

Utilizing the AZD7442 popPK Model to Accelerate Development of New YTE mAbs

O. Stepanov¹, M. Learoyd¹, L. Clegg², U. Wählby Hamrén³, I. Pouliquen¹

¹ Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Cambridge, UK;

² Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gaithersburg, MD, USA;

³ Clinical Pharmacology and Quantitative Pharmacology, Clinical Pharmacology & Safety Sciences, R&D, AstraZeneca, Gothenburg, Sweden

Introduction

Due to the coronavirus disease 2019 (COVID-19) pandemic and the rise of anti-microbial resistance, the rapid development of neutralizing monoclonal antibodies (mAbs) for the prevention and passive immunization of infectious diseases (ID) is urgently needed. Our study aimed to investigate and compare the pharmacokinetic profiles of mAbs featuring YTE-modification (substitution within its Fc region, which enhances affinity to the neonatal Fc receptor, thereby extending the half-life) across diverse ID indications and species. We also demonstrate the practical utility of a population Pharmacokinetic (popPK) model established for mAbs with YTE modification in inform first time in-human dose selection and accelerated development for a novel YTE-mAb with AZD5148 as an example.

Data and Methods

Data from cynomolgus monkey and humans for three drugs were used for this analysis:

- AZD7442 is a combination of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralizing antibodies with YTE modification, AZD8895 (tixagevimab) and AZD1061 (cilgavimab), developed for pre-exposure prophylaxis (PrEP) and treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents. [1].
- MEDI8897(Nirsevimab) is a mAb with YTE modification, developed for the prevention of respiratory syncytial virus (RSV) disease in all infants [2].
- AZD5148 is a mAb with YTE modification that binds to and neutralizes *Clostridium difficile* (*C. difficile*) toxin B, the key virulence factor in *C. difficile* infection (CDI) pathogenesis.

The popPK model was developed for AZD7442 using data from eight clinical trials. The final model was a two-compartmental model with first-order absorption and elimination, including standard allometric exponents for the effect of body weight on clearance and volume.

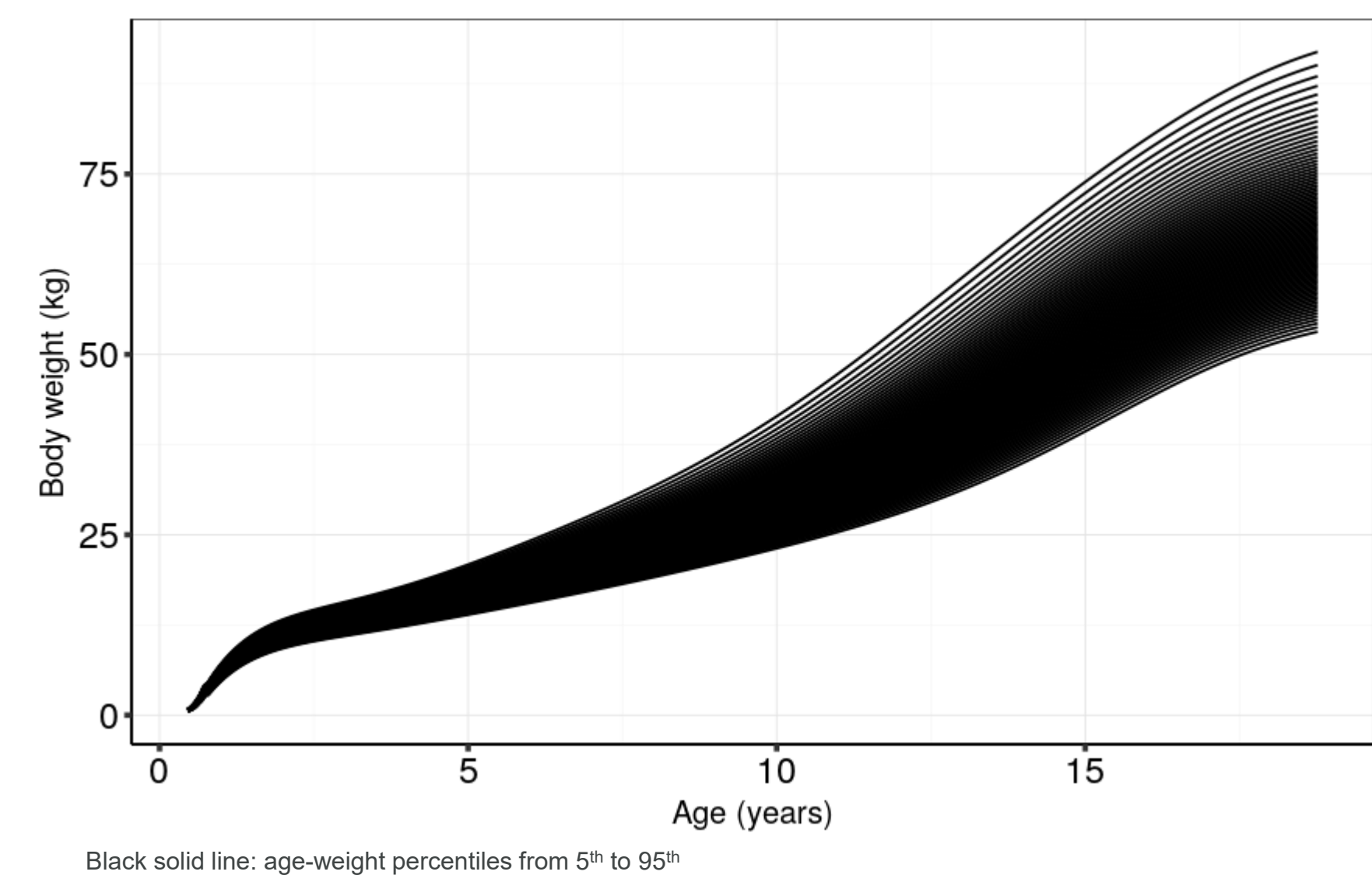
To accurately predict paediatric data, it is essential to consider both body weight and age-related (maturation) effects when describing mAb clearance. The following function described the age-maturation, with parameters taken from the nirsevimab popPK model[2]:

$$CL_{tv} = CL_{pop} * \left(\frac{WT}{70}\right)^{\Theta_{WT}} * \left(1 - (1 - \beta_{CL}) * e^{\left(-\left(PAGE - \frac{40}{4.35}\right) * \frac{LN(2)}{T50CL}\right)}\right)$$

PAGE is the post menstrual age in months, T50CL denotes the maturation half-life, and Θ_{WT} is the estimated CL allometric scaling exponent.

Continuous age-weight distribution from CDC growth charts (childsds R package v0.8.0) to account for weight change over time for children was used (Figure 1).

Figure 1. Age-Weight Distribution from Birth to 18 Years



Black solid line: age-weight percentiles from 5th to 95th

References

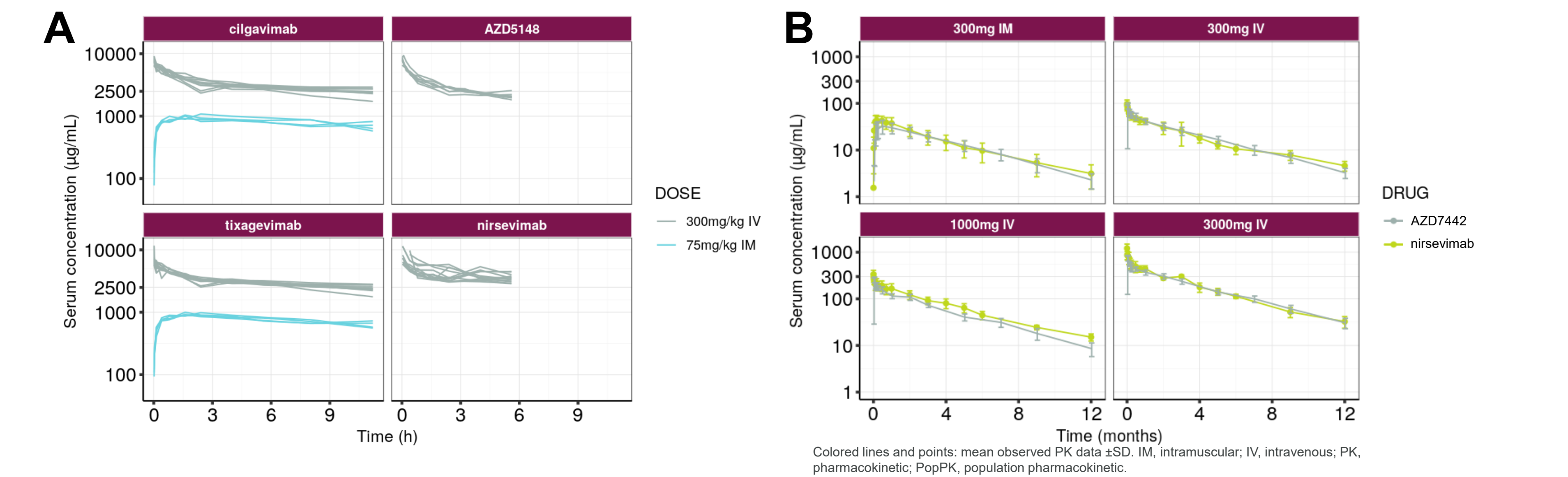
- Clegg LE, Stepanov O, Schmidt H, Tang W, Zhang H, Webber C, Cohen TS, Esser MT, Nâgård M.2024.Accelerating therapeutics development during a pandemic: population pharmacokinetics of the long-acting antibody combination AZD7442 (tixagevimab/cilgavimab) in the prophylaxis and treatment of COVID-19. Antimicrob Agents Chemother68:e01587-23
- Clegg L., Freshwater, E., Leach, A., Villafana, T. and Hamrén, U.W. (2024). Population Pharmacokinetics of Nirsevimab in Preterm and Term Infants. J Clin Pharm. 64: 555-567.
- Forte-Soto P,Albayaty M, Brooks D, Arends RH, Tillinghast J, Aksyuk AA, Bouquet J, Chen C, Gebre A, Kubiak RJ, Pilla Reddy V, Seegobin S, Streicher K, Templeton A, Esser MT. Safety, Tolerability and Pharmacokinetics of Half-Life Extended Severe Acute Respiratory Syndrome Coronavirus 2 Neutralizing Monoclonal Antibodies AZD7442 (Tixagevimab-Cilgavimab) in Healthy Adults. J Infect Dis. 2023 May 12;227(10):1153-1163.
- Griffin MP, Khan AA, Esser MT, Jensen K, Takas T, Kankam MK, Villafana T, Dubovsky F. Safety, Tolerability, and Pharmacokinetics of MEDI8897, the Respiratory Syncytial Virus Prefusion F-Targeting Monoclonal Antibody with an Extended Half-Life, in Healthy Adults. Antimicrob Agents Chemother. 2017 Feb 23;61(3):e01714-16.

Results: PK Comparison for cilgavimab, tixagevimab, nirsevimab and AZD5148

mAbs with YTE modification were found to have extended half-life and similar PK properties:

- All 4 molecules had similar PK profiles in cynomolgus monkey studies with comparable half-life estimates of 19, 19, 21 and 23 days for cilgavimab, tixagevimab, nirsevimab and AZD5148 respectively (Figure 2A).
- Serum concentrations of AZD7442 (sum of cilgavimab and tixagevimab) and nirsevimab in Phase I clinical studies in adults (Figure 2B), showed similar PK profiles and their half-life estimates were respectively 80 to 95 days [3] and 85 to 117 days [4].

