Supplementary Information S2: Evofosfamide compound file and trial simulation settings for the base model of simulations on interaction potential via CYP3A induction

Evofosfamide compound file for modeling induction of CYP3A. For file development and validation, see text and supplementary material S1

Parameter	**Value**
Setup: Is small molecule	Yes
mol. wt. (g/mol)	449
log P	0.92
Compound type	Neutral
B:P ratio	1.61
fu,p	0.455
Main plasma binding protein	Human serum albumin
fu_{gut}	1
Distribution Model	Minimal PBPK Model
V_{SS} (L/kg)	0.43
CV V_{SS} (%)	79.0
CL_{iv} (L/h)	63.6
CV CL_{iv} (%)	54.0
CL_R (L/h)	0
Enzyme	CYP3A4
Ind_{max}	8
$IndC_{50}$ (µM)	2.5
Enzyme	CYP3A5
Ind_{max}	8
$IndC_{50}$ (µM)	2.5

B:P ratio, blood to plasma concentration ratio; CL_{IV}, clearance after intravenous administration; CL_R, renal clearance; CV, coefficient of variation; CYP, cytochrome P450 enzyme; fu_{gut}, fraction unbound in enterocytes; fu,p, fraction unbound in plasma; $IndC_{50}$, concentration that gives half maximal fold induction; Ind_{max}, maximal fold induction; logP, octanol-water partition coefficient; mol. wt., molecular weight; V_{ss}, volume of distribution at steady state

The midazolam PK was described using the “Sim-Midazolam” compound file provided within the Simcyp simulator software. The “Sim-Midazolam” file was used without any further modification.

Trial simulation settings for induction base model

Parameter	Value
Midazolam	5 mg SD orally, 3 h after start of evofosfamide infusion
Evofosfamide	340 mg/m² SD, as 30 min infusion
Number of subjects x trials	10 x 10
Population	North European Caucasian
Age range (years)	18 - 80
Proportion of females	0.5
Prandial state	Fasted
Duration (h)	27
PKPD Profiles simulated	Yes

PKPD Profiles, time courses of PK and/or PD endpoints; SD, single dose

The models for multiple dosing, sensitivity analyses, etc. were derived from the base model by adjusting the respective parameters as described in the text.