2.6.5.4 薬物動態試験：反復投与後の吸収

Test Article: Upadacitinib (A-1293543; ABT-494)

2.6.7.2「トキシコキネティクス試験の一覧表」及び 2.6.7.3「トキシコキネティクス試験成績の一覧」を参照

2.6.5.5 薬物動態試験：組織分布 **Test Article:** Upadacitinib (A-1293543; ABT-494)

Study No. R&D/14/1115

Species: Long Evans (pigmented) rats
Gender (M/F)/Number of Animals: M/10 (1/timepoint)
Feeding Condition: fasted
Vehicle/Formulation: Solution in ethanol, PEG-400 and 5% dextrose in water (10: 40: 50, by volume); 1 mL/kg
Method of Administration: oral gavage
Dose (mg/kg): 5 (~100 µCi/kg)
Radionuclide: [^{14}C]A-1293543 **Assay:** QWBA
Specific Activity: 50.2 mCi/mmol (lot [redacted])
Sampling Time: 0.5, 1, 2, 4, 8, 24, 48, 96, 168, 192 hr

	Concentration (ng-eq/g)									
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**24 hr**	**48 hr**	**96 hr**	**168 hr**	**192 hr**
Adrenal gland(s)	22200[a]	19500	11100	6530[a]	2410	BLQ	ND	ND	ND	ND
Arterial wall	3110	2580	1110	518	118	84.8	71.1	88.8	96.1	65.5
Bile	38100	31600	10000	ND	ND	ND	ND	ND	ND	ND
Blood	1560	905	410	189	BLQ	ND	ND	ND	ND	ND
Bone	202	90.7	BLQ	ND	ND	ND	ND	ND	ND	ND
Bone marrow	1310	658	328	159	BLQ	ND	ND	ND	ND	ND
Brain cerebellum	BLQ	BLQ	ND	ND	ND	ND	ND	ND	ND	ND
Brain cerebrum	BLQ	BLQ	ND	ND	ND	ND	ND	ND	ND	ND
Brain choroid plexus	747	628	261	ND	ND	ND	ND	ND	ND	ND
Brain medulla	BLQ	BLQ	ND	ND	ND	ND	ND	ND	ND	ND
Brain olfactory lobe	BLQ	BLQ	ND	ND	ND	ND	ND	ND	ND	ND
Bulbo-urethral gland	2030	1040	481	160	BLQ	ND	ND	ND	ND	ND
Cecum	1380	889	467	277	ND[b]	52.2	ND	ND	ND	ND

All footnotes are located at the end of the table; table continues on next page…

2.6.5.5 薬物動態試験：組織分布（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/14/1115

	Concentration (ng-eq/g)									
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**24 hr**	**48 hr**	**96 hr**	**168 hr**	**192 hr**
Diaphragm	1830	1000	392	270	BLQ	ND	ND	ND	ND	ND
Epididymis	755[a]	619	375	225	ND	ND	ND	ND	ND	ND
Esophagus	1810	870	401	211	BLQ	ND	ND	ND	ND	ND
Exorbital lacrimal gland	1920	1180	512	199	BLQ	ND	ND	ND	ND	ND
Eye lens	BLQ	BLQ	ND	ND	ND	ND	ND	ND	ND	ND
Eye uveal tract	3500	4210	3300	4710	3420	2470	765	544	218	214
Eye vitreous humor	58.5	88.4	BLQ	BLQ	ND	ND	ND	ND	ND	ND
Eye(s)	399	495	351	637	413	240	94.2	BLQ	BLQ	BLQ
Fat (abdominal)	232	145	BLQ	ND	ND	ND	ND	ND	ND	ND
Fat (brown)	1280	763	267	105	ND	ND	ND	ND	ND	ND
Harderian gland	2080	1570	510	243	BLQ	ND	ND	ND	ND	ND
Intervertebral disc(s)	4250	3070	1430	1080	145	125	137	151	160	136
Intra-orbital lacrimal gland	2060	1360	540	231	BLQ	ND	ND	ND	ND	ND
Kidney cortex	5990	3320	1380	710	164	91.5	71.2	54.5	65.5	BLQ
Kidney medulla	10700	5730	1950	1570	285	117	118	57.8	BLQ	BLQ
Kidney(s)	8740	4850	1730	1250	236	106	101	54.8	57.7	BLQ
Large intestine	2100	1660	943	528	111	156	BLQ	ND	ND	ND
Liver	15300	8810	4520	2480	656	290	232	100	140	BLQ
Lung(s)	1870	955	442	211	BLQ	ND	ND	ND	ND	ND
Lymph node(s)	1380	897	426	167	ND	ND	ND	ND	ND	ND
Muscle	1290	837	363	156	BLQ	ND	ND	ND	ND	ND
Myocardium	2020	1170	477	203	BLQ	ND	ND	ND	ND	ND

All footnotes are located at the end of the table; table continues on next page…

2.6.5.5 薬物動態試験：組織分布（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/14/1115

	Concentration (ng-eq/g)									
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**24 hr**	**48 hr**	**96 hr**	**168 hr**	**192 hr**
Nasal turbinates	444	284	150	117	ND	ND	ND	ND	ND	ND
Pancreas	2380	1240	487	222	52.8	BLQ	ND	ND	ND	ND
Pituitary gland	2000	1270	621	218	BLQ	ND	ND	ND	ND	ND
Preputial gland	1170[a]	630[a]	294[a]	222[a]	104	ND[a]	ND	ND	ND	ND
Prostate gland	1240	905	352	147	BLQ	ND	ND	ND	ND	ND
Salivary gland(s)	1960	1190	481	227	BLQ	ND	ND	ND	ND	ND
Seminal vesicle(s)	623	402	382	272	BLQ	ND	ND	ND	ND	ND
Skin (nonpigmented)	1270	1130	451	209	BLQ	ND	ND	ND	ND	ND
Skin (pigmented)	1300	1330	730	629	198	74.3	BLQ	ND	ND	ND
Small intestine	2290	1810	530	447	65.5	BLQ	ND	ND	ND	ND
Spinal cord	BLQ	BLQ	ND	ND	ND	ND	ND	ND	ND	ND
Spleen	1710	947	379	188	BLQ	ND	ND	ND	ND	ND
Stomach	1690	1340	444	363	BLQ	ND	ND	ND	ND	ND
Testis(es)	241	288	242	177	BLQ	ND	ND	ND	ND	ND
Thymus	1200	920	361	175	BLQ	ND	ND	ND	ND	ND
Thyroid	1730	1080	522	175	BLQ	ND	ND	ND	ND	ND
Urinary bladder	1130	ND[c]	ND[c]	ND[c]	70.1	BLQ	ND	ND	ND	ND
Urine	158000	166000	163000[d]	130000	1290	61.9	BLQ	ND	ND	ND

