SUPPLEMENTARY MATERIAL FOR *EUROPEAN JOURNAL OF DRUG METABOLISM AND PHARMACOKINETICS*

Assessment of the effects of inhibition or induction of CYP2C19 and CYP2C9 enzymes, or inhibition of OAT3, on the pharmacokinetics of abrocitinib and its metabolites in healthy individuals

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Pharmacokinetic Sampling

Blood samples for pharmacokinetic analysis were collected into appropriately labeled tubes containing dipotassium ethylenediaminetetraacetic acid. Each blood collection tube was gently inverted 8-10 times to completely mix the blood. The blood sample was centrifuged as soon as possible for about 10 minutes at approximately 1700 ×*g* in a refrigerated centrifuge at 4°C to harvest the plasma. Using a new disposable transfer pipette for each time point, plasma was transferred into prelabeled storage tubes that were stored at approximately −20°C or below within 60 minutes of collection. Samples were shipped on dry ice to the analytical laboratory.

In study NCT03634345, blood samples (3 mL) were collected to provide a minimum of 1 mL of plasma. For the fluvoxamine cohort, blood samples were collected at pre-dose (within 15 min prior to abrocitinib dosing), 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours (only occurred if patients were discharged after completion of Period 1) post-dose on Period 1 Day 1, and pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, and 48 hours post-dose on Period 2 Day 8. For the fluconazole cohort, blood samples were collected at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36 and 48 hours (only occurred if patients were discharged after completion of Period 1), post-dose on Period 1 Day 1, and pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 hours post-dose on Period 2 Day 5.

In study NCT03637790 (rifampin study), blood samples (6 mL) were collected to provide approximately 2.5 mL of plasma. Blood samples were collected at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours post-dose on Period 1 Day 1 and Period 2 Day 8.

In study NCT03937258 (probenecid study), blood samples (10 mL) were collected to provide approximately 4 mL of plasma. Blood samples were collected pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 36, and 48 hours after dosing on Period 1 Day 1, Period 2 Day 4, and Period 3 Day 2.

Table S1. Summary of subject metabolizer status

	Fluvoxamine cohort (*N* = 12)	Fluconazole cohort (*N* = 12)	Rifampin study (*N* = 12)	Probenecid study (*N* = 12)
CYP2C19 metabolizer status, *n*				
Ultra-rapid metabolizer	1	1	0	0
Rapid metabolizer	2	2	2	4
Extensive metabolizer	5	4	7	5
Intermediate metabolizer	4	5	2	3
Poor metabolizer	0	0	1	0
CYP2C9 metabolizer status, *n*				
Rapid metabolizer	0	0	0	0
Extensive metabolizer	9	7	7	10
Intermediate metabolizer	3	4	5	2
Poor metabolizer	0	1	0	0

Table S2. Summary of pharmacokinetics parameters for abrocitinib parent drug and active moiety in the presence and absence of fluvoxamine

	Abrocitinib 100 mg single dose (*N* = 12)	**Abrocitinib 100 mg single dose + fluvoxamine 50 mg QD (*N* = 12)**	**Abrocitinib 100 mg single dose (*N* = 12)**	**Abrocitinib 100 mg single dose + fluvoxamine 50 mg QD (*N* = 12)**
	Total abrocitinib pharmacokinetics		**Unbound active moiety pharmacokinetics**	
AUC_{inf}, ng·h/mL	1578 (21)	4343 (30)	3500 (10)	6703 (24)
AUC_{last}, ng·h/mL	1551 (21)	4308 (30)	3313 (11)	6374 (25)
C_{max}, ng/mL	420.2 (50)	775.0 (48)	807.4 (43)	1074 (48)
T_{max}, h	1.00 (0.500–2.02)	0.750 (0.5003.00)–		
$t_{1/2}$, h	4.332 ± 2.7930	5.181 ± 2.2197		
CL/F, mL/min	63.41 (21)	23.03 (30)		
V_z/F, L	323.3 (70)	156.7 (54)		

Data are expressed as geometric mean (geometric % coefficient of variation) for all except T_{max} and $t_{1/2}$. T_{max} is median (range) and $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; QD, once daily; T_{max}, time for C_{max}; $t_{1/2}$, terminal plasma half-life; V_Z/F, apparent volume of distribution following oral administration.

