CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Integrated Review	
NDA Number:	211675
Associated IND:	114717
Link to EDR:	\\CDSESUB1\evsprod\NDA211675\0002
Submissions Date:	12/18/2018
Submission Type:	Priority, 505(b)(1)
Proposed Brand Name:	Rinvoq
Generic Name:	Upadacitinib
Applicant:	Abbvie
Route of Administration:	Oral
Dosage Form and strength:	Extended-release tablets, 15 mg
Proposed Dosing Regimen:	The recommended oral dose is 15 mg once daily with or without food. May be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs.
Proposed Indication(s):	(b) (4)
OCP Review Team:	Lei He, PhD.; Jing Niu, MD.; Manuela Grimstein, PhD.; Robert Schuck, PhD.; Christian Grimstein, PhD.; Xinyuan Zhang, PhD.; Jingyu Yu, PhD.; Anshu Marathe PhD.
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1. EXECUTIVE SUMMARY

Abbvie submitted NDA 211675 on December 18, 2018 seeking the marketing approval for upadacitinib as monotherapy or in combination with methotrexate (MTX) and/or other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) for the treatment of moderately to severely active rheumatoid arthritis (RA). Upadacitinib (also known as A-1293543 and ABT-494), is claimed to be a Janus kinase (JAK) inhibitor.

The proposed commercial upadacitinib drug product is formulated as 15 mg extended-release (ER) tablet for oral administration. The proposed dosing regimen is 15 mg once daily (QD) regardless of food.

NDA 211675 consists of thirty clinical and clinical pharmacology studies, including twenty-two Phase 1 studies, two Phase 2 studies, one supportive Phase2b/3 study in Japan, and five Phase 3 studies. Eight in-vitro study reports were submitted characterizing protein binding, metabolism, and drug-drug interaction (DDI) potential. In addition, three population PK, exposure-response, and physiological-based pharmacokinetic (PBPK) analysis reports were submitted.

Results from Phase 2 dose-ranging studies using immediate-release (IR) formulation showed that upadacitinib 6 mg and 12 mg twice daily (BID) dosing regimens were both efficacious in RA patients. While 12 mg BID dosing produced a slight increase in efficacy as compared to 6 mg BID dosing, no additional increase in efficacy was observed for doses higher than 12 mg BID. Therefore, upadacitinib 6 mg and 12 mg BID dosing regimens using IR formulation were selected as the target exposure for doses in Phase 3 studies. To enhance patient compliance, an ER tablet formulation has been developed. Upadacitinib doses of 15 mg QD and 30 mg QD using the ER formulation provided comparable systemic exposure to 6 mg BID and 12 mg BID using IR formulation, respectively, and were investigated in Phase 3 study evaluations. In Phase 3 studies, upadacitinib 15 mg QD dosing provided significantly greater probability of ACR20 response at the prespecified primary time point comparing with the placebo group or active comparator groups. Although there were numerical trends of dose response towards greater ACR response for 30 mg QD dosing, the safety profile of upadacitinib has demonstrated a dose-dependent increase in the number of reported adverse events. Exposure-response analysis for efficacy and safety were consistent with the observed dose-response. Overall, results from Phase 3 studies and exposure-response analysis support the proposed 15 mg QD dosing regimen as it provides the optimal benefit-risk balance in patients with moderately to severely active RA.

1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP2) has reviewed NDA 211675 Clinical Pharmacology data submitted on December 18, 2018 and recommends approval. The key review issues with specific recommendations/comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	• Five Phase 3 studies provide primary evidence (refer to the clinical review by medical officer Dr. Keith Hull and the statistical review by Dr. William Koh). • Exposure-response analyses for efficacy is consistent with the observed dose-response.

General dosing instructions	• The proposed 15 mg QD dosing regimen is acceptable based on Phase 2 and 3 studies. See Section 2.2.1 for details on dose/exposure-response.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Upadacitinib is not recommended to be co-administered with strong CYP3A4 inducers. • The sponsor's proposal that upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors is acceptable. • The sponsor's proposal that no dose adjustment is needed for subjects with mild, moderate, or severe renal impairment and mild or moderate hepatic impairment is acceptable. • PBPK analysis adequately bridged the clinical DDI effect of strong CYP3A4 modulator (inducer or inhibitor) observed with upadacitinib IR formulation to the ER formulation See section 2.2.2.
Bridge between the "to-be-marketed" and clinical trial formulations	• Bioequivalence was established between the to-be-marketed ER tablets and the ER tablets used in Phase 3 studies.
Labeling	See section 2.4 for labeling.

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Upadacitinib is an oral Janus kinase (JAK) inhibitor. The clinical pharmacokinetics of upadacitinib is summarized as below:

Absorption: Following a single dose administration of upadacitinib, the median Tmax was 2-3 hours. High-fat and high-caloric meal increased upadacitinib Cmax and AUC0-inf by 40% and 30%, respectively. Following QD dosing, steady state was achieved within 4 days with minimal accumulation. Upadacitinib Cmax and AUC were approximately dose-proportional over evaluated dose ranges.

Distribution: Upadacitinib is approximately 52% bound to human plasma proteins. The blood to plasma ratio is 1.0 in human. For a typical patient with RA with body weight of 74 kg, upadacitinib volume of distribution at steady state is estimated to be 224 L following the administration of ER formulation.

Elimination: Upadacitinib mean terminal elimination t1/2 ranged from 8 to 14 hours following the administration of ER formulation. The typical clearance of upadacitinib was 40.9 L/h in patients with RA as estimated by population PK analysis.

Metabolism: Upadacitinib is metabolized by CYP3A4 and to a minor extent, by CYP2D6. In the mass balance study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma. There are no known active metabolites.

Excretion: In the mass balance study, approximately 53% and 43% of the administered dose was excreted in feces and urine, respectively. Upadacitinib was eliminated predominantly as the unchanged parent drug in feces (38%) and urine (24%), and approximately 34% of upadacitinib dose was excreted as metabolites.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The proposed dosing regimen for upadacitinib is 15 mg ER tablets QD as monotherapy or in combination with MTX and/or other csDMARDs for the treatment of moderately to severely active RA. In Phase 2 dose-ranging studies using IR formulation, while the ACR20 response rates at Week 12 with 12 mg BID were slightly higher as compared to 6 mg BID, both 6 mg BID and 12 mg BID dosing regimens were significantly higher than placebo and no additional significant increase in ACR20 response rates were observed with doses higher than 12 mg BID. Therefore, upadacitinib 6 mg and 12 mg BID dosing regimens using IR formulation were selected as the target exposure for Phase 3 studies. To enhance patient compliance, an ER tablet formulation has then been developed. Upadacitinib doses of 15 mg QD and 30 mg QD using the ER formulation provided comparable systemic exposure to 6 mg BID and 12 mg BID using IR formulation, respectively, and were investigated in five Phase 3 studies in patients with RA, including Studies M13-545 (n=945), M13-549 (n=661), M14-465 (n=1629), M15-555 (n=648), and M13-542 (n=498). In the Phase 3 studies, there were significantly greater probability of ACR20 response at the prespecified primary time point comparing upadacitinib 15 mg QD with the placebo group or active comparator groups (MTX monotherapy). In studies evaluating both upadacitinib 15 mg and 30 mg QD doses (except for ACR20 in Study M13-542), there were numerical trends of dose response towards greater ACR response for the higher upadacitinib dosing (30 mg QD), which is not clinically significant. Preliminary review of the upadacitinib safety profile has demonstrated a dose-dependent increase in the number of reported adverse events, i.e. the percentage of subjects with adverse events or serious adverse events with 30 mg QD dosing was greater than subjects with 15 mg QD dosing. In addition, results from the exposure-response analysis for efficacy and safety were consistent with the observed dose-response relationship. All these results support the proposed 15 mg QD dosing regimen for the treatment of patients with moderately to severely active RA. For details regarding efficacy and safety, refer to the clinical review by Dr. Keith Hull and the statistical review by Dr. William Koh.

2.2.2 Therapeutic individualization

When upadacitinib was co-administered with ketoconazole (a strong CYP3A4 inhibitor), upadacitinib exposure increased by 75% for AUC0-inf and 70% for Cmax. Upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors.

When upadacitinib was co-administered with rifampin (a strong CYP3A4 inducer), upadacitinib exposure decreased by 61% for AUC0-inf and 51% for Cmax, which may result in inefficacious concentrations and consequently decrease the efficacy. Therefore, upadacitinib is not recommended to be co-administered with strong CYP3A4 inducers.

No dose adjustment is needed for subjects with mild, moderate, or severe renal impairment and mild or moderate hepatic impairment. Upadacitinib has not been evaluated in patients with severe hepatic impairment and is not recommended for these patients.

2.3 Outstanding Issues

There was no Clinical Pharmacology-related outstanding issue for this submission.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

Label Section	Recommendations
7.2 Drug interactions	• Upadacitinib is not recommended to be co-administered with strong CYP3A4 inducers.
8.6 Renal impairment	• The predicted impact of hemodialysis on upadacitinib PK should not be included.
12.2 Pharmacodynamics	• Cardioelectrophysiology labeling language should be updated based on QT-IRT review.
12.3 Pharmacokinetics	• Include both positive and pertinent negative in vitro study results regarding DDI potential. • Clinical recommendations based on PK or PD data should not be included in section 12.3.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Drug product

Upadacitinib drug substance is manufactured as a hemihydrate (Figure 1). The proposed drug product is an extended-release, (b) (4) tablet containing 15 mg of upadacitinib.

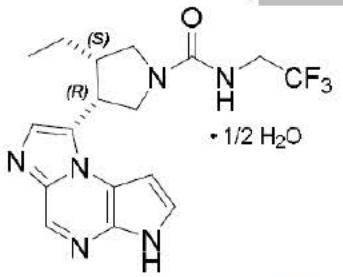


Figure 1. Structure of upadacitinib hemihydrate
(Source: Figure 1 of Quality Overall Summary-Drug Substance)

Table 1. Physicochemical properties of upadacitinib

Molecular Formula	$C_{17}H_{19}F_3N_6O$ • 1/2 H_2O (hemihydrate)
Molecular Weight	389.38 g/mol (hemihydrate); 380.38 g/mol (anhydrate)
Dissociation Constants	pKa=4.7
Solubility at 37°C	433 mg/L in ethanol (absolute); 0.2 mg/mL in water; 95 mg/mL in tetrahydrofuran
Permeability	Papp = 11.5×10^{-6} cm/sec, pH 6.5
Partition Coefficient	2.5 (n-octanol/buffer, pH 7.4)

Regulatory background

To date, there are two approved JAK inhibitors in the U.S.: 1) XELJANZ (tofacitinib, tablets and extended-release tablets, Pfizer) is currently approved for the treatment of RA, psoriatic arthritis, and ulcerative colitis; and 2) OLUMIANT (baricitinib, tablets, Eli Lilly) is currently approved the treatment of RA.

Upadacitinib, a JAK inhibitor, has been developed as monotherapy or in combination with MTX and/or other csDMARDs for the treatment of moderately to severely active RA. The relevant regulatory history is summarized in the table below. The NDA was submitted on December 18, 2018 and is reviewed under priority review timelines.

NDA 211675 consists of thirty clinical and clinical pharmacology studies, including twenty-two Phase 1 studies, two Phase 2 studies, one supportive Phase 2b/3 study in Japan, and five Phase 3 studies (Table 3). Eight in-vitro study reports were submitted characterizing protein binding, metabolism, and DDI potential. In addition, three population PK, exposure-response, and PBPK analysis reports were submitted.

Table 2. Summary of regulatory history relevant to clinical pharmacology

End-of-Phase 2 meeting (10/2015)	• The Agency recommended to finish the dedicated PK studies in renal and hepatic impairment subjects before enrolling patients with hepatic or/and renal impairment in Phase 3 studies. • To bridge the proposed Phase 3 ER tablet to the Phase 2 IR capsule, the least common dosing interval should be used for PK comparison in the proposed comparability study. • The sponsor believed that results from Phase 1 studies did not demonstrate a potential effect of upadacitinib on the QT interval and planned not to conduct a thorough QT study. The Agency recommended to submit data for review. • Based on the results from Phase 2 studies, 6 mg and 12 IR capsule BID doses appear to be a reasonable goal to base future development. However, the Agency could not agree with the proposed dose selection with ER formulation for Phase 3 studies at the time of the meeting due to insufficient data to bridge the Phase 2 IR capsule and the proposed Phase 3 ER tablet.
Pre-NDA meeting (05/2018)	• The Agency agreed that the clinical pharmacology information is adequate to support the filing of the NDA. The adequacy of the information will be a review issue. • The Agency recommended to submit a justification for the dose selection and thorough analyses of dose- and exposure-response for both efficacy and safety, including laboratory parameters, to further support the NDA.

Table 3. Summary of submitted clinical studies

Study #	Study ID	Study Objectives	Study Design	Formulation	Study population	Treatment
	Phase 1 Studies					
1	M13-547	Relative BA and food effect	SD, OL, R, 4-P CO (part 1), 2-P CO (part2)	IR capsule, ER formulations	HS (n=33)	IR 24 mg; ER 24 mg
2	M14-677	Relative BA and food effect	SD, OL, R, 4-P, 8-S, incomplete CO	IR tablet and capsule	HS (n=24)	IR tablet or capsule 24 mg
3	M14-174	Relative BA and food effect	SD, OL, R, CO	IR capsule, ER formulations	HS (n=30)	IR 24 mg; ER 24 mg
4	M14-680	Relative BA, food effect, PK, safety, tolerability	SD or MD, OL, R, CO	IR capsule ER tablets	HS (n=81)	IR 3 and 12 mg ER 15 and 30 mg
5	M14-678	Relative BA	SD, OL, R, 2-P CO	IR capsule, ER tablet	HS (n=12)	IR 3 mg ER 7.5 mg
6	M14-679	Relative BA	SD, OL, R, CO	ER formulations	HS (n=73)	ER 15 and 30 mg
7	M15-878	Phase 3 and commercial ER bridge, food effect	SD, OL, R, CO	ER tablets	HS (n=82)	ER 15 and 30 mg
8	M16-552	Relative BA	SD, OL, R, 2-P, 2-S, CO	Oral solution and tablet	HS (n=24)	Oral solution, 2×6 mg; tablet 15 mg
9	M16-094	Relative BA, food effect	SD, OL, R, 3-P, 6-S	Tablet formulations	HS (n=24)	tablets 45 mg
10	M15-868	Relative BA	SD, OL, R, 5-P CO	IR and ER formulations	HS (n=20)	IR 24 mg ER 30 mg
11	M13-401	SAD, food effect, effect of ketoconazole	SD, R, DB or OL,	IR capsules	HS (n=68)	1, 3, 6, 12, 24, 36, and 48 mg
12	M13-845	MAD, safety, tolerability, PK	R, DB, PC, MAD	IR capsules	HS and RA (on MTX) (n=67)	3, 6, 12, and 24 mg BID
13	M13-548	Mass balance study	SD, OL	Oral solution	HS (n=4)	[^{14}C]UPA oral solution, 30 mg
14	M13-543	SAD, MAD	R, DB, PC, SAD, MAD	IR capsules	Japanese and Chinese HS (n=45)	3, 6, 24 mg; 18 mg BID, 14 days
15	M13-539	Hepatic impairment study	SD, OL	ER tablets	Normal adults or with HI (n=18)	15 mg
16	M13-551	Renal impairment study	SD, OL	ER tablets	Normal adults or with RI (n=24)	15 mg
17	M15-558	MD study	R, DB, PC, MD	ER tablets	Chinese HS (n=36)	15, 30, 45 mg QD, 7 days
18	M13-540	Effect of rifampin	OL, 2-P, sequential design	IR capsules	HS (n=12)	12 mg
19	M13-541	Effect of UPA on rosuvastatin and atorvastatin PK	OL, 2-part, 2-P	ER tablets	HS (n=36)	30 mg
20	M14-624	Effect of UPA on CYP substrates	MD, OL, 2-P	ER tablets	HS (n=20)	30 mg
21	M14-625	Effect of UPA on thinylestradiol and levonorgestrel	MD, OL, 2-P	ER tablets	HS (n=20)	30 mg
22	M17-221	Effect of UPA on bupropion PK	MS, OL, 2-P	ER tablets	HS (n=22)	30 mg
	Phase 2 Studies					

23	M13-537	Dose ranging	R, DB, PG, PC	IR capsules	RA on MTX, no adequate response to MTX alone (n=299)	3, 6, 12, 18 mg BID 12 weeks; 24 mg QD 12 weeks
24	M13-550	Dose ranging	R, DB, PG, PC	IR capsules	RA on MTX, inadequate response or intolerance to anti-TNF biologics (n=276)	3, 6, 12, 18 mg BID 12 weeks
	Phase 3 Studies					
25	M14-663	Supportive Phase 2b/3 dose ranging (Japan)	R, DB, PG, PC	ER tablets	Japanese RA on stable csDMARDs, inadequate response to csDMARDs (n=197)	7.5, 15, 30 mg QD
26	M13-549	Efficacy and safety	R, DB, PG, PC	ER tablets	RA on stable csDMARDs, inadequate response to csDMARDs (n=661)	15, 30 mg QD
27	M15-555	Efficacy and safety	R, DB, PG,	ER tablets	RA, inadequate response to MTX	15, 30 mg QD
28	M13-542	Efficacy and safety	R, DB, PG, PC	ER tablets	RA on stable csDMARDs, inadequate response to bDMARDs (n=499)	15, 30 mg QD
29	M14-465	Efficacy and safety	R, DB, PG, PC, active comparator	ER tablets	RA on stable MTX, inadequate response to MTX (n=1629)	15 mg QD
30	M13-545	Efficacy and safety	R, DB, PG, MTX-controlled	ER tablets	RA, MTX-naïve (n=947)	7.5(Japan only), 15, 30 mg QD

UPA: upadacitinib; BA: bioavailability; IR: immediate release; ER: extend release; SD: single dose; MD: multiple dose; P: period; S: sequence; CO: crossover; OL: open label; R: randomized; HS: healthy subjects; PC: placebo controlled; PG: parallel group; MTX: methotrexate; Sub.: substudy; HI: hepatic impairment; RI: renal impairment; bDMARD = biologic disease-modifying antirheumatic drug; TNF = tumor necrosis factor; csDMARD = conventional synthetic disease-modifying antirheumatic drug;

3.2 General Pharmacological and Pharmacokinetic Characteristics

SUMMARY OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology	
Review Issues	**Recommendations and Comments**
Mechanism of action	Upadacitinib is an oral JAK inhibitor.
Active moieties	Upadacitinib parent drug is the active moiety. There are no active metabolites.
QT prolongation	A lack of clinically relevant effect on the QTc interval was observed at the maximum upadacitinib exposure level in the QT assessment (314 ng/mL, approximately 6 times the mean maximum exposure of the 15 mg once daily dose). Refer to QT-IRT review by Dr. Nan Zhang dated 05/09/2019.
General Information	
Bioanalysis	Upadacitinib concentrations in human plasma and urine were measured using validated HPLC tandem mass spectrometric

	methods.	
Healthy volunteers vs. Patients	Based on population pharmacokinetic analyses, subjects with RA are estimated to have 25% lower upadacitinib CL/F (leading to 33% higher estimated AUC) compared to healthy subjects.	
Drug exposure at steady state following the therapeutic dosing regimen	Based on population PK model, the estimated median $C_{max,ss}$, $C_{ave,ss}$, and $C_{min,ss}$ was 41.1 ng/mL (95% CI: 28.2-56.0 ng/mL), 15.1 ng/mL (95% CI: 9.0-32.7 ng/mL), 3.82 ng/mL (95% CI: 1.28-21.3 ng/mL), respectively, for 15 mg QD dosing in RA patients.	
Dose proportionality	Upadacitinib Cmax and AUC were approximately dose-proportional over single and multiple IR (1-48 mg) (Studies M13-401 and M13-845) and ER (7.5-45 mg) dose ranges (Studies M14-678, M14-680, and M16-094).	
Accumulation	Following QD dosing, steady state was achieved within 4 days with minimal accumulation (Study M14-680).	
Variability	In healthy subjects, the between-subject variability (CV %) of upadacitinib AUC and Cmax was approximately 20% to 35% for the clinically relevant regimens. Based on population PK analysis, the between-subject variability for CL/F is estimated to be 37% in RA patients.	
Absorption		
T_{max} [oral]	Following a single dose administration of upadacitinib, the median Tmax was 2-3 hours (range 1-4 hours) under the fasted condition and was 6 hours (range 1.5-10 hours) under fed condition (Study M15-878).	
Food effect (high-fat and high-caloric) GMR (fed/fasted, 90% CI) (Study M15-878)	AUC_{0-inf}	C_{max}
	1.29 (1.23, 1.36)	1.39 (1.28, 1.51)
Distribution		
Volume of distribution	For a typical RA patient with body weight of 74 kg, upadacitinib volume of distribution at steady state is estimated to be 224 L following the administration of ER formulation (Population PK Report R&D/18/0165).	
Plasma protein binding	Upadacitinib is approximately 52% bound to human plasma proteins (Study R&D/17/0325).	
Blood to plasma ratio	In vitro study showed the mean blood-to-plasma ratios of upadacitinib is 1.0 in human (Study R&D/17/0325). In ADME study, mean C_{max} and AUC_{∞} for total radioactivity were 15% and 19%, respectively, higher in plasma than in blood (Study M13-548).	
Substrate transporter systems	Upadacitinib is a substrate of P-gp and BCRP. However, modulation of P-gp or BCRP transporters is expected to have minor effect on upadacitinib exposures in vivo based on PBPK simulations.	
Elimination		
Mean terminal elimination half-life	Upadacitinib mean terminal elimination t1/2 ranged from 8 to 14 hours following the administration of the extended-release formulation.	
Metabolism		
Primary metabolic pathway(s)	In vitro metabolism studies indicated that upadacitinib metabolism is mediated by CYP3A4 with a potential minor contribution from	

	CYP2D6. In human ADME study, unchanged upadacitinib accounted for 79% of the total radioactivity in plasma while the two main metabolites detected (M4 (products of monooxidation followed by glucuronidation) and M11 (monooxidation followed by ring opening)) accounted for 13% and 7.1% of the total plasma radioactivity, respectively (Study M13-548).
Inhibitor/Inducer	Ketoconazole (strong CYP3A4 inhibitor) increased upadacitinib exposure by 75% (StudyM13-401). Rifampin (strong CYP3A4 inducer) decreased upadacitinib exposure by 61% (Study M13-540). Therefore, upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors and is not recommended to be co-administered with strong CYP3A4 inducers. Methotrexate (potential concomitant medication) or OATP1B inhibitor (rifampin) do not have clinically meaningful effect on upadacitinib PK (Studies M13-845 and M13-540). Upadacitinib does not have clinical meaningful effect on midazolam (CYP3A4 substrate), caffeine (CYP1A2 substrate), dextromethorphan (CYP2D6 substrate), S-warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), bupropion (CYP2B6 substrate), or potential concomitant medications, including methotrexate, rosuvastatin, atorvastatin, ethinylestradiol, levonorgestrel (Studies M14-624, M17-221, M13-845, M13-541, and M14-625).
Excretion	
Primary excretion pathway	Following single dose administration of 30 mg (100 μCi) [^{14}C]upadacitinib IR solution, 96% of the radioactivity was recovered in urine and feces within 216 hours after dosing, in which ~53% was recovered in feces and 43% was recovered in urine. Upadacitinib was eliminated predominantly as the unchanged parent drug in urine (24%) and feces (38%), and approximately 34% of upadacitinib dose was excreted as metabolites (Study M13-548).

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

Yes, the clinical pharmacology information provides supportive evidence of effectiveness.

Phase 2 dose-ranging study

Two Phase 2 dose-ranging studies (Studies M13-537 and M13-550) using IR formulation explored the treatment effect of upadacitinib BID dosing regimens (ACR response at Week 12 as primary endpoint) in RA patients. The primary efficacy results of different treatment groups from these studies are shown in Table 4. In both dose-ranging studies, while the ACR20 response rates at Week 12 with 12 mg BID were slightly higher as compared to 6 mg BID, both 6 mg BID and 12 mg BID were significantly higher than placebo and no additional increase in ACR20 response was observed with doses higher than 12 mg BID.

The same trend has also been observed in the exposure-response analysis for ACR20/50/70 using data from Phase 2 dose-ranging studies (Figure 2). Therefore, 6 mg BID and 12 mg BID were selected as the target exposure for Phase 3 studies.

Bridging IR formulation and ER formulation

To enhance patient compliance, an ER tablet formulation has been developed. Upadacitinib PK was compared between using IR formulation and ER formulation in a dedicated, randomized, open-label, two-period, two-sequence, crossover, relative bioavailability study (Study M14-680). Following multiple dose administration, upadacitinib doses of 15 mg QD and 30 mg QD using the ER formulation provided comparable systemic exposure at steady state to 6 mg BID and 12 mg BID using IR formulation, respectively, and therefore were predicted to provide similar efficacy to 6 mg BID and 12 mg BID, respectively, using IR formulation (Table 5).

Table 4. Summary of the primary efficacy results from three Phase 2 dose-ranging studies

Study ID	Patient Population	Formulation	ACR Response Rate at Week 12*					
			placebo	3 mg BID	6 mg BID	12 mg BID	18 mg BID	24 mg QD
M13-537	RA with inadequate resp. to MTX (n=299)	IR	50% (23/46)	64.6% (31/48) (n.s.)	73.5% (36/49) (p=0.018)	81.6% (40/49) (p=0.001)	76.6% (36/47) (p=0.008)	81.6% (40/49) (p=0.001)
M13-550	RA on MTX, inadequate resp. to anti-TNF biologics (n=276)	IR	35.2% (19/54)	55.6% (30/54) (p=0.033)	63.5% (33/52) (p=0.004)	72.7% (40/55) (p<0.001)	70.9% (39/55) (p<0.001)	--

* listed as response rate (%) calculated by response patient number/total patient number; p value is the comparison of ACR 20 between treatment group and placebo.

Table 5. Upadacitinib PK comparison (geometric mean ratio (90% CI)) using IR and ER formulation (Study M14-680)

PK	ER 15 mg QD (T) *vs* IR 6 mg BID (R)	ER 15 mg QD (T) *vs* IR 6 mg BID (R)
Cmax	0.91 (0.74, 1.12)	0.90 (0.73, 1.11)
AUC0-24h	0.94 (0.84, 1.05)	0.97 (0.87, 1.09)
Cmin	1.09 (0.85, 1.40)	0.87 (0.75, 1.02)

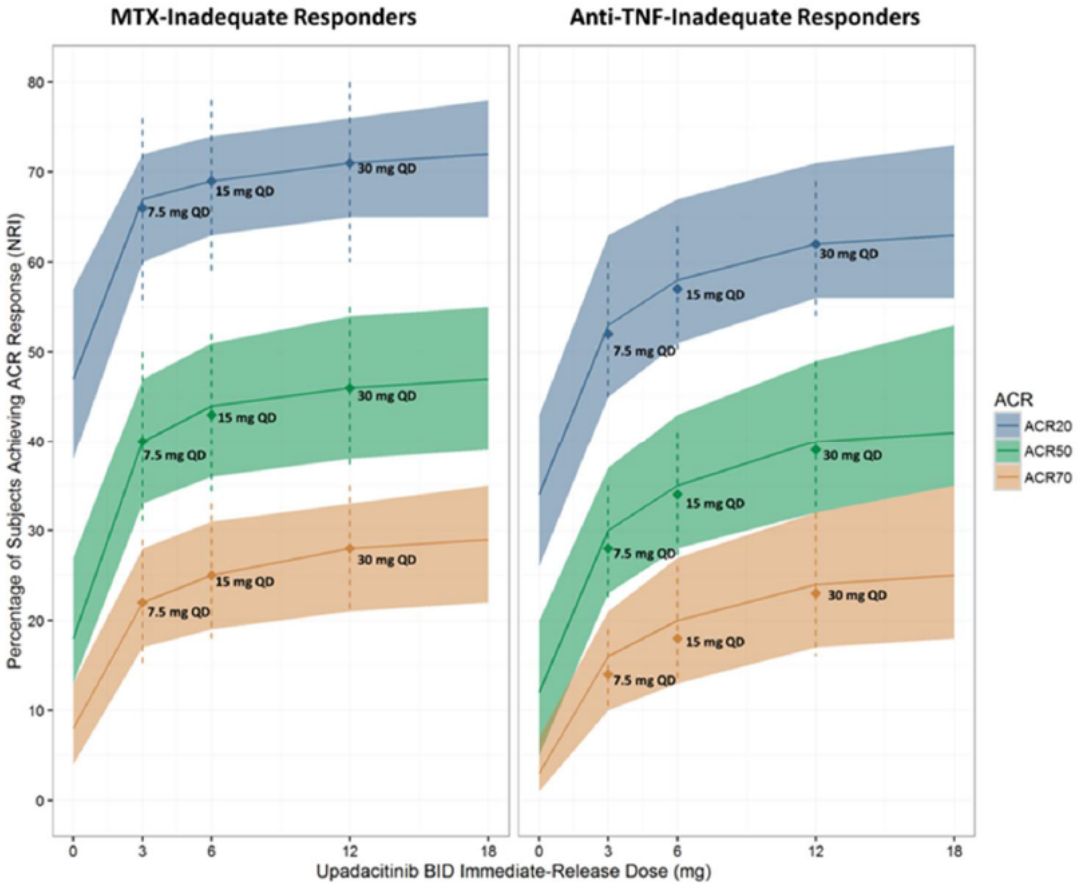


Figure 2. Simulated median and 90% prediction intervals ACR responses at Week 12 for the IR BID regimens evaluated in Studies M13-537 and M13-550 and the ER QD dosing regimens based on Phase 2 exposure-response analyses
(Source: Figure 8 of Summary of Clinical Pharmacology)

Effects of upadacitinib on ex-vivo IL-6-induced pSTAT3 and IL-7-induced pSTAT5

The effects of upadacitinib on ex-vivo markers of JAK activity have been explored in healthy volunteers (Study M13-401). Following a single dose administration of upadacitinib using IR formulation, the inhibition of IL-6 (JAK1/JAK2) - induced STAT3 and IL-7 (JAK1/JAK3)-induced STAT5 phosphorylation was shown in a dose-dependent manner and the maximal inhibition was observed 1 hour after dosing which returned to near baseline by the end of dosing interval (Figure 3). However, the clinical meaning of these ex vivo results is unclear.

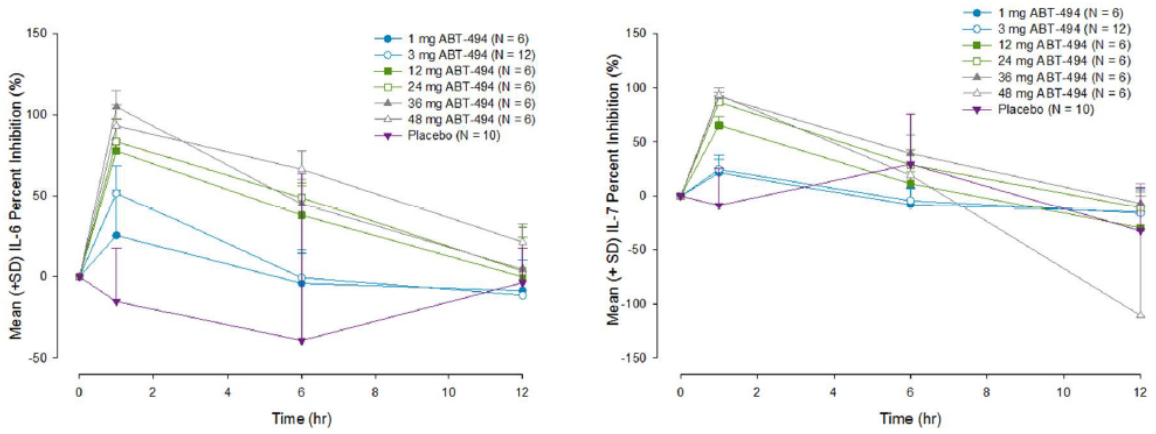


Figure 3. Mean (+ SD) percent inhibition of ex-vivo IL-6-induced STAT3 phosphorylation and IL-7-induced STAT5 phosphorylation relative to baseline following single dose administration of upadacitinib (IR) or placebo to healthy subjects (Study M13-401)
(Source: Figure 6 of Summary of Clinical Pharmacology)

3.3.2 Is the proposed general dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed general dosing regimen is appropriate.

The efficacy of upadacitinib was exposure-dependent. Exposure-efficacy analysis for ACR responses, low disease activity (LDA), and clinical remission (CR) described placebo responses and response to upadacitinib treatment in subjects with RA reasonably well using data from Phase 2 and 3 studies. Results of the exposure-efficacy simulations demonstrate that upadacitinib at the 30 mg QD dose provides only a small incremental efficacy benefit compared to 15 mg QD (Table 6). The applicant's exposure response analysis for efficacy is consistent with the observed efficacy data.

No exposure-response relationship was observed between upadacitinib exposure and the occurrence of serious infections (Week 12/14), pneumonia, herpes zoster infection, changes in platelet count, lymphopenia (Grade 4 or higher), and neutropenia. Increased upadacitinib exposures were associated with higher incidence of hemoglobin decrease from baseline (> 1 g/dL and > 2 g/dL) for both Week 12/14 and Week 24/26, higher incidence of lymphopenia (grade 3 or higher) for Week 12/14, and increased incidence of serious infections up to Week 24/26. 15 mg QD is predicted to be associated with lower incidence of reduction in hemoglobin, lymphopenia, or serious infections as compared to 30 mg QD. The applicant's exposure response analysis for safety is consistent with the observed safety data.

Refer to the clinical review and statistical review by Dr. Keith Hull and Dr. William Koh, respectively, for more details for the observed efficacy and safety data. Refer to the pharmacometrics review (section 4.3) for the technical details for the exposure-response analyses for efficacy and safety.

Table 6. Model-simulated clinical efficacy responses following placebo and upadacitinib 15 mg and 30 mg QD dosing regimens (based on exposure-response analyses of Phase 2 and 3 Studies)

Population	Clinical Efficacy Response Variable[a]	Upadacitinib Dosing Regimen		
		Placebo	15 mg QD	30 mg QD
MTX-IR on Background MTX	ACR20	40 (34, 47)	66 (60, 71)	68 (62, 74)
	ACR50	17 (12, 22)	41 (35, 48)	45 (39, 52)
	ACR70	6 (3, 11)	23 (18, 29)	26 (21, 33)
	LDA	19 (13, 24)	45 (40, 52)	50 (44, 57)
	CR	11 (8, 16)	31 (25, 36)	34 (29, 41)
bDMARD-IR on Background MTX	ACR20	36 (30, 43)	58 (52, 65)	61 (54, 67)
	ACR50	14 (8, 19)	34 (27, 42)	38 (32, 45)
	ACR70	5 (2, 9)	18 (13, 24)	21 (16, 26)
	LDA	18 (14, 24)	40 (34, 47)	45 (39, 51)
	CR	11 (7, 15)	27 (21, 33)	31 (25, 36)
MTX-IR on Upadacitinib Monotherapy	ACR20	36 (29, 44)	65 (58, 72)	68 (61, 75)
	ACR50	12 (8, 16)	42 (36, 49)	45 (38, 52)
	ACR70	3 (1, 7)	24 (18, 30)	27 (20, 33)
	LDA	17 (12, 23)	50 (44, 58)	55 (48, 62)
	CR	11 (7, 16)	36 (31, 44)	40 (34, 47)

MTX-IR = Methotrexate inadequate responder; bDMARD-IR = Biologic disease-modifying anti-rheumatic drug inadequate responder

a. Data are presented as median (5^{th}, 95^{th} percentiles).

(Source: Summary of Clinical Pharmacology Studies, Module 2.7.2)

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

No alternative dosing regimen and management strategy is required for subpopulations based on intrinsic factors. There is no clinically relevant effect of mild, moderate, or severe renal impairment and mild or moderate hepatic impairment on upadacitinib exposure. Upadacitinib has not been evaluated in patients with severe hepatic impairment and is not recommended for these patients.

3.3.3.1 Renal impairment

The mass balance study (Study M13-548) demonstrated that ~43% of total orally administered upadacitinib was excreted in the urine. The impact of various degrees of renal impairment (based on estimated glomerular filtration rate (eGFR)) on upadacitinib PK was assessed in a dedicated, open-label, single dose study (Study M13-551). Following the administration of a single dose of 15 mg upadacitinib under fasted conditions, upadacitinib Cmax remained similar while AUC were up to 19%, 33% and 45% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. The sponsor's proposal that no dose adjustment is needed for subjects with mild, moderate, or severe renal impairment is reasonable. Refer to Individual Study Review in Appendix 4.1.2 for more details.

Table 7. Summary of upadacitinib PK comparison (geometric mean ratio (90% CI)) in subjects with impaired renal function based on eGFR

Group comparison* (Test *vs* Reference)	N	Cmax	AUC0-t	AUC0-inf
Mild *vs* Normal	6/6	1.06 (0.92, 1.23)	1.19 (1.06, 1.32)	1.18 (1.06, 1.32)
Moderate *vs* Normal	5/6	1.11 (0.87, 1.40)	1.33 (1.11, 1.60)	1.32 (1.11, 1.59)
Severe *vs* Normal	6/6	1.14 (0.84, 1.56)	1.45 (1.14, 1.84)	1.44 (1.14, 1.82)

*Normal renal function: eGFR≥90 mL/min/1.73m^2; mild renal impairment: eGFR 60-89 mL/min/1.73m^2; moderate renal impairment: eGFR 30-59 mL/min/1.73m^2; severe renal impairment: eGFR 15-29 mL/min/1.73m^2.
(Data source: Table 7 of Study M13-551 CSR)

3.3.3.2 Hepatic impairment

The mass balance study (Study M13-548) demonstrated that ~53% of total orally administered upadacitinib was excreted in the feces. In a dedicated, open-label, single dose study (Study M13-539), following the administration of a single dose of 15 mg upadacitinib under fasted conditions, upadacitinib Cmax was similar in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment, and upadacitinib AUC was 28% and 25% higher in subjects with mild and moderate hepatic impairment, respectively, as compared to subjects with normal hepatic function. The use of upadacitinib in subjects with severe hepatic impairment has not been proposed. The sponsor's proposal that no dose adjustment is needed for subjects with mild and moderate hepatic impairment is reasonable. Refer to Individual Study Review in Appendix 4.1.2 for more details.

Table 8. Summary of upadacitinib PK comparison (geometric mean ratio (90% CI)) in subjects with impaired hepatic function according to Child-Pugh classification

Group comparison* (Test *vs* Reference)	N	Cmax	AUC0-t	AUC0-inf
Mild *vs* Normal	6/6	1.04 (0.77, 1.39)	1.27 (0.91, 1.79)	1.28 (0.91, 1.79)
Moderate *vs* Normal	5/6	1.43 (1.05, 1.95)	1.25 (0.87, 1.78)	1.24 (0.87, 1.76)

*Mild hepatic impairment: Child-Pugh A, score 5-6; moderate hepatic impairment: Child-Pugh B, score 7-9.
(Data source: Table 6 of Study M13-539 CSR)

3.3.3.3 CYP2D6 genotype

The in-vitro studies showed minor contribution of CYP2D6 in upadacitinib metabolism and the impact of CYP2D6 genotype on upadacitinib PK has been assessed.

DNA was extracted from whole blood in healthy subjects (Studies M13-401, M13-845, M13-543) and RA patients (studies M13-537 and M13-550) and CYP2D6 genotyping was performed to determine the presence of gene duplication, gene deletion, and multiple single nucleotide polymorphisms (CYP2D6*3, CYP2D6*4, CYP2D6*6, CYP2D6*7, CYP2D6*9, CYP2D6*10, CYP2D6**17, CYP2D6*29, and CYP2D6*41). CYP2D6 genotype-inferred phenotypes were determined for a total of 588 subjects using methods previously reported in the literature. The impact of CYP2D6 genotype-inferred phenotype on upadacitinib CL/F of the immediate-release formulation was assessed in the population pharmacokinetic model. In the combined dataset there were 355 (62%) normal metabolizers, 36 (6%) intermediate metabolizers, 29 poor metabolizers (5%), and 7 (1%) ultra-rapid metabolizers. CYP2D6 genotype-inferred phenotype did not correlate with upadacitinib CL/F, and therefore was not included in the full model.

Consistent with the lack of a CYP2D6 genotype effect on CL/F, concomitant use of CYP2D6 inhibitors was not correlated with updatacitinib CL/F.

3.3.3.4 Other intrinsic factors from population PK analysis

Population PK analysis showed that body weight, gender, race, ethnicity, and age did not have a clinically meaningful effect on upadacitinib exposure. Refer to the Pharmacometrics Review in the Appendix for more details.

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

There is no clinically relevant food-drug interaction. Upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors. Upadacitinib is not recommended to be co-administered with strong CYP3A4 inducers.

