

Addressing variability and uncertainty in pooled pre-clinical data improved the quality of compound selection of a gamma secretase modulator in Alzheimer’s Disease

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Introduction

Efficient selection of compounds in discovery/early development requires optimal use of data (exposure, safety and efficacy) to make rational decisions. However, with many drug properties still being unknown experiments might not be optimally designed eventuating in differences in the quality/informativeness of the data.

Objective

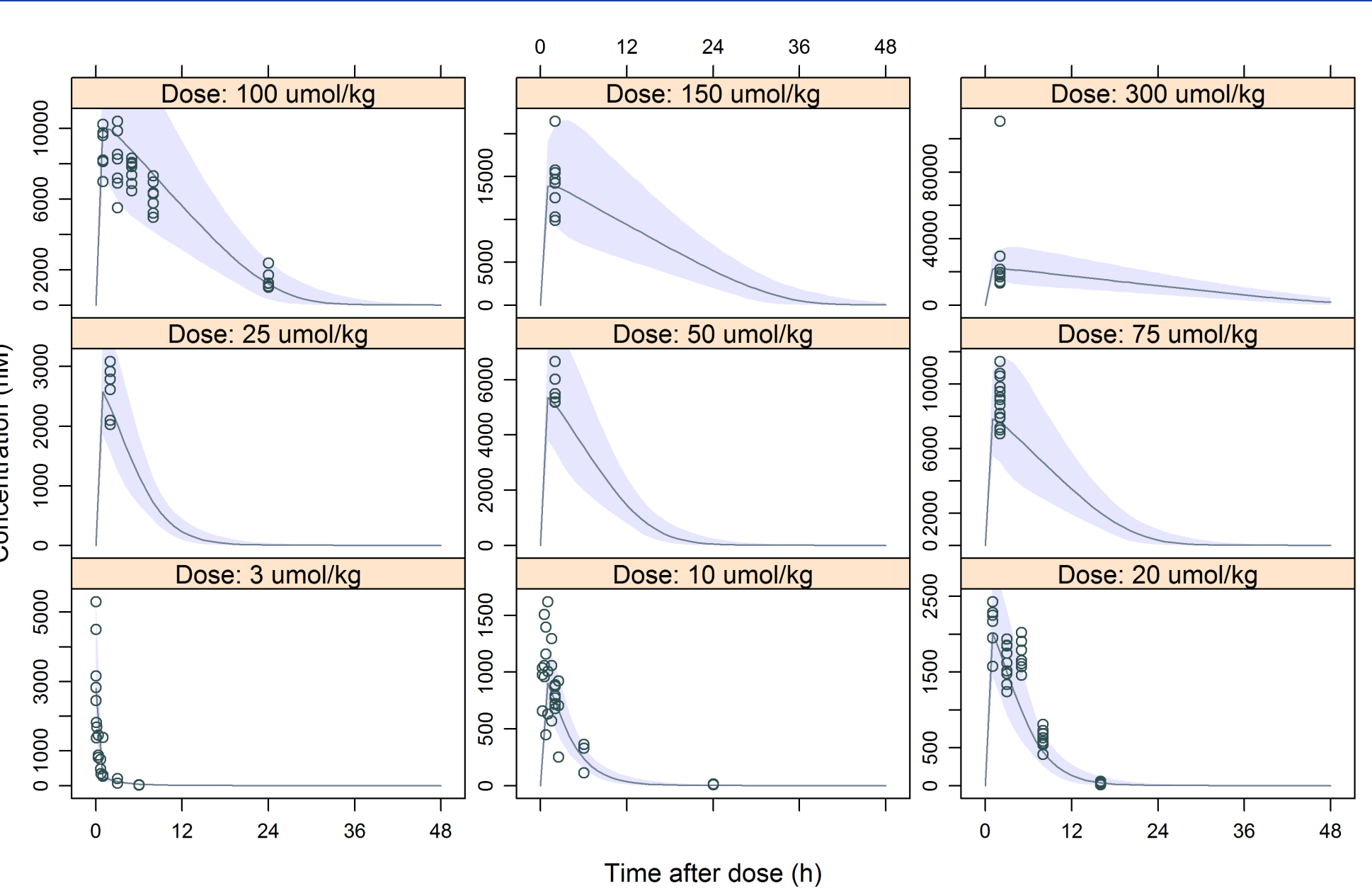
- Analyze exposure and efficacy data from several centrally active gamma secretase modulators (GSMs) using an integrated approach. GSMs are developed to inhibit the formation of Aβ42, a fragment of the amyloid precursor protein, which is hypothesized to play a key role in Alzheimer’s Disease pathology [1].
- Address all sources of variability and uncertainty.
- Present the results in a comprehensive manner to improve the quality of decision making.