N = Total number of participants in the treatment group in the indicated population.

Table S3. Summary of pharmacokinetics parameters for abrocitinib parent drug and active moiety in the presence and absence of fluconazole

	Abrocitinib 100 mg single dose (*N* = 12)	**Abrocitinib 100 mg single dose + fluconazole 200 mg QD (*N* = 12)**	**Abrocitinib 100 mg single dose (*N* = 12)**	**Abrocitinib 100 mg single dose + fluconazole 200 mg QD (*N* = 12)**
	Total abrocitinib pharmacokinetics		**Unbound active moiety pharmacokinetics**	
AUC_{inf}, ng·h/mL	1549 (75)	7482 (36)	3359 (41)	7959 (-)
AUC_{last}, ng·h/mL	1537 (75)	7453 (36)	3244 (42)	8879 (33)
C_{max}, ng/mL	519.8 (79)	998.5 (38)	960.3 (54)	1186 (36)
T_{max}, h	0.525 (0.500–2.02)	1.00 (0.500–2.00)		
$t_{1/2}$, h	3.094 ± 1.3542	6.142 ± 1.1937		
CL/F, mL/min	64.53 (75)	13.36 (35)		
V_z/F, L	263.7 (57)	116.6 (29)		

Data are expressed as geometric mean (geometric % coefficient of variation) for all except T_{max} and $t_{1/2}$. T_{max} is median (range) and $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; QD, once daily; T_{max}, time for C_{max}; $t_{1/2}$, terminal plasma half-life; V_Z/F, apparent volume of distribution following oral administration**.**

N = Total number of participants in the treatment group in the indicated population.

Table S4. Summary of pharmacokinetics parameters for abrocitinib parent drug and active moiety in the presence and absence of rifampin

	Abrocitinib 200 mg single dose (*N* = 12, *n* = 10)	**Abrocitinib 200 mg single dose + Rifampin 600 mg QD (*N* = 12, *n* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12, *n* = 10)**	**Abrocitinib 200 mg single dose + Rifampin 600 mg QD (*N* = 12, *n* = 12)**
	Total abrocitinib pharmacokinetics		**Unbound active moiety pharmacokinetics**	
AUC_{inf}, ng·h/mL	3883 (44)	468.7 (82)	7829 (22)	3374 (22)
AUC_{last}, ng·h/mL	3593 (48)	462.2 (82)	7311 (30)	3291 (23)
C_{max}, ng/mL	934.5 (72)	194.9 (92)	1621 (67)	1117 (44)
T_{max}, h	0.750 (0.500–2.10)	1.00 (0.500–1.00)		
$t_{1/2}$, h	4.270 ± 2.7210	2.144 ± 1.4279		
CL/F, L/hr	51.50 (44)	426.6 (82)		
V_z/F, L	270.3 (81)	1127 (90)		

Data are expressed as geometric mean (geometric % coefficient of variation) for all except T_{max} and $t_{1/2}$. T_{max} is median (range) and $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; QD, once daily; T_{max}, time for C_{max}; $t_{1/2}$, terminal plasma half-life; V_Z/F, apparent volume of distribution following oral administration.

N = Total number of participants in the treatment group in the indicated population.

n = Total number of participants contributing to the summary statistics for $t_{1/2}$, AUCinf, CL/F and Vz/F.

