DDI precipitant risk assessment for examplinib and M1

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Introduction

This drug-drug interaction (DDI) precipitant risks assessment report for examplinib and M1 is based on the ICH M12 guidance document.

All calculations were done using the `ddir` package, version 0.15.0.

Drug properties

The following physico-chemical, ADME and clinical exposure data were used for the calculation of the relevant precipitant drug concentrations:

Table 1: Compound parameters for examplinib

parameter	value	source
oral	TRUE	
MW (g/mol)	492.6	
$dose$ (mg)	450	clinical dose
$C_{max,ss}$ (ng/ml)	3530	study 001
f_u	0.023	study 002
$f_{u,mic}$	1	default
R_B	1	study 003
F_a	0.81	study 003
F_g	1	default
k_a (1/min)	0.00267	unknown
$solubility$ (mg/l)	Inf	default

Table 2: Compound parameters for M1

parameter	value	source
oral	FALSE	
MW (g/mol)	506.56	
$dose$ (mg)	NA	
$C_{max,ss}$ (ng/ml)	1038	study 001
f_u	0.012	study 002
$f_{u,mic}$	1	default
R_B	1	study 002
$solubility$ (mg/l)	Inf	default

Key perpetrator concentrations

The following perpetrator concentrations were calculated as described in Appendix 1:

Table 3: Key perpetrator concentrations for examplinib

parameter	value (ng/ml)	value (uM)
I_{gut}	1800000.0	3654.080
$I_{max,ss,u}$	81.2	0.165
$I_{max,inlet,u}$	95.0	0.193
$I_{max,intestinal}$	3244.1	6.586

Table 4: Key perpetrator concentrations for M1

parameter	value (ng/ml)	value (uM)
I_{gut}	0.0	0.0000
$I_{max,ss,u}$	12.5	0.0246
$I_{max,inlet,u}$	12.5	0.0246
$I_{max,intestinal}$	12.5	0.0246

DDI risk as inhibitor or inducer of drug-metabolizing enzymes

Basic modeling of CYP inhibition

Reversible inhibition

Following the basic modeling approach (refer to Section 2.1.2.1 of the ICH M12 guideline), the relevant metric for the assessment of the direct CYP inhibition risk is $R = [I]/K_{i,u}$ with the inhibitor concentration $[I]$ being $C_{max,ss,u}$ for hepatic CYP enzymes and I_{gut} for intestinal CYP enzymes.

R values of $R \geq 0.02$ and $R \geq 10$ for hepatic and intestinal enzymes are considered to indicate a potential clinical risk.

Table 5: Risk for direct CYP inhibition by examplinib, basic model

CYP	K_i (μM)	$K_{i,u}$ (μM)	R	risk (hepatic)	R_{gut}	risk (intestinal)
CYP1A2	NA	NA	NA	NA		
CYP2B6	NA	NA	NA	NA		
CYP2C8	11.0	11.0	0.015	FALSE		
CYP2C9	13.5	13.5	0.012	FALSE		
CYP2C19	15.0	15.0	0.011	FALSE		
CYP2D6	NA	NA	NA	NA		
CYP3A4	12.5	12.5	0.013	FALSE	292.3	TRUE

Table 6: Risk for direct CYP inhibition by M1, basic model

CYP	K_i (μM)	$K_{i,u}$ (μM)	R	risk (hepatic)	R_{gut}	risk (intestinal)
CYP2C9	4.4	4.4	0.006	FALSE		

Time-dependent inhibition

As per the ICH M12 guideline, the risk for time-dependent inhibition (TDI) of CYP enzymes is assessed based on the formula given in Appendix 1, where $R \geq 1.25$ suggest a clinically relevant DDI potential that requires further investigation.

