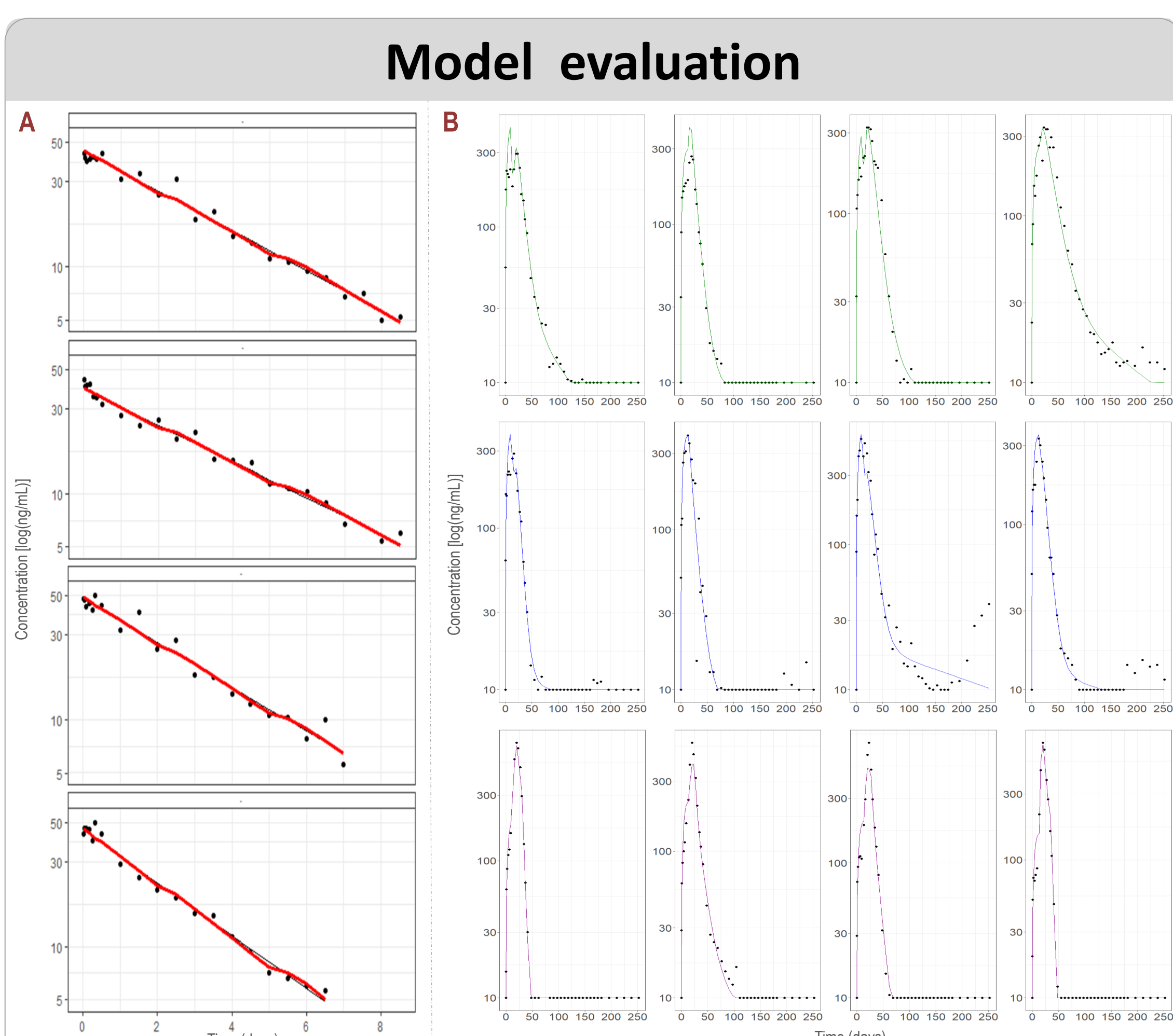


Figure 3. **A:** Concentration vs time profiles of the first 8 days after IV administration. Black circles, raw data profiles. Black lines, model prediction. Red lines, model prediction with EHC. **B:** Individual fit and observations of concentration vs time profiles (IM formulation). Black circles, raw data profiles. Solid lines, individual prediction of the target (green), faster release (blue) and slower release (purple) formulations.