3.3.4.1 Food-drug interaction

In a dedicated food effect study (Study M15-878 Part 1), following a single 30 mg dose of upadacitinib ER tablet administered after high-fat and high-calorie meal, upadacitinib Cmax, AUC0-t, and AUC0-inf increased 39%, 30%, and 29%, respectively, as compared to fasted conditions. Refer to Individual Study Review in Appendix 4.1.2 for more details.

Table 9. Summary of upadacitinib PK comparison under fasted and fed conditions

Parameters	**Geometric means**		**Geometric mean ratio (90% CI) (Test/Reference)**
	Fed (Test)	**Fasted (Reference)**	
Cmax (ng/mL)	77.2	55.6	1.39 (1.28, 1.51)
AUC0-t (h*ng/mL)	603	462	1.30 (1.24, 1.37)
AUC0-inf (h*ng/mL)	612	474	1.29 (1.23, 1.36)

(Data source: Table 7 of Study M15-878 CSR)

3.3.4.2 Drug-drug interactions

In-vitro studies indicated that upadacitinib is metabolized by CYP3A4 and to a minor extent by CYP2D6. Upadacitinib increased mRNA expression of CYP3A and CYP2B6 in vitro in a concentration-dependent manner and resulted in a minor increase in CYP1A2 mRNA. Upadacitinib is a weak inhibitor of P-gp, BCRP, and OATP1B1, but no interactions are expected at therapeutic levels with 15 mg QD dosing regimen. Upadacitinib is a substrate for P-gp and BCRP efflux transporters. However, modulation of P-gp or BCRP transporters is expected to have minor effect on upadacitinib exposures in vivo based on PBPK simulation (see PBPK review in Appendix 4.4).

Effects of concomitant medications on pharmacokinetics of upadacitinib

The effect of CYP3A4 inhibitor or inducer on the PK of updacitinib was evaluated in clinical studies using the IR formulation of upadacitinib. PBPK analysis has adequately bridged the clinical DDI effect of strong CYP3A4 modulator (inducer or inhibitor) observed with upadacitinib IR formulation to the ER formulation. Refer to PBPK review in Appendix 4.4 for details.

When upadacitinib was co-administered with ketoconazole (a strong CYP3A4 inhibitor), upadacitinib exposure increased by 75% for AUC0-inf and 70% for Cmax (Study M13-401, Table 10). Upadacitinib should be used with caution if patients receive chronic treatment with strong CYP3A4 inhibitors.

When upadacitinib was co-administered with rifampin (a strong CYP3A4 inducer), upadacitinib exposure decreased by 61% for AUC0-inf and 51% for Cmax, which may result in inefficacious concentrations and consequently decrease the efficacy (Study M13-540, Table 10). Therefore, we recommend that upadacitinib should not be co-administered with strong CYP3A4 inducers.

When upadacitinib was co-administered with methotrexate (potential concomitant medication) or OATP1B inhibitor (rifampin), there was no clinically meaningful difference in upadacitinib PK.

Effects of upadacitinib on pharmacokinetics of concomitant medications

When upadacitinib was co-administered with midazolam (a CYP3A4 substrate), caffeine (a CYP1A2 substrate), dextromethorphan (a CYP2D6 substrate), S-warfarin (a CYP2C9 substrate), omeprazole (a CYP2C19 substrate), bupropion (a CYP2B6 substrate), or potential concomitant medications, including methotrexate, rosuvastatin, atorvastatin, ethinylestradiol, levonorgestrel, there was no clinically meaningful effect of upadacitinib on the PK of these concomitant medications (Table 11).

Refer to Individual Study Review in Appendix 4.1.2 for more details.

Table 10. Effect of concomitant medications on upadacitinib plasma exposure

Co-administered drug	**Regimen of Co-administered drug**	**Mean Ratio (90% CI)**		**Reference**
		C_{max}	**AUC**	
CYP3A4 inhibitor: Ketoconazole	400 mg once daily x 6 days	1.70 (1.55-1.89)	1.75 (1.62-1.88)	Study M13-401
CYP3A4 inducer: Rifampin	600 mg once daily x 9 days	0.49 (0.44-0.55)	0.39 (0.37-0.42)	Study M13-540
Potential comedication: Methotrexate*	Stable dose of 10-25 mg/week	0.97 (0.86, 1.09)	0.99 (0.93, 1.06)	Study M13-845
OATP1B inhibitor: Rifampin	600 mg single dose	1.14 (1.02, 1.28)	1.07 (1.01, 1.14)	Study M13-540

* Upadacitinib IR formulation was administered as BID regimen alone on Day 28 (reference) and co-administered with methotrexate on Day 29 (test). The effect of methotrexate on upadacitinib steady-state AUC12 was evaluated.

Table 11. Effect of upadacitinib on plasma exposures of concomitant medications

Coadministered Drug	Upadacitinib Regimen	Point Estimate (90% Confidence Interval)		Reference
		C_{max}	AUC	
Methotrexate; Observed	6 mg to 24 mg BID Immediate-Release	1.03 (0.86, 1.23)	1.14 (0.91, 1.43)	R&D/18/0624
Sensitive CYP1A2 Substrate Caffeine; Observed	30 mg QD Extended-Release	1.13 (1.05, 1.22)	1.22 (1.15, 1.29)	Study M14-624
Sensitive CYP3A Substrate Midazolam; Predicted based on PBPK	15 mg QD Extended-Release	0.91 (0.91, 0.92)	0.85 (0.84, 0.86)	R&D/17/1073
Sensitive CYP3A Substrate Midazolam; Observed	30 mg QD Extended-Release	0.84 (0.68, 0.80)	0.74 (0.68, 0.80)	Study M14-624
Sensitive CYP2D6 Substrate Dextromethorphan, Observed	30 mg QD Extended-Release	1.09 (0.98, 1.21)	1.07 (0.95, 1.22)	Study M14-624
Sensitive CYP2C9 Substrate S-Warfarin; Observed	30 mg QD Extended-Release	1.07 (1.02, 1.11)	1.11 (1.07, 1.15)	Study M14-624
Sensitive CYP2C19 Marker 5-OH Omeprazole to Omeprazole metabolic ratio; Observed	30 mg QD Extended-Release	--	1.09 (1.00, 1.19)	Study M14-624
CYP2B6 Substrate Bupropion; Observed	30 mg QD Extended-Release	0.87 (0.79, 0.96)	0.92 (0.87, 0.98)	Study M17-221
Rosuvastatin; Observed	30 mg QD Extended-Release	0.77 (0.63, 0.94)	0.67 (0.56, 0.82)	Study M13-541
Atorvastatin; Observed	30 mg QD Extended-Release	0.88 (0.79, 0.97)	0.77 (0.70, 0.85)	Study M13-541
Ethinylestradiol; Observed	30 mg QD Extended-Release	0.96 (0.89, 1.02)	1.11 (1.04, 1.19)	Study M14-625
Levonorgestrel; Observed	30 mg QD Extended-Release	0.96 (0.87, 1.06)	0.96 (0.85, 1.07)	Study M14-625

(Source: Table 28 of Summary of Clinical Pharmacology)

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

Upadacitinib IR capsule formulations have been used in Phase 1 studies and Phase 2 dose-ranging studies, while ER tablet formulations have been used in Phase 1 studies and Phase 3 studies (Table 12). The proposed to-be-marketed formulation is 15 mg strength of ER tablet formulation (ER17).

(b) (4) have been changed between the proposed to-be-marketed 15 mg ER tablet formulation (ER17) and the 15 mg ER tablet formulation used in Phase 3 clinical studies (ER7). The sponsor conducted a two-period, two-sequence, randomized, crossover bioequivalence study (Study M15-878 Part 2) in healthy subjects (n=40) to demonstrate the bioequivalence between the to-be-marketed formulation and Phase 3 study formulation under fasted condition. Following a single 15 mg dose administration of upadacitinib with to-be-marketed 15 mg ER formulation (ER17) and Phase 3 study 15 mg ER tablet formulation (ER7) under fasted condition, the 90% CIs of the geometric mean ratios of

upadacitinib Cmax, AUC0-t, and AUC0-inf are well within 80-125% limit, indicating the to-be-marketed tablet is bioequivalent to the clinical study tablet (Figure 4 and Table 13).

A request to inspect the clinical facility and bioanalytical facility was sent to the Office of Study Integrity and Surveillance (OSIS) and OSIS recommended accepting the study data. For more detailed information, refer to the review memo for clinical facility inspection by Dr. Nicola Fenty-Stewart dated April 03, 2019, and the review memo for bioanalytical facility inspection by Dr. Yiyue Zhang dated February 28, 2019.

Table 12. Summary of clinically relevant formulations evaluated in Phase 1, Phase 2, and Phase 3, and the proposed commercial formulations

Upadacitinib Formulation	Strength (Dosage Form)	Phase 1 Studies	Phase 2 Studies	Phase 3 Studies
Immediate-release Capsules ((b) (4) API)	0.5 mg and/or 3 mg (capsules)	M13-401[a] M14-678[a] M14-680[a] M13-543[d]	M13-537 M13-538 M13-550	
	12 mg (capsules)	M14-680,[a] M13-540,[b] M13-547,[a] M14-174,[a] M14-677,[a] M15-868,[a]	M13-537 M13-538 M13-550	
Extended-release tablets	7.5 mg (ER9)	M14-678[a]		M13-545 M14-663
	15 mg (ER7)	M14-679,[a] M14-680,[a] M15-878,[c] M17-221,[b] M13-539,[d] M13-551,[d] M15-558,[d] M16-094,[a] M16-552[a]	M13-538	M13-542, M13-545, M14-663, M15-555, M15-925, M13-549, M14-465
	30 mg (ER8)	M13-541,[b] M14-624,[b] M14-625,[b] M14-679,[a] M14-680,[a] M15-878,[c] M15-558,[d] M16-094[a]	M13-538	M13-542, M13-545, M14-663, M15-555, M15-925, M13-549
	30 mg (ER18Y)	M15-868[a,e]		
Proposed Commercial Formulation Extended-release tablets	15 mg (ER17) 30 mg (ER18)	M15-878[c]		

a. BA and/or Food effect study.

b. DDI study.

c. BE and/or Food effect study.

d. Special Population: Asian, Hepatic, or Renal Impairment Subjects.

e. "Y" in ER18Y indicates a yellow coating and no debossment.

Note: Study M13-538 is a Phase 2, multicenter, open-label extension study in RA patients who have completed a preceding Phase 2 randomized controlled trial with UPA.

(Source: Table 2 of Summary of Biopharmaceutic Studies and Associated Analytical Methods)

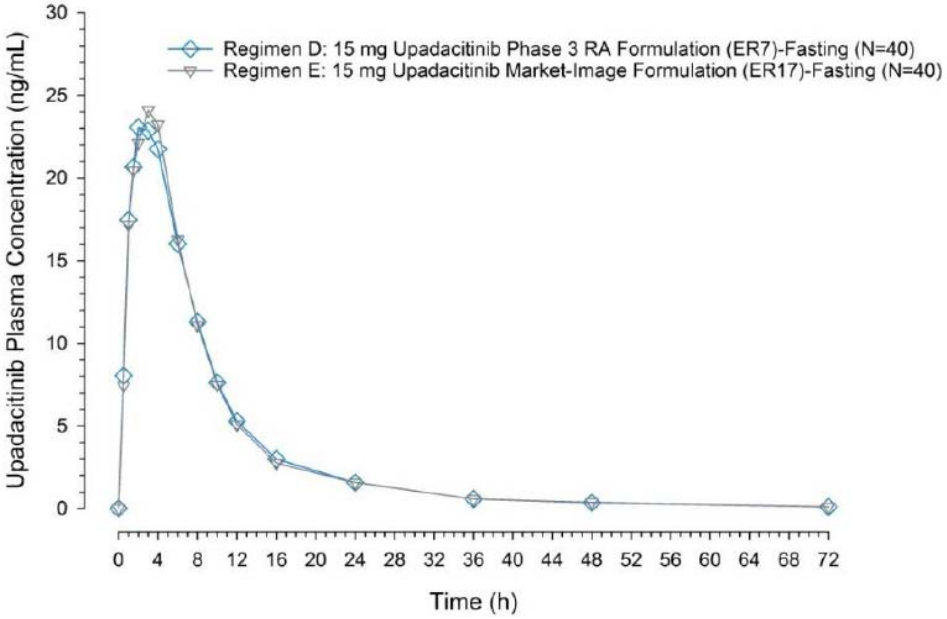


Figure 4. Mean upadacitinib plasma concentrations versus time profiles following administration of single dose of 15 mg strength of the to-be-marketed ER formulation (ER17) and Phase 3 clinical study ER formulation (ER7) under fasted conditions (Study M15-878, Part 2)
(Source: adapted form Figure 2 of Study M15-878 CSR)

Table 13. Summary of upadacitinib PK comparison using the to-be-marketed formulation and Phase 3 clinical study formulation under fasted condition (Study M15-878, Part 2)

Parameters	Geometric means		Geometric mean ratio (90% CI) (Test/Reference)
	To-be-marketed formulation (Test)	Phase 3 study formulation (Reference)	
Cmax (ng/mL)	25.0	24.4	1.02 (0.94, 1.11)
AUC0-t (h*ng/mL)	222	219	1.02 (0.97, 1.06)
AUC0-inf (h*ng/mL)	228	224	1.02 (0.97, 1.07)

(Source: Adapted from Table 9 of Study M15-878 CSR)

4. Appendix

4.1 Appendix – Individual Study Review

Note that upadacitinib is also known as A-1293543 and ABT-494.

4.1.1 *In-vitro* Studies

A total of 8 *in-vitro* studies using human biomaterials were submitted under NDA 211675. The brief conclusions are summarized in the table below.

Table 4.1.1-1. List of *In Vitro* Studies with Human Biomaterials

Study	Study Report #	Study Title
1	RD170325	Determination of the Unbound Fraction of A-1293543 in Plasma and Microsomal Protein and Blood-to-Plasma Concentration Ratios
2	Memo-06	Assessment of A-1293543 Stability in Hepatic Enzyme Systems
3	Memo-09	Assessment of the Enzymes Involved in the Metabolism of [14C]A-1293543 using Recombinant Enzymes
4	RD12256	In Vitro Biotransformation of [14C]A-1293543
5	RD170324	Assessment of Inhibitory Effects on Drug Metabolizing Enzyme Activity by A-1293543
6	RD161011	Assessment of Cytochrome P450 mRNA Induction by A-1293543 in Cultured Human Hepatocytes
7	RD160380	A-1293543: In Vitro Drug Transporter Assessment
8	RD170322	Pharmacokinetic Drug-Drug Interactions: Metabolism and Transporters

Table 4.1.1-2. Results Summary of Upadacitinib *in vitro* Studies Using Human Biomaterials

Study	Study Report	Study Conclusions
Distribution	RD170325	• No concentration dependence in plasma binding was observed with upadacitinib concentrations ranging from 0.1 to 100 µM for any species. • The mean unbound fraction (fu) of upadacitinib (at 1 µM) was 0.28, 0.41, 0.69, 0.47 and 0.48 for mouse, rat, dog, monkey and human plasma respectively. • The mean blood-to-plasma ratios of upadacitinib are 0.99, 1.28, 1.18,1.31 and 1.00 in mouse, rat, dog, monkey and human, respectively.
Metabolism	Memo-06	• The scaled intrinsic clearance of upadacitinib (1µM concentration) was 25.6, 4.07, 0.413, 0.415 and 0.366 L/h/kg in mouse, rat, monkey, dog and human hepatocytes, respectively.
	Memo-09	• Upadacitinib is a substrate for in vitro metabolism by cytochrome P450 3A (CYP3A) with a potential very minor contribution of CYP2D6. • The apparent Km for CYP3A4 and 2D6 were estimated to be 8.32 µM and 165.3 µM, respectively.
	RD12256	• The in vitro metabolism of [14C]A-1293543 was investigated using liver cytosol and hepatocytes from mouse, rat, dog, monkey and human, as well as recombinant human cytochrome P450 enzymes (CYP 2D6, 3A4 and 3A5). • There was no metabolism of [14C]A-1293543 in incubations with liver cytosols across species. • In hepatocytes, a total of five metabolites were characterized across species, four of them were detected in human. • Seven metabolites were observed in incubations of [14C]A-1293543 with recombinant

		human CYP3A4, six in CYP3A5, and three in CYP2D6. M11, a major metabolite, was proposed to be formed via oxidation at the pyrrolopyrazine moiety, followed by ring opening.
Drug-drug interactions	RD170324	• Upadacitinib was not an inhibitor in vitro of drug metabolizing enzymes or transporters at clinically-relevant concentrations. • In the direct inhibition assays, upadacitinib inhibited CYP2C9 with an IC50 value of 40.3 μM and inhibited CYP3A4 with IC50 values of 181 μM and 212 μM when using midazolam and testosterone as substrates, respectively. Upadacitinib exhibited IC50 values >250 μM for all other tested isoforms (CYP1A2, 2B6,2C8, 2C19, 2D6). • Upadacitinib caused no detectable time-dependent inhibition of any isoform tested up to a concentration of 50 μM.
	RD161011	• In vitro, upadacitinib increased mRNA expression of CYP3A and CYP2B6 in a concentration-dependent manner and resulted in a minor increase in CYP1A2 mRNA.
	RD160380	• Upadacitinib is a substrate for P-gp and BCRP. Upadacitinib is not a substrate for OATP1B1, OATP1B3 or OCT1. • A-1293543 is an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OAT3, MATE1 and MATE2K, with IC50 values of 510 μM, 120 μM, 220 μM, 48 μM, 35 μM, 10 μM and 10 μM, respectively. • A-1293543 shows <10% inhibition of OATP1B3, OCT1, OCT2 and OAT1 at 3 and 30 μM, therefore the IC50 values for these transporters were >30 μM.
	RD170322	This integrated report summarized the metabolism and drug transporter interactions for upadacitinib: • At 15 mg and 30 mg QD doses, upadacitinib Cmax,ss is 41.3 ng/mL (0.109 μM) and 83.4 ng/mL (0.219 μM), respectively. • The metabolism of upadacitinib is attributed predominantly to CYP3A4. The exposure of upadacitinib is predicted to be affected by coadministration of strong CYP3A4 inhibitors or inducers. • At 15 mg, upadacitinib is not predicted to be an inhibitor or inducer of the CYP enzymes evaluated. • Upadacitinib is a substrate for the efflux transporters P-gp and BCRP. • Upadacitinib is not predicted to inhibit efflux transporters, P-gp and BCRP, hepatic transporters, OATP1B1, OATP1B3 and OCT1, and renal transporters OCT2, OAT1, OAT3, MATE1 and MATE2K based on the clinical dose and exposures (15 mg and 30 mg).

(Source: summarized from in-vitro study reports)

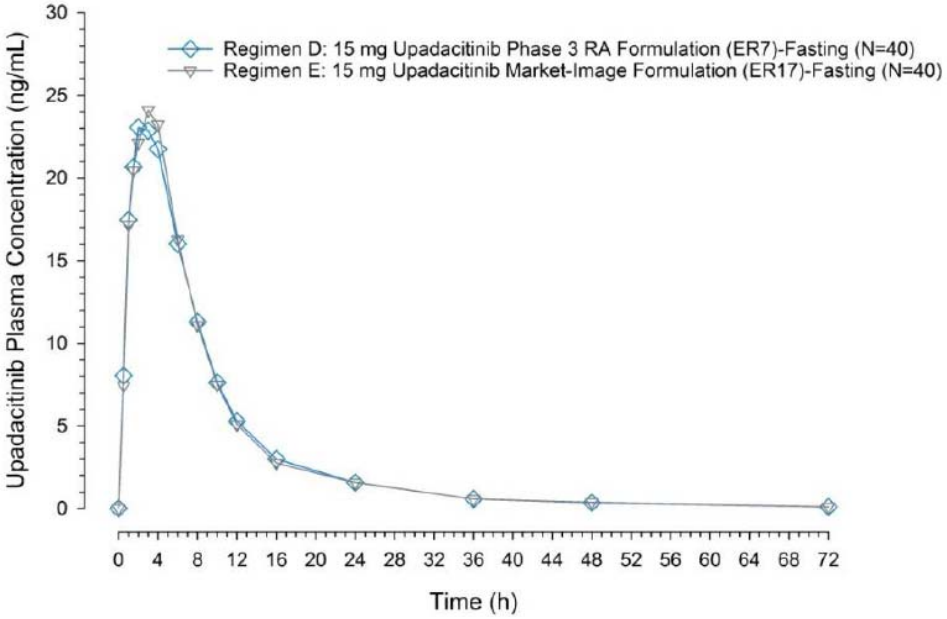


Figure 4. Mean upadacitinib plasma concentrations versus time profiles following administration of single dose of 15 mg strength of the to-be-marketed ER formulation (ER17) and Phase 3 clinical study ER formulation (ER7) under fasted conditions (Study M15-878, Part 2)
(Source: adapted form Figure 2 of Study M15-878 CSR)

Table 13. Summary of upadacitinib PK comparison using the to-be-marketed formulation and Phase 3 clinical study formulation under fasted condition (Study M15-878, Part 2)

Parameters	Geometric means		Geometric mean ratio (90% CI) (Test/Reference)
	To-be-marketed formulation (Test)	Phase 3 study formulation (Reference)	
Cmax (ng/mL)	25.0	24.4	1.02 (0.94, 1.11)
AUC0-t (h*ng/mL)	222	219	1.02 (0.97, 1.06)
AUC0-inf (h*ng/mL)	228	224	1.02 (0.97, 1.07)

(Source: Adapted from Table 9 of Study M15-878 CSR)

4. Appendix

4.1 Appendix – Individual Study Review

Note that upadacitinib is also known as A-1293543 and ABT-494.

4.1.1 *In-vitro* Studies

A total of 8 *in-vitro* studies using human biomaterials were submitted under NDA 211675. The brief conclusions are summarized in the table below.

Table 4.1.1-1. List of *In Vitro* Studies with Human Biomaterials

Study	Study Report #	Study Title
1	RD170325	Determination of the Unbound Fraction of A-1293543 in Plasma and Microsomal Protein and Blood-to-Plasma Concentration Ratios
2	Memo-06	Assessment of A-1293543 Stability in Hepatic Enzyme Systems
3	Memo-09	Assessment of the Enzymes Involved in the Metabolism of [14C]A-1293543 using Recombinant Enzymes
4	RD12256	In Vitro Biotransformation of [14C]A-1293543
5	RD170324	Assessment of Inhibitory Effects on Drug Metabolizing Enzyme Activity by A-1293543
6	RD161011	Assessment of Cytochrome P450 mRNA Induction by A-1293543 in Cultured Human Hepatocytes
7	RD160380	A-1293543: In Vitro Drug Transporter Assessment
8	RD170322	Pharmacokinetic Drug-Drug Interactions: Metabolism and Transporters

Table 4.1.1-2. Results Summary of Upadacitinib *in vitro* Studies Using Human Biomaterials

Study	Study Report	Study Conclusions
Distribution	RD170325	• No concentration dependence in plasma binding was observed with upadacitinib concentrations ranging from 0.1 to 100 µM for any species. • The mean unbound fraction (fu) of upadacitinib (at 1 µM) was 0.28, 0.41, 0.69, 0.47 and 0.48 for mouse, rat, dog, monkey and human plasma respectively. • The mean blood-to-plasma ratios of upadacitinib are 0.99, 1.28, 1.18,1.31 and 1.00 in mouse, rat, dog, monkey and human, respectively.
Metabolism	Memo-06	• The scaled intrinsic clearance of upadacitinib (1µM concentration) was 25.6, 4.07, 0.413, 0.415 and 0.366 L/h/kg in mouse, rat, monkey, dog and human hepatocytes, respectively.
	Memo-09	• Upadacitinib is a substrate for in vitro metabolism by cytochrome P450 3A (CYP3A) with a potential very minor contribution of CYP2D6. • The apparent Km for CYP3A4 and 2D6 were estimated to be 8.32 µM and 165.3 µM, respectively.
	RD12256	• The in vitro metabolism of [14C]A-1293543 was investigated using liver cytosol and hepatocytes from mouse, rat, dog, monkey and human, as well as recombinant human cytochrome P450 enzymes (CYP 2D6, 3A4 and 3A5). • There was no metabolism of [14C]A-1293543 in incubations with liver cytosols across species. • In hepatocytes, a total of five metabolites were characterized across species, four of them were detected in human. • Seven metabolites were observed in incubations of [14C]A-1293543 with recombinant

		human CYP3A4, six in CYP3A5, and three in CYP2D6. M11, a major metabolite, was proposed to be formed via oxidation at the pyrrolopyrazine moiety, followed by ring opening.
Drug-drug interactions	RD170324	• Upadacitinib was not an inhibitor in vitro of drug metabolizing enzymes or transporters at clinically-relevant concentrations. • In the direct inhibition assays, upadacitinib inhibited CYP2C9 with an IC50 value of 40.3 μM and inhibited CYP3A4 with IC50 values of 181 μM and 212 μM when using midazolam and testosterone as substrates, respectively. Upadacitinib exhibited IC50 values >250 μM for all other tested isoforms (CYP1A2, 2B6,2C8, 2C19, 2D6). • Upadacitinib caused no detectable time-dependent inhibition of any isoform tested up to a concentration of 50 μM.
	RD161011	• In vitro, upadacitinib increased mRNA expression of CYP3A and CYP2B6 in a concentration-dependent manner and resulted in a minor increase in CYP1A2 mRNA.
	RD160380	• Upadacitinib is a substrate for P-gp and BCRP. Upadacitinib is not a substrate for OATP1B1, OATP1B3 or OCT1. • A-1293543 is an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OAT3, MATE1 and MATE2K, with IC50 values of 510 μM, 120 μM, 220 μM, 48 μM, 35 μM, 10 μM and 10 μM, respectively. • A-1293543 shows <10% inhibition of OATP1B3, OCT1, OCT2 and OAT1 at 3 and 30 μM, therefore the IC50 values for these transporters were >30 μM.
	RD170322	This integrated report summarized the metabolism and drug transporter interactions for upadacitinib: • At 15 mg and 30 mg QD doses, upadacitinib Cmax,ss is 41.3 ng/mL (0.109 μM) and 83.4 ng/mL (0.219 μM), respectively. • The metabolism of upadacitinib is attributed predominantly to CYP3A4. The exposure of upadacitinib is predicted to be affected by coadministration of strong CYP3A4 inhibitors or inducers. • At 15 mg, upadacitinib is not predicted to be an inhibitor or inducer of the CYP enzymes evaluated. • Upadacitinib is a substrate for the efflux transporters P-gp and BCRP. • Upadacitinib is not predicted to inhibit efflux transporters, P-gp and BCRP, hepatic transporters, OATP1B1, OATP1B3 and OCT1, and renal transporters OCT2, OAT1, OAT3, MATE1 and MATE2K based on the clinical dose and exposures (15 mg and 30 mg).

(Source: summarized from in-vitro study reports)

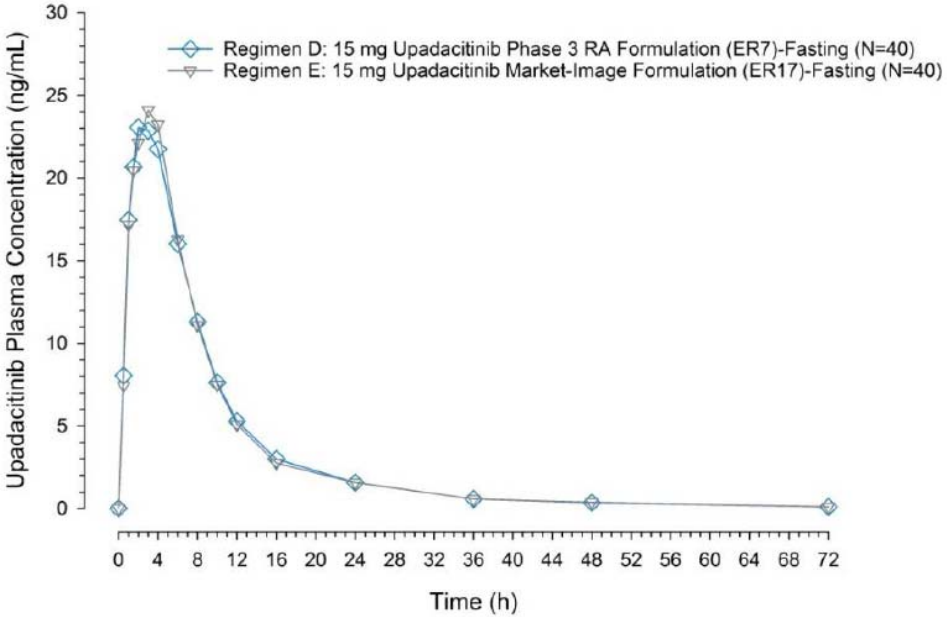


Figure 4. Mean upadacitinib plasma concentrations versus time profiles following administration of single dose of 15 mg strength of the to-be-marketed ER formulation (ER17) and Phase 3 clinical study ER formulation (ER7) under fasted conditions (Study M15-878, Part 2)
(Source: adapted form Figure 2 of Study M15-878 CSR)

Table 13. Summary of upadacitinib PK comparison using the to-be-marketed formulation and Phase 3 clinical study formulation under fasted condition (Study M15-878, Part 2)

Parameters	Geometric means		Geometric mean ratio (90% CI) (Test/Reference)
	To-be-marketed formulation (Test)	Phase 3 study formulation (Reference)	
Cmax (ng/mL)	25.0	24.4	1.02 (0.94, 1.11)
AUC0-t (h*ng/mL)	222	219	1.02 (0.97, 1.06)
AUC0-inf (h*ng/mL)	228	224	1.02 (0.97, 1.07)

(Source: Adapted from Table 9 of Study M15-878 CSR)

4. Appendix

4.1 Appendix – Individual Study Review

Note that upadacitinib is also known as A-1293543 and ABT-494.

4.1.1 *In-vitro* Studies

A total of 8 *in-vitro* studies using human biomaterials were submitted under NDA 211675. The brief conclusions are summarized in the table below.

Table 4.1.1-1. List of *In Vitro* Studies with Human Biomaterials

Study	Study Report #	Study Title
1	RD170325	Determination of the Unbound Fraction of A-1293543 in Plasma and Microsomal Protein and Blood-to-Plasma Concentration Ratios
2	Memo-06	Assessment of A-1293543 Stability in Hepatic Enzyme Systems
3	Memo-09	Assessment of the Enzymes Involved in the Metabolism of [14C]A-1293543 using Recombinant Enzymes
4	RD12256	In Vitro Biotransformation of [14C]A-1293543
5	RD170324	Assessment of Inhibitory Effects on Drug Metabolizing Enzyme Activity by A-1293543
6	RD161011	Assessment of Cytochrome P450 mRNA Induction by A-1293543 in Cultured Human Hepatocytes
7	RD160380	A-1293543: In Vitro Drug Transporter Assessment
8	RD170322	Pharmacokinetic Drug-Drug Interactions: Metabolism and Transporters

Table 4.1.1-2. Results Summary of Upadacitinib *in vitro* Studies Using Human Biomaterials

Study	Study Report	Study Conclusions
Distribution	RD170325	• No concentration dependence in plasma binding was observed with upadacitinib concentrations ranging from 0.1 to 100 µM for any species. • The mean unbound fraction (fu) of upadacitinib (at 1 µM) was 0.28, 0.41, 0.69, 0.47 and 0.48 for mouse, rat, dog, monkey and human plasma respectively. • The mean blood-to-plasma ratios of upadacitinib are 0.99, 1.28, 1.18,1.31 and 1.00 in mouse, rat, dog, monkey and human, respectively.
Metabolism	Memo-06	• The scaled intrinsic clearance of upadacitinib (1µM concentration) was 25.6, 4.07, 0.413, 0.415 and 0.366 L/h/kg in mouse, rat, monkey, dog and human hepatocytes, respectively.
	Memo-09	• Upadacitinib is a substrate for in vitro metabolism by cytochrome P450 3A (CYP3A) with a potential very minor contribution of CYP2D6. • The apparent Km for CYP3A4 and 2D6 were estimated to be 8.32 µM and 165.3 µM, respectively.
	RD12256	• The in vitro metabolism of [14C]A-1293543 was investigated using liver cytosol and hepatocytes from mouse, rat, dog, monkey and human, as well as recombinant human cytochrome P450 enzymes (CYP 2D6, 3A4 and 3A5). • There was no metabolism of [14C]A-1293543 in incubations with liver cytosols across species. • In hepatocytes, a total of five metabolites were characterized across species, four of them were detected in human. • Seven metabolites were observed in incubations of [14C]A-1293543 with recombinant

		human CYP3A4, six in CYP3A5, and three in CYP2D6. M11, a major metabolite, was proposed to be formed via oxidation at the pyrrolopyrazine moiety, followed by ring opening.
Drug-drug interactions	RD170324	• Upadacitinib was not an inhibitor in vitro of drug metabolizing enzymes or transporters at clinically-relevant concentrations. • In the direct inhibition assays, upadacitinib inhibited CYP2C9 with an IC50 value of 40.3 μM and inhibited CYP3A4 with IC50 values of 181 μM and 212 μM when using midazolam and testosterone as substrates, respectively. Upadacitinib exhibited IC50 values >250 μM for all other tested isoforms (CYP1A2, 2B6,2C8, 2C19, 2D6). • Upadacitinib caused no detectable time-dependent inhibition of any isoform tested up to a concentration of 50 μM.
	RD161011	• In vitro, upadacitinib increased mRNA expression of CYP3A and CYP2B6 in a concentration-dependent manner and resulted in a minor increase in CYP1A2 mRNA.
	RD160380	• Upadacitinib is a substrate for P-gp and BCRP. Upadacitinib is not a substrate for OATP1B1, OATP1B3 or OCT1. • A-1293543 is an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OAT3, MATE1 and MATE2K, with IC50 values of 510 μM, 120 μM, 220 μM, 48 μM, 35 μM, 10 μM and 10 μM, respectively. • A-1293543 shows <10% inhibition of OATP1B3, OCT1, OCT2 and OAT1 at 3 and 30 μM, therefore the IC50 values for these transporters were >30 μM.
	RD170322	This integrated report summarized the metabolism and drug transporter interactions for upadacitinib: • At 15 mg and 30 mg QD doses, upadacitinib Cmax,ss is 41.3 ng/mL (0.109 μM) and 83.4 ng/mL (0.219 μM), respectively. • The metabolism of upadacitinib is attributed predominantly to CYP3A4. The exposure of upadacitinib is predicted to be affected by coadministration of strong CYP3A4 inhibitors or inducers. • At 15 mg, upadacitinib is not predicted to be an inhibitor or inducer of the CYP enzymes evaluated. • Upadacitinib is a substrate for the efflux transporters P-gp and BCRP. • Upadacitinib is not predicted to inhibit efflux transporters, P-gp and BCRP, hepatic transporters, OATP1B1, OATP1B3 and OCT1, and renal transporters OCT2, OAT1, OAT3, MATE1 and MATE2K based on the clinical dose and exposures (15 mg and 30 mg).

(Source: summarized from in-vitro study reports)

4.1.2 *In-vivo* Clinical Studies

4.1.2-1 Study M14-680--Phase 1 BA and PK Study

Title: Pharmacokinetics, Safety and Tolerability of Single and Multiple Doses of ABT-494 Once-Daily Tablet and Immediate-Release Capsule Formulations, and Assessment of the Effect of Food on the Pharmacokinetics of the Once-Daily Tablet Formulation in Healthy Volunteers

Objectives

- Part 1: relative BA of 15 mg ER tablet (ER7) to 12 mg IR capsule under fasting condition
- Part 2: relative BA of 30 mg ER tablet (ER8) to 2×12 mg IR capsules under fasting condition; food effect
- Part 3: PK, safety and tolerability of ER tablet
- Part 4: PK, safety and tolerability of IR capsule
- Part 5: relative BA of 15 mg ER tablet (ER7) QD to 6mg IR capsule BID following multiple doses under fasting condition
- Part 6: relative BA of 30 mg ER tablet (ER8) QD to 12 mg IR capsules BID following multiple doses under fasting condition

Study population: healthy subjects (Part 1: n=11; Part 2: n=12; Part 3: n=32; Part 4: n=0 (cancelled); Part 5: n=12; Part 6: n=11)

Drug product:

	Placebo	ABT-494 Formulations			
Dosage Form	Tablet	Capsule	Capsule	Tablet	Tablet
Formulation	NA	IR	IR	ER7	ER8
Strength	NA	3 mg	12 mg	15 mg	30 mg
MMID	D1600025	G1300260	G1300261	20006408	20006409
Bulk Product Lot Number	15-005363	15-000645	14-004208	15-005364	15-005365
Retest Date	30 Sep 2017	28 Feb 2018	31 Jan 2017	30 Jun 2016	30 Jun 2016

NA = Not applicable; MMID = Material Master Identification

Study design:

Part 1 (N = 11) was a single dose, open-label, randomized study conducted according to a two-period, two-sequence, crossover design. Study drug was administered in the morning on Day 1.

Part 1:

Regimen A: Single 12 mg dose of ABT-494 immediate-release capsule administered under fasting conditions (Reference for B).

Regimen B: Single 15 mg dose of ABT-494 once-daily tablet formulation (ER7) administered under fasting conditions (Test for A).

Part 2 (N = 12) was a single dose, open-label, randomized study conducted according to a three-period, two-sequence, crossover design. Period 3 also evaluated the food effect of ABT-494 once-daily tablet formulation. Study drug was administered in the morning on Day 1.

Part 2:

Regimen C: Single 24 mg dose (2 × 12 mg) of ABT-494 immediate-release capsules administered under fasting conditions (Reference for D).

Regimen D: Single 30 mg dose of ABT-494 once-daily tablet formulation (ER8) administered under fasting conditions (Test for C and Reference for E).

Regimen E: Single 30 mg dose of ABT-494 once-daily tablet formulation (ER8) administered after high fat/high calorie breakfast (Test for D).

Part 3 (N = 34) was a multiple dose, randomized, double-blind, placebo-controlled design conducted in 3 parallel groups of subjects. Study drug was administered in the morning on Days 1 through 7.

Regimen F: 15 mg ABT-494 once-daily tablet formulation (ER7) administered QD for 7 days under non-fasting conditions.

Regimen G: 30 mg ABT-494 once-daily tablet formulation (ER8) administered QD for 7 days under non-fasting conditions.

Regimen H: Matching placebo administered QD for 7 days under non-fasting conditions.

Part 4 was cancelled because thorough evaluation of ABT-494 PK for the IR formulation had been achieved.

Parts 5 (N = 12) and 6 (N = 12) were conducted as multiple-dose, randomized, open-label, two-period, two-sequence, crossover designs. In Parts 5 and 6, study drug was administered on Days 1 through 7 in each Period.

Part 5:

Regimen K: 6 mg (2 × 3 mg) ABT-494 immediate-release capsules administered BID for 7 days under fasting conditions.

Regimen L: 15 mg ABT-494 once-daily tablet formulation (ER7) administered QD for 7 days under fasting conditions.

Part 6:

Regimen M: 12 mg ABT-494 immediate-release capsule administered BID for 7 days under fasting conditions.

Regimen N: 30 mg ABT-494 once-daily tablet formulation (ER8) administered QD for 7 days under fasting conditions.

PK sampling:

Part 1 and 2: predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing on Day 1 in each Period.

Part 3: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing on Day 1. Predose on Days 3, 4, 5 and 6. Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing on Day 7.

Part 5 and 6:

Regimens K and M: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 21 and 24 hours after the morning dose on Day 1. Predose on Days 3, 4, 5 and 6. Predose and 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 12.5, 13, 13.5, 14, 15, 16, 18, 21, 24, 36, 48 and 72 hours after the morning dose on Day 7.

Regimens L and N: predose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16 and 24 hours after dosing on Day 1. Predose on Days 3, 4, 5 and 6.

Results

Part 1

Under fasting conditions, single 15 mg dose of ABT-494 once-daily ER tablet formulation (Regimen B) provided equivalent AUC and 63% lower Cmax compared to single 12 mg dose of ABT-494 IR capsule (Regimen A).