Table S5. Summary of pharmacokinetics parameters for abrocitinib parent drug and active moiety in the presence and absence of probenecid

	Abrocitinib 200 mg single dose (*N* = 12)	**Abrocitinib 200 mg single dose + Probenecid 1000 mg BID (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg single dose + Probenecid 1000 mg BID (*N* = 12)**
	Total abrocitinib pharmacokinetics		**Unbound active moiety pharmacokinetics**	
AUC_{inf}, ng·h/mL	3902 (26)	4020 (69)	7968 (16)	11390 (40)
AUC_{last}, ng·h/mL	3189 (57)	4003 (69)	6739 (35)	11120 (41)
C_{max}, ng/mL	756.5 (60)	918.2 (64)	1410 (56)	1835 (44)
T_{max}, h	1.00 (0.500–4.00)	2.00 (0.500–4.00)		
$t_{1/2}$, h	5.907 ± 3.0829	4.339 ± 2.6190		
CL/F, L/hr	51.24 (26)	49.75 (69)		
V_z/F, L	375.2 (62)	261.3 (87)		

Data are expressed as geometric mean (geometric % coefficient of variation) for all except T_{max} and $t_{1/2}$. T_{max} is median (range) and $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; CL/F, apparent oral clearance; C_{max}, maximum observed plasma concentration; QD, once daily; T_{max}, time for C_{max}; $t_{1/2}$, terminal plasma half-life; V_Z/F, apparent volume of distribution following oral administration.

Table S6. Influence of fluvoxamine on the pharmacokinetics of abrocitinib metabolites M1, M2, and M4

	Abrocitinib 100 mg single dose (*N* = 12)	**Abrocitinib 100 mg single dose + fluvoxamine 200 mg QD (*N* = 12)**	**Abrocitinib 100 mg single dose (*N* = 12)**	**Abrocitinib 100 mg single dose + fluvoxamine200 mg QD (*N* = 12)**	**Abrocitinib 100 mg single dose (*N* = 12)**	**Abrocitinib 100 mg single dose + fluvoxamine 200 mg QD (*N* = 12)**
	M1		**M2**		**M4**	
AUC_{inf}, ng·h/mL	565.6 (19)	452.0 (28)	532.9 (17)	630.8 (19)	807.3 (20)	1080 (25)
AUC_{last}, ng·h/mL	548.2 (19)	420.4 (29)	482.0 (20)	511.5 (23)	793.7 (21)	1060 (26)
C_{max}, ng/mL	138.6 (49)	57.68 (76)	95.83 (47)	68.32 (47)	147.4 (47)	131.3 (50)
$t_{1/2}$, h	4.348 ± 2.7452	5.739 ± 2.4642	2.862 ± 0.55279	4.776 ± 2.4429	4.748 ± 2.4240	6.161 ± 2.6169

Data are expressed as geometric mean (geometric % coefficient of variation) for all except $t_{1/2}$. $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; QD, once daily; $t_{1/2}$, terminal plasma half-life.

Table S7. Influence of fluconazole on the pharmacokinetics of abrocitinib metabolites M1, M2, and M4

	Abrocitinib 100 mg single dose (*N* = 12)	**Abrocitinib 100 mg single dose + fluconazole 200 mg QD (*N* = 12)**	**Abrocitinib 100 mg single dose (*N* = 12)**	**Abrocitinib 100 mg single dose + fluconazole 200 mg QD (*N* = 12)**	**Abrocitinib 100 mg single dose (*N* = 12)**	**Abrocitinib 100 mg single dose + fluconazole 200 mg QD (*N* = 12)**
	M1		**M2**		**M4**	
AUC_{inf}, ng·h/mL	481.7 (21)	135.8 (31)	468.0 (24)	289.0 (-)[a]	713.9 (40)	1385 (26)
AUC_{last}, ng·h/mL	467.6 (21)	91.84 (45)	428.6 (26)	177.0 (49)	695.1 (41)	1368 (27)
C_{max}, ng/mL	144.5 (49)	13.73 (47)	99.77 (41)	23.77 (50)	161.7 (51)	128.7 (40)
$t_{1/2}$, h	3.100 ± 1.1892	5.792 ± 1.9266	2.790 ± 0.54413	4.630[a]	3.551 ± 1.2132	6.867 ± 1.1639

Data are expressed as geometric mean (% coefficient of variation) for all except $t_{1/2}$. $t_{1/2}$ is arithmetic mean ± standard deviation. [a]$n = 1$ for these $t_{1/2}$ and AUC_{inf} calculations. AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; QD, once daily; $t_{1/2}$, terminal plasma half-life.

