2.6.7.1 Toxicology - Overview

Test Article: Upadacitinib

Study Type	Species and Strain	Route (Method) of Administration	Duration of Dosing	Doses (mg/kg/day [a])	GLP Compliant	Test Facility	Report Number (Module)
Single-Dose Toxicity	-	-	-	-	-	-	-
Repeated-Dose Toxicity	Mouse Tg(HRAS)	Oral (gavage)	7 days	0, 30, 50, 70, 100	No	AbbVie	R&D/15/0789 (4.2.3.2-1)
	Mouse Tg(HRAS)	Oral (gavage)	28-29 days	0, 10, 20, 30, 40	Yes	AbbVie	R&D/15/1235 (4.2.3.2-2)
	Rat Sprague-Dawley	Oral (gavage)	29-30 days	0, 10, 50, 100, 200 [b]	Yes	Abbott	R&D/11/1044 (4.2.3.2-3)
	Rat Sprague-Dawley	Oral (gavage)	26 weeks	0, 5, 20, 50	Yes	[redacted]	R&D/12/544 (4.2.3.2-4)
	Dog, Beagle	Oral (capsule)	28 days	5	No	Abbott	R&D/11/517 (4.2.3.2-5)
	Dog, Beagle	Oral (capsule)	28-31 days	0, 0.5, 1.5, 3, 5	Yes	Abbott	R&D/11/1001 (4.2.3.2-6)
	Dog, Beagle	Oral (capsule)	39 weeks	0, 0.1, 0.5, 1.5	Yes	AbbVie	R&D/12/324 (4.2.3.2-7)

Footnotes at end of table.

2.6.7.1 Toxicology - Overview (Cont.)

Test Article: Upadacitinib

Study Type	Species and Strain	Route (Method) of Administration	Duration of Dosing	Doses (mg/kg/day [c])	GLP Compliant	Test Facility	Report Number (Modele)
Genotoxicity							
Bacterial Reverse Mutation Test	S. typhimurium/ E. coli	In vitro ±S9	NA	1.5, 5.0, 15, 50, 150, 500, 1500, 5000 µg/plate	Yes	[redacted]	R&D/11/1293 (4.2.3.3.1-1)
Chromosome Aberration Test	Human Peripheral Blood Lymphocytes (HPBL)	In vitro -S9	20 h	25, 50, 100 µg/mL	Yes	[redacted]	R&D/11/1294 (4.2.3.3.1-2)
		In vitro -S9	4 h (with 16 h recovery)	400, 512, 640 µg/mL			
		In vitro +S9	4 h (with 16 h recovery)	327, 400, 512 µg/mL			
Micronucleus Test	Rat Sprague-Dawley	Oral (gavage)	single dose	0, 37.5, 75, 150	Yes	[redacted]	R&D/12/350 (4.2.3.3.2-1)
Carcinogenicity	Mouse Tg(HRAS)	Oral (gavage)	26 weeks	0, 5, 10, 20	Yes	[redacted]	R&D/16/0988 (4.2.3.4.2-1)
	Rat Sprague-Dawley	Oral (gavage)	104 weeks	M: 0, 4, 7.5, 15 F: 0, 3, 7.5, 20	Yes	[redacted]	R&D/15/0464 (4.2.3.4.1-1)

Footnotes at end of table.

2.6.7.1 Toxicology - Overview (Cont.)

Test Article: Upadacitinib

Study Type	Species and Strain	Route (Method) of Administration	Duration of Dosing	Doses (mg/kg/day [a])	GLP Compliant	Test Facility	Report Number (Module)
Reproductive and Developmental Toxicity Studies							
Fertility and Early Embryonic Development	Rat Sprague-Dawley	Oral (gavage)	14 days prior to mating through euthanasia (M) or GD 7 (F)	0, 5, 25 50/75 for fertility (M/F)	Yes	[redacted]	R&D/13/1006 (4.2.3.5.1-1)
Embryofetal Development	Rat Female Sprague-Dawley	Oral (gavage)	GD 6 through GD 17	0, 50, 100, 150/75	No	[redacted]	R&D/12/875 (4.2.3.5.2-1)
	Rat Female Sprague-Dawley	Oral (gavage)	GD 6 through GD 17	0, 5, 25, 75 (maternal) ≤ 5 (fetal)	Yes	[redacted]	R&D/12/1109 (4.2.3.5.2-2)
	Rat Female Sprague-Dawley	Oral (gavage)	GD 6 through GD 17	0, 1.5, 4 (maternal) 1.5 (fetal)	Yes	[redacted]	R&D/17/0574 (4.2.3.5.2-3)
	Rabbit Female New Zealand White	Oral (gavage)	GD 7 through GD 19	0, 5, 20, 50	No	[redacted]	R&D/12/1007 (4.2.3.5.2-4)
	Rabbit Female New Zealand White	Oral (gavage)	GD 7 through GD 19	0, 2.5, 10 (maternal and fetal), 25	Yes	[redacted]	R&D/13/335 (4.2.3.5.2-5)
Pre- and Postnatal Development	Rat Sprague-Dawley	Oral (gavage)	GD 6 through LD 20	0, 2.5, 5, 10 (F0 and F1)	Yes	[redacted]	R&D/16/1460 (4.2.3.5.3-1)

Footnotes at end of table.

2.6.7.1 Toxicology - Overview (Cont.)

Test Article: Upadacitinib

Study Type	Species and Strain	Route (Method) of Administration	Duration of Dosing	Doses (mg/kg [a,c])	GLP Compliant	Test Facility	Report Number (Module)
Studies in Juvenile Animals	Rat Sprague-Dawley	Oral (gavage)	PND 15 through PND 29	0, 50, 100, 150	No	[redacted]	R&D/17/0266 (4.2.3.5.4-1)
	Rat Sprague-Dawley	Oral (gavage)	PND 15 through PND 63	0, 5, 20, 50	Yes	[redacted]	R&D/17/0588 (4.2.3.5.4-2)
Local Tolerance	-	-	-	-	-	-	-
Other Toxicity Studies							
T-cell Dependent Antibody Response Assay	Rat Sprague-Dawley	Oral (gavage)	4 or 8 weeks	0, 5, 30, 60	Yes	AbbVie	R&D/15/0592 (4.2.3.7.2-1)
Phototoxicity Assay	Mouse fibroblasts	In vitro	-	Concentration range 1.78-100 µg/mL	Yes	[redacted]	R&D/13/991 (4.2.3.7.7-1)

GD = Gestation Day; LD = Lactation Day; PND = Postnatal Day; NA = Not Applicable

a. The highest No-Observed-Adverse-Effect Level (NOAEL) in repeated-dose, reproductive toxicity, and juvenile studies is underlined, where applicable.

b. Due to toxicity, the 200 mg/kg/day dose was a single dose.

c. Unless otherwise specified.

2.6.7.2 Toxicokinetics - Overview of Toxicokinetics Studies

Test Article: Upadacitinib

Test System	Study Type	Route (Method) of Administration	Doses (mg/kg/day)	GLP Compliant	Report Number (Module)
Mouse, Tg(HRAS)	4-week repeat dose toxicity	Oral (gavage)	10, 20, 30, 40	Yes	R&D/15/1235 (4.2.3.2-2)
	26-week carcinogenicity	Oral (gavage)	5, 10, 20	Yes	R&D/16/0988 (4.2.3.4.2-1)
Rat, Sprague-Dawley	4-week repeat dose toxicity	Oral (gavage)	10, 50, 100	Yes	R&D/11/1044 (4.2.3.2-3)
	26-week repeat dose toxicity	Oral (gavage)	5, 20, 50	Yes	R&D/12/544 (4.2.3.2-4)
	104-week carcinogenicity	Oral (gavage)	4, 7.5, 15 (male) 3, 7.5, 20 (female)	Yes	R&D/15/0464 (4.2.3.4.1-1)
	embryofetal development	Oral (gavage)	5, 25, 75	Yes	R&D/12/1109 (4.2.3.5.2-2)
	embryofetal development	Oral (gavage)	1.5, 4	Yes	R&D/17/0574 (4.2.3.5.2-3)
Rabbit, New Zealand White	embryofetal development	Oral (gavage)	2.5, 10, 25	Yes	R&D/13/335 (4.2.3.5.2-5)
Dog, Beagle	4-week repeat dose toxicity	Oral (capsule)	0.5, 1.5, 3, 5	Yes	R&D/11/1001 (4.2.3.2-6)
	39-week repeat dose toxicity	Oral (capsule)	0.1, 0.5, 1.5	Yes	R&D/12/324 (4.2.3.2-7)

2.6.7.3 Toxicokinetics - Overview of Toxicokinetics Data

Test Article: Upadacitinib

Dose (mg/kg/day)	Steady-State AUC (µg•hr/mL)								
	Mice		Rats		Dogs		Pregnant Rats	Pregnant Rabbits	Humans
	Males	Females	Males	Females	Males	Females			
0.1					0.0484[e]	0.0597[e]			
0.5					0.270[d], 0.350[e]	0.408[d], 0.278[e]			
1.5					1.24[d], 0.937[e]	1.17[d], 0.850[e]	0.115[i]		
2.5								0.145[j]	
3				0.468[g]	2.13[d]	2.16[d]			
4			0.302[g]				0.629[i]		
5	0.0917[f]	0.153[f]	0.462[c]	1.39[c]	3.52[d]	4.68[d]	0.680[h]		
7.5			0.733[g]	1.13[g]					
10	0.193[a], 0.284[f]	0.248[a], 0.271[f]	1.49[b]	2.28[b]				0.881[j]	
15			1.67[g]						
20	0.641[a], 0.844[f]	0.689[a], 1.44[f]	3.83[c]	6.84[c], 4.17[g]					
25							8.72[h]	5.95[j]	
30	1.16[a]	1.19[a]							
40	2.25[a]	1.80[a]							
50			16.8[b], 12.1[c]	33.2[b], 22.1[c]					
75							33.4[h]		
100			40.8[b]	63.8[b]					

a. R&D/15/1235 (TD15-070): 4 week Tg (HRAS) mouse
b. R&D/11/1044 (TA11-224): 4 week rat
c. R&D/12/544 (TA12-067): 26 week rat
d. R&D/11/1001 (TB11-225): 4 week dog
e. R&D/12/324 (TB12-042): 39 week dog
f. R&D/16/0988 (TD16-088): 26 week Tg(Hras) mouse
g. R&D/15/0464 (TA15-032): 104 week rat
h. R&D/12/1109 (TA12-095): developmental rat
i. R&D/17/0574 (TA17-026): developmental rat
j. R&D/13/335 (TE12-096): developmental rabbit

2.6.7.4 Toxicology - Drug Substance

Test Article: Upadacitinib

Batch Number	Potency (%) [a]	AM*	AN*	E*	D*	B*	Report Number (Module)	Study Type
Commercial Acceptance Criterion:	NLT 97.0 (assay, anhydrous)	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted]%	NMT [redacted] ppm		
[redacted]	99.0%	NR	NR	NT	NT	NT	R&D/11/517 (4.2.3.2-5)	4-week oral toxicity study in dogs (non-GLP)
[redacted]	98.8%	NR	ND	NT	NT	NT	R&D/11/1001 (4.2.3.2-6)	4-week oral toxicity study in dogs with recovery (GLP)
							R&D/11/1044 (4.2.3.2-3)	4-week oral toxicity study in rats with recovery (GLP)
							R&D/11/1293 (4.2.3.3.1-1)	Bacterial reverse mutation assay
							R&D/11/1294 (4.2.3.3.1-2)	Chromosomal aberrations assay in human peripheral lymphocytes
							R&D/12/350 (4.2.3.3.2-1)	In vivo rat micronucleus assay
[redacted] [b]	61.6	NR	ND	NT	ND	ND	R&D/12/324 (4.2.3.2-7)	39-week oral toxicity study in dogs (GLP)
[redacted] [b]	59.2	NR	ND	NT	ND	ND	R&D/12/544 (4.2.3.2-4)	26-week oral toxicity study in rats (GLP)
							R&D/12/875 (4.2.3.5.2-1)	Embryofetal development DRF in rats (non-GLP)
							R&D/12/1109 (4.2.3.5.2-2)	Embryofetal development in rats (GLP)

Footnotes at end of table.

*新薬承認情報提供時に置換

2.6.7.4 Toxicology - Drug Substance (Cont.)

Test Article: Upadacitinib

Batch Number	Potency (%) [a]	AM*	AN*	E*	D*	B*	Report Number (Module)	Study Type
[redacted] [b]	59.2	NR	ND	NT	ND	ND	R&D/12/1007 (4.2.3.5.2-4)	Embryofetal development DRF in rabbits (non-GLP)
							R&D/13/335 (4.2.3.5.2-5)	Embryofetal development in rabbits (GLP)
[redacted] [b]	62.5	NR	<[redacted]% [c]	NT	ND	ND	R&D/13/1006 (4.2.3.5.1-1)	Fertility and early embryonic development in rats (GLP)
							R&D/13/991 (4.2.3.7.7-1)	In vitro 3T3 phototoxicity assay (GLP)
[redacted]	97.3	NR	ND	NT	ND	ND	R&D/15/0789 (4.2.3.2-1)	7-day oral dose DRF study in CByB6F1-Tg(HRAS)2Jic Wild Type (non-transgenic littermates) mice (non-GLP)
							R&D/15/1235 (4.2.3.2-2)	4-week oral toxicity study in CByB6F1-Tg(HRAS)2Jic Wild Type (non-transgenic littermates) mice (GLP)
							R&D/15/0592 (4.2.3.7.2-1)	T cell-dependent antibody response assay in rats (GLP)
							R&D/15/0464 (4.2.3.4.1-1)	2-year carcinogenicity study in rats (GLP)

Footnotes at end of table.

*新薬承認情報提供時に置換

2.6.7.4 Toxicology - Drug Substance (Cont.)

Test Article: Upadacitinib

Batch Number	Potency (%) [a]	AM*	AN*	E*	D*	B*	Report Number (Module)	Study Type
[redacted]	97.3	NR	< [redacted] % [c]	NT	ND	< [redacted] ppm	R&D/16/0988 (4.2.3.4.2-1)	26-week carcinogenicity study in Model 001178-T (Hemizygous) CByB6F1-Tg(HRAS)2Jic mice (GLP)
							R&D/16/1460 (4.2.3.5.3-1)	Pre-/Postnatal development in rats (GLP)
							R&D/17/0574 (4.2.3.5.2-3)	Embryofetal development in rats at low doses (GLP)
							R&D/17/0266 (4.2.3.5.4-1)	Oral DRF toxicity study in juvenile rats (non-GLP)
							R&D/17/0588 (4.2.3.5.4-2)	Oral toxicity study in juvenile rats (GLP)

ND = Not Detected; NR = Not Reported; NT = Not Tested; NMT = Not More Than; NLT = Not Less Than

Reference: Module 3.2.S.4.4 GLP Toxicology Batches Section 2.2

a. Assigned chemical potency for batches used in toxicology studies.

b. Manufactured as tartrate salt

c. AN* is Unknown M on Certificate of Analysis

*新薬承認情報提供時に置換

2.6.7.5 Single-Dose Toxicity - No Studies Conducted

2.6.7.6 Repeat-Dose Toxicity - Nonpivotal Studies

Test Article: Upadacitinib

Species and Strain	Route (Method) of Administration (Vehicle/Formulation)	Duration of Dosing	Doses (mg/kg/day)	Sex and Number per Group (satellites)	NOAEL (mg/kg)	Noteworthy Findings	Report Number (Module)
Mouse CByB6F1-Tg(HRAS)2Jic Wild Type (non-transgenic littermates)	Oral (gavage) (0.2% (high-viscosity) hydroxypropyl methylcellulose (HPMC); Dose volume = 20 mL/kg)	7 days	0, 30, 50, 70, 100	Males: 5 (3 or 9) Females: 5 (3 or 9)	NA	**30 and 50 mg/kg/day:** adverse liver degeneration, necrosis, or single cell necrosis (primarily in periportal areas) in males and females **50 mg/kg/day:** males- adverse tubular degeneration/regeneration in the kidneys; ↑ ALKP and total bilirubin **50, 70 and 100 mg/kg/day**: not tolerated	R&D/15/0789 (4.2.3.2-1)
Dog Beagle	Oral (capsule) (PEG 400: Tween 20 (70:30, w/w) acidified with p-toluenesulfonic acid monohydrate; Dose volume = 1 mL/kg)	28 days	5	Males: 2 Females: 2	NA	mixed cellular infiltration in popliteal (2M/2F) lymph node capsule, minimal to moderate	R&D/11/517 (4.2.3.2-5)

NOAEL = No-Observed-Adverse-Effect Level; NA = not applicable, since NOAEL determination was not a study endpoint.