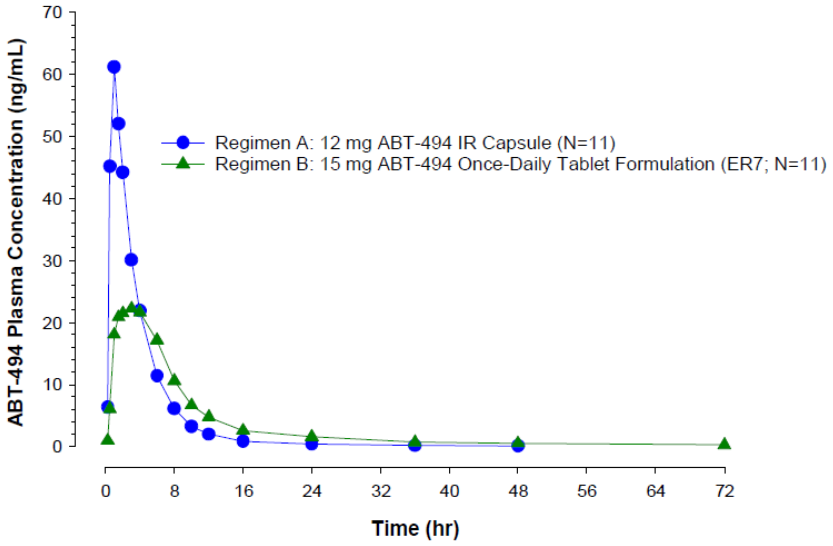


Figure 4.1.2-1. Mean ABT-494 PK Profiles Following Administration of Single Doses of 12 mg ABT-494 IR Capsule and 15 mg ABT-494 Once-Daily Tablet Formulation (ER7) Under Fasting Conditions, Linear Scale

(Source: Figure 1 of Study M14-680 CSR)

Table 4.1.2-1. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Single Doses of 12 mg IR Capsule and 15 mg of the Once-Daily Tablet Formulation (ER7) Under Fasting Conditions

Pharmacokinetic Parameters (units)	Regimen A: Single 12 mg Dose of ABT-494 Immediate-Release Capsule (N = 11)	Regimen B: Single 15 mg Dose of ABT-494 Once-Daily Tablet Formulation (ER7) (N = 11)
C_{max} (ng/mL)	64.6 ± 10.3	26.0 ± 9.65*
T_{max}[a] (h)	1.0 (0.5 – 1.5)	3.0 (1.0 – 4.0)*
AUC_t (ng•h/mL)	231 ± 34.5	227 ± 60.0
AUC_∞ (ng•h/mL)	234 ± 34.6	242 ± 63.6
$t_{1/2}$[b] (h)	9.23 ± 11.0	12.5 ± 11.2

Regimen A = Single 12 mg dose of ABT-494 immediate-release capsule formulation under fasting conditions (Reference for B).

Regimen B = Single 15 mg dose of ABT-494 once-daily tablet formulation (ER7) under fasting conditions (Test for A).

* Statistically significantly different from reference regimen (Regimen A, $p < 0.05$).

a. Median (range).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 10 of Study M14-680 CSR)

Table 4.1.2-2. PK Comparison between a Single 15 mg Dose of ABT-494 Once-Daily Tablet Formulation (ER7) and 12 mg ABT-494 IR Capsule Under Fasting Conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B	C_{max}	23.86	63.93	0.373	0.312 – 0.446
vs.	AUC_t	214.88	228.92	0.939	0.869 – 1.013
Regimen A	AUC_∞	229.81	231.69	0.992	0.909 – 1.082

Regimen A = Single 12 mg dose of ABT-494 immediate-release capsule formulation under fasting conditions (Reference for B).

Regimen B = Single 15 mg dose of ABT-494 once-daily tablet formulation (ER7) under fasting conditions (Test for A).
(Source: Table 11 of Study M14-680 CSR)

Part 2

Under fasting conditions, single 30 mg dose of ABT-494 once-daily tablet formulation (Regimen D) provided equivalent AUC and 63% lower Cmax compared to single 24 mg dose of ABT-494 IR capsule formulation (Regimen C).

Administration of 30 mg ABT-494 once-daily tablet formulation after a high-fat breakfast (Regimen E) increased ABT-494 Cmax and AUC∞ by 20% and 17%, respectively relative to administration under fasting conditions (Regimen D).

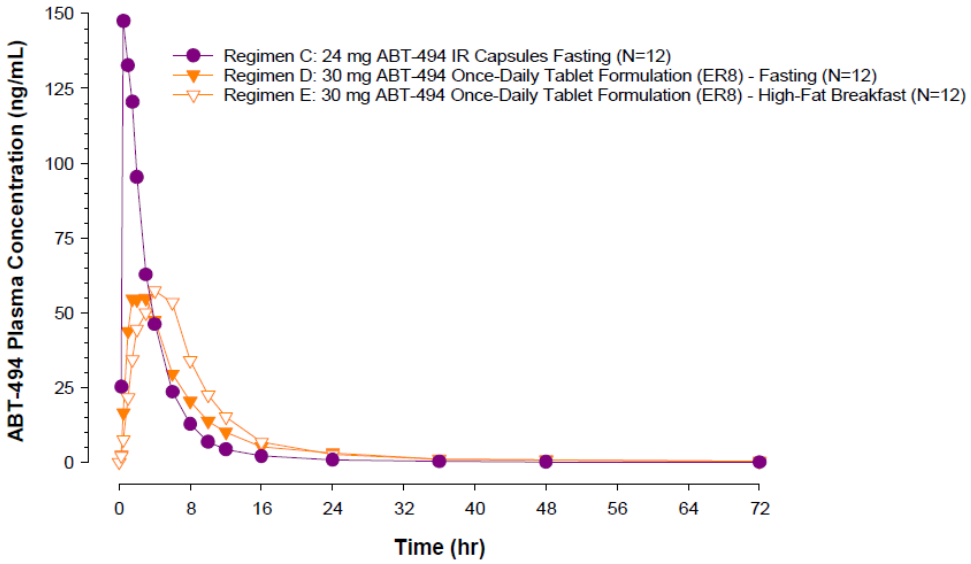


Figure 4.1.2-2. Mean ABT-494 PK Profiles Following Administration of Single Doses of 24 mg ABT-494 IR Capsule Formulation and 30 mg ABT-494 Once-Daily Tablet Formulation (ER8) Under Fasting Conditions and After High-Fat Meal, Linear Scale
(Source: Figure 2 of Study M14-680 CSR)

Table 4.1.2-3. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Single Doses of 24 mg IR Capsule and 30 mg of the Once-Daily Tablet Formulation (ER8) Under Fasting Conditions and After High-Fat Breakfast

Pharmacokinetic Parameters (units)	Regimen C: Single 24 mg Dose of ABT-494 Immediate-Release Capsule Fasting (N = 12)	Regimen D: Single 30 mg Dose of ABT-494 Once-Daily Tablet (ER8) Fasting (N = 12)	Regimen E: Single 30 mg Dose of ABT-494 Once-Daily Tablet (ER8) High Fat Breakfast (N = 12)
C_{max} (ng/mL)	176 ± 65.6	63.7 ± 21.1*	76.8 ± 29.6
T_{max}[a] (h)	0.5 (0.5 – 1.5)	2.0 (1.5 – 4.0)*	4.0 (1.5 – 8.0)**
AUC_t (ng•h/mL)	520 ± 130	477 ± 130	564 ± 145**
AUC_∞ (ng•h/mL)	524 ± 133	491 ± 133	577 ± 157**
$t_{1/2}$[b] (h)	9.86 ± 5.16	10.8 ± 7.25	11.9 ± 6.12

Regimen C = Single 24 mg dose of ABT-494 (2 × 12 mg immediate-release capsules) under fasting conditions (Reference for D).

Regimen D = Single 30 mg dose of ABT-494 once-daily tablet formulation (ER8) under fasting conditions (Test for C and Reference for E).

Regimen E = Single 30 mg dose of ABT-494 once-daily tablet formulation (ER8) following a high-fat/high-calorie breakfast (Test for D).

* Statistically significantly different from reference regimen (Regimen C, $p < 0.05$).

** Statistically significantly different from reference regimen (Regimen D, $p < 0.05$).

a. Median (range).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 12 of Study M14-680 CSR)

Table 4.1.2-4. PK Comparison between a Single 30 mg Dose of ABT-494 Once-Daily Tablet Formulation (ER8) and 24 mg ABT-494 IR Capsule Formulation Under Fasting Conditions and Single 30 mg Dose of ABT-494 Once-Daily Tablet (ER8) After High-Fat High-Calorie Meal Relative to Fasting Conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen D	C_{max}	60.48	164.41	0.368	0.326 – 0.415
vs.	AUC_t	460.49	505.11	0.912	0.828 – 1.004
Regimen C	AUC_∞	474.54	508.78	0.933	0.845 – 1.029
Regimen E	C_{max}	72.40	60.48	1.197	1.027 – 1.395
vs.	AUC_t	545.07	460.49	1.184	1.042 – 1.344
Regimen D	AUC_∞	555.84	474.54	1.171	1.035 – 1.326

(Source: Table 13 of Study M14-680 CSR)

Part 3

Following multiple QD doses of ABT-494 ER tablet formulation, steady state was achieved by Day 4. ABT-494 PK are linear between 15 mg and 30 mg QD doses using the once-daily ER formulation. There was minimal accumulation for ABT-494 with repeated administration of the once-daily formulation.

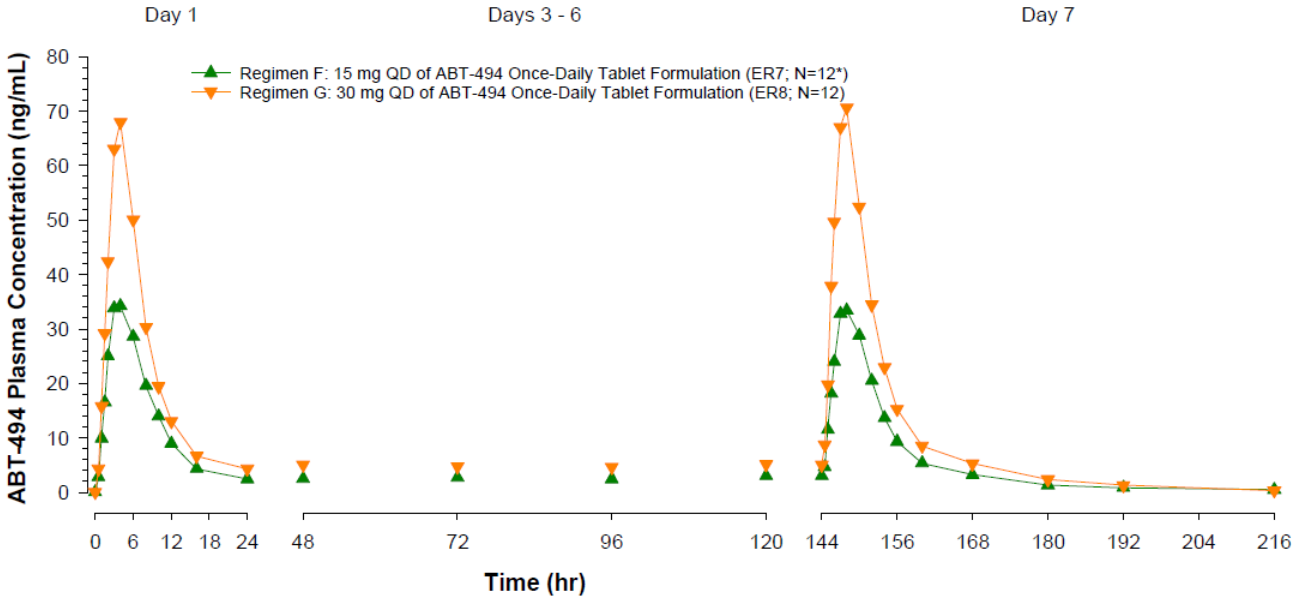


Figure 4.1.2-3. Mean ABT-494 PK Profiles Following Administration of Multiple QD Doses of 15 mg (ER7) and 30 mg (ER8) of ABT-494 Once-Daily Tablet Formulation Under Non-Fasting Conditions, Linear Scale

(Source: Figure 3 of Study M14-680 CSR)

Table 4.1.2-5. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Multiple QD Doses of 15 mg (ER7) and 30 mg (ER8) of ABT-494 Once-Daily Tablet Formulation Under Non-Fasting Conditions

	Regimen F: 15 mg QD of ABT-494 Once-Daily Tablet Formulation (ER7)		Regimen G: 30 mg QD of ABT-494 Once-Daily Tablet Formulation (ER8)	
Pharmacokinetic Parameters (units)	**Day 1 (N = 12)**	**Day 7 (N = 11)**	**Day 1 (N = 12)**	**Day 7 (N = 12)**
C_{max} (ng/mL)	36.8 ± 9.41	36.0 ± 8.79	74.3 ± 24.1	79.5 ± 31.8
T_{max}[a] (h)	4.0 (3.0 – 6.0)	4.0 (2.0 – 6.0)	4.0 (2.0 – 6.0)	4.0 (1.5 – 6.0)
$t_{1/2}$[b] (h)	--	9.43 ± 7.18	--	10.4 ± 4.62
AUC_{0-24} (ng•h/mL)	305 ± 72.0	317 ± 68.1	517 ± 155	582 ± 172
C_{24} (ng/mL)	2.42 ± 1.08	3.22 ± 1.48	4.27 ± 2.05	5.25 ± 2.33
C_{min} (ng/mL)	--	2.80 ± 1.16	--	4.62 ± 1.77
DFL	--	2.51 ± 0.356	--	3.06 ± 0.526
R_{ac} C_{max}[a]	--	1.0 (0.84 – 1.3)	--	1.0 (0.82 – 1.4)
R_{ac} AUC_{0-24}[a]	--	1.0 (0.91 – 1.4)	--	1.2 (0.92 – 1.3)

Regimen F = 15 mg QD of ABT-494 once-daily tablet formulation (ER7) × 7 days under non-fasting conditions.

Regimen G = 30 mg QD of ABT-494 once-daily tablet formulation (ER8) × 7 days under non-fasting conditions.

a. Median (range).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 14 of Study M14-680 CSR)

Part 5

Multiple dosing with 15 mg QD regimen of ABT-494 once-daily formulation provided equivalent AUC and slightly lower Cmax as compared to 6 mg BID of ABT-494 IR capsule formulation under fasting

conditions. The slightly higher C_{24} for 6 mg BID compared to 15 mg QD regimen is likely due to the short fasting period (only 3 hours) prior to the evening dose of the 6 mg BID regimen.

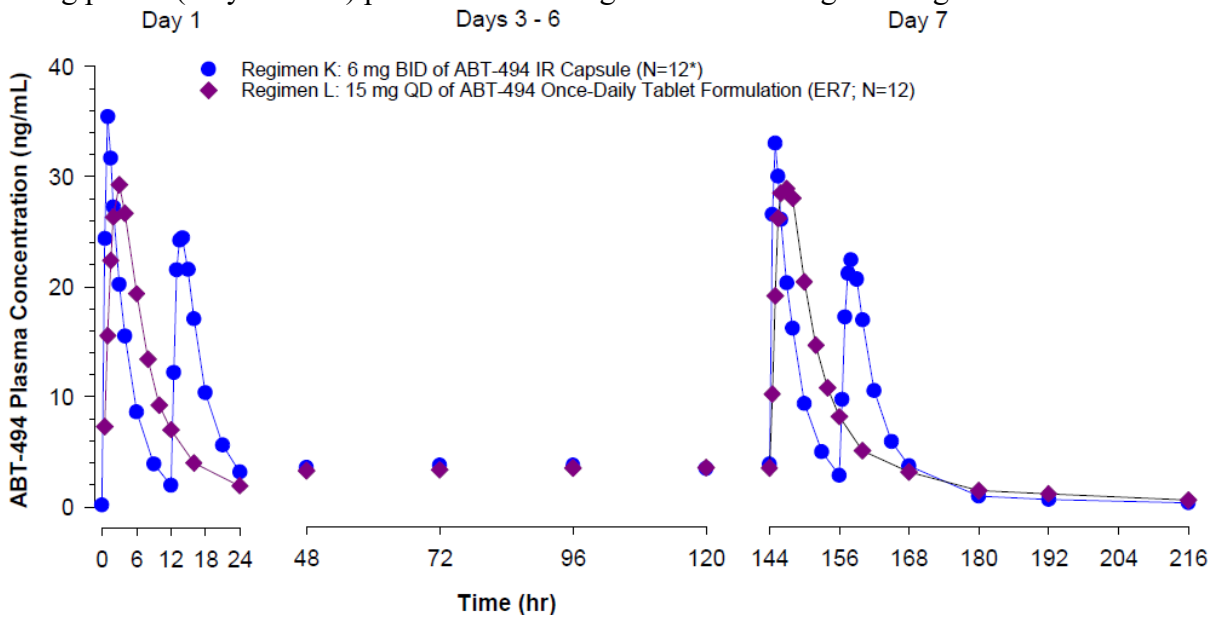


Figure 4.1.2-4. Mean ABT-494 PK Profiles Following Administration of Multiple Doses of 15 mg QD of the Once-Daily Tablet Formulation (ER7) Compared to 6 mg BID of the IR Capsule Formulation Under Fasting Conditions, Linear

(Source: Figure 4 of Study M14-680 CSR)

Table 4.1.2-6. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Multiple Doses of 15 mg QD of the Once-Daily Tablet Formulation (ER7) Compared to 6 mg BID of the IR Capsule Formulation Under Fasting Conditions

	Regimen K: 6 mg BID of ABT-494 Immediate-Release Capsule Formulation		Regimen L: 15 mg QD of ABT-494 Once-Daily Tablet Formulation (ER7)	
Pharmacokinetic Parameters (units)	**Day 1 (N = 12)**	**Day 7 (N = 11)**	**Day 1 (N = 12)**	**Day 7 (N = 12)**
C_{max} (ng/mL)	36.5 ± 9.03	33.9 ± 8.76	31.7 ± 12.6	31.9 ± 11.2
T_{max}[a] (h)	1.0 (1.0 – 13.0)	1.0 (0.5 – 14.0)	3.0 (1.5 – 6.0)	2.5 (1.5 – 4.0)
AUC_{0-24} (ng•h/mL)	289 ± 61.7	288 ± 63.5	249 ± 71.9	279 ± 71.4
C_{24} (ng/mL)	3.17 ± 1.13	3.63 ± 0.841	1.94 ± 0.811	3.09 ± 1.15
C_{min} (ng/mL)	--	2.71 ± 0.627	--	3.05 ± 1.13
DFL		2.59 ± 0.331	--	2.46 ± 0.517
$t_{1/2}$[b] (h)	--	14.7 ± 11.6	--	10.4 ± 7.49
R_{ac} C_{max}[a]	--	0.97 (0.68 – 1.2)	--	1.0 (0.65 – 3.0)
R_{ac} AUC[a]	--	1.0 (0.88 – 1.1)	--	1.1 (0.87 – 2.0)

Regimen K = 6 mg BID of ABT-494 (2 × 3 mg immediate-release capsules) × 7 days under fasting conditions (Reference).

Regimen L = 15 mg QD of ABT-494 once-daily tablet formulation (ER7) × 7 days under fasting conditions (Test).

a. Median (range).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 15 of Study M14-680 CSR)

Table 4.1.2-7. PK Comparison between Multiple Doses of 15 mg QD of the Once-Daily Tablet Formulation (ER7) and 6 mg BID of the IR Capsule Formulation Under Fasting Conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen L	C_{max}	30.34	33.40	0.909	0.736 – 1.122
vs.	AUC_{0-24}	270.63	288.29	0.939	0.837 – 1.053
Regimen K	C_{24}	2.90	3.51	0.826	0.646 – 1.057
	C_{min}	2.86	2.62	1.090	0.852 – 1.395

Regimen K = 6 mg BID of ABT-494 (2 × 3 mg immediate-release capsules) × 7 days under fasting conditions (Reference for L).

Regimen L = 15 mg QD of ABT-494 once-daily tablet formulation (ER7) × 7 days under fasting conditions (Test for K).

(Source: Table 17 of Study M14-680 CSR)

Part 6

Administration of multiple 30 mg QD doses of ABT-494 once-daily tablet formulation provided equivalent AUC0-24 and slightly lower Cmax as compared to 12 mg BID of ABT-494 IR capsule formulation under fasting conditions. The higher C24 on Day 7 for 12 mg BID compared to 30 mg QD regimen is likely due to the short fasting period (only 3 hours) prior to the evening dose of the 12 mg BID regimen.

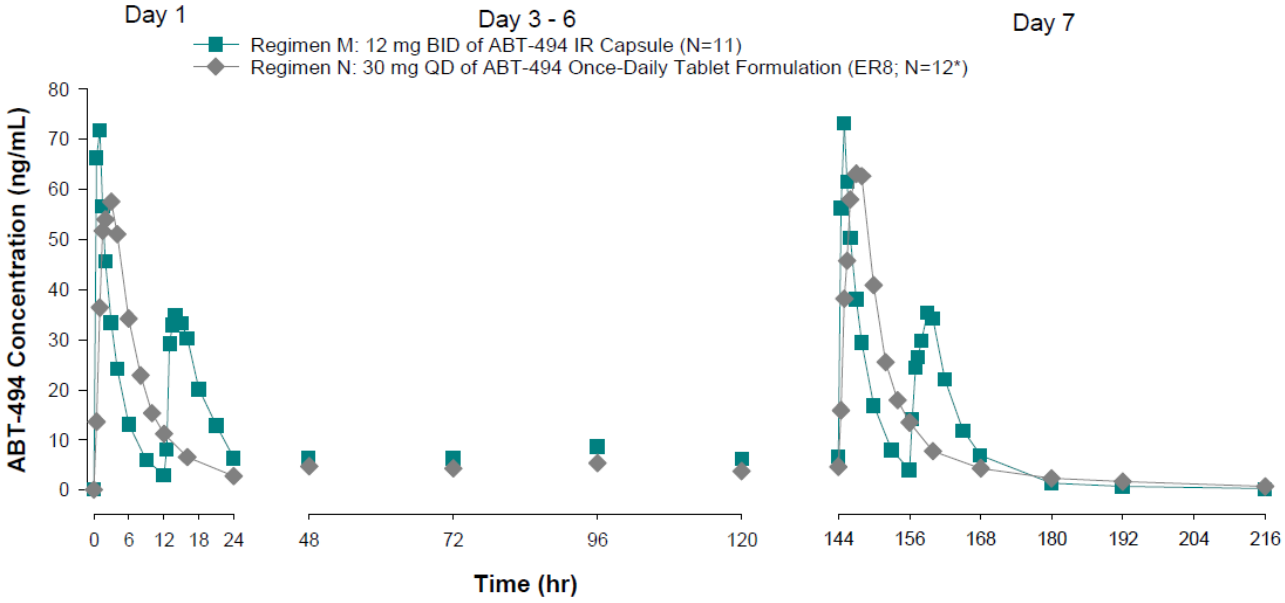


Figure 4.1.2-5. Mean ABT-494 PK Profiles Following Administration of Multiple Doses of 30 mg QD of the Once-Daily Tablet Formulation (ER8) Compared to 12 mg BID of the IR Capsule Formulation Under Fasting Conditions, Linear Scale

(Source: Figure 15 of Study M14-680 CSR)

Table 4.1.2-8. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Multiple Doses of 30 mg QD of the Once-Daily Tablet Formulation (ER8) Compared to 12 mg BID of the IR Capsule Formulation Under Fasting Conditions

Pharmacokinetic Parameters (units)	Regimen M: 12 mg BID of ABT-494 Immediate-Release Capsule Formulation		Regimen N: 30 mg QD of ABT-494 Once-Daily Tablet Formulation (ER8)	
	Day 1 (N = 11)	Day 7 (N = 11)	Day 1 (N = 12)	Day 7 (N = 11)
C_{max} (ng/mL)	80.8 ± 18.9	73.9 ± 14.2	65.7 ± 14.2	68.2 ± 20.5
T_{max}[a] (h)	1.0 (0.5 – 13.0)	1.0 (0.5 – 1.5)	2.5 (1.5 – 4.0)	3.0 (2.0 – 4.0)
$t_{1/2}$[b] (h)	--	7.26 ± 4.38	--	14.4 ± 9.27
AUC_{0-24} (ng•h/mL)	497 ± 74.8	534 ± 97.8	454 ± 102	525 ± 123
C_{24} (ng/mL)	6.48 ± 3.49	6.94 ± 2.57	2.75 ± 1.03	4.35 ± 1.71*
C_{min} (ng/mL)	--	3.84 ± 2.22	--	3.79 ± 1.63
DFL	--	3.17 ± 0.438	--	2.91 ± 0.491
R_{ac} C_{max}[a]	--	0.98 (0.65 – 1.2)	--	1.0 (0.40 – 1.8)
R_{ac} AUC[a]	--	1.1 (0.97 – 1.2)	--	1.1 (0.79 – 1.7)

Regimen M = 12 mg BID of ABT-494 immediate-release capsules × 7 days under fasting conditions (Reference for N).

Regimen N = 30 mg QD of ABT-494 once-daily tablet formulation (ER8) × 7 days under fasting conditions (Test for M).

* Statistically significantly different from reference regimen (Regimen M, $p < 0.05$).

a. Median (range).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 18 of Study M14-680 CSR)

Table 4.1.2-9. PK Comparison between Multiple Doses of 30 mg QD of the Once-Daily Tablet Formulation (ER8) and 12 mg BID of the IR Capsule Formulation Under Fasting Conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen N	C_{max}	64.83	72.04	0.900	0.732 – 1.107
vs.	AUC_{0-24}	511.26	524.76	0.974	0.869 – 1.092
Regimen M	C_{24}	4.03	6.53	0.617	0.499 – 0.764
	C_{min}	3.48	3.99	0.874	0.747 – 1.022

Regimen M = 12 mg BID of ABT-494 immediate-release capsules × 7 days under fasting conditions (Reference for N).

Regimen N = 30 mg QD of ABT-494 once-daily tablet formulation (ER8) × 7 days under fasting conditions (Test for M).

(Source: Table 20 of Study M14-680 CSR)

Conclusions

ABT-494 15 mg ER tablet (ER7) and 30 mg ER tablet (ER8) were used in Phase 3 studies.

- Following single dose administration under fasting condition, ABT-494 15 mg ER tablet (ER7) and 30 mg ER tablet (ER8) provided comparable AUC and 63% lower Cmax compared to 12 mg IR tablet and 2×12 mg IR tablet, respectively.
- High-fat breakfast increased ABT-494 ER8 tablet Cmax and AUC∞ by 20% and 17%, respectively, as compared to fasting condition.
- Following QD dosing with ER tablet (ER7 and ER8), the steady state was achieved by 4 days.
- Following multiple dosing, ABT-494 15 mg ER7 QD regimen provided comparable systemic exposure at steady state as compared to ABT-494 6 mg IR BID regimen.

- Following multiple dosing, ABT-494 30 mg ER8 QD regimen provided comparable systemic exposure at steady state as compared to ABT-494 12 mg IR BID regimen.

4.1.2-2 Study M14-678--Phase 1 BA and PK Study

Title: A Bioavailability Study of a Single Dose of 7.5 mg ABT-494 Once-Daily Tablet Formulation Relative to Two Doses of 3 mg ABT-494 Immediate-Release Capsule Formulation in Healthy Adults

Objectives: relative BA of ER tablets (7.5 mg, ER9)

Study population: healthy subjects (n=12)

Drug product:

	ABT-494 Formulations	
	Immediate Release	**Extended Release-Formulation 9 (ER9)**
Dosage Form	Capsule	Tablet
Strength	3 mg	7.5 mg
MMID	G1300206	20007621
Bulk Product Lot Number	15-000645	15-006685
Retest Date	28-Feb-2018	30-June-2017

MMID = Material Master Identification

Study design: Phase 1, single-dose, open-label, randomized study was conducted according to a two-regimen, two-period, crossover design.

Sequence Group	Number of Subjects	Regimens	
		Period 1	**Period 2**
1	6	A	B
2	6	B	A

Study drug was administered on Day 1 of each period as follows:

Regimen A: Two 3 mg doses of ABT-494 immediate-release capsule formulation administered 12 hours apart under fasting conditions (reference).

Regimen B: Single 7.5 mg dose of ABT-494 once-daily tablet formulation (ER9) administered under fasting conditions (test).

PK sampling:

- Regimen A: Prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 (prior to the evening dose), 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, 21, 24, 36, 48 and 72 hours after the morning dose.
- Regimen B: Prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing.

Results: The PK results are shown as below:

Table 4.1.2-10. PK Parameters (Mean ± SD) of ABT-494 Following Administration of 3 mg ABT-494 IR Capsule Every 12 Hours (Two Doses) and Single 7.5 mg Dose of ABT-494 Once-Daily Tablet (ER9) Under Fasting Conditions

Pharmacokinetic Parameters (Units)	Regimen A: ABT-494 3 mg Immediate-Release Capsule Q12H (Two Doses)[a] (N = 12)	Regimen B: Single 7.5 mg Dose of ABT-494 Once-Daily Tablet (ER9) (N = 12)
C_{max} (ng/mL)	21.2 ± 6.56	14.4 ± 7.47
T_{max}[b] (h)	1.0 (0.5 – 13.0)	3.0 (1.5 – 4.0)
$t_{1/2}$[c] (h)	8.44 (5.78)	12.3 (7.39)
AUC_t (ng•h/mL)	159 ± 41.7[d]	139 ± 45.5
AUC_∞ (ng•h/mL)	162 ± 42.8[d]	145 ± 51.0
CL/F (L/h)	39.3 ± 9.65[d]	56.5 ± 16.5

a. See Table 5 for parameters after morning and evening doses.
b. Median (Minimum – Maximum).
c. Harmonic mean (Pseudo SD).
d. N = 11 after 12 hour for 3 mg Q12H (IR) regimen. Data from one subject were excluded from calculations of AUCt, AUC∞ and CL/F because the subject's plasma concentrations versus time profile suggests that the subject did not take the evening dose.
(Source: Table 6 of Study M14-678 CSR)

Table 4.1.2-11. PK Comparison between A Single 7.5 mg Dose of ABT-494 Once-Daily Tablet (ER9) and 3 mg ABT-494 IR Capsule Every 12 Hours (Two Doses) Under Fasting Conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter (unit)	Central Values		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
B vs. A	C_{max} (ng/mL)	13.4	20.4	0.657	0.569 – 0.758
	AUC_t (ng•h/mL)	133	158	0.842	0.774 – 0.915
	AUC_∞ (ng•h/mL)	138	160	0.860	0.797 – 0.928

(Source: Table 7 of Study M14-678 CSR)

Conclusions

- The relative BA of a single dose of 7.5 mg ER tablet (ER9) to 2 doses of 3 mg IR capsule (every 12 hours) is about 66%-86%.

4.1.2-3 Study M15-878--Phase 1 BA and PK Study

Title: A Phase 1 Study to Evaluate the Bioavailability of Upadacitinib (ABT-494) Market-Image Formulation Relative to the Formulation Utilized in Upadacitinib Phase 3 Rheumatoid Arthritis Trials and to Assess the Effect of High-Fat Meal on Upadacitinib Exposure from the Market-Image Formulation

Objectives

- Part 1: The relative BA of the market-image (to-be-marketed) formulation at 30 mg strength (ER18) to Phase 3 30 mg ER formulation (ER8), food effect
- Part 2: The relative BA of the market-image (to-be-marketed) formulation at 15 mg strength (ER17) to Phase 3 15 mg ER formulation (ER7)

Study population: healthy subjects (n=82)

Drug product:

	Upadacitinib Formulations			
	Regimen A (Reference)	**Regimen B, C (Test)**	**Regimen D (Reference)**	**Regimen E (Test)**
Dosage Form	Tablet	Tablet	Tablet	Tablet
Formulation	ER8 Phase 3 RA Formulation	ER18 Market-image Formulation	ER7 Phase 3 RA Formulation	ER17 Market-image Formulation
Strength (mg)	30	30	15	15
MMID	20012626	20015271	20012388	20015270
Bulk Product Lot Number	17-001119	1000186484	17-002018	1000186479
Batch Size	(b) (4) tablets	(b) (4) tablets	(b) (4) tablets	(b) (4) tablets
Retest Date	31-Mar-2020	30-Sep-2019	31-Mar-2020	30-Sep-2019

MMID = Material Master Identification

Study design:

Part 1 was a three-period, six-sequence, randomized, crossover study (n= 42). Part 2 was a two-period, two-sequence, randomized, crossover study (n= 40).

			Regimens		
Part	**Sequence**	**Number of Subjects**	**Period 1**	**Period 2**	**Period 3**
1	1	7	A	B	C
	2	7	B	C	A
	3	7	C	A	B
	4	7	A	C	B
	5	7	B	A	C
	6	7	C	B	A
2	1	20	D	E	--
	2	20	E	D	--

Regimen A: Single 30 mg dose of upadacitinib Phase 3 RA formulation (ER8) administered under fasting conditions (reference for B).

Regimen B: Single 30 mg dose of upadacitinib market-image formulation (ER18) administered under fasting conditions (test for A, reference for C).

Regimen C: Single 30 mg dose of upadacitinib market-image formulation (ER18) administered after high-fat/high-calorie meal (test for B).

Regimen D: Single 15 mg dose of upadacitinib Phase 3 RA formulation (ER7) administered under fasting conditions (reference for E).

Regimen E: Single 15 mg dose of upadacitinib market-image formulation (ER17) administered under fasting conditions (test for D).

PK sampling: extensive blood samples were collected predose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing in each period.

Results

Part 1: Results indicated that the 30 mg strength of market-image upadacitinib formulation (ER18) was bioequivalent to upadacitinib 30 mg strength of Phase 3 RA formulation (ER8). High-fat/high-calorie increased Cmax by 40% and AUC by 30% in relative to fasting conditions.

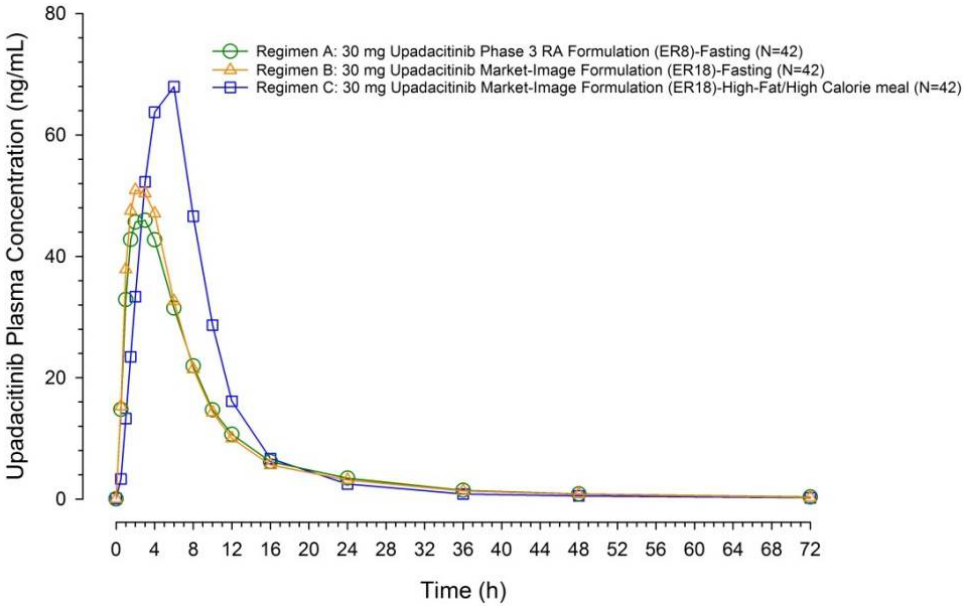


Figure 4.1.2-6. Mean Upadacitinib PK Profiles Following Administration of Single Doses of 30 mg Strength Upadacitinib Formulations Under Fasting Conditions or After a High-Fat/High-Calorie Meal (Linear Scale)

(Source: adapted form Figure 1 of Study M15-878 CSR)

Table 4.1.2-12. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of Single 30 mg Doses of the Upadacitinib Formulations Under Fasting Conditions and After High-Fat/High-Calorie Meal (Part 1)

Pharmacokinetic Parameters (Units)	Regimen A Phase 3 RA Formulation ER8 Fasting (N = 42)	Regimen B Market-Image Formulation ER18 Fasting (N = 42)	Regimen C Market-Image Formulation ER18 High-Fat/High-Calorie Meal (N = 42)
C_{max} (ng/mL)	53.3 ± 13.6	58.2 ± 17.5	78.9 ± 17.5
T_{max}[a] (h)	2.0 (1.0 – 8.0)	2.0 (1.0 – 4.0)	6.0 (1.5 – 10.0)
AUC_t (ng•h/mL)	465 ± 109	474 ± 114	615 ± 128
AUC_{inf} (ng•h/mL)	479 ± 112	486 ± 115	624 ± 128
AUC_{0-12} (ng•h/mL)	336 ± 84.1	356 ± 96.2	496 ± 96.9
AUC_{12-t} (ng•h/mL)	129 ± 55.5	118 ± 40.5	119 ± 50.1
$t_{1/2}$[b] (h)	10.4 (7.04)	10.6 (6.06)	10.8 (6.81)

a. Median (minimum through maximum). b. Harmonic mean (pseudo-standard deviation).

(Source: Table 6 of Study M15-878 CSR)

Table 4.1.2-13. PK Comparison between a Single 30 mg Dose of Upadacitinib Market-Image Formulation (ER18) and the Upadacitinib Phase 3 RA Formulation (ER8) Under Fasting Conditions and Single 30 mg Dose of Upadacitinib Market-Image Formulation After High-Fat/High-Calorie Meal Relative to Fasting (Part 1)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen B vs. A	C_{max}	55.6	51.7	1.075	0.990 – 1.166
	AUC_t	462	453	1.019	0.968 – 1.073
	AUC_∞	474	466	1.017	0.968 – 1.069
	AUC_{0-12}	344	327	1.051	0.988 – 1.118
	AUC_{12-t}	111	116	0.960	0.866 – 1.063
Regimen C vs. B	C_{max}	77.2	55.6	1.389	1.280 – 1.508
	AUC_t	603	462	1.305	1.239 – 1.374
	AUC_∞	612	474	1.293	1.230 – 1.358

(Source: Table 7 of Study M15-878 CSR)

Part 2: Results indicated that the 15 mg strength of market-image upadacitinib formulation (ER17) was bioequivalent to upadacitinib 15 mg strength of Phase 3 RA formulation (ER7).

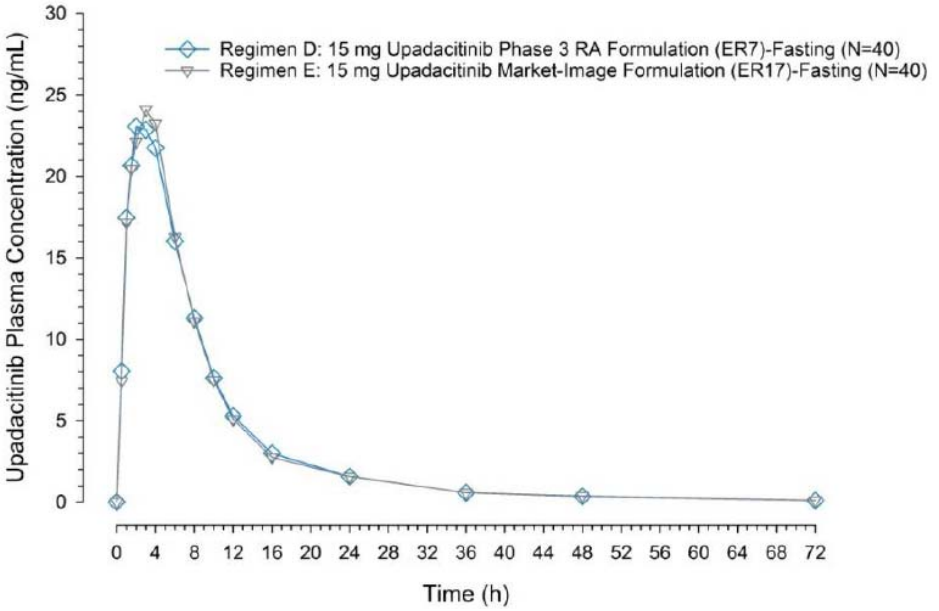


Figure 4.1.2-7. Mean Upadacitinib PK Profiles Following Administration of Single Doses of 15 mg Strength Upadacitinib Formulations Administered Under Fasting Conditions (Part 2) (Linear Scale)

(Source: adapted form Figure 2 of Study M15-878 CSR)

Table 4.1.2-14. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of Single Doses of 15 mg Strength Upadacitinib Formulations Under Fasting Conditions (Part 2)

Pharmacokinetic Parameters (units)	Regimen D: Phase 3 RA Formulation ER7 Fasting (N = 40)	Regimen E: Market-Image Formulation ER17 Fasting (N = 40)
C_{max} (ng/mL)	25.9 ± 8.93	26.3 ± 8.64
T_{max}[a] (h)	2.0 (1.0 – 4.0)	3.0 (1.0 – 4.0)
AUC_t (ng•h/mL)	228 ± 71.6	229 ± 55.4
AUC_{inf} (ng•h/mL)	234 ± 73.5	235 ± 59.7
AUC_{0-12} (ng•h/mL)	171 ± 49.4	173 ± 43.0
AUC_{12-t} (ng•h/mL)	57.1 ± 30.0	55.8 ± 26.3
$t_{1/2}$[b] (h)	8.09 ± 4.72	8.25 ± 4.72

a. Median (minimum through maximum). b. Harmonic mean (pseudo-standard deviation).
(Source: Table 8 of Study M15-878 CSR)

Table 4.1.2-15. PK Comparison between a Single 15 mg Dose of Upadacitinib Market-Image Formulation (ER17) and the Upadacitinib Phase 3 RA Formulation (ER7) Under Fasting Conditions (Part 2)

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen E vs. D	C_{max}	25.0	24.4	1.023	0.939 – 1.113
	AUC_t	222	219	1.017	0.972 – 1.064
	AUC_∞	228	224	1.016	0.969 – 1.066
	AUC_{0-12}	168	165	1.018	0.960 – 1.080
	AUC_{12-t}	49.4	50.0	0.987	0.886 – 1.100

Regimen D: Single 15 mg dose of upadacitinib Phase 3 RA formulation (ER7) administered under fasting conditions (reference for E).