Table S8. Influence of rifampin on the pharmacokinetics of abrocitinib metabolites M1, M2, and M4

	Abrocitinib 200 mg single dose (*N* = 12)	**Abrocitinib 200 mg single dose + Rifampin 600 mg QD (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg single dose + Rifampin 600 mg QD (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg single dose + Rifampin 600 mg QD (*N* = 12)**
	M1		**M2**		**M4**	
AUC_{inf}, ng·h/mL	824.9 (45)	810.1 (43)	1207 (16)	872.3 (16)	2048 (29)	864.8 (38)
AUC_{last}, ng·h/mL	810.2 (44)	800.2 (43)	1044 (29)	842.9 (18)	1760 (35)	854.8 (38)
C_{max}, ng/mL	194.0 (82)	326.6 (71)	171.1 (73)	248.9 (43)	306.7 (77)	265.6 (49)
$t_{1/2}$, h	4.202 ± 2.5635	2.984 ±1.5784	4.332 ± 3.2071	2.633 ± 1.5052	4.451 ± 2.1802	2.908 ± 1.5808

Data are expressed as geometric mean (geometric % coefficient of variation) for all except $t_{1/2}$. $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; QD, once daily; $t_{1/2}$, terminal plasma half-life.

Table S9. Influence of probenecid on the pharmacokinetics of abrocitinib metabolites M1, M2, and M4

	Abrocitinib 200 mg single dose (*N* = 12)	**Abrocitinib 200 mg single dose + Probenecid 1000 mg BID (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg single dose + Probenecid 1000 mg BID (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg single dose + Probenecid 1000 mg BID (*N* = 12)**
	M1		**M2**		**M4**	
AUC_{inf}, ng·h/mL	998.5 (48)	1742 (42)	1197 (23)	2157 (42)	2042 (14)	3756 (47)
AUC_{last}, ng·h/mL	978.9 (40)	1712 (43)	948.5 (36)	2050 (45)	1719 (40)	3709 (48)
C_{max}, ng/mL	210.2 (86)	287.3 (57)	162.1 (65)	218.2 (50)	287.8 (60)	416.8 (51)
$t_{1/2}$, h	4.153 ± 2.6427	6.011 ± 3.4644	3.899 ± 2.2215	7.007 ± 3.1531	4.953 ± 2.4198	6.928 ± 2.3519

Data are expressed as geometric mean (geometric % coefficient of variation) for all except t_{max} and $t_{1/2}$. t_{max} is median (range) and $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; AUC_{last}, area under the concentration-time curve from time 0 to the time of last quantifiable concentration; C_{max}, maximum observed plasma concentration; QD, once daily; $t_{1/2}$, terminal plasma half-life, t_{max}, time to C_{max}.

Table S10. Ratio of the unadjusted geometric means for abrocitinib metabolites M1, M2, M4 to parent drug for C_{max} in the presence of fluvoxamine, fluconazole, rifampin, and probenecid

	M1/parent			M2/parent			M4/parent		
	Ref	**Test**	**Test/Ref**	**Ref**	**Test**	**Test/Ref**	**Ref**	**Test**	**Test/Ref**
Effect of fluvoxamine	0.3142	0.07092	0.2257	0.2173	0.08402	0.3868	0.3344	0.1614	0.4828
Effect of fluconazole	0.2649	0.01309	0.04941	0.1829	0.02268	0.1240	0.2962	0.1228	0.4144
Effect of rifampin	0.1978	1.597	8.074	0.1744	1.217	6.977	0.3128	1.299	4.153
Effect of probenecid	0.2650	0.2981	1.125	0.2041	0.2264	1.109	0.3626	0.4323	1.192

Ref represents the reference value for a single dose of abrocitinib. Test represents a single dose of abrocitinib in the presence of fluvoxamine, fluconazole, rifampin, or probenecid.