All footnotes are located at the end of the table; table continues on next page…

2.6.5.5 薬物動態試験：組織分布（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/14/1115

	Concentration (ng-eq/g)									
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**24 hr**	**48 hr**	**96 hr**	**168 hr**	**192 hr**
Blood‡	1320	740	417	167	42.2	8.00	5.78	4.63	BLQ	BLQ
Plasma‡	1420	774	433	129	25.1	7.52	BLQ	BLQ	BLQ	BLQ
Blood:Plasma Ratio	0.930	0.956	0.963	1.29	1.68	1.06	NA	NA	NA	NA

Additional Information: ‡Blood and plasma concentrations determined by liquid scintillation counting; NA – not applicable

BLQ below the limit of quantitation (< 51.9 ng-eq/g for tissues; 4.53 ng-eq/g in blood and 4.89 ng-eq/g in plasma)

ND Not Detectable (sample shape not discernible from background or surrounding tissue);

a. Tissue appeared to be fat soaked.

b. Tissue unable to be sampled due to flare from the gastrointestinal contents.

c. Tissue was unable to be sampled due to flare from urine.

d. Value may have been affected by smearing of gastrointestinal contents

2.6.5.6 薬物動態試験：血漿タンパク結合及び全血中分布

Test Article: Upadacitinib (A-1293543; ABT-494)

Study System: *In vitro*

Target Entity, Test System and Method: Equilibrium dialysis technique (mouse, rat, dog, monkey and human plasma)

	f_u (Mean [SD])						
Species	**0.1 µM**	**1 µM**	**3 µM**	**10 µM**	**30 µM**	**100 µM**	**Study No.**
Mouse	0.23 (0.01)	0.28 (0.13)	0.22 (0.01)	0.23 (0.01)	0.23 90.02)	0.26 (0.02)	
Rat	0.34 (0.02)	0.41 (0.14)	0.35 (0.02)	0.36 (0.02)	0.35 (0.02)	0.37 (0.02)	
Dog	0.50 (0.04)	0.69 (0.23)	0.55 (0.03)	0.51 (0.05)	0.49 (0.05)	0.41 (0.05)	R&D/17/0325
Monkey	0.33 (0.03)	0.47 (0.16)	0.46 (0.05)	0.47 (0.02)	0.40 (0.01)	0.46 (0.01)	
Human	0.41 (0.03)	0.48 (0.09)	0.48 (0.03)	0.46 (0.02)	0.45 (0.02)	0.43 (0.04)	
Blood-to-plasma concentration ratios in mouse, rat, dog, monkey and human whole blood	1 µM (0.381 µg/mL)		The mean A-1293543 blood-to-plasma concentration ratios averaged 0.99, 1.28, 1.18, 1.31 and 1.00 in mouse, rat, dog, monkey and human, respectively.				R&D/17/0325

Additional Information: 0.1, 1, 3, 10, 30 and 100 µM A-1293543 corresponds to 0.038, 0.381, 1.14, 3.81, 11.4 and 38.1 µg/mL, respectively.

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験

Test Article: Upadacitinib (A-1293543; ABT-494)
Study No. R&D/16/1391

Species: Sprague Dawley Rat
Gender (M/F)/Number of Animals: Pregnant female, time mated (Gestation Day 18) / 9 (1 per time point)
Feeding Condition: ad libitum
Vehicle/Formulation: Solution in ethanol, PEG-400 and 5% dextrose in water (10: 40: 50, by volume); 1 mL/kg
Method of Administration: Oral
Dose (mg/kg): 10 (~200 µCi/kg)
Radionuclide: [^{14}C]A-1293543 **Assay:** QWBA
Specific Activity: 43.05 mCi/mmol (lot [redacted])
Sampling Time: 0.5, 1, 2, 4, 8, 12, 24, 48, 72 hours post dose

	Concentration (ng-eq/g)								
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**	**48 hr**	**72 hr**
Adrenal gland	26900	9900	5750[a]	3340[a]	1360	1200	1900	ND	ND
Amniotic fluid	153	BLQ	ND	ND	ND	ND	ND	ND	ND
Amniotic sac	2760	737	1330	328	312	163	154	ND	ND
Arterial wall	3810	871	770	253	168	210	ND	ND	ND
Bile	33300	5630	10500	2000	895	ND	ND	ND	ND
Blood	2950	336	482	119	BLQ	ND	ND	ND	ND
Bone	226	BLQ	ND	ND	ND	ND	ND	ND	ND
Bone marrow	3080	327	509	82.8	BLQ	ND	ND	ND	ND
Brain cerebellum	136	BLQ	ND	ND	ND	ND	ND	ND	ND
Brain cerebrum	92.4	BLQ	ND	ND	ND	ND	ND	ND	ND

All footnotes are located at the end of the table; table continues on the next page…

