***Calculation methods of reference fm,CYP values for compounds 8, 10 and 11***

Compound 8 was mainly metabolized by CYP1A2 and also showed induction potential for CYP1A2 in human hepatocytes *in vitro*, with an EC50 of 2.21 µM and Emax of 9.9. The decrease in systemic exposure over the time was observed after multiple oral administration indicating an auto-induction potential for CYP1A2. The compound file was developed using Simcyp, where fm,CYP1A2 and fm,CYP3A4 were set to 70% and 30%, respectively. These fmCYP values were obtained from the chemical inhibition data with the cross-reactivity correction factors (Table 6). The decrease in systemic exposure in time- and dose-dependent manner then can be predicted. It was assumed that a reference *in vivo* fm,CYP1A2 for compound 8 were identical with the *in vitro* fm,CYP1A2 in the HLM incubation. This assumption appears to be reasonable, as the magnitude of the auto-induction potential by Simcyp was under-estimated compared to the observations in the clinical PK study, when fm,CYP1A2 is set to be less than 70% in the PBPK model.

For compound 10 which was metabolized by CYP2C19 and CYP3A4, the PK profiles were investigated in healthy volunteers including carriers of CYP2C19\*2 and CYP2C19\*17 alleles. Since the CYP2C19\*2 allele produces an inactive protein due to a splicing effect, homozygous \*2/\*2 subjects have no CYP2C19 activity. Heterozygous wild type (wt)/\*2 subjects can be assumed to show half of the CYP2C19 activity in wt/wt subjects. The CYP2C19\*17 allele is associated with an increase in CYP2C19 expression due to a change in the 5’-flanking region of the gene. Heterozygous wt/\*17 subjects can be assumed to show half the gain in CYP2C19 activity compared to homozygous \*17/\*17 subjects, taking wt/wt subjects as reference. Assuming that the CLint,u for CYP3A4 was not affected by the CYP2C19 genotypes, the CLint,u values in HLM mediated by CYP3A4 and CYP2C19 in wt/wt subjects were separately estimated. Hence, the fm,CYP3A4 and fm,CYP2C19 were calculated to be ~17% and ~83%, respectively.

The systemic exposure of compound 11 after single administration was observed to be 1.91-fold higher in the presence of co-administration of ketoconazole (200 mg p.o., b.i.d.). Since a gut first pass effect was not expected for this compound due to high permeability indicated in Caco-2 cells, the DDI observation is likely due to the inhibition effect of ketoconazole on the hepatic metabolism by CYP3A. The rhCYP data indicated no CYP3A5 contribution to the metabolism. Therefore, assuming complete inhibition of the CYP3A4 activity by treatment with ketoconazole, the *in vivo* fm,CYP3A4 (at most ~ 48%) could be derived according to equation 3:

 (S1)

where AUCR is an AUC ratio of a victim drug in the presence and absence of co-administration of a perpetrator drug. As this compound was found to be mainly metabolized by CYP3A4 and CYP2C9, the *in vivo* fm,CYP2C9 value as reference was estimated to be ~52% (= 100 - 48), assuming that contributions of other CYP enzymes were relatively minor.