Human PK/PD profiles of CKD517, a new drug candidate targeting hypercholesterolemia by inhibiting cholesteryl ester transfer protein (CEPT), were predicted using NONMEM and allometric scaling with animal data. Although the manuscript predicted PK and PD profiles of CKD517 in humans, discrepancies were found between predicted and observed data. The manuscript needs to be improved by considering the following points:

Major comments

1. As authors mentioned, the exponent value for CL by simple allometric scaling was less than 0.55, indicating that the correction with brain weight or MLP is not applicable to predict human CL of the drug (CKD519). According to the rule of exponents, corrections with MLP and brain weight could improve predictability of human CL only when the exponent value is between 0.71 and 1.0 and between 1.0 and 1.3, respectively. The allometric scaling is not recommended to predict human PK profile if the exponent value is out of these ranges ( < 0.55 or > 1.3). Please provide a rationale on the purpose of the study. It is contradictory as the authors already found discrepancies in PK and PD profiles (Figure 6).

2. The method for statistical analysis is not described in the text, and only OFV values are shown in Tables 2 and 3. The criteria for statistical analysis should be mentioned in the main text.

3. There is no description on how drug concentrations in biological samples were measured. Since the manuscript includes animal data, the information on the animal protocol approval by IACUC should be described in the main text. If the animal data were obtained from other sources or institutions, it has to be declared in the main text.

4. Due to a small size of hamsters, it is difficult to collect blood samples serially from one animal, and the serial blood sampling could affect pharmacokinetics of drug in small animals if sampling volume is significant. Please confirm whether the blood samples were serially collected from each hamster. If the blood sampling was not serially taken from each hamster, the authors need to refit the data with new data file.

5. In Table 1, samples sizes for some subgroups are less than 2, which is not enough size to calculate standard deviation. Moreover, it is not clear how the authors obtained $C_{\text{max}}$ for IV injected subgroups, as $C_{\text{max}}$ is not obtainable after IV injection. Delete $C_{\text{max}}$ for IV subgroups.

6. Provide other PK parameters including $T_{\text{max}}$ and elimination rate constant ($k_e$) of the drug in Table 1.

7. The unit for plasma concentration of drug was shown as ng/mL in figures. Since the unit for IC50 was nM scale in the text, please confirm whether the conversion equation using molecular weight of CKD 517 was included in the NONMEM script for PK/PD.
8. Again, it is not clear how the authors calculated standard deviation for the group, which had a small sample size (<3), in Figure 1. Furthermore, Y-axis needs to be in log-scale, and sample sizes for each dose have to be shown beside each dose in Figure 1.

Minor comments

1. A bracket is missing in Equation 4 and Table 4.

2. How were the brain weight and maximum lifespan potential for each animal species calculated? Describe how these values were obtained in the main text.

3. In Figure 2, the equation for “F” is not consistent with Equation 4.

4. Both 22 and 37 nM were used to predict the inhibitory effect of CKD517 on CETP activity by both simple allometry and brain weight-incorporated allometry (Table 7). However, it is not clearly tabulated in Table 7; 22 nM for simple allometry and 37 nM for brain weight-incorporated allometry. Revise the table to clarify this point.

5. In Figure 5, the figure legends in the panels are covering the data. Shift the legends to the other side.