Methods

For three GSMs data from pharmacokinetic (PK) and efficacy studies in mouse were pooled per compound and analyzed using mixed-effects turn-over models linking the inhibition of Aβ42 in the brain to the predicted brain and plasma PK. Dense PK observations in plasma were available for a small set of animals (typically n=6) for each compound, divided equally in two groups for intravenous and oral administration. For the majority of the animals a single observation of PK and PD (brain Aβ42) was available. NONMEM version 7.2 was used for estimating the parameters of the mixed-effect models by fitting the available PK and PD data simultaneously.

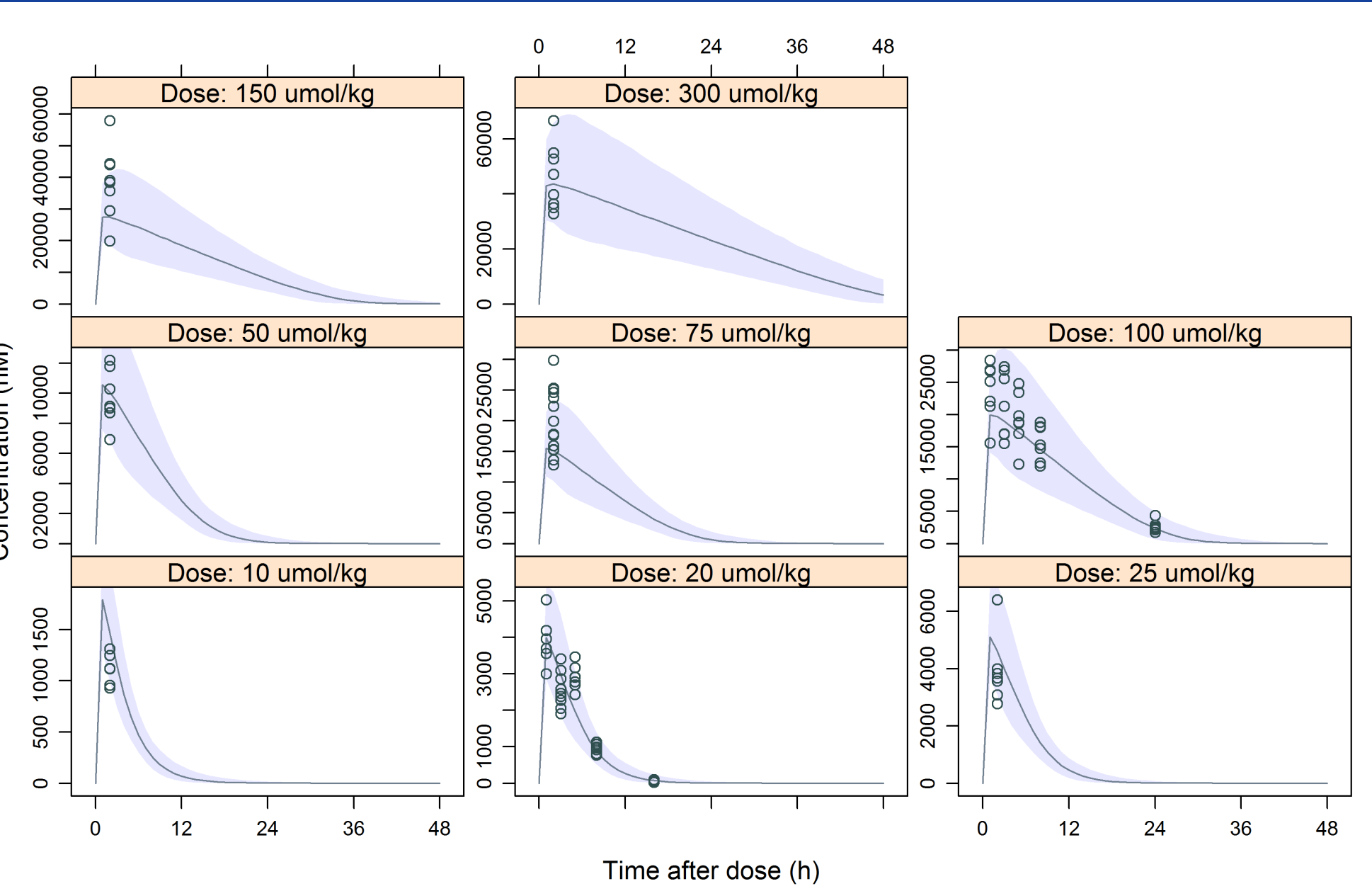
The PK properties were evaluated for nonlinear bioavailability and elimination. The distribution from plasma to the brain were evaluated using linear, nonlinear and/or delayed relationships. Typically, inter-individual variability (IIV) was evaluated on clearance or volume of distribution. Brain Aβ42 levels were determined using ELISA. For each time-point Aβ42 levels were measured after vehicle exposure. Ideally, the variability between baseline Aβ42 measurements would be described using a variability parameter but this is currently not supported in NONMEM for the number of individuals in this analysis. Instead, the mean of the baseline Aβ42 levels per time point was estimated using a separate baseline parameter. Direct and indirect E_{max}-type response models linking predicted compound concentrations in brain with observed Aβ42 levels in brain were applied to assess the pharmacokinetic-pharmacodynamic (PKPD) properties of the compounds.