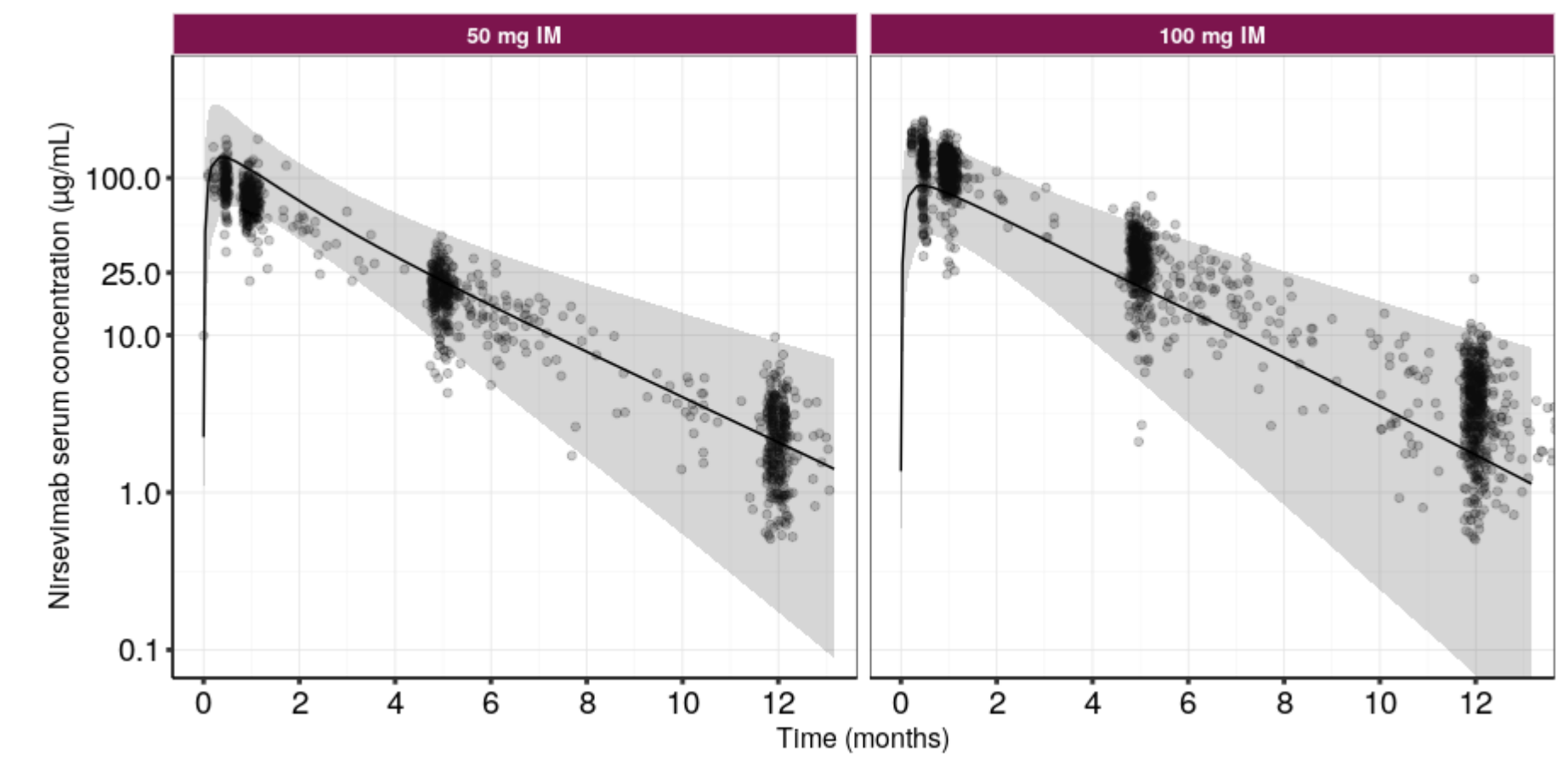
Figure 2. Comparison of serum concentrations for cilgavimab, tixagevimab, nirsevimab and AZD5148 in cynomolgus monkeys (A) and AZD7442 vs nirsevimab in clinical phase I adult studies (B)



Results: Comparison of model predictions with pediatric clinical study data for AZD7442 and nirsevimab