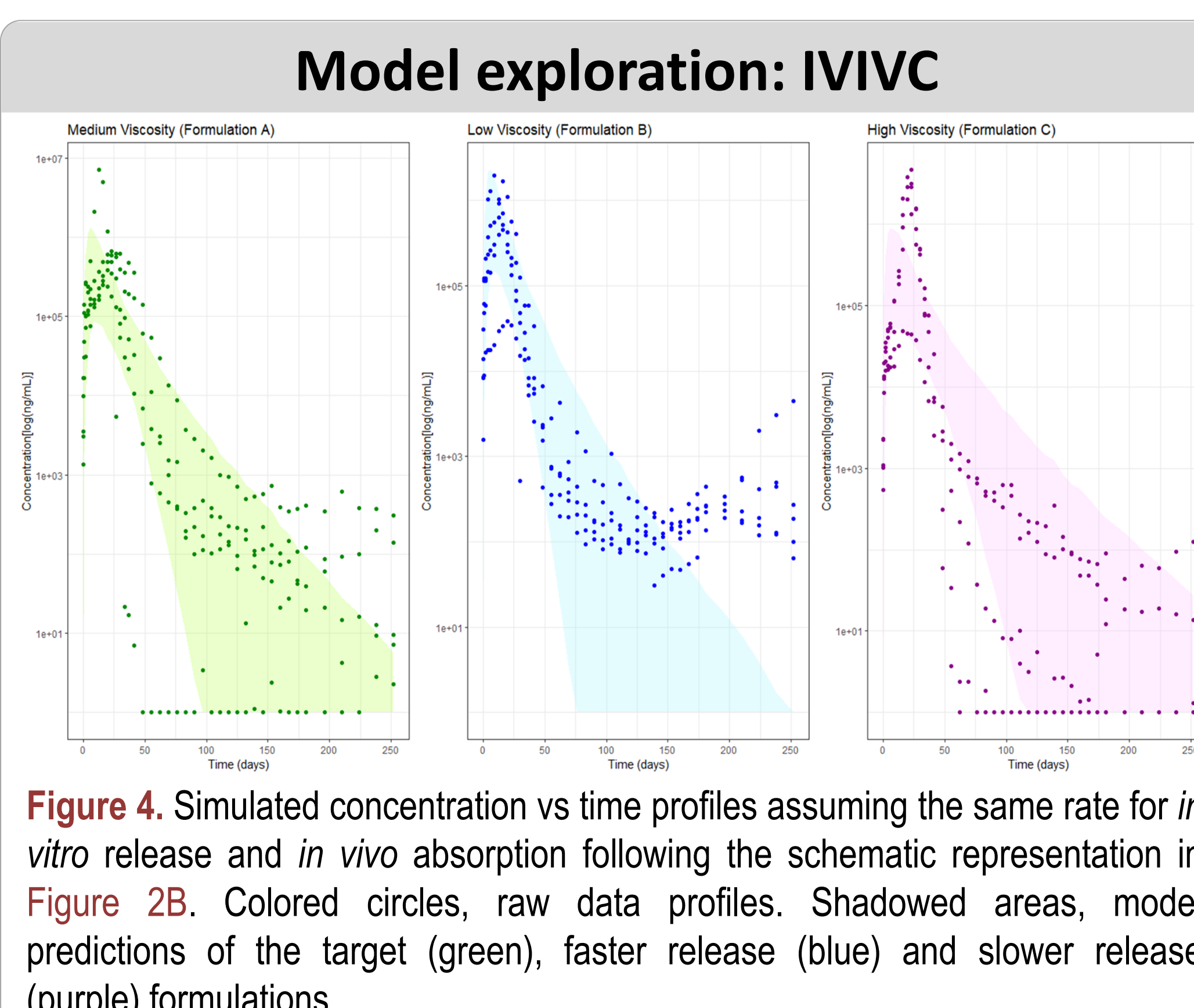


Figure 4. Simulated concentration vs time profiles assuming the same rate for *in vitro* release and *in vivo* absorption following the schematic representation in **Figure 2B**. Colored circles, raw data profiles. Shaded areas, model predictions of the target (green), faster release (blue) and slower release (purple) formulations.

REFERENCES

- [1] Subramani, R. et al. (2017).
- [2] SEOM clinical guidelines in advanced and recurrent breast cancer (2018).
- [3] Vademecum Letrozole.
- [4] Yusuf, M. et al. (2021).
- [5] Chaudhary, K. et al. (2019).
- [6] Bao, Q. et al. (2022).
- [7] Mast, M. et al. (2021).
- [8] Alimpertis, N. et al. (2024).
- [9] Ibarra, M. et al. (2014).

CONCLUSIONS

The nlme approach was successfully applied to *in vivo* pharmacokinetic data obtained after intramuscular administration of Letrozole ISM[®] to Beagle dogs, allowing the characterization of pharmacokinetic differences when altering the formulation CQAs controlling the release of the active compound. This evaluation, together with the analysis of the Letrozole ISM[®] *in vitro* release characteristics, constitutes a further step to establish an IVIVC from *in vitro*, preclinical and clinical data.

Email : acastineiras@rovi.es
Website: <http://rovi.es> ; <http://unav.edu/psp>