Figure 1. Pharmacokinetics of AZ1 – Plasma



Visual Predictive Check of the PK in plasma for AZ1. Circles represent observed AZ1 concentrations. Solid lines show the median prediction of the PK model. Shaded grey area represent the 80% prediction interval of the PK model

Figure 2. Pharmacokinetics of AZ1 – Brain



Visual Predictive Check of the PK in brain for AZ1. Circles represent observed AZ1 concentrations. Solid lines show the median prediction of the PK model. Shaded grey area represent the 80% prediction interval of the PK model

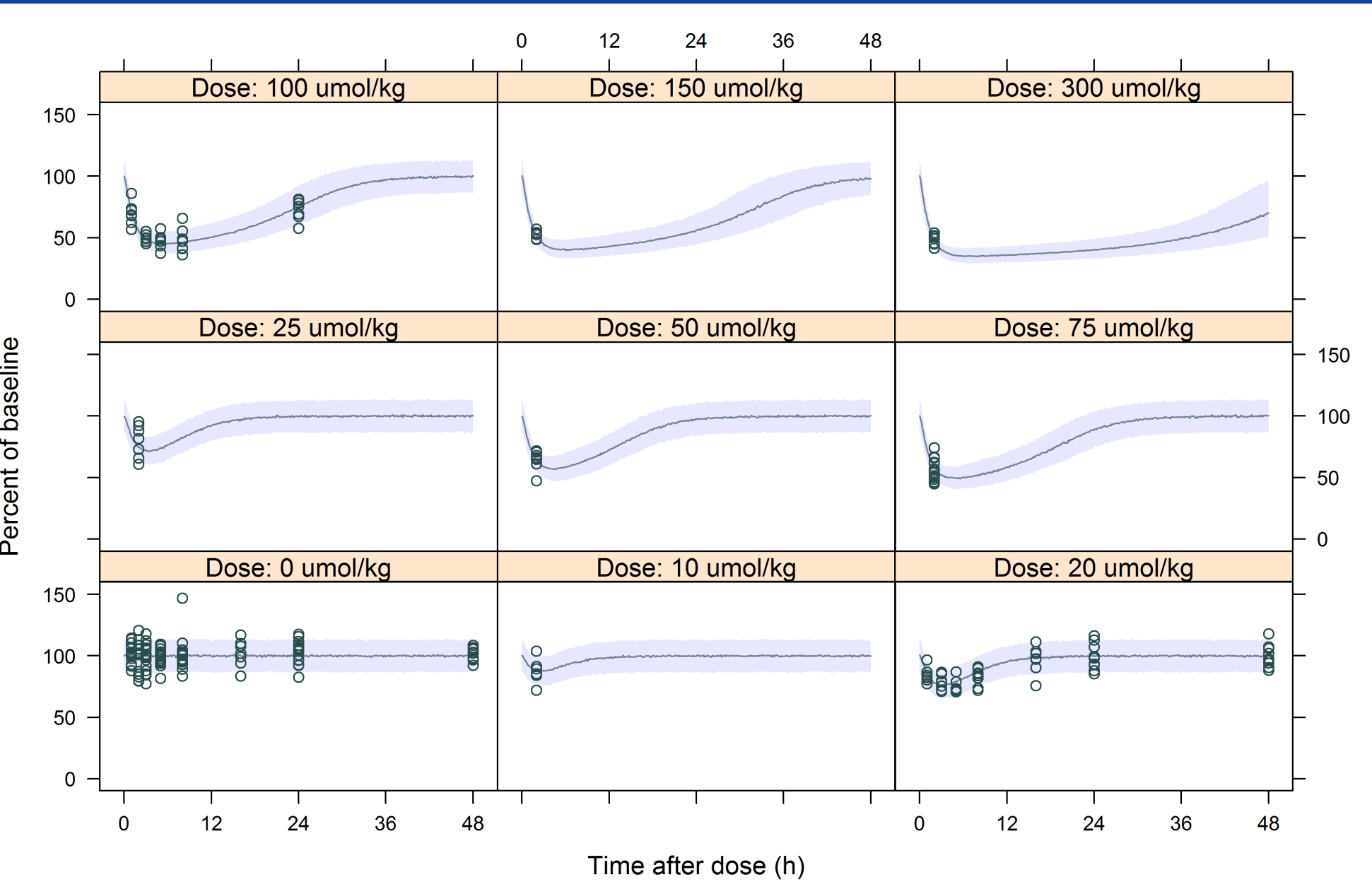
Results

Pharmacokinetics: The plasma concentrations for all three compounds were best described using two-compartment models with nonlinear elimination. Nonlinear bioavailability (lower at higher doses) was identified for compound AZ1.

Compound AZ1 showed a simple proportional relationship between plasma and brain PK at all concentration levels. AZ2 showed a distinct non-linear relation between plasma and brain PK. For AZ3, a time-delay in the decline of the brain concentrations was necessary to adequately link plasma and brain observations.

