

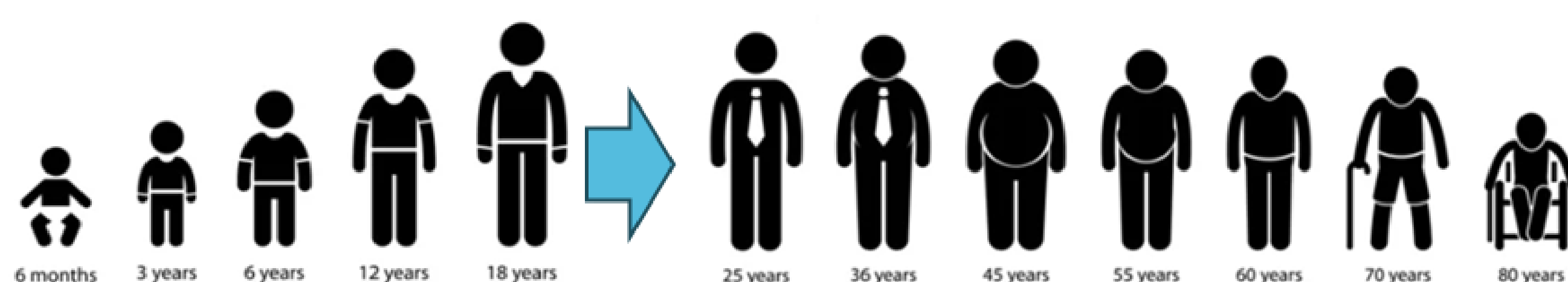
Defining Adult Dosing of Midazolam Oromucosal Solution for Prolonged Seizures Using