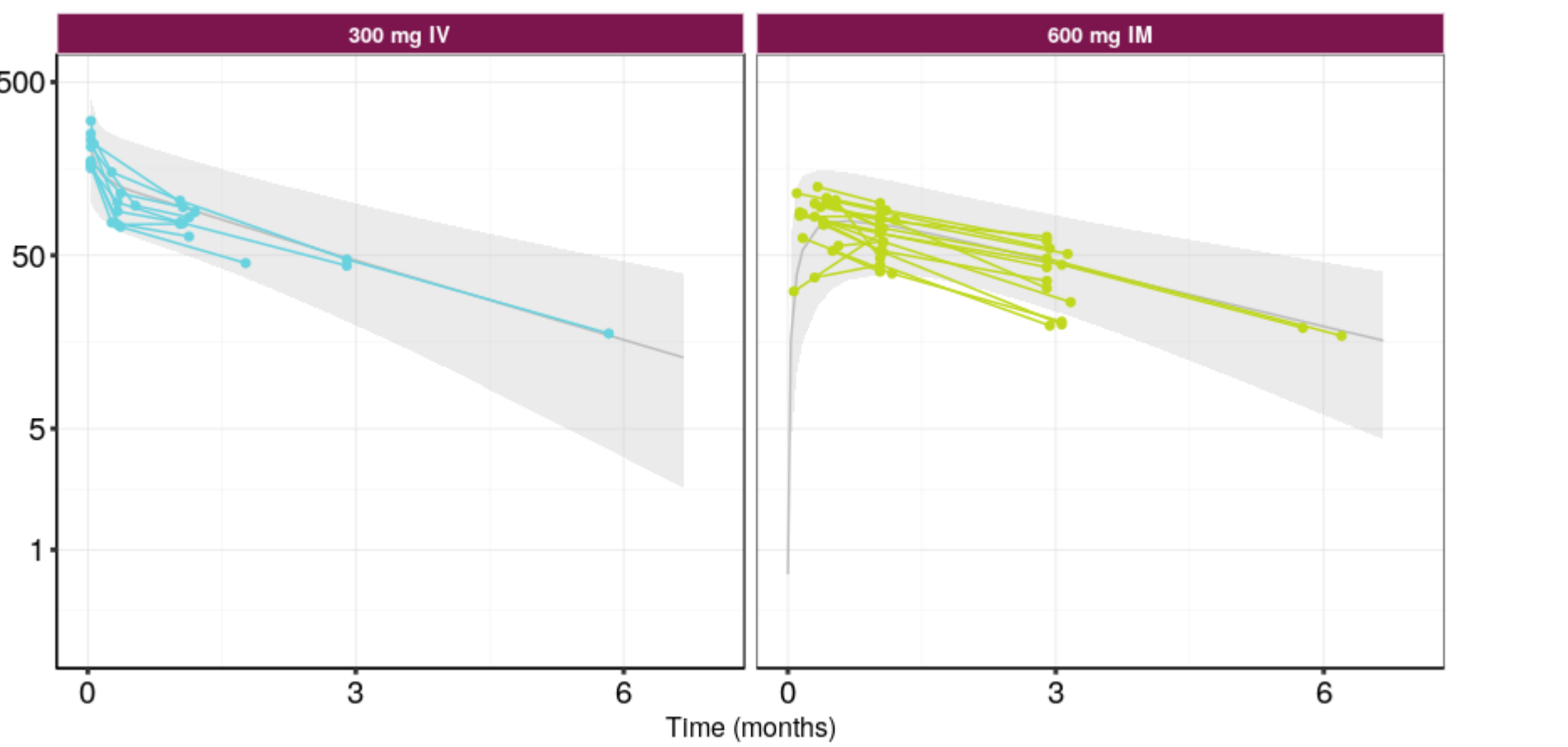
- Each simulation scenario contains 1000 subjects for each dose group and uniform distribution for baseline bodyweight
- Comparison of model prediction with observed nirsevimab data from MELODY study in infants [2] (Figure3)
 - Simulated doses were 50mg for body weight less than 5kg and 100 mg for body weight more or equal to 5kg
 - Model predictions align with observed data; small differences could be explained by difference in initial bodyweight distribution for clinical data and simulated data (equal vs log-normal).
- Comparison of model prediction with AZD7442 interim TRUST pediatric study data [1] (Figure4)
 - Simulated doses 300mg for body weight 15 - 40kg and 600 mg for body weight more or equal to 40kg
 - Model predictions align with observed data.

Figure 3. PopPK-predicted and observed (MELODY Season 1 study data) nirsevimab serum concentrations in healthy term and preterm infants ≥35 wGA



Black solid line: median predicted concentration. Ribbon: 90% prediction interval. Points: observed PK data. IM, intramuscular; IV, intravenous; PK, pharmacokinetic; PopPK, population pharmacokinetic; wGA, weeks gestational age.

Figure 4. PopPK-predicted and observed (interim TRUST study data) serum AZD7442 concentrations in adolescents and children by body weight band