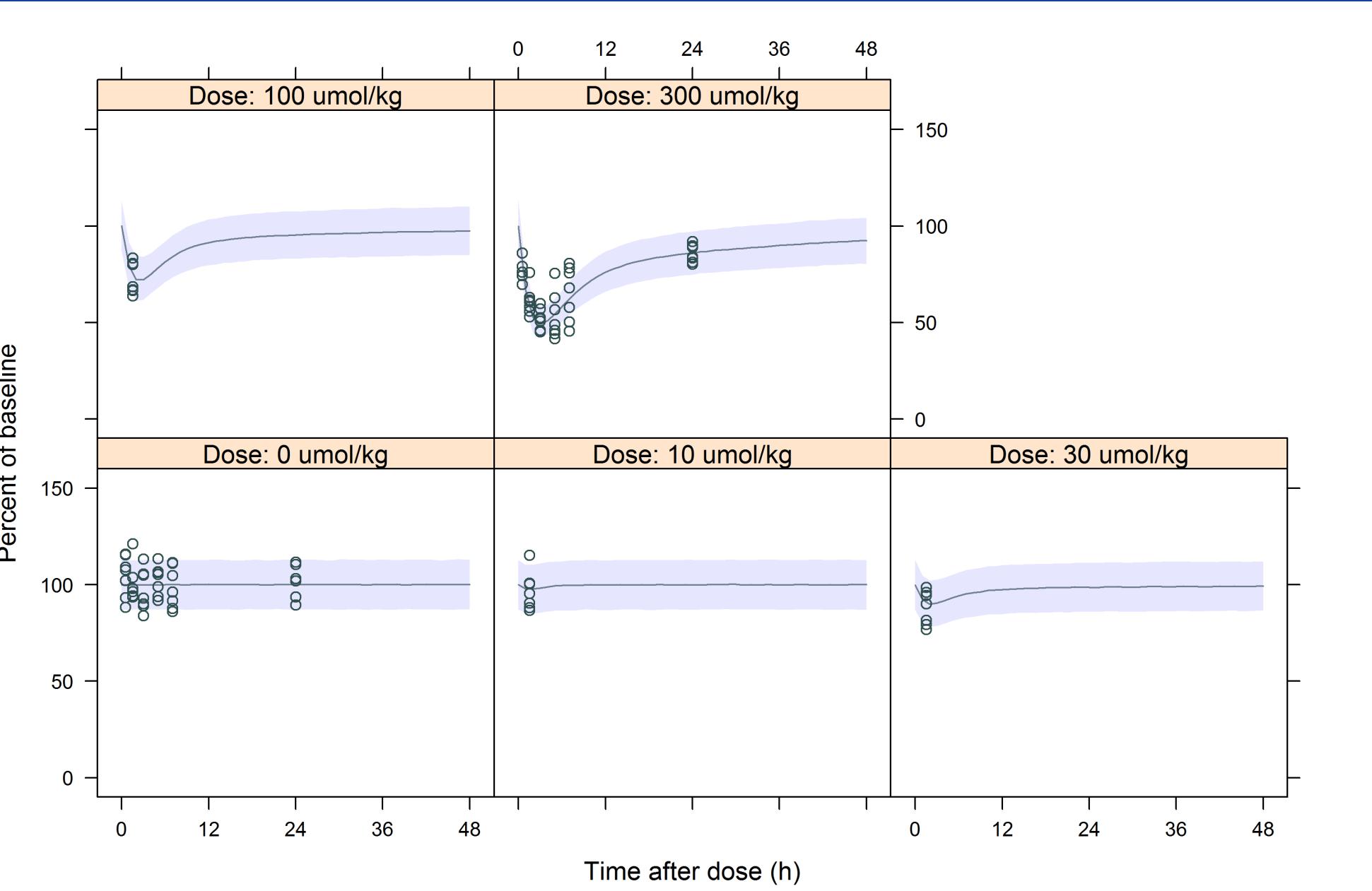
Visual predictive checks of plasma and brain concentrations for AZ1 can be seen in figures 1 and 2. For AZ2 and AZ3 similar results were obtained (data not shown).