Table S11. Ratio of the unadjusted geometric means for abrocitinib metabolites M1, M2, M4 to parent drug for AUC_{inf} in the presence of fluvoxamine, fluconazole, rifampin, and probenecid

	M1/parent			M2/parent			M4/parent		
	Ref	**Test**	**Test/Ref**	**Ref**	**Test**	**Test/Ref**	**Ref**	**Test**	**Test/Ref**
Effect of fluvoxamine	0.3419	0.09643	0.2820	0.3173	0.1389	0.4379	0.4880	0.2370	0.4857
Effect of fluconazole	0.2961	0.01755	0.05927	0.2878	0.04270	0.1484	0.4388	0.1764	0.4019
Effect of rifampin	0.2025	1.648	8.137	0.3132	1.773	5.660	0.5279	1.759	3.332
Effect of probenecid	0.2435	0.4129	1.695	0.2992	0.5114	1.709	0.5052	0.8904	1.763

Ref represents the reference value for a single dose of abrocitinib. Test represents a single dose of abrocitinib in the presence of fluvoxamine, fluconazole, rifampin, or probenecid.

Table S12. Summary of pharmacokinetics parameters for abrocitinib parent drug, metabolites M1, M2, and M4, and active moiety with single or multiple dosing of abrocitinib

	Abrocitinib 200 mg single dose (*N* = 12)	**Abrocitinib 200 mg once daily dose (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg once daily dose (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg once daily dose (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg once daily dose (*N* = 12)**	**Abrocitinib 200 mg single dose (*N* = 12)**	**Abrocitinib 200 mg once daily dose (*N* = 12)**
	Parent drug		**M1**		**M2**		**M4**		**Active moiety**	
AUC_{tau}, ng·h/mL	3092 (55)	4752 (57)	956.3 (43)	869.1 (42)	968.3 (38)	1020 (30)	1644 (40)	2171 (32)	6634 (35)	8693 (35)
C_{max}, ng/mL	756.5 (60)	1184 (44)	210.2 (86)	193.7 (60)	162.1 (65)	166.9 (44)	287.8 (60)	386.7 (29)	1410 (56)	1927 (28)
T_{max}, h	1.00 (0.500–4.00)	1.50 (0.500–3.00)	1.00 (0.500–4.00)	1.50 (0.500–3.00)	2.00 (0.500–4.00)	2.00 (0.500–4.00)	2.00 (0.500–4.00)	2.00 (0.500–3.00)	-	-
$t_{1/2}$, h	5.907 ± 3.0829	5.958 ± 4.4495	4.153 ± 2.6427	6.265 ± 4.6527	3.899 ± 2.2215	4.556 ± 2.1682	4.953 ± 2.4198	5.827 ± 2.5947	-	-
R_{ac}	-	1.537 (22)	-	0.9094 (14)	-	1.053 (15)	-	1.322 (17)	-	1.165 (12)
$R_{ac,Cmax}$	-	1.565 (46)	-	0.9212 (33)	-	1.030 (34)	-	1.342 (36)	-	1.309 (19)
R_{ss}	-	1.468 (20)	-	0.8513 (13)	-	0.9911 (16)	-	1.183 (12)	-	1.367 (43)

Data are expressed as geometric mean (geometric % coefficient of variation) for all except T_{max} and $t_{1/2}$. T_{max} is median (range) and $t_{1/2}$ is arithmetic mean ± standard deviation.