Table 7: Risk for CYP TDI by examplinib, basic model

CYP	K_I (μM)	f_u	k_{inact} (1/h)	k_{deg} (1/h)	source	R	risk
CYP3A4	0.17	0.02	0.04	0.02	study 001	3.06	TRUE

Modeling of CYP induction

Basic 'fold-change' method

The basic 'fold-change' approach evaluates whether the maximal change in CYP mRNA expression is > 2-fold at concentrations up to 50-fold of the expected unbound systemic concentration of the drug (refer to Section 2.1.4.1 of th ICH M12 guidance document).

Basic modeling as per the FDA guideline results in the following risk assessment:

Table 8: Risk for hepatic CYP induction by examplinib, basic static model

CYP	E_{max}	$maxc$ (μM)	source	$maxc/C_{max,ss,u}$	risk	notes
CYP1A2	1.00	5	study 007	30.3	FALSE	Maximal tested concentration (maxc) is below guideline expectations
CYP2B6	1.00	5	study 007	30.3	FALSE	Maximal tested concentration (maxc) is below guideline expectations
CYP3A4	7.35	3	study 007	18.2	TRUE	Maximal tested concentration (maxc) is below guideline expectations

Table 9: Risk for hepatic CYP induction by M1, basic static model

CYP	E_{max}	$maxc$ (μM)	source	$maxc/C_{max,ss,u}$	risk	notes
CYP1A2	1.00	5	study 007	203.3	FALSE	
CYP2B6	6.98	5	study 007	203.3	TRUE	
CYP3A4	22.70	5	study 007	203.3	TRUE	

Basic kinetic method

The basic kinetic method for the assessment of CYP induction is based on the EC_{50} and E_{max} parameters derived from in vitro studies (refer to Section 'Basic kinetic modeling of CYP induction' in Appendix 1). For $R < 0.8$, an in vivo induction risk cannot be excluded:

Table 10: Risk for CYP induction by examplinib, basic kinetic model

CYP	E_{max}	EC_{50} (μM)	source	R	risk
CYP1A2	1.00	NA	study 007	NA	NA
CYP2B6	1.00	NA	study 007	NA	NA
CYP3A4	7.35	1.64	study 007	0.21	TRUE

CYP	E_{max}	EC_{50} (μM)	source	R	risk

Table 11: Risk for CYP induction by M1, basic kinetic model

CYP	E_{max}	EC_{50} (μM)	source	R	risk
CYP1A2	1.00	NA	study 007	NA	NA
CYP2B6	6.98	1.86	study 007	0.55	TRUE
CYP3A4	22.70	1.10	study 007	0.19	TRUE

Mechanistic static modeling

Using the mechanistic static modeling approach (refer to Section 7.5.1.2 of the ICH M12 guideline, AUC ratios for specific sensitive CYP substrates are calculated, considering the available in vitro data for both direct and time-dependent inhibition, and mRNA induction (refer to Section 'Mechanistic static modeling of CYP modulation' in Appendix 1).

Mechanistic static modeling may be used to investigate CYP inhibition alone, or both inhibition and induction effects.

CYP inhibition only

Table 12: Mechanistic static modeling of the CYP inhibition risk for examplinib

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP1A2	NA	tizanidine	1.00	0.95	0.98	1.000	1.000	1.000	1.000	1.000	1.000	1.00	FALSE
CYP2B6	NA	NA	NA	NA	NA	1.000	1.000	1.000	1.000	1.000	1.000	NA	NA
CYP2C8	11.0	repaglinide	1.00	1.00	0.61	0.626	0.983	1.000	1.000	1.000	1.000	1.01	FALSE
CYP2C9	13.5	S-warfarin	1.00	1.00	0.91	0.672	0.986	1.000	1.000	1.000	1.000	1.01	FALSE
CYP2C19	15.0	omeprazole	1.00	1.00	0.87	0.695	0.987	1.000	1.000	1.000	1.000	1.01	FALSE
CYP2D6	NA	NA	NA	NA	NA	1.000	1.000	1.000	1.000	1.000	1.000	NA	NA
CYP3A4	12.5	midazolam	0.57	0.96	1.00	0.655	0.985	0.435	0.476	1.000	1.000	2.95	TRUE