Figure 3. Pharmacodynamics of AZ1 – Aβ42 levels in brain



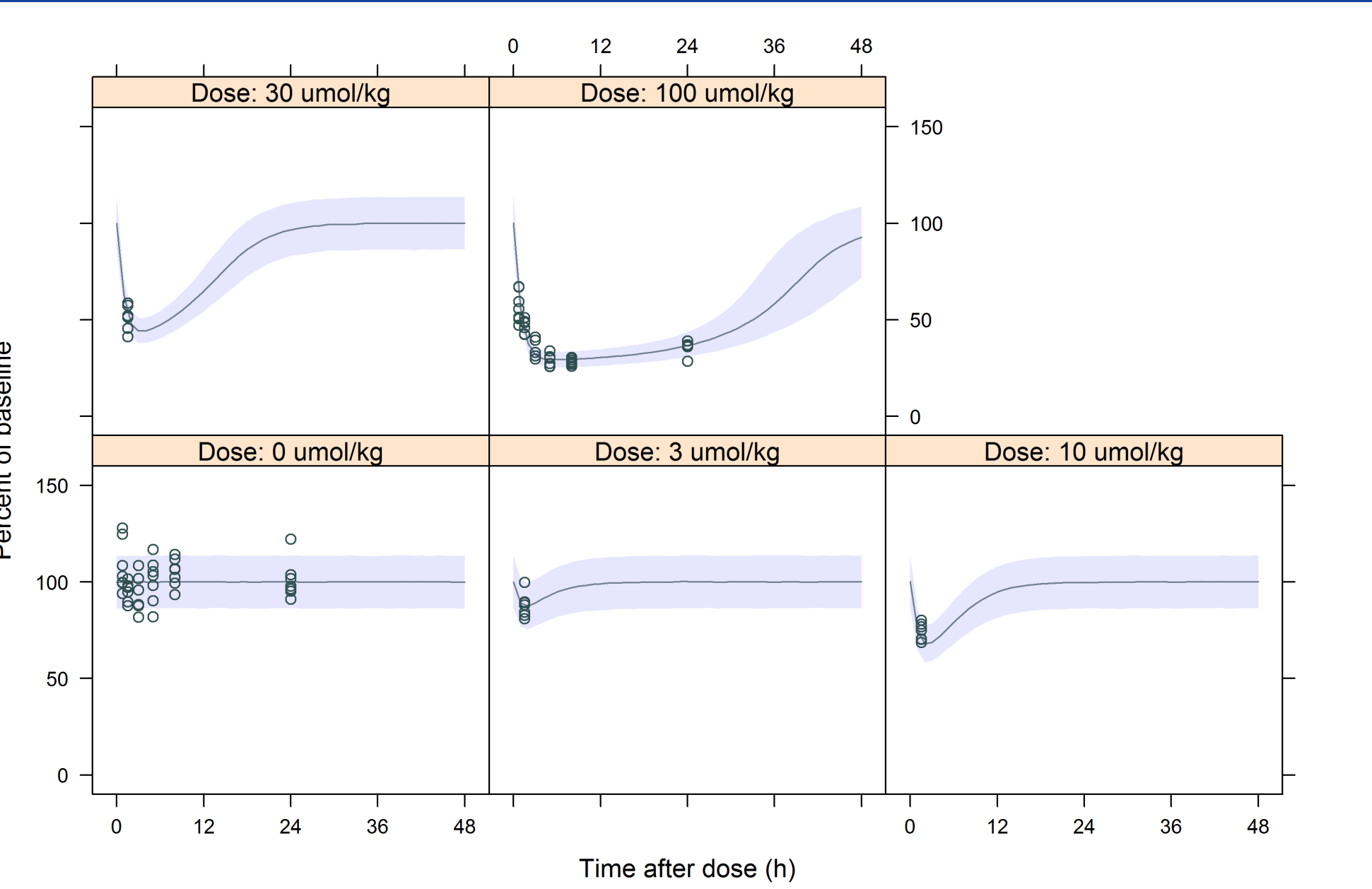
Visual Predictive Check for the change in brain Aβ42 after single oral dose AZ1. Circles represent observed baseline and vehicle group adjusted Aβ42 levels. Solid lines show the median prediction of the PKPD model. Shaded grey area represent the 80% prediction interval of the PKPD model

Figure 4. Pharmacodynamics of AZ2 – Aβ42 levels in brain



Visual Predictive Check for the change in brain Aβ42 after single oral dose AZ2. Circles represent observed baseline and vehicle group adjusted Aβ42 levels. Solid lines show the median prediction of the PKPD model. Shaded grey area represent the 80% prediction interval of the PKPD model