Regimen E: Single 15 mg dose of upadacitinib market-image formulation (ER17) administered under fasting conditions (test for D).

(Source: Table 9 of Study M15-878 CSR)

Conclusions

Uupadacitinib 15 mg ER formulation (ER17) is the proposed to-be-marketed formulation.

- Uupadacitinib 15 mg ER formulation (ER17) is bioequivalent to upadacitinib 15 mg ER formulation (ER7) used in Phase 3 RA studies.
- 30 mg strength of market-image upadacitinib formulation (ER18) was bioequivalent to upadacitinib 30 mg ER formulation (ER8) used in Phase 3 RA studies. High-fat/high-calorie did not result in a clinically relevant effect on upadacitinib exposure with the market-image formulation (40% increase in Cmax and 30% increase in AUC relative to the fasting conditions).

4.1.2-4 Study M16-552--Phase 1 BA and PK Study

Title: A Phase 1 Study in Healthy Adults to Evaluate the Bioavailability of Upadacitinib (ABT-494) Oral Solution Formulation Relative to the Once-Daily Tablet Formulation used in Phase 3 Rheumatoid Arthritis Studies

Objectives: the relative BA and PK of ABT-494 oral solution formulation

Study population: healthy subjects (n=24)

Drug product:

	Upadacitinib Regimens	
	Regimen A (Test)	**Regimen B (Reference)**
Active ingredient	ABT-494 (Upadacitinib)	ABT-494 (Upadacitinib)
Mode of Administration	Oral	Oral
Formulation	Upadacitinib Oral Solution (1 mg/mL)	ER7
Dose Strength	6 mg	15 mg
Dosage Form	Solution	Tablet
Drug Preparation	Extemporaneous Dose Preparation (EDP)	Tablets in bottle
Item ID	20010871	20006408
Bulk Lot	FT00183222	16-005249
Packaged Lot	AB20171214-03	17-006998
Expiration/Retest Date	31-JUL-2020	30-SEP-2019

Study design: This was a Phase 1, open-label, randomized, two-period, two-sequence crossover study in 24 subjects.

Regimen A Two 6 mg doses of the upadacitinib (ABT-494) oral solution (1 mg/mL) formulation administered 12 hours apart under fasting conditions (test for B).

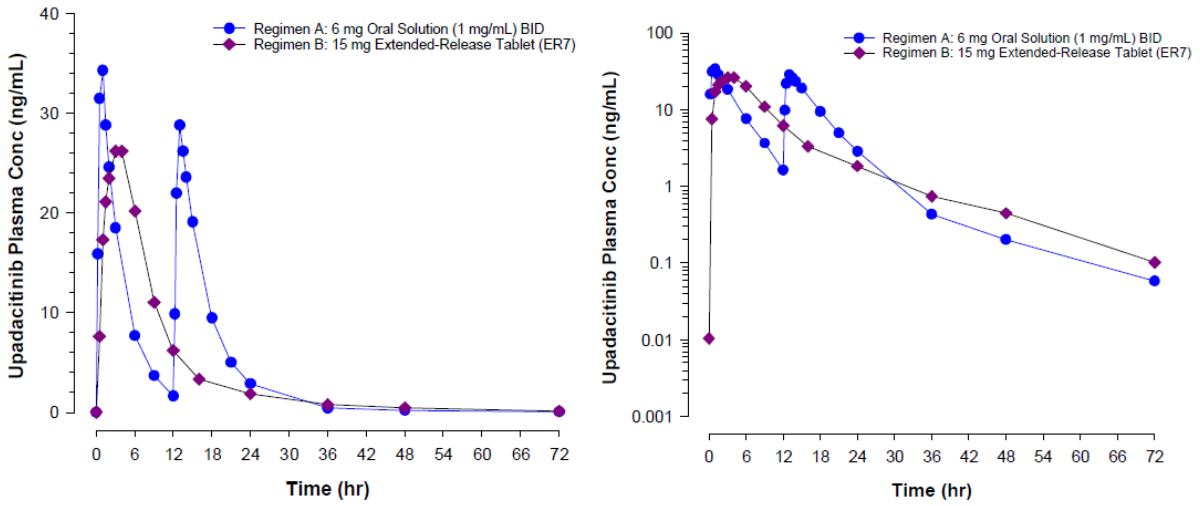
Regimen B Single 15 mg dose of the upadacitinib once-daily tablet formulation (ER7) administered under fasting conditions (reference for A).

PK sampling:

- Regimen A: prior to dosing (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 6, 9, 12 (prior to the evening dose), 12.25, 12.5, 13, 13.5, 14, 15, 18, 21, 24, 36, 48 and 72 hours after the morning dose.
- Regimen B: prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 36, 48 and 72 hours after dosing.

Results

Under fasting conditions, administration of two 6 mg doses of upadacitinib oral solution (1 mg/mL) 12 hours apart resulted in 30% higher Cmax and 17% higher AUC0-inf relative to administration of a single 15 mg upadacitinib ER tablet (ER7 formulation).



Note: N = 23 for Regimen A and Regimen B. Data from one subject was excluded due to premature discontinuation in the middle of Period 1.

Figure 4.1.2-8. Upadacitinib PK Profiles Following Administration of Two 6 mg Doses of Upadacitinib Oral Solution Formulation (Regimen A) 12 Hours Apart and a Single Dose 15 mg Dose of Upadacitinib ER Tablet Formulation (ER7; Regimen B) under Fasting Conditions, Linear and Log-Linear Scale

(Source: Figure 2 of Study M16-552)

Table 4.1.2-16. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of Two 6 mg Doses of Upadacitinib Oral Solution Formulation (Regimen A) 12 Hours Apart and a Single 15 mg Dose of Upadacitinib ER Tablet Formulation (ER7; Regimen B) under Fasting Conditions

Pharmacokinetic Parameters (units)	Regimen A:[c] Oral Solution (Test) Two 6 mg doses (N = 23)	Regimen B: Once-Daily Tablet (Reference) 15 mg dose (N = 23)
C_{max} (ng/mL)	38.1 (8.99)	29.8 (9.75)
T_{max}[a] (h)	1.0 (0.5 – 13.5)	3.0 (1.5 - 6.0)
$t_{1/2}$[b] (h)	6.39 (3.7)	8.67 (5.3)
AUC_t (ng•h/mL)	307 (61.8)	266 (78.8)
AUC_{inf} (ng•h/mL)	309 (61.6)	271 (81.9)

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

c. Parameters estimated from the full profile. See Table 5 for parameters after morning and evening doses.

Note: One subject discontinued prematurely in the middle of Period 1 and was excluded from the summary statistics.

(Source: Table 4 of Study M16-552)

Table 4.1.2-17. PK Comparison between Two 6 mg Doses of Upadacitinib Oral Solution Formulation (1 mg/mL) and a Single 15 mg Dose of Upadacitinib ER Tablet Formulation (ER7) under Fasting Conditions

Regimens Test vs. Reference	Pharmacokinetic Parameter	Point Estimate	90% Confidence Interval
Regimen A vs. Regimen B	C_{max} (ng/mL)[a]	1.301	1.164, 1.453
	AUC_t (ng•h/mL)	1.184	1.102, 1.272
	AUC_{inf} (ng•h/mL)	1.169	1.087, 1.258

(Source: Table 6 of Study M16-552)

Conclusions

- Under fasting conditions, administration of two 6 mg doses of upadacitinib oral solution (1 mg/mL) resulted in 30% higher Cmax and 17% higher AUC0-inf relative to administration of a single 15 mg upadacitinib ER tablet (ER7).

4.1.2-5 Study M16-094--Phase 1 BA and PK Study

Title: A Phase 1 Study to Evaluate the Bioavailability of the 45 mg ABT-494 Dose when Administered as a Single Tablet Relative to when Administered Using the 30 mg Strength (ER8 Formulation) and the 15 mg Strength (ER7 Formulation) Tablets and Assessment of the Effect of Food on the Bioavailability of the 45 mg Single Tablet

Objectives: relative BA and food effect

Study population: healthy subjects (n=24)

Drug product:

	Upadacitinib (Test/Reference)	Upadacitinib (Reference)	
Formulation	ER19Y	ER7	ER8
(b) (4) Content	(b) (4)%	(b) (4)%	(b) (4)%
Formulation Process	(b) (4)	(b) (4)	(b) (4)
Strength (mg)	45	15	30

Study design: Single-dose, open-label, randomized study conducted according to a three-period, six-sequence crossover design in 24 healthy adult subjects.

- Regimen A: Single dose of upadacitinib 45 mg strength tablet (ER19Y) administered under fasting conditions (Test for Regimen B and Reference for Regimen C)
- Regimen B: Single dose of upadacitinib 45 mg administered as 15 mg (ER7) and 30 mg (ER8) strength tablets administered under fasting conditions (Reference for Regimen A)
- Regimen C: Single dose of upadacitinib 45 mg strength tablet (ER19Y) administered after high-fat/high-calorie meal (Test for Regimen A)

PK sampling: blood samples were collected prior to dosing (0-hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 and 72 hours after dosing in each study period.

Results

A single 45 mg upadacitinib dose of the ER19Y tablet formulation provided comparable AUC and Cmax to a 45 mg upadacitinib dose administered as one 15 mg (ER7) and one 30 mg (ER8) tablet under fasting conditions. High-fat/high-calorie meal increased upadacitinib Cmax and AUCinf by 18% and 30% respectively.

Table 4.1.2-18. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of Single 45 mg Doses of Upadacitinib Under Fasting Conditions or After a High-Fat Meal

Pharmacokinetic Parameters	(Units)	Regimen A ER19Y Fasting (N = 24)	Regimen B ER7 & ER8 Fasting (N = 24)	Regimen C ER19Y High-Fat Meal (N = 24)
C_{max}	(ng/mL)	98.1 ± 29.7	88.2 ± 26.8	114 ± 25.5
T_{max}[a]	(h)	2.5 (1.0 – 4.0)	3.0 (1.0 – 4.0)	4.0 (2.0 – 10)
AUC_t	(ng•h/mL)	719 ± 167	735 ± 188	941 ± 189
AUC_{inf}	(ng•h/mL)	735 ± 169	751 ± 195	952 ± 189
$t_{1/2}$[b]	(h)	11.5 (5.88)	10.9 (6.41)	10.8 (5.92)

a. Median (minimum through maximum).
b. Harmonic mean (pseudo-standard deviation).
(Source: Table 6 of Study M16-094 CSR)

Table 4.1.2-19. PK Comparison of Upadacitinib Following Administration of Single 45 mg Dose of Upadacitinib ER19Y Formulation Relative to a Single 45 mg Dose Administered as ER7 and ER8 Under Fasting Conditions and the Effect of High-Fat Meal on the ER19Y Formulation

Regimens Test vs. Reference	Pharmacokinetic Parameter[a]	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
Regimen A	C_{max}	94.1	84.3	1.116	0.998 – 1.247
vs.	AUC_t	702	709	0.990	0.935 – 1.048
Regimen B	AUC_{inf}	717	724	0.992	0.935 – 1.051
Regimen C	C_{max}	111	94.1	1.176	1.053 – 1.314
vs.	AUC_t	921	702	1.313	1.239 – 1.390
Regimen A	AUC_{inf}	933	717	1.301	1.227 – 1.379

a. Cmax and AUC units are ng/mL and ng•h/mL, respectively.
(Source: Table 7 of Study M16-094 CSR)

Conclusions

- A single 45 mg upadacitinib dose of the ER19Y tablet formulation provided comparable AUC and Cmax to a 45 mg upadacitinib dose administered as one 15 mg (ER7) and one 30 mg (ER8) tablet under fasting conditions. High-fat/high-calorie meal increased upadacitinib Cmax and AUCinf by 18% and 30%, respectively.

4.1.2-6 Study M13-401--Phase 1 PK and Safety Study

Title: A Study in Healthy Adults to Evaluate the Safety, Tolerability, and Pharmacokinetics After Single Ascending Doses of ABT-494 and to Evaluate the Effects of Food and Ketoconazole on the Safety and Pharmacokinetics of ABT-494 in Healthy Adults

Objectives: safety, tolerability, and PK, food effect, effect of ketoconazole (CYP3A inhibitor)

Study population: healthy subjects (n=67)

Drug product: ABT-494 oral capsule 0.5 mg and 3 mg (Bulk Product Lot Number 12-002767, 12-002768, 12-002768)

Study design:

- Substudy 1 was a randomized, double-blind, placebo-controlled study designed to assess the safety, tolerability and PK of single ascending doses (1, 3, 6, 12, 24, 36 and 48 mg) of ABT-494 in healthy subjects (8/group, 6 ABT-494 and 2 placebo).
- Substudy 2 was an open-label, randomized study with two parts:
  - Part 1 was a two-period crossover investigation designed to assess the effect of food on the safety and PK of a single oral dose of ABT-494 in healthy adult subjects.
  - Part 2 was a single period investigation designed to assess the potential metabolic interaction between ketoconazole and ABT-494. All subjects received 400 mg ketoconazole under fasting conditions once a day for 6 days (Study Days 1 – 6) and a single dose of ABT-494 on Study Day 4.

				Part 1		Part 2
Group	**Sequence**	**N**	**Subject Numbers**	**Period 1**	**Period 2**	**Period 3**
6	I	6	(b) (6)	ABT-494 Fasting	ABT-494 Nonfasting	ABT-494 with Ketoconazole Fasting
	II	6		ABT-494 Nonfasting	ABT-494 Fasting	ABT-494 with Ketoconazole Fasting

Note: The dose administered in Substudy 2 was based on review of data from the single ascending dose study (Substudy 1).

a. Subject (b) (6) was prematurely discontinued after completion of Period 2.

PK sampling:

Substudy 1 (SAD): predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48 and 72 hours post dose
Substudy 2 Part 1 (food effect): predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48 and 72 hours post dose for Periods 1 and 2
Substudy 2 Part 2 (DDI): 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48 and 72 hours post dose

Results

Substudy 1 SAD

Following single dose of ABT-494 capsules, ABT-494 plasma concentrations reached maximum levels at ~1 hour (T_{max}). The apparent terminal elimination half-life ($t_{1/2}$) was estimated to be ~3 to 15 hours.

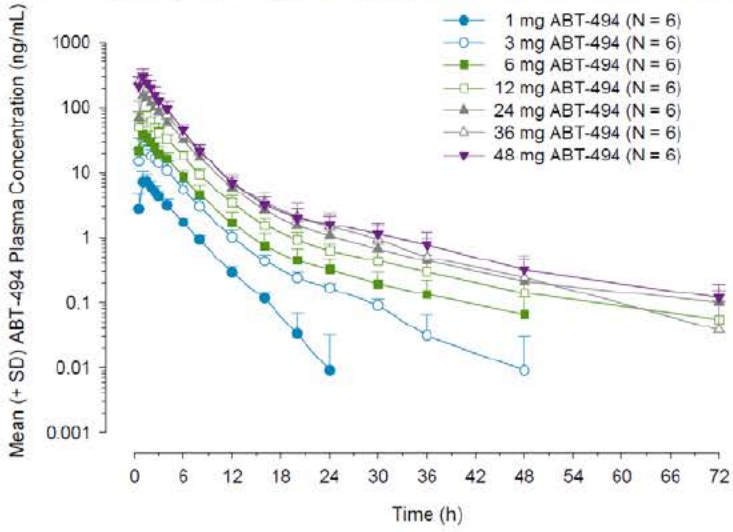


Figure 4.1.2-9. ABT-494 PK Profiles, Log-Linear Scales (Substudy 1)
(Source: Figure 3 of Study M13-401 CSR)

Table 4.1.2-20. PK Parameters of ABT-494 (Substudy 1)

Pharmacokinetic Parameters (Units)	Group 1 1 mg ABT-494 (N = 6)	Group 2 3 mg ABT-494 (N = 6)	Group 3 6 mg ABT-494 (N = 6)	Group 4 12 mg ABT-494 (N = 6)	Group 5 24 mg ABT-494 (N = 6)	Group 7 36 mg ABT-494 (N = 6)	Group 8 48 mg ABT-494 (N = 6)
C_{max} (ng/mL)	7.72 ± 2.36	25.0 ± 6.88	38.9 ± 9.96	82.9 ± 12.1	158 ± 18.4	277 ± 44.5	314 ± 81.9
T_{max} (h)	1.3 ± 0.4	1.1 ± 0.2	1.1 ± 0.2	1.2 ± 0.4	1.3 ± 0.3	0.8 ± 0.3	0.8 ± 0.3
$t_{1/2}$ (h)[a]	2.6 ± 0.4	5.9 ± 2.4	11.0 ± 3.4	12.1 ± 7.4	14.5 ± 9.0	6.4 ± 4.0	12.2 ± 3.52
AUC_t (ng•h/mL)	29.8 ± 5.78	102 ± 27.5	159 ± 37.5	329 ± 48.9	612 ± 78.6	909 ± 201	1032 ± 174
AUC_∞ (ng•h/mL)	30.1 ± 5.72	103 ± 27.6	160 ± 37.6	331 ± 49.8	615 ± 78.1	911 ± 202	1035 ± 174
CL/F (L/h)	34.3 ± 6.89	31.3 ± 10.4	39.1 ± 9.06	37.0 ± 6.32	39.5 ± 4.92	41.1 ± 8.35	47.6 ± 8.97
Vd_β/F (L)	128 ± 18.3	295 ± 129	666 ± 262	821 ± 429	981 ± 400	446 ± 176	872 ± 177
C_{max}/Dose (ng/mL)/mg	7.72 ± 2.36	8.33 ± 2.29	6.48 ± 1.66	6.91 ± 1.01	6.58 ± 0.77	7.69 ± 1.24	6.54 ± 1.71
AUC_t/Dose (ng•h/mL)/mg	29.8 ± 5.78	34.1 ± 9.18	26.5 ± 6.24	27.4 ± 4.07	25.5 ± 3.27	25.3 ± 5.60	21.5 ± 3.62
AUC_∞/Dose (ng•h/mL)/mg	30.1 ± 5.72	34.3 ± 9.20	26.7 ± 6.27	27.6 ± 4.15	25.6 ± 3.25	25.3 ± 5.62	21.6 ± 3.63
CL_r (L/h)	5.80 ± 2.87	4.60 ± 1.07	5.89 ± 0.38	7.35 ± 1.00	7.29 ± 0.55	8.05 ± 2.29	7.60 ± 2.30
f_e (%)	17.7 ± 9.58	15.6 ± 4.44	15.6 ± 3.49	19.9 ± 2.26	18.6 ± 3.08	20.8 ± 9.25	16.4 ± 5.48

a. Harmonic mean ± pseudo-standard deviation.
(Source: Table 13 of Study M13-401 CSR)

Substudy 2: Food effect and Ketoconazole DDI

Administration of ABT-494 oral capsules under nonfasting conditions resulted in ~23% decrease in C_{max} compared to fasting conditions. Following concomitant administration of ABT-494 and ketoconazole the mean ABT-494 C_{max}, AUC_t and AUC_{inf} values were ~70%, 76% and 75% higher, respectively, compared to ABT-494 administered alone.

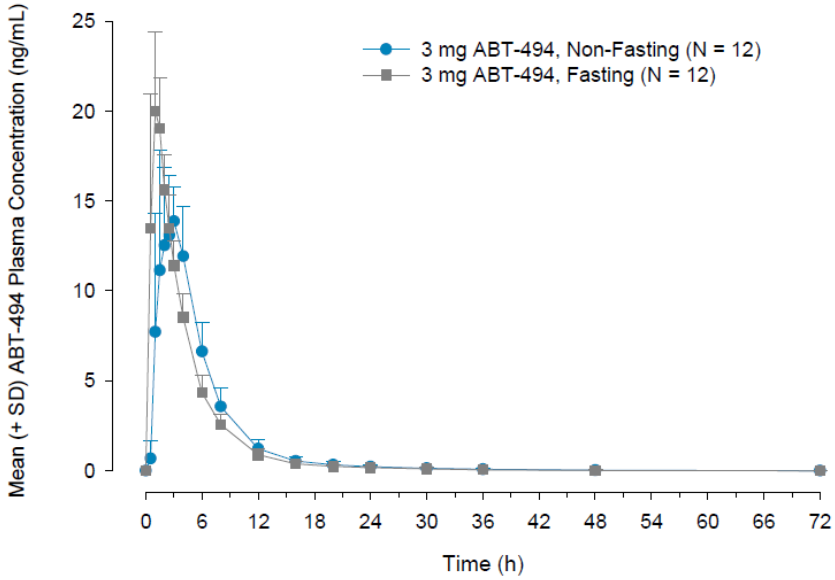


Figure 4.1.2-10. ABT-494 PK Profiles After Administration of ABT-494 under Fasting and Nonfasting Conditions
(Source: Figure 5 of Study M13-401 CSR)

Table 4.1.2-21. PK Parameters of ABT-494 After Administration under Fasting and Nonfasting Conditions

Pharmacokinetic Parameters (Units)	3 mg ABT-494 Nonfasting Alone[a] (N = 12)	3 mg ABT-494 Fasting Alone[a] (N = 12)
C_{max} (ng/mL)	16.4 ± 3.56[c]	21.4 ± 4.18
T_{max} (h)	2.7 ± 1.0[c]	1.1 ± 0.3
$t_{1/2}$ (h)[b]	7.6 ± 4.1	8.5 ± 3.8
AUC_t (ng•h/mL)	85.8 ± 12.0	86.5 ± 12.8
AUC_∞ (ng•h/mL)	86.9 ± 12.5	87.7± 12.6

a. ABT-494 administered as one 3 mg capsule under nonfasting or fasting conditions on Study Day 1 of Period 1 or Period 2.

b. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

c. Statistically significantly different from reference fasting alone regimen (ANOVA, $p < 0.05$).

(Source: Table 15 of Study M13-401 CSR)

Table 4.1.2-22. Effect of Food on ABT-494 PK

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value[a]		Ratio of Central Values (Test/Reference)	
		Test	Reference	Point Estimate[b]	90% Confidence Interval
Nonfasting vs. Fasting	C_{max}	16.08	21.01	0.766	0.662 – 0.885
	AUC_t	85.13	85.70	0.993	0.933 – 1.057
	AUC_∞	86.11	86.91	0.991	0.929 – 1.056

a. Antilogarithm of the least squares means for logarithms.

b. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

Cross reference: Table 14.2__3.1

Note: ABT-494 administered as one 3 mg capsule under nonfasting or fasting conditions on Study Day 1 of Period 1 or Period 2.

(Source: Table 17 of Study M13-401 CSR)

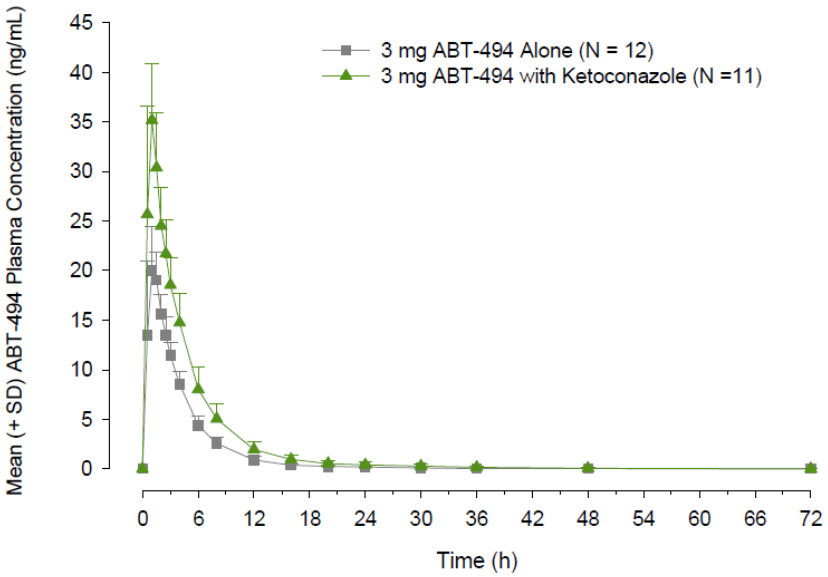


Figure 4.1.2-11. ABT-494 PK Profiles After Administration of ABT-494 With and Without Ketoconazole

(Source: Figure 6 of Study M13-401 CSR)

Table 4.1.2-23. PK Parameters of ABT-494 After Administration With and Without Ketoconazole

Pharmacokinetic Parameters (Units)	3 mg ABT-494 Fasting Alone[a] (N = 12)	3 mg ABT-494 Fasting with Ketoconazole[b] (N = 11)
C_{max} (ng/mL)	21.4 ± 4.18	36.3 ± 6.34[d]
T_{max} (h)	1.1 ± 0.3	0.9 ± 0.2[d]
$t_{1/2}$ (h)[c]	8.5 ± 3.8	7.4 ± 3.0
AUC_t (ng•h/mL)	86.5 ± 12.8	155 ± 31.6[d]
AUC_∞ (ng•h/mL)	87.7 ± 12.6	156 ± 31.8[d]

a. ABT-494 administered as one 3 mg capsule under fasting conditions on Study Day 1 of Period 1 or Period 2.

b. Ketoconazole administered as two 200 mg tablets under fasting conditions once a day for 6 days on Study Days 1 – 6 and a single dose of ABT-494 administered as one 3 mg capsule on Study Day 4 in Period 3.

c. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

d. Statistically significantly different from reference fasting alone regimen (ANOVA, $p < 0.05$).

(Source: Table 18 of Study M13-401 CSR)

Table 4.1.2-24. Effect of Ketoconazole on ABT-494 PK

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value[c]		Ratio of Central Values (Test/Reference)	
		Test[a]	Reference[b]	Point Estimate[d]	90% Confidence Interval
ABT-494 Administered with Ketoconazole vs. ABT-494 Administered Alone	C_{max}	35.63	21.01	1.696	1.546 – 1.886
	AUC_t	150.82	85.70	1.760	1.633 – 1.897
	AUC_∞	151.64	86.91	1.745	1.620 – 1.879

a. Ketoconazole administered as two 200 mg tablets under fasting conditions once a day for 6 days on Study Days 1 – 6 and a single dose of ABT-494 administered as one 3 mg capsule on Study Day 4 in Period 3.

b. ABT-494 administered as one 3 mg capsule under nonfasting or fasting conditions on Study Day 1 of Period 1 or Period 2.

c. Antilogarithm of the least squares means for logarithms.

d. Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

(Source: Table 20 of Study M13-401 CSR)

Conclusions

- Following single dose of ABT-494 IR capsules, ABT-494 Tmax is ~1 hour. The apparent terminal elimination half-life ($t_{1/2}$) was estimated to be ~3 to 15 hours. Upadacitinib Cmax and AUC were approximately dose-proportional.
- Following concomitant administration of ABT-494 IR capsule and ketoconazole, the mean ABT-494 C_{max}, AUC_t and AUC_{inf} values were approximately 70%, 76% and 75% higher, respectively, compared to ABT-494 administered alone.

4.1.2-7 Study M13-845--Phase 1 PK and Safety Study

Title: A Study in Healthy Adult Volunteers and Adult Subjects with Rheumatoid Arthritis to Evaluate the Safety, Tolerability, and Pharmacokinetics After Multiple Dosing of ABT-494

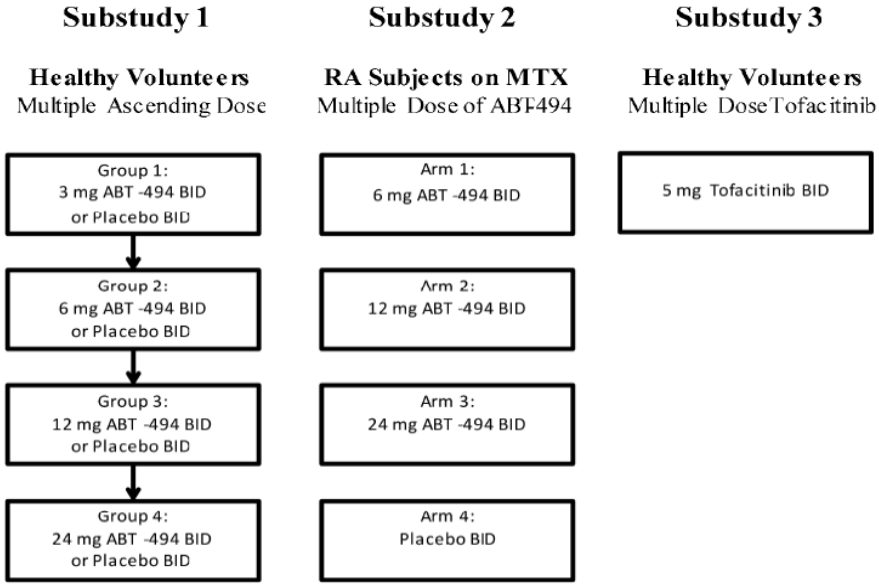
Objectives: safety, tolerability, PK, DDI with MTX

Study population: 53 healthy volunteers in Substudies 1 and 3 and 14 subjects with RA in Substudy 2

Drug product: ABT-494 oral capsule 3 mg (Bulk Product Lot Number 12-002768, 12-008070)

Study design: This Phase 1 study consisted of three substudies:

- Substudy 1 was a randomized, double-blind, placebo-controlled study.
- Substudy 2 was a randomized, double-blind, parallel-group, placebo-controlled study.
- Substudy 3 was a single-arm, open-label study.



Substudy 1 (MAD/HV)	
Group 1:	Daily doses of ABT-494 3 mg (one 3 mg capsule) or matching placebo given twice a day on Study Days 1 – 13 and once on Day 14 under non-fasting conditions.
Group 2:	Daily doses of ABT-494 6 mg (two 3 mg capsules) or matching placebo given twice a day on Study Days 1 – 13 and once on Day 14 under non-fasting conditions.
Group 3:	Daily doses of ABT-494 12 mg (four 3 mg capsules) or matching placebo given twice a day on Study Days 1 – 13 and once on Day 14 under non-fasting conditions.
Group 4:	Daily doses of ABT-494 24 mg (eight 3 mg capsules) or matching placebo given twice a day on Study Days 1 – 13 and once on Day 14 under non-fasting conditions.
Substudy 2 (MD/RA)	
Arm 1:	Daily doses of ABT-494 6 mg (two 3 mg capsules) given twice a day on Study Days 3 – 28 and once on Day 29.
Arm 2:	Daily doses of ABT-494 12 mg (four 3 mg capsules) given twice a day on Study Days 3 – 28 and once on Day 29.
Arm 3:	Daily doses of ABT-494 24 mg (eight 3 mg capsules) given twice a day on Study Days 3 – 28 and once on Day 29.
Arm 4:	Matching placebo of ABT-494 given twice a day on Study Days 3 – 28 and once on Day 29.
Substudy 3 (Tofa/HV)	
Group 1	Daily doses of tofacitinib 5 mg (one 5 mg tablet) given twice a day on Study Days 1 – 13 and once on Day 14 under non-fasting conditions.

In Substudy 2, subjects continued their weekly stable doses of MTX on Study Days 1, 8, 15, 22 and 29.

Blood PK sampling:

Substudy 1 (MAD/HV) for ABT-949 PK:

- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post Day 1 morning dose.
- Prior to the morning dose on Study Days 5, 6, 7, 13.
- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, and 72 hours post Day 14 morning dose.

Substudy 2 (MD/RA):
ABT-949 PK

- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post Day 3 morning dose.
- Prior to study drug and MTX being administered together on Study Days 8, 15 and 22.
- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post Day 28 morning dose.
- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36 and 48 hours post Day 29 morning dose.

MTX PK

- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 hours after the MTX dose on Day 1.
- Prior to study drug and MTX being administered together on Study Days 8, 15 and 22.
- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 24 and 48 hours after the MTX dose on Day 29.

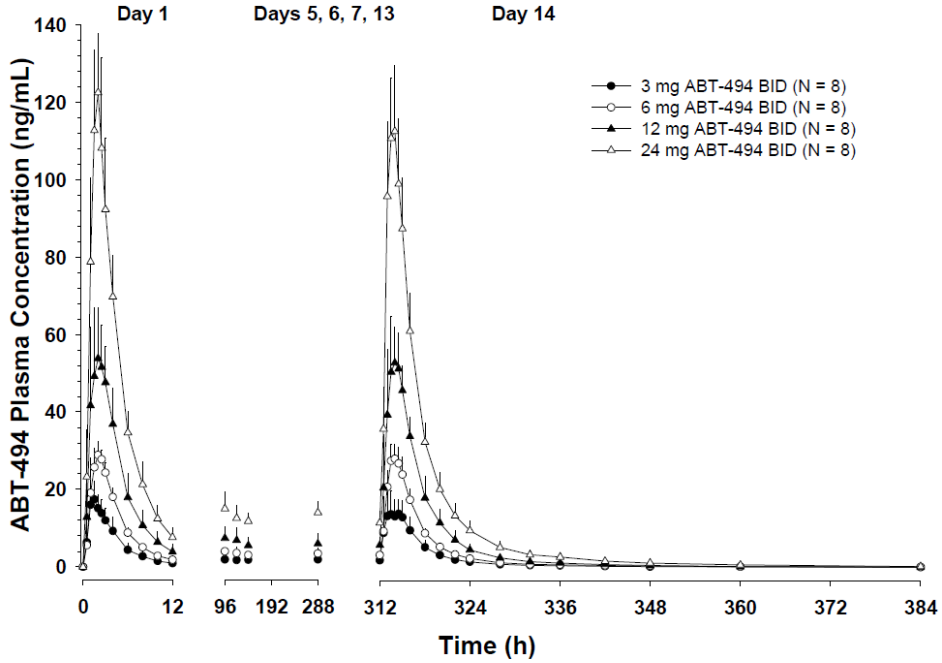
Substudy 3 (Tofa/HV) for tofacitinib PK:

- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post Day 1 morning dose.
- Predose, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, and 72 hours post Day 14 morning dose.

Results

Substudy 1

ABT-494 plasma concentrations reached peak levels at ~2 hours after dosing on Days 1 and 14 under non-fasting conditions. The mean terminal elimination half-life of ABT-494 after multiple BID dosing ranged from 8 to 16 hours.



Note: ABT-494 was administered BID on Study Days 1 – 13, single dose of ABT-494 was administered in the morning on Study Day 14.

Figure 4.1.2-12. ABT-494 PK Profiles Following Administration of Multiple Twice-Daily Oral Doses to Healthy Subjects, Linear Scale (Substudy 1)
(Source: Figure 3 of Study M13-845 CSR)

Table 4.1.2-25. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Multiple Twice-Daily Oral Doses to Healthy Subjects (Substudy 1)

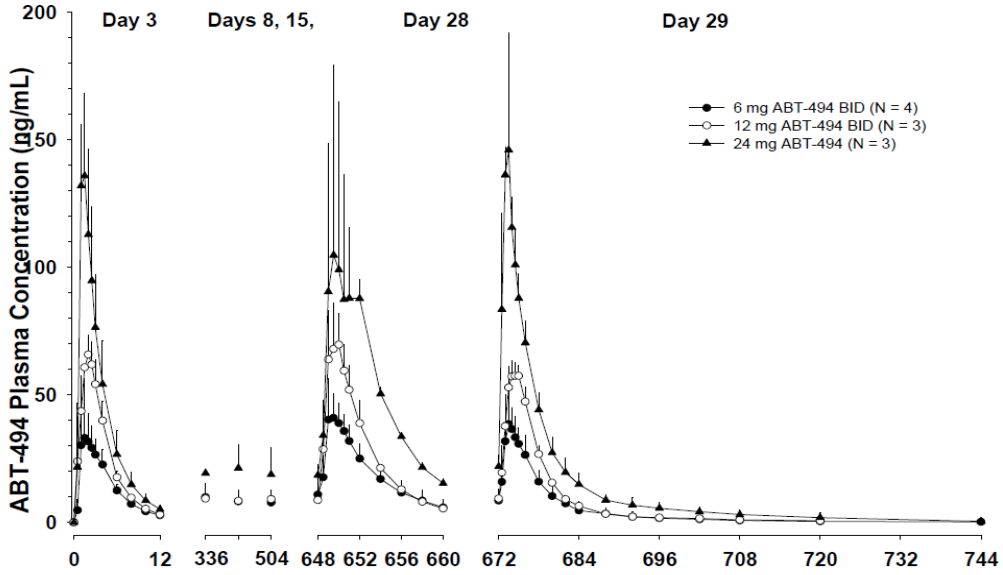
	Substudy 1[a]			
Pharmacokinetic Parameters (Units)	**Group 1 3 mg BID ABT-494 (N = 8)**	**Group 2 6 mg BID ABT-494 (N = 8)**	**Group 3 12 mg BID ABT-494 (N = 8)**	**Group 4 24 mg BID ABT-494 (N = 8)**
	Study Day 1			
C_{max} (ng/mL)	19.0 ± 5.02	29.4 ± 3.16	58.1 ± 10.9	126 ± 18.1
T_{max} (h)	1.6 ± 0.8	2.0 ± 0.3	1.9 ± 0.7	1.9 ± 0.4
AUC_{0-12} (ng•h/mL)	75.3 ± 20.5	134 ± 15.9	270 ± 63.2	540 ± 74.0
C_{max}/Dose (ng/mL)/mg	6.33 ± 1.67	4.91 ± 0.53	4.84 ± 0.91	5.25 ± 0.75
AUC_{0-12}/Dose (ng•h/mL)/mg	25.1 ± 6.83	22.3 ± 2.64	22.5 ± 5.26	22.5 ± 3.08
	Study Day 14			
C_{max} (ng/mL)	18.5 ± 5.41	28.8 ± 3.67	57.6 ± 11.0	119 ± 16.9
T_{max} (h)	1.7 ± 0.9	2.1 ± 0.4	2.2 ± 0.5	1.8 ± 0.3
AUC_{0-12} (ng•h/mL)	78.3 ± 20.3	138 ± 16.7	271 ± 52.7	529 ± 62.6
C_{trough} (ng/mL)	1.46 ± 0.50	2.29 ± 0.41	4.54 ± 1.55	9.50 ± 2.57
$t_{1/2}$ (h)[b,c]	15.7 ± 10.6	13.6 ± 8.5	7.6 ± 4.8	8.0 ± 4.2
$t_{1/2}F$ (h)[b,d]	3.2 ± 0.4	3.3 ± 0.3	3.2 ± 0.5	3.3 ± 0.4
CL/F (L/h)	40.7 ± 10.6	43.9 ± 5.35	45.5 ± 8.04	46.1 ± 6.40
C_{max}/Dose (ng/mL)/mg	6.16 ± 1.80	4.80 ± 0.61	4.80 ± 0.91	4.95 ± 0.71
AUC_{0-12}/Dose (ng•h/mL)/mg	26.1 ± 6.75	23.1 ± 2.78	22.6 ± 4.39	22.0 ± 2.61
C_{trough}/Dose (ng•h/mL)/mg	0.49 ± 0.17	0.38 ± 0.07	0.38 ± 0.13	0.40 ± 0.11
CL_r (L/h)	7.46 ± 2.34	8.05 ± 1.83	9.70 ± 2.28	8.58 ± 2.78
f_e (%)	18.8 ± 4.99	18.7 ± 5.76	21.4 ± 3.80	18.7 ± 5.92
R_{ac} C_{max}[e]	0.9 (0.7 – 1.3)	1.0 (0.8 – 1.1)	1.0 (0.8 – 1.3)	1.0 (0.8 – 1.0)
R_{ac} AUC_{0-12}[f]	1.1 (0.9 – 1.2)	1.0 (0.9 – 1.2)	1.0 (0.9 – 1.1)	1.0 (0.8 – 1.3)

a. ABT-494 administered BID under non-fasting conditions on Study Days 1 – 13, single dose administered on Study Day 14.
b. Harmonic mean ± pseudo-standard deviation.
c. Terminal elimination half-life.
d. Functional half-life calculated as: $\ln(2)/[\ln(C_{max}/C_{trough})/12]$.
e. R_{ac} C_{max} = Accumulation ratio (calculated as the ratio of C_{max} on Study Day 14 to C_{max} on Study Day 1); median and range (minimum to maximum) are presented.
f. R_{ac} AUC_{0-12} = Accumulation ratio (calculated as the ratio of AUC_{0-12} on Study Day 14 to AUC_{0-12} on Study Day 1); median and range (minimum to maximum) are presented.

(Source: Table 15 of Study M13-845 CSR)

Substudy 2: ABT-494 PK

In subjects with RA on stable MTX doses, ABT-494 Tmax was at 1 to 2 hours after dosing on Days 3, 28, and 29. The mean terminal elimination half-life of ABT-494 ranged from 9.5 to 14.4 hours. The median accumulation ratio of ABT-494 on Study Day 28 was 0.8 to 1.4. The median ratio of ABT-494 Cmax and AUC0-12 on Study Day 29 (when administered with MTX) to Study Day 28 (when administered without MTX) ranged from 0.9 to 1.2.



Note: ABT-494 administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

Figure 4.1.2-13. ABT-494 PK Profiles Following Administration of Multiple Twice-Daily Oral Doses of ABT-494 to Subjects with Mild to Moderate RA on Stable Doses of MTX, Linear Scale (Substudy 2)

(Source: Figure 6 of Study M13-845 CSR)

Table 4.1.2-26. ABT-494 PK Parameters (Mean ± SD) Following Administration of Multiple Twice-Daily Oral Doses of ABT-494 to Subjects with Mild to Moderate RA on Stable Doses of MTX (Substudy 2)

	Substudy 2[a]		
Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**
	Study Day 3		
C_{max} (ng/mL)	39.4 ± 17.7	66.3 ± 6.77	150 ± 8.39
T_{max} (h)	2.3 ± 1.3	1.8 ± 0.3	1.3 ± 0.3
AUC_{0-12} (ng•h/mL)	169 ± 43.1	296 ± 43.8	492 ± 111
C_{max}/Dose (ng/mL)/mg	6.56 ± 2.94	5.53 ± 0.56	6.24 ± 0.35
AUC_{0-12}/Dose (ng•h/mL)/mg	28.2 ± 7.18	24.7 ± 3.65	20.5 ± 4.62
CL_r (L/h)	5.82 ± 2.06	3.57 ± 0.40[b]	8.58 ± 1.02
f_e (%)	15.7 ± 4.3	8.38 ± 0.69[b]	17.3 ± 2.16
	Study Day 28		
C_{max} (ng/mL)	47.1 ± 7.47	71.1 ± 14.8	129 ± 39.0
T_{max} (h)	1.5 ± 0.4	1.8 ± 0.3	2.3 ± 1.4
AUC_{0-12} (ng•h/mL)	231 ± 48.5	334 ± 49.4	637 ± 143
C_{trough} (ng/mL)	5.81 ± 3.06	5.41 ± 0.98	15.3 ± 1.86
CL/F (L/h)	26.7 ± 4.96	36.4 ± 5.44	39.1 ± 9.79
C_{max}/Dose (ng/mL)/mg	7.84 ± 1.25	5.93 ± 1.23	5.37 ± 1.62
AUC_{0-12}/Dose (ng•h/mL)/mg	38.5 ± 8.09	27.9 ± 4.12	26.5 ± 5.94
C_{trough}/Dose (ng•h/mL)/mg	0.97 ± 0.51	0.45 ± 0.08	0.64 ± 0.08
CL_r (L/h)	6.94 ± 4.04	6.27 ± 2.79	6.31 ± 0.96
f_e (%)	24.7 ± 13.7	17.4 ± 7.81	16.7 ± 4.56
R_{ac} C_{max}[b]	1.3 (0.9 – 1.9)	1.1 (0.9 – 1.2)	0.8 (0.7 – 1.1)
R_{ac} AUC_{0-12}[c]	1.4 (1.0 – 1.8)	1.2 (0.9 – 1.4)	1.3 (1.2 – 1.4)

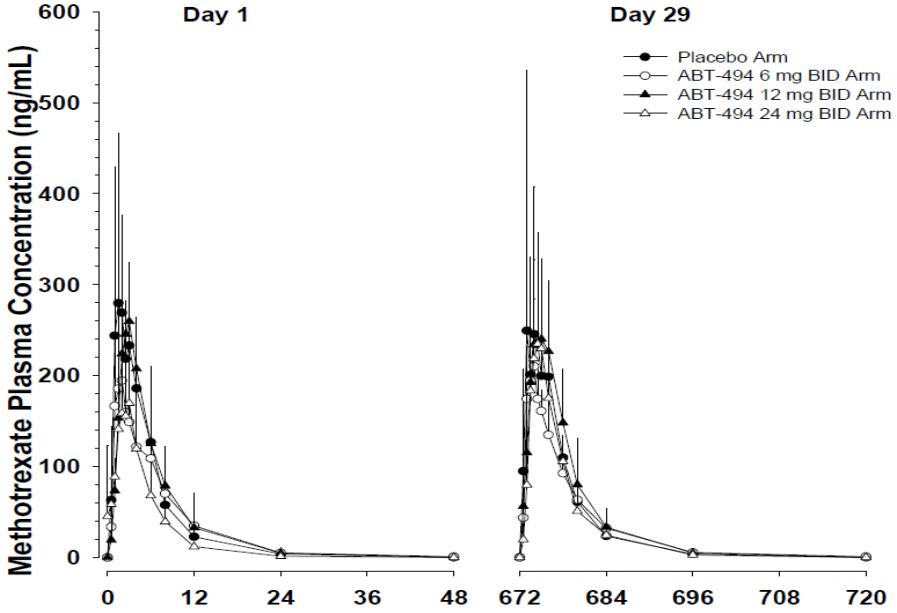
	Study Day 29		
C_{max} (ng/mL)	42.4 ± 8.85	60.8 ± 4.01	154 ± 39.5
T_{max} (h)	2.1 ± 0.8	2.2 ± 0.8	1.0 ± 0.5
AUC_{0-12} (ng•h/mL)	215 ± 49.2	338 ±14.5	665 ± 89.8
C_{trough} (ng/mL)	4.63 ± 3.48	6.44 ± 1.09	14.9 ± 4.37
$t_{1/2}$ (h)[b,c]	9.5 ± 3.6	14.4 ± 5.3	11.5 ± 7.6
$t_{1/2}F$ (h)[b,d]	3.5 ± 0.9	3.7 ± 0.2	3.6 ± 0.1
CL/F (L/h)	29.0 ± 5.92	35.6 ± 1.56	36.5 ± 4.70
C_{max}/Dose (ng/mL)/mg	7.06 ± 1.48	5.07 ± 0.33	6.40 ± 1.64
AUC_{0-12}/Dose (ng•h/mL)/mg	35.8 ± 8.19	28.1 ± 1.21	27.7 ± 3.74
C_{trough}/Dose (ng•h/mL)/mg	0.77 ± 0.58	0.54 ± 0.09	0.62 ± 0.18
CL_r (L/h)	4.93 ± 2.41	4.96 ± 3.34	8.60 ± 1.30
f_e (%)	16.1 ± 5.33	14.2 ± 9.76	23.6 ± 1.80
Day 29/Day 28 C_{max} Ratio[e]	0.9 (0.8 – 1.1)	0.9 (0.7 – 1.0)	1.2 (1.1 – 1.4)
Day 29/Day 28 AUC_{0-12} Ratio[e]	0.9 (0.9 – 1.0)	1.0 (0.9 – 1.1)	1.0 (0.9 – 1.2)

a. ABT-494 administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.
b. Harmonic mean ± pseudo-standard deviation.
c. Terminal elimination half-life.
d. Functional half-life.
e. Median and range (minimum to maximum) are presented.

(Source: Table 17 of Study M13-845 CSR)

Substudy 2: MTX PK

The median AUC_∞ ratio of Day 29 (with ABT-494) to Day 1 (without ABT-494) ranged from 0.9 to 1.1. and the median ratio of Day 29 to Day 1 MTX C_{max} ranged from 0.8 to 1.2.



Note: ABT-494 or placebo administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

Figure 4.1.2-14. Methotrexate PK Profiles Following Administration With (Study Day 29) and Without (Study Day 1) ABT-494 to Subjects With Mild to Moderate RA, Linear Scale (Substudy 2)

(Source: Figure 9 of Study M13-845 CSR)

Table 4.1.2-27. PK Parameters of MTX (Substudy 2)

Substudy 2[a]				
Pharmacokinetic Parameters (Units)	**Arm 1: 6 mg BID ABT-494 (N = 4)**	**Arm 2: 12 mg BID ABT-494 (N = 3)**	**Arm 3: 24 mg BID ABT-494 (N = 3)**	**Arm 4: ABT-494 Placebo (N = 4)**
		Study Day 1		
C_{max} (ng/mL)	245 ± 63.6	278 ± 44.0	196 ± 58.6	318 ± 138
T_{max} (h)	3.1 ± 2.0	2.7 ± 0.6	2.0 ± 1.7	2.0 ± 0.7
AUC_t (ng•h/mL)	1450 ± 510	1640 ± 381	945 ± 350	1620 ± 479
AUC_∞ (ng•h/mL)	1470 ± 494	1670 ± 393	966 ± 365	1640 ± 470
$t_{1/2}$ (h)[b]	4.0 ± 2.6	4.0 ± 0.3	3.0 ± 1.1	3.9 ± 0.5
CL/F (L/h)	11.8 ± 6.43	8.36 ± 1.28	16.9 ± 8.89	11.2 ± 3.81
C_{max}/Dose (ng/mL)/mg	18.0 ± 10.0	20.7 ± 4.61	13.9 ± 4.29	18.8 ± 9.50
AUC_t /Dose (ng•h/mL)/mg	97.2 ± 36.0	120 ± 19.7	67.8 ± 27.4	97.4 ± 39.3
AUC_∞ /Dose (ng•h/mL)/mg	98.9 ± 35.6	122 ± 20.0	69.3 ± 28.1	98.7 ± 38.8
CL_r (L/h)	6.63 ± 3.79	6.13 ± 1.93	7.46 ± 0.70	4.32 ± 1.12
f_e (%)	58.0 ± 28.6	74.3 ± 18.6	53.9 ± 25.1	44.9 ± 25.1
		Study Day 29		
C_{max} (ng/mL)	228 ± 23.0	255 ± 99.9	256 ± 29.3	354 ± 182
T_{max} (h)	1.6 ± 0.5	2.7 ± 0.3	2.5 ± 0.5	2.1 ± 1.4
AUC_t (ng•h/mL)	1480 ± 426	1750 ± 784	1340 ± 315	1570 ± 462
AUC_∞ (ng•h/mL)	1490 ± 424	1780 ± 791	1373 ± 324	1590 ± 458
$t_{1/2}$ (h)[b]	4.7 ± 1.3	4.2 ± 0.6	3.1 ± 1.3	3.8 ± 0.3
CL/F (L/h)	10.9 ± 3.43	8.14 ± 1.03	10.6 ± 1.61	11.3 ± 2.66
C_{max}/Dose (ng/mL)/mg	16.2 ± 7.21	18.0 ± 2.11	18.1 ± 1.75	21.3 ± 13.1
AUC_t/Dose (ng•h/mL)/mg	96.5 ± 25.4	122 ± 14.4	94.1 ± 16.0	92.1 ± 28.9
AUC_∞/Dose (ng•h/mL)/mg	97.5 ± 25.4	124 ± 14.7	96.4 ± 16.1	93.2 ± 28.4
CL_r (L/h)	5.43 ± 2.02	4.78 ± 2.28	6.43 ± 0.75	5.80 ± 1.08
f_e (%)	51.1 ± 20.1	58.8 ± 25.8	62.6 ± 3.99	56.5 ± 26.4
C_{max} Ratio[c]	1.0 (0.8 – 1.1)	0.8 (0.8 – 1.1)	1.2 (1.0 – 2.2)	1.1 (1.0 – 1.2)
AUC_∞ Ratio[d]	1.0 (0.8 – 1.4)	0.9 (0.9 – 1.3)	1.1 (1.0 – 3.1)	0.9 (0.8 – 1.2)

a. ABT-494 or placebo administered BID under non-fasting conditions on Study Days 3 – 28, single dose administered on Study Day 29; weekly stable doses of MTX administered on Study Days 1, 8, 15, 22 and 29.

b. Harmonic mean ± pseudo-standard deviation.

c. C_{max} Ratio = calculated as the ratio of C_{max} on Study Day 29 to C_{max} on Study Day 1; median and range (minimum to maximum) are presented.

d. AUC_∞ Ratio = calculated as the ratio of AUC_∞ on Study Day 29 to AUC_∞ on Study Day 1; median and range (minimum to maximum) are presented.

(Source: Table 19 of Study M13-845 CSR)

Substudy 3: Tofacitinib PK

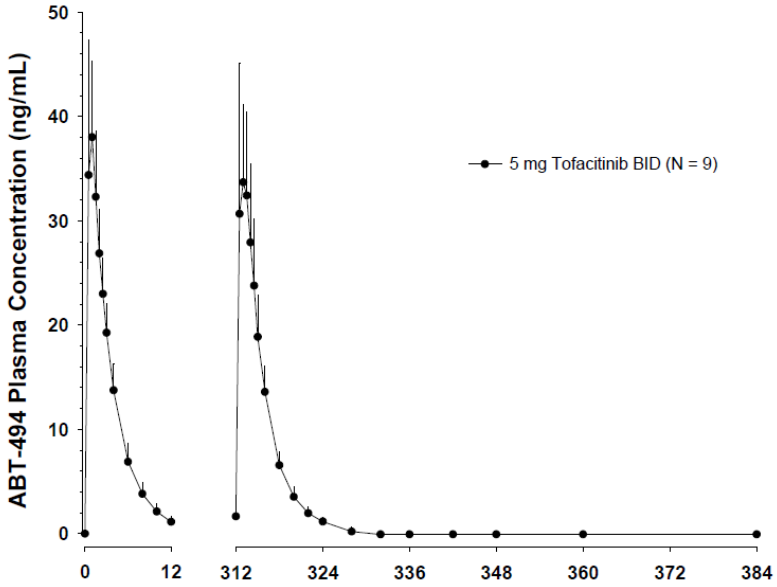


Figure 4.1.2-15. Tofacitinib PK Profiles Following Administration of Multiple Twice-Daily Oral Doses of Tofacitinib to Healthy Subjects, Linear Scale (Substudy 3)

Note: Tofacitinib was administered BID on Study Days 1 – 13, single dose of Tofacitinib was administered in the morning on Study Day 14
(Source: Figure 11 of Study M13-845 CSR)

Table 4.1.2-28. PK Parameters (Mean ± SD) of Tofacitinib Following Administration of Multiple Twice-Daily Oral Doses of Tofacitinib to Healthy Subjects (Substudy 3)

	Substudy 3[a]	
	5 mg BID Tofacitinib (N = 9)	
Pharmacokinetic Parameters (Units)	**Day 1**	**Day 14**
C_{max} (ng/mL)	42.0 ± 10.0	40.9 ± 6.29
T_{max} (h)	0.8 ± 0.3	0.9 ± 0.5
AUC_{0-12} (ng•h/mL)	139 ± 13.4	135 ± 14.2
C_{trough} (ng/mL)	--	1.23 ± 0.44
$t_{1/2}$ (h)[b]	--	2.3 ± 0.4
CL/F (L/h)	--	37.4 ± 4.05
C_{max}/Dose (ng/mL)/mg	8.39 ± 2.00	8.19 ± 1.26
AUC_{0-12}/Dose (ng•h/mL)/mg	27.8 ± 2.68	27.0 ± 2.84
C_{trough}/Dose (ng•h/mL)/mg	--	0.25 ± 0.09

a. Tofacitinib was administered BID on Study Days 1 – 13, single dose of Tofacitinib was administered in the morning on Study Day 14.

b. Harmonic mean ± pseudo-standard deviation.

(Source: Table 21 of Study M13-845 CSR)

Conclusions

- In healthy subjects, following multiple BID dosing of ABT-494 IR capsule, ABT-494 Cmax and AUC were approximately dose-proportional over tested doses.
- In subjects with RA, co-administration of MTX did not have clinically meaning effect of ABT-494 PK. Co-administration of ABT-494 did not have clinically meaning effect of MTX PK.

4.1.2-8 Study M13-548—Phase 1 ADME Study

Title: Absorption, Distribution, Metabolism and Excretion Study of [^{14}C] ABT-494 in Healthy Male Subjects Following Single Oral Dose Administration

Objectives: evaluate the absorption, distribution, metabolism and excretion of ABT-494

Study population: healthy male subjects (N=4)

Drug product: [^{14}C] ABT-494 oral solution, 30 mg active (free base equivalent)

Study design: This was a Phase 1, single-dose, open-label, single-center, ADME, mass balance study in healthy adult male subjects (N = 4). Each subject received a single 30 mg dose of ABT-494 (~100 g of oral solution) containing approximately 100 µCi (actual = 108 µCi) [14C] ABT-494.

PK sampling:

Blood Samples for ABT-494 Assay, Total Radioactivity Determination and Metabolite Profiling and Identification:

Blood samples were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 18, 24, 48, 72, 96, 120, 144, 168, 192, and 216 hours after dosing on Study Day 1. Blood sampling stopped after 168 hours post dose if either greater than 90% of the administered radioactivity had been recovered or less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods.

Urine Samples for Total Radioactivity Determination and Metabolite Profiling and Identification

Urine for total radioactivity determination and metabolite profiling or identification was collected into a collection container without preservatives over the following intervals:0-6, 6-12, 12-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, 168-192, and 192-216 hours after dosing on Study Day 1. Urine collection stopped after 168 hours post-dose if either greater than 90% of the administered radioactivity had been recovered or less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods.

Fecal Samples for Total Radioactivity Determination and Metabolite Profiling and Identification

Fecal samples were collected pre-dose (upon check-in before dosing) and quantitatively for the following intervals after dosing: 0-24, 24-48, 48-72, 72-96, 96-120, 120-144, 144-168, and 168-192 hours after dosing on Study Day 1. Fecal samples collection stopped after 168 hours post-dose if either greater than 90% of the administered radioactivity had been recovered or less than 1% of the radioactive dose had been recovered in two consecutive 24-hour urine and fecal collection periods.

Results

Following administration of a single oral dose of 30 mg (100 µCi) [14C] ABT-494, 96% of the radioactivity was recovered in urine and feces within 216 hours of dosing. Of the total administered radioactive dose, approximately 53% was recovered in feces and 43% was recovered in urine.

In plasma, unchanged ABT-494 accounted for 79% of the total radioactivity while metabolites M4 (product of monooxidation followed by glucuronidation) and M11 (product of monooxidation followed by ring-opening) accounted for 13% and 7.1% of the total plasma radioactivity, respectively.

Approximately 61% of the administered radioactive dose was excreted in urine and feces as parent ABT-494 and 34% was excreted as metabolites. Approximately 24% of the administered radioactive dose was

recovered as unchanged parent drug in urine and 9.6% and 3.6% of the dose were recovered as M4 and M10 (product of monooxidation), respectively. In feces, approximately 38% of the total radioactive dose was recovered as parent drug and 6.3% was recovered as M11 metabolite.

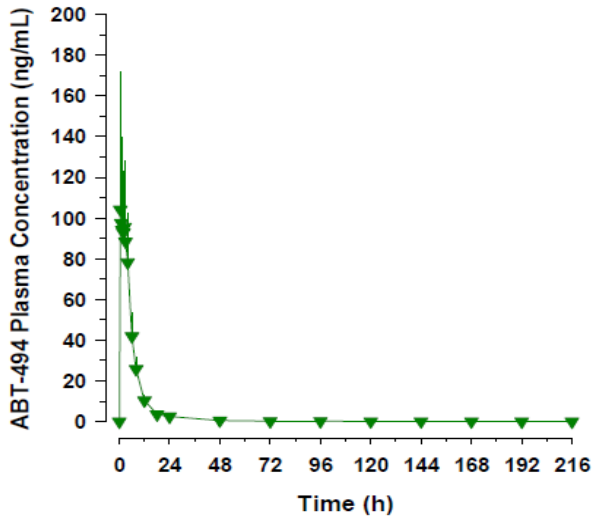


Figure 4.1.2-16. ABT-494 PK Profiles After Administration of a Single Oral Dose of 30 mg ABT-494 (n=4)

(Source: Figure 2 of Study M13-548 CSR)

Table 4.1.2-29. PK Parameters (Mean ± SD) of ABT-494 After Administration of a Single Oral Dose of 30 mg ABT-494

Pharmacokinetic Parameters (units)		ABT-494 (N = 4)
C_{max}	ng/mL	122 ± 44.1
T_{max}	h	1.0 ± 1.0
AUC_t	ng•h/mL	712 ± 141
AUC_∞	ng•h/mL	717 ± 143
$t_{1/2}$[a]	h	11.7 ± 7.0
CL/F	L/h	43.0 ± 7.90
C_{max}/D	(ng/mL)/mg	4.08 ± 1.47
AUC_∞/D	(ng•h/mL)/mg	23.9 ± 4.78

a. Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

(Source: Figure 2 of Study M13-548 CSR)

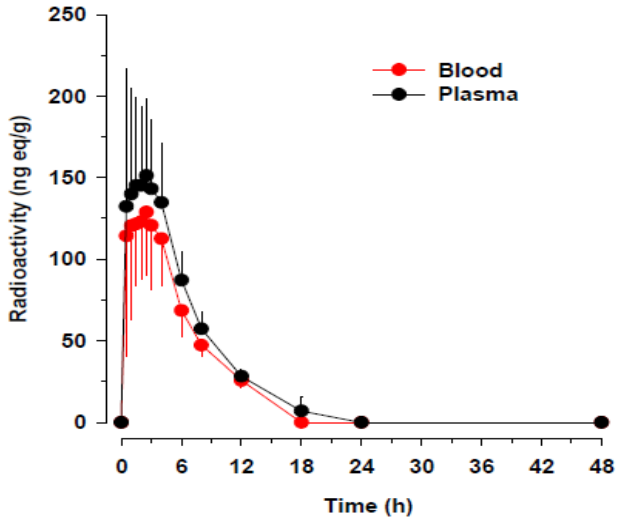


Figure 4.1.2-17. Total Radioactivity (Mean + SD) Versus Time Profiles After Administration of a 30 mg (100 µCi) Single Dose of [14C] ABT-494
(Source: Figure 3 of Study M13-548 CSR)

Table 4.1.2-30. PK Parameters (Mean ± SD) of Total Radioactivity in Blood and Plasma After Administration of 30 mg (100 µCi) [14C] ABT-494

		Total Radioactivity N = 4	
Pharmacokinetic Parameters (units)		**Blood**	**Plasma**
C_{max}	(ng eq/g)	144 ± 40.4	165 ± 48.8
T_{max}	(h)	1.9 ± 1.7	1.6 ± 1.7
AUC_t	(ng eq•h/g)	894 ± 186	1130 ± 205
AUC_∞	(ng eq•h/g)	1050 ± 163	1250 ± 219

(Source: Table 7 of Study M13-548 CSR)

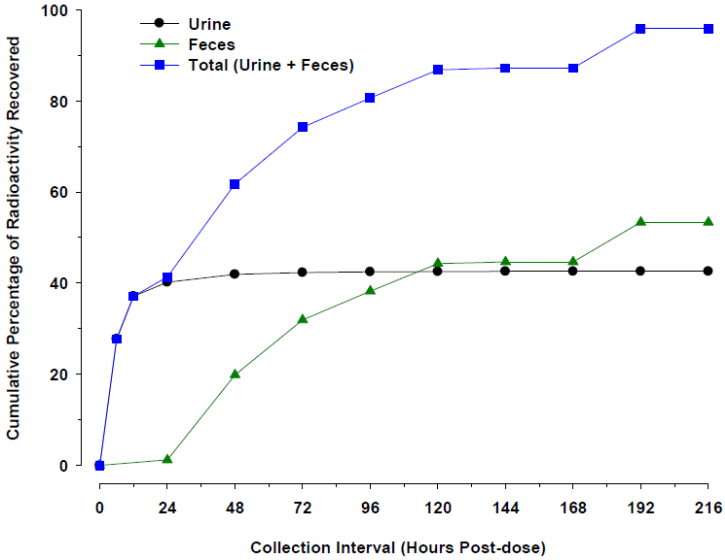


Figure 4.1.2-18. Mean Cumulative Percent of Total Radioactivity Recovered in Urine and Feces After Administration of 30 mg (100 µCi) [14C] ABT-494
(Source: Figure 4 of Study M13-548 CSR)

Table 4.1.2-31. Mean ± SD Cumulative Percent Recovery of Radioactive Dose for [14C] ABT-494 in Feces and Urine up to 216 Hours After Administration

	ABT-494
Feces	53.4 ± 10.8
Urine	42.6 ± 13.6
Total	95.9 ± 2.75

(Source: Table 8 of Study M13-548 CSR)

Table 4.1.2-32. Identification of Major (> 10%) ABT-494 Related Compounds in Circulation

Compound[a]	Identification
A-1293543 (ABT-494)[b]	Parent, $C_{17}H_{20}F_3N_6O^+$
M4[c]	$C_{23}H_{28}F_3N_6O_8^+$

M4 = Metabolite 4

a. Only compounds that represent > 10% of the total drug related radioactive materials in circulation are listed.

b. Observed in plasma, urine, and feces.

c. Observed in plasma and urine.

(Source: Table 9 of Study M13-548 CSR)

Table 4.1.2-33. Total Percent Recovery of Radioactive Dose for [14C] ABT-494 and Metabolites in Pooled Feces and Urine

Compound		Parent	M1	M2	M3	M4	M6/M8[a]	M8	M10	M11	M22	M23	UNK	Total Radioactivity[b]
Feces[c]	0 – 192 h	37.8	0.0	0.6	ND	ND	ND	0.0	ND	6.3	0.0	0.0	8.3	53.0
Urine[d]	0 – 48 h	23.6	ND	0.1	0.1	9.6	2.6	ND	3.6	0.1	0.0	ND	2.2	41.9
Total[e]	**0 – 192 h**	**61.4**	**0.0**	**0.7**	**0.1**	**9.6**	**2.6**	**0.0**	**3.6**	**6.4**	**0.0**	**0.0**	**10.5**	**94.9**

ND = Not detected; M1 = Metabolite 1; M2 = Metabolite 2; M3 = Metabolite 3; M4 = Metabolite 4; M6 = Metabolite 6; M8 = Metabolite 8; M10 = Metabolite 10; M11 = Metabolite 11; M22 = Metabolite 22; M23 = Metabolite 23; UNK = Unknown metabolites

a. M6 and M8 co-eluted in urine in one chromatographic fraction.

b. Total radioactivity is the sum of radioactivity from parent ABT-494 and all metabolites in pooled feces and urine.

c. Sum of radioactivity dose recovery from 0 – 192 hours for pooled feces.

d. Sum of radioactivity dose recovery from 0 – 48 hours for pooled urine.

e. Total calculated as sum of urine and feces.

(Source: Table 11 of Study M13-548 CSR)

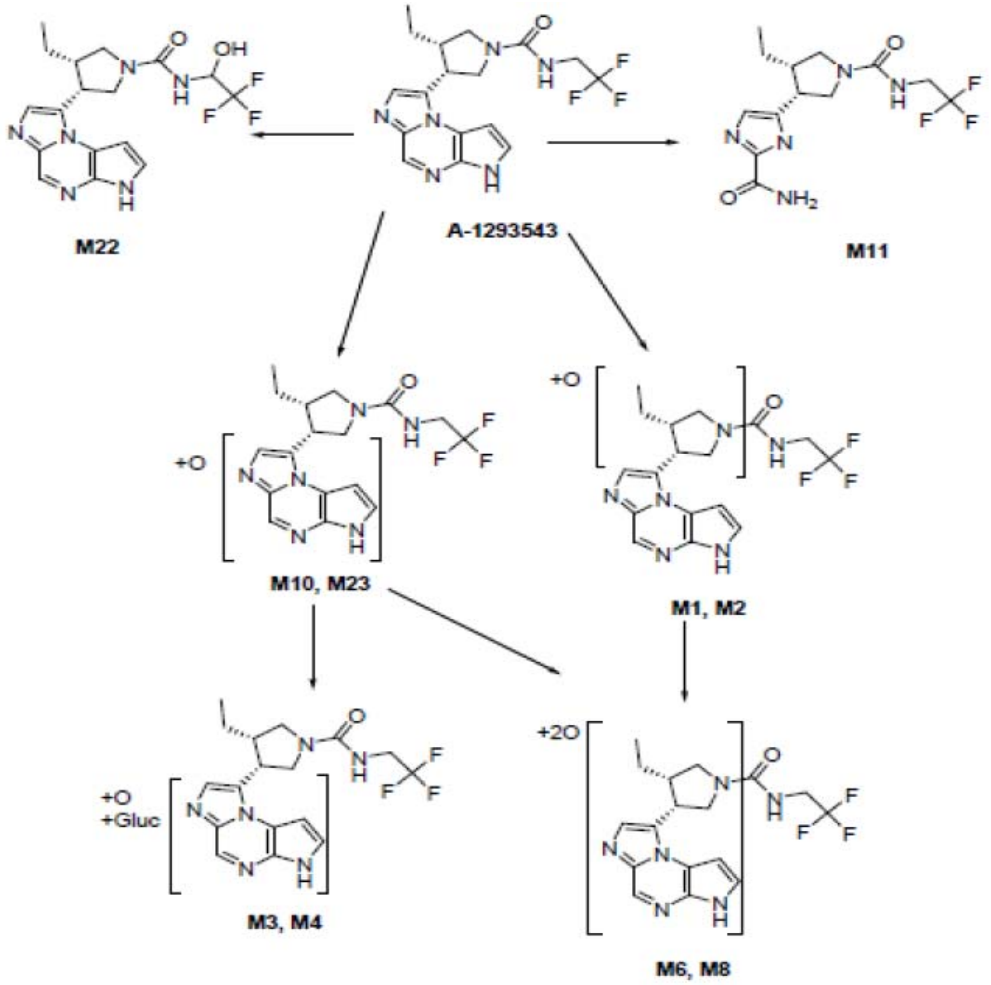


Figure 4.1.2-19. Proposed Metabolic Pathway for ABT-494 and Proposed Structures of ABT-494 Metabolites
(Source: Figure 5 of Study M13-548 CSR)

Conclusions

- Following administration of a single oral dose of 30 mg (100 µCi) [14C] ABT-494, 96% of the radioactivity was recovered in urine and feces within 216 hours of dosing. Of which approximately 53% was recovered in feces and 43% was recovered in urine.
- In plasma, unchanged ABT-494 accounted for 79% of the total radioactivity while metabolites M4 (product of monooxidation followed by glucuronidation) and M11 (product of monooxidation followed by ring-opening) accounted for 13% and 7.1% of the total plasma radioactivity, respectively.
- In urine, approximately 24% of the administered radioactive dose was recovered as unchanged parent drug and 9.6% and 3.6% of the dose were recovered as M4 and M10 (product of monooxidation), respectively.
- In feces, approximately 38% of the total radioactive dose was recovered as parent drug and 6.3% was recovered as M11 metabolite.

4.1.2-9 Study M13-543--Phase 1 Intrinsic Factor PK Study

Title: A Double-Blinded, Randomized, Placebo-Controlled Phase 1 Study in Healthy Japanese and Chinese Adults to Evaluate the Safety, Tolerability and Pharmacokinetics of Single and Multiple Doses of ABT-494

Objectives: safety, tolerability, and PK of ABT-494 under non-fasting conditions after single ascending and multiple doses of ABT-494 in healthy adult Japanese and Chinese subjects

Study population: healthy adult Japanese and Chinese subjects (n=24 (part 1), 20 (part 2))

Drug product:

	ABT-494	
Dosage Form	Capsule	Capsule
Strength (mg)	12	3
Mode of Administration	Oral	Oral
Finishing Lot	14-001276	14-001274

Study design: This was a Phase 1, double-blinded, single-center study of single ascending and multiple oral doses of ABT-494. This study consisted of two parts.

In Part 1, single ABT-494 doses were assessed in ascending order in three sequential groups. Each dose was taken orally under non-fasting conditions (~30 minutes after a meal).

Group[a]	Treatment and Number of Subjects[b]	
1	Japanese: ABT-494 3 mg, n = 6	Placebo, n = 2
2	Japanese: ABT-494 6 mg, n = 6	Placebo, n = 2
3	Japanese: ABT-494 24 mg, n = 6	Placebo, n = 2

a. Subjects participated in one group only.

b. ABT-494 was administered as 3 mg capsules or 12 mg capsules.

In Part 2, multiple administrations of ABT-494 at 18 mg dose for 14 days in two groups (Groups 4 and 5) were assessed. Each dose of study drug was taken under non-fasting conditions (~30 minutes after a meal).

Group[a]	Treatment and Number of Subjects[b]	
4	Japanese: ABT-494 18 mg BID × 14 days, n = 8	Placebo, n = 3
5	Chinese: ABT-494 18 mg BID × 14 days, n = 8	Placebo, n = 3

a. Subjects participated in one group either in Part 1 or Part 2.

b. ABT-494 was administered as 3 mg and 12 mg capsules.

PK sampling:

Part 1:

- Pre-dose (0 hour) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 20, 24, 30, 36, 48, and 72 hours after dosing on Study Day 1.

Part 2:

- Day 1: pre-dose (0-hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, and 12 hours post Day 1 morning dose. pre-dose for the evening dose.
- Days 5, 6, 7, and 13: pre-dose for morning dose.
- Day 14: pre-dose (0-hour) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, 24, 30, 36, 48, and 72 hours post Day 14 morning dose.

Results

Part 1

ABT-494 Tmax was approximately 2 hours. The mean terminal phase elimination half-life ($t_{1/2}$) ranged from 6 to 9 hours. Cmax and AUC increase dose-proportionally.

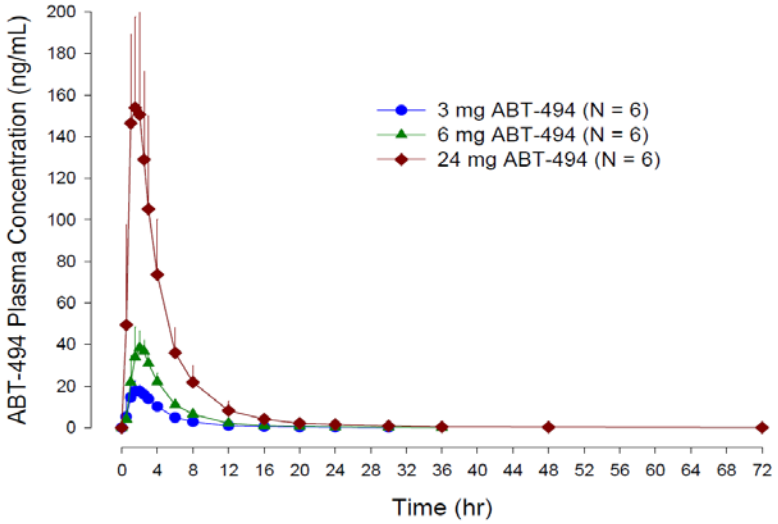


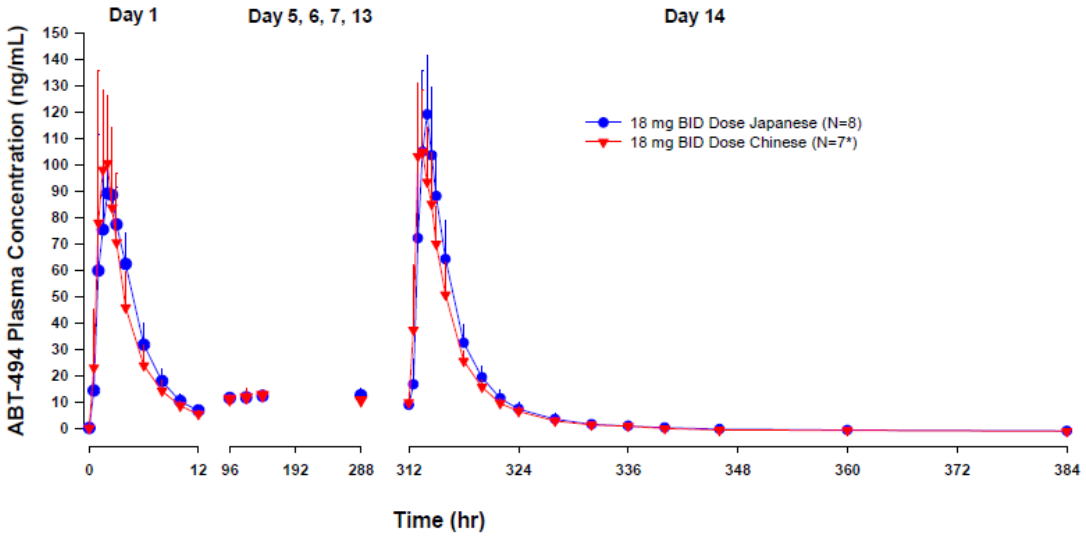
Figure 4.1.2-20. ABT-494 PK Profiles Following Administration of Single Doses to Healthy Japanese Subjects, Linear Scale – Part 1
(Source: Figure 2 of Study M13-543 CSR)

Table 4.1.2-34. PK Parameters (Mean ± SD) of ABT-494 Following Administration of Single Doses to Healthy Japanese Subjects –Part 1

Pharmacokinetic Parameters (units)		Regimens		
		Group 1 ABT-494 3 mg (N = 6)	Group 2 ABT-494 6 mg (N = 6)	Group 3 ABT-494 24 mg (N = 6)
C_{max}	(ng/mL)	19.5 ± 5.3	42.5 ± 5.4	173 ± 36.6
T_{max}	(h)	1.9 ± 0.8	2.0 ± 0.4	1.5 ± 0.4
AUC_t	(ng•h/mL)	87.9 ± 14.8	185 ± 21.4	723 ± 229
AUC_∞	(ng•h/mL)	88.8 ± 14.8	187 ± 21.8	728 ± 228
$t_{1/2}$[a]	(h)	6.63 ± 2.07	5.53 ± 2.19	9.12 ± 9.65
C_{max}/Dose	(ng/mL/mg)	6.51 ± 1.75	7.08 ± 0.902	7.19 ± 1.52
AUC_t/Dose	(ng•h/mL/mg)	29.3 ± 4.93	30.9 ± 3.56	30.1 ± 9.56
AUC_∞/Dose	(ng•h/mL/mg)	29.6 ± 4.93	31.1 ± 3.63	30.3 ± 9.51
f_e[b]	(%)	25.4 ± 3.48	24.4 ± 3.73	26.9 ± 4.89
CL_R[c]	(L/h)	8.76 ± 1.48	7.99 ± 1.55	9.46 ± 2.58

a. Harmonic mean ± pseudo-standard deviation.
b. f_e calculated as the amount recovered in urine divided by ABT-494 dose.
c. CL_R calculated as the amount recovered in urine within 72 hour interval divided by AUC_{0-72}.
(Source: Table 12 of Study M13-543 CSR)

Part 2



* In the Chinese group, N = 7 on Days 1, 5, 6, and 7 and N = 6 on Days 13 and 14.

Figure 4.1.2-21. ABT-494 PK Profiles Following Administration of Multiple Twice Daily Oral Doses to Healthy Japanese and Chinese Subjects, Linear Scale – Part 2
(Source: Figure 5 of Study M13-543 CSR)

Table 4.1.2-35. ABT-494 PK Parameters (Mean ± SD) Following Administration of 18 mg Twice Daily Oral Doses to Healthy Japanese and Chinese Subjects – Part 2

Pharmacokinetic Parameters (units)		Group 4[a] Japanese Subjects	Group 5[a] Chinese Subjects
		Study Day 1	
N		8	7
C_{max}	(ng/mL)	107 ± 38.9	116 ± 45.3
T_{max}	(h)	2.1 ± 0.6	1.7 ± 0.5
AUC_{0-12}	(ng•h/mL)	440 ± 80.2	410 ± 87.6
		Study Day 14	
N		8	6
C_{max}	(ng/mL)	128 ± 23.4	118 ± 26.9
T_{max}	(h)	2.1 ± 0.5	1.6 ± 0.6
C_{trough}	(ng/mL)	8.61 ± 2.83	7.70 ± 1.68
AUC_{0-12}	(ng•h/mL)	522 ± 76.2	466 ± 48.2
CL/F	(L/h)	35.2 ± 5.38	39.0 ± 3.81
$t_{1/2}$[b]	(h)	9.5 ± 6.6	6.9 ± 3.7
$t_{1/2F}$[b,c]	(h)	3.1 ± 0.52	3.1 ± 0.46
R_{ac} C_{max}[d]		1.21 (0.62 – 1.97)	1.07 (0.68 – 1.30)
R_{ac} AUC_{0-12}[e]		1.19 (1.03 – 1.47)	1.15 (0.98 – 1.33)
f_e[f]	(%)	25.7 ± 9.81	30.9 ± 5.01
CL_R[g]	(L/h)	8.84 ± 3.26	12.0 ± 1.97

a. ABT-494 was administered in both groups as 18 mg BID dose.

b. Harmonic mean ± pseudo standard deviation.

c. Functional half-life calculated as: $\ln(2)/[\ln(C_{max}/C_{trough})/12]$.

d. R_{ac} C_{max} = Accumulation ratio (calculated as the ratio of C_{max} on Study Day 14 to C_{max} on Study Day 1); median and range (minimum to maximum) are presented.

e. R_{ac} AUC_{0-12} = Accumulation ratio (calculated as the ratio of AUC_{0-12} on Study Day 14 to AUC_{0-12} on Study Day 1) median and range (minimum to maximum) are presented.

f. f_e calculated as the amount recovered in urine divided by ABT-494 dose 18 mg.

g. CL_R calculated as the amount recovered in urine within AM dosing interval divided by AUC_{0-12} on Day 14.

(Source: Table 14 of Study M13-543 CSR)

Conclusions

- Following multiple BID dosing of ABT-494 IR capsule, steady state appeared to be achieved within 5 days. ABT-494 PK are generally comparable between Japanese and Chinese subjects.

4.1.2-10 Study M13-539--Phase 1 Intrinsic Factor PK Study

Title: A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of ABT-494 in Subjects with Mild or Moderate Hepatic Impairment

Objectives: PK and safety of upadacitinib following oral administration of a single dose of upadacitinib in subjects with hepatic impairment

Study population: subjects with hepatic impairment (n=18)

Drug product: Upadacitinib 15 mg [redacted] (b) (4) tablet (ER7) (Bulk Product Lot Number 15-005421)

Study design: This was a Phase 1, single-dose, open-label, multicenter study to assess the PK and safety of upadacitinib following oral administration of a single 15 mg dose of upadacitinib once-daily tablet (ER7) in subjects with mild and moderate hepatic impairment (according to Child-Pugh classification) relative to healthy subjects. Six subjects were enrolled into each of the three groups: normal hepatic function (Group 1); mild hepatic impairment (Group 2); and moderate hepatic impairment (Group 3).

PK sampling: pre-dose (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96, and 120 hours post-dose

Results

Upadacitinib AUC was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function. Upadacitinib Cmax was similar in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.

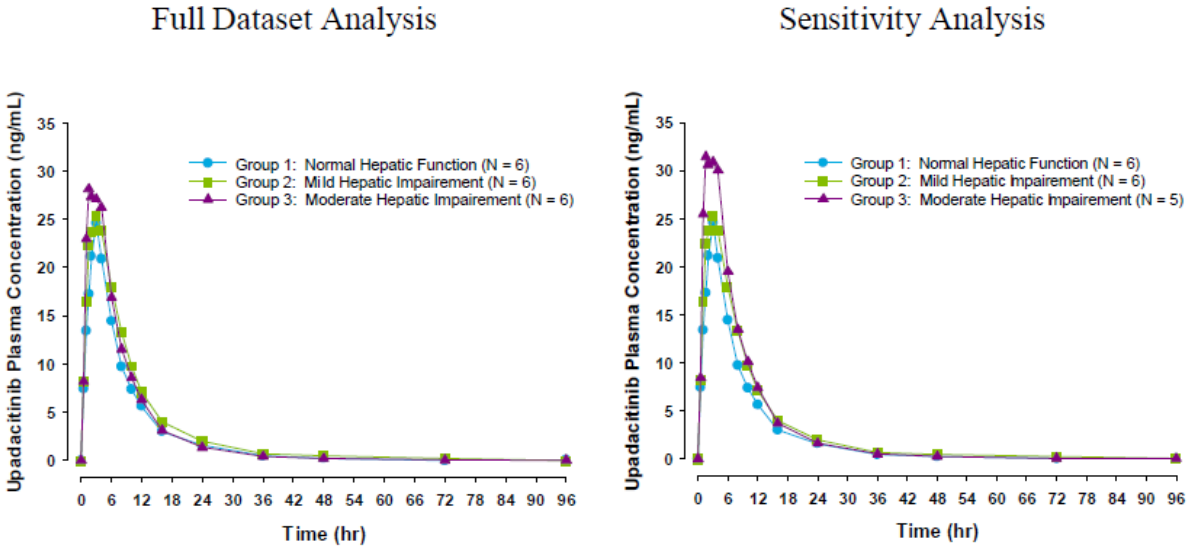


Figure 4.1.2-22. Upadacitinib PK Profiles Following Administration of 15 mg Dose of Upadacitinib in Subjects with Normal and Impaired Hepatic Function Under Fasting Conditions

Sensitivity Analysis excludes Subject [redacted] (b) (6) with low exposures from moderate hepatic impairment group.
(Source: adapted from Figure 1 of Study M13-539 CSR)

Table 4.1.2-36. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of a Single 15 mg Dose of Upadacitinib to Subjects with Normal and Impaired Hepatic Function Under Fasting Conditions

Pharmacokinetic Parameters (units)	Group 1 Subjects with Normal Hepatic Function (N = 6)	Group 2 Subjects with Mild Hepatic Impairment (N = 6)	Group 3 Subjects with Moderate Hepatic Impairment (N = 6)	Group 3 Sensitivity Analysis: Subjects with Moderate Hepatic Impairment (N = 5)[a]
C_{max} (ng/mL)	26.6 ± 8.39	27.3 ± 6.98	33.0 ± 13.1	37.2 ± 8.94
T_{max}[b] (h)	2.5 (1.5 to 3.0)	2.5 (1.5 to 3.0)	1.5 (1.5 to 4.0)	1.5 (1.5 to 4.0)
AUC_t (ng•h/mL)	212 ± 56.5	270 ± 75.0	251 ± 157	289 ± 141
AUC_{inf} (ng•h/mL)	215 ± 56.1	274 ± 74.5	252 ± 157	290 ± 141
$t_{1/2}$[c] (h)	8.93 ± 4.87	7.99 ± 4.60	4.06 ± 1.27	4.14 ± 1.46
CL/F (L/h)	74.5 ± 21.6	58.1 ± 15.4	94.8 ± 80.9	64.1 ± 32.9

a. Sensitivity analysis excluding Subject (b) (6)

b. Median (minimum to maximum).

c. Harmonic mean ± pseudo-standard deviation.

(Source: Table 4 of Study M13-539 CSR)

Table 4.1.2-37. Effect of Hepatic Function on Upadacitinib Pharmacokinetic Parameters –Full Analysis Dataset

Hepatic Function Test vs. Reference	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
		Test	Reference	Point Estimate	90% Confidence Interval
Mild vs. Normal[a]	C_{max}	26.4	25.4	1.038	0.702, 1.536
	AUC_t	312	245	1.274	0.796, 2.038
	AUC_{inf}	316	248	1.278	0.800, 2.041
Moderate vs. Normal[b]	C_{max}	30.1	25.4	1.185	0.800, 1.753
	AUC_t	243	245	0.991	0.620, 1.586
	AUC_{inf}	243	248	0.983	0.616, 1.570

a. Upadacitinib 15 mg single dose in subjects with mild hepatic impairment (Test) relative to upadacitinib 15 mg single dose in subjects with normal hepatic function (Reference).

b. Upadacitinib 15 mg single dose in subjects with moderate hepatic impairment (Test) relative to upadacitinib 15 mg single dose in subjects with normal hepatic function (Reference).

(Source: Table 5 of Study M13-539 CSR)

Table 4.1.2-38. Effect of Hepatic Function on Upadacitinib Pharmacokinetic Parameters – Sensitivity Analysis Excluding Outlier Subject (3004) with Low Exposures from the Moderate Hepatic Impairment Group

Hepatic Function Test vs. Reference	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
		Test	Reference	Point Estimate	90% Confidence Interval
Mild vs. Normal[a]	C_{max}	26.4	25.4	1.038	0.773, 1.394
	AUC_t	303	238	1.274	0.909, 1.787
	AUC_{inf}	307	240	1.278	0.913, 1.789
Moderate vs. Normal[b]	C_{max}	36.4	25.4	1.431	1.051, 1.950
	AUC_t	296	238	1.248	0.875, 1.779
	AUC_{inf}	297	240	1.237	0.870, 1.760

a. Upadacitinib 15 mg single dose in subjects with mild hepatic impairment (Test) relative to upadacitinib 15 mg single dose in subjects with normal hepatic function (Reference).

b. Upadacitinib 15 mg single dose in subjects with moderate hepatic impairment (Test) relative to upadacitinib 15 mg single dose in subjects with normal hepatic function (Reference).

One subject (Subject (b) (6)) in the moderate hepatic impairment group (Group 3) had 72% lower upadacitinib AUC compared to the mean AUC in subjects with normal hepatic function group (Group 1). Additionally, the subject's upadacitinib Cmax and AUC were noticeably lower than all other subjects in the study.
(Source: Table 6 of Study M13-539 CSR)

Conclusions

Following a single dose of upadacitinib 15 mg ER tablet,

- Upadacitinib Cmax was similar in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.
- Upadacitinib AUC was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function.

4.1.2-11 Study M13-551--Phase 1 Intrinsic Factor PK Study

Title: A Phase 1 Study to Evaluate the Safety and Pharmacokinetics of a Single Dose of ABT-494 in Subjects with Normal and Impaired Renal Function

Objectives: PK and safety of a single upadacitinib dose in subjects with normal renal function, and in subjects with mild, moderate and severe renal impairment

Study population:

Group	Description	eGFR (mL/min/1.73 m^2)	N
1	Normal renal function	≥ 90	6
2	Mild renal impairment	60 – 89	6
3	Moderate renal impairment	30 – 59	6
4	Severe renal impairment	15 – 29	6

eGFR = Glomerular filtration rate as calculated by the Modification of Diet in Renal Disease (MDRD) equation

Drug product:
Upadacitinib 15 mg extended-release tablet (Bulk Product Lot Number 15-005421)

Study design: This was a Phase 1, single-dose, open-label, multicenter study. Upadacitinib 15 mg was taken orally after an approximate 10-hour fast and 4 hours before lunch.

PK sampling:
Blood samples were collected prior to dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours after dosing.

Urine samples were collected 0 to 12, 12 to 24, 24 to 48, 48 to 72, 72 to 96, and 96 to 120 hours after dosing.

Results
Upadacitinib mean Cmax were similar and mean AUCinf were 18%, 33% and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function.

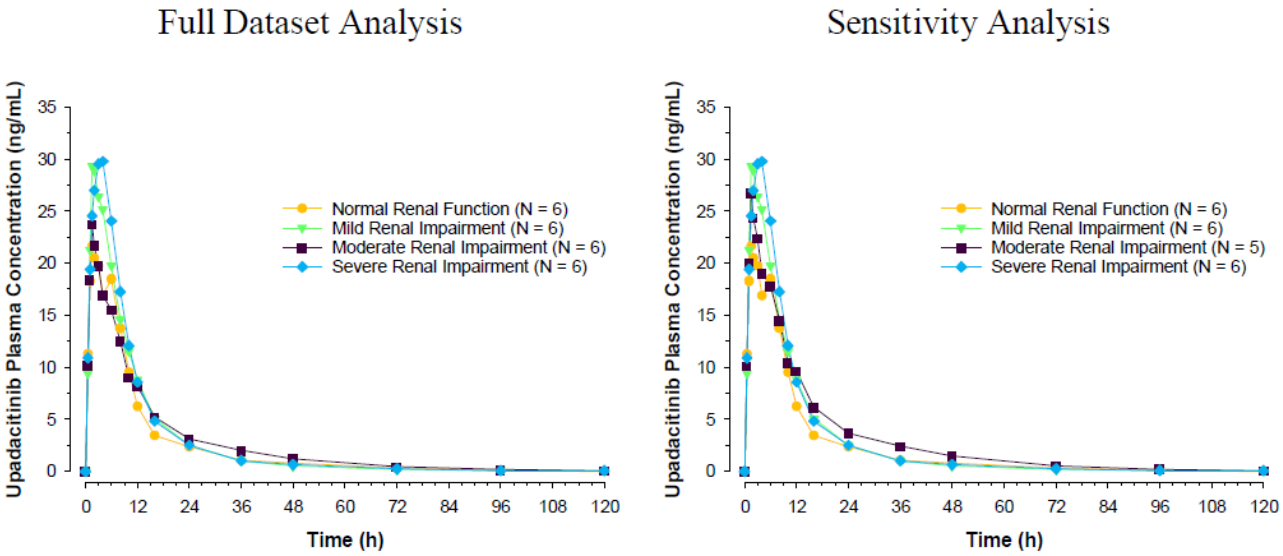


Figure 4.1.2-23. Upadacitinib PK Profiles Following Administration of a Single 15 mg Dose of Upadacitinib in Subjects with Normal and Impaired Renal Function Under Fasting Conditions, Linear Scale

One subject (Subject (b) (6)) in the moderate renal impairment group (Group 3) had 77% lower upadacitinib AUC compared to the mean AUC in subjects with normal renal function group (Group 1). Additionally, the subject's upadacitinib Cmax and AUC were noticeably lower than all other subjects with moderate renal impairment (Group 3).
(Source: Figure 1 of Study M13-551 CSR)

Table 4.1.2-39. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of a Single 15 mg Dose of Upadacitinib in Subjects with Normal and Impaired Renal Function Under Fasting Conditions

Pharmacokinetic Parameter (units)	Subject Group Group 1 Normal Renal Function (N = 6)	Group 2 Mild Renal Impairment (N = 6)	Group 3 Moderate Renal Impairment (N = 6)	Group 3 Sensitivity Analysis: Moderate Renal Impairment (N = 5)[a]	Group 4 Severe Renal Impairment (N = 6)
C_{max} (ng/mL)	31.1 ± 11.8	32.5 ± 10.2	25.2 ± 10.2	28.2 ± 8.05	33.7 ± 5.96
T_{max}[b] (h)	1.8 (1.0 – 6.0)	2.5 (1.5 – 6.0)	1.5 (0.5 – 6.0)	1.5 (1.0 – 6.0)	3.5 (2.0 – 6.0)
AUC_t (ng•h/mL)	265 ± 75.5	314 ± 87.9	309 ± 144	358 ± 85.8	337 ± 63.6
AUC_{inf} (ng•h/mL)	270 ± 77.7	323 ± 90.7	311 ± 145	361 ± 86.9	341 ± 63.2
$t_{1/2}$[c] (h)	11.0 ± 5.51	10.5 ± 7.00	8.14 ± 7.08	10.4 ± 11.2	8.63 ± 4.43
f_e (%)	9.91 ± 4.05	7.03 ± 3.05	4.10 ± 2.02	4.76 ± 1.34	2.48 ± 1.62
CL_R (L/h)	5.64 ± 2.13	3.42 ± 1.53	2.10 ± 0.837	2.14 ± 0.930	1.06 ± 0.547

a. Sensitivity analysis excluding Subject (b) (6) who had distinctively low upadacitinib exposure.

b. Median (minimum through maximum).

c. Harmonic mean (pseudo-standard deviation); evaluations of $t_{1/2}$ were based on statistical tests for β (BETA).

(Source: Table 5 of Study M13-551 CSR)

Table 4.1.2-40. Effect of Renal Impairment on Upadacitinib Cmax and AUC [Full Dataset Analysis]

Group Test vs. Reference	Parameter	Regression Analysis of eGFR Point Estimate	90% CI	Regression Analysis of CL_{cr} Point Estimate	90% CI	ANCOVA Point Estimate	90% CI
Mild vs Normal	C_{max}	1.060	0.899 – 1.250	1.102	0.947 – 1.281	1.071	0.789 – 1.453
	AUC_t	1.150	0.966 – 1.371	1.202	1.029 – 1.404	1.211	0.846 – 1.735
	AUC_{inf}	1.146	0.961 – 1.367	1.201	1.027 – 1.404	1.224	0.854 – 1.755
Moderate vs Normal	C_{max}	1.102	0.837 – 1.451	1.175	0.914 – 1.511	0.702	0.514 – 0.960
	AUC_t	1.263	0.943 – 1.691	1.358	1.048 – 1.760	0.885	0.612 – 1.278
	AUC_{inf}	1.255	0.936 – 1.683	1.357	1.046 – 1.759	0.882	0.610 – 1.275
Severe vs Normal	C_{max}	1.134	0.793 – 1.622	1.233	0.890 – 1.710	1.225	0.900 – 1.668
	AUC_t	1.355	0.927 – 1.980	1.489	1.063 – 2.085	1.432	0.996 – 2.059
	AUC_{inf}	1.344	0.917 – 1.968	1.487	1.060 – 2.084	1.424	0.989 – 2.050

CI = Confidence Interval

(Source: Table 6 of Study M13-551 CSR)

Table 4.1.2-41. Effect of Renal Impairment on Upadacitinib Cmax and AUC [Sensitivity Analysis Excluding an Outlier with Low Exposure in the Moderate Renal Impairment Category]

Group Test vs. Reference	Parameter	Regression Analysis of eGFR		Regression Analysis of CL_{cr}		ANCOVA	
		Point Estimate	90% CI	Point Estimate	90% CI	Point Estimate	90% CI
Mild vs Normal	C_{max}	1.064	0.923 – 1.226	1.097	0.964 – 1.249	1.046	0.765 – 1.430
	AUC_t	1.187	1.064 – 1.325	1.200	1.088 – 1.322	1.229	0.952 – 1.588
	AUC_{inf}	1.184	1.062 – 1.319	1.198	1.088 – 1.320	1.248	0.970 – 1.605
Moderate vs Normal	C_{max}	1.109	0.875 – 1.404	1.167	0.941 – 1.448	0.926	0.667 – 1.285
	AUC_t	1.331	1.108 – 1.598	1.354	1.151 – 1.593	1.359	1.042 – 1.772
	AUC_{inf}	1.325	1.106 – 1.587	1.352	1.150 – 1.589	1.348	1.038 – 1.750
Severe vs Normal	C_{max}	1.144	0.841 – 1.555	1.223	0.924 – 1.619	1.127	0.824 – 1.541
	AUC_t	1.450	1.143 – 1.839	1.483	1.201 – 1.832	1.326	1.029 – 1.708
	AUC_{inf}	1.441	1.140 – 1.822	1.480	1.200 – 1.826	1.323	1.031 – 1.699

(Source: Table 7 of Study M13-551 CSR)

Conclusions

Following a single dose of upadacitinib 15 mg ER tablet,

- Upadacitinib Cmax were similar in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.
- Upadacitinib AUCinf were 18%, 33% and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function

4.1.2-12 Study M15-558--Phase 1 Intrinsic Factor PK Study

Title: A Double-Blind, Randomized, Placebo-Controlled Phase 1 Study in Healthy Chinese Adults to Evaluate the Safety, Tolerability and Pharmacokinetics of Multiple Doses of ABT-494

Objectives: safety, tolerability and PK of multiple once-daily oral doses of upadacitinib (ABT-494) in healthy Chinese subjects

Study population: healthy Chinese subjects (n=36)

Drug product: Upadacitinib ER tables 15 mg (ER7, Bulk Lot 16-005249) and 30 mg (ER8, Bulk Lot 16-005870)

Study design: This was a Phase 1, double-blind, randomized, placebo-controlled study in 36 healthy Chinese adults residing in China. Subjects were given multiple doses of upadacitinib 15 mg, 30 mg, and 45 mg QD for 7 days.

Group	Treatment	
1	Upadacitinib 15 mg QD, N = 9	Placebo QD, N = 3
2	Upadacitinib 30 mg QD, N = 9	Placebo QD, N = 3
3	Upadacitinib 45 mg QD, N = 9	Placebo QD, N = 3

PK sampling:
Day 1: predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after dosing;
Day 7: predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, and 72 hours after dosing;
Days 3, 4, 5, 6: predose

Results
Upadacitinib PK in healthy Chinese subjects were consistent with previous studies in healthy Western subjects.

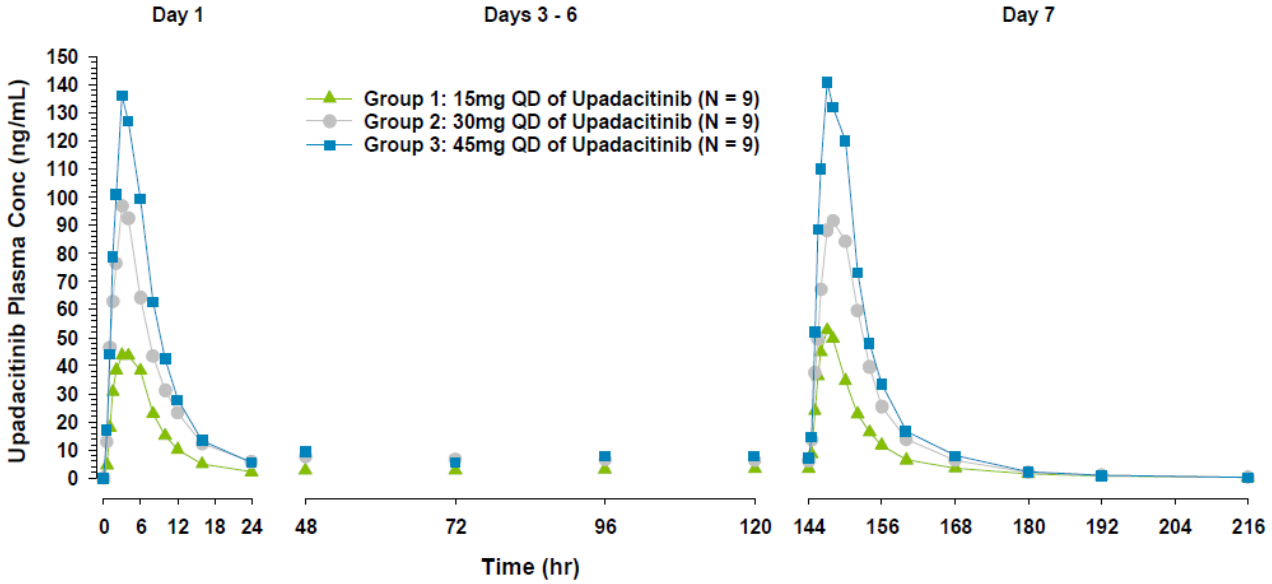


Figure 4.1.2-24. Upadacitinib PK Profiles Following Administration of Multiple Doses of 15 mg, 30 mg, or 45 mg Using Upadacitinib ER Tablet Formulation in Healthy Chinese Subjects Under Non-Fasting Conditions, Linear Scale
(Source: Figure 1 of Study M15-558 CSR)

Table 4.1.2-42. PK Parameters (Mean ± SD) of Upadacitinib Following Administration of Multiple Doses of 15 mg, 30 mg, or 45 mg of Upadacitinib ER Tablet Formulation in Chinese Subjects Under Non-Fasting Conditions

Pharmacokinetic Parameters (units)	Group 1: 15 mg QD (N = 9)	Group 2: 30 mg QD (N = 9)	Group 3: 45 mg QD (N = 9)
Study Day 1			
C_{max} (ng/mL)	52.3 ± 11.1	99.2 ± 30.8	157 ± 25.0
T_{max}[a] (h)	4.0 (1.5 - 6.0)	3.0 (3.0 - 4.0)	3.0 (3.0 - 6.0)
C_{24} (ng/mL)	2.17 ± 1.20	5.71 ± 2.66	5.69 ± 1.35
AUC_{0-24} (ng•h/mL)	386 ± 98.7	798 ± 273	1070 ± 223
Study Day 7			
C_{max} (ng/mL)	56.2 ± 9.76	103 ± 24.5	168 ± 28.5
T_{max}[a] (h)	3.0 (1.5 - 6.0)	4.0 (3.0 - 6.0)	4.0 (1.5 - 6.0)
C_{24} (ng/mL)	3.52 ± 1.42	6.37 ± 3.68	7.93 ± 2.72
C_{min} (ng/mL)	2.99 ± 1.71	5.92 ± 3.59	6.87 ± 2.67
AUC_{0-24} (ng•h/mL)	431 ± 93.2	878 ± 241	1220 ± 241
CL/F (L/h)	36.4 ± 8.47	35.8 ± 7.01	38.3 ± 7.85
$t_{1/2}$[b] (h)	9.81 (5.15)	7.82 (3.69)	6.63 (2.63)
C_{max}/Dose (ng/mL/mg)	3.74 ± 0.65	3.43 ± 0.82	3.74 ± 0.63
C_{24}/Dose (ng/mL/mg)	0.24 ± 0.09	0.21 ± 0.12	0.18 ± 0.06
AUC_{0-24}/Dose (ng•h/mL/mg)	28.7 ± 6.22	29.3 ± 8.03	27.0 ± 5.35
DFL	3.03 ± 0.61	2.69 ± 0.33	3.21 ± 0.28
R_{ac} AUC_{0-24}[c]	1.07 (0.92 - 1.70)	1.06 (0.96 - 1.37)	1.12 (0.98 - 1.37)
R_{ac} C_{max}[d]	1.02 (0.89 - 1.38)	1.03 (0.87 - 1.37)	1.05 (0.92 - 1.43)
f_e[e] (%)	20.0 ± 5.04	24.0 ± 7.86	21.0 ± 5.31
CL_R[f] (L/h)	7.08 ± 1.44	8.26 ± 2.20	7.96 ± 2.20

a. Median (minimum through maximum).
b. Harmonic mean (pseudo-standard deviation).
c. R_{ac} AUC_{0-24} = AUC_{0-24}_Day 7/AUC_{0-24}_Day 1; median and range (minimum through maximum) are presented.
d. R_{ac} C_{max} = C_{max}_Day 7/C_{max}_Day 1; median and range (minimum through maximum) are presented.
e. f_e calculated as the amount recovered in urine on Day 7 divided by upadacitinib dose.
f. CL_R calculated as the amount recovered in urine on Day 7 within the dosing interval of 24 hours divided by AUC_{0-24}.

(Source: Table 5 of Study M15-558 CSR)

Table 4.1.2-43. Comparison of Day 7 Dose-Normalized Upadacitinib PK Parameters Between Healthy Chinese and Western Subjects Under Non-Fasting Conditions

Test vs. Reference	Pharmacokinetic Parameter[a]	Central Values		Point Estimate	95% Confidence Interval
		Test	Reference		
Healthy Chinese (Test) vs. Healthy Western (Reference)	Dose-normalized C_{max}	3.19	2.42	1.316	1.142, 1.516
	Dose-normalized AUC_{0-24}	24.7	19.6	1.256	1.101, 1.433
	Dose-normalized C_{24}	0.168	0.174	0.965	0.739, 1.259

a. Dose-normalized C_{max} and C_{24} units are (ng/mL)/mg and dose-normalized AUC units are (ng•h/mL)/mg.

(Source: Table 6 of Study M15-558 CSR)

Conclusions

- Upadacitinib PK in healthy Chinese subjects were consistent with previous studies in healthy Western subjects.

4.1.2-13 Study M13-540--Phase 1 Extrinsic Factor PK Study

Title: A Phase 1 Study to Evaluate the Effects of the Co-Administration of Rifampin on the Pharmacokinetics and Safety of a Single Dose of ABT-494 in Healthy Adult Subjects

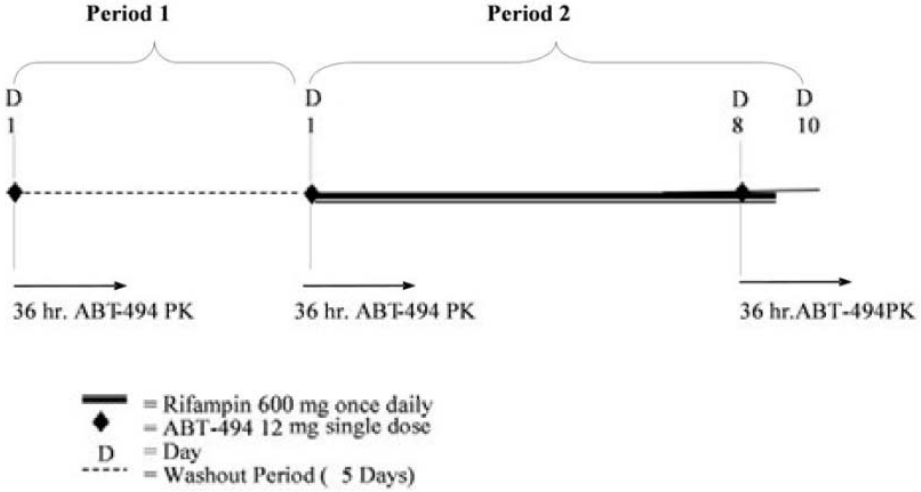
Objectives: PK, safety and tolerability of ABT-494 (a CYP3A substrate) when administered with rifampin (a potent CYP3A inducer)

Study population: healthy adult subjects (n=12)

Drug product: ABT-494 capsule 12 mg (Bulk Product Lot Number 13-003488)

Study design:
This Phase 1, open-label study was conducted according to a two-period, sequential design to evaluate the effects of rifampin on a single dose of ABT-494.

Period 1	One 12 mg ABT-494 capsule on Study Day 1.
Period 2	One 12 mg ABT-494 capsule on Study Days 1 and 8. Two 300 mg rifampin capsules administered once daily on Study Days 1 through 9. (Both rifampin and ABT-494 were administered at the same time on Study Days 1 and 8).



PK sampling:
Predose and 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 15, 18, 24, 30 and 36 hours after ABT-494 dosing on Study Day 1 of Period 1 and Study Days, 1 and 8 of Period 2.

Blood samples were obtained for the rifampin assay 2 hours after rifampin dosing on Study Days 1, 4, 6, and 8 of Period 2.

Results

Single doses of rifampin had no clinically meaningful effect on ABT-494 exposure. Administration of ABT-494 on Day 8 of a 9-day regimen of rifampin decreased the central values of ABT-494 C_{max} and AUC by approximately 50% and 60%, indicating that administration of ABT-494 with repeated doses of a strong CYP3A inducer results in a moderate decrease in ABT-494 exposure.

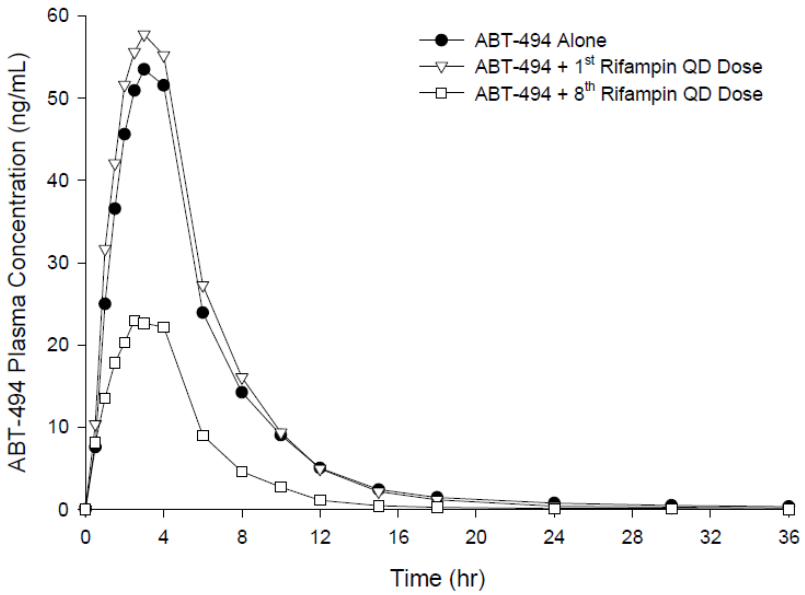


Figure 4.1.2-25. ABT-494 PK Profiles Following Administration of ABT-494 Alone and with Single and Multiple QD Doses of Rifampin to Healthy Subjects, Linear Scale
(Source: Figure 3 of Study M13-540 CSR)

Table 4.1.2-44. PK Parameters (Mean ± SD) of ABT-494 Following Administration of ABT-494 Alone and with Single and Multiple QD Doses of Rifampin to Healthy Subjects

Pharmacokinetic Parameters (Units)		Regimens[a]		
		ABT-494 Alone Period 1, Day 1 (N = 12)	ABT-494 + Rifampin (Single Dose) Period 2, Day 1 (N = 12)	ABT-494 + Rifampin (QD) Period 2, Day 8 (N = 12)
C_{max}	(ng/mL)	62.0 ± 10.9	71.3 ± 15.5	31.7 ± 11.5[d]
T_{max}	(h)	2.9 ± 1.1	2.8 ± 1.0	2.8 ± 0.9
AUC_t	(ng•h/mL)	329 ± 74.1	355 ± 80.2	130 ± 28.1[d]
AUC_∞	(ng•h/mL)	334 ± 76.1	357 ± 80.9	131 ± 27.9[d]
$t_{1/2}$[b]	(h)	6.5 ± 3.0	5.9 ± 3.1	4.9 ± 2.7
CL/F[c]	(L/h)	37.3 ± 6.64	34.9 ± 6.48	95.2 ± 19.4

a ABT-494 was administered as a single 12 mg tablet in Period 1 on Study Day 1 and in Period 2 on Study Days 1 and 8; two 300 mg rifampin capsules were administered once daily on Study Days 1 through 9 in Period 2.

b Harmonic mean ± pseudo-standard deviation; evaluations of $t_{1/2}$ were based on statistical tests for β.

c Parameter was not tested statistically.

d Statistically significantly different from reference regimen (ABT-494 Alone, ANOVA, $p < 0.05$).

(Source: Table 5 of Study M13-540 CSR)

Table 4.1.2-45. Bioavailability of ABT-494 When Administered with Single and Multiple Doses of Rifampin Relative to that When Administered Alone

Regimens[a] Test vs. Reference	Pharmacokinetic Parameter[b]	Central Value[c]		Relative Bioavailability	
		Test	Reference	Point Estimate[d]	90% Confidence Interval
ABT-494 + Rifampin SD	C_{max}	69.7	61.1	1.142	1.015 – 1.284
vs.	AUC_t	348	323	1.078	1.014 – 1.147
ABT-494 Alone	AUC_∞	350	327	1.070	1.006 – 1.138
ABT-494 + Rifampin QD	C_{max}	30.0	61.1	0.491	0.436 – 0.552
vs.	AUC_t	128	323	0.395	0.372 – 0.420
ABT-494 Alone	AUC_∞	129	327	0.393	0.369 – 0.418

SD = single dose; QD = multiple once-daily dose

a ABT-494 was administered as a single 12 mg tablet in Period 1 on Study Day 1 and in Period 2 on Study Days 1 and 8; two 300 mg rifampin capsules were administered once daily on Study Days 1 through 9 in Period 2.

b Units presented for C_{max} and AUC are ng/mL and ng•h/mL, respectively.

c Antilogarithm of the least squares means for logarithms.

d Antilogarithm of the difference (test minus reference) of the least squares means for logarithms.

(Source: Table 7 of Study M13-540 CSR)

Conclusions

- Single doses of rifampin (as an OATP1B inhibitor) had no clinically meaningful effect on ABT-494 exposure.
- Administration of repeated doses of rifampin as a strong CYP3A inducer decreased ABT-494 C_{max} and AUC by approximately 50% and 60%.

4.1.2-14 Study M13-541--Phase 1 Extrinsic Factor PK Study

Title: A Phase 1 Study to Assess the Effects of Co-Administration of ABT-494 on the Pharmacokinetics of Select Statins

Objectives: PK and safety of rosuvastatin and atorvastatin when administered in combination with ABT-494; effect of single doses of rosuvastatin and atorvastatin on the steady-state PK of ABT-494

Study populations: healthy subjects (n=12)

Drug product: ABT-494 (b) (4) tablet, 30 mg (Bulk Product Lot Number 15-005425)

Study design:
This was a Phase 1, single center, two-part, study. Each Study Part followed a single-sequence 2-period, open-label design.

Part	N	Period 1	Period 2
1	12	Day 1: A single dose of rosuvastatin 5 mg followed by a washout interval of 5 days	Days 1 – 10: ABT-494 30 mg QD; Day 7: A single dose of rosuvastatin 5 mg administered 1 hour after ABT-494 dose
2	24	Day 1: A single dose of atorvastatin 10 mg followed by a washout interval of 5 days	Days 1 – 10: ABT-494 30 mg QD; Day 7: A single dose of atorvastatin 10 mg administered 1 hour after ABT-494 dose

PK sampling:

Rosuvastatin Assay (Part 1)

- Day 1, Period 1: Prior to rosuvastatin dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 11, 15, 23, 36, 48, 72 and 96 hours after rosuvastatin dosing.
- Day 7, Period 2: Prior to rosuvastatin dosing (0 hour) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 11, 15, 23, 36, 48, 72 and 96 hours after rosuvastatin dosing.

Atorvastatin and Ortho-Hydroxyatorvastatin Assay (Part 2)

- Day 1, Period 1: Prior to atorvastatin dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11, 15, 23, 36, 48, 72 and 96 hours after atorvastatin dosing.
- Day 7, Period 2: Prior to atorvastatin dosing (0 hour) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 11, 15, 23, 36, 48, 72 and 96 hours after atorvastatin dosing.

ABT-494 Assay (Parts 1 and 2)

- Day 6, Period 2: Prior to ABT-494 dosing (0 hour) and at 0.5, 1, 2, 3, 4, 7, 9, 12, and 16 hours after ABT-494 dosing.
- Day 7, Period 2: Prior to ABT-494 dosing (0 hour; 24 hours after Day 6 ABT-494 dose) and at 0.5, 1 (prior to the statin dose), 2, 3, 4, 7, 9, 12, 16, 24 hours after ABT-494 dosing.

Results

Following the administration of rosuvastatin or atorvastatin on Day 7 of a 10-Day multiple-dose regimen (30 mg QD using IR formulation) of ABT-494, the ratios for concomitant administration with ABT-494 relative to administration alone were 0.77, 0.71, and 0.67 for rosuvastatin Cmax, AUCt, and AUCinf and 0.88, 0.77, and 0.77 for atorvastatin Cmax, AUCt, and AUCinf, respectively. Administration of single doses of 5 mg rosuvastatin or 10 mg atorvastatin had no relevant effect on ABT-494 AUC0-24 and Cmax at steady-state.

<u>Rosuvastatin PK (Part 1)</u>

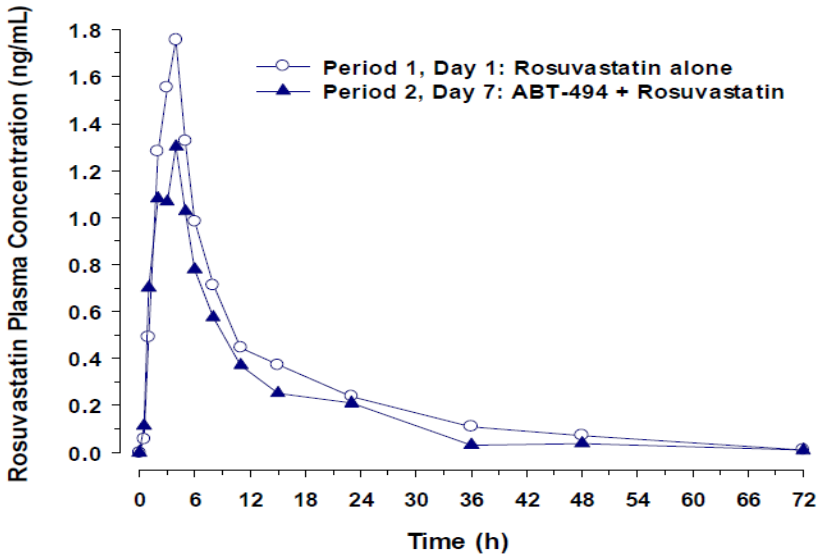


Figure 4.1.2-26. Rosuvastatin PK Profiles Following Administration of 5 mg Single Doses of Rosuvastatin Alone and with a Multiple-Dose Regimen of ABT-494 30 mg QD

Period 1, Day 1: Rosuvastatin 5 mg single dose
Period 2, Day 7: ABT-494 30 mg QD + rosuvastatin 5 mg single dose

(Source: Figure 1 of Study M13-541)

Table 4.1.2-46. PK Parameters of Rosuvastatin Following Administration of 5 mg Single Doses of Rosuvastatin Alone and with a Multiple-Dose Regimen of ABT-494 30 mg QD

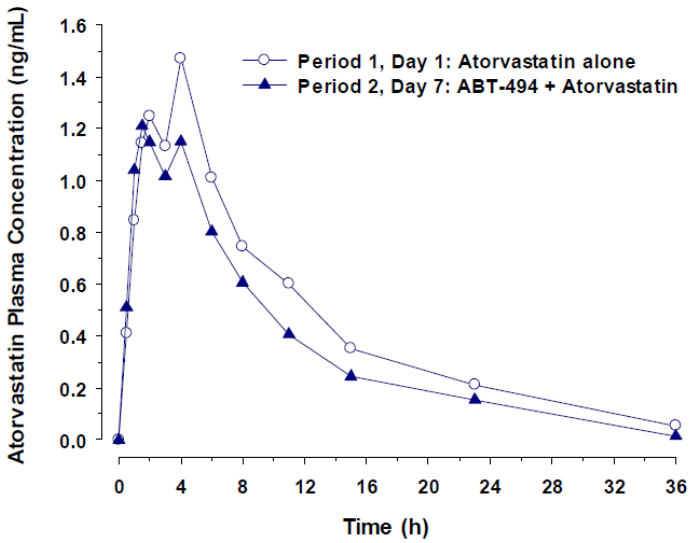
Pharmacokinetic Parameters (units)	Period 1 – Day 1: Rosuvastatin 5 mg Alone (N = 12)	Period 2 – Day 7 ABT-494 30 mg QD + Rosuvastatin 5 mg (N = 12)
C_{max} (ng/mL)	1.91 ± 0.699	1.43 ± 0.404
T_{max} [a] (h)	4.0 (1.0 to 4.0)	4.0 (1.0 to 4.0)
AUC_t (ng•h/mL)	17.5 ± 6.53	12.8 ± 5.73
AUC_{inf} (ng•h/mL)	22.8 ± 6.69	15.9 ± 6.62
$t_{1/2}$ [b] (h)	18.8 (9.89)	10.2 (5.14)

a. Median (minimum to maximum).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 4 of Study M13-541)

Atorvastatin and Ortho-Hydroxyatorvastatin (Part 2)



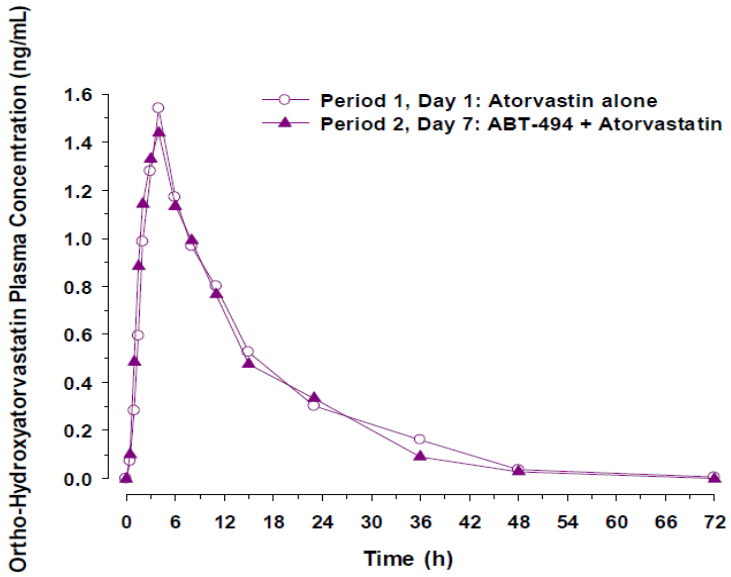


Figure 4.1.2-27. Atorvastatin and Ortho-Hydroxyatorvastatin PK Profiles Following Administration of 10 mg Single Doses of Atorvastatin Alone and with a Multiple-Dose Regimen of ABT-494 30 mg QD

Period 1, Day 1: Atorvastatin 10 mg single dose
Period 2, Day 7: ABT-494 30 mg QD + atorvastatin 10 mg single dose
(Source: Figure 2 of Study M13-541)

Table 4.1.2-47. PK Parameters of Atorvastatin and Ortho-Hydroxyatorvastatin Following Administration of 10 mg Single Doses of Atorvastatin Alone and with a Multiple-Dose Regimen of ABT-494 30 mg QD

Pharmacokinetic Parameters (units)	Period 1 – Day 1: Atorvastatin 10 mg Alone (N = 24)	Period 2 – Day 7 ABT-494 30 mg QD + Atorvastatin 10 mg (N = 24)
	Atorvastatin	
C_{max} (ng/mL)	1.67 ± 0.828	1.50 ± 0.813
T_{max}[a] (h)	3.5 (0.5 to 4.0)	1.5 (0.5 to 4.0)
AUC_t (ng•h/mL)	15.6 ± 8.43	11.9 ± 6.72
AUC_{inf} (ng•h/mL)	17.8 ± 8.72	13.6 ± 6.98
$t_{1/2}$[b] (h)	8.15 (3.42)	7.28 (2.00)
	Ortho-hydroxyatorvastatin	
C_{max} (ng/mL)	1.58 ± 0.716	1.54 ± 0.610
T_{max}[a] (h)	4.0 (2.0 to 8.0)	4.0 (2.0 to 8.0)
AUC_t (ng•h/mL)	19.4 ± 9.50	19.0 ± 7.61
AUC_{inf} (ng•h/mL)	22.8 ± 9.68	22.1 ± 7.66
$t_{1/2}$[b] (h)	11.1 (3.92)	10.0 (2.60)
Ortho-Hydroxyatorvastatin to Atorvastatin AUC_t Ratio[c]	1.33 ± 0.492	1.73 ± 0.517
Ortho-Hydroxyatorvastatin to Atorvastatin AUC_{inf} Ratio[d]	1.39 ± 0.499	1.74 ± 0.440

a. Median (minimum to maximum).
b. Harmonic mean (pseudo-standard deviation).
c. Ratio of metabolite (ortho-hydroxyatorvastatin) AUC_t to parent drug (atorvastatin) AUC_t.
d. Ratio of metabolite (ortho-hydroxyatorvastatin) AUC_{inf} to parent drug (atorvastatin) AUC_{inf}.

(Source: Table 5 of Study M13-541)

Table 4.1.2-48. PK Comparison of Rosuvastatin, Atorvastatin and Ortho-Hydroxyatorvastatin when Administered with a 30 mg Multiple-Dose Regimen of ABT-494 Relative to when Administered Alone

Compound	Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
			Test	Reference	Point Estimate	90% Confidence Interval
Rosuvastatin	Period 2, Day 7 vs. Period 1 Day 1[a]	C_{max}	1.37	1.78	0.770	0.628, 0.943
		AUC_t	11.8	16.5	0.714	0.642, 0.794
		AUC_{inf}	14.7	21.8	0.673	0.556, 0.815
Atorvastatin	Period 2, Day 7 vs. Period 1 Day 1[b]	C_{max}	1.33	1.51	0.878	0.791, 0.974
		AUC_t	10.6	13.8	0.767	0.693, 0.848
		AUC_{inf}	12.4	16.0	0.771	0.698, 0.852
Ortho-hydroxyatorvastatin	Period 2, Day 7 vs. Period 1 Day 1[b]	C_{max}	1.45	1.46	0.988	0.935, 1.044
		AUC_t	17.6	17.3	1.014	0.937, 1.098
		AUC_{inf}	20.8	21.0	0.988	0.921, 1.060
Ortho-hydroxyatorvastatin to Atorvastatin Ratio	Period 2, Day 7 vs. Period 1 Day 1[b]	AUC_t	1.66	1.25	1.323	1.227, 1.427
		AUC_{inf}	1.68	1.31	1.281	1.186, 1.385

a. Period 2, Day 7: ABT-494 30 mg QD + rosuvastatin 5 mg single dose (Test) versus Period 1, Day 1: Rosuvastatin 5 mg single dose (Reference).

b. Period 2, Day 7: ABT-494 30 mg QD + atorvastatin 10 mg single dose (Test) versus Period 1, Day 1: Atorvastatin 10 mg single dose (Reference).

(Source: Table 6 of Study M13-541)

ABT-494 PK

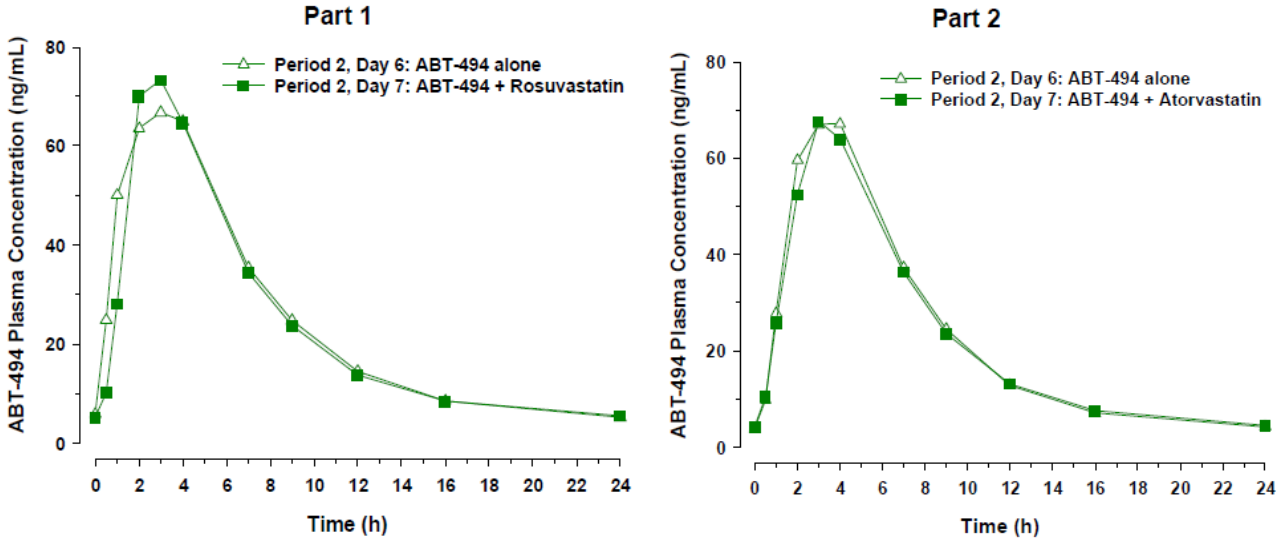


Figure 4.1.2-28. Mean Steady-State ABT-494 Plasma Concentration Versus Time Profiles Following Administration of ABT-494 30 mg QD Alone and with Single Doses of Rosuvastatin (Part 1) and Atorvastatin (Part 2)

Part 1: Period 2, Day 6: ABT-494 30 mg QD alone
Part 1: Period 2, Day 7: ABT-494 30 mg QD + rosuvastatin 5 mg single dose
Part 2: Period 2, Day 6: ABT-494 30 mg QD alone
Part 2: Period 2, Day 7: ABT-494 30 mg QD + atorvastatin 10 mg single dose
(Source: Figure 4 of Study M13-541)

Table 4.1.2-49. Steady-State PK Parameters of ABT-494 Following Administration of ABT-494 30 mg QD Alone and with Single Doses of Rosuvastatin (Part 1) and Atorvastatin (Part 2)

	Part 1		Part 2	
Pharmacokinetic Parameters (units)	Period 2 – Day 6 ABT-494 30 mg QD Alone (N = 12)	Period 2 – Day 7 ABT-494 30 mg QD + Rosuvastatin 5 mg Single Dose (N = 12)	Period 2 – Day 6 ABT-494 30 mg QD Alone (N = 24)	Period 2 – Day 7 ABT-494 30 mg QD + Atorvastatin 10 mg Single Dose (N = 24)
C_{max} (ng/mL)	73.0 ± 23.6	80.9 ± 21.2	76.5 ± 16.1	73.2 ± 17.1
T_{max}[a] (h)	3.0 (1.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 4.0)	3.0 (2.0 to 7.0)
AUC_{0-24} (ng•h/mL)	585 ± 153	567 ± 131	547 ± 112	533 ± 103
C_{24} (ng/mL)	5.17 ± 1.56	5.56 ± 1.52	4.30 ± 1.74	4.61 ± 1.67
CL/F (L/h)	54.6 ± 14.4	55.9 ± 14.7	57.2 ± 12.3	58.4 ± 11.7

a. Median (minimum to maximum).

(Source: Table 7 of Study M13-541)

Table 4.1.2-50. Steady-State ABT-494 PK Comparison when Administered with Rosuvastatin and Atorvastatin Relative to when Administered Alone

Compound (Part)	Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
			Test	Reference	Point Estimate	90% Confidence Interval
ABT-494 (Part 1)	Period 2, Day 7 vs. Period 2 Day 6[a]	C_{max}	78.3	69.6	1.124	0.982, 1.287
		AUC_{0-24}	552	567	0.975	0.880, 1.080
ABT-494 (Part 2)	Period 2, Day 7 vs. Period 2 Day 6[b]	C_{max}	71.5	74.9	0.954	0.898, 1.013
		AUC_{0-24}	524	536	0.977	0.916, 1.042

a. Period 2, Day 7: ABT-494 30 mg QD + rosuvastatin 5 mg single dose (Test) versus Period 2, Day 6: ABT-494 30 mg QD (Reference).

b. Period 2, Day 7: ABT-494 30 mg QD + atorvastatin 10 mg single dose (Test) versus Period 2, Day 6: ABT-494 30 mg QD (Reference).

(Source: Table 8 of Study M13-541)

Conclusions

- Following the administration of rosuvastatin or atorvastatin on Day 7 of a 10-Day multiple-dose regimen (30 mg QD using ER) of ABT-494, co-administration of ABT-494 had no clinically meaningful effect on rosuvastatin and atorvastatin exposure.
- Co-administration of single dose of 5 mg rosuvastatin or 10 mg atorvastatin had no clinically meaningful effect on ABT-494 AUC0-24 and Cmax at steady-state.

4.1.2-15 Study M14-624--Phase 1 Extrinsic Factor PK Study

Title: A Phase 1 Study to Evaluate the Effect of Multiple Doses of ABT-494 on the Pharmacokinetics and Safety of Cytochrome P450 Substrates Midazolam, Caffeine, Warfarin, Omeprazole, and Dextromethorphan in Healthy Adult Subjects

Objectives: the effect of repeated doses of ABT-494 on the PK of specific substrates of CYP enzymes

Study population: healthy subjects (n=20)

Drug product: ABT-494 tablets, 30 mg (Bulk Product Lot Number 15-005424)

Study design: This single-center, multiple-dose, open-label, single-arm study evaluated the impact of co-administration of multiple-doses of ABT-494 on specific probe drug substrates for different CYP enzymes.

		Period 1			Period 2			
Drug	**CYP**	**Day 1**	**Day 2**	**Day 3 – 6**	**Day 1 – 10**	**Day 11**	**Day 12**	**Day 13 – 15**
ABT-494 (30 mg)					x	x	x	x
Midazolam (5 mg)	3A	x				x		
Caffeine (200 mg)	1A2		x				x	
Warfarin (10 mg) + vitamin K (10 mg)	2C9		x				x	
Omeprazole (40 mg)	2C19		x				x	
Dextromethorphan (30 mg)	2D6		x				x	

PK sampling:

Blood Samples for CYP Probe Substrates Assays

Midazolam: Period 1 Day 1 and Period 2 Day 11: predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing.

Caffeine: Period 1 Day 2 and Period 2 Day 12: predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, and 36 hours after dosing.

Omeprazole and 5-hydroxy-omeprazole (omeperazole metabolite): Period 1 Day 2 and Period 2 Day 12: predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours after dosing.

Dextromethorphan: Period 1 Day 2 and Period 2 Day 12: predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, and 72 hours after dosing.

Warfarin: Period 1 Day 2 and Period 2 Day 12: predose and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, and 96 hours after dosing.

Urine Samples for Dextromethorphan and Dextrorphan Assays

Urine was collected in containers without preservatives over the following intervals: 0 to 6 and 6 to 12 hours Period 1 Day 2 and Period 2 Day 12.

Results

Administration of multiple 30 mg QD doses of ABT-494 resulted in 26% decrease in AUC and C_{max} of midazolam, a very sensitive CYP3A substrate, and no clinically relevant effect on exposure of the sensitive in vivo probe substrates/markers for CYP1A2, CYP2C9, CYP2C19, and CYP2D6.

Table 4.1.2-51. Effect of ABT-494 on Pharmacokinetic Parameters of CYP Probe Substrates

Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Relative Bioavailability	
		Test	Reference	Point Estimate	90% Confidence Interval
	Midazolam (CYP3A Probe Substrate)				
Administration with ABT-494[a] vs. Administration without ABT-494[b]	C_{max}	22.2	30.1	0.737	0.680 – 0.799
	AUC_t	58.3	78.9	0.738	0.683 – 0.798
	AUC_∞	59.4	80.8	0.735	0.680 – 0.795
	Caffeine (CYP1A2 Probe Substrate)				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	C_{max}	4640	4100	1.131	1.051 – 1.216
	AUC_t	39700	32700	1.212	1.147 – 1.282
	AUC_∞	40700	33400	1.216	1.149 – 1.286
	S-Warfarin (CYP2C9 Probe Substrate)				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	C_{max}	665	624	1.065	1.018 – 1.114
	AUC_t	19900	18300	1.090	1.058 – 1.124
	AUC_∞	25000	22600	1.105	1.066 – 1.146
	R-Warfarin				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	C_{max}	682	644	1.060	1.025 – 1.096
	AUC_t	28700	26300	1.094	1.073 – 1.115
	AUC_∞	41600	36100	1.152	1.106 – 1.200
	Dextromethorphan (CYP2D6 Probe Substrate)				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	C_{max}	2.76	2.54	1.086	0.978 – 1.206
	AUC_t	34.6	31.5	1.101	0.974 – 1.246
	AUC_∞	41.4	38.6	1.073	0.947 – 1.217
	Omeprazole				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	C_{max}	580	667	0.870	0.719 – 1.052
	AUC_t	1440	1650	0.874	0.770 – 0.992
	AUC_∞	1510	1830	0.824	0.720 – 0.944

	5-Hydroxy-Omeprazole				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	C_{max}	374	405	0.922	0.798 – 1.066
	AUC_t	1130	1220	0.919	0.852 – 0.991
	AUC_∞	1140	1240	0.922	0.857 – 0.993
	Dextromethorphan to Dextrorphan Molar Urine Recovery Ratio (CYP2D6 Activity Marker)				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	Ratio	0.361	0.309	1.171	0.972 – 1.410
	5-Hydroxy-Omeprazole to Omeprazole AUC Ratio (CYP2C19 Activity Marker)				
Administration with ABT-494[c] vs. Administration without ABT-494[d]	AUC_t Ratio	0.851	0.808	1.053	0.974 – 1.138
	AUC_∞ Ratio	0.834	0.764	1.091	0.998 – 1.192

a. Period 2 Day 11 (P2D11): midazolam 5 mg + ABT-494 30 mg QD (test).

b. Period 1 Day 1 (P1D1): midazolam 5 mg (reference).

c. Period 2 Day 12 (P2D12): CYP cocktail (caffeine 200 mg + omeprazole 40 mg + warfarin 10 mg + dextromethorphan 30 mg) + ABT-494 30 mg QD (test).

d. Period 1 Day 2 (P1D2): CYP cocktail (caffeine 200 mg + omeprazole 40 mg + warfarin 10 mg + dextromethorphan 30 mg) (reference).

(Source: Table 9 of Study M14-624 CSR)

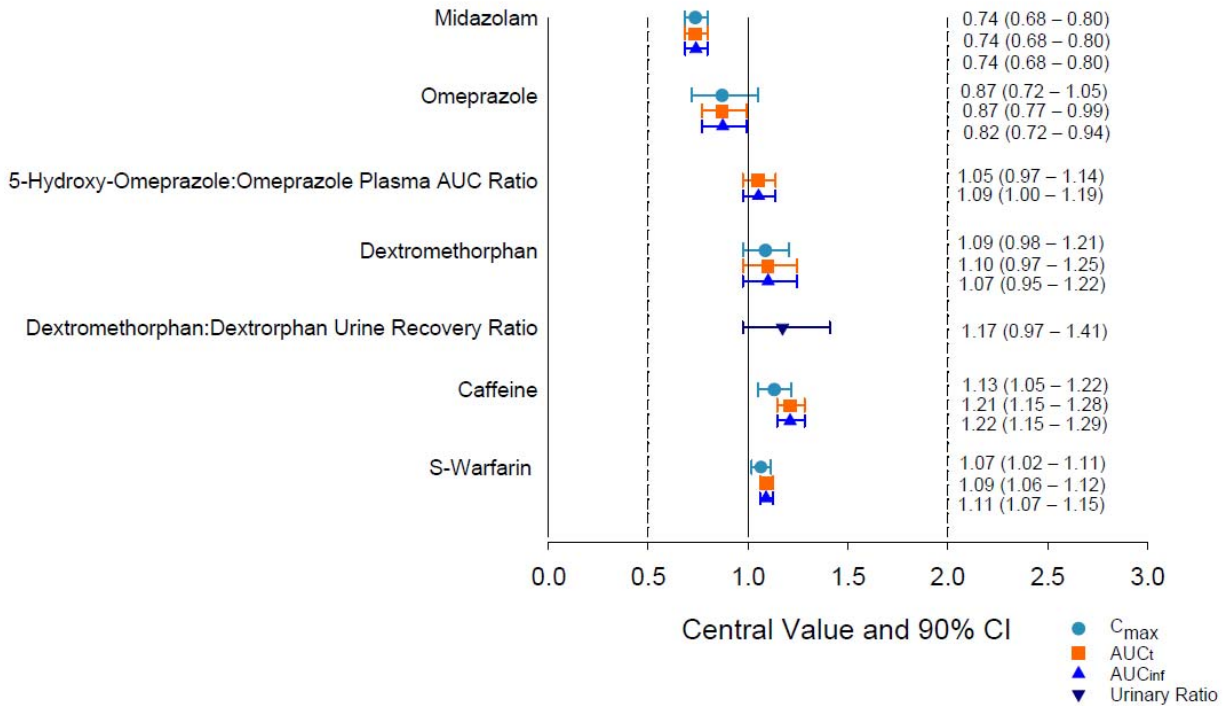


Figure 4.1.2-29. Point Estimate and 90% Confidence Intervals for the Effect of ABT-494 on PK Parameters of CYP Probe Substrates

(Source: Figure 6 of Study M14-624 CSR)

Midazolam PK

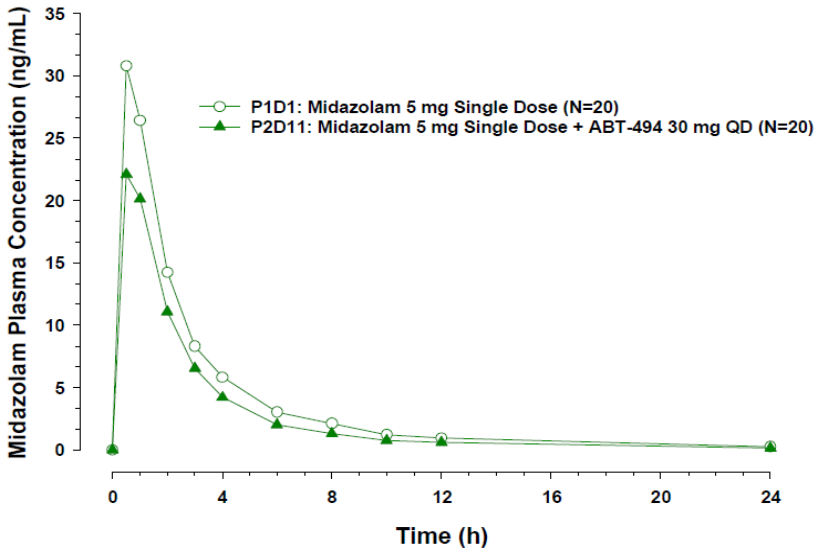


Figure 4.1.2-30. Mean Midazolam PK Profiles Following Administration of a Single Dose of 5 mg Midazolam Alone and with Repeated ABT-494 30 mg QD

(Source: Figure 1 of Study M14-624 CSR)

Table 4.1.2-52. PK Parameters of Midazolam Following Administration of a Single Dose of 5 mg Midazolam Alone and with Repeated ABT-494 30 mg QD

Pharmacokinetic Parameters (Units)	Period 1 Day 1 Midazolam 5 mg (N = 20)	Period 2 Day 11 Midazolam 5 mg + ABT-494 30 mg QD (N = 20)
C_{max} (ng/mL)	32.6 ± 14.1	23.9 ± 9.83
T_{max} (h)[a]	0.5 (0.5 – 1.0)	0.5 (0.5 – 1.0)
AUC_t (ng•h/mL)	87.5 ± 44.5	63.2 ± 29.6
AUC_∞ (ng•h/mL)	90.3 ± 49.0	64.6 ± 30.9
$t_{1/2}$ (h)[b]	4.65 (2.51)	4.08 (2.33)

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 4 of Study M14-624 CSR)

Caffeine PK

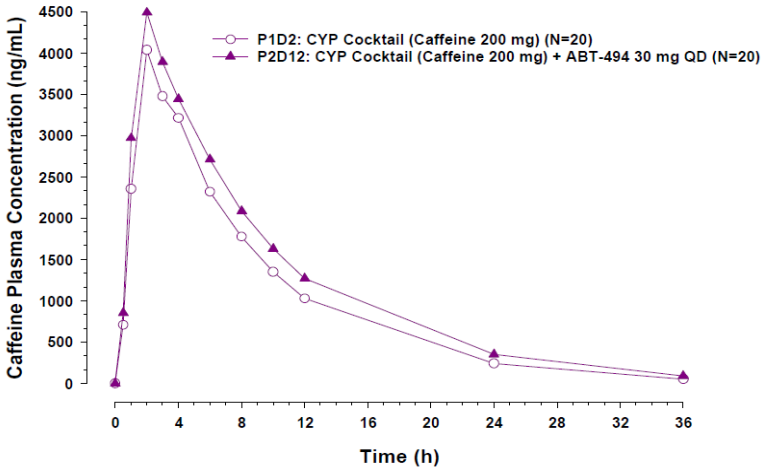


Figure 4.1.2-31. Mean Caffeine PK Profiles Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD
(Source: Figure 2 of Study M14-624 CSR)

Table 4.1.2-53. PK Parameters of Caffeine Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD

Pharmacokinetic Parameters (Units)	Period 1 Day 2 CYP Cocktail (Caffeine 200 mg) (N = 20)	Period 2 Day 12 CYP Cocktail (Caffeine 200 mg) + ABT-494 30 mg QD (N = 20)
C_{max} (ng/mL)	4190 ± 826	4790 ± 1230
T_{max} (h)[a]	2.0 (1.0 to 3.0)	2.0 (1.0 to 4.0)
AUC_t (ng•h/mL)	35500 ± 13900	42500 ± 16100
AUC_∞ (ng•h/mL)	36200 ± 14300	43800 ± 17100
$t_{1/2}$ (h)[b]	4.52 (1.50)	5.28 (1.50)

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 5 of Study M14-624 CSR)

Warfarin PK

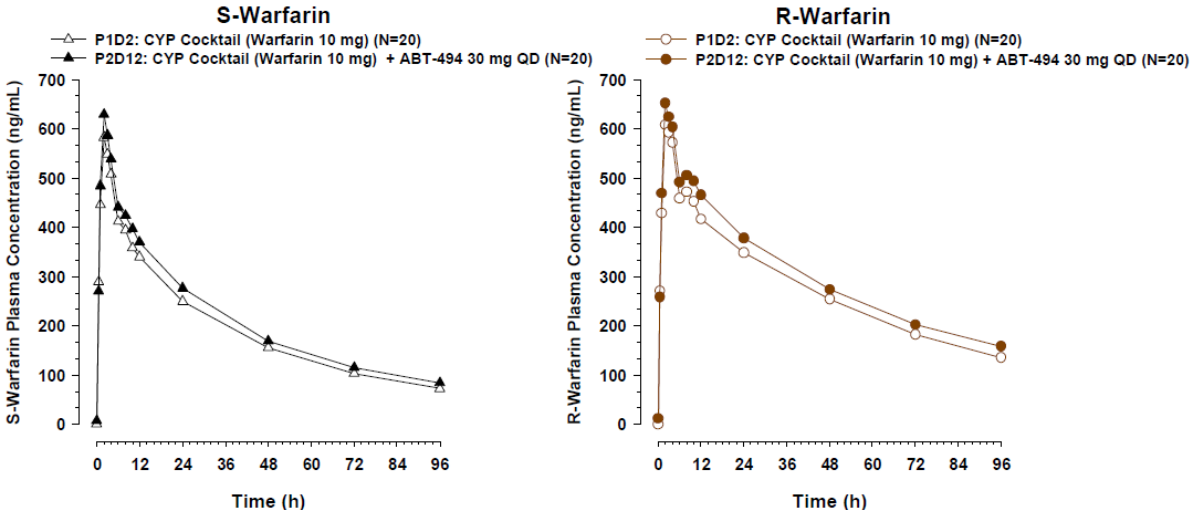


Figure 4.1.2-32. Mean S-Warfarin and R-Warfarin PK Profiles Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD
(Source: Figure 3 of Study M14-624 CSR)

Table 4.1.2-54. PK Parameters of Warfarin Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD

Pharmacokinetic Parameters (Units)	Period 1 Day 2 CYP Cocktail (Warfarin 10 mg) + (N = 20)		Period 2 Day 12 CYP Cocktail (Warfarin 10 mg) + ABT-494 30 mg QD (N = 20)	
	S-Warfarin	R-Warfarin	S-Warfarin	R-Warfarin
C_{max} (ng/mL)	630 ± 84.4	649 ± 88.1	675 ± 121	690 ± 109
T_{max} (h)[a]	2.0 (0.5 – 4.0)	2.0 (0.5 – 4.0)	2.0 (0.5 – 3.0)	2.0 (0.5 – 3.0)
AUC_t (ng•h/mL)	18600 ± 3860	26600 ± 4170	20400 ± 5010	29000 ± 4330
AUC_∞ (ng•h/mL)	23800 ± 9030	37000 ± 8540[b]	26700 ± 11800	42700 ± 10400[b]
$t_{1/2}$ (h)[c]	38.6 (8.80)	49.1 (9.52)	39.7 (10.1)	54.4 (11.6)

a. Median (minimum through maximum).

b. The percentage of the contribution of AUC_{ext} to the overall AUC_∞ exceeded 20% for R-warfarin in the majority of subjects.

c. Harmonic mean (pseudo-standard deviation).

(Source: Table 6 of Study M14-624 CSR)

Dextromethorphan PK

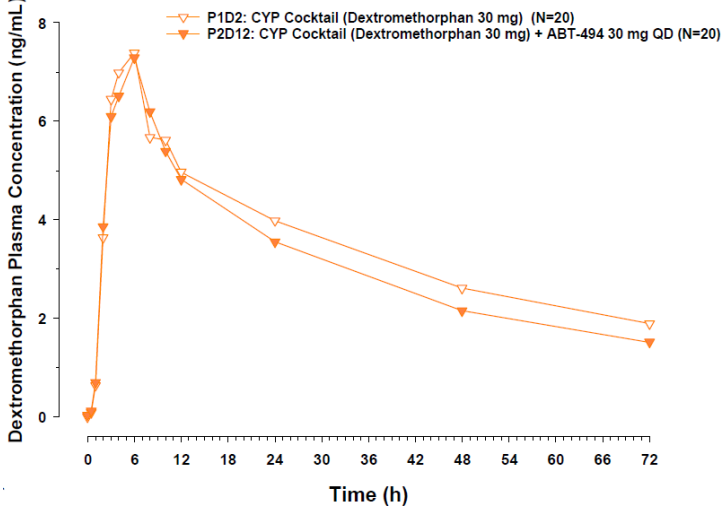


Figure 4.1.2-33. Mean Dextromethorphan PK Profiles Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD

(Source: Figure 4 of Study M14-624 CSR)

Table 4.1.2-55. PK Parameters of Dextromethorphan Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD

Pharmacokinetic Parameters (Units)	Period 1 Day 2 CYP Cocktail (Dextromethorphan 30 mg) (N = 20)	Period 2 Day 12 CYP Cocktail (Dextromethorphan 30 mg) + ABT-494 30 mg QD (N = 20)
C_{max} (ng/mL)	7.77 ± 10.1	7.64 ± 9.54
T_{max} (h)[a]	3.5 (2.0 – 8.0)	3.5 (2.0 – 6.0)
AUC_t (ng•h/mL)	250 ± 397	225 ± 347
AUC_∞ (ng•h/mL)	403 ± 706	328 ± 552
$t_{1/2}$ (h)[b]	6.82 (4.68)	7.26 (5.08)
Dextromethorphan to Dextrorphan Molar Urinary Ratio[a,c]	0.263 (0.0190 – 116)	0.263 (0.0289 – 90.9)

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

c. N = 17; three subjects had no detectable levels of dextrorphan in urine.

(Source: Table 7 of Study M14-624 CSR)

PK of Omeprazole and its metabolite 5-Hydroxy-Omeprazole

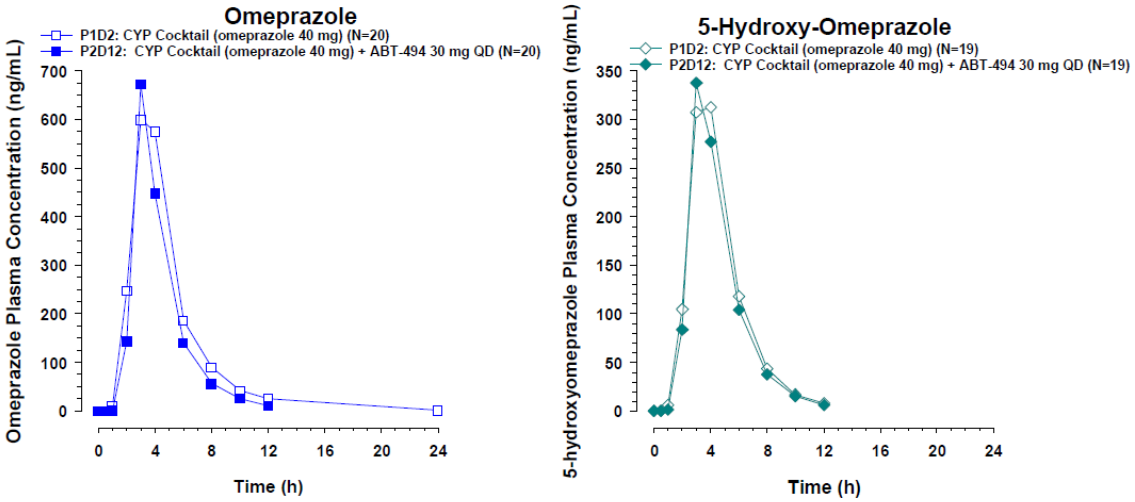


Figure 4.1.2-34. Mean Omeprazole and 5-Hydroxy-Omeprazole PK Profiles Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD
(Source: Figure 5 of Study M14-624 CSR)

Table 4.1.2-56. PK Parameters of Omeprazole and 5-Hydroxy-Omeprazole Following Administration of CYP Cocktail Alone and with Repeated ABT-494 30 mg QD

Pharmacokinetic Parameters (Units)	Period 1 Day 2 CYP Cocktail (Omeprazole 40 mg) (N = 20)	Period 2 Day 12 CYP Cocktail (Omeprazole 40 mg) + ABT-494 30 mg QD (N = 20)
	Omeprazole	
C_{max} (ng/mL)	855 ± 544	731 ± 484
T_{max} (h)[a]	3.0 (2.0 – 4.0)	3.0 (2.0 – 6.0)
AUC_t (ng•h/mL)	2520 ± 2750	2000 ± 1820
AUC_∞ (ng•h/mL)	2890 ± 2870	2080 ± 1860
$t_{1/2}$ (h)[b]	1.13 (0.400)	1.14 (0.386)
	5-Hydroxy-Omeprazole[d]	
C_{max} (ng/mL)	435 ± 155	389 ± 116
T_{max} (h)[a]	3.0 (2.0 – 6.0)	3.0 (2.0 – 6.0)
AUC_t (ng•h/mL)	1270 ± 359	1160 ± 292
AUC_∞ (ng•h/mL)	1290 ± 364	1180 ± 302
$t_{1/2}$ (h)[b]	1.36 (0.293)	1.37 (0.319)
5-hydroxy-omeprazole to omeprazole AUC_t Ratio[a,c]	0.921 (0.192 – 1.91)	1.04 (0.324 – 1.74)
5-hydroxy-omeprazole to omeprazole AUC_∞ Ratio[a,c]	0.708 (0.194 – 1.60)	0.999 (0.339 – 1.74)

a. Median (minimum through maximum).
b. Harmonic mean (pseudo-standard deviation).
c. Ratio of metabolite (5-hydroxy-omeprazole) AUC to parent drug (omeprazole) AUC.
d. N = 19 for 5-hydroxy-omeprazole. Plasma concentrations of 5-hydroxy-omeprazole could not be measured for Subject 113.

(Source: Table 8 of Study M14-624 CSR)

Conclusions

- Administration of multiple 30 mg QD doses of ABT-494 resulted in 26% decrease in AUC and C_{max} of midazolam, a very sensitive CYP3A substrate, and no clinically relevant effect on exposure of the sensitive in vivo probe substrates/markers for CYP1A2, CYP2C9, CYP2C19, and CYP2D6.

4.1.2-16 Study M14-625--Phase 1 Extrinsic Factor PK Study

Title: A Phase 1 Study to Assess the Effect of Multiple Doses of ABT-494 on the Pharmacokinetics of Ethinylestradiol and Levonorgestrel

Objectives: the effect of multiple doses of upadacitinib on the pharmacokinetics of ethinylestradiol and levonorgestrel in healthy female subjects

Study populations: healthy female subjects (n=20)

Drug product: Upadacitinib ER tablets 30 mg (ER8) (Bulk Product Lot Number 15-005425)

Study design: This was a Phase 1, single center, open-label study.

Initial Confinement	**Period 1**		**Period 2**			
Day –1	**Day 1**	**Days 2 – 5**	**Days 1 – 11**	**Day 12**	**Days 13 – 14**	**Days 15 – 16**
	Ethinylestradiol/ levonorgestrel 0.03/0.15 mg			Ethinylestradiol/levonorgestrel 0.03/0.15 mg		
			Upadacitinib 30 mg QD			

PK sampling:
Blood samples for ethinylestradiol and levonorgestrel were collected pre-dose (0 hour) and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 48, 72 and 96 hours.

Results
Administration of multiple doses of upadactinib 30 mg QD does not have clinical meaningful effect on plasma exposures of ethinylestradiol or levonorgestrel.

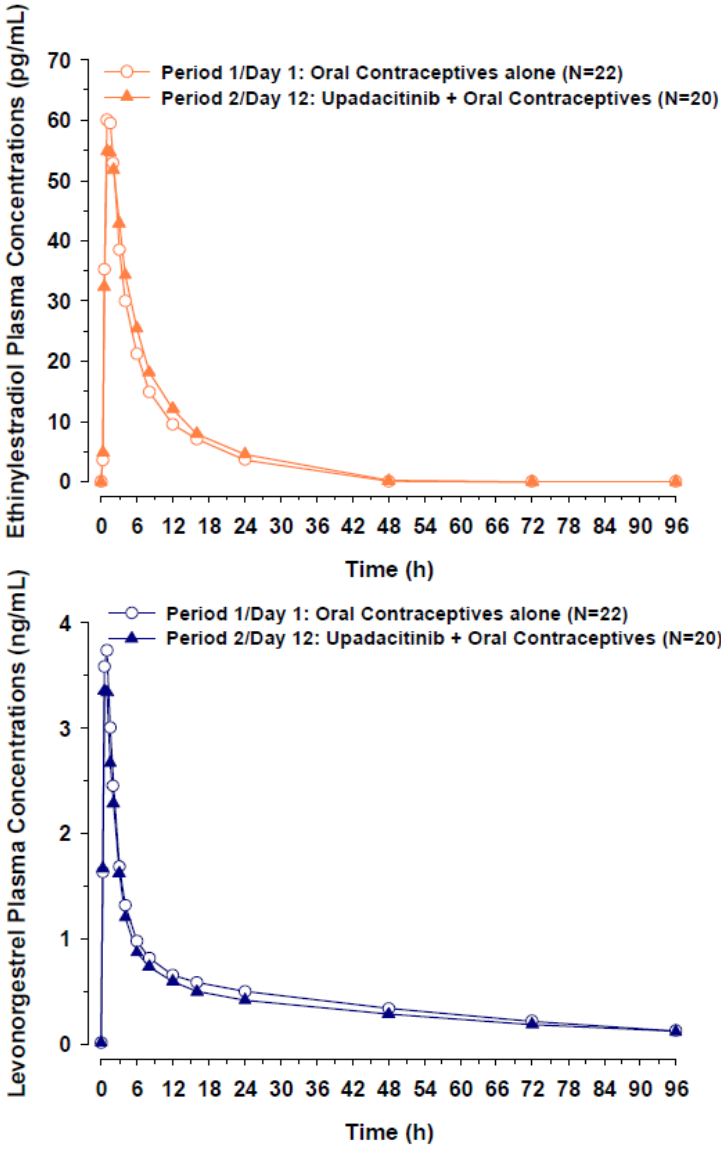


Figure 4.1.2-35. Mean Ethinylestradiol and Levonorgestrel PK Profiles Following Administration of Single Doses of 0.03 mg Ethinylestradiol and 0.15 mg Levonorgestrel Alone and With Repeated Administration of Upadacitinib 30 mg QD

(Source: Figure 2 of Study M14-625 CSR)

Table 4.1.2-57. PK Parameters of Ethinylestradiol and Levonorgestrel Following Administration of Single Doses of 0.03 mg Ethinylestradiol and 0.15 mg Levonorgestrel Alone and With Repeated Administration of Upadacitinib 30 mg QD

Pharmacokinetic Parameters (units)	Period 1/Day 1: Ethinylestradiol/Levonorgestrel 0.03/0.15 mg (N = 22)	Period 2/Day 12: Upadacitinib 30 mg QD + Ethinylestradiol/Levonorgestrel 0.03/0.15 mg (N = 20)
	Ethinylestradiol	
C_{max} (pg/mL)	62.7 ± 24.3	59.0 ± 20.5
T_{max}[a] (h)	1.5 (1.0 to 2.0)	1.5 (1.0 to 3.0)
AUC_t (pg•h/mL)	378 ± 154	426 ± 137
AUC_{inf} (pg•h/mL)	441 ± 193	492 ± 166
$t_{1/2}$[b] (h)	7.01 (3.39)	7.65 (2.36)
	Levonorgestrel	
C_{max} (ng/mL)	3.94 ± 1.38	3.68 ± 1.05
T_{max}[a] (h)	0.8 (0.5 to 2.0)	0.8 (0.5 to 2.0)
AUC_t (ng•h/mL)	43.0 ± 18.4	38.7 ± 12.1
AUC_{inf} (ng•h/mL)	51.7 ± 22.0	49.5 ± 20.4
$t_{1/2}$[b] (h)	33.1 (12.4)	37.1 (15.1)

a. Median (minimum to maximum).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 3 of Study M14-625 CSR)

Table 4.1.2-58. Effect of Upadacitinib 30 mg QD on Ethinylestradiol and Levonorgestrel PK

Compound	Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
			Test	Reference	Point Estimate	90% Confidence Interval
Ethinylestradiol	Period 2/ Day 12 vs. Period 1/ Day 1	C_{max}	55.3	57.9	0.955	0.893, 1.022
		AUC_t	390	348	1.121	1.043, 1.205
		AUC_{inf}	445	402	1.108	1.036, 1.186
Levonorgestrel	Period 2/ Day 12 vs. Period 1/ Day 1	C_{max}	3.59	3.74	0.961	0.873, 1.059
		AUC_t	36.3	39.6	0.916	0.828, 1.014
		AUC_{inf}	45.5	47.6	0.955	0.851, 1.071

Period 2/Day 12: Upadacitinib 30 mg QD + ethinylestradiol/levonorgestrel 0.03/0.15 mg (Test)

Period 1/Day 1: Ethinylestradiol/levonorgestrel 0.03/0.15 mg (Reference)

(Source: Table 4 of Study M14-625 CSR)

Conclusions

- Administration of multiple doses of upadactinib 30 mg QD does not have clinical meaningful effect on plasma exposures of ethinylestradiol or levonorgestrel.