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1391

Tissues/Organs	Concentration (ng-eq/g)								
	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr	72 hr
Brain choroid plexus	1050	124	248	ND	ND	ND	ND	ND	ND
Brain medulla	65.7	BLQ	ND	ND	ND	ND	ND	ND	ND
Brain olfactory lobe	112	BLQ	ND	ND	ND	ND	ND	ND	ND
Cecum	4290	NR	ND[b]	ND[b]	ND[b]	ND[b]	ND[b]	ND	ND
Diaphragm	4000	514	638	200	BLQ	ND	ND	ND	ND
Esophagus	2520	476	622	129	70.7	150	154	BLQ	ND
Exorbital lacrimal gland	3910	383	578	115	BLQ	ND	ND	ND	ND
Eye	218	76.9	BLQ	ND	ND	ND	ND	ND	ND
Eye lens	56.1	BLQ	ND	ND	ND	ND	ND	ND	ND
Eye uveal tract	1810	261	186	78.2	ND	ND	ND	ND	ND
Fat (abdominal)	231	BLQ	ND	ND	ND	ND	ND	ND	ND
Fat (brown)	2600	235	353	63.4	ND	ND	ND	ND	ND
Fat (subcutaneous)	254	BLQ	ND	ND	ND	ND	ND	ND	ND
Fetal blood	1260	357	365	120	ND	ND	ND	ND	ND
Fetal brain	307	BLQ	ND	ND	ND	ND	ND	ND	ND
Fetal eye	713	173	238	79.4	ND	ND	ND	ND	ND
Fetal gastrointestinal tract	1010	320	548	173	ND	ND	ND	ND	ND
Fetal heart	1180	235	404	117	ND	ND	ND	ND	ND
Fetal kidney	2160	293	443	109	ND	ND	ND	ND	ND
Fetal liver	2050	289	416	109	ND	ND	ND	ND	ND
Fetal lung	1410	224	294	73.9	ND	ND	ND	ND	ND
Fetal muscle	1930	299	423	157	ND	ND	ND	ND	ND
Fetal spinal cord	136	BLQ	64.3	BLQ	ND	ND	ND	ND	ND
Fetus	1780	248	323	100	BLQ	ND	ND	ND	ND

All footnotes are located at the end of the table; table continues on the next page…

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1391

Tissues/Organs	Concentration (ng-eq/g)								
	0.5 hr	1 hr	2 hr	4 hr	8 hr	12 hr	24 hr	48 hr	72 hr
Harderian gland	5520	665	780	154	BLQ	ND	ND	ND	ND
Intervertebral disc	4110	1270	768	474	277	388	212	130	ND
Intra-orbital lacrimal gland	2370	423	642	188	ND	ND	ND	ND	ND
Kidney	23100	1420	2630	494	344	290	214	227	138
Kidney cortex	18100	1420	2780	537	391	322	233	203	193
Kidney medulla	21400	1410	2330	433	191	228	170	BLQ	67.3
Large intestine	2990	451	432	133	165	168	61.0	ND	ND
Liver	16000	2660	4280	935	458	500	333	150	97.7
Lung	1770	382	625	133	BLQ	ND	ND	ND	ND
Lymph node(s)	2210	403	507	115	ND	ND	ND	ND	ND
Mammary gland	4210	1560	3180	2520	440	489	526	100	BLQ
Muscle	1600	317	396	79.6	BLQ	ND	ND	ND	ND
Myocardium	2900	473	750	133	BLQ	ND	ND	ND	ND
Nasal turbinates	647	118	168	75.2	BLQ	ND	ND	ND	ND
Ovary	2640[a]	616[a]	2150[a]	431[a]	112	145[a]	70.8[a]	ND	ND
Pancreas	3270	576	994	237	BLQ	71.1	BLQ	ND	ND
Pituitary gland	2480	393	638	152	BLQ	59.2	ND	ND	ND
Placenta	1420	291	441	90.8	BLQ	ND	ND	ND	ND
Preputial gland	2900	NR	521	300	177	108[a]	146	65.9	BLQ
Salivary gland	3060	470	780	ND	ND	ND	ND	ND	ND
Skin (non-pigmented)	1290	332	413	120	BLQ	ND	ND	ND	ND
Small intestine	2990	1490	812	NDb	170	116	153	ND	ND
Spinal cord	56.4	BLQ	ND	ND	ND	ND	ND	ND	ND
Spleen	2570	451	656	144	BLQ	65.4	ND	ND	ND

All footnotes are located at the end of the table; table continues on the next page…

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1391

	Concentration (ng-eq/g)								
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**	**48 hr**	**72 hr**
Stomach	3700	546	977	295	50.8	95.5	57.0	ND	ND
Thymus	2190	401	510	118	ND	ND	ND	ND	ND
Thyroid	2500	480	695	188	ND	ND	ND	ND	ND
Urinary bladder	1510	378	473	175	ND[c]	51.8[a]	76.6	ND	ND
Urine	240000	12400	29500	NR	1130	1850	1840	ND	ND
Uterus	1970	377	400	249	BLQ	73.0	BLQ	ND	ND
Blood‡	2290	404	516	145	50.0	51.5	34.7	5.48	BLQ
Plasma‡	2470	407	492	118	32.7	33.0	21.0	BLQ	BLQ
Blood:Plasma Ratio	0.928	0.994	1.05	1.23	1.53	1.56	1.65	NA	NA

BLQ Below the limit of quantitation (49.3 ng-eq/g for tissues, 4.93 ng-eq/g for blood and 4.46 ng-eq/g for plasma).

ND Not detectable (sample shape not discernible from background or surrounding tissue).

NR Not represented (tissue not present in section).

NA Not applicable

‡ Concentrations determined by liquid scintillation counting (LSC).

a Tissue appeared to be fat-soaked.

b Tissue not detectable due to flare from gastrointestinal contents.

c Tissue not detectable due to flare from urine.