Table 13: Mechanistic static modeling of the CYP inhibition risk for M1

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP2C9	4.4	S-warfarin	1	1	0.91	0.994	0.994	1.000	1.000	1.000	1.000	1.01	FALSE

CYP inhibition and induction

Table 14: Mechanistic static modeling of the CYP inhibition risk for examplinib

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP1A2	NA	tizanidine	1.00	0.95	0.98	1.000	1.000	1.000	1.000	1.000	1.000	1.000	FALSE
CYP2C8	11.0	repaglinide	1.00	1.00	0.61	0.626	0.983	1.000	1.000	1.000	1.000	1.011	FALSE
CYP2C9	13.5	S-warfarin	1.00	1.00	0.91	0.672	0.986	1.000	1.000	1.000	1.000	1.013	FALSE
CYP2C19	15.0	omeprazole	1.00	1.00	0.87	0.695	0.987	1.000	1.000	1.000	1.000	1.011	FALSE
CYP3A4	12.5	midazolam	0.57	0.96	1.00	0.655	0.985	0.435	0.476	6.885	1.774	0.845	FALSE

Table 15: Mechanistic static modeling of the CYP inhibition risk for M1

CYP	$K_{i,u}$	substrate	F_{gut}	f_m	$f_{m,CYP}$	A_g	A_h	B_g	B_h	C_g	C_h	AUCR	risk
CYP2C9	4.4	S-warfarin	1	1	0.91	0.994	0.994	1.000	1.000	1.000	1.000	1.01	FALSE

Basic modeling of UGT inhibition

The relevant metric for basic modeling of the UGT inhibition risk is $R = C_{max,ss,u}/K_{i,u}$ (refer to Section 2.1.2.1 of the ICH M12 guidance document) for details.

$R > 0.02$ is considered to indicate a potential UGT inhibition risk.

Note that in in vitro UGT inhibition studies, often IC_{50} rather than K_i values are reported. Assuming that substrate concentrations close to K_m are used, K_i is calculated as $K_i = IC_{50}/2$ (refer to Cheng, Prusoff 1973).

Basic modeling of UGT inhibition results in the following risk assessment:

Table 16: Risk for UGT inhibition by examplinib, basic model

UGT	$K_{i,u}$	R	risk
UGT1A1	7.50	0.022	TRUE
UGT1A3	7.50	0.022	TRUE
UGT1A4	7.50	0.022	TRUE
UGT1A6	7.50	0.022	TRUE
UGT1A9	1.90	0.087	TRUE
UGT2B7	7.50	0.022	TRUE
UGT2B15	7.50	0.022	TRUE
UGT2B17	3.05	0.054	TRUE

Table 17: Risk for UGT inhibition by M1, basic model

UGT	$K_{i,u}$	R	risk
UGT1A1	0.55	0.045	TRUE
UGT1A3	2.90	0.008	FALSE
UGT1A4	3.10	0.008	FALSE
UGT1A6	7.50	0.003	FALSE
UGT1A9	1.80	0.014	FALSE

UGT	$K_{i,u}$	R	risk
UGT2B7	7.50	0.003	FALSE
UGT2B15	4.80	0.005	FALSE

DDI risk as inhibitor of drug transporters

The metric for the assessment of the drug transporter inhibition risk is $R = [I]/K_i$. For the relevant perpetrator concentrations, refer to Appendix 1, Section 'Inhibition of drug transporters'.