Figure 5. Pharmacodynamics of AZ3 – Aβ42 levels in brain



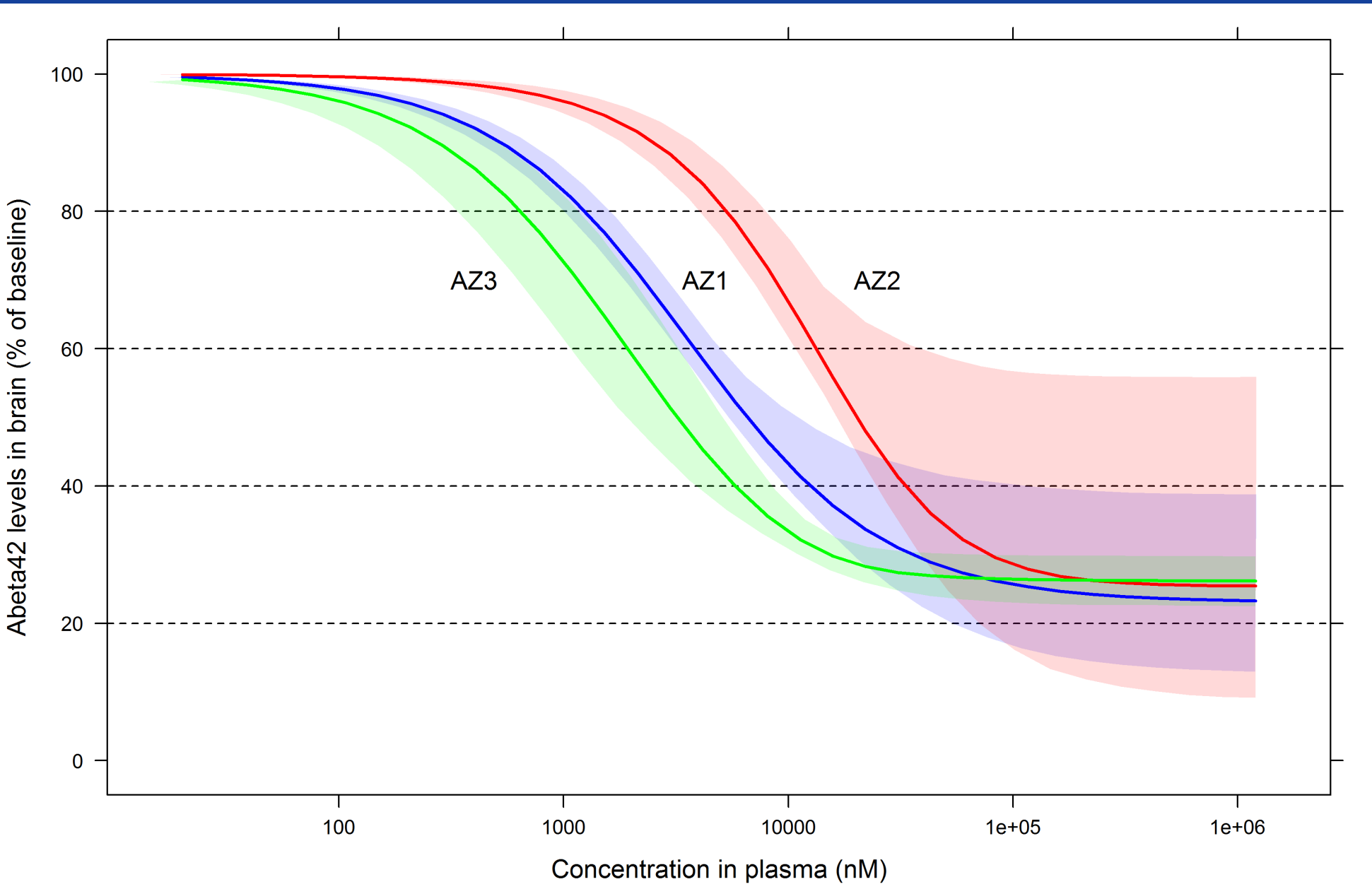
Visual Predictive Check for the change in brain Aβ42 after single oral dose. Circles represent observed baseline and vehicle group adjusted Aβ42 levels. Solid lines show the median prediction of the PKPD model. Shaded grey area represent the 80% prediction interval of the PKPD model

Pharmacodynamics: The effect was best described using indirect response models for all three compounds with turn-over half-lives between 0.64 and 0.87 hours and a maximum effect (E_{max}) of approx. 75% for all three compounds (figures 3-5)

Figures 6 and 7 show the steady state concentration-effect relationships for plasma and brain. The plasma PK – brain PD relation was calculated using the estimated link between plasma and brain concentrations (linear, nonlinear and delayed) in addition to the E_{max}-type model between brain concentration and Aβ42 inhibition.