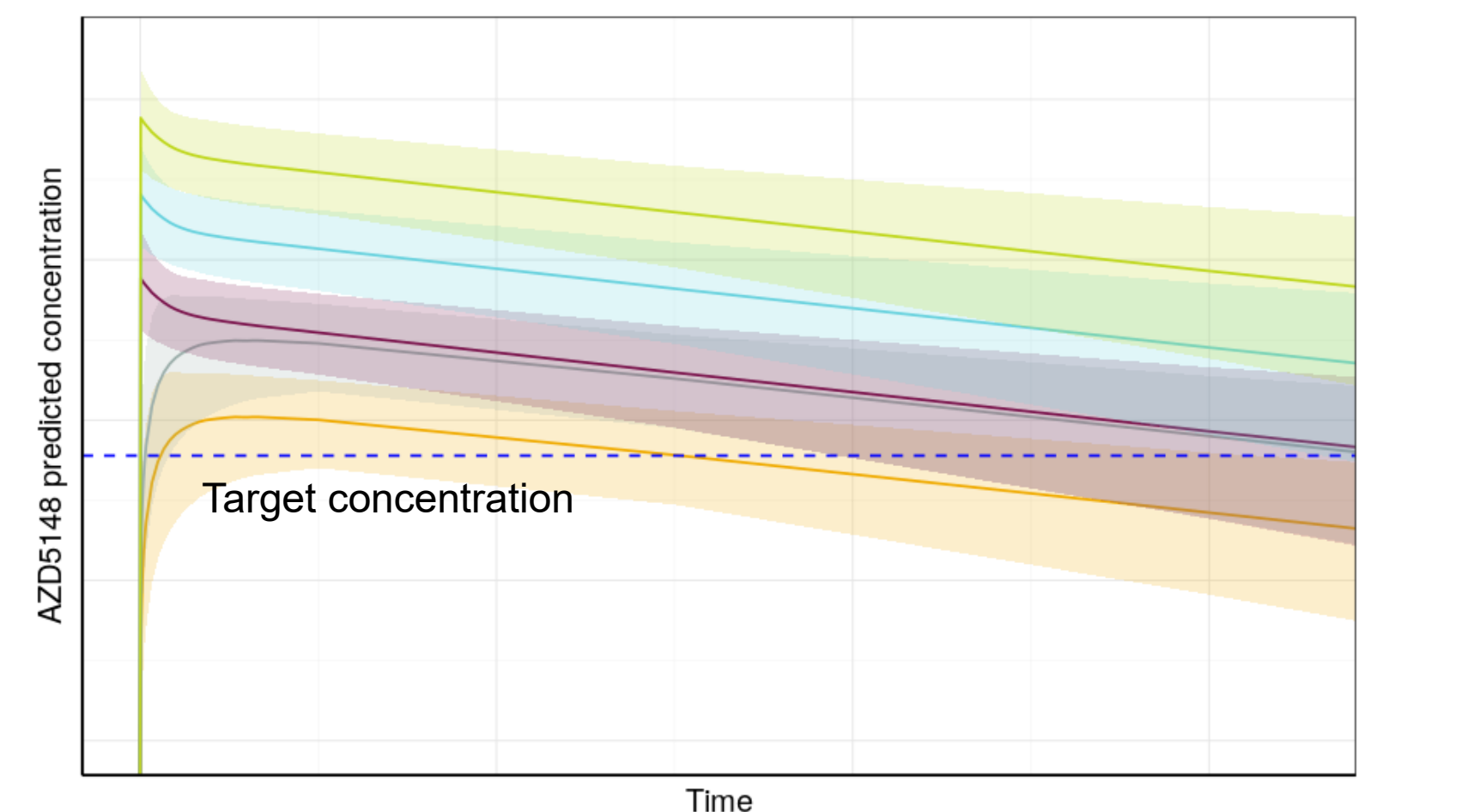
Gray solid line: median predicted concentration. Ribbon: 90% prediction interval. Colored lines and points: observed PK data. IM, intramuscular; IV, intravenous; PK, pharmacokinetic; PopPK, population pharmacokinetic.

Results: Application of the AZD7442 popPK model for AZD5148 clinical development

Given the similarity of PK properties for mAb with YTE modification, the AZD7442 popPK model was used to guide and accelerate AZD5148 clinical development:

- Based on the therapeutic target serum concentration and model predictions, first time in human study doses and potential efficacious dose were selected 1 year prior to Phase I study initiation.
- Model simulations allowed acceleration of the clinical development plan.
- PK sampling collection time for first time in human study reduced by >40% compared to AZD7442 and nirsevimab.

Figure 5. Predicted AZD5148 Serum Concentrations for Phase I doses compared to the target serum concentration



Colored solid lines: median predicted concentration. Ribbon: 90% prediction interval.

Conclusions

A combination of the AZD7442 popPK model with the nirsevimab age-maturation function created a modelling platform at the preclinical stage enabling a PK profile prediction of new mAbs with YTE modification in both adults and children. This accelerated the new drug development program by facilitating:

- The selection of first-in-human doses.
- The optimisation of clinical trials design and reducing the need for extensive pharmacokinetic sampling, thereby decreasing participants' burden, as well as increasing efficiency and cost-effectiveness.
- Early initiation of paediatric study plans (PSP) and paediatric investigation plans (PIP).

Disclosures

These analyses were funded by AstraZeneca. Oleg Stepanov (and any other authors) are employees of, and may or may not hold stock in, AstraZeneca