2.6.5.7 薬物動態試験：妊娠又は授乳動物における試験（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1391

Species: Sprague-Dawley Rat
Gender (M/F)/Number of Animals: Lactating female / 27 (3 per time point; dosed 7–8 days after parturition)
Feeding Condition: ad libitum
Vehicle/Formulation: Solution in ethanol, PEG-400 and 5% dextrose in water (10: 40: 50, by volume); 1 mL/kg
Method of Administration: Oral
Dose (mg/kg): 10 (~200 µCi/kg)
Radionuclide: [^{14}C]A-1293543 **Assay:** QWBA (tissues) and LCS (total radioactivity; blood and plasma)
Specific Activity: 43.05 mCi/mmol (lot [redacted])
Sampling Time: 0.5, 1, 2, 4, 8, 12, 24, 48 and 72 hours post dose

	Mean Concentration (ng-eq/g; n = 3 per time point)									Pharmacokinetic Parameters				
Tissues/Organs	**0.5 hr**	**1 hr**	**2 hr**	**4 hr**	**8 hr**	**12 hr**	**24 hr**	**48 hr**	**72 hr**	**C_{max}**	**T_{max}**	**$t_{1/2}$**	**AUC_{0-t}**	**AUC_{0-inf}**
Blood	628	358	248	126	49.7	24.8	9.33	2.84	1.59	628	0.5	18.9	1990	2030
Plasma	658	348	226	92.5	29.5	15.4	3.80	BLQ	BLQ	657	0.5	5.5	1470	1500
Milk	5170	6880	6760	4510	2020	710	38.9	BLQ	BLQ	6880	1.0	2.8	45400	45500
Blood: plasma ratio	0.957	1.03	1.11	1.37	1.74	1.61	1.90	NA	NA					
Milk: plasma ratio	7.96	19.0	31.7	51.1	70.4	45.5	8.50	NA	NA					

Additional information: Units: C_{max} (ng-eq/g); T_{max} (hr); $t_{1/2}$ (hr); AUC (ng-eq•hr/g); NA: Not Applicable.

BLQ: below the limit of quantitation; the lower limits of quantitation for blood, plasma and milk were 6.93, 4.69 and 4.46 ng-eq/g, respectively.

2.6.5.8 薬物動態試験：その他の分布試験

Test Article: Upadacitinib (A-1293543; ABT-494)

その他の分布試験は実施していない。

2.6.5.9a 薬物動態試験：*In vivo* における代謝

Test Article: Upadacitinib (A-1293543; ABT-494)

Species	CByB6F1-Tg(HRAS)2Jic (Wild-type) Mouse	Sprague-Dawley Rat			Beagle Dog	Human
Gender/ Number of Animals	Male/Female 12/12	Male 3	Male 3	Female 3	Male 3	Male 4
Feeding condition	non-fasted	fasted	fasted	non-fasted	fasted	non-fasted
Vehicle/Formulation	(a)/suspension	(b)/solution	(b)/solution	(c)/solution	(c)/solution	(d)/solution
Method of Administration	PO	IV	PO	PO	PO	PO
Dose (mg/kg)	30	3	3	10	5	30 mg
Sample	plasma	plasma, urine, feces, bile		plasma, milk	plasma, urine, feces	
Radionucleotide	na	[^{14}C]A-1293543	[^{14}C]A-1293543	[^{14}C]A-1293543	[^{14}C]A-1293543	[^{14}C]A-1293543
Lot Number	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Specific Activity	na	0.0464 Ci/mmol	0.0464 Ci/mmol	0.04305 Ci/mmol	0.0502 Ci/mmol	3.62 µCi/mg
Assay	HPLC-MS/MS	HPLC-MS/MS and Radioassay				
Study Number	R&D/16/0480	R&D/12/255		R&D/16/1391 R&D/16/1392	R&D/15/0801	R&D/15/0180 R&D/15/0181

Additional Information:

(a) Suspension of A-1293543 in 0.2% HPMC

(b) A-1293543 was dissolved in a mixture of 10% ethanol, 40% propylene glycol and 50% D5W (5% dextrose in water)

(c) A-1293543 was dissolved in a mixture of 10% ethanol, 40% PEG-400 and 50% D5W (5% dextrose in water)

(d) A-1293543 was dissolved in water containing 0.11% sodium hydroxide (w/v) and 0.96% citric acid (w/v)

2.6.5.9b 薬物動態試験：*In vivo* における代謝－血漿中代謝物

Test Article: Upadacitinib (A-1293543; ABT-494)

	% Peak Area*	Percent of Radioactivity in AUC Pooled Plasma or Milk						
Species (Gender)	**CByB6F1-Tg(HRAS)2Jic (Wild-type) Mouse**	**Sprague-Dawley Rat (male)**			**Sprague-Dawley Rat (female)**		**Beagle Dog (male)**	**Human (male)**
Radionucleotide	na	[^{14}C]A-1293543			[^{14}C]A-1293543		[^{14}C]A-1293543	[^{14}C]A-1293543
Administration	PO	IV	IV	PO	PO		PO	PO
Sample	Plasma (M/F)	Plasma (1hr)	Plasma	Plasma	Plasma	Milk	Plasma	Plasma
A-1293543	81.2/77.5	82.6	87.7	84.8	82.8	96.7	87.7	79.4
M1	-	6.4	-	-	3.1	0.8	1.5	-
M2	-	3.0	-	-	1.6	0.6	5.3	-
M3	-	-	-	-	MS	-	-	-
M4	-	2.4	-	-	MS	-	0.9	13.4
M11	18.9/22.6	5.7	12.3	15.2	9.2	1.5	3.4	7.1
M21	-	-	-	-	-	-	1.2	-
M22	-	-	-	-	3.3	0.5	-	-
Study Number	R&D/16/0480	R&D/12/255			R&D/16/1392		R&D/15/0801	R&D/15/0181

Additional Information: - not detected; * estimated from MS peak areas; M/F (male/female); MS (detected by MS only)

2.6.5.9c 薬物動態試験：*In vivo* における代謝－排泄物中代謝物

Test Article: Upadacitinib (A-1293543; ABT-494)