Table 18: Risk for drug transporter inhibition by examplinib

transporter	IC_{50}	source	R	threshold	risk
Pgp_int	0.41	study 005	8912.39	10.00	TRUE
Pgp_sys	0.41	study 005	0.40	0.02	TRUE
BCRP_int	1.90	study 005	1923.20	10.00	TRUE
BCRP_sys	1.90	study 005	0.09	0.02	TRUE
OATP1B1	177.00	study 006	0.00	0.10	FALSE
OATP1B3	35.00	study 006	0.01	0.10	FALSE
OAT1	271.00		0.00	0.10	FALSE
OAT3	300.00		0.00	0.10	FALSE
BSEP	12.80		0.01	0.10	FALSE
OCT2	67.00	study 006	0.00	0.10	FALSE
MATE1	3.60	study 006	0.05	0.02	TRUE
MATE2k	1.10	study 006	0.15	0.02	TRUE
OCT1	2.30	study 006	NA	NA	NA

Appendix 1: Calculations and formulae

Relevant precipitant drug concentrations

Gut concentration

The maximal gut concentration (I_{gut}) for the orally administered compounds is the administered dose dissolved in 250 ml.

$$I_{gut} = \frac{D}{250}$$

Systemic concentration

The unbound systemic ($C_{max,ss,u}$) concentration is considered the relevant precipitant concentration for hepatic enzyme inhibition and induction:

$$C_{max,ss,u} = I_{max,ss} * f_u$$

Hepatic inlet concentration

The hepatic inlet concentration is considered the relevant perpetrator concentration for inhibition of the hepatic uptake transporters OATPB1B1 and OATP1B3, and for the hepatic terms in the mechanistic static modeling equation (refer to Section '[Mechanistic static modeling of CYP inhibition/induction]').

The hepatic inlet concentration is composed of the systemic concentration and the portal contribution. For orally administered drugs, the portal term is calculated as:

$$portal\ term = D * \frac{F_a * F_g * k_a}{Q_h * R_B} * 1000\ ng/ml$$

with

- D the administered dose in mg
- F_a the fraction absorbed after oral administration
- F_g the fraction available after gut metabolism
- k_a the absorption rate
- Q_h the hepatic blood flow
- R_B the blood-to-plasma ratio.

The standard hepatic blood flow is assumed as 97 l/h/70 kg or 1.61 l/min/70 kg.

The relevant hepatic inlet ($I_{max,inlet,u}$, also called I_h in the mechanistic static modeling equations) concentration is the sum of the maximal systemic plasma concentration and the portal contribution:

$$I_{max,inlet,u} = (C_{max,ss} + portal\ term) * f_u$$

Enteric concentration

For the parent compound, the villous concentration in the gut ($I_{enteric}$, also called I_g in the mechanistic static modeling equations) is calculated as:

$$I_{enteric,u} = D * \frac{F_a * k_a}{Q_{ent}} * 1000\ ng/ml$$

with

- F_a the fraction absorbed after oral administration
- k_a the absorption rate constant
- Q_{ent} the enteric villous blood flow

Note that as per the ICH M12 guideline and Rostami-Hodjegan and Tucker, 2004 the blood-to-plasma distribution ratio and the plasma binding of the drug are not applicable for the calculation of the villous concentration.

The standard villous blood flow is assumed as 18 l/h/70 kg or 0.3 l/min/70 kg.

Basic modeling of enzyme inhibition

Reversible inhibition

For the basic modeling of direct (reversible) enzyme inhibition, the ratios of the relevant inhibitor concentration to the K_i are considered (refer to Section 2.1.2.1 of the ICH M12 guidance document).

R values larger than 0.02 (liver) or 10 (gut), are considered to indicate a potential clinical enzyme inhibition risk using this method.

Liver

$$R = \frac{C_{max,ss,u}}{K_{i,u}}$$

Gut wall

$$R_{gut} = \frac{I_{gut}}{K_{i,u}}$$

Time-dependent CYP inhibition

For the basic modeling of the potential for time-dependent CYP inhibition (TDI), the following metric is considered:

$$R = \frac{k_{obs} + k_{deg}}{k_{deg}}$$

with

$$k_{obs} = \frac{5 * k_{inact} * C_{max,u}}{K_{I,u} + 5 * C_{max,u}}$$

The CYP degradation constant, k_{deg} is a physiological constant that should be derived from the scientific literature. In this DDI assessment report, standard values are used unless otherwise indicated.

