2.6.7.17 Other Toxicity Studies

2.6.7.17.1 Other Toxicity Studies - Immunotoxicity - Report Title: T-cell Dependent Antibody Response Assay using A-1293543 Free Base (Hemihydrate) in Sprague-Dawley Rats (R&D/15/0592)

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

Species and Strain	Route (Method) of Administration	Duration of Dosing	Doses (mg/kg/day)	Sex and Number per Group	Noteworthy Findings	Report Number (Module)
Rat Sprague-Dawley [Crl:CD(SD)]	Oral (gavage) (A-1293543.0 hemihydrate in 2% (high-viscosity) hydroxypropyl methylcellulose (HPMC)) Dose Volume = 10 mL/kg	Main phase animals were dosed with upadacitinib for 8 weeks with TDAR conducted during last four weeks of dosing phase Recovery phase animals were dosed with upadacitinib for 4 weeks, then entered 16-week recovery phase with TDAR conducted during last four weeks of recovery phase	0, 5, 30, 60	Main phase was 10/sex/group at all dose levels Recovery phase was 10/sex/group at 0 and 60 mg/kg/day only	Upadacitinib suppressed the anti-KLH IgM and IgG T-cell dependent antibody response at all doses under the conditions of this study.	R&D/15/0592 (4.2.3.7.2-1) GLP

2.6.7.17.2 Other Toxicity Studies - Impurities - Bacterial Mutation Assays for Potential Impurities

Impurity	Highest Concentration Tested (µg/well)	Result	GLP Compliant	Test Facility	Report Number (Module)
I*	1000	Negative	Yes	AbbVie	R&D/15/1066 (4.2.3.7.6-1)
K*	1000	Negative	Yes	AbbVie	R&D/15/1172 (4.2.3.7.6-2)
L*	1000	Negative			
M*	1000	Negative			
N*	1000	Negative			
G*	1000	Positive	Yes	AbbVie	R&D/15/1263 (4.2.3.7.6-3)
O*	1000	Positive			
P*	1000	Negative			
Q*	1000	Negative			
R*	1000	Negative	Yes	AbbVie	R&D/16/0016 (4.2.3.7.6-4)
S*	1000	Negative	Yes	AbbVie	R&D/16/0218 (4.2.3.7.6-5)
T*	1000	Negative	Yes	AbbVie	R&D/16/0407 (4.2.3.7.6-6)
V*	600	Negative	Yes	AbbVie	R&D/16/0457 (4.2.3.7.6-7)
W*	1000	Negative	Yes	AbbVie	R&D/16/0855 (4.2.3.7.6-8)
X*	1000	Negative	Yes	AbbVie	R&D/16/1066 (4.2.3.7.6-9)

*新薬承認情報提供時に置換

2.6.7.17.2 Other Toxicity Studies - Impurities - Bacterial Mutation Assays for Potential Impurities (Cont.)

Impurity	Highest Concentration Tested	Result	GLP Compliant	Test Facility	Report Number (Module)
Impurities Tested Negative in GLP Ames Assay					
B*	1000	Negative	Yes	AbbVie	R&D/17/0261 (4.2.3.7.6-10)
AA*	1000	Negative	Yes	AbbVie	R&D/17/0367 (4.2.3.7.6-11)
AB*	1000	Negative	Yes	AbbVie	R&D/17/0445 (4.2.3.7.6-12)
AC*	1000	Negative	Yes	AbbVie	R&D/17/0568 (4.2.3.7.6-13)
AD*	1000	Negative	Yes	AbbVie	R&D/17/0650 (4.2.3.7.6-14)
AE*	1000	Negative			
AF*	1000	Negative	Yes	AbbVie	R&D/17/0746 (4.2.3.7.6-15)
AG*	1000	Negative	Yes	AbbVie	R&D/17/1097 (4.2.3.7.6-16)
AI*	1000	Negative	Yes	AbbVie	R&D/16/0552 (4.2.3.7.6-17)
AJ*	1000	Negative	Yes	AbbVie	R&D/16/0682 (4.2.3.7.6-18)

*新薬承認情報提供時に置換

2.6.7.17.3 Other Toxicity Studies - Other - Report Title: Neutral Red Uptake Phototoxicity Assay of A-1293543 Tartrate in Balb/c 3T3 Mouse Fibroblasts (R&D/13/991)

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

Test for Induction of:	Phototoxicity In Vitro	**Number of Independent Assays:**	2	**Report Number:**	R&D/13/991
				(Module)	(4.2.3.7.7-1)
Species/Strain:	Mouse/Balb/c 3T3 fibroblasts	**Number of Replicate Cultures:**	N/A	**Study Number:**	TX13-260
Metabolizing System:	None	**Number of Cells Analyzed/Culture:**	N/A	[redacted] **Study Number:**	[redacted]
Vehicles:	**For Test Article:** DPBS-DMSO	**For Positive Controls:**	DPBS-DMSO	**GLP Compliant:**	Yes
Treatment:	90 minutes followed by 26-27 minutes irradiation			**Date of Treatment:**	[redacted] 20[redacted]
Phototoxic Effects:	None				

Assay	Test Article	Concentration Range (µg/mL)	IC_{50} -UVR (µg/mL)	IC_{50} +UVR (µg/mL)	Photoirritancy Factor	Mean Photo Effect
Assay 1	A-1293543	1.78 - 100	-	-	*1	0.013
Assay 2	A-1293543	1.78 - 100	-	-	*1	0.024
Positive Control	Promethazine	0.032 - 100	54.3	0.7787	69.745	0.496

Abbreviations: DPBS-DMSO = Dulbecco's phosphate-buffered saline with calcium and magnesium/dimethyl sulfoxide.

*1: Both IC_{50}(-UVR) and IC_{50}(+UVR) could not be calculated, this indicated a lack of phototoxic potential.

Criteria

Mean Photo Effect (MPE)	Photoirritancy Factor (PIF)	Phototoxic Potential
< 0.1	< 2	Non-Phototoxic
> 0.1 and < 0.15	> 2 and < 5	Probably Phototoxic
> 0.15	> 5	Phototoxic