	Recovery (% of Dose)									
Species	**Sprague-Dawley Rat (IV)**			**Sprague-Dawley Rat (PO)**			**Beagle Dog**		**Human**	
Sample	**Bile (0-6hr)**	**Urine (0-24hr)**	**Feces (0-24hr)**	**Bile (0-6hr)**	**Urine (0-24hr)**	**Feces (0-24hr)**	**Urine (0-24hr)**	**Feces (0-48hr)**	**Urine (0-48hr)**	**Feces (0-192hr)**
A-1293543	24.6	18.9	9.6	18.5	8.9	21.4	36.2	20.6	23.6	38.5
M1 (monooxidation)	2.1	1.1	0.1	4.9	0.3	2.9	1.5	2.6	-	0.0
M2 (monooxidation)	3.0	0.6	0.2	2.6	0.2	0.1	4.2	9.5	0.1	0.2
M3 (monooxidation + glucuronidation)	4.0	0.6	-	7.5	0.4	-	0.5	1.6	0.1	-
M4 (monooxidation + glucuronidation)	1.2	MS	-	1.5	0.2	-	MS	-	9.6	-
M6/M8 (dioxidation)*	-	-	-	-	-	-	-	-	2.6	-
M8 (dioxidation)	0.6	-	-	1.5	-	-	-	-	*	0.0
M10 (monooxidation)	3.5	MS	-	3.2	0.3	-	-	-	3.6	-
M11 (monooxidation + ring opening)	4.5	1.1	0.2	4.7	0.5	0.3	1.1	2.9	0.1	6.2
M12 (uncharacterized)	MS	1.2	-	MS	MS	-	-	-	-	-
M13 (uncharacterized)	1.5	MS	-	MS	MS	-	-	-	-	-
M19 (mono-oxidation + glucuronidation)	-	-	-	-	-	-	0.5	-	-	-
M20 (glucuronidation)	-	-	-	-	-	-	0.8	2.5	-	-
M21 (N-methylation)	-	-	-	-	-	-	0.2	1.6	-	-
M22 (monooxidation)	-	-	-	-	-	-	-	-	0.0	0.0
M23 (monooxidation)	-	-	-	-	-	-	-	-	-	0.0

Table continues on next page…

2.6.5.9c 薬物動態試験：*In vivo* における代謝－排泄物中代謝物（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

	Species	Recovery (% of Dose)									
		Sprague-Dawley Rat (IV)			Sprague-Dawley Rat (PO)			Beagle Dog		Human	
Sample		Bile (0-6hr)	Urine (0-24hr)	Feces (0-24hr)	Bile (0-6hr)	Urine (0-24hr)	Feces (0-24hr)	Urine (0-24hr)	Feces (0-48hr)	Urine (0-48hr)	Feces (0-192hr)
Unks		2.4	-	-	5.5	-	-	-	-	2.2	8.1
Unk1		-	-	-	-	-	-	-	4.8	-	-
Unk2		-	-	-	-	-	-	-	6.0	-	-
Unk3		-	-	-	-	-	-	-	1.0	-	-
Unk4		-	-	-	-	-	-	-	0.8	-	-
Study No.		R&D/12/255						R&D/15/0801		R&D/15/0181	

- not detected; MS: Detected by MS only; * M6 & M8 are co-eluting metabolites

2.6.5.10a 薬物動態試験：*In vitro* における代謝

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. 1293543-memo-06

Type of Study: *In vitro* metabolic stability of A-1293543 across species

Method: Metabolic stability in hepatocytes

Conditions: 1 µM substrate; 0.5 million cells/mL

Species	CL_{int} (µL/min × 10^6 cells)	$t_{1/2}$ (minutes)	Scaled CL_{int} (L/hr/kg)
Mouse	49.7*	29.1*	25.6*
Rat	14.2 (1.36)**	98.8 (9.18)**	4.07 (0.386)**
Dog	1.81*	786*	0.415*
Monkey	2.32*	609*	0.413*
Human	2.09 (0.599)**	688 (171)**	0.366 (0.098)**

Additional Information: * average (n=2); ** averaged (SD; $n \geq 3$)

2.6.5.10a 薬物動態試験：*In vitro* における代謝（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. 1293543-memo-09

Type of Study: Drug metabolizing enzyme phenotyping in recombinant enzymes

Method: Metabolism of A-1293543 in baculovirus infected insect cells over expressing human CYPs ([redacted]).

Enzyme	% of Parent Remaining (Mean)	V_{max} (pmol/min/pmol CYP)	K_m (µM)
Control (Insect)	100.0		
1A2 + OR	100.0		
2B6 + OR + b5	100.0		
2C8 + OR + b5	100.0		
2C9 + OR + b5	98.7		
2C18 + OR + b5	100.0		
2C19 + OR + b5	100.0		
2D6 + OR	73.4	3.1	165.3
2J2 + OR+ b5	98.7		
3A4 + OR + b5	36.0	0.71	8.32
3A5 + OR + b5	80.6		
FMO1	100.0		
FMO3	100.0		

Additional Information: + OR – Co-expressed with cytochrome P450 reductase; + OR + b5 – Co-expressed with cytochrome P450 reductase and cytochrome b5

Experimental conditions for enzyme phenotyping consisted of 100 pmol/mL CYPs or 0.5 mg/mL FMOs with 2 µM [^{14}C]A-1293543 in 50 mM phosphate buffer pH 7.4; reaction was initiated with 1 mM NADPH.

2.6.5.10b 薬物動態試験：*In vitro* における代謝ー代謝物プロファイリング

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/12/256

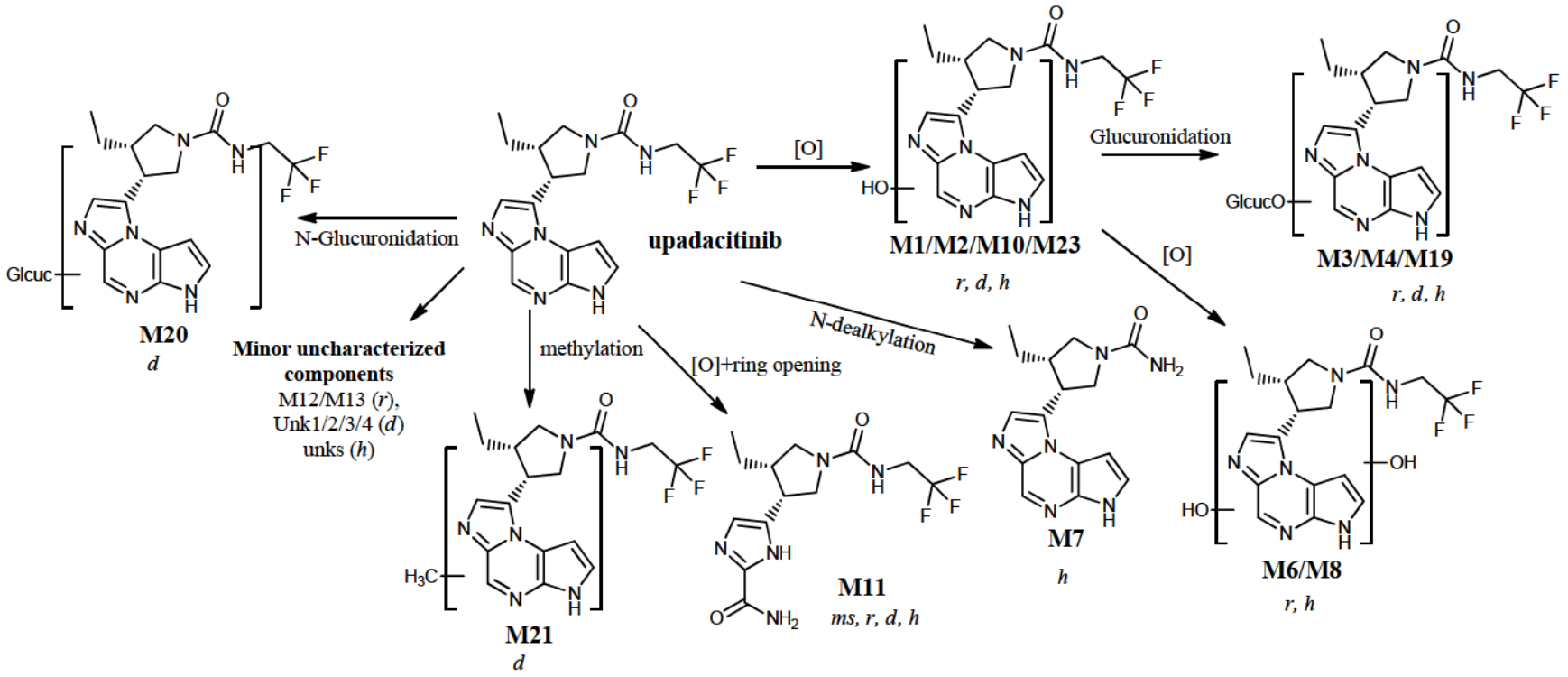
Purpose: Metabolite profiling following incubation in hepatocytes and [redacted]

Radionucleotide: [^{14}C]A-1293543 (lot [redacted]; 0.0464 Ci/mmol)

Study system:	**Hepatocytes:** 10 µM substrate; 0.5 million cells/mL; 4 hr; 37°C					[redacted]: 2 µM substrate; 100 pmol/mL [redacted]; 1 hr; 37°C		
Metabolite	**Mouse**	**Rat**	**Dog**	**Monkey**	**Human**	**CYP2D6**	**CYP3A4**	**CYP3A5**
A-1293543	77.9	96.8	100	96.0	100	71.7	41.9	73.4
M1	5.9	-	MS	1.9	MS	-	MS	MS
M2	-	MS	MS	MS	MS	-	9.4	MS
M3	6.3	MS	-	-	MS			
M4	-	MS	MS	MS	MS			
M6						2.1	3.5	2.7
M7						-	MS	-
M8						2.3	3.2	2.5
M10	MS	-	-	-	-	-	3.3	MS
M11						23.9	38.7	21.4
Unknown	9.9	3.2	-	2.1	-			

Additional Information: - Not detected; MS: only detected by mass spectrometry, below limit of quantitation of radiodetection. Metabolite profile expressed as percent parent drug remaining (A-1293543) or percent metabolite formation as a fraction of the area counts for the total radiochromatogram.

2.6.5.11 薬物動態試験：推定代謝経路



r - *rat, ms - mouse, d- dog, h- human*

2.6.5.12a 薬物動態試験：薬物代謝酵素の阻害

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/17/0324

Type of Study: *In vitro* CYP inhibition

Method: Assessment of the effect of upadacitinib on the activity of CYPs in human liver microsomes

		Positive Control	Upadacitinib	
Isoform	**Positive Control**	**IC_{50} (μM)‡**	**% Inhibition Max Concentration‡**	**IC_{50} (μM)**
CYP1A2	Furafylline	2.6, 2.3	30.4, 21.4	>250
CYP2B6	Ticlopidine	0.062, 0.066	26.8, 21.8	>250
CYP2C8	Quercetin	0.85, 0.83	17.0, 20.2	>250
CYP2C9	Sulfaphenazole	0.18, 0.17	77.0, 82.4	40.3
CYP2C19	Tranylcypromine	5.1, 4.4	46.9, 20.4	>250
CYP2D6	Quinidine	0.033, 0.034	49.1, 45.2	>250
CYP3A4 (midazolam)	Ketoconazole	0.0081, 0.0066	57.0, 60.6	181
CYP3A4 (testosterone)	Ketoconazole	0.0087, 0.0093	58.8, 51.9	212

Additional Information: ‡ values from two independent experiments

2.6.5.12a 薬物動態試験：薬物代謝酵素の阻害（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/17/0324

Type of Study: *In vitro* CYP inhibition

Method: Assessment of CYP time-dependent inhibition potential by upadacitinib in human liver microsomes

	Positive Controls					Upadacitinib			
			CYP activity remaining vs. DMSO (%)				CYP activity remaining vs. DMSO (%)		
Isoform	Reference compound	Conc (μM)	0 min	30 min	0 and 30 min difference	Conc (μM)	0 min	30 min	0 and 30 min difference
CYP1A2	Furafylline	10	79.0 (2.6)	11.7 (0.6)	67.3	50	91.3 (1.5)	83.7 (2.1)	7.6
CYP2B6	Ticlopidine	10	55.0 (2.0)	9.7 (0.2)	45.3	50	93.7 (0.6)	87.7 (1.5)	6.0
CYP2C8	Gemfibrozil 1-O-β-glucuronide	50	76.0 (3.6)	18.3 (0.6)	57.7	50	100 (0.0)	98.0 (2.0)	2.0
CYP2C9	Tienilic acid	10	75.7 (2.1)	13.0 (0.0)	62.7	50	95.3 (1.2)	93.7 (1.5)	1.6
CYP2C19	Ticlopidine	10	64.3 (0.6)	27.3 (0.6)	37.0	50	103 (5.8)	103 (5.8)	0.0
CYP2D6	Paroxetine	10	40.7 (0.6)	11.0 (0.0)	29.7	50	95.0 (1.0)	92.3 (0.6)	2.7
CYP3A4 (M)	Troleandomycin	10	100 (0.0)	51.0 (1.0)	49.0	50	103 (5.8)	97.3 (2.1)	5.7
CYP3A4 (T)	Troleandomycin	10	100 (0.0)	29.3 (0.6)	70.7	50	94.7 (1.5)	82.7 (2.1)	12.0

Additional Information: Data provided as the Mean (SD)

(M) midazolam; (T) testosterone

2.6.5.12b 薬物動態試験：薬物代謝酵素の誘導

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1011

Type of Study: *in vitro* incubations in cultured human hepatocytes

Study: An investigation of CYP induction (mRNA) by A-1293543 in cultured human hepatocytes

Test Compound	Conc (μM)	Mean Fold Induction Over Vehicle Control (± SD)								
		Donor FOS			Donor MMM			Donor CRT		
		CYP3A4	CYP2B6	CYP1A2	CYP3A4	CYP2B6	CYP1A2	CYP3A4	CYP2B6	CYP1A2
A-1293543	0.3	1.1 (0.2)	1.1 (0.3)	0.9 (0.1)	1.4 (0.2)	1.1 (0.2)	1.2 (0.2)	0.8 (0.3)	1.4 (0.1)	1.2 (0.6)
	1	1.0 (0.1)	0.6 (0.1)	0.9 (0.1)	1.3 (0.1)	1.0 (0.1)	1.1 (0.0)	1.0 (0.2)	2.0 (0.3)	1.0 (0.2)
	3	1.2 (0.1)	0.7 (0.1)	1.1 (0.2)	2.0 (0.4)	1.5 (0.2)	1.3 (0.3)	1.8 (0.3)	3.0 (0.3)	1.1 (0.1)
	10	2.5 (0.0)	1.8 (0.5)	0.9 (0.1)	5.0 (0.7)	5.1 (0.4)	2.2 (0.2)	5.0 (0.9)	9.0 (1.6)	1.7 (0.1)
	30	8.0 (0.0)	6.7 (0.9)	1.3 (0.1)	6.3 (1.0)	18 (3.8)	4.1 (0.2)	9.9 (1.1)	22 (1.3)	3.1 (0.8)
	50	12 (0.7)	8.6 (0.6)	1.4 (0.2)	6.2 (0.7)	21 (1.1)	4.0 (0.4)	12 (2.5)	40 (5.0)	3.4 (0.8)
	75	17 (0.5)	16 (1.0)	1.7 (0.0)				20 (1.5)	92 (2.8)	2.7 (0.3)
	100	16 (2.1)	22 (1.9)	1.6 (0.2)		‡			‡	
Positive Controls#	10-50#	34 (3.0)	16 (1.9)[a] 16 (4.1)[b]	53 (4.2)	25 (1.0)	19 (0.8)[a] 26 (3.3)[b]	72 (10)	74 (8.5)	22 (3.5)[a] 17 (1.6)[b]	109 (6.4)
Probenecid (Negative Control)	10	1.1 (0.0)	0.8 (0.1)	1.2 (0.4)	1.1 (0.3)	1.1 (0.2)	1.1 (0.2)	1.7 (0.2)	2.0 (0.3)	1.0 (0.2)

Data are presented as mean fold induction over vehicle ± standard deviation (in triplicate)

Vehicle control: 0.1% (v/v) DMSO; ‡ Data were excluded from analysis due to decreased cell viability

50 μM omeprazole (CYP1A2), 50 μM phenytoin (CYP2B6, [a]), 0.1 μM CITCO (CYP2B6, [b]) or 10 μM rifampin (CYP3A4)

2.6.5.12b 薬物動態試験：薬物代謝酵素の誘導（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1011

Type of Study: *in vitro* incubations in cultured human hepatocytes

Study: An investigation of CYP induction (mRNA) by A-1293543 in cultured human hepatocytes

Test Compound	Conc (μM)	Mean % Induction of Positive Control Response (± SD)								
		Donor FOS			Donor MMM			Donor CRT		
		CYP3A4	CYP2B6	CYP1A2	CYP3A4	CYP2B6	CYP1A2	CYP3A4	CYP2B6	CYP1A2
A-1293543	0.3	0.3 (0.7)	0.6 (2.2)	-0.2 (0.2)	1.9 (0.9)	0.8 (1.2)	0.3 (0.3)	-0.3 (0.4)	1.8 (0.5)	0.2 (0.5)
	1	-0.1 (0.3)	-2.4 (0.5)	-0.1 (0.2)	1.1 (0.3)	-0.1 (0.3)	0.1 (0.0)	0.0 (0.3)	4.7 (1.3)	0.0 (0.2)
	3	0.7 (0.2)	-1.8 (0.6)	0.2 (0.4)	4.3 (1.8)	2.6 (1.4)	0.5 (0.4)	1.0 (0.4)	9.5 (1.5)	0.1 (0.1)
	10	4.6 (0.1)	5.3 (3.2)	-0.1 (0.2)	17 (2.9)	23 (2.5)	1.6 (0.2)	5.5 (1.2)	38 (7.5)	0.7 (0.1)
	30	21 (0.1)	39 (6.0)	0.6 (0.2)	22 (4.1)	100 (22)	4.3 (0.2)	12 (1.5)	100 (6.0)	2.0 (0.7)
	50	32 (2.1)	51 (4.1)	0.9 (0.3)	22 (3.1)	116 (6.2)	4.3 (0.6)	15 (3.4)	184 (24)	2.3 (0.8)
	75	47 (1.5)	104 (7.0)	1.3 (0.1)				26 (2.1)	431 (13)	1.5 (0.3)
	100	46 (6.5)	141 (13)	1.2 (0.4)		‡			‡	
Positive Controls#	10-50#	100	100	100	100	100	100	100	100	100
Probenecid (Negative Control)	10	0.2 (0.1)	-1.3 (0.9)	0.3 (0.8)	0.3 (1.3)	0.8 (0.9)	0.1 (0.3)	0.9 (0.2)	5.0 (1.4)	0.0 (0.1)