AUC_{tau}, area under the concentration-time curve from time 0 to time tau (24 hours for QD dosing); C_{max}, maximum observed plasma concentration; QD, once daily; R_{ac}, observed accumulation ratio; $R_{ac,Cmax}$, observed accumulation ratio for C_{max}; R_{ss}, observed steady-state accumulation ratio; $t_{1/2}$, terminal plasma half-life, T_{max}, time to C_{max}.

Table S13. Ratio of the unadjusted geometric means for abrocitinib metabolites M1, M2, M4 to parent drug for C_{max} and AUC_{tau} with single or multiple dosing of abrocitinib

	M1/parent			M2/parent			M4/parent		
	Ref	**Test**	**Test/Ref**	**Ref**	**Test**	**Test/Ref**	**Ref**	**Test**	**Test/Ref**
C_{max}	0.2650	0.1558	0.5879	0.2041	0.1344	0.6583	0.3626	0.3113	0.8585
AUC_{tau}	0.2945	0.1744	0.5921	0.2984	0.2046	0.6856	0.5062	0.4356	0.8605

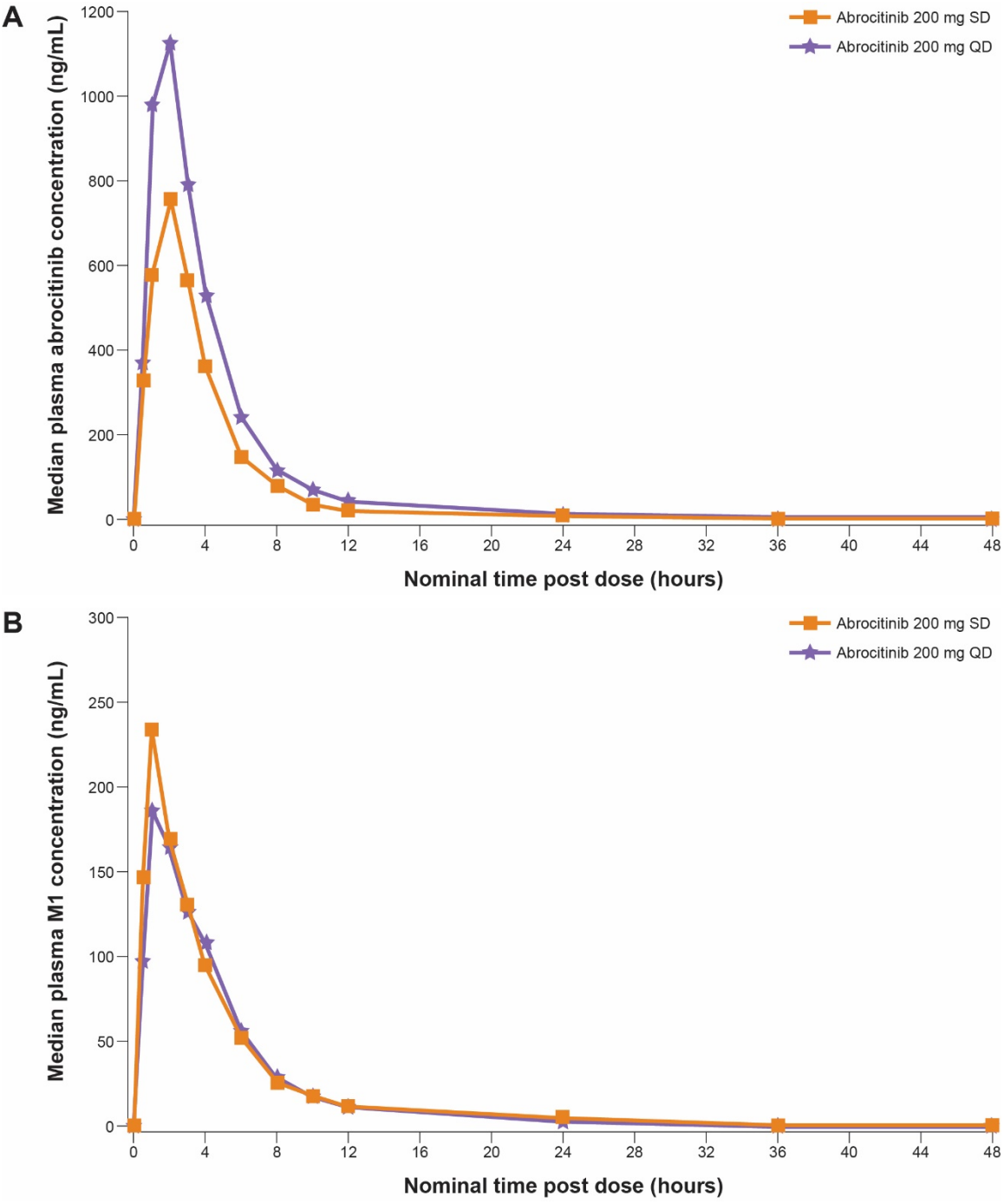
Ref represents the reference value for a single dose of abrocitinib 200 mg. Test represents a daily dose of abrocitinib 200 mg.