Population PK Modeling

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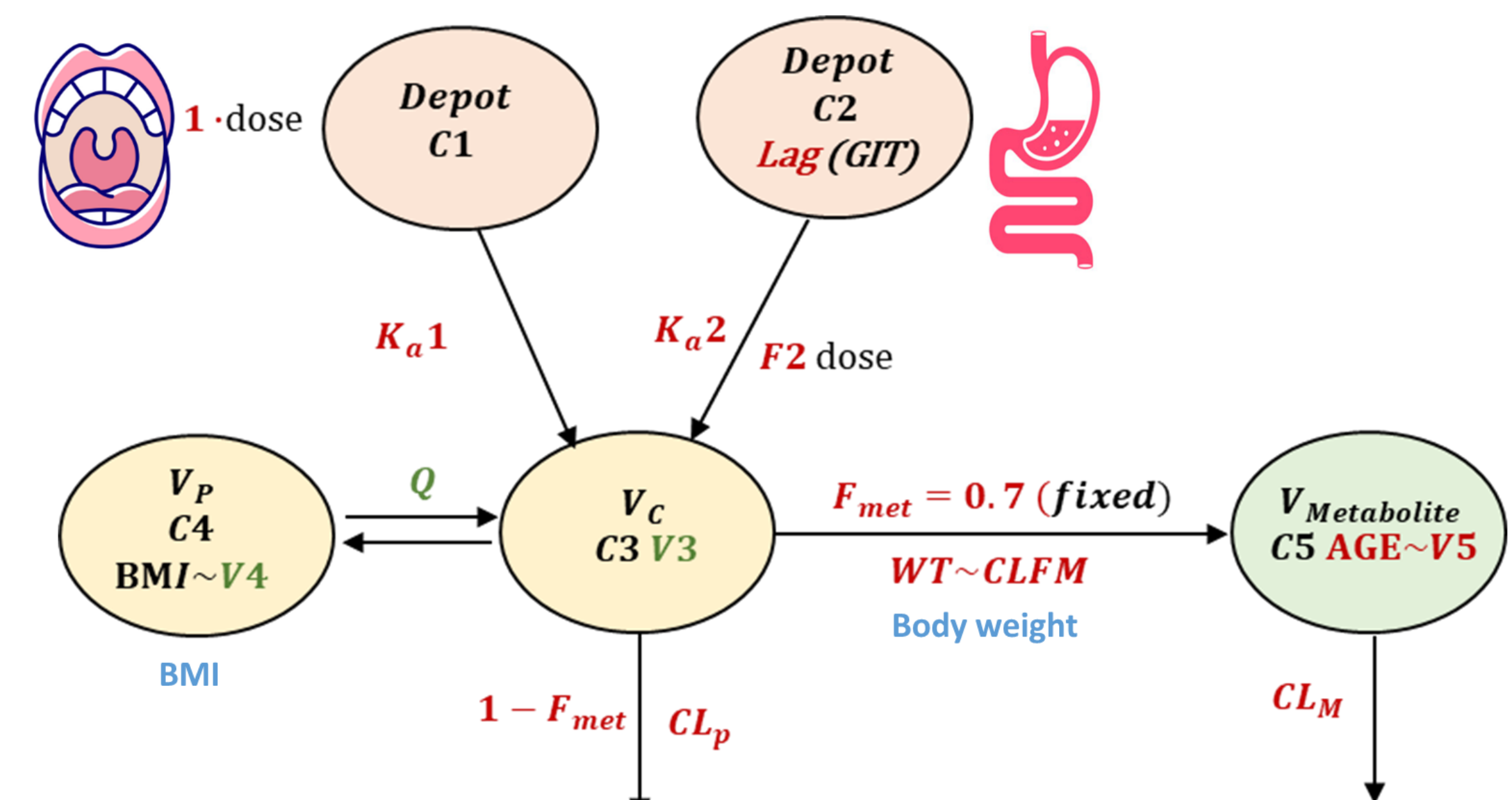
INTRODUCTION