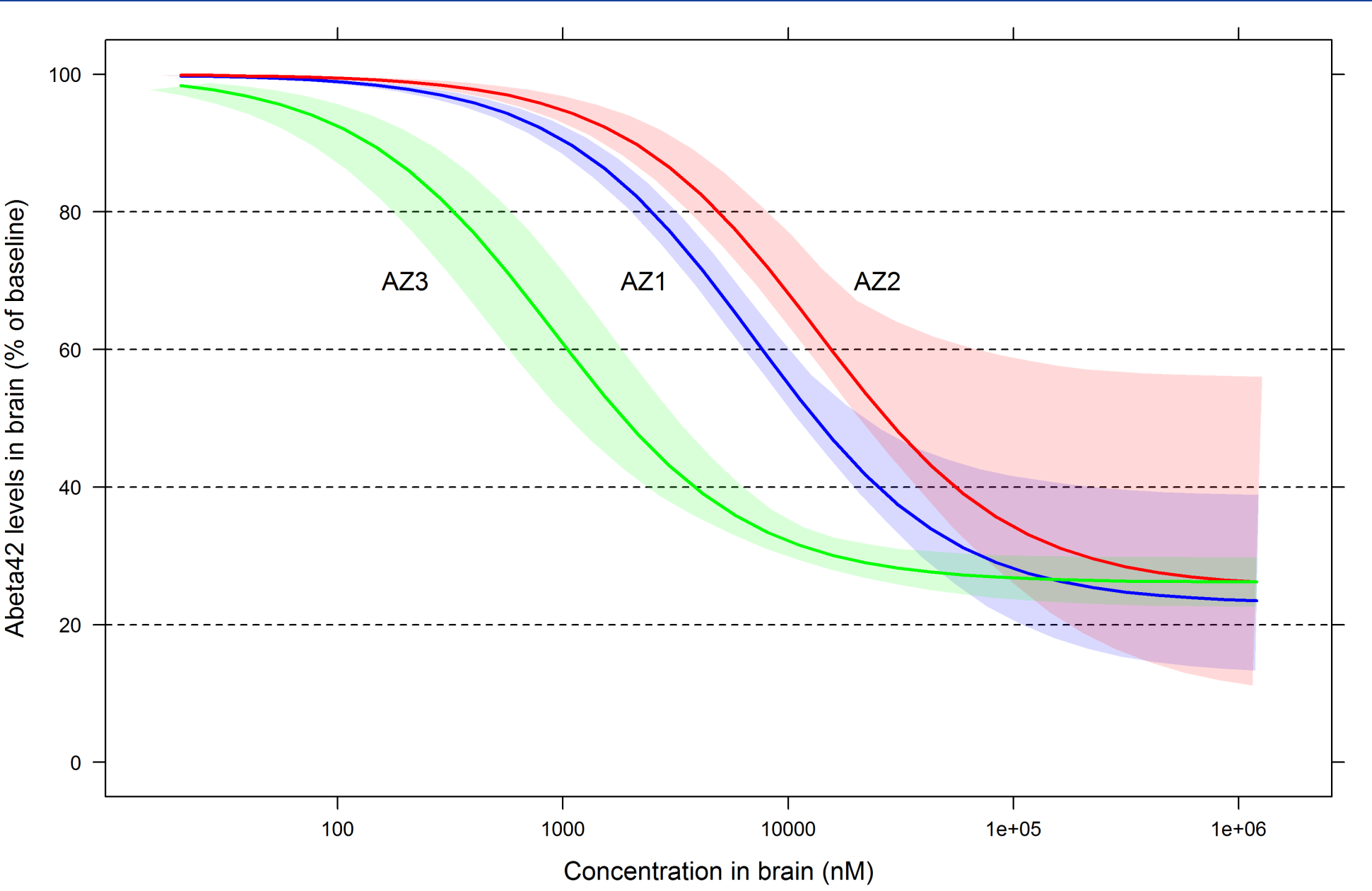
The potency is best characterized for AZ1 with a narrow 95% confidence interval at low to modest inhibition levels while E_{max} is less well defined. AZ3 shows the opposite pattern with very well estimated E_{max} and lower precision for the estimate of its potency. AZ2 show medium to low precision in both efficacy and potency.

Figure 6. Concentration-effect relationship for plasma



Solid lines represent the median predictions of the baseline adjusted Aβ42 levels for each compound. Shaded areas show the 95% confidence intervals of the concentration-effect curves.

Figure 7. Concentration-effect relationship for brain



Solid lines represent the median predictions of the baseline adjusted Aβ42 levels for each compound. Shaded areas show the 95% confidence intervals of the concentration-effect curves.

Conclusion

Using an integrated modeling & simulation approach to show the uncertainty in the concentration-effect relationships from different GSMs allowed to quantitatively compare their potency and efficacy. This facilitated compound selection for further development in an intuitive and comprehensive manner.

References

1. Richter L, Munter LM, Ness J, Hildebrand PW, Dasari M, Unterreitmeier S, Bulic B, Beyermann M, Gust R, Reif B, Weggen S, Langosch D, Multhaup G. Amyloid beta 42 peptide (Abeta42)-lowering compounds directly bind to Abeta and interfere with amyloid precursor protein (APP) transmembrane dimerization. Proc Natl Acad Sci USA. 2010;107(33):14597-602.