Values of $R \geq 1.25$ is considered to indicate a clinically relevant TDI potential and suggest the need for further investigation.

Basic kinetic modeling of CYP induction

For the basic kinetic modeling of the CYP induction potential, the following metric is considered:

$$R = \frac{1}{1 + d * \frac{E_{max} * 10 * C_{max,ss,u}}{EC_{50} + 10 * C_{max,ss,u}}}$$

with d a scaling factor that has a standard value of 1. A different value can be used if warranted by prior experience with the experimental conditions.

$R \leq 0.8$ suggest a relevant in vivo CYP induction potential.

Mechanistic static modeling of CYP modulation

In this approach, AUC ratios for specific DDI object substrates are projected based on their known intestinal and hepatic metabolism. Both direct (competitive) and time-dependent inhibition, as well as enzyme induction are considered. AUC ratios are calculated according to the below formula (refer to Section 7.5.1.2 of the ICH M12 guideline):

$$AUCR = \frac{1}{A_g * B_g * C_g * (1 - F_g) + F_g} * \frac{1}{A_h * B_h * C_h * f_m + (1 - f_m)}$$

This calculation is applied for typical probe substrates for which F_g, i.e., the fraction escaping gut metabolism and f_m, i.e., the fraction metabolized are known.

Note that the f_m is composed of the overall fraction metabolized for the respective probe substrate, and the fraction metabolized by the CYP enzyme in questions:

$$f_m = f_{m,overall} * f_{m,CYP}$$

The individual terms in the AUC calculation are:

Reversible inhibition

$$A_g = \frac{1}{1 + \frac{I_g}{K_i}}$$

$$A_h = \frac{1}{1 + \frac{I_h}{K_i}}$$

Time-dependent inhibition

$$B_g = \frac{k_{deg,g}}{k_{deg,g} + \frac{I_g * k_{inact}}{I_g + K_I}}$$

$$B_h = \frac{k_{deg,h}}{k_{deg,h} + \frac{I_h * k_{inact}}{I_h + K_I}}$$

Induction

$$C_g = 1 + \frac{d * E_{max} * I_g}{I_g + EC_{50}}$$

$$C_h = 1 + \frac{d * E_{max} * I_h}{I_h + EC_{50}}$$

with the hepatic inlet concentration $I_h = I_{max,inlet,u}$ and the intestinal concentration $I_g = I_{enteric}$ (see above). d is an induction scaling factor (assumed to be 1 but can be adjusted based on the experimental conditions).

Inhibition of drug transporters

The metric for the assessment of the drug transporter inhibition risk is:

$$R = [I]/K_i$$

with the following relevant precitipant concentrations $[I]$ and regulatory thresholds of concern:

I	transporter	threshold
I_{gut}	P-gp and BRCR when drugs are orally administered	10
$C_{max,ss,u}$	P-gp and BRCR when drugs are administered parenterally or for drug metabolites	0.02
$I_{max,inlet,u}$	hepatic basolateral transporters OCT1, OATP1B1 and OATP1B3	0.1
$C_{max,ss,u}$	renal basolateral transporters OAT1, OAT3 and OCT2	0.1
$C_{max,ss,u}$	apical transporters MATE1 and MATE2-K	0.02

Refer to Section 'Relevant precipitant drug concentrations' for the calculation of the relevant precipitant concentrations.

Appendix 2: R Session Info

This document was created using R version 4.4.1 (2024-06-14) and the following packages:

name	version
ddir	0.15.0
knitrdata	0.6.1
knitr	1.48
lubridate	1.9.3
forcats	1.0.0
stringr	1.5.1
dplyr	1.1.4
purrr	1.0.2
readr	2.1.5
tidyr	1.3.1
tibble	3.2.1
ggplot2	3.5.1
tidyverse	2.0.0