- Midazolam oromucosal solution (MOS) (Buccolam®, Neuraxpharm) 10 mg has been recently approved for the treatment of prolonged, acute convulsive seizures in adults.
- Objective:** support the selection of an appropriate adult dose by leveraging exposure matching from pediatric therapeutic doses—an established efficacy extrapolation approach when similarity in disease progression and response to intervention can be supported.



MATERIALS AND METHODS

- A two-absorption population PK model for midazolam (MDZ) and its active metabolite (1-OH-MDZ) was developed using data from a 15 mg single-dose study in adults up to 70 years and a BMI <34 kg/m².
- Key covariates: BMI on distribution volume; Body weight on metabolite formation; Age on metabolite distribution. These effects were incorporated using a power model.



The model was built in NONMEM® (v7.4.4, Icon Plc) using first-order conditional estimation with interaction (FOCE-I).

RESULTS AND DISCUSSION

The 10 mg dose in adults lead to similar total AUC_{0-inf} in adults to that of pediatrics at the therapeutic doses in all the reference age groups

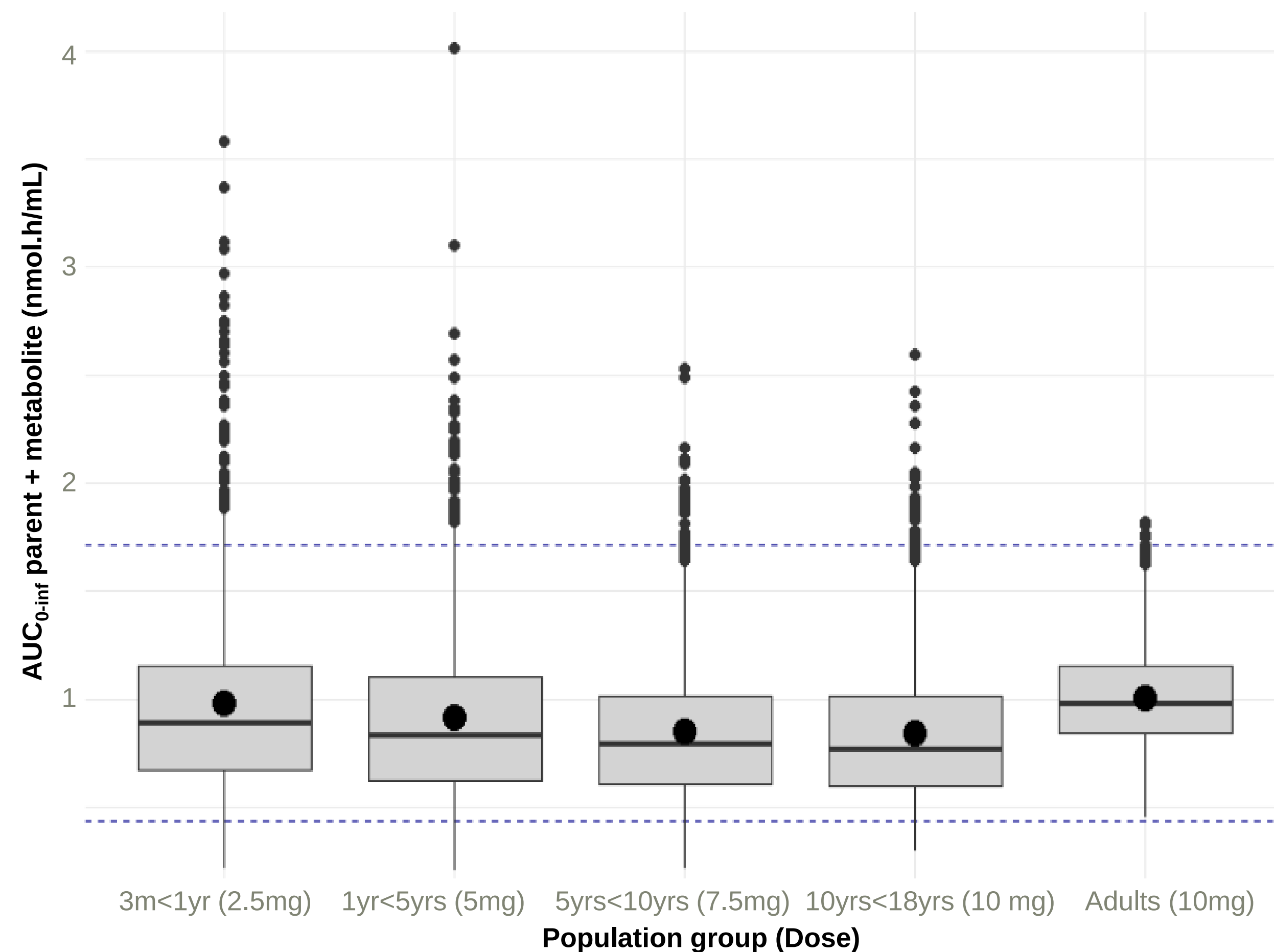


Figure 1. Simulated total exposure to the sum of parent and metabolite as AUC_{0-inf} in nmol.h/mL in pediatrics and adults after the administration of Buccolam® 10 mg

Note: The dashed blue lines correspond to the 5th and 95th percentiles of the pediatric reference range considering age <10 years. AUC_{0-inf}, area under the curve of plasma concentrations versus time from time zero to infinity.

