

## **Extrahepatic metabolism of ibrutinib**

Johannes J.M. Rood, Amer Jamalpoor, Stephanie van Hoppe, Matthijs J. van Haren, Roeland E. Wasmann, Manoe J. Janssen, Alfred H. Schinkel, Rosalinde Masereeuw, Jos H. Beijnen, Rolf W. Sparidans

## **Supplemental Tables**

**Supplemental Table 1:** Patient data for 24 samples of 2 patients (A and B) for ibrutinib, DHI, IGSH, ICGS, and ICYS.

Index	Patient	Sample ID	T (h)	Dose	Group	Analyte	Concentration (nM)
1	A	5	0.5	1xdd 420mg	abs	ibru	11.8
2	A	3	0.8	1xdd 560mg	abs	ibru	3.5
3	A	21	0.8	1xdd 420mg	abs	ibru	143.2
4	A	6	0.8	1xdd 420mg	abs	ibru	14.6
5	A	18	1.2	1xdd 420mg	abs	ibru	117.5
6	A	2	1.4	1xdd 420mg	abs	ibru	6.6
7	A	16	1.5	1xdd 420mg	abs	ibru	11.6
8	B	12	2.4	1xdd 560mg	max	ibru	551.2
9	A	13	2.5	1xdd 420mg	max	ibru	683.1
10	B	4	2.8	1xdd 560mg	max	ibru	234.3
11	B	1	3.3	1xdd 560mg	max	ibru	309.2
12	A	14	3.8	1xdd 420mg	max	ibru	151.2
13	B	20	3.8	1xdd 560mg	max	ibru	195.7
14	B	17	3.9	1xdd 560mg	max	ibru	578.0
15	B	23	4.1	1xdd 560mg	max	ibru	497.1
16	B	7	4.1	1xdd 560mg	max	ibru	359.7
17	B	24	4.4	1xdd 560mg	max	ibru	323.2
18	B	9	4.4	1xdd 560mg	max	ibru	192.3
19	A	10	22.2	1xdd 420mg	trough	ibru	7.0
20	A	11	22.6	1xdd 420mg	trough	ibru	4.3
21	A	8	22.7	1xdd 420mg	trough	ibru	8.9
22	A	19	23.3	1xdd 420mg	trough	ibru	5.5
23	A	15	NA	1xdd 420mg	<sup>a</sup>	ibru	15.8
24	A	22	NA	1xdd 420mg	<sup>a</sup>	ibru	0.9
25	A	5	0.5	1xdd 420mg	abs	dhi	51.6
26	A	3	0.8	1xdd 560mg	abs	dhi	17.5
27	A	21	0.8	1xdd 420mg	abs	dhi	188.2
28	A	6	0.8	1xdd 420mg	abs	dhi	48.3
29	A	18	1.2	1xdd 420mg	abs	dhi	137.1
30	A	2	1.4	1xdd 420mg	abs	dhi	43.9
31	A	16	1.5	1xdd 420mg	abs	dhi	24.0
32	B	12	2.4	1xdd 560mg	max	dhi	449.9
33	A	13	2.5	1xdd 420mg	max	dhi	403.7
34	B	4	2.8	1xdd 560mg	max	dhi	345.6
35	B	1	3.3	1xdd 560mg	max	dhi	419.9
36	A	14	3.8	1xdd 420mg	max	dhi	195.3
37	B	20	3.8	1xdd 560mg	max	dhi	524.1
38	B	17	3.9	1xdd 560mg	max	dhi	542.0
39	B	23	4.1	1xdd 560mg	max	dhi	468.0

40	B	7	4.1	1xdd 560mg	max	dhi	523.3
41	B	24	4.4	1xdd 560mg	max	dhi	484.1
42	B	9	4.4	1xdd 560mg	max	dhi	393.3
43	A	10	22.2	1xdd 420mg	trough	dhi	90.7
44	A	11	22.6	1xdd 420mg	trough	dhi	45.3
45	A	8	22.7	1xdd 420mg	trough	dhi	86.6
46	A	19	23.3	1xdd 420mg	trough	dhi	30.5
47	A	15	NA	1xdd 420mg	<sup>a</sup>	dhi	59.3
48	A	22	NA	1xdd 420mg	<sup>a</sup>	dhi	<LLOQ
49	A	5	0.5	1xdd 420mg	abs	igsh	<LLOQ
50	A	3	0.8	1xdd 560mg	abs	igsh	0.5
51	A	21	0.8	1xdd 420mg	abs	igsh	<LLOQ
52	A	6	0.8	1xdd 420mg	abs	igsh	<LLOQ
53	A	18	1.2	1xdd 420mg	abs	igsh	<LLOQ
54	A	2	1.4	1xdd 420mg	abs	igsh	<LLOQ
55	A	16	1.5	1xdd 420mg	abs	igsh	<LLOQ
56	B	12	2.4	1xdd 560mg	max	igsh	0.8
57	A	13	2.5	1xdd 420mg	max	igsh	1.5
58	B	4	2.8	1xdd 560mg	max	igsh	3.5
59	B	1	3.3	1xdd 560mg	max	igsh	2.6
60	A	14	3.8	1xdd 420mg	max	igsh	0.5
61	B	20	3.8	1xdd 560mg	max	igsh	0.8
62	B	17	3.9	1xdd 560mg	max	igsh	1.9
63	B	23	4.1	1xdd 560mg	max	igsh	2.2
64	B	7	4.1	1xdd 560mg	max	igsh	1.5
65	B	24	4.4	1xdd 560mg	max	igsh	1.4
66	B	9	4.4	1xdd 560mg	max	igsh	0.8
67	A	10	22.2	1xdd 420mg	trough	igsh	<LLOQ
68	A	11	22.6	1xdd 420mg	trough	igsh	<LLOQ
69	A	8	22.7	1xdd 420mg	trough	igsh	<LLOQ
70	A	19	23.3	1xdd 420mg	trough	igsh	<LLOQ
71	A	15	NA	1xdd 420mg	<sup>a</sup>	igsh	<LLOQ
72	A	22	NA	1xdd 420mg	<sup>a</sup>	igsh	<LLOQ
73	A	5	0.5	1xdd 420mg	abs	icgs	5.4
74	A	3	0.8	1xdd 560mg	abs	icgs	9.7
75	A	21	0.8	1xdd 420mg	abs	icgs	11.9
76	A	6	0.8	1xdd 420mg	abs	icgs	7.3
77	A	18	1.2	1xdd 420mg	abs	icgs	11.1
78	A	2	1.4	1xdd 420mg	abs	icgs	6.7
79	A	16	1.5	1xdd 420mg	abs	icgs	2.2
80	B	12	2.4	1xdd 560mg	max	icgs	73.2
81	A	13	2.5	1xdd 420mg	max	icgs	412.5

82	B	4	2.8	1xdd 560mg	max	icgs	159.9
83	B	1	3.3	1xdd 560mg	max	icgs	97.1
84	A	14	3.8	1xdd 420mg	max	icgs	72.5
85	B	20	3.8	1xdd 560mg	max	icgs	78.0
86	B	17	3.9	1xdd 560mg	max	icgs	226.1
87	B	23	4.1	1xdd 560mg	max	icgs	238.6
88	B	7	4.1	1xdd 560mg	max	icgs	190.9
89	B	24	4.4	1xdd 560mg	max	icgs	160.2
90	B	9	4.4	1xdd 560mg	max	icgs	88.1
91	A	10	22.2	1xdd 420mg	trough	icgs	3.7
92	A	11	22.6	1xdd 420mg	trough	icgs	3.0
93	A	8	22.7	1xdd 420mg	trough	icgs	5.6
94	A	19	23.3	1xdd 420mg	trough	icgs	0.6
95	A	15	NA	1xdd 420mg	<sup>a</sup>	icgs	5.1
96	A	22	NA	1xdd 420mg	<sup>a</sup>	icgs	<LLOQ
97	A	5	0.5	1xdd 420mg	abs	icys	5.1
98	A	3	0.8	1xdd 560mg	abs	icys	3.9
99	A	21	0.8	1xdd 420mg	abs	icys	12
100	A	6	0.8	1xdd 420mg	abs	icys	5.6
101	A	18	1.2	1xdd 420mg	abs	icys	9.9
102	A	2	1.4	1xdd 420mg	abs	icys	5.0
103	A	16	1.5	1xdd 420mg	abs	icys	2.3
104	B	12	2.4	1xdd 560mg	max	icys	209.5
105	A	13	2.5	1xdd 420mg	max	icys	185.8
106	B	4	2.8	1xdd 560mg	max	icys	92.8
107	B	1	3.3	1xdd 560mg	max	icys	77.1
108	A	14	3.8	1xdd 420mg	max	icys	32.1
109	B	20	3.8	1xdd 560mg	max	icys	78.7
110	B	17	3.9	1xdd 560mg	max	icys	143.4
111	B	23	4.1	1xdd 560mg	max	icys	194.3
112	B	7	4.1	1xdd 560mg	max	icys	170.3
113	B	24	4.4	1xdd 560mg	max	icys	210.5
114	B	9	4.4	1xdd 560mg	max	icys	89.2
115	A	10	22.2	1xdd 420mg	trough	icys	5.0
116	A	11	22.6	1xdd 420mg	trough	icys	4.7
117	A	8	22.7	1xdd 420mg	trough	icys	6.4
118	A	19	23.3	1xdd 420mg	trough	icys	2.6
119	A	15	NA	1xdd 420mg	<sup>a</sup>	icys	12.1
120	A	22	NA	1xdd 420mg	<sup>a</sup>	icys	< LLOQ

---

<sup>a</sup> omitted (no group)

**Supplemental Table 2:** Concomitant drugs for the 73 yr. old patient receiving a lowered dose due to co-administration of a potent CYP3A4-inhibitor.

Drug	DD	Dose	Route	Inhibits	Metabolism
Clemastine	2	1 mg	IV	CYP2D6	-
Cyanocobalamin	1	6 mg	n.g.	-	-
Enteral feeding	continuous	-	n.g.	-	-
Furosemide	continuous	2 mg/h	IV	-	-
Glucose 5%	continuous	42 ml/h	IV	-	-
Haloperidol	1	1 mg	IV	CYP2D6	<b>CYP3A4</b>
Ibrutinib	1	140 mg	n.g.	-	<b>CYP3A4,</b> 2D6
Macrogol	2	2 sachets	n.g.	-	-
Magnesium sulphate	1	15 mg	n.g.	-	-
Metoclopramide	3	10 mg	IV	-	<i>CYP2D6</i>
Midazolam	continuous	10 mg/h	IV	-	<b>CYP3A4</b>
Monosodium phosphate	continuous	2 mmol/h	IV	-	-
Nadroparin	1	2850 IE	SC	-	-
Parenteral nutrition	continuous	84 ml	IV	-	-
Propofol	continuous	100 mg/h	IV	-	-
Salbutamol/ipratropium 1/0,2mg/ml	1-2	2.5 ml	IH	-	-
Sufentanil	continuous	10 µg/h	IV	-	<i>CYP3A4</i>
Tobramycin/colistin/ amphotericin B oral paste	4	1 g	Oral	-	-
Tobramycin/colistin/ amphotericin B oral suspension	4	10 mL	n.g.	-	-
Voriconazole	2	340 mg	IV (1h)	<u>CYP3A4,</u> CYP2C9, CYP2C19	<b>CYP3A4,</b> <b>CYP2C9,</b> <b>CYP2C19</b>

DD: number of daily doses, IH: inhaled (after nebulizing), IV: intravenous, n.g.: nasogastric tube, SC: sub-cutaneous, **BOLD**: relevant interaction by strong inhibitors of that enzyme\*, *italicized*: deemed not-relevant\* Underlined: relevant for ibrutinib. (\* Relevance as evaluated by the Royal Dutch Pharmacists Association (kennisbank.knmp.nl, visited 17-06-2018)).