2.6.7 Repeat-Dose Toxicity

2.6.7.1 Repeat-Dose Toxicity - Report Title: Four-Week Oral Toxicity Study of A-1293543 Free Base (Hemihydrate) in CByB6F1-Tg(HRAS)2Jic Wild Type (non-Transgenic Littermates) Mice (R&D/15/1235)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Mice/CByB6F1-Tg (HRAS)2 Jic Wild Type (non-Transgenic Littermates)	**Duration of Dosing:**	28 to 29 consecutive days	**Report Number (Module):**	R&D/15/1235 (4.2.3.2-2)
Initial Age:	10 weeks at start of dosing	**Duration of Postdose:**	NA	**Study Number:**	TD15-070
Date of First Dose:	[redacted] 20[redacted]	**Route (Method) of Administration:**	Oral (gavage)	**GLP Compliant:**	Yes

Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (HPMC) in water; Dose volume = 20 mL/kg

Special Features: NA

MTD: 40 mg/kg/day

2.6.7.7.1 Repeat-Dose Toxicity - Report R&D/15/1235 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Daily Dose (mg/kg/day)	**0**	**10**	**20**	**30**	**40**	**0**	**10**	**20**	**30**	**40**
Number of Main Study Animals	10	10	10	10	10	10	10	10	10	10
Number of Animals (Toxicokinetics - Satellite) [a]	5	5	5	5	5	5	5	5	5	5
Toxicokinetics [b]**:**										
Day 1: C_{max} (µg/mL)	BQL	0.0905	0.267	0.528	0.919	BQL	0.123	0.338	0.843	0.994
Day 28: C_{max} (µg/mL)	BQL	0.108	0.439	0.677	1.48 [a]	BQL	0.203	0.529	1.13	1.67 [a]
Day 1: AUC (µg•hr/mL)	NA	0.143	0.415	0.866	1.42	NA	0.248	0.444	1.13	1.35
Day 28: AUC (µg•hr/mL)	NA	0.193	0.641	1.16	2.25 [a]	NA	0.248	0.689	1.19	1.80 [a]

2.6.7.7.1 Repeat-Dose Toxicity - Report R&D/15/1235 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Daily Dose (mg/kg/day)	**0**	**10**	**20**	**30**	**40**	**0**	**10**	**20**	**30**	**40**
Number of Main Study Animals	10	10	10	10	10	10	10	10	10	10
Noteworthy Findings:										
Mortality [a]	-	-	-	-	-	-	-	-	-	-
Body Weight (g [c]**)**	25.95	-	-	-	-	21.68	-	-	-	-
Food Consumption (g/day [d]**)**	4.12	-	-	-	-	4.16	-	-	-	-
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Hematology [e]										
Lymphocytes (E9/L)	2.331	2.083	2.174	1.544	1.779	4.293	2.592	2.642	2.443	2.328
Serum Chemistry	-	-	-	-	-	-	-	-	-	-
Organ Weights	-	-	-	-	-	-	-	-	-	-
Gross Observations	-	-	-	-	-	-	-	-	-	-
Microscopic Observations	-	-	-	-	-	-	-	-	-	-
Not planned per Study Protocol										
Coagulation										
Urinalysis										

2.6.7.7.1 Repeat-Dose Toxicity - Report R&D/15/1235 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit
MTD	Maximum Tolerated Dose
NA	Not applicable
-	No noteworthy findings
*	$p < 0.05$
**	$p < 0.01$
+	Mild
++	Moderate
+++	Marked

a. Serial microsampling from satellite animals was used for toxicokinetic calculations. On Day 28, n = 4 for both males and females in Group 5. Satellite Animal 5026 was euthanized in moribund condition on Day 3. The cause of moribundity could not be identified at necropsy. Satellite Animal 5027 was excluded from the statistical analysis due to a missing concentration at the T_{max} (0.25 hr).

b. Mean AUC and C_{max} are presented.

c. Group mean body weight at the end of the dosing period is presented for control mice.

d. Group mean food consumption at the end of the dosing period is presented for control mice.

e. Absolute values are presented.

2.6.7.7.2 Repeat-Dose Toxicity - Report Title: Four-Week Oral Toxicity Study of A-1293543 in Sprague-Dawley Rats (with a Four-Week Recovery Period) (R&D/11/1044)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Rat/Sprague-Dawley	**Duration of Dosing:**	29-30 days	**Report Number:** (Module)	R&D/11/1044 (4.2.3.2-3)
Initial Age:	9 weeks	**Duration of Postdose:**	29 days	**Study Number:**	TA11-224
Date of First Dose:	[redacted] 20[redacted]	**Route (Method) of Administration:**	Oral (gavage)	**GLP Compliant:**	Yes

Vehicle/Formulation: PEG-400:Tween 20 (70:30, w/w) acidified with 1 molar equivalent p-toluenesulfonic acid monohydrate; Dose volume = 2 mL/kg

Special Features: Peripheral blood lymphocyte immunophenotyping

NOAEL: 50 mg/kg/day

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**		**200** [a]	
Number of Animals [b]	M:15 (5)	F:15 (5)	M:10 (5)	F:10 (5)	M:15 (5)	F:15 (5)	M:15 (5)	F:15 (5)	M:15 (5)	F:15 (5)
Toxicokinetics:										
Day 1: C_{max} (µg/mL)	BQL	BQL	0.224	0.468	3.03	5.16	3.91	13.5	7.25	18.2
Day 29: C_{max} (µg/mL)	BQL	BQL	0.329	0.652	2.32	8.85	5.72	14.9	NA	NA
Day 1: AUC (µg•hr/mL)	NA	NA	1.39	1.87	15.9	22.4	24.9	54.1	50.4	108
Day 29: AUC (µg•hr/mL)	NA	NA	1.49	2.28	16.8	33.2	40.8	63.8	NA	NA

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**		**200** [a]	
Number of Animals - Main Study (Recovery)	M:10 (5)	F:10 (5)	M:10	F:10	M:10 (5)	F:10 (5)	M:10 (5)	F:10 (5)	M:10 (5)	F:10 (5)
Noteworthy Findings Dosing Phase:										
Mortality [c]	0	0	0	0	1	0	5	0	15	15
Body Weight	-	-	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-	-	-
Clinical Observations [d]										
Decreased activity	-	-	-	-	-	-	1+,1++,2+++	-	-	6+++
Weakness	-	-	-	-	-	-	-	-	-	3++,1+++
Decreased reactivity to noise	-	-	-	-	-	-	3	1	6	2
Dark-colored urine	-	-	-	-	-	-	9	1	3	-
Red urine	-	-	-	-	-	-	1	-	-	-
Squinting eyes	-	-	-	-	-	-	1+,2++	3+,2++	-	3+,2++
Rough hair	-	-	-	-	-	-	3+,4++	1++	-	1+++
Stained anogenital hair										
Red staining	-	-	-	-	-	-	4+,3++,1+++	1+	-	-
Yellow staining	-	-	-	-	-	-	1+,1++	1+	-	-
Increased salivation	-	-	-	-	-	-	3++,1+++	2++	-	-

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**		**200** [a]	
Number of Animals - Main Study (Recovery)	M:10 (5)	F:10 (5)	M:10	F:10	M:10 (5)	F:10 (5)	M:10 (5)	F:10 (5)	M:10 (5)	F:10 (5)
Noteworthy Findings Dosing Phase:										
Clinical Observations [d]										
Red-stained hair										
Muzzle	-	-	-	-	-	2+	4+,1++,1+++	5+,1++	-	-
Ears	-	1+	-	-	-	2+	-	2+	-	-
Forepaws	-	-	-	-	-	-	1+,1++	2+,1++	-	-
Slow skin turgor, dehydrated	-	-	-	-	-	-	7	1	-	-
Sunken eyes, recumbency	-	-	-	-	-	-	1 [e]	-	-	-
Lost righting reflex, labored breathing	-	-	-	-	-	-	1 [e]	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-
Recovery Phase										
Clinical Observations [d]										
Stained anogenital hair (red)	-	-	NA	NA	-	-	1+,1++	-	NA	NA
Red-stained hair (ears)	-	-	NA	NA	-	1+	-	-	NA	NA

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**	
Number of Animals	M:10	F:10	M:10	F:10	M:10	F:10	M:7	F:10
Noteworthy Findings Dosing Phase:								
Hematology [f]								
White blood cells (E9/L)	12.207	7.598	7.359***	5.707	5.016***	4.174***	4.241***	2.948***
Lymphocytes (E9/L)	10.197	6.489	5.744	4.556	3.645	3.171	2.986	1.905
RBC (E12/L)	8.580	8.346	8.329	8.122	8.356	7.923	8.219	7.300***
HGB (g/dL)	15.80	15.53	14.98*	15.32	15.31	14.86	14.84*	13.62***
HCT (%)	49.78	48.10	47.71	46.77	48.86	45.82	47.20	41.58***
Immunophenotyping cells/µL [g]								
Mature T cells	2752	1886	1270	1348	818	759	503	388
Helper T cells	1784	1241	911	976	630	576	393	312
Cytotoxic T cells	966	635	343	359	177	177	100	68
Mature B cells	3664	1837	1460	1100	931	884	752	450
NK cells	520	273	125	85	50	38	27	18
Coagulation	-	-	-	-	-	-	-	-
Serum Chemistry [f]								
Phosphorous (mg/dL)	9.34	9.06	9.78	9.39	9.74	9.00	10.23	9.63

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**	
Number of Animals	M:14	F:9	M:9	F:7	M:14	F:8	M:4	F:4
Noteworthy Findings Dosing Phase:								
Urinalysis [h]								
UA Protein								
Negative	6	2	1	0	0	0	0	0
30 mg/dL	8	7	7	7	1	0	0	0
100 mg/dL	0	0	1	0	11	3	0	0
≥ 500 mg/dL	0	0	0	0	2	5	4	4
UA Bilirubin								
Negative	13	5	6	3	0	1	0	0
Small	1	1	2	1	0	0	0	0
Moderate	0	1	1	2	7	1	0	2
Large	0	2	0	1	7	6	4	2
UA Blood								
Negative	14	9	7	7	0	0	0	0
Small	0	0	2	0	14	8	4	4
UA Urobilinogen								
≤ 2 mg/dL	14	7	9	6	3	3	1	2
4 mg/dL	0	0	0	1	4	1	0	1
8 mg/dL	0	2	0	0	7	4	3	1

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**	
Number of Animals	M:14	F:9	M:9	F:7	M:14	F:8	M:4	F:4
Noteworthy Findings **Dosing Phase:**								
Urinalysis [h]								
Color								
Straw	8	5	0	2	0	0	0	0
Yellow	6	4	6	2	0	0	0	0
Amber	0	0	1	1	0	0	0	0
Brown	0	0	2	2	1	4	0	1
Black	0	0	0	0	13	4	4	3

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**	
Number of Animals	M:10	F:10	M:10	F:10	M:10	F:10	M:7	F:10
Noteworthy Findings Dosing Phase:								
Organ Weights (%) [i]								
Thymus (g)	0.4777	0.4257	-37***	-21	-56***	-67***	-71***	-76***
Spleen (g)	0.7659	0.4992	-26***	-15*	-37***	-30***	-49***	-37***
Gross Observations	-	-	-	-	-	-	-	-
Microscopic Observations [h]								
Liver (Only unscheduled deaths)								
Necrosis [j]								
Moderate	NA	NA	NA	NA	NA	NA	1	NA
Marked	NA	NA	NA	NA	NA	NA	2	NA
Kidney								
Degeneration/ regeneration								
Minimal	0	0	0	0	0	0	3	1
Mild	0	0	0	0	0	0	1	0
Moderate	0	0	0	0	0	0	1	3
Marked	0	0	0	0	0	0	0	1

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)		**0**		**10**		**50**		**100**	
Number of Animals		M:10	F:10	M:10	F:10	M:10	F:10	M:7	F:10
Noteworthy Findings **Dosing Phase:**									
Microscopic Observations [h]									
Thymus									
Decreased numbers, lymphocytes, cortex									
	Minimal	0	0	0	0	1	2	0	0
	Mild	0	0	0	0	5	6	2	4
	Moderate	0	0	0	0	0	0	5	5
Decreased numbers, lymphocytes, medulla									
	Minimal	0	0	0	0	1	2	0	0
	Mild	0	0	0	0	5	6	2	4
	Moderate	0	0	0	0	0	0	2	4
Spleen									
Decreased numbers, lymphocytes, marginal zone									
	Minimal	0	0	0	0	0	0	2	0
	Moderate	0	0	0	0	0	0	1	0
Bone Marrow									
Hypocellularity									
	Minimal	0	0	0	0	0	0	5	5
	Mild	0	0	0	0	0	0	1	0

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**10**		**50**		**100**	
Number of Animals	M:5	F:5	M:0	F:0	M:4	F:5	M:3	F:5
Noteworthy Findings Recovery Phase:								
Hematology [k]								
White blood cells (E9/L)	12.676	7.680	NA	NA	10.013	7.218	9.817	5.772 *
Lymphocytes (E9/L)	10.134	6.152	NA	NA	8.153	5.768	7.147	4.684
RBC (E12/L)	9.154	8.322	NA	NA	8.473	7.958	8.363	8.250
HGB (g/dL)	15.80	15.48	NA	NA	15.00	14.98	14.77	15.60
HCT (%)	50.12	47.98	NA	NA	48.25	45.98	47.80	48.40
Serum Chemistry [k]								
Phosphorous (mg/dL)	7.94	7.74	NA	NA	9.28*	8.20	9.47*	8.28
Urinalysis	-	-	NA	NA	-	-	-	-
Organ Weights	-	-	NA	NA	-	-	-	-
Microscopic Observations								
Kidney	-	-	NA	NA	-	-	-	-
Thymus	-	-	NA	NA	-	-	-	-
Immunophenotyping, cells/µL [g]								
Cytotoxic T cells	1553	889	NA	NA	842	744	510	484
Mature B cells	2261	1329	NA	NA	2135	975	1545	729

2.6.7.7.2 Repeat-Dose Toxicity - Report R&D/11/1044 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit
NA	Not Applicable
NOAEL	No-Observed-Adverse-Effect Level
-	No noteworthy findings
*	$p < 0.05$
**	$p < 0.01$
***	$p < 0.001$
+, ++, +++	Mild, Moderate, Marked

a. Rats in the 200 mg/kg/day group died or were euthanized on Study Days 1-3 due to excessive toxicity.
b. Five rats per sex per group within the control, 50, 100 and 200 mg/kg/day groups were designated recovery animals to be maintained for one month without dosing after the treatment period. Animal numbers within parentheses denote satellite subgroups used for measurement of plasma upadacitinib concentrations.
c. Cause of death of male in 50 mg/kg/day group was not upadacitinib-related. Deaths of five males at 100 mg/kg/day (three main study, two recovery) were considered upadacitinib-related and occurred on Dosing Days 1, 3, 4, 18, and 26. Due to excessive toxicity at 200 mg/kg/day, four males and six females were found dead or euthanized in moribund condition on Dosing Day 1, and the remaining animals in the group were euthanized on Dosing Days 2 and 3.
d. Number of animals with each upadacitinib-related clinical observation followed by severity score (i.e., 5+++ means 5 animals had the clinical finding with marked severity).
e. Moribund animals only
f. Absolute values of group means listed from Dosing Day 30.
g. Absolute values of group means at the end of the Dosing period.
h. Number indicates incidence of finding.
i. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data not on the percent differences. Both absolute and relative weights differed from controls in the direction indicated
j. Finding observed in early death animals only. Similar liver necrosis not observed among animals administered 100 mg/kg/day upadacitinib that survived to scheduled necropsy at the end of the Dosing or Recovery period.
k. Absolute values of group means listed from Recovery Day 29.

2.6.7.7.3 Repeat-Dose Toxicity - Report Title: 26-Week Oral Dose Toxicity Study with A-1293543 Tartrate in Sprague-Dawley Rats (R&D/12/544)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain: Rat/CD®[Crl:CD® (SD)]	**Duration of Dosing:** 26 weeks	**Report Number:**	R&D/12/544
		(Module)	(4.2.3.2-4)
Initial Age: 8 weeks (start of dosing)	**Duration of Postdose:** NA	**Study Number:**	TA12-067
Date of First Dose: [redacted] 20[redacted]	**Route (Method) of Administration:** Oral (gavage)	[redacted] **Study Number:**	[redacted]
Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (HPMC) in deionized water; Dose volume = 10 mL/kg		**GLP Compliant:**	Yes

Special Features: None

NOAEL: 20 mg/kg/day

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals [a]	20	20	20	20	20	20	20	20
Toxicokinetics: [b]								
C_{max} (µg/mL)								
Day 1	BQL	0.0626	0.552	2.62	BQL	0.266	1.67	6.44
Day 51	BQL	0.0909	1.05	3.92	BQL	0.342	1.82	5.10
Day 178	BQL	0.0997	1.11	4.22	BQL	0.522	2.24	5.26
AUC (µg•hr/mL)								
Day 1	NA	0.248	1.48	6.35	NA	0.596	3.29	15.7
Day 51	NA	0.405	2.80	13.3	NA	0.977	5.15	26.2
Day 178	NA	0.462	3.83	12.1	NA	1.39	6.84	22.1

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males				Females			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	20	20	20	20	20	20	19	20
Noteworthy Findings:								
Mortality[c]	0	0	0	0	0	0	1	0
Clinical Observations	-	-	-	-	-	-	-	-
Body Weight	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Ophthalmology	-	-	-	-	-	-	-	-
Hematology[d]								
Leukocytes (10^3/µL)								
Week 13	9.78	-23†	-45†	-54†	7.33	-24†	-48†	-54†
Terminal	10.27	-17†	-39†	-46†	7.72	-26†	-38†	-39†
Lymphocytes (10^3/µL)								
Week 13	8.048	-32†	-56†	-69†	6.059	-35†	-56†	-70†
Terminal	8.197	-26†	-48†	-58†	6.155	-35†	-49†	-51†
Eosinophils (10^6/µL)								
Week 13	0.136	-24†	-43†	-51†	0.099	-16†	-42†	-32†
Terminal	0.133	-	-30	-50†	0.100	-11	-39†	-33†
Hemoglobin (g/dL)								
Week 13	15.58	-	-4†	-6†	14.93	-	-	-4†
Terminal	15.18	-	-4†	-7†	14.78	-	-	-6†

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	20	20	20	20	20	20	20	20
Noteworthy Findings:								
Hematology [d]								
RDW (%)								
Week 13	12.72	-	+4†	+8†	11.91	-	-	+5†
Terminal	12.96	-	+5†	+7†	11.39	-	-	+9†
Reticulocytes (10^3/µL)								
Week 13	174.10	-	-	-14†	154.94	-	-	-20†
Terminal	197.92	-	-	-	187.77	-	-	-
Platelets (10^3/µL)								
Week 13	836.1	-	-	-	863.4	-	-	-
Terminal	1110.4	-	-	+27†	972.4	-	+15†	+34†
Coagulation	-	-	-	-	-	-	-	-
Clinical Chemistry	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males				Females			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	20	20	20	20	20	20	20	20
Noteworthy Findings:								
Organ Weights [e]								
Spleen (g)	1.008	0.812**	0.630**	0.560**	0.604	0.428**	0.402**	0.378**
Thymus (g)	0.415	0.380	0.349	0.272**	0.263	0.276	0.245	0.204
Gross Observations								
Stomach, nonglandular								
Focus/foci, tan								
Mild	0	0	0	1	0	0	0	0
Irregular surface								
Moderate	0	0	0	1	0	0	0	0
Histopathology [f]								
Number Examined	20	20	20	20	20	20	20	20
Kidneys								
Degeneration/regeneration, tubular								
Minimal	0	0	0	9	0	0	0	4
Mild	0	0	0	6	0	0	0	4
Moderate	0	0	0	1	0	0	0	0
Thymus								
Depletion, lymphoid, generalized								
Minimal	0	8	14	7	0	0	2	6
Mild	0	1	0	8	0	0	0	8
Moderate	0	0	0	1	0	0	0	2

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	20	20	20	20	20	20	20	20
Noteworthy Findings:								
Histopathology [f]								
Spleen								
Depletion, lymphoid, generalized								
minimal	0	4	6	3	0	10	7	4
mild	0	1	7	14	0	0	8	13
moderate	0	0	0	2	0	0	0	2
Lymph nodes								
Mandibular								
Depletion, lymphoid, generalized								
minimal	0	0	0	2	0	0	0	3
mild	0	0	1	0	0	0	0	1
moderate	0	0	0	1	0	0	0	0
Medial iliac								
Depletion, lymphoid, generalized								
minimal	0	0	2	0	0	0	0	2
mild	0	0	1	3	0	0	0	2
moderate	0	0	0	7	0	0	0	0

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Noteworthy Findings:								
Histopathology [f]								
Lymph nodes								
Mediastinal								
Depletion, lymphoid, generalized								
minimal	0	0	0	2	0	0	1	3
mild	0	0	0	0	0	0	0	1
Mesenteric								
Depletion, lymphoid, generalized								
minimal	0	0	0	2	0	0	0	0

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Noteworthy Findings:								
Histopathology [f]								
Stomach, non-glandular								
Ulcer, limiting ridge, focal								
minimal	0	0	1	0	0	0	0	1
Ulcer, multifocal								
mild	0	0	0	1	0	0	0	0
Ulcer, focal								
mild	0	0	0	0	0	0	0	1
Erosion, limiting ridge, focal								
minimal	0	0	0	4	0	0	0	4
Erosion, focal								
minimal	0	0	0	1	0	0	0	0
Tongue								
Erosion, focal								
minimal	0	0	0	0	0	0	0	1
mild	0	0	0	0	0	0	0	1

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**5**	**20**	**50**	**0**	**5**	**20**	**50**
Number of Animals	**20**	**20**	**20**	**20**	**20**	**20**	**20**	**20**
Noteworthy Findings:								
Histopathology [f]								
Tongue								
Erosion, multifocal								
minimal	0	0	0	1	0	0	0	1
Inflammation, subacute/chronic								
minimal	1	0	2	0	0	0	0	1
mild	0	1	1	4	0	0	0	5
moderate	0	0	0	2	0	0	0	1

2.6.7.7.3 Repeat-Dose Toxicity - Report R&D/12/544 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit
NA	Not applicable
NOAEL	No-Observed-Adverse-Effect Level
-	No noteworthy findings
*	Statistically different from control; $p < 0.05$
**	Statistically different from control; $p < 0.01$
†	Statistically different from control

a. Blood samples for plasma upadacitinib concentration analysis were collected from cohorts of three to four surviving animals/sex/group/time point.

b. Group means are shown for treated groups; the control group was only analyzed for plasma concentration.

c. One female at 20 mg/kg/day was found dead on Day 80; the death was not considered upadacitinib-related due to the single incidence and dose level (mid-dose) of this animal.

d. Group means are shown for control. For upadacitinib dosed groups, difference from controls is shown. Values differed from controls in the direction indicated. Number indicates percent change from control group mean.

e. Group means are shown.

f. Reported as number observed.

2.6.7.7.4 Repeat-Dose Toxicity - Report Title: Four-Week Oral Toxicity Study of A-1293543 in Beagle Dogs with a Four-Week Recovery Period (R&D/11/1001)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Dog/Beagle	**Duration of Dosing:**	28-31 days	**Report Number:**	R&D/11/1001
				(Module)	(4.2.3.2-6)
Initial Age:	6-7 months	**Duration of Postdose:**	29 days	**Study Number:**	TB11-225
Date of First Dose:	[redacted], 20[redacted]	**Route (Method) of Administration:**	Oral (capsule)	**GLP Compliant:**	Yes

Vehicle/Formulation: PEG 400: Tween 20 (70:30, by weight) acidified with 1 molar equivalent of p-toluenesulfonic acid monohydrate; Dose volume = 1 mL/kg

Special Features: Peripheral Blood Lymphocyte Immunophenotyping

NOAEL: 1.5 mg/kg/day

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals	M:6	F:6	M:4	F:4	M:6	F:6	M:4	F:4	M:6	F:6
Toxicokinetics										
Day 1: C_{max} (ng/mL)	BQL	BQL	91.7	131	415	394	598	636	1270	1200
Day 28: C_{max} (ng/mL)	BQL	BQL	61.8	90.8	290	303	514	581	751	1290
Day 1: AUC (ng•hr/mL)	NA	NA	292	427	1460	1430	2120	2280	4270	4590
Day 28: AUC (ng•hr/mL)	NA	NA	270	408	1240	1170	2130	2160	3520	4680

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	0		0.5		1.5		3		5	
Noteworthy Findings Dosing Phase										
Number of Animals (Main Study)	M:6	F:6	M:4	F:4	M:6	F:6	M:4	F:4	M:6	F:6
Mortality	-	-	-	-	-	-	-	-	-	-
Body Weight, kg (%) [a]	8.572	6.8817	+(1.12)	+(1.00)	-(0.702)	-(2.468)	-(0.047)	+(3.184)	-(3.859)	-(1.313)
Body Weight Gain, kg [b]	0.2002	0.2250	0.0445	0.2522	0.1806	0.1988	0.1370	0.2555	-(0.0260)	0.1870
Food Consumption, g/day (%) [a]	249.73	187.50	+(0.8)	+(20.9)	-(7.7)	+(28.1)	+(3.3)	+(26.5)	+(1.1)	+(8.2)
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Ophthalmoscopy	-	-	-	-	-	-	-	-	-	-
Electrocardiography	-	-	-	-	-	-	-	-	-	-

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals (Main Study)	M:6	F:6	M:4	F:4	M:6	F:6	M:4	F:4	M:6	F:6
Hematology [c]										
Red blood cells (E12/L) [d]	-5 to +17	-9 to +17	-	-	-14 (1 of 6)	-	-15 to -18 (4 of 4)	-14 (1 of 4)	-13 to -25 (5 of 6)	-15 to -27 (5 of 6)
Hemoglobin (g/dL) [d]	-4 to +18	-9 to +19	-	-	-14 (1 of 6)	-	-16 to -20 (4 of 4)	-15 (1 of 4)	-15 to -25 (5 of 6)	-17 to -29 (5 of 6)
Hematocrit (%) [d]	-9 to +12	-13 to +13	-	-	-15 to -18 (2 of 6)	-	-21 to -23 (4 of 4)	-17 (1 of 4)	-16 to -29 (6 of 6)	-20 to -32 (5 of 6)
Reticulocytes (E9/L) [d]	-4 to +46	-26 to +42	-40 (1 of 4)	-57 (1 of 4)	-40 to -65 (3 of 6)	-33 to -37 (2 of 6)	-41 to -59 (4 of 4)	-30 to -61 (3 of 4)	-45 to -68 (5 of 6)	-30 to -67 (6 of 6)
Lymphocyte counts (E9/L)	0 to +24	-17 to +15	-	-	-	-	-	-	-27 to -37 (3 of 6)	-20 to -31 (3 of 6)

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals (Main Study)	M:6	F:6	M:4	F:4	M:6	F:6	M:4	F:4	M:6	F:6
Hematology										
Immunophenotyping cells/µL[e]										
Mature T cells, pre-dose	1357	1491	1289	1394	1198	1612	1213	1303	1519	1622
Mature T cells, end of dosing	1856	1438	869	1304	1032	1397	838	1170	1004	1036
Cytotoxic T cells, pre-dose	379	444	352	389	342	391	305	321	468	436
Cytotoxic T cells, end of dosing	424	381	224	270	192	247	174	222	165	208
Cytotoxic T cells (% of gated), pre-dose	18.59	19.74	17.14	19.37	17.72	17.64	17.62	18.23	21.68	20.04
Cytotoxic T cells (% of gated), end of dosing	20.52	21.28	17.21	18.89	13.94	13.56	14.22	13.51	13.63	15.40
Coagulation	-	-	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-	-	-

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals (Main Study)	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Organ Weights [f] (%)										
Thymus	7.5315	6.1523	-27	-28	-37	-10	-37	+35	-32	-35
Spleen	66.3473	68.4023	-28	-24	-7	-20	-17	-6	-14	-26
Gross Observations	-	-	-	-	-	-	-	-	-	-
Microscopic Observations [g]										
Spleen										
Decreased number, lymphocytes, follicles										
Minimal, diffuse	0	0	0	0	0	0	1	0	1	0
Thymus										
Decreased number, lymphocytes, cortex										
Minimal, diffuse	0	0	0	0	0	1	1	1	1	3
Mild, diffuse	0	0	0	0	0	0	2	0	1	0
Moderate, diffuse	0	0	0	1	0	0	0	0	0	0
Lymph node, popliteal [h]										
Infiltration, mixed cell, capsule										
Minimal, locally extensive	0	0	0	0	0	0	0	0	1	0
Minimal, multifocal	0	0	1	0	1	0	0	0	0	2
Mild, multifocal (males), focal (females)	0	0	0	0	0	0	1	1	0	0

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals (Main Study)	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Microscopic Observations [g]										
Lymph node, popliteal [h]										
Infiltration, mixed cell, multi-focal, sinus(es), subcapsular										
Minimal	0	0	0	0	0	0	0	0	0	1
Moderate	0	0	0	0	0	0	1	0	1	0
Lymph node, mandibular										
Decreased number, lymphocytes, cortex										
Mild	0	0	0	0	1	0	0	1	0	0
Moderate	0	0	0	0	0	0	1	0	1	1
Decreased number, lymphocytes, medulla										
Mild	0	0	0	0	1	1	0	1	0	0
Moderate	0	0	0	0	0	0	1	0	1	1
Lymph node, mesenteric										
Decreased number, lymphocytes, cortex										
Mild	0	0	0	0	0	0	0	0	2	0
Moderate	0	0	0	1	0	0	0	0	0	0
Decreased number, lymphocytes, medulla										
Mild	0	0	0	0	0	0	0	0	1	0

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals (Main Study)	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4	M:4	F:4
Microscopic Observations [g]										
Lymph node, tracheobronchial										
Decreased number, lymphocytes, cortex										
Minimal	0	0	0	0	0	0	0	0	1	0
Mild	0	0	0	1	0	0	1	0	0	0
Marked	0	0	0	0	0	0	0	0	1	0
Decreased number, lymphocytes, medulla										
Mild	0	0	0	0	0	0	1	0	0	0
Marked	0	0	0	0	0	0	0	0	1	0
Bone marrow, hypocellularity										
Minimal	0	0	0	0	0	0	2	0	3	1
Mild	0	0	0	0	0	0	0	0	0	1

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**0.5**		**1.5**		**3**		**5**	
Number of Animals (Recovery)	M:2	F:2	M:0	F:0	M:2	F:2	M:0	F:0	M:2	F:2
Noteworthy Findings Recovery Phase										
Hematology	-	-	NE	NE	-	-	NE	NE	-	-
Microscopic Observations [g]										
Spleen	-	-	NA	NA	-	-	NA	NA	-	-
Thymus										
Decreased number, lymphocytes, cortex, marked, diffuse	0	0	NA	NA	0	0	NA	NA	1	0
Lymph node, popliteal [h]										
Infiltration, mixed cell, capsule, minimal, multifocal	0	0	NE	NE	0	0	NE	NE	0	1
Infiltration, mixed cell, multifocal, sinus(es), sub-capsular, mild	0	0	NE	NE	0	0	NE	NE	1	0
Lymph node, mandibular	-	-	NE	NE	-	-	NE	NE	-	-
Lymph node, mesenteric	-	-	NE	NE	-	-	NE	NE	-	-
Lymph node, tracheobronchial	-	-	NE	NE	-	-	NE	NE	-	-
Bone marrow, hypocellularity	-	-	NE	NE	-	-	NE	NE	-	-
Organ Weights [f] **(%)**										
Thymus	8.9330	-	NE	NE	-25	-	NE	NE	-45	-
Spleen	-	-	NE	NE	-	-	NE	NE	-	-

2.6.7.7.4 Repeat-Dose Toxicity - Report R&D/11/1001 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit
F	Female
M	Male
NA	Not applicable
NE	Not examined
NOAEL	No-Observed-Adverse-Effect Level
-	No noteworthy findings

a. Measured on Day 28. For controls, group means are shown. For dosed groups, percent change relative to baseline values is shown.

b. Body weight gain between Days 1 and 28. Group mean values shown for both control and treated groups.

c. Dosing Day 29. Range expressed as the percent change from individual baseline values including incidence (in parentheses) for affected upadacitinib treated animals.

d. Decreases considered adverse at 3 and 5 mg/kg/day.

e. Absolute values of group means pre-dose or at the end of the dosing period.

f. Both absolute and relative weights differed from controls in the direction indicated. For controls, number listed is mean absolute weight (g). For upadacitinib-dosed groups, number indicates percent difference from control absolute organ weight mean.

g. Number indicates incidence of finding.

h. Finding considered adverse at 3 and 5 mg/kg/day at the end of the dosing phase and at 5 mg/kg/day at the end of the recovery phase due to extension of the infiltrate into the pericapsular tissue.

2.6.7.7.5 Repeat-Dose Toxicity - Report Title: Thirty-Nine Week Oral Toxicity Study of A-1293543 Tartrate in Beagle Dogs (R&D/12/324)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Dog/Beagle	**Duration of Dosing:**	39 weeks (273 to 275 days)	**Report Number:** (Module)	R&D/12/324 (4.2.3.2-7)
Initial Age:	8 months	**Duration of Post-dose:**	NA	**Study Number:**	TB12-042
Date of First Dose:	[redacted]20[redacted]	**Route (Method) of Administration:**	Oral (capsule)	**GLP Compliant:**	Yes
Vehicle/Formulation:	0.2% hydroxypropyl methylcellulose (HPMC) in sterile water; Dose volume = 1 mL/kg				
NOAEL:	1.5 mg/kg/day				

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**0.1**	**0.5**	**1.5**	**0**	**0.1**	**0.5**	**1.5**
Number of Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Toxicokinetics [a]								
Day 272: C_{max} (ng/mL)	BQL	11.8	82.3	210	BQL	17.0	69.4	214
Day 272: AUC (ng•hr/mL)	NA	48.4	350	937	NA	59.7	278	850

2.6.7.7.5 Repeat-Dose Toxicity - Report R&D/12/324 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males				Females			
Daily Dose (mg/kg/day)	**0**	**0.1**	**0.5**	**1.5**	**0**	**0.1**	**0.5**	**1.5**
Number of Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Dosing Phase, Noteworthy Findings								
Mortality	0	0	0	0	0	0	0	0
Body Weight	-	-	-	-	-	-	-	-
Food Consumption	-	-	-	-	-	-	-	-
Clinical Observations								
Paw swelling [b]	2 (6)	0	2 (36)	3 (204)	0	3 (18)	2 (13)	2 (138)
Ophthalmoscopy [c]	-	-	-	-	-	-	-	-
Electrocardiography [c]	-	-	-	-	-	-	-	-

2.6.7.7.5 Repeat-Dose Toxicity - Report R&D/12/324 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**0.1**	**0.5**	**1.5**	**0**	**0.1**	**0.5**	**1.5**
Number of Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Clinical Pathology [d]								
Hematology								
Red blood cell count (E12/L)								
Dosing Day 28	-7 to +3	-3 to +3	-13 to +1	-12 to -8	-4 to +8	-5 to +2	-9 to +2	-13 to +1
Dosing Day 91	-1 to +8	-3 to +1	-15 to +6	-21 to -13	-7 to +6	-9 to +9	-11 to +4	-20 to 0
Dosing Day 182	-5 to +2	-4 to -1	-16 to +4	-18 to -8	-12 to +7	-12 to +5	-13 to +2	-15 to 0
Dosing Day 265	+4 to +11	-1 to +9	-12 to +5	-14 to -4	-10 to +12	-5 to +8	-10 to -5	-10 to +7
Hemoglobin (g/dL)								
Dosing Day 28	-6 to +2	-2 to +2	-13 t +2	-13 to -9	-2 to +9	-6 to +2	-8 to +4	-13 to +2
Dosing Day 91	-1 to +9	-2 to +3	-15 to +7	-23 to -11	-5 to +11	-8 to +10	-11 to +9	-20 to +2
Dosing Day 182	-3 to +3	-1 to 0	-16 to +4	-19 to -5	-11 to +11	-10 to +9	-10 to +8	-15 to +3
Dosing Day 265	+5 to +11	0 to +9	-13 to +5	-14 to -1	-6 to +14	-4 to +14	-9 to -1	-12 to +11
Hematocrit (%)								
Dosing Day 28	-7 to 0	-5 to 0	-13 to 0	-13 to -9	-4 to +8	-7 to +1	-10 to +1	-15 to -2
Dosing Day 91	-2 to +6	-5 to 0	-15 to +6	-22 to -9	-8 to +7	-9 to +7	-12 to +5	-21 to -2
Dosing Day 182	-6 to -1	-7 to -5	-17 to +2	-19 to -6	-14 to +7	-13 to +3	-12 to +3	-15 to 0
Dosing Day 265	+3 to +9	-1 to +5	-11 to +5	-14 to -1	-9 to +12	-6 to +10	-9 to -1	-10 to +8

2.6.7.7.5 Repeat-Dose Toxicity - Report R&D/12/324 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males				Females			
Daily Dose (mg/kg/day)	**0**	**0.1**	**0.5**	**1.5**	**0**	**0.1**	**0.5**	**1.5**
Number of Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Clinical Pathology [d]								
Hematology (Dosing Day 265)								
White blood cells (E9/L)	-20 to +15	-20 to -9	-40 to +3	+52 to +83	-15 to -4	-17 to +20	-36 to 0	-14 to +39
Neutrophils (E9/L)	-20 to +32	-16 to +6	-30 to +35	+87 to +132	-19 to +6	-16 to +50	-27 to +13	-1 to +71
Coagulation	-	-	-	-	-	-	-	-
Serum Chemistry	-	-	-	-	-	-	-	-
Urinalysis	-	-	-	-	-	-	-	-

2.6.7.7.5 Repeat-Dose Toxicity - Report R&D/12/324 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males				Females			
Daily Dose (mg/kg/day)	**0**	**0.1**	**0.5**	**1.5**	**0**	**0.1**	**0.5**	**1.5**
Number of Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Organ Weights (%)	-	-	-	-	-	-	-	-
Gross Observations [e]								
Skin								
Abnormal surface (Interdigital cysts)								
Present	0	0	1	2	1	1	2	0
Moderate	0	0	0	1	0	0	0	0
Microscopic Observations [f]								
Skin, interdigital								
Inflammation, mixed cell								
Minimal	2	0	1	0	0	1	1	0
Mild	1	1	1	0	3	2	0	4
Moderate	1	3	2	1	1	0	2	0
Marked	0	0	0	3	0	1	1	0
Arthropod (Demodex spp.) Present	0	0	0	4	0	0	0	4

2.6.7.7.5 Repeat-Dose Toxicity - Report R&D/12/324 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**				**Females**			
Daily Dose (mg/kg/day)	**0**	**0.1**	**0.5**	**1.5**	**0**	**0.1**	**0.5**	**1.5**
Number of Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Microscopic Observations [f]								
Lymph node								
Prescapular								
Inflammation, mixed cell								
Minimal	0	0	0	1	0	0	1	0
Mild	0	0	0	1	0	0	0	0
Popliteal								
Inflammation, mixed cell								
Minimal	0	1	2	1	1	0	2	1
Mild	0	0	0	1	0	0	0	1
Moderate	0	0	0	1	0	0	0	0
Marked	0	0	0	1	0	0	0	0

2.6.7.7.5 Repeat-Dose Toxicity - Report R&D/12/324 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit (< 1.27 ng/mL)
NA	Not applicable
-	No noteworthy findings
NOAEL	No-Observed-Adverse-Effect Level

a. Day 272 plasma upadacitinib exposures (C_{max} and AUC) were similar, by dose level, to Days 1, 35, and 218. Upadacitinib was not detected in the plasma samples from control animals.

b. Number of animals (total number of observations in parenthesis). The total number of observations includes all observations of paw swelling, which may have been more than one paw on a given day. For Animal 4005 (male at 1.5 mg/kg/day), upadacitinib administration was suspended on Day 219 due to clinical findings (increased neutrophil counts, paw swelling, and demodicosis) that were considered secondary to upadacitinib administration. Animal 4005 was maintained on study without dose administration and provided necessary veterinary care until the scheduled necropsy on Day 275. Clinical observation data from Animal 4005 that was recorded on/after Day 219 is not presented in this table.

c. Ophthalmoscopic examinations were conducted on Day 267 and electrocardiographic tracings were recorded on Days 6 and 265.

d. Red blood cell mass (red blood cell count, hemoglobin, and hematocrit), white blood cell and neutrophil counts expressed as the range of percent change for individual animals as compared to respective mean baseline values.

e. Findings at necropsy.

f. Incidence of noteworthy microscopic observations, by severity.

2.6.7.8 Genotoxicity: In Vitro

2.6.7.8.1 Genotoxicity: In Vitro - Report Title: Bacterial Reverse Mutation Assay with A 1293543 Free Form (R&D/11/1293)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Test for Induction of:	Reverse mutation in bacterial cells	**Number of Independent Assays:**	2	**Report Number:**	R&D/11/1293
				(Module)	(4.2.3.3.1-1)
Species/Strain:	S. typhimurium, E. coli	**Number of Replicate Plates:**	2	**Study Number:**	TX11-235
				[redacted] **Study Number:**	[redacted]
Metabolizing System:	Aroclor™ 1254-induced rat liver S9			**GLP Compliant:**	Yes
Vehicles:	**For Test Article:** Dimethyl sulfoxide (DMSO)	**For Positive Controls:**	DMSO, except water for sodium azide		
Treatment:	Plate incorporation for initial toxicity-mutation assay			**Date of Treatment:**	[redacted] 20[redacted]
Cytotoxic Effects:	None				
Genotoxic Effects:	None				

2.6.7.8.1 Genotoxicity: In Vitro - Report R&D/11/1293 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Metabolic Activation	Test Article	Concentration Level (µg/plate)	Initial Toxicity-Mutation Assay Revertant Colony Counts (Mean ±SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without Activation	DMSO[a]	50 µL	15 ± 6	129 ± 6	9 ± 1	8 ± 1	45 ± 4
	A-1293543	1.5	18 ± 3	114 ± 16	13 ± 3	6 ± 2	36 ± 7
		5.0	18 ± 4	109 ± 13	10 ± 1	5 ± 3	41 ± 10
		15	18 ± 4	90 ± 11	10 ± 4	5 ± 3	42 ± 14
		50	17 ± 3	103 ± 11	7 ± 3	10 ± 3	47 ± 8
		150	20 ± 1	106 ± 1	7 ± 0	8 ± 1	26 ± 4
		500	17 ± 3	118 ± 18	6 ± 4	10 ± 2	37 ± 5
		1500	16 ± 4	98 ± 11	7 ± 4	6 ± 1	36 ± 4
		5000	13 ± 3	97 ± 3	11 ± 3	6 ± 3	32 ± 9
	2NF[b]	1.0	224 ± 11				
	SA[c]	1.0		722 ± 134	563 ± 8		
	9AAD[d]	75				416 ± 21	
	MMS[e]	1000					527 ± 30

a. DMSO: dimethyl sulfoxide
b. 2NF: 2-nitrofluorene
c. SA: sodium azide
d. 9AAD: 9-aminoacridine
e. MMS: methyl methanesulfonate

2.6.7.8.1 Genotoxicity: In Vitro - Report R&D/11/1293 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Metabolic Activation	Test Article	Concentration Level (µg/plate)	Initial Toxicity-Mutation Assay Revertant Colony Counts (Mean ±SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
With Activation	DMSO[a]	50 µL	18 ± 2	133 ± 21	9 ± 0	10 ± 2	43 ± 7
	A-1293543	1.5 µg	16 ± 6	134 ± 1	11 ± 4	4 ± 4	42 ± 6
		5.0 µg	21 ± 5	126 ± 7	11 ± 2	3 ± 2	51 ± 4
		15 µg	22 ± 4	134 ± 6	10 ± 1	5 ± 0	46 ± 11
		50 µg	25 ± 1	135 ± 6	12 ± 0	6 ± 3	49 ± 6
		150 µg	23 ± 16	120 ± 7	9 ± 5	7 ± 2	35 ± 2
		500 µg	14 ± 2	140 ± 2	16 ± 1	8 ± 6	38 ± 1
		1500 µg	19 ± 6	112 ± 3	10 ± 7	7 ± 2	50 ± 1
		5000 µg	15 ± 3	126 ± 0	10 ± 2	5 ± 0	40 ± 2
	2AA[b]	1.0 µg	332 ± 33		51 ± 2	56 ± 8	
	2AA	2.0 µg		796 ± 19			
	2AA	15 µg					297 ± 4

a. DMSO: dimethyl sulfoxide

b. 2AA: 2-aminoanthracene

2.6.7.8.1 Genotoxicity: In Vitro - Report R&D/11/1293 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Test for Induction of:	Reverse mutation in bacterial cells	**Number of Independent Assays:**	2	**Report Number:**	R&D/11/1293
				(Module)	(4.2.3.3.1-1)
Species/Strain:	S. typhimurium, E. coli	**Number of Replicate Plates:**	3	**Study Number:**	TX11-235
				[redacted] **Study Number:**	[redacted]
Metabolizing System:	Aroclor™ 1254-induced rat liver S9			**GLP Compliant:**	Yes
Vehicles:	**For Test Article:** Dimethyl sulfoxide (DMSO)	**For Positive Controls:**		DMSO, except water for sodium azide	
Treatment:	Preincubation for 60 ± 2 minutes at 37°C for confirmatory mutagenicity assay			**Date of Treatment:**	[redacted] 20[redacted]
Cytotoxic Effects:	Toxicity was observed beginning at 1500 µg per plate with tester strains TA100 and TA1537 in the absence of S9 activation.				
Genotoxic Effects:	None				

2.6.7.8.1 Genotoxicity: In Vitro - Report R&D/11/1293 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Metabolic Activation	Test Article	Concentration Level (µg/plate)	Confirmatory Mutagenicity Assay Revertant Colony Counts (Mean ±SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
Without Activation	DMSO[a]	50 µL	16 ± 2	101 ± 10	15 ± 5	8 ± 2	21 ± 5
	A-1293543	50 µg	19 ± 0	114 ± 4	12 ± 3	4 ± 1	20 ± 4
		150 µg	14 ± 3	106 ± 7	10 ± 6	6 ± 2	21 ± 7
		500 µg	16 ± 5	111 ± 5	16 ± 8	6 ± 2	27 ± 2
		1500 µg	7 ± 4	74 ± 10	10 ± 5	3 ± 2	30 ± 3
		5000 µg[b]	15 ± 1	102 ± 6	10 ± 3	4 ± 3	26 ± 8
	2NF[c]	1.0 µg	647 ± 28				
	SA[d]	1.0 µg		886 ± 95	890 ± 13		
	9AAD[e]	75 µg				736 ± 146	
	MMS[f]	1000 µg					858 ± 68

a. DMSO: dimethyl sulfoxide
b. Precipitate
c. 2NF: 2-nitrofluorene
d. SA: sodium azide
e. 9AAD: 9-aminoacridine
f. MMS: methyl methanesulfonate

2.6.7.8.1 Genotoxicity: In Vitro - Report R&D/11/1293 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Metabolic Activation	Test Article	Concentration Level (µg/plate)	Confirmatory Mutagenicity Assay Revertant Colony Counts (Mean ±SD)				
			TA98	TA100	TA1535	TA1537	WP2*uvr*A
With Activation	DMSO[a]	50 µL	26 ± 6	149 ± 6	15 ± 2	7 ± 2	32 ± 6
	A-1293543	50 µg	25 ± 7	161 ± 8	9 ± 2	8 ± 2	34 ± 3
		150 µg	30 ± 4	152 ± 7	10 ± 3	7 ± 1	39 ± 9
		500 µg	28 ± 4	154 ± 9	10 ± 4	6 ± 6	38 ± 12
		1500 µg	25 ± 10	121 ± 22	10 ± 3	7 ± 2	25 ± 8
		5000 µg	21 ± 2	124 ± 10	9 ± 2	7 ± 4	40 ± 12
	2AA[b]	1.0 µg	474 ± 17		643 ± 324	412 ± 71	
	2AA	2.0 µg		737 ± 93			
	2AA	15 µg					111 ± 7

a. DMSO: dimethyl sulfoxide

b. 2AA: 2-aminoanthracene

2.6.7.8.2 Genotoxicity: In Vitro - Report Title: In Vitro Mammalian Chromosome Aberration Test with A-1293543 Free Form (R&D/11/1294)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Test for Induction of:	Chromosome aberrations	**Number of Independent Assays:**	1	**Report Number:**	R&D/11/1294
				(Module)	(4.2.3.3.1-2)
Strains:	Human Peripheral Blood Lymphocytes (HPBL)	**Number of Replicate Cultures:**	2	**Study Number:**	TX11-236
				[redacted] **Study Number:**	[redacted]
Metabolizing System:	Aroclor-induced rat liver S9	**Number of Cells Analyzed/Culture:**	A-1293543: 100 for structural, 100 for numerical; Positive controls: 50 for structural, 100 for numerical		
Vehicles:	For Test Article: DMSO	**For Positive Controls:**	Water (MMC CP)	**GLP Compliant:**	Yes
Treatment:	20 hr without S9; 4 hr with 16 hr recovery period with and without S9	**Date of Treatment:**	[redacted] 20[redacted] (Definitive Assay)		

Cytotoxic Effects: Reduction in mitotic index in all three treatment conditions.

Genotoxic Effects: Negative for the induction of structural aberrations. Positive for the induction of numerical aberrations.

DMSO: dimethyl sulfoxide
MMC: mitomycin C
CP: cyclophosphamide

2.6.7.8.2 Genotoxicity: In Vitro - Report R&D/11/1294 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Metabolic Activation	Test Article	Dose µg/mL	Cytotoxicity[a] (% of Control)	Aberrant Cells		Aberrations per Cell[b,d]	Total Polyploid Cells (Mean %)	Total Endoreduplicated Cells (Mean %)
				Structural (Mean %)[b]	Numerical (Mean %)[c]			
20-hr Continuous	DMSO	NA	NA	0.0	0.5	0.000 ± 0.000	0.5	0.0
Treatment	A-1293543	25	16	0.0	3.0	0.000 ± 0.000	3.0	0.0
Without	A-1293543	50	26	0.0	7.0**	0.000 ± 0.000	7.0	0.0
Activation	A-1293543	100	55	0.0	1.5	0.000 ± 0.000	1.5	0.0
	MMC	0.3	50	30.0**	0.0	0.370 ± 0.661	0.0	0.0
4-hr Treatment	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0	0.0
With 16 hr Recovery	A-1293543	400	9	0.0	3.5*	0.000 ± 0.000	3.5	0.0
Without	A-1293543	512	10	0.5	3.5*	0.005 ± 0.071	3.5	0.0
Activation	A-1293543	640	51	0.0	0.5	0.000 ± 0.000	0.5	0.0
	MMC	0.6	58	25.0**	1.0	0.350 ± 0.796	1.0	0.0
4-hr Treatment	DMSO	NA	NA	0.0	0.0	0.000 ± 0.000	0.0	0.0
With 16 hr Recovery	A-1293543	327	-1	0.0	0.0	0.000 ± 0.000	0.0	0.0
With	A-1293543	400	12	1.5	0.0	0.015 ± 0.122	0.0	0.0
Activation	A-1293543	512	57	1.5	0.0	0.015 ± 0.122	0.0	0.0
	CP	5	59	14.0**	1.0	0.150 ± 0.386	1.0	0.0

DMSO: Dimethyl sulfoxide; MMC: Mitomycin C; CP: Cyclophosphamide; NA: Not Applicable; Fisher's Exact Test: * $p \leq 0.05$; ** $p \leq 0.01$.

a. Based on mitotic inhibition at least 500 cells analyzed.

b. Does not include cells with only gaps.

c. Includes polyploid and endoreduplicated cells.

d. Severely damaged cells counted as 10 aberrations

2.6.7.9 Genotoxicity: In Vivo

2.6.7.9.1 Genotoxicity: In Vivo - Report Title: Rat Bone Marrow Micronucleus Test with A-1293543 Free Form (R&D/12/350)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Test for Induction of: Micronuclei in bone marrow
Treatment Schedule: Single dose
Report Number: R&D/12/350
(Module) (4.2.3.3.2-1)
Species/Strain: Rat/HsdSD Sprague-Dawley
Route (Method) of Administration: Oral (gavage)
Study Number: TA12-044
Age/weight: 7 weeks
212.3 – 230.5 grams
Date of Dosing: [redacted] 20[redacted]
Study Number: [redacted]
Sampling Times: 24 and 48 hours post-dose
Cells Evaluated: Polychromatic erythrocytes (PCE)
GLP Compliant: Yes
Vehicles: **For Test Article:** PEG 400: Tween 20 (70:30 w/w) with 1M equivalent p-toluenesulfonic acid **For Positive Controls:** Sterile water for injection
Number of Cells Analyzed/Animal: 1000 (PCEs + NCEs) for bone marrow proliferation, 2000 PCEs for micronuclei screening
Cytotoxic Effects: None
Evidence of Exposure: Plasma exposure to test article
Genotoxic Effects: None

Controls/Test Article	Dose (mg/kg)	Number/ Sex of Animals	Micronucleus Test			
			PCEs/EC Ratio (Mean±SD)		mn-PCEs/Total PCEs/Group	
			Sampling Time (hours)		Sampling Time (hours)	
			24	48	24	48
Vehicle*	0	5/Male	0.447 ± 0.02	0.485 ± 0.03	5/10,000	4/10,000
A-1293543	37.5	5/Male	0.448 ± 0.04	NA	8/10,000	NA
A-1293543	75	5/Male	0.484 ± 0.03	NA	5/10,000	NA
A-1293543	150	5/Male	0.435 ± 0.02	0.517 ± 0.02	4/10,000	6/10,000
Cyclophosphamide	40	5/Male	0.425 ± 0.06	NA	**285/10,000	NA

*Vehicle = PEG400: Tween20 (70:30 w/w) with 1M equivalent p-toluenesulfonic acid.
** Statistically significant increase compared to the vehicle control, $p \leq 0.05$ (Kastenbaum-Bowman Tables).

N/A = not applicable; NCE = normochromatic erythrocytes; mn-PCEs = micronucleated polychromatic erythrocytes; EC = erythrocytes

2.6.7.10 Carcinogenicity

2.6.7.10.1 Carcinogenicity - Report Title: A-1293543 Free Form [ABT-494]: A 26-Week Oral Gavage Carcinogenicity Study in Model 001178-T (Hemizygous) CByB6F1-Tg(HRAS)2Jic Mice (R&D/16/0988)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Mice/Taconic Model 001178-T (hemizygous), CByB6F1-Tg(HRAS)2Jic	**Duration of Dosing:**	26 weeks	**Report Number:** (Module)	R&D/16/0988 (4.2.3.4.2-1)
Initial Age:	Approximately 6 weeks of age	**Route (Method) of Administration:**	Oral (gavage)	**Study Number:**	TD16-088
Date of First Dose:	[redacted] 20[redacted]	**Duration of Postdose:**	NA	[redacted] **Study Number:**	[redacted]
Vehicle:	0.2% hydroxypropyl methylcellulose (HPMC) in deionized water; Dose volume = 10 mL/kg			**GLP Compliant:**	Yes
Positive Control:	N-nitroso-N-methylurea (also known as N-methyl-N-nitrosurea or MNU)				
Special Features:	None				

Basis for High Dose Selection: Dose levels were selected based upon results of a 4-week toxicity study with upadacitinib in CByB6F1-Tg(HRAS)2Jic wildtype mice, with subsequent presentation and approval of an integrated dose selection justification to the FDA Carcinogenicity Assessment Committee.

Conclusion: Upadacitinib did not produce any evidence of a carcinogenic effect in Model 00178-T (Hemizygous) CByB6F1-Tg(HRAS)2Jic mouse model system following daily administration for 26 weeks.

2.6.7.10.1 Carcinogenicity - Report R&D/16/0988 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose Level (mg/kg/day)	**0**	**5**	**10**	**20**	**75 (mg/kg)** [a]	**0**	**5**	**10**	**20**	**75 (mg/kg)** [a]
Number of TK Animals	**6**	**18**	**18**	**18**	**0**	**6**	**18**	**18**	**18**	**0**
Toxicokinetics [b]**:**										
Mortality	0	0	0	0	NA	0	0	0	0	NA
C_{max} (ng/mL): Day 91	BQL	75.9	364	1170	NA	BQL	104	397	2590	NA
AUC (ng•hr/mL): Day 91	NA	91.7	284	844	NA	NA	153	271	1440	NA

2.6.7.10.1 Carcinogenicity - Report R&D/16/0988 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose Level (mg/kg/day)	**0**	**5**	**10**	**20**	**75 (mg/kg)** [a]	**0**	**5**	**10**	**20**	**75 (mg/kg)** [a]
Number of Animals	**25**	**25**	**25**	**25**	**15**	**25**	**25**	**25**	**25**	**15**
At Start of Study	25	25	25	25	15	25	25	25	25	15
Mortality[c]	2	0	1	1	4	0	1	0	1	6
Terminal Sacrifice	23	25	24	24	11	25	24	25	24	9
Survival of Carcinogenicity Animals (%)	92	100	96	96	73	100	96	100	96	60
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Body Weight [d] **(g) (%)**										
Week 26	26.44	-3	-2	-2	+10	21.02	-2	-5*	-4	+11
Food Consumption	-	-	-	-	-	-	-	-	-	-
Mass Findings	-	-	-	-	-	-	-	-	-	-
Not Planned per Study Protocol										
Ophthalmology										
Hematology										
Total Number of Neoplastic Lesions [e]										
Drug-related	0	0	0	0	25	0	0	0	0	33
Incidental	6	3	1	2	NA	2	3	2	3	NA
Number of Animals with Neoplastic Lesions [f]										
Adipose tissue										
Hemangiosarcoma, malignant, multicentric	0 (n=0)	0 (n=0)	1 (n=1)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)
Gallbladder										
Carcinoma, squamous cell, malignant, secondary	1 (n=23)	0	0 (n=24)	0 (n=24)	0 (n=0)	0	0	0	0	0 (n=0)

2.6.7.10.1 Carcinogenicity - Report R&D/16/0988 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose Level (mg/kg/day)	**0**	**5**	**10**	**20**	**75 (mg/kg) [a]**	**0**	**5**	**10**	**20**	**75 (mg/kg) [a]**
Number of Animals	**25**	**25**	**25**	**25**	**15**	**25**	**25**	**25**	**25**	**15**
Harderian glands										
Adenoma, benign, primary	0	2	0	0	0 (n=0)	0	1	0	2	0 (n=0)
Lung										
Adenoma, bronchiolar alveolar, benign, primary	0	1	0	0	4	0	1	0	1	2
Carcinoma, bronchiolar alveolar, malignant, primary	1	0	0	0	0	1	0	0	0	0
Carcinoma, squamous cell, malignant, secondary	1	0	0	0	0	0	0	0	0	0
Lymph node										
Carcinoma, squamous cell, malignant, secondary	1 (n=1)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)
Mesentery/peritoneum										
Carcinoma, squamous cell, malignant, secondary	1 (n=1)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)
Multicentric neoplasm										
Hemangiosarcoma, malignant, multicentric	0 (n=0)	0 (n=0)	1 (n=1)	1 (n=1)	0 (n=4)	1 (n=1)	0 (n=0)	2 (n=2)	0 (n=0)	1 (n=7)
Lymphoma, malignant, multicentric	0 (n=0)	0 (n=0)	0 (n=1)	0 (n=1)	4 (n=4)	0 (n=1)	0 (n=0)	0 (n=2)	0 (n=0)	6 (n=7)
Skin										
Papilloma, squamous cell, benign, primary	0	0	0	0	3 (n=3)	0	0	0	0	7 (n=7)
Small intestine, duodenum										
Adenoma, benign, primary	0 (n=24)	0	0	0	0 (n=0)	0	0	0	0	1 (n=1)
Stomach, nonglandular										
Carcinoma, squamous cell, malignant, primary	1	0	0	0	2	0	0	0	0	0
Papilloma, squamous cell, benign, primary	0	0	0	0	12	0	0	0	0	11
Spleen										
Hemangiosarcoma, malignant, multicentric	0	0	0	1 (n=24)	0	1	0	2	0	1

2.6.7.10.1 Carcinogenicity - Report R&D/16/0988 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose Level (mg/kg/day)	**0**	**5**	**10**	**20**	**75 (mg/kg)** [a]	**0**	**5**	**10**	**20**	**75 (mg/kg)** [a]
Number of Animals	**25**	**25**	**25**	**25**	**15**	**25**	**25**	**25**	**25**	**15**
Thymus										
Thymoma, benign, primary	0	0	0	1	0 (n=14)	0	1	0	0	0
Uterus with cervix										
Papilloma, squamous cell, benign, primary	NA	NA	NA	NA	NA	0	0	0	0	1 (n=5)
Polyp, glandular, benign, primary	NA	NA	NA	NA	NA	0	0	0	0	4 (n=5)
Noteworthy Findings:										
Gross Pathology	-	-	-	-	-	-	-	-	-	-
Non-neoplastic Histopathology [e]										
Number Examined	25	25	25	25	15	25	25	25	25	15
Liver										
necrosis, single cell										
mild	0	0	0	0	0	0	0	0	2	0

2.6.7.10.1 Carcinogenicity - Report R&D/16/0988 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit
NA	Not applicable
TK	Toxicokinetic
-	No noteworthy findings
*	Significantly different from control; ($p < 0.05$)

a. The positive control N-nitroso-N-methylurea (MNU) was administered by intraperitoneal injection once on Day 1 at a dose volume of 10 mL/kg.

b. The control group was analyzed for plasma concentration; however, group means were not calculated.

c. Unscheduled deaths in the vehicle control group and upadacitinib-treated groups were considered incidental or accidental. Early deaths in the positive control group were primarily attributed to lymphoid or gastrointestinal tumors, with two exceptions (one thoracic cavity inflammation and one cause of death undetermined). The incidence of neoplasms in the positive control group was typical of this mouse model.

d. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data not on the percent differences. All percent difference values are rounded to the nearest whole number.

e. Reported as number observed.

f. For neoplastic lesions, the numbers within parentheses indicate the number of animals examined. Without parentheses, tissues from all the animals were examined.

2.6.7.10.2 Carcinogenicity - Report Title: 104-Week Oral Dose (Gavage) Carcinogenicity Study with A-1293543 Hydrate C in Sprague-Dawley Rats (R&D/15/0464)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Rat/CD® [Crl:CD®(SD)]	**Duration of Dosing:**	Up to 101 weeks	**Report Number (Module):**	R&D/15/0464 (4.2.3.4.1-1)
Initial Age:	Approximately 6 weeks at receipt	**Duration of Postdose:**	NA	**Study Number:**	TA15-032
Acclimation Period:	18 days	**Route (Method) of Administration:**	Oral (gavage)	[redacted] **Study Number:**	[redacted]
Date of First Dose:	[redacted] 20[redacted]			**GLP Compliant:**	Yes

Vehicle [a]: 0.2% hydroxypropyl methylcellulose (HPMC) in deionized water; Dose volume = 10 mL/kg

Special Features: None

Basis for High Dose Selection Dose levels were selected based upon results of a 26-week rat toxicity study with upadacitinib, with subsequent presentation and approval of an integrated dose selection justification to the FDA Carcinogenicity Assessment Committee.

Conclusion: Once daily oral administration of upadacitinib in rats for up to 101 weeks at dose levels of 4, 7.5, and 15 mg/kg/day in males and 3, 7.5, and 20 mg/kg/day in females did not result in any upadacitinib-related carcinogenic or non-neoplastic effects.

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of TK Animals	6	6	6	6	6	6	6	6	6	6
Toxicokinetics [c]:										
Mortality	0	0	0	0	0	0	0	0	0	0
$AUC_{0\text{-}24}$ (µg•hr/mL)										
Day 92	NA	NA	0.302 ± 0.158	0.733 ± 0.433	1.67 ± 0.890	NA	NA	0.468 ± 0.211	1.13 ± 0.452	4.17 ± 2.03
C_{max} (µg/mL)										
Day 92	BQL	BQL	0.0865 ± 0.0531	0.168 ± 0.106	0.483 ± 0.369	BQL	BQL	0.141 ± 0.0667	0.249 ± 0.107	1.24 ± 0.581
T_{max} (hr)										
Day 92	NA	NA	1.4 ± 0.9	1.0 ± 0.0	1.0 ± 0.0	NA	NA	1.0 ± 0.0	1.8 ± 1.1	1.0 ± 0.0

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Mortality[d]	60	57	55	54	55	56	58	55	50	53
Terminal Sacrifice	10	13	15	16	15	14	12	15	20	17
Survival of Carcinogenicity Animals [e] (%)										
Week 92	31		36	47	36	29		37	34	31
Terminal	16		21	23	21	19		21	29	24
Clinical Observations	-	-	-	-	-	-	-	-	-	-
Body Weight [f] (g) (%)										
Week 4	458.79		-2	-4	-5	266.06		0	0	-1
Week 13	623.94		-3	-7**	-8**	324.59		-1	-1	-1
Week 26	743.94		-3	-6**	-9**	382.71		-3	-2	0
Week 38	832.17		-3	-7**	-10**	441.66		-4	-4	-2
Week 50	898.04		-5**	-8**	-12**	480.50		-6*	-2	-1
Week 66	957.41		-6**	-11**	-14**	519.41		-8**	-3	-3
Week 78	950.36		-5**	-11**	-12**	530.67		-10**	-3	-6**
Week 98	916.48		-8**	-12**	-16**	552.15		-15**	-10**	-13**

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Caged Food Consumption [f] (g/animal/day) (%)										
Week 4	29.00		-3*	-7**	-8**	18.73		-1	0	-3
Week 13	28.37		-4**	-8**	-9**	17.56		0	+1	-1
Week 26	27.43		-6**	-7**	-10**	17.81		-8	-2	-3
Week 38	27.83		-9**	-12**	-12**	18.12		-6**	-11**	-3
Week 50	27.47		-5*	-9**	-11**	17.71		-9**	0	-3
Week 66	28.68		-5	-12**	-12**	18.49		-8*	-5	-1
Week 78	21.16		+30**	+22**	+19*	18.49		-12*	-9	-10*
Week 98	24.70		+6	0	-15	18.90		-21*	-9	-17
Mass Findings	-	-	-	-	-	-	-	-	-	-
Total Number of Neoplastic Lesions [g]										
Drug-related	0	0	0	0	0	0	0	0	0	0
Incidental/Spontaneous	109	116	111	116	109	142	166	158	129	124
Number of Animals with Neoplastic Lesions [h]										
Adrenal glands										
Adenoma, cortical, benign, primary	1	2	1	0	1	0	0	1	0	0
Carcinoma, squamous cell, malignant, secondary	0	0	0	0	0	0	0	0	0	1
Pheochromocytoma, benign, primary	11	6	5	8	2	2	3	1	0	1
Pheochromocytoma, malignant, primary	0	0	1	1	1	0	0	0	0	0

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Bone, mandible										
Osteosarcoma, malignant, primary	0 (n=0)	1 (n=1)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)
Brain										
Carcinoma, pars distalis, malignant, secondary	1	0	0	1	0	2	4	5	8	0
Glioma, malignant, primary	0	1	3	2	0	0	1	0	1	0
Granular cell tumor, benign, primary	0	2	0	1	2	0	0	0	1	0
Meningioma, malignant, primary	1	0	0	0	0	0	0	0	0	0
Mixed glioma, malignant, primary	0	0	0	0	0	0	2	0	1	0
Oligodendroglioma, malignant, primary	0	0	0	0	1	0	0	0	0	1
Schwannoma, malignant, primary	0	1	0	0	0	0	0	0	0	0
Cavity, abdominal										
Lipoma, benign, primary	0 (n=2)	0 (n=2)	0 (n=0)	0 (n=0)	0 (n=2)	0 (n=2)	0 (n=0)	0 (n=1)	0 (n=1)	1 (n=2)
Sarcoma, undifferentiated, malignant, primary	0 (n=2)	0 (n=2)	0 (n=0)	0 (n=0)	0 (n=2)	0 (n=2)	0 (n=0)	1 (n=1)	0 (n=1)	0 (n=2)
Schwannoma, malignant, secondary	0 (n=2)	0 (n=2)	0 (n=0)	0 (n=0)	0 (n=2)	0 (n=2)	0 (n=0)	0 (n=1)	0 (n=1)	1 (n=2)
Cavity, thoracic										
Adenocarcinoma, malignant, secondary	0 (n=2)	0 (n=1)	0 (n=0)	0 (n=2)	0 (n=1)	1 (n=5)	0 (n=0)	0 (n=1)	0 (n=4)	0 (n=1)
Eyes										
Carcinoma, squamous cell, malignant, primary	0	1	0	0	0	0	0	0 (n=69)	0	0

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Heart										
Adenocarcinoma, malignant, secondary	0	0	0	0	0	1	0	0	0	0
Carcinoma, squamous cell, malignant, secondary	0	0	0	0	0	0	0	0	0	1
Mesothelioma, atriocaval, malignant, primary	1	0	0	1	0	0	0	0	0	0
Sarcoma, undifferentiated, malignant, secondary	0	0	0	0	0	0	0	1	0	0
Schwannoma, malignant, primary	1	0	0	0	1	0	0	0	0	0
Kidneys										
Adenoma, renal tubule, amphophilic-vacuolar (av) type, be	0	0	0	0	2	0	1	0	0	1
Carcinoma, squamous cell, malignant, secondary	0	0	0	0	0	0	0	0	0	1
Liposarcoma, malignant, primary	2	0	0	0	0	0	1	0	0	0
Papilloma, transitional cell, benign, primary	0	0	0	0	1	0	0	0	0	0
Sarcoma, undifferentiated, malignant, secondary	0	0	0	0	0	0	0	1	0	0
Liver										
Adenoma, hepatocellular, benign, primary	0	1	1	0	0	0	0	1	0	0
Carcinoma, squamous cell, malignant, secondary	0	0	0	0	0	0	0	0	0	1
Cholangioma, benign, primary	1	0	0	0	0	0	0	0	0	0
Hemangiosarcoma, malignant, secondary	0	0	0	0	1	0	0	0	0	0

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Lung										
Adenocarcinoma, malignant, secondary	0	0	0	0	0	2	0	0	0	0
Adenoma, bronchiolar alveolar, benign, primary	1	1	1	0	0	0	0	0	0	0
Carcinoma, bronchiolar alveolar, malignant, primary	0	0	0	0	0	1	0	0	0	0
Carcinoma, c-cell, malignant, secondary	0	1	0	0	0	0	0	0	0	0
Carcinoma, pars distalis, malignant, secondary	0	0	0	0	0	0	0	0	1	0
Carcinoma, squamous cell, malignant, secondary	0	0	0	0	0	0	0	0	0	1
Hemangiosarcoma, malignant, secondary	1	0	0	0	0	0	0	0	0	0
Sarcoma, undifferentiated, malignant, secondary	0	0	0	0	0	0	0	1	0	0
Lymph node, mandibular										
Carcinoma, c-cell, malignant, secondary	0	1	0	0	0 (n=69)	0	0	0	0	0 (n=69)
Lymph node, mesenteric										
Hemangioma, benign, primary	0	0	0	0 (n=69)	1 (n=68)	0	0	0	0	0
Hemangiosarcoma, malignant, primary	1	1	1	1 (n=69)	1 (n=68)	1	0	1	0	0
Mammary gland										
Adenocarcinoma, malignant, primary	1 (n=69)	0 (n=67)	0 (n=69)	1 (n=68)	0	15	23	30	14	14
Adenolipoma, benign, primary	0 (n=69)	0 (n=67)	0 (n=69)	0 (n=68)	0	0	0	1	0	0
Adenoma, benign, primary	0 (n=69)	0 (n=67)	0 (n=69)	0 (n=68)	1	1	0	0	0	0
Fibroadenoma, benign, primary	0 (n=69)	0 (n=67)	1 (n=69)	0 (n=68)	0	35	35	23	15	13
Mesentery/peritoneum										
Mesothelioma, malignant, primary	0 (n=0)	0 (n=3)	0 (n=1)	0 (n=1)	0 (n=4)	0 (n=2)	0 (n=3)	1 (n=3)	0 (n=3)	0 (n=2)

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Multicentric neoplasm										
Leukemia, granulocytic, malignant, multicentric	1 (n=3)	0 (n=4)	0 (n=1)	0 (n=4)	3 (n=8)	0 (n=2)	0 (n=3)	0 (n=0)	0 (n=1)	0 (n=1)
Leukemia, large granular lymphocyte, malignant, multicentric	0 (n=3)	0 (n=4)	0 (n=1)	1 (n=4)	1 (n=8)	0 (n=2)	0 (n=3)	0 (n=0)	0 (n=1)	0 (n=1)
Lymphoma, malignant, multicentric	2 (n=3)	2 (n=4)	0 (n=1)	1 (n=4)	1 (n=8)	2 (n=2)	2 (n=3)	0 (n=0)	1 (n=1)	1 (n=1)
Sarcoma, histiocytic, malignant, multicentric	0 (n=3)	2 (n=4)	1 (n=1)	2 (n=4)	3 (n=8)	0 (n=2)	1 (n=3)	0 (n=0)	0 (n=1)	0 (n=1)
Ovaries										
Sex-cord/stromal tumor, benign, primary	NA	NA	NA	NA	NA	0	0	1	0	0
Pancreas										
Adenoma, acinar cell, benign, primary	0	0	0	0	1	0	0	0	0	0
Adenoma, islet cell, benign, primary	4	5	8	5	5	1	2	1	1	0
Carcinoma, acinar cell, malignant, primary	0	1	0	1	0	0	0	0	0	0
Carcinoma, islet cell, malignant, primary	2	2	1	1	1	2	0	0	0	0
Parathyroid glands										
Adenoma, benign, primary	0 (n=57)	1 (n=61)	2 (n=62)	0 (n=62)	0 (n=64)	1 (n=62)	1 (n=57)	1 (n=57)	0 (n=63)	0 (n=61)
Pituitary gland										
Adenoma, pars distalis, benign, primary	47	47	50	53	44	50	61	56	56	62
Adenoma, pars intermedia, benign, primary	1	1	0	0	2	0	0	0	0	1
Carcinoma, pars distalis, malignant, primary	0	0	0	1	0	2	4	5	9	0
Prostate gland										
Adenoma, benign, primary	0	0	0	0	1	NA	NA	NA	NA	NA

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Skin										
Adenoma, basal cell, benign, primary	1	1	2	0	0	0	1	0	0	0
Adenoma, sebaceous cell, benign, primary	0	0	0	2	0	0	0	0	0	0
Carcinoma, basal cell, malignant, primary	0	0	0	0	0	0	0	0	1	0
Carcinoma, sebaceous cell, malignant, primary	0	0	1	0	0	0	0	0	0	1
Carcinoma, squamous cell, malignant, primary	1	0	0	1	0	0	0	0	0	0
Hair follicle tumor, benign, primary	2	0	2	2	0	1	0	1	0	0
Hair follicle tumor, malignant, primary	1	1	0	0	0	0	0	1	0	0
Keratoacanthoma, benign, primary	4	1	4	2	1	1	0	0	0	0
Papilloma, fibrous, benign, primary	0	1	0	0	0	0	0	0	0	0
Papilloma, squamous cell, benign, primary	1	2	1	1	0	0	0	0	0	0
Skin, subcutis										
Carcinoma, c-cell, malignant, secondary	0 (n=7)	1 (n=20)	0 (n=9)	0 (n=12)	0 (n=12)	0 (n=4)	0 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Fibroma, benign, primary	3 (n=7)	6 (n=20)	4 (n=9)	5 (n=12)	3 (n=12)	1 (n=4)	1 (n=5)	1 (n=4)	0 (n=2)	2 (n=6)
Fibrosarcoma, malignant, primary	0 (n=7)	3 (n=20)	2 (n=9)	2 (n=12)	1 (n=12)	1 (n=4)	2 (n=5)	2 (n=4)	0 (n=2)	1 (n=6)
Hemangiosarcoma, malignant, primary	2 (n=7)	1 (n=20)	0 (n=9)	1 (n=12)	0 (n=12)	0 (n=4)	0 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Lipoma, benign, primary	0 (n=7)	2 (n=20)	2 (n=9)	2 (n=12)	2 (n=12)	0 (n=4)	1 (n=5)	0 (n=4)	1 (n=2)	2 (n=6)
Liposarcoma, malignant, primary	0 (n=7)	3 (n=20)	0 (n=9)	0 (n=12)	1 (n=12)	0 (n=4)	0 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Osteosarcoma, malignant, primary	0 (n=7)	0 (n=20)	1 (n=9)	0 (n=12)	0 (n=12)	0 (n=4)	0 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Papilloma, fibrous, benign, primary	0 (n=7)	0 (n=20)	0 (n=9)	0 (n=12)	0 (n=12)	0 (n=4)	1 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Sarcoma, undifferentiated, malignant, primary	0 (n=7)	1 (n=20)	0 (n=9)	1 (n=12)	0 (n=12)	0 (n=4)	0 (n=5)	1 (n=4)	0 (n=2)	0 (n=6)

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Skin, subcutis (cont.)										
Schwannoma, benign, primary	1 (n=7)	0 (n=20)	1 (n=9)	0 (n=12)	0 (n=12)	0 (n=4)	0 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Schwannoma, malignant, primary	0 (n=7)	0 (n=20)	1 (n=9)	0 (n=12)	0 (n=12)	0 (n=4)	0 (n=5)	0 (n=4)	0 (n=2)	0 (n=6)
Small intestine, ileum										
Leiomyoma, benign, primary	0	0	0	0	0	0	0	0	1	0
Small intestine, jejunum										
Adenocarcinoma, malignant, primary	0	0	0	0	0	0	1	0	0	0
Spinal cord, thoracic										
Glioma, malignant, primary	0	0	0	0	0	1	0	0	0	0
Spleen										
Hemangiosarcoma, malignant, primary	1	0	0	0	2	1	0	1	0	0
Leiomyosarcoma, malignant, primary	1	0	0	1	1	0	1	0	0	1
Liposarcoma, malignant, primary	0	1	0	0	0	0	0	0	0	0
Testes										
Adenoma, leydig cell, benign, primary	1	0	1	2	2	NA	NA	NA	NA	NA
Thymus										
Carcinoma, squamous cell, malignant, primary	0 (n=68)	0	0 (n=66)	0 (n=68)	1 (n=69)	0	0	0	0	0 (n=69)
Thymoma, benign, primary	0 (n=68)	0	0 (n=66)	0 (n=68)	0 (n=69)	0	1	1	0	1 (n=69)
Thymoma, malignant, primary	0 (n=68)	0	0 (n=66)	0 (n=68)	1 (n=69)	0	0	0	1	0 (n=69)

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Males					Females				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Thyroid gland										
Adenoma, c-cell, benign, primary	6	6	6	8	8 (n=69)	7	6	5	13	4
Adenoma, follicular cell, benign, primary	1	2	1	4	4 (n=69)	0	1	1	0	0
Carcinoma, c-cell, malignant, primary	1	2	2	0	1 (n=69)	0	2	2	0	1
Carcinoma, follicular cell, malignant, primary	1	1	1	1	2 (n=69)	2	0	0	0	0
Ganglioneuroma, benign, primary	1	1	1	0	1 (n=69)	0	0	2	0	0
Ganglioneuroma, malignant, primary	0	0	0	0	0 (n=69)	0	0	1	0	0
Urinary bladder										
Carcinoma, squamous cell, malignant, secondary	0	0	0	0	0	0	0	0	0	1 (n=69)
Uterus with cervix										
Carcinoma, squamous cell, malignant, primary	NA	NA	NA	NA	NA	0	0	0	1	1
Granular cell tumor, benign, primary	NA	NA	NA	NA	NA	2	1	0	1	0
Hemangiosarcoma, malignant, primary	NA	NA	NA	NA	NA	0	0	1	0	0
Leiomyoma, benign, primary	NA	NA	NA	NA	NA	0	0	1	0	0
Leiomyosarcoma, malignant, primary	NA	NA	NA	NA	NA	0	0	0	0	1
Polyp, endometrial stromal, benign, primary	NA	NA	NA	NA	NA	3	3	4	1	3
Sarcoma, undifferentiated, malignant, secondary	NA	NA	NA	NA	NA	0	0	1	0	0
Schwannoma, malignant, primary	NA	NA	NA	NA	NA	1	0	0	1	2

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Males**					**Females**				
Dose [b] (mg/kg/day)	**0**	**0**	**4**	**7.5**	**15**	**0**	**0**	**3**	**7.5**	**20**
Number of Main Study Animals	70	70	70	70	70	70	70	70	70	70
Vagina										
Carcinoma, squamous cell, malignant, secondary	NA	NA	NA	NA	NA	0	0	0	0	1
Granular cell tumor, benign, primary	NA	NA	NA	NA	NA	1	3	0	0	0
Granular cell tumor, malignant, primary	NA	NA	NA	NA	NA	1	0	0	0	0
Schwannoma, malignant, secondary	NA	NA	NA	NA	NA	0	0	0	0	1
Zymbal`s gland										
Carcinoma, zymbals gland, malignant, primary	0 (n=0)	0 (n=0)	2 (n=2)	0 (n=0)	1 (n=1)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)	0 (n=0)
Gross Pathology	-	-	-	-	-	-	-	-	-	-
Non-neoplastic Histopathology	-	-	-	-	-	-	-	-	-	-

2.6.7.10.2 Carcinogenicity - Report R&D/15/0464 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit; quantitation limit = 0.00526 µg A-1293543/mL
NA	Not applicable
TK	Toxicokinetic
-	No noteworthy findings
*	Significantly different from control; ($p < 0.05$)
**	Significantly different from control; ($p < 0.01$)

a. Vehicle 1 (Group 1) and Vehicle 2 (Group 2) both received 0.2% HPMC in deionized water.

b. Dose levels were corrected for assigned chemical potency.

c. Group means are shown. There were no quantifiable levels of upadacitinib in any samples from the control groups.

d. There was no upadacitinib-related effect on survival.

e. Respective survival percentage calculations include/reflect either death or necropsy at Weeks 92 to 104 and the terminal necropsy (Weeks 99, 100, or 101) of the study for groups surviving to scheduled terminal necropsy. Control calculations were performed on the combined control groups that were administered the vehicle (Group 1 and Group 2). Early terminal necropsies were triggered for all groups based on achieving the survival criteria and Sponsor consultation with the U.S. FDA. In males, dosing was terminated at Week 99 among rats administered 4 mg/kg/day when the number of surviving animals reached 15, and remaining males in the rest of the groups were terminated after Week 100 was reached (during Week 101). In females, all groups were terminated when Week 100 was reached, after the number of surviving females at 3 mg/kg/day reached 15.

f. For controls, combined group least square means are shown for vehicle 1 and vehicle 2 control groups. For treated groups, percent differences from combined controls are shown. Statistical significance is based on actual data not on the percent differences. All percent difference values are rounded to the nearest whole number.

g. All neoplastic findings were considered typical of those seen in rats of this strain and age and were considered incidental to upadacitinib administration.

h. For neoplastic lesions, the numbers within parentheses indicate the number of animals examined. Without parentheses, tissues from all the animals were examined.

2.6.7.11 Reproductive and Developmental Toxicity - Nonpivotal Studies

Test Article: Upadacitinib

Species and Strain	Route (Method) of Administration (Vehicle/Formulation)	Dosing Period	Doses (mg/kg/day)	Number per Group	Noteworthy Findings	Report Number (Module)
Rat CD®[Crl:CD®(SD)]	Oral (gavage) (0.2% hydroxypropyl methylcellulose (HPMC) (high-viscosity) in deionized water); Dose volume = 10 mL/kg	Gestation Day (GD) 6 to 17	0, 50, 100, or 150/75[a]	6 time-mated females	**≥100 mg/kg/day:** ↓ fetal weights (6-13% of the controls) **150 mg/kg/day**: death in 1 animal after two days of dosing.[a] dose was lowered to 75 mg/kg/day. **150/75 mg/kg/day:** ↑ post implantation loss, red discoloration of the skin over the entire body, ↓ gestation body weight gain (39% lower than controls) and food consumption (10% lower than controls).	R&D/12/875 (4.2.3.5.2-1)

a. Due to mortality (1 animal)-at 150 mg/kg/day after two days of treatment, the dose level was reduced to 75 mg/kg/day on GD 8 and referred to as 150/75 mg/kg/day.

2.6.7.11 Reproductive and Developmental Toxicity - Nonpivotal Studies (Cont.)

Test Article: Upadacitinib

Species and Strain	Route (Method) of Administration (Vehicle/Formulation)	Dosing Period	Doses (mg/kg/day)	Number per Group	Noteworthy Findings	Report Number (Module)
Rabbit New Zealand White Hra:(NZW)SPF	Oral (gavage) (0.2% hydroxypropyl methylcellulose (HPMC) (high-viscosity) in deionized water); Dose volume = 5 mL/kg	Gestation Day (GD) 7 to 19	0, 5, 20 or 50	6 time-mated females	**5 and 20 mg/kg/day**: no maternal effects, all survived to scheduled termination. ↓ fetal body weights (7 and 12 % lower than controls) **50 mg/kg/day:** GD 14/15 early termination 3 euthanized due to declining clinical condition (↓activity, tremors, skin discolored red on the ears, feces few/absent, blue colored material in the cage pan), weight loss, low food consumption	R&D/12/1007 (4.2.3.5.2-4)

2.6.7.12 Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development

2.6.7.12.1 Reproductive and Developmental Toxicity - Fertility and Early Embryonic Development - Report Title: An Oral Fertility Study with A-1293543 Tartrate in Rats (R&D/13/1006)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Rat/CD®[Crl:CD® (SD)]	**Duration of Dosing:**	**M:** 14 days prior to pairing to euthanasia	**Report Number:** (Module)	R&D/13/1006 (4.2.3.5.1-1)
Initial Age:	Approximately 9 weeks at dosing		**F:** 14 days prior to pairing to Gestation Day (GD) 7	**Study Number:**	TA13-312
Date of First Dose:	[redacted] 20[redacted]	**Day of Mating:**	GD 0	[redacted] **Study Number:**	[redacted]
		Day of Uterine Examination:	GD 13	**GLP Compliant:**	Yes
Special Features:	None	**Route (Method) of Administration:**	Oral (gavage) (10 mL/kg)		

Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (high-viscosity) in deionized water; Dose volume = 10 mL/kg

NOAEL:

General Toxicity: 25 mg/kg/day (females); not achieved in males

Reproductive performance and fertility parameters in males and females at all dose levels were unaffected by treatment with upadacitinib.

2.6.7.12.1 Reproductive and Developmental Toxicity - Report R&D/13/1006 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose Level (mg/kg/day)	0	5	25	50	75
Males					
Number Evaluated	25	25	25	25	NA
Mortality	0	0	0	0	NA
Clinical Observations	-	-	-	-	NA
Body Weight [a] (g) (%)					
Day 15	388.8	-1	-3	-4*	NA
Day 22	416.2	-2	-4*	-6**	NA

2.6.7.12.1 Reproductive and Developmental Toxicity - Report R&D/13/1006 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose Level (mg/kg/day)	0	5	25	50	75
Males					
Body Weight Change [a] (g) (%)					
Days 11-15	22.3	-7	-28**	-29**	NA
Food Consumption	-	-	-	-	NA
Number of Males Mated	24	25	25	23	NA
Number of Males Impregnating a Female	21	23	21	19	NA
Organ Weights	-	-	-	-	NA
Necropsy Observations	-	-	-	-	NA

2.6.7.12.1 Reproductive and Developmental Toxicity - Report R&D/13/1006 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose Level (mg/kg/day)	0	5	25	50	75
Females					
Number Evaluated	25	25	25	NA	25
Mortality	0	0	0	NA	0
Clinical Observations	-	-	-	NA	-
Premating Body Weight [a] (g) (%)					
Day 4	221.5	0	0	NA	-5**
Gestation Body Weight [a] (g) (%)					
Day 3	269.6	0	+2	NA	-4*
Day 13	323.6	-2	0	NA	-9**
Premating Body Weight Change[a] (g) (%)					
Days 1-4	12.3	-18	-9	NA	-74**
Gestation Body Weight Change [a] (g) (%)					
Day 7-10	20.8	-21*	-21	NA	-49**
Day 0-13	72.2	-11*	-9	NA	-23**

2.6.7.12.1 Reproductive and Developmental Toxicity - Report R&D/13/1006 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose Level (mg/kg/day)	0	5	25	50	75
Females					
Gestation Food Consumption	-	-	-	NA	-
Organ Weights	-	-	-	NA	-
Necropsy Observations	-	-	-	NA	-
Mean Cycle Length (Days)	4.4	4.5	4.1	NA	4.2
Mean Number of Cycles (Count)	2.8	2.6	2.7	NA	2.7
Mean Copulatory Interval (Days)	2.6	2.7	2.5	NA	2.3
Number of Females with Confirmed Mating Days	23	24	25	NA	23
Cesarean Section Observations					
Number Evaluated	20	23	21	NA	19
Number Pregnant	21	23	21	NA	19
Number Total Resorption of Litter	0	0	0	NA	6
Mean Number Corpora Lutea	16.3	16.6	16.2	NA	14.2 [b]
Mean Number Implantation Sites	15.3	14.3*	14.3	NA	10.8**
Mean % Preimplantation Loss	5.40	12.26	11.18	NA	18.37 [b]
Mean Number Viable Embryos	14.6	13.4	11.5**	NA	2.0**
Mean % Postimplantation Loss	4.83	5.83	20.40**	NA	82.58**
Litter Size (Mean Number per Animal)	14.6	13.4	11.5**	NA	2.0**
Mean Number Early + Late Resorptions	0.8	0.8	2.9**	NA	8.8**

2.6.7.12.1 Reproductive and Developmental Toxicity - Report R&D/13/1006 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
GD	Gestation Day
NA	Not applicable
NOAEL	No-Observed-Adverse-Effect Level
-	No noteworthy findings
*	$p < 0.05$
**	$p < 0.01$

a. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data not on the percent differences. All percent difference values are rounded to the nearest whole number.

b. Number evaluated = 13, 6 females with total litter resorptions.

2.6.7.13 Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development

2.6.7.13.1 Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development - Report Title: An Oral Developmental Toxicity Study with A-1293543 Tartrate in Rats, Including a Toxicokinetic Evaluation (R&D/12/1109)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain: Rat/CD®[Crl:CD® (SD)]	**Dosing Period:** Gestation Day (GD) 6 to 17	**Report Number:** (Module)	R&D/12/1109 (4.2.3.5.2-2)
Initial Age: Approximately 8 to 10 weeks at receipt	**Day of Mating:** GD 0	**Study Number:**	TA12-095
Date of First Dose: [redacted] 20[redacted]	**Day of Cesarean Section:** GD 20	[redacted] **Study Number:**	[redacted]
	Route (Method) of Administration: Oral (gavage)	**GLP Compliant:**	Yes

Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (HPMC, high viscosity) in deionized water; Dose volume = 10 mL/kg

Special Features: None

NOAEL:

Maternal Toxicity: 75 mg/kg/day

Developmental Toxicity and Teratogenicity: Not established, and should be considered < 5 mg/kg/day.

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**5**	**25**	**75**
Number of Toxicokinetic Animals	**5**	**5**	**5**
Toxicokinetics: [a]			
C_{max} (µg/mL)			
GD 6	0.182	3.34	12.3
GD 16	0.262	2.07	6.46
$AUC_{0\text{-}24hr}$ (µg•hr/mL)			
GD 6	0.429	7.48	39.2
GD 16	0.680	8.72	33.4
Plasma Concentrations (GD 17) [a]			
Fetal (µg/mL)	0.266	2.80	7.45
Dam (µg/mL)	0.104	1.34	5.34
Fetal/Dam Ratio	2.81	2.14	1.45

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**	**5**	**25**	**75**
Maternal Females				
Main Study:				
Number of Main Study Animals	25	25	25	25
Mortality	0	0	0	0
Gestation Clinical Observations	-	-	-	-
Gestation Body Weight	-	-	-	-
Gestation Body Weight Change	-	-	-	-
Gestation Food Consumption	-	-	-	-
Gravid Uterine Weight	-	-	-	-
Final Body Weight	-	-	-	-
Adjusted Final Body Weight	-	-	-	-
Adjusted Body Weight Change From Day 0	-	-	-	-
Necropsy Observations	-	-	-	-

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	0	5	25	75
Maternal Females				
Main Study:				
Cesarean Section Observations				
Number Evaluated	25	25	24	25
Number Pregnant	25	25	24	25
Number with Total Resorption of Litter	0	0	0	0
Pregnancy Index (%)	100.0	100.0	96.0	100.0
Number Females with Viable Fetuses Day 20 Gestation	25	25	24	25
Mean Number Corpora Lutea	13.0	12.6	12.7	13.6
Mean Number Implantation Sites	11.8	11.9	12.3	12.8
Mean % Preimplantation Loss	8.69	4.97	2.97*	5.15
Mean Number Viable Fetuses	11.2	11.1	11.3	12.0
Mean Fetal Sex Ratio (% Males)	49.2	49.9	49.5	53.0
Mean % Postimplantation Loss	5.04	6.73	9.81	6.27
Mean Number Nonviable Fetuses	0.0	0.0	0.0	0.0
Litter Size (Mean Number per Animal)	11.2	11.1	11.3	12.0
Mean Number Resorptions (Early + Late)	0.6	0.8	1.0	0.8
Mean Number Early Resorptions	0.6	0.8	1.0	0.8
Mean Number Late Resorptions	0.0	0.0	0.0	0.0

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	0	5	25	75
Fetuses				
Number Litters/Fetuses Evaluated	25/279	25/278	24/270	25/300
Fetal Body Weight (least square mean) (g) [a]				
Males	4.35	4.33	4.24	4.05**
Females	4.11	4.12	4.02	3.83**
Males + Females	4.23	4.22	4.14	3.95**
Fetal Observations				
External Observations	-	-	-	-
Visceral Observations	-	-	-	-
Skeletal Malformations				
Number Litters/Fetuses Evaluated	25/140	25/141	24/137	25/151
Humerus, Bent				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Number Fetuses (%)#	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Humerus, Misshapen				
Number Litters (%)	0 (0.0)	1 (4.0)	6 (25.0)**	16 (64.0)**
Number Fetuses (%)#	0 (0.0)	1 (0.7)	9 (6.6)	38 (25.2)

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	0	5	25	75
Fetuses				
Fetal Observations				
Skeletal Malformations				
Number Litters/Fetuses Evaluated	25/140	25/141	24/137	25/151
Radius, Bent				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (12.0)
Number Fetuses (%)[#]	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)
Ulna, Bent				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Number Fetuses (%)[#]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)
Femur, Bent				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	4 (16.0)
Number Fetuses (%)[#]	0 (0.0)	0 (0.0)	0 (0.0)	11 (7.3)
Fibula, Bent				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.0)
Number Fetuses (%)[#]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	0	5	25	75
Fetuses				
Fetal Observations				
Skeletal Malformations				
Number Litters/Fetuses Evaluated	25/140	25/141	24/137	25/151
Scapula, Bent				
Number Litters (%)	0 (0.0)	1 (4.0)	6 (25.0)**	15 (60.0)**
Number Fetuses (%)#	0 (0.0)	1 (0.7)	9 (6.6)	39 (25.8)
Rib(s), Absent				
Number Litters (%)	0 (0.0)	1 (4.0)	0 (0.0)	1 (4.0)
Number Fetuses (%)#	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)
Rib(s), Branched				
Number Litters (%)	0 (0.0)	1 (4.0)	0 (0.0)	2 (8.0)
Number Fetuses (%)#	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.3)
Rib(s), Fused				
Number Litters (%)	0 (0.0)	1 (4.0)	0 (0.0)	1 (4.0)
Number Fetuses (%)#	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.7)
Skeletal Variations				
Number Litters/Fetuses Evaluated	25/140	25/141	24/137	25/151
Rib(s), Bent				
Number Litters (%)	2 (8.0)	3 (12.0)	14 (58.3)**	18 (72.0)**
Number Fetuses (%)#	3 (2.1)	6 (4.3)	27 (19.7)	67 (44.4)

2.6.7.13.1 Reproductive and Developmental Toxicity - Report R&D/12/1109 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
GD	Gestation day
NOAEL	No-Observed-Effect Level
-	No noteworthy findings
*	$p < 0.05$
**	$p < 0.01$
#	Not statistically analyzed

a. Group means are shown.

2.6.7.13.2 Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development - Report Title: A-1293543 Free Form: A Low-Dosage Oral Developmental Toxicity Study in Rats, Including a Toxicokinetic Evaluation (R&D/17/0574)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Rat/CD®[Crl:CD® (SD)]	**Duration of Dosing:**	Gestation Day (GD) 6 through 17	**Report Number:** (Module)	R&D/17/0574 (4.2.3.5.2-3)
Initial Age:	~8 weeks	**Day of Mating:**	GD 0	**Study Number:**	TA17-026
Date of First Dose:	[redacted] 20[redacted]	**Day of C- Section:**	GD 20	[redacted] **Study Number:**	[redacted]
		Route (Method) of Administration:	Oral (gavage)	**GLP Compliant:**	Yes

Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (high viscosity) in deionized water; Dose volume = 10 mL/kg

Special Features: None

NOAEL:

Maternal Toxicity: 4 mg/kg/day

Developmental Toxicity: 1.5 mg/kg/day

2.6.7.13.2 Reproductive and Developmental Toxicity - Report R&D/17/0574 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	Females		
Dose (mg/kg/day)	**0**	**1.5**	**4.0**
Number of TK Animals	3	3	3
Toxicokinetics: [a]			
C_{max} (ng/mL)			
GD 6	BQL	33.1	120
GD 17	BQL	64.7	344
$AUC_{0\text{-}9hr}$ (ng hr•/mL)			
GD 6	NA	64.0	196
GD 17	NA	115	629
Mean Plasma Concentrations:			
Fetal GD 18 (ng/mL)	BQL	26.9	126
Dam GD 18 (ng/mL)	BQL	72.4	286
Ratio	NA	0.345	0.505

2.6.7.13.2 Reproductive and Developmental Toxicity - Report R&D/17/0574 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose (mg/kg/day)	0	1.5	4
Maternal Females			
Main Study:			
Number of Main Study Animals	25	25	25
Mortality	0	0	0
Clinical Observations	-	-	-
Gestation Body Weight	-	-	-
Gestation Body Weight Change	-	-	-
Gestation Food Consumption	-	-	-
Gravid Uterine Weight	-	-	-
Adjusted Body Weight	-	-	-
Adjusted Body Weight Change	-	-	-
Necropsy Observations	-	-	-

2.6.7.13.2 Reproductive and Developmental Toxicity - Report R&D/17/0574 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose (mg/kg/day)	0	1.5	4
Maternal Females			
Main Study:			
Cesarean Section Observations	-	-	-
Number Evaluated	25	25	25
Number Not Pregnant	0	1	1
Number Pregnant	25	24	24
Number Aborted or with Total Resorption of Litter	0	0	0
Pregnancy Index Percent	100.0	96.0	96.0
Number Females with Viable Fetuses on GD 20	25	24	24
Mean Number Corpora Lutea	15.1	15.6	14.3
Mean Number Implantation Sites	13.3	12.6	13.1
Mean % Preimplantation Loss	11.68	17.61	8.22
Mean Number Viable Fetuses	12.4	12.3	12.2
Mean Fetal Sex Ratio (% Males)	50.9	52.6	53.0
Mean % Postimplantation Loss	7.26	2.74	9.10
Mean Number Nonviable Fetuses	0.0	0.0	0.0
Mean Litter Size	12.4	12.3	12.2
Resorptions: Early + Late	0.9	0.4	1.0
Mean Number Early Resorptions	0.8	0.4	0.9
Mean Number Late Resorptions	0.0	0.0	0.0

2.6.7.13.2 Reproductive and Developmental Toxicity - Report R&D/17/0574 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose (mg/kg/day)	0	1.5	4
Maternal Females			
Main Study:			
Number of Main Study Animals	25	25	25
Fetuses			
Number Litters/Fetuses Evaluated	25/310	24/294	24/292
Mean Fetal Body Weight (Males;g least square means)	4.49	4.55	4.46
Mean Fetal Body Weight (Females;g, least square means)	4.21	4.33	4.26
Mean Fetal Body Weight (Males + Females;g; least square means)	4.35	4.44	4.34
Fetal Observations			
External Malformations and Variations	-	-	-
Visceral Malformations and Variations	-	-	-
Skeletal Malformations			
Number Litters/Fetuses Evaluated	25/154	23/147	23/146
Humerus, Bent			
Number Litters (%)	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%) [b]	0 (0.0)	0 (0.0)	1 (0.7)
Radius, Bent			
Number Litters (%)	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%) [b]	0 (0.0)	0 (0.0)	1 (0.7)

2.6.7.13.2 Reproductive and Developmental Toxicity - Report R&D/17/0574 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Dose (mg/kg/day)	0	1.5	4
Maternal Females			
Main Study:			
Number of Main Study Animals	25	25	25
Fetuses			
Fetal Observations			
Skeletal Malformations			
Ulna, Bent			
Number Litters (%)	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%) [b]	0 (0.0)	0 (0.0)	1 (0.7)
Scapula, Bent			
Number Litters (%)	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%) [b]	0 (0.0)	0 (0.0)	1 (0.7)
Tympanic ring, Misshapen			
Number Litters (%) [b]	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%)	0 (0.0)	0 (0.0)	1 (0.7)
Neural arch(es), Fused (Cervical vertebra(e))			
Number Litters (%)	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%) [b]	0 (0.0)	0 (0.0)	1 (0.7)
Neural arch(es), Misshapen (Thoracic vertebra(e))			
Number Litters (%)	0 (0.0)	0 (0.0)	1 (4.3)
Number Fetuses (%) [b]	0 (0.0)	0 (0.0)	1 (0.7)
Skeletal Variations	-	-	-

2.6.7.13.2 Reproductive and Developmental Toxicity - Report R&D/17/0574 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES

Abbreviation	Definition
BQL	Below the Quantitation Limit
GD	Gestation Day
NA	Not applicable
TK	Toxicokinetic
NOAEL	No-Observed-Adverse-Effect Level
-	No noteworthy findings

a. Group means are shown; the control group was analyzed for plasma concentration; however group means were not calculated.

b. Not statistically analyzed.

2.6.7.13.3 Reproductive and Developmental Toxicity - Effects on Embryo-Fetal Development - Report Title: An Oral Developmental Toxicity Study with A-1293543 Tartrate in Rabbits, Including a Toxicokinetic Evaluation (R&D/13/335)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain: Rabbit/New Zealand White Hra:(NZW)SPF

Dosing Period: Gestation Day (GD) 7 to 19

Report Number: R&D/13/335 (Module) (4.2.3.5.2-5)

Initial Age: Approximately 6.5 to 7 months at receipt

Day of Mating: GD 0

Study Number: TE12-096

Date of First Dose: [redacted] 20[redacted]

Day of Cesarean Section: GD 29

[redacted] **Study Number:** [redacted]

Route (Method) of Administration: Oral (gavage)

GLP Compliant: Yes

Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (HPMC, high viscosity) in deionized water; Dose volume = 5 mL/kg

Special Features: None

NOAEL: 10 mg/kg/day (maternal toxicity, developmental toxicity, and teratogenicity)

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Sex	**Females**		
Daily Dose Level (mg/kg/day)	**2.5**	**10**	**25**
Number of Toxicokinetic Animals	**5**	**5**	**5**
Toxicokinetics: [a]			
C_{max} (ng/mL)			
GD 7	54.4	411	2030
GD 18	84.1	482	2690
$AUC_{0\text{-}24hr}$ (ng•hr/mL)			
GD 7	95.5	799	3670
GD 18	145	881	5950
Plasma Concentrations GD 19 (ng/mL)			
Fetal	0.00	0.884	21.7
Dam	25.0	189	1030
Ratio	0.00	0.00326	0.0206

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose Level (mg/kg/day)	0	2.5	10	25
Maternal Females				
Main Study:				
Number of Main Study Animals	20	20	20	20
Mortality	0	0	0	0
Clinical Observations	-	-	-	-
Gestation Body Weight [b] (kg) (%)				
GD 10	3.441	0	0	-2
GD 13	3.505	-1	0	-4
GD 20	3.642	0	+2	-4
Gestation Body Weight Change [b] (kg) (%)				
GD 10 to 13	0.064	-17	+39	-119**
GD7 to 20	0.239	+13	+46	-35
Gestation Food Consumption [b] (g/animal/day) (%)				
GD 7 to 20	150.6	-4	+2	-20*

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose Level (mg/kg/day)	0	2.5	10	25
Maternal Females				
Main Study:				
Gravid Uterine Weight [b] (kg) (%)	0.564	-6	-6	-13*
Final Body Weight [b] (kg) (%)	3.794	0	0	-1
Adjusted Body Weight [b] (kg) (%)	3.230	+1	+1	+1
Adjusted Body Weight Change From Day 0 [b] (kg) (%)	0.064	+13	+14	+52
Necropsy Observations	-	-	-	-
Cesarean Section Observations				
Number Evaluated	20	19	17	15
Number Pregnant	20	20	18	19
Number Not Pregnant	0	0	2	1
Pregnancy Index (%)	100.0	100.0	90.0	95.0
Number Aborted	0	0	0	4
Number Early Deliveries	0	1	1	0
Number Females with Viable Fetuses GD 29	20	19	17	15

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose Level (mg/kg/day)	0	2.5	10	25
Maternal Females				
Main Study:				
Cesarean Section Observations				
Mean Number Corpora Lutea	10.1	10.1	10.1	10.1
Mean Number Implantation Sites	9.7	9.4	9.0	9.5
Mean % Preimplantation Loss	4.66	6.96	10.92	5.05
Mean Number Viable Fetuses	9.4	9.0	8.8	8.1
Mean Fetal Sex Ratio (% Males)	50.2	50.5	42.6	42.8
Mean % Postimplantation Loss	2.51	4.12	2.62	14.83**
Mean Number Nonviable Fetuses	0.0	0.0	0.0	0.0
Litter Size (Mean Number per Animal)	9.4	9.0	8.8	8.1
Mean Number Early + Late Resorptions	0.3	0.4	0.2	1.5**
Mean Number Early Resorptions	0.1	0.2	0.1	0.4*
Mean Number Late Resorptions	0.2	0.3	0.2	1.1

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose Level (mg/kg/day)	0	2.5	10	25
Fetuses				
Number Litters/Fetuses Evaluated	20/188	19/171	17/149	15/121
Mean Fetal Body Weight [a] (Males) (g) Least square means	44.85	43.60	43.15	41.11*
Mean Fetal Body Weight [a] (Females) (g) Least square means	43.09	42.26	42.75	39.29*
Mean Fetal Body Weight [a] (Males + Females) (g) Least square means	43.85	43.00	43.03	40.03**
Fetal Observations				
External Malformations	-	-	-	-
External Variations	-	-	-	-
Visceral Malformations				
Aortic arch, dilated				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	3 (20.0)
Number Fetuses (%)[#]	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.5)
Heart - entire, persistent truncus arteriosis				
Number Litters (%)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)
Number Fetuses (%)[#]	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Interventricular septum, absent				
Number Litters (%)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)
Number Fetuses (%)[#]	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose Level (mg/kg/day)	0	2.5	10	25
Fetuses				
Fetal Observations				
Visceral Malformations				
Interventricular septum, discontinuous				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Number Fetuses (%)#	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Pulmonary trunk, constricted				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Number Fetuses (%)#	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Pulmonary trunk, smaller than normal				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Number Fetuses (%)#	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Pulmonary valve, absent				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Number Fetuses (%)#	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)
Ventricle, larger than normal				
Number Litters (%)	0 (0.0)	0 (0.0)	0 (0.0)	2 (13.3)
Number Fetuses (%)#	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Visceral Variations	-	-	-	-
Skeletal Malformations	-	-	-	-
Skeletal Variations	-	-	-	-

2.6.7.13.3 Reproductive and Developmental Toxicity - Report R&D/13/335 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
GD	Gestation Day
NA	Not applicable
NOAEL	No Observed Adverse Effect Level
-	No noteworthy findings
*	$p < 0.05$
**	$p < 0.01$
#	Not statistically analyzed

a. Group means are shown.

b. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data not on the percent differences. All percent difference values are rounded to the nearest whole number.