Adults up to 70 years old and with a BMI<34 do not require dose adjustment

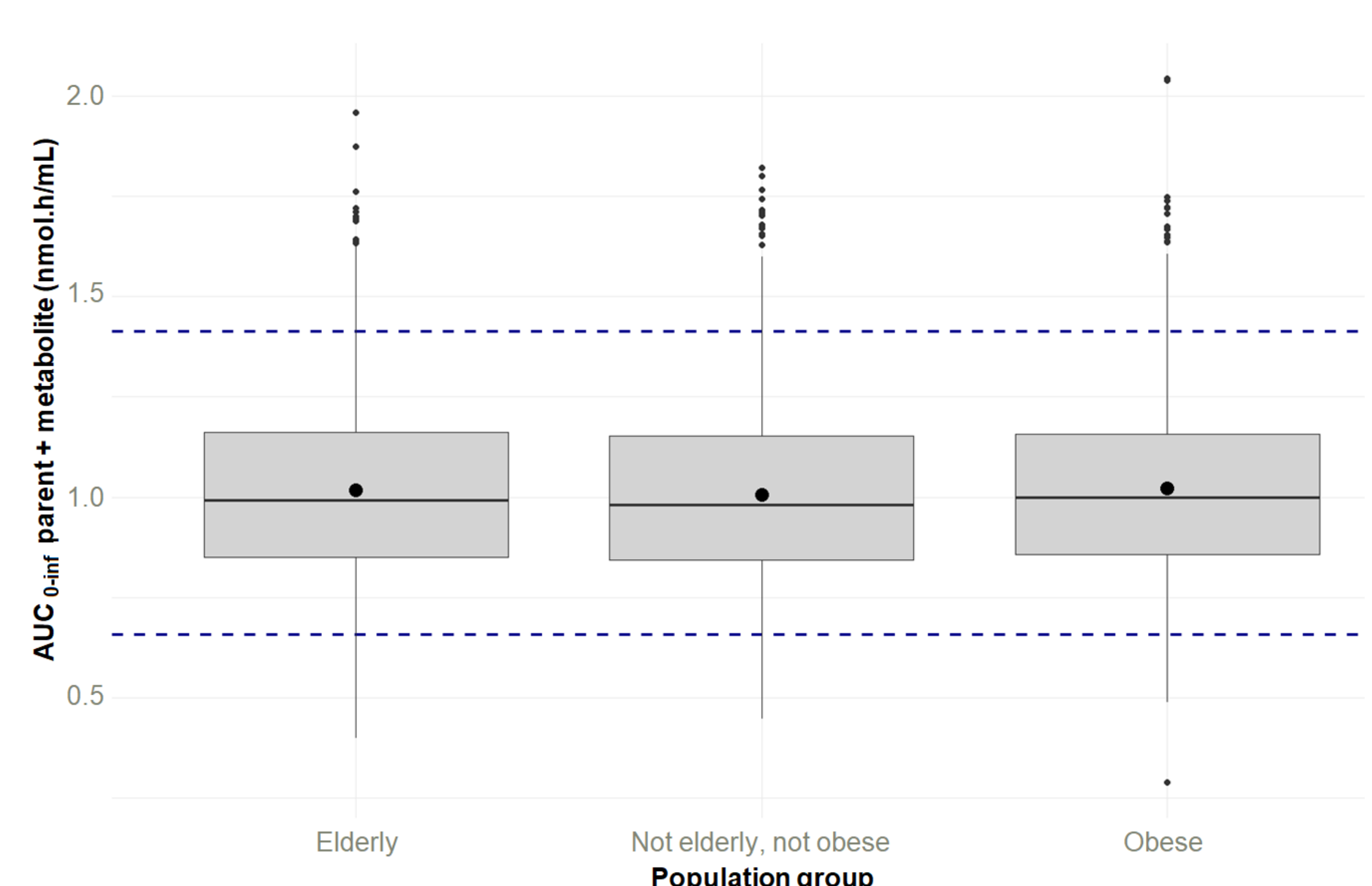


Figure 2. Simulated total exposure to the sum of parent and metabolite as AUC_{0-inf} in nmol.h/mL in adults after the administration of Buccolam® 10 mg

Note: The dashed blue lines correspond to the 5th and 95th percentiles of the first adult group (not elderly, not obese) to visualize as a total AUC reference range. AUC_{0-inf}, area under the curve of plasma concentrations versus time from time zero to infinity. The results are presented separately by subgroups: Adults (not elderly, not obese), obese (34>BMI>30) and elderly (70>Age≥65 years) (n=1000 per group).

CONCLUSIONS

- The 10 mg dose in adults up to 70 years and with BMI <34 yields exposures consistent with those of demonstrated efficacy in children.
- The finding is in line with the recommendations from many national guidelines for the management of prolonged seizures and as reflected in several publications describing the use and effectiveness of 10 mg buccal midazolam to stop seizures in adults.
- Based on the above simulations and clinical practice considerations, the 10 mg dose is therefore proposed as the optimal, efficacious, and safe dose for Buccolam® to treat adults with prolonged acute convulsive seizures.

REFERENCES

All the bibliographical references consulted in this work can be viewed through the following QR code:

