Supplementary materials

Effects of cytochrome P450 3A4 induction and inhibition on the pharmacokinetics of BI 425809, a novel glycine transporter 1 inhibitor

Michael Desch, PhD[1], Glen Wunderlich, PhD[2], Markus Goettel, MD[3], Sophia Goetz, Dipl.-Math[1], Karl-Heinz Liesenfeld, Dipl.-Ing. (FH)[1], Tom Chan, PhD[4], Holger Rosenbrock, PhD[1], Regina Sennewald, MD[1], Jasmin Link, MS[1], Sascha Keller, PhD[1], Sven Wind, PhD[1]

Affiliations:

[1]Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riss, Baden Württemberg, Germany; [2]Boehringer Ingelheim Canada Ltd, Burlington, ON, Canada; [3]Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [4]Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, CT, USA.

Corresponding author:

Dr Michael Desch,
Translational Medicine and Clinical Pharmacology,
Boehringer Ingelheim Pharma GmbH & Co. KG,
Birkendorfer Str. 65, 88397
Biberach an der Riss, Germany.
Tel.: +49 (7351) 54-145070,
Fax: +49 (7351) 83-145070,
Email: michael.desch@boehringer-ingelheim.com
ORCID ID: 0000-0003-0205-1592

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Supplementary Table 1 Final recombinant CYPs concentration

CYP isoform	Final rCYP concentration (pmol/mL)
1A2	149
2B6	100
2C8	100
2C9	478/579
2C19	234/355
2D6	155
3A4	234
3A5	153

rCYP, recombinant cytochrome P450

Supplementary Table 2 BI 425809 PK sampling times for study NCT02342717 (DDI with itraconazole)

BI 425809 PK sampling		
Planned time relative to BI 425809 administration (h:min)	**BI 425809 single dose**	**BI 425809 single dose + itraconazole multiple dose**
-2:00	X[a]	X[a]
0:30	X	X
1:00	X	X
1:30	X	X
2:00	X	X
2:30	X	X
3:00	X	X
3:30	X	X
4:00	X	X
4:30	X	X
5:00	X	X
6:00	X	X
7:00	X	X
8:00	X	X
10:00	X	X
12:00	X	X
24:00	X	X
34:00	X	X
47:00	X	X
71:00	X	X
95:00	X	X
119:00	X	X
143:00	X	X
167:00	X	X
191:00	X	X
239:00	–	X
287:00	–	X
335:00	–	X

[a]The time was approximate; the procedure was to be performed and completed within 3 h prior to drug administration

DDI, drug–drug interaction; PK, pharmacokinetic

Supplementary Table 3 BI 425809 PK sampling times for study NCT03082183 (DDI with rifampicin)

BI 425809 PK sampling		
Planned time relative to BI 425809 administration (h:min)	**BI 425809 single dose**	**BI 425809 single dose + rifampicin multiple dose**
-2:00	X[a]	X[a]
0:30	X	X
1:00	X	X
1:30	X	X
2:00	X	X
2:30	X	X
3:00	X	X
3:30	X	X
4:00	X	X
4:30	X	X
5:00	X	X
6:00	X	X
8:00	X	X
10:00	X	X
12:00	X	X
24:00	X	X
34:00	X	X
48:00	X	X
72:00	X	X
96:00	X	X
168:00	X[b]	X[b]
216:00	X[b]	–
264:00	X[b]	–
336:00	X[b]	–
408:00	X[b]	–
504:00	X[b]	–

[a]The time was approximate; the procedure was to be performed and completed within 3 h prior to drug administration; [b]The time was approximate; the procedure was to be performed and completed within ±3 h of planned time

DDI, drug–drug interaction; PK, pharmacokinetic

Supplementary Table 4 In vitro metabolism of BI 425809 by recombinant CYP isoforms[a]

CYP isoform	% In vitro CYP contribution		
	Formation[b]	Depletion	Average
3A4	96.6	96.1	96.4
3A5	3.41	3.87	3.64
All	100	100	100

[a]In vitro percent contribution of CYP3A4 and CYP3A5 to CYP metabolism using depletion of BI 425809 and semiquantitative formation of metabolites by rCYPs. No detectable depletion of BI 425809 or formation of its metabolites was observed using other rCYPs (1A2, 2B6, 2C8, 2C9, 2C19, and 2D6)
[b]Formation was based on all metabolites observed (M526, M530, and M544)
CYP, cytochrome P450

Supplementary Table 5 Inhibition of in vitro BI 425809 metabolism by erythromycin (30 µM) in human hepatocytes

BI 425809 concentration (µM)	CL_{int} (µL/h/million cells)		
	Control	Inhibited	% CYP3A inhibition
0.2	155	No turnover	100
2	364	25.5	93
10	392	31	92.1

CL_{int}, intrinsic clearance; CYP, cytochrome P450

Supplementary Table 6 Baseline demographics and clinical characteristics (TS)

Parameter	DDI with itraconazole N=16	DDI with rifampicin N=16
Number of participants, N (%)	16 (100)	16 (100)
Sex, n (%)		
Male	16 (100)	16 (100)
Race, n (%)		
White	16 (100)	16 (100)
Hispanic/Latino, n (%)		
No	16 (100)	16 (100)
Age (years), mean (SD)	40.1 (7.9)	38.1 (10.8)
BMI (kg/m^2), mean (SD)	26.4 (1.9)	25.0 (2.1)
Smoking history, n (%)		
Never smoked	8 (50.0)	9 (56.3)
Ex-smoker	5 (31.3)	6 (37.5)
Currently smokes	3 (18.8)	1 (6.3)
Alcohol history, n (%)		
Non-drinker	2 (12.5)	4 (25.0)
Drinks − possible interference	14 (87.5)	12 (75.0)
Drinks − no interference	0 (0)	0 (0)
Participants with any concomitant diagnosis, n (%)		
No	16 (100)	16 (100)
Participants receiving any concomitant therapy, n (%)		
Yes	3 (18.8)	3 (18.8)
No	13 (81.3)	13 (81.3)

BMI, body mass index; DDI, drug–drug interaction; SD, standard deviation; TS, treated set