Data are presented as mean percent induction of positive control response ± standard deviation (in triplicate)

Vehicle control: 0.1% (v/v) DMSO

50 μM omeprazole (CYP1A2), 50 μM phenytoin (CYP2B6) or 10 μM rifampin (CYP3A4)

‡ Data were excluded from analysis due to decreased cell viability

2.6.5.12b 薬物動態試験：薬物代謝酵素の誘導（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/1011

Type of Study: *in vitro* incubations in cultured human hepatocytes

Results: Summary of CYP3A4 and CY2B6 mRNA Induction EC_{50} and E_{max}

	CYP3A4		CYP2B6	
Donor	**EC_{50} (μM)**	**E_{max} (fold)**	**EC_{50} (μM)**	**E_{max} (fold)**
FOS	40	20	57	24
MMM	6.6	6.3	17	22
CRT	36	22	51	95

Additional Information: EC_{50} and E_{max} values were determined with four parameter hill equation.

2.6.5.13 薬物動態試験：排泄

Test Article: Upadacitinib (A-1293543; ABT-494)

Species	**Rat**				**Rat**				**Dog**		
Gender (M/F) / No. Animals	M/2				M/3				M/3		
Feeding Condition	fasted				fasted				fasted		
Vehicle/Formulation	(a)/solution				(a)/solution				(b)/solution		
Method of Administration	IV				PO				PO		
Dose (mg/kg)	3				3				5		
Analyte	% ^{14}C Dose				% ^{14}C Dose				% ^{14}C Dose		
Excretion Route	**Urine**	**Feces**	**Bile**	**Total[c]**	**Urine**	**Feces**	**Bile**	**Total[c]**	**Urine**	**Feces**	**Total[c]**
0-6 h	ns	ns	47.6	47.6	ns	ns	49.8	49.8	45.5	49.1	97.9
0-24 hr	22.9	10.1	49.3	91.3	11.0	22.0	52.4	93.7	46.7	54.0	104.6
0-48 hr	23.7	11.3	49.7	96.0	11.1	22.5	52.6	96.8	46.9	54.6	105.7
Study Number	R&D/12/255				R&D/12/255				R&D/15/0801		

Additional Information:

(a) A-1293543 was dissolved in a mixture of 10% ethanol, 40% propylene glycol and 50% D5W (5% dextrose in water)

(b) A-1293543 was dissolved in a mixture of 10% ethanol, 40% PEG-400 and 50% D5W (5% dextrose in water)

(c) Includes cage wash

all calculations performed prior to rounding; ns (no sample)

2.6.5.13 薬物動態試験：排泄（続き）

Test Article: Upadacitinib (A-1293543; ABT-494)

Species		**Human**	
Gender (M/F) / No. Animals		M/4	
Feeding Condition		non-fasted	
Vehicle/Formulation		(a)/solution	
Method of Administration		PO	
Dose (mg/kg)		30 mg	
Analyte		% ^{14}C Dose	
Excretion Route	**Urine**	**Feces**	**Total**
0-24 hr	40.2	1.17	41.4
0-48 hr	41.9	19.9	61.8
0-72 hr	42.3	31.9	74.2
0-144 hr	42.6	44.7	87.2
0-216 hr	42.6	53.4	95.9
Study Number		R&D/15/0180	

Additional Information:

(a) A-1293543 was dissolved in water containing 0.11% sodium hydroxide (w/v) and 0.96% citric acid (w/v)

all calculations performed prior to rounding; ns (no sample)

2.6.5.14 薬物動態試験：胆汁中排泄

Test Article: Upadacitinib (A-1293543; ABT-494)

ウパダシチニブの胆汁中排泄に関しては 2.6.5.9c 及び 2.6.5.13 に示す。

2.6.5.15a 薬物動態試験：薬物相互作用－トランスポーターの基質としての評価

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/0380

Type of Study: *In vitro* drug transporter substrate assessment

Method: Assessment of transport specific uptake for upadacitinib

Transporter	A-1293543	Reference Compound
MDR1/P-gp	Substrate: $K_{m, app}$ > 860 µM	Quinidine: $K_{m, app}$ 1.4 µM
BCRP	Substrate: $K_{m, app}$ 220 µM	Prazosin: $K_{m, app}$ 3.9 µM
OATP1B1	Not a substrate	
OATP1B3	Not a substrate	
OCT1	Not a substrate	

Additional Information:

2.6.5.15b 薬物動態試験：薬物相互作用－トランスポーターの阻害

Test Article: Upadacitinib (A-1293543; ABT-494)

Study No. R&D/16/0380

Type of Study: *In vitro* drug transporter inhibition

Method: Assessment of drug transporter inhibition potential by upadacitinib

	IC_{50}	
Transporter	**A-1293543**	**Reference Inhibitor**
OATP1B1	48 µM	0.71 µM (Rifampicin)
OATP1B3	< 10% inhibition at 30 µM	74% inhibition at 30 µM (BSP) 88% inhibition at 30 µM (Rifampicin)
OCT1	< 10% inhibition at 30 µM	77% inhibition at 200 µM (Quinidine) 83% inhibition at 100 µM (Pyrimethamine)
OCT2	< 10% inhibition at 30 µM	50% inhibition at 200 µM (Quinidine) 77% inhibition at 100 µM (Pyrimethamine)
OAT1	< 10% inhibition at 30 µM	≥ 82% inhibition at 100 µM (Probenecid)
OAT3	35 µM	4.6 µM (Probenecid)
MATE1	10 µM	0.11 µM (Pyrimethamine)
MATE2K	10 µM	0.043 µM (Pyrimethamine)
MDR1/P-gp	510 µM	4.2 µM (Cyclosporine A)
BCRP	120 µM	0.13 µM (Ko143)
BSEP	220 µM	0.15 µM (Cyclosporine A)

Additional Information:

2.6.5.16 薬物動態試験：その他

Test Article: Upadacitinib (A-1293543; ABT-494)

その他の試験は実施していない。