AUC_{tau}, area under the concentration-time curve from time 0 to time tau (24 hours for QD dosing); C_{max}, maximum observed plasma concentration

Figure legend

Figure S1. Median plasma concentration-time curves for abrocitinib parent drug (**A**) and metabolites M1 (**B**), M2 (**C**), and M4 (**D**) with single and multiple dosing of abrocitinib. QD, once daily [multiple dosing]; SD, single dose.

Figure S1


A
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600
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200
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0
4
8
12
16
20
24
28
32
36
40
44
48
Nominal time post dose (hours)
Abrocitinib 200 mg SD
Abrocitinib 200 mg QD
B
Median plasma M1 concentration (ng/mL)
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200
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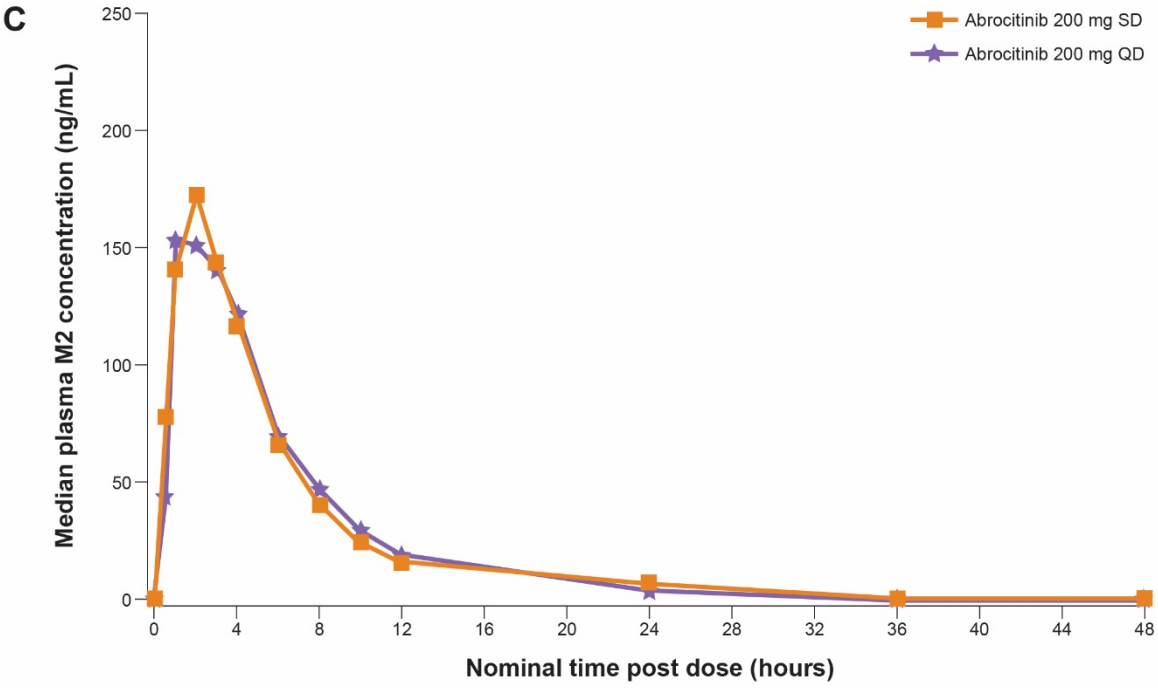
100
50
0
Nominal time post dose (hours)
Abrocitinib 200 mg SD
Abrocitinib 200 mg QD