2.6.7.14 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function

2.6.7.14.1 Reproductive and Developmental Toxicity - Effects on Pre- and Postnatal Development, Including Maternal Function - Report Title: An Oral (Gavage) Pre-/Postnatal Developmental Toxicity Study of A-1293543 (ABT-494) in Rats, Including a Postnatal Behavioral/Functional Evaluation (R&D/16/1460)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Rat/Crl:CD(SD)	**Duration of Dosing:**	Once daily Gestation Day (GD) 6 through Lactation Day (LD) 20	**Report Number:** **(Module)**	R&D/16/1460 (4.2.3.5.3-1)
Initial Age:	62 to 80 days	**Day of Mating:**	Day 0	**Study Number:**	TA16-197
Date of First Dose:	[redacted] 20[redacted]	**Route (Method) of Administration:**	Oral (gavage)	[redacted] **Study Number:**	[redacted]
		Litters Culled/Not Culled:	Not culled	**GLP Compliant:**	Yes

Vehicle/Formulation: 0.2% hydroxypropyl methylcellulose (HPMC); Dose volume = 5 mL/kg

NOAEL:

F_0 Females: 10 mg/kg/day

F_1 Males: 10 mg/kg/day

F_1 Females: 10 mg/kg/day

2.6.7.14.1 Reproductive and Developmental Toxicity - Report R&D/16/1460 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)		**0**	**2.5**	**5**	**10**
F_0 Females:	Toxicokinetics:				
	LD 14 C_{max} (ng/mL)	BQL	81.4	121	334
	LD 14 AUC (ng•hr/mL)	NA	203	321	1090
	Number Pregnant	22	22	22	22
	Mortality	0	0	0	0
	Number Aborted or with Total Resorption of Litter	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Gestation Body Weight (g, %) [a]	357.5	-0.7	+1.5	+2.5
	Lactation Body Weight (g, %) [a]	308.7	+1.4	+3.1	+4.8
	Gestation Food Consumption (g, %) [b]	49.6	+4.6	+7.0	+6.8
	Lactation Food Consumption (g, %) [c]	59.2	-1.0	-1.2	-5.2
	Mean Duration of Gestation (days)	22.2	22.3	22.4	22.3
	Abnormal Parturition	-	-	-	-

2.6.7.14.1 Reproductive and Developmental Toxicity - Report R&D/16/1460 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)		**0**	**2.5**	**5**	**10**
F_1Litters:	Number Litters Evaluated	22	22	22	22
(Preweaning)	Mean Number of Implantations	13.3	12.8	12.8	13.1
	Mean Number Pups/Litter	12.5	11.9	12.3	12.1
	Mean Number Liveborn Pups/Litter	12.5	11.9	12.3	12.0
	Number of Litters with Stillborn Pups	1	0	0	3
	Postnatal Survival to Day 4	99.3	99.2	99.6	98.9
	Postnatal Survival to Weaning	99.6	100	100	100
	Number of Total Litters Losses	0	0	0	0
	Pup Body Weights LD 21(g, %)[a]	45.1	+3.3	-0.2	+0.2
	Pup Sex Ratios LD 21 (% males)	46.8	50.6	52.9	48.8
	Pup Clinical Signs	-	-	-	-
	Pup Necropsy Observations	-	-	-	-

2.6.7.14.1 Reproductive and Developmental Toxicity - Report R&D/16/1460 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)		**0**	**2.5**	**5**	**10**
F_1 Males:	Number Evaluated Postweaning	22	22	22	22
(Postweaning)	**Mortality**	0	0	0	0
	Clinical Observations	-	-	-	-
	Necropsy Observations	-	-	-	-
	Organ Weights	-	-	-	-
	Body Weight Change (g, %) [d]	522.8	+1.0	+0.9	-2.1
	Food Consumption (g, %) [e]	54.9	+1.6	-0.5	+2.0
	Mean Age of Preputial Separation (Days)	43.8	42.8	43.6	45.0
	Acoustic Startle	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and memory	-	-	-	-
	Mean Number Days Prior to Mating	2.5	3.2	2.8	2.4
	Number of Males that Mated	22	22	21	22
	Number of Fertile Males	20	21	21	20

2.6.7.14.1 Reproductive and Developmental Toxicity - Report R&D/16/1460 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)		**0**	**2.5**	**5**	**10**
F_1 Females:	Number Evaluated	22	22	22	22
(Postweaning)	**Mortality**	0	0	0	0
	Clinical Observations:	-	-	-	-
	Necropsy Observations	-	-	-	-
	Organ Weights	-	-	-	-
	Premating Body Weight [f] (g, %)	302.4	-3.1	-3.0	-4.6
	Gestation Body Weight [f] (g, %)	374.2	-2.8	-2.7	-3.7
	Premating Food Consumption (g, %) [f]	40.5	+0.7	-3.7	-2.5
	Gestation Food Consumption (g, %) [f]	26.9	+0.4	-1.1	+0.7
	Mean Age of Vaginal Patency (days)	32.6	32.8	32.8	32.3
	Acoustic Startle	-	-	-	-
	Motor Activity	-	-	-	-
	Learning and memory	-	-	-	-
	Mean Number Days Prior to Mating	2.5	3.2	2.8	3.0
	Number of Females Sperm Positive	22	22	21	22
	Number of Pregnant Females	20	21	21	20
	Mean Number Corpora Lutea	17.2	17.6	17.8	17.0
	Mean Number Implantations	16.6	17.1	16.9	16.1
	Mean % Preimplantation Loss	3.1	2.8	4.7	5.3

2.6.7.14.1 Reproductive and Developmental Toxicity - Report R&D/16/1460 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)		**0**	**2.5**	**5**	**10**
F1Litters:	Mean Number Viable Embryos/Litter	16.0	16.3	16.2	14.9
	Number of Litters with Nonviable Embryos	11	12	10	13
	Mean Number Nonviable Embryos	0.7	0.8	0.7	1.2
	Mean % Postimplantation Loss	4.2	4.8	4.5	7.8

2.6.7.14.1 Reproductive and Developmental Toxicity - Report R&D/16/1460 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES	
Abbreviation	**Definition**
BQL	Below the Quantitation Limit
GD	Gestation Day
LD	Lactation Day
NA	Not Applicable
NOAEL	No-Observed-Adverse-Effect Level
-	No noteworthy findings

a. At end of gestation or lactation or pups bodyweight on LD 21. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b. From GD 6-18

c. From LD 1 to 14

d. From weaning to mating, LD 21 to post-partum day 95.

e. At the end of postweaning period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

f. At the end of premating (post-partum day 92) or gestation (GD 13). For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

2.6.7.15 Studies in Juvenile Animals

2.6.7.15.1 Studies in Juvenile Animals - Report Title: A Dose Range-Finding Toxicity Study of A-1293543 by Oral Gavage in Juvenile Rats (R&D/17/0266)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species and Strain	Route (Method) of Administration (Vehicle/Formulation)	Dosing Period	Doses (mg/kg/day)	Number per Group	Noteworthy Findings	Report Number (Module)
Rat Crl:CD (SD)	Oral (gavage) (0.2% hydroxypropyl methylcellulose (HPMC)); Dose volume = 5 mL/kg	PND 15 to PND 29	0, 50, 100, 150	5 males/ 5 females main study 3 or 6 males/ 3 or 6 females for TK	**50 mg/kg**: males ↓ body weight gains. **100 mg/kg**: 2 males, 2 females found dead from the main study and TK groups. One male, one female euthanized on PND 22 and 18, due to clinical signs and body weight loss. ↓ body weight gain in males and females. **150 mg/kg**: 9 males, 6 females found dead from the main study and TK groups. Remaining animals in group terminated on PND 18 due to excessive mortality, clinical signs and reduced body weights.	R&D/17/0266 (4.2.3.5.4-1) Non-GLP

PND = Postnatal Day
TK = Toxicokinetic

2.6.7.15.2 Studies in Juvenile Animals - Report Title: Juvenile Toxicity Study of A-1293543 Hemihydrate by Oral Gavage in Rats (R&D/17/0588)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Species/Strain:	Rat/Crl:CD (SD)	**Duration of Dosing:**	PND 15 to 63	**Report Number:** **(Module)**	R&D/17/0588 (4.2.3.5.4-2)
Initial Age:	7 to 10 days of age at arrival	**Day of Post Dose:**	NA	**Study Number:**	TA17-024
Date of First Dose:	[redacted] 20[redacted]	**Route (Method) of Administration:**	Oral (gavage)	[redacted] **Study Number:**	[redacted]
Vehicle/Formulation:	0.2% (w/v) hydroxypropyl methylcellulose in deionized water; Dose Volume = 5 mL/kg			**GLP Compliant:**	Yes
Special Features:	TDAR, immunophenotyping and toxicokinetics				
NOAEL:	20 mg/kg/day				

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**5**		**20**		**50**	
Total Number of Animals (PND 15 & 63)	M:6	F:6	M:27	F:27	M:27	F:27	M:27	F:27
Toxicokinetics								
PND 15/Number of Animals	3	3	18	18	18	18	18	18
$AUC_{0\text{-}24hr}$ (µg•hr/mL)	NA	NA	8.10	8.41	34.0	22.9	85.7	68.0
C_{max} (µg/mL)	NA	NA	1.63	1.77	5.49	4.73	9.97	9.07
PND 63/Number of Animals	3	3	9	9	9	9	9	9
AUC (µg•hr/mL)	NA	NA	0.462	0.622	2.74	4.69	9.53	7.93
C_{max} (µg/mL)	NA	NA	0.335	0.378	1.34	3.13	4.10	2.08

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**5**		**20**		**50**	
Number of Animals Subset 1	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Mortality	0	0	0	0	0	0	0	0
Clinical Observations	-	-	-	-	-	-	-	-
Body Weight PND 64 (g, %) [a]	404.4	235.4	-4.3	+0.4	-7.8	-0.9	-12.6*	-10.5**
Food Consumption PND 21 to 63 (g/day, %) [a]	22.6	16.7	-1.8	-0.6	+2.6	+4.8	-3.5	-3.0
Sexual Maturation	-	-	-	-	-	-	-	-
Clinical Pathology [b]								
Hematology PND 64								
White Blood Cells	-	-	0.60**	0.53**	0.37**	0.36**	0.36**	0.28**
Lymphocytes (absolute)	-	-	0.53**	0.52**	0.28**	0.32**	0.23**	0.19**
Monocytes (absolute)	-	-	0.68*	0.67	0.65*	0.64*	0.71	0.62*
Eosinophils (absolute)	-	-	-	0.50*	0.61	0.40**	0.36	0.30**
Red Blood Cells	-	-	-	-	0.93	-	0.94	0.92
Hemoglobin	-	-	-	-	0.91	-	0.94	0.94
Hematocrit	-	-	-	-	0.91*	-	0.94	0.94
Reticulocytes (absolute)	-	-	-	-	0.89	-	0.87*	-
Coagulation PND 64								
PT	-	-	-	0.95**	-	0.95**	0.94*	0.94**
APTT	-	-	-	-	-	0.94*	-	0.89**

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**5**		**20**		**50**	
Number of Animals Subset 1	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Clinical Chemistry PND 64								
ALP	-	-	-	-	-	-	-	1.42**
Total Protein	-	-	-	-	-	-	-	0.92**
Albumin	-	-	-	-	-	-	-	0.93*
Globulin	-	-	-	-	-	-	-	0.91*
Gross Pathology	-	-	-	-	-	-	-	-
Organ Weights (g, %) [a]								
Spleen								
Absolute Weight	0.8164	0.5676	-28**	-34**	-43**	-41**	-51**	-44**
% of Body Weight	0.203	0.241	-25**	-34**	-38**	-40**	-42**	-36**
Percent of Brain Weight	39.155	32.389	-26**	-40**	-40**	-44**	-49**	-47**
Thymus								
Absolute	0.7923	0.5969	-16**	-11	-37**	-13	-54**	-53**
% of Body Weight	0.196	0.253	-12	-11	-31**	-13	-47**	-47**
Percent of Brain Weight	37.942	34.162	-13*	-20	-33**	-19	-53**	-56**

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**5**		**20**		**50**	
Number of Animals Subset 1	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Histopathology (Total Incidence of Finding)								
Spleen - Decreased Lymphoid Cellularity								
Minimal	0	0	5	8	10	5	0	1
Mild	0	0	0	0	0	5	8	9
Moderate	0	0	0	0	0	0	2	0
Thymus								
Decreased Lymphoid Cellularity								
Minimal	0	0	0	0	9	0	0	0
Mild	0	0	0	0	0	5	10	9
Moderate	0	0	0	0	0	0	0	1
Increased Lymphocyte Apoptosis								
Minimal	0	0	2	0	6	0	7	0
Mesenteric Lymph Node								
Decreased Lymphoid Cellularity								
Minimal	0	0	1	0	7	3	0	6
Mild	1	0	0	0	1	0	7	0
Moderate	0	0	0	0	0	0	2	0

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**5**		**20**		**50**	
Number of Animals Subset 1	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Histopathology (Total Incidence of Finding)								
GALT								
Decreased Lymphoid Cellularity								
Minimal	0	0	0	0	0	2	1	4
Mild	0	0	0	0	0	0	5	1
BALT								
Decreased Lymphoid Cellularity								
Minimal	0	0	0	0	4	2	2	6
Mild	0	0	0	0	0	1	7	4
Bone Marrow								
Decreased Hematopoiesis								
Minimal	0	0	0	0	5	0	9	4

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

Daily Dose (mg/kg/day)	**0**		**5**		**20**		**50**	
Number of Animals - Subset 1	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
Mortality	0	0	0	0	0	0	2 [c]	2 [c]
Immunophenotyping (PND 64)								
Total T Cells (CD3+) (thous/µL, %) [d]	6.05	5.83	-39.2	-39.5	-66.4	-61.9	-72.1	-75.1
T Helper Cells (CD3+CD4+) (thous/µL, %) [d]	3.98	4.06	-32.7	-33.3	-60.3	-56.2	-64.1	-69.0
T Cytotoxic Cells (CD3+CD8+) (thous/µL, %) [d]	2.01	1.68	-52.2	-51.8	-78.1	-73.8	-86.6	-89.3
B Cells (CD3-CD45RA+) (thous/µL, %) [d]	5.57	4.99	-56.9	-63.5	-75.8	-73.3	-82.6	-86.8
NK Cells (CD3-CD161a+) (thous/µL, %) [d]	0.10	0.10	-70.0	-80.0	-90.0	-80.0	-90.0	-90.0
NKT Cells (CD3+CD161a+) (thous/µL, %) [d]	0.24	0.23	-62.5	-56.5	-83.3	-78.3	-83.3	-87.0
Number of Animals - Subset 4	M:10	F:10	M:10	F:10	M:10	F:10	M:10	F:10
TDAR								
IgG KLH (ng/mL, %) PND 59	4566.44	4327.51	<LLOQ	-75.0	<LLOQ	<LLOQ	<LLOQ	<LLOQ
IgM KLH (ng/mL) PND 50	7303.17	1822.89	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ	<LLOQ

2.6.7.15.2 Studies in Juvenile Animals - Report R&D/17/0588 (Cont.)

Test Article: Upadacitinib; **Lot Number:** [redacted]

GLOSSARY and ENDNOTES

Abbreviation	Definition
BALT	Bronchial associated lymphoid tissue
GALT	Gut-associated lymphoid tissue
LLOQ	Lower Limit of Quantification
NA	Not applicable
NOAEL	No-Observed-Adverse Effect Level
PND	Postnatal Day
-	No noteworthy findings
*	$p < 0.05$
**	$p < 0.01$

a. At end of dosing period. For controls, group means are shown. For treated groups, percent differences from controls are shown. Statistical significance is based on actual data (not on the percent differences).

b. Numerical values indicate fold changes of treated group value relative to reference item group mean value.

c. One male and one female in Subset 4 in the 50 mg/kg/day dose group were found dead on PND 22 and PND 18, respectively. Although the cause of death of these animals could not be determined, a relationship to upadacitinib could not be discounted. In addition, one male and one female in Subset 4 in the 50 mg/kg/day dose group were found dead on PND 20 and PND 18, respectively, due to a gavage error, and five males and three females from the positive control group were found dead or euthanized due to adverse clinical signs on PND 54.

d. For controls, group means are shown. For treated groups, percent differences from controls are shown.

2.6.7.16 Local Tolerance - No Studies Conducted