C
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Abrocitinib 200 mg QD
Median plasma M2 concentration (ng/mL)
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200
150
100
50
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0
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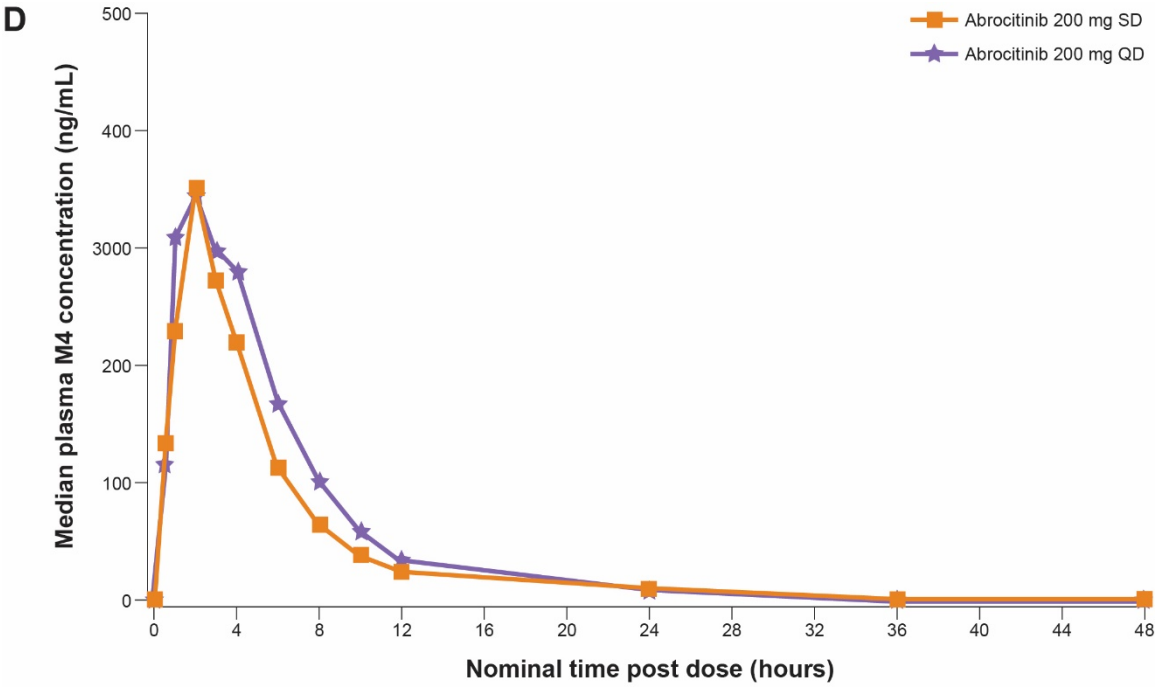
8
12
16
20
24
28
32
36
40
44
48
Nominal time post dose (hours)


D
Abrocitinib 200 mg SD
Abrocitinib 200 mg QD
Median plasma M4 concentration (ng/mL)
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400
3000
200
100
0
0
4
8
12
16
20
24
28
32
36
40
44
48
Nominal time post dose (hours)