4.1.2-17 Study M17-221--Phase 1 Extrinsic Factor PK Study

Title: A Phase 1 Study to Evaluate the Effect of Multiple Doses of Upadacitinib on the Pharmacokinetics of Bupropion in Healthy Adult Subjects

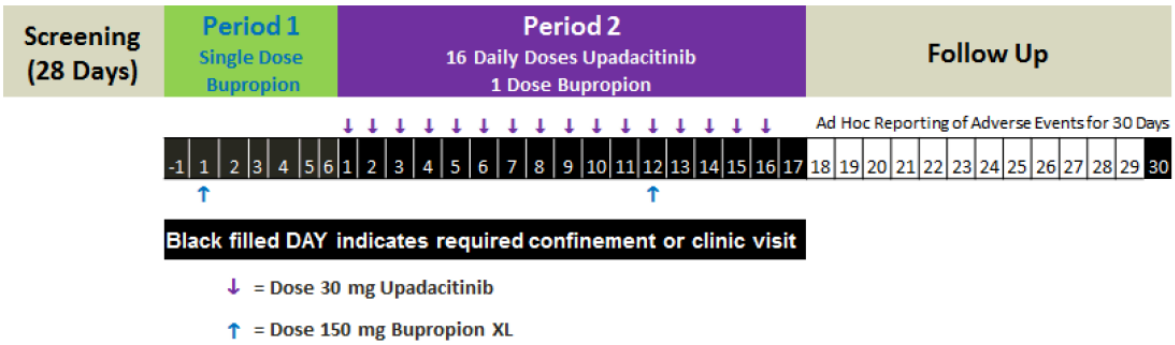
Objectives: the effect of multiple doses of upadacitinib on PK bupropion, a probe CYP2B6 substrate

Study population: healthy subjects (n=22)

Drug product: Upadacitinib ER tablet 15 mg (ER7) (Bulk Product Lot Number 16-005249)

Study design: This Phase 1, single-center, multiple-dose, open-label, two-period, one sequence study was conducted in 22 healthy adult male and female subjects.

- Period 1: Bupropion 150 mg single dose was administered under fasting conditions on Day 1.
- Period 2: Upadacitinib 30 mg (2 × 15 mg ER tablets) was administered in the morning under non-fasting conditions on Days 1 - 11 and Days 13 - 16. Bupropion 150 mg single dose was co-administered with upadacitinib 30 mg in the morning under fasting conditions on Day 12.



PK sampling:
Blood samples for assay of bupropion and hydroxybupropion (metabolite of bupropion formed mainly through CYP2B6) were collected pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 36, 48, 72, 96 and 120 hours after the morning dose on Day 1 in Period 1 and on Day 12 in Period 2.

Blood samples for assay of upadacitinib were collected pre-dose (0 hour) and at 1.5, 3, 4, 6, 8, 12 and 24 hours after the morning dose on Day 11 in Period 2.

Results
Upadacitinib had no clinically relevant impact on bupropion exposure, suggesting that 30 mg upadacitinib QD dose does not induce CYP2B6 activity.

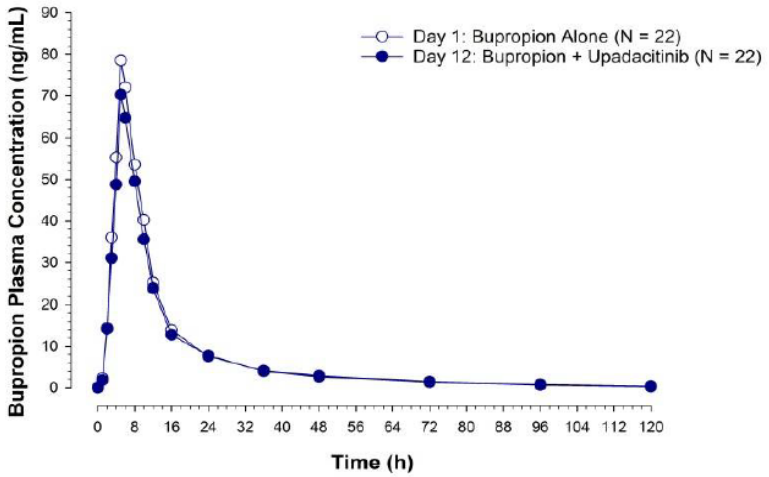


Figure 4.1.2-36. Mean Bupropion PK Profiles Following Administration of Bupropion Alone and With a Multiple-Dose Regimen of Upadacitinib 30 mg QD
(Source: Figure 2 of Study M17-221 CSR)

Table 4.1.2-59. PK Parameters of Bupropion Following Administration of Bupropion Alone and After Multiple Doses of Upadacitinib 30 mg QD Doses

Pharmacokinetic Parameters (units)	Period 1 – Day 1: Bupropion 150 mg Alone (N = 22)	Period 2 – Day 12 Upadacitinib 30 mg QD + Bupropion 150 mg (N = 22)
	Bupropion	
C_{max} (ng/mL)	83.5 ± 26.2	72.9 ± 20.8
T_{max}[a] (h)	5.0 (3.0 to 10.0)	5.0 (3.0 to 8.0)
AUC_t (ng•h/mL)	869 ± 271	795 ± 210
AUC_{inf} (ng•h/mL)	898 ± 281	826 ± 215
$t_{1/2}$[b] (h)	23.3 ± 10.4	23.8 ± 8.26

a. Median (minimum through maximum).

b. Harmonic mean (pseudo-standard deviation).

(Source: Table 4 of Study M17-221 CSR)

Table 4.1.2-60. Point Estimates and 90% Confidence Intervals for the Pharmacokinetic Parameters of Bupropion when Administered on Day 12 of 16-day Multiple-Dose Regimen of Upadacitinib 30 mg Relative to when Administered Alone

Compound	Regimens Test vs. Reference	Pharmacokinetic Parameter	Central Value		Ratio of Central Values	
			Test	Reference	Point Estimate	90% Confidence Interval
Bupropion	Period 2, Day 12 vs. Period 1 Day 1[a]	C_{max}	69.3	79.8	0.868	0.787, 0.957
		AUC_t	763	830	0.919	0.868, 0.974
		AUC_{inf}	794	859	0.924	0.873, 0.979

a. Period 2, Day 12: Upadacitinib 30 mg QD + Bupropion 150 mg single dose (Test) versus Period 1, Day 1: Bupropion 150 mg single dose (Reference).

(Source: Table 5 of Study M17-221 CSR)

Conclusions

- Administration of multiple doses of upadactinib 30 mg QD does not have clinical meaningful effect on plasma exposures of ethinylestradiol or levonorgestrel.

4.1.2-18 Study M13-537--Phase 2 Dose-Ranging Study

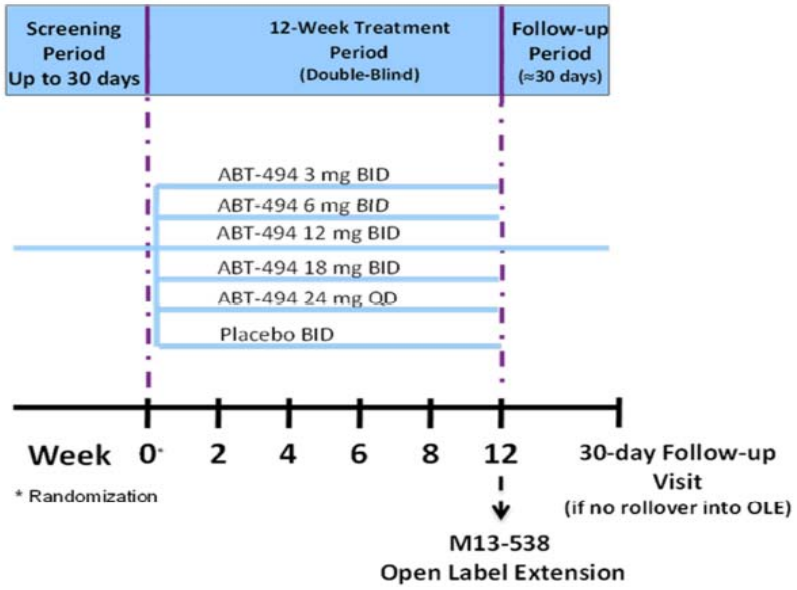
Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Investigate the Safety and Efficacy of ABT-494 with Background Methotrexate (MTX) in Subjects with Active Rheumatoid Arthritis (RA) Who Have Had an Inadequate Response to MTX Alone

Objectives: efficacy and safety

Study population: subjects with moderately to severely active RA who had shown inadequate response to MTX and were naïve to biologic therapy (n=299, (50 placebo; 249 ABT-494))

Drug product:
ABT-494 3 mg IR capsules for oral administration; Bulk lot number: 13-004590; 15-000327
ABT-494 12 mg IR capsules for oral administration; Bulk lot number: 13-004770; 15-000395

Study design: This was a Phase 2, randomized, double-blind, parallel-group, placebo-controlled multicenter study comparing the safety and efficacy of multiple doses of ABT-494 versus placebo administered for 12 weeks in subjects with moderately to severely active RA who had shown inadequate response to MTX and were naïve to biologic therapy. Subjects were randomized in a 1:1:1:1:1:1 ratio to 1 of 6 treatment arms. The primary efficacy endpoint was the ACR20 response rate at Week 12.



PK sampling:

- PK trough (prior to morning dose) samples were collected at each visit.
- If a visit could not be scheduled in the morning, the subject was instructed to take the morning dose at the regular schedule, and the PK sample was to be collected at any time during the visit, preferably within 1 to 8 hours after dose.
- For ~30% of subjects, in addition to trough PK samples at each visit, PK samples were collected on Day 1 (Baseline) and Week 8 at 1, 2, and 3 hours post-morning dose.

Results

Efficacy:

Table 4.1.2-61. ACR20 Response Rates at Week 12 (mITT Population; LOCF)

		ABT-494				
Variable at Week 12	**Placebo**	**3 mg BID**	**6 mg BID**	**12 mg BID**	**18 mg BID**	**24 mg QD**
ACR20 response rate						
N	46	48	49	49	47	49
Responder, n (%)	23 (50.0)	31 (64.6)	36 (73.5)	40 (81.6)	36 (76.6)	40 (81.6)
P value[a]	-	n.s.	0.018	0.001	0.008	0.001

n.s. = not statistically significant ($P > 0.05$)

a. *P* value for comparison between ACR20 response rate for treatment group and placebo group was calculated using a chi-square test or Fisher's exact test (if ≥ 20% of the cells had expected counts less than 5).

Note: The primary analysis was performed using LOCF missing data imputation but with the as-observed approach for joints not assessed and replaced (i.e., not imputed).

(Source: Table 9 of Study M13-537 CSR)

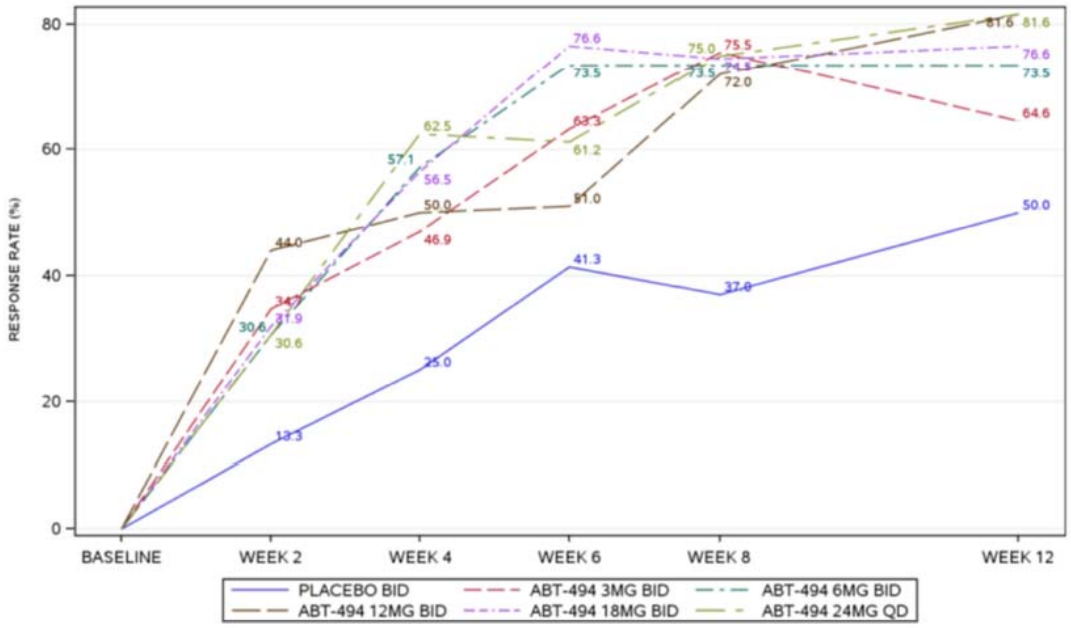


Figure 4.1.2-37. ACR20 Response Rates from Baseline Through Week 12 (mITT Population; LOCF)
(Source: Figure 3 of Study M13-537 CSR)

PK
ABT-494 mean (SD) plasma concentrations are summarized by dose group and time window in the table as below. The drug concentration levels were also included in ABT-494 exposure-response analyses.

Table 4.1.2-62. ABT-494 Plasma Concentrations Categorized by Treatment and Time from Previous Dose

ABT-494 Dose Group	Time Categories (h)	Number of Samples	Mean (SD)	
			Time from Previous ABT-494 Dose (h)	ABT-494 Concentration (ng/mL)
3 mg BID	> 0 – 2	29	1.48 (0.65)	16.6 (11.9)
	> 2 – 6	26	3.05 (0.48)	18.3 (11.2)
	> 6 – 12	25	10.1 (1.75)	5.00 (4.82)
	> 12 – 16	39	13.9 (1.10)	3.24 (4.16)
	> 16 – 24	14	18.2 (1.65)	1.37 (0.77)
	> 24	3	33.0 (6.63)	1.09 (1.29)
6 mg BID	> 0 – 2	29	1.47 (0.66)	32.8 (21.5)
	> 2 – 6	27	2.95 (0.53)	33.7 (13.4)
	> 6 – 12	24	10.9 (1.01)	8.58 (9.58)
	> 12 – 16	33	14.0 (1.07)	4.44 (3.53)
	> 16 – 24	12	18.7 (2.06)	6.12 (5.88)
	> 24	7	35.1 (4.46)	5.99 (5.41)
12 mg BID	> 0 – 2	33	1.36 (0.71)	59.3 (46.7)
	> 2 – 6	29	3.14 (0.56)	67.8 (39.0)
	> 6 – 12	28	10.9 (1.03)	18.6 (20.1)
	> 12 – 16	36	13.7 (1.03)	12.0 (19.6)
	> 16 – 24	9	18.5 (2.19)	21.6 (28.8)
	> 24	3	35.6 (2.25)	16.8 (17.9)
18 mg BID	> 0 – 2	30	1.25 (0.70)	61.6 (64.0)
	> 2 – 6	28	3.42 (0.88)	74.1 (46.8)
	> 6 – 12	22	10.5 (1.40)	23.5 (17.8)
	> 12 – 16	35	14.0 (1.13)	20.0 (30.7)
	> 16 – 24	9	17.5 (1.06)	18.7 (21.1)
	> 24	3	35.7 (1.15)	4.51 (1.56)
24 mg QD	> 0 – 2	32	1.46 (0.63)	94.2 (86.9)
	> 2 – 6	27	3.25 (0.73)	99.4 (68.7)
	> 6 – 12	21	10.7 (1.14)	8.44 (22.2)
	> 12 – 16	35	13.9 (1.05)	7.58 (29.6)
	> 16 – 24	6	17.0 (1.16)	17.2 (42.1)
	> 24	2	26.3 (1.06)	35.7 (48.6)

(Source: Table 24 of Study M13-537 CSR)

Table 4.1.2-63. ABT-494 Cmax and Tmax on Day 1 and at Week 8 in Subjects Who Participated in the Intensive PK Sampling Cohort

ABT-494 Dose Group	Day 1			Week 8		
	N	T_{max} (h) Median (range)	C_{max} (ng/mL) Mean (SD)	N	T_{max} (h) Median (range)	C_{max} (ng/mL) Mean (SD)
3 mg BID	23	1.0 (1.0 – 3.0)	30.6 (11.2)	23	1.0 (0.0 – 3.0)	23.7 (9.91)
6 mg BID	22	1.0 (1.0 – 3.0)	46.6 (14.9)	20	1.0 (0.0 – 3.0)	54.1 (13.7)
12 mg BID	23	2.0 (1.0 – 3.0)	112 (39.4)	24	1.0 (0.0 – 3.0)	105 (45.5)
18 mg BID	20	1.0 (1.0 – 3.0)	139 (49.9)	18	2.0 (1.0 – 3.0)	135 (58.0)
24 mg QD	22	1.0 (1.0 – 3.0)	201 (65.2)	19	1.0 (1.0 – 3.0)	172 (58.5)

(Source: Table 25 of Study M13-537 CSR)

Conclusions

- While the ACR20 response rates at Week 12 with 12 mg BID were slightly higher as compared to 6 mg BID, both 6 mg BID and 12 mg BID were significantly higher than placebo and no additional increase in ACR20 response was observed with doses higher than 12 mg BID.

4.1.2-19 Study M13-550--Phase 2 Dose-Ranging Study

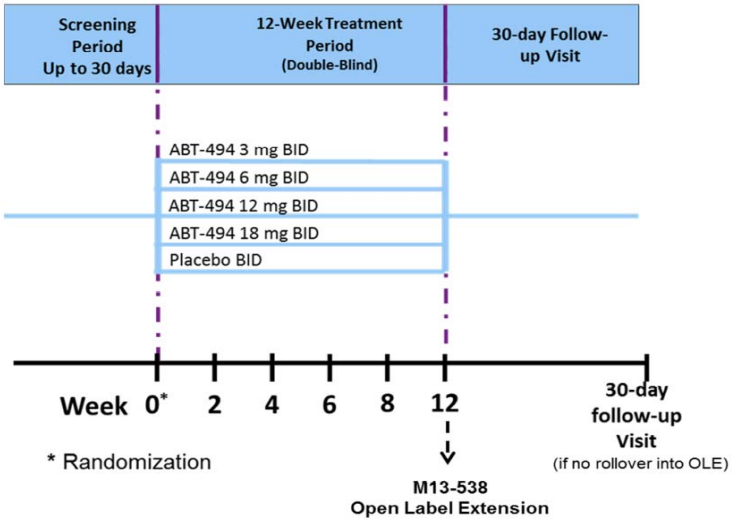
Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study to Investigate the Safety and Efficacy of ABT-494 Given with Methotrexate (MTX) in Subjects with Moderately to Severely Active Rheumatoid Arthritis (RA) Who Have Had an Inadequate Response or Intolerance to Anti-TNF Biologic Therapy

Objectives: efficacy and safety

Study population: subjects with moderately to severely active RA on stable background MTX therapy who had shown an inadequate response or intolerance to anti-TNF biologic therapy (n=276 (56 placebo; 220 ABT-494))

Drug product:
ABT-494 3 mg IR capsules for oral administration; Bulk lot number: 13-003339; 13-004590.
ABT-494 12 mg IR capsules for oral administration; Bulk lot number: 13-003488; 13-004770

Study design:
This was a Phase 2, randomized, double-blind, parallel-group, placebo-controlled multicenter study comparing the safety and efficacy of multiple doses of ABT-494 versus placebo administered for 12 weeks in subjects with moderately to severely active RA who had an inadequate response or intolerance to anti-TNF biologic therapy. Study drug was to be taken BID orally for 12 weeks. The primary endpoint was the ACR20 response rate at Week 12.



PK sampling:

- PK trough (prior to morning dose) samples were collected at each visit.
- If a visit could not be scheduled in the morning, the subject was instructed to take the morning dose at the regular schedule, and the PK sample was to be collected at any time during the visit, preferably within 1 to 8 hours after dose.

- For ~30% of subjects, in addition to trough PK samples at each visit, PK samples were collected on Day 1 (Baseline) and Week 8 at 1, 2, and 3 hours post-morning dose.

Results

Efficacy

Table 4.1.2-64. ACR20 Response Rates at Week 12 (mITT Population; LOCF)

		ABT-494			
Variable at Week 12	**Placebo**	**3 mg BID**	**6 mg BID**	**12 mg BID**	**18 mg BID**
ACR20 response rate					
N	54	54	52	55	55
Responder, n (%)	19 (35.2)	30 (55.6)	33 (63.5)	40 (72.7)	39 (70.9)
P value[a]	--	0.033	0.004	< 0.001	< 0.001

a. Comparison between ACR20 response rate for treatment group and placebo group using a chi-square test or Fisher's exact test (if 20% of the cells had expected counts less than 5).

Note: The primary analysis was performed using LOCF missing data imputation but with the as observed approach for joints not assessed and replaced (i.e., not imputed).

(Source: Table 9 of Study M13-550 CSR)

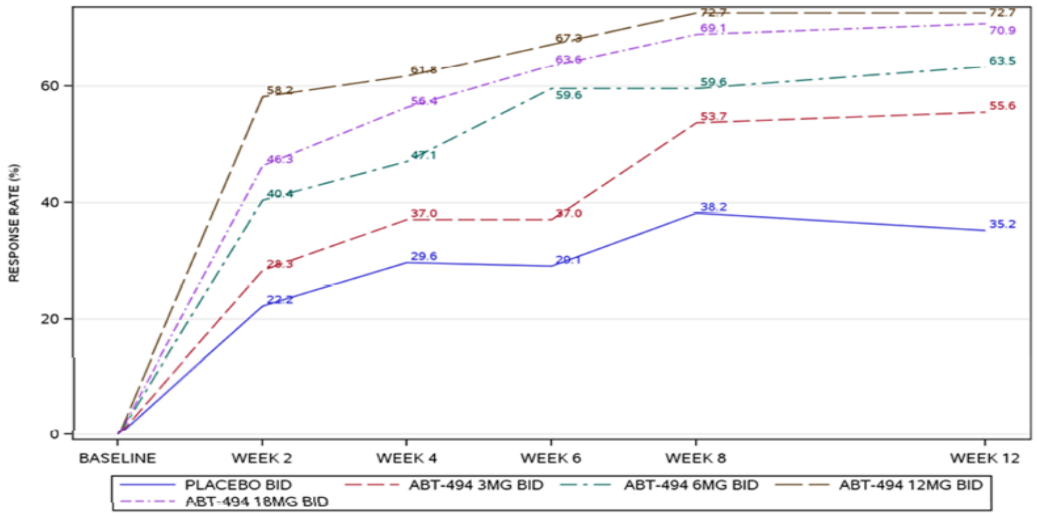


Figure 4.1.2-38. ACR20 Response Rates from Baseline through Week 12 (mITT Population; LOCF)

(Source: Figure 3 of Study M13-550 CSR)

PK

ABT-494 mean (SD) plasma concentrations are summarized by dose group and time window in the table as below.

Table 4.1.2-65. ABT-494 Plasma Concentrations Categorized by Treatment and Time from Previous Dose

ABT-494 Dose Group	Time Categories (h)	Number of Samples	Mean (SD)	
			Time from Previous ABT-494 Dose (h)	ABT-494 Concentration (ng/mL)
3 mg BID	> 0 – 2	27	1.56 (0.60)	19.5 (11.0)
	> 2 – 6	26	3.13 (0.61)	15.8 (7.02)
	> 6 – 12	31	10.3 (1.34)	4.48 (6.16)
	> 12 – 16	38	13.7 (0.89)	4.18 (5.03)
	> 16 – 24	10	17.1 (0.84)	4.49 (6.45)
	> 24	5	34.2 (6.33)	2.64 (3.07)
6 mg BID	> 0 – 2	23	1.50 (0.59)	30.6 (16.4)
	> 2 – 6	24	3.13 (0.61)	27.8 (11.7)
	> 6 – 12	25	10.2 (1.38)	9.44 (11.3)
	> 12 – 16	37	13.6 (1.03)	6.88 (10.9)
	> 16 – 24	12	18.4 (2.40)	4.84 (6.23)
	> 24	2	30.1 (5.89)	10.6 (14.1)
12 mg BID	> 0 – 2	33	1.71 (0.46)	72.6 (39.6)
	> 2 – 6	34	3.09 (0.45)	56.2 (30.5)
	> 6 – 12	28	10.6 (1.23)	13.7 (17.5)
	> 12 – 16	36	13.9 (1.10)	13.8 (19.1)
	> 16 – 24	16	17.5 (1.35)	7.58 (5.64)
	> 24	3	33.0 (6.48)	3.73 (4.11)
18 mg BID	> 0 – 2	30	1.73 (0.46)	103 (56.9)
	> 2 – 6	28	3.16 (0.71)	70.3 (39.3)
	> 6 – 12	31	10.2 (1.58)	25.5 (32.8)
	> 12 – 16	43	13.8 (1.03)	24.8 (39.5)
	> 16 – 24	17	18.1 (2.01)	15.7 (21.3)
	> 24	6	30.7 (5.78)	8.75 (9.65)

(Source: Table 23 of Study M13-550 CSR)

Table 4.1.2-66. ABT-494 Cmax and Tmax on Day 1 and at Week 8 in Subjects Who Participated in the Intensive PK Sampling Cohorts

ABT-494 Dose Group	Day 1			Week 8		
	N	T_{max} (h) Median (Range)	C_{max} (ng/mL) Mean (SD)	N	T_{max} (h) Median (Range)	C_{max} (ng/mL) Mean (SD)
3 mg BID	30	1.0 (0.0 – 3.0)	23.4 (8.78)	25	1.0 (0.0 – 3.0)	25.6 (11.2)
6 mg BID	25	1.0 (0.0 – 3.0)	41.9 (16.7)	22	1.0 (0.0 – 3.0)	46.5 (14.5)
12 mg BID	32	1.0 (1.0 – 3.0)	99.0 (37.9)	30	1.0 (0.0 – 3.0)	87.3 (39.0)
18 mg BID	33	1.0 (1.0 – 3.0)	148 (58.5)	29	1.0 (0.0 – 2.0)	137 (73.2)

(Source: Table 24 of Study M13-550 CSR)

Conclusions

- While the ACR20 response rates at Week 12 with 12 mg BID were slightly higher as compared to 6 mg BID, both 6 mg BID and 12 mg BID were significantly higher than placebo and no additional increase in ACR20 response was observed with doses higher than 12 mg BID.

4.1.2-20 Study M14-663--Phase 2 Dose-Ranging Study (Japan)

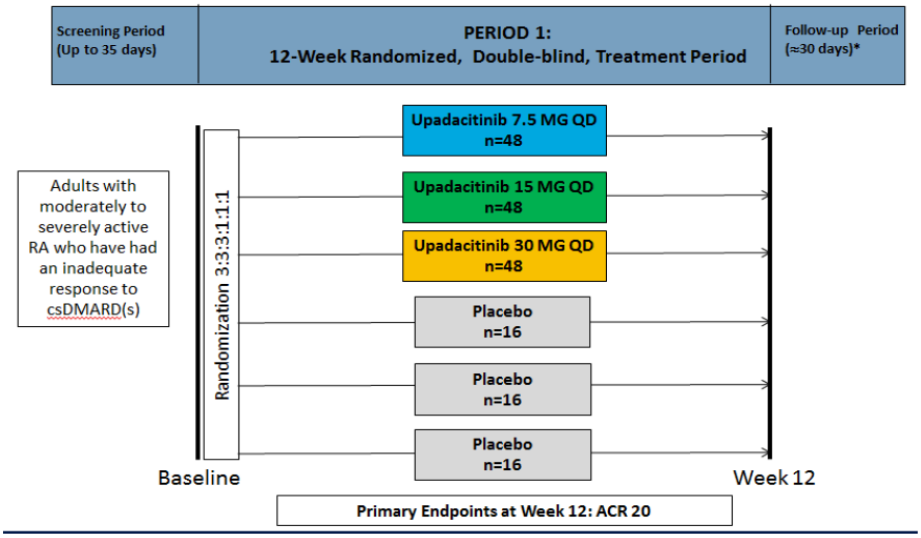
Title: A Phase 2b/3, Randomized, Double-Blind Study Comparing Upadacitinib (ABT-494) to Placebo in Japanese Subjects with Moderately to Severely Active Rheumatoid Arthritis Who Are on a Stable Dose of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs (csDMARDs) and Have an Inadequate Response to csDMARDs

Objectives: efficacy, safety and tolerability

Study population: Japanese subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs (n=197)

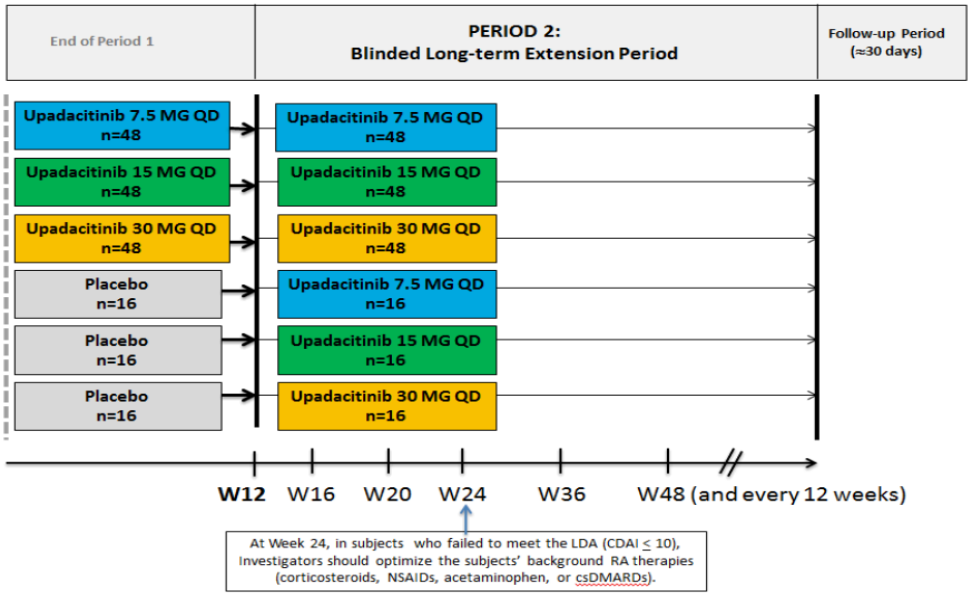
Drug product:
Upadacitinib 7.5 mg ER tablets (bulk lot number: 15-006685, 16-001353, 16-004623)
Upadacitinib 15 mg ER tablets (bulk lot number: 15-006832, 16-001357, 17-000986)
Upadacitinib 30 mg ER tablets (bulk lot number: 15-006955, 16-001431, 17-000991)

Study design:
This is a Phase 2b/3 multicenter study that included two periods. Period 1 was a 12-week, randomized, double-blind, parallel-group, placebo-controlled period designed to compare the safety and efficacy of upadacitinib 7.5 mg QD, 15 mg QD, and 30 mg QD versus placebo for the treatment of signs and symptoms of subjects with moderately to severely active RA who were on a stable dose of csDMARDs and had an inadequate response to csDMARDs. Period 2 is a blinded long-term extension period.
The primary efficacy endpoint collected in Period 1 was the proportion of subjects achieving ACR 20 response at Week 12.



ACR20 = American College of Rheumatology 20 response; csDMARD(s) = conventional synthetic disease modifying anti-rheumatic drug(s); QD = once daily; RA = rheumatoid arthritis

* The follow-up period was for subjects who did not enter Period 2 or prematurely discontinued study drug and study participation.



CDAI = Clinical Disease Activity Index; csDMARDs = conventional synthetic disease modifying anti-rheumatic drugs; LDA = low disease activity; NSAIDs = non-steroidal anti-inflammatory drugs; QD = once daily; RA = rheumatoid arthritis; W = week

The follow-up period was for subjects who completed Period 2 or prematurely discontinued study drug and study participation.

PK sampling:

- At Weeks 1 and 2 prior to dosing in all subjects;
- At Weeks 4, 8, and 12 at any time during the visit in all subjects.
- Prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12 and 24 hours after dose in ~32 subjects who participate in the intensive PK study.

Results

Efficacy

Table 4.1.2-67. Summary of ACR20 Response Rate at Week 12 with Cochran-Armitage Test

Treatment	N	Responder n (%)	Responder Rate (95% CI)[a]	Response Rate Difference (Upadacitinib – Placebo) Point Estimate	95% CI[b]	P-value[c]	P-value[d]
Placebo	49	21 (42.9)	42.9 (29.0, 56.7)				
Upadacitinib 7.5 mg QD	49	37 (75.5)	75.5 (63.5, 87.6)	32.7	(14.3, 51.0)	< 0.001***	< 0.001***
Upadacitinib 15 mg QD	49	41 (83.7)	83.7 (73.3, 94.0)	40.8	(23.5, 58.1)	< 0.001***	
Upadacitinib 30 mg QD	50	40 (80.0)	80.0 (68.9, 91.1)	37.1	(19.4, 54.9)	< 0.001***	

a. 95% confidence intervals (CIs) for response rate were calculated based on normal approximation to the binominal distribution.

b. 95% CIs for response rate difference were calculated based on normal approximation using Proc Freq.

c. Nominal p-value was constructed using Cochran-Mantel-Haenszel test adjusted for stratification factor prior bDMARD use.

d. P-value was constructed using Cochran-Armitage trend test for dose-response.

***, **, * Statistically significant at 0.001, 0.01, and 0.05 level, respectively.

(Source: Table 9 of Study M140663 CSR)

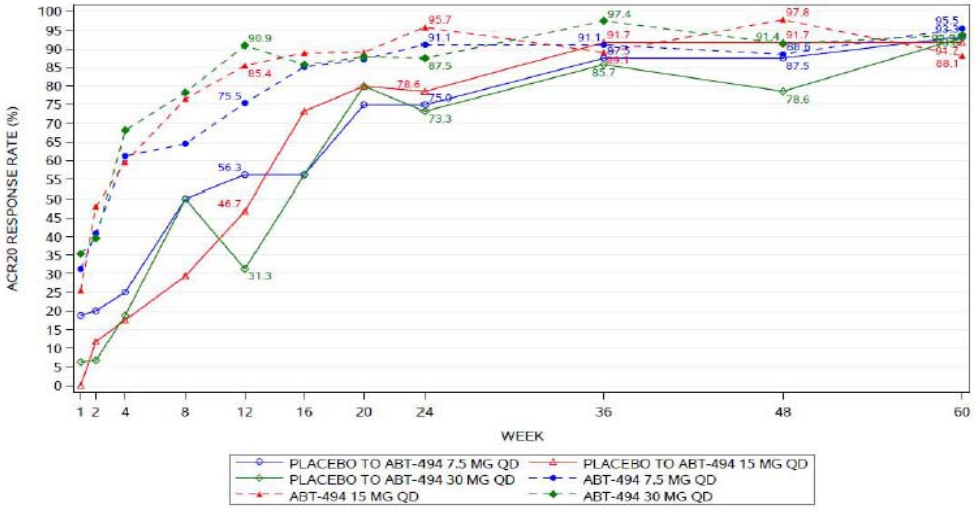


Figure 4.1.2-39. ACR20 Response Rate Over Time- Long-Term (Up to Week 60) (FAS)
(Source: Figure 3 of Study M140663 CSR)

PK

Upadacitinib mean (SD) plasma concentrations are summarized by dose group and time window in the table below.

Table 4.1.2-68. Upadacitinib Plasma Concentrations Categorized by Treatment and Time from Previous Dose

Upadacitinib Dose Group	Time Categories (h)	Number of Samples	Number of Subjects	Mean (SD)	
				Time from Previous Upadacitinib Dose (h)	Upadacitinib Concentration (ng/mL)
7.5 mg QD	> 0 – 2	7	5	1.58 (0.153)	23.4 (6.72)
	> 2 – 6	19	11	3.14 (0.826)	23.8 (9.14)
	> 6 – 12	9	5	8.87 (2.49)	15.5 (5.22)
	> 12 – 16	38	11	14.6 (1.40)	7.08 (2.52)
	> 16 – 24	33	12	19.7 (3.05)	3.98 (3.07)
	> 24 – 48	137	36	27.4 (1.79)	2.98 (3.61)
15 mg QD[b]	> 0 – 2	4	4	0.675 (0.603)	24.0 (23.4)
	> 2 – 6	12	8	3.94 (1.12)	48.1 (12.7)
	> 12 – 16	15	6	14.4 (0.604)	11.6 (5.05)
	> 16 – 24	30	19	22.2 (2.44)	6.20 (4.90)
	> 24 – 48	177	46	27.3 (2.46)	6.07 (7.27)[a]
30 mg QD	> 0 – 2	8	5	1.26 (0.478)	82.0 (46.8)
	> 2 – 6	16	10	3.75 (1.25)	105 (33.5)
	> 6 – 12	3	2	6.48 (0.448)	83.8 (48.3)
	> 12 – 16	22	7	14.7 (1.10)	28.3 (10.3)
	> 16 – 24	48	20	20.2 (2.79)	13.5 (6.45)
	> 24 – 48	139	39	27.2 (2.16)	11.4 (19.2)

h = hour; QD = once daily; SD = standard deviation

a. Number of samples = 176.

b. No samples were collected between 6 to 12 hours after dosing in the 15 mg QD group.

(Source: Table 18 of Study M140663 CSR)

Table 4.1.2-69. PK Parameters of Upadacitinib Following Administration of Multiple Doses of 7.5 mg QD, 15 mg QD, and 30 mg QD of Upadacitinib

Pharmacokinetic Parameters (Units)	Upadacitinib 7.5 mg QD (N = 6)[b]	Upadacitinib 15 mg QD (N = 13)[b]	Upadacitinib 30 mg QD (N = 10)
C_{max} (ng/mL)	31.9 ± 4.12	61.0 ± 19.5	111 ± 46.9
T_{max} (h)[a]	2.0 (1.0 - 4.0)	2.0 (1.5 - 6.0)	2.0 (1.0 – 4.0)
AUC_{24} (ng•h/mL)	272 ± 59.3	520 ± 215	900 ± 290
C_{min} (ng/mL)	1.87 ± 0.34	4.64 ± 2.75	7.47 ± 4.61
C_{24} (ng/mL)	2.42 ± 1.04	4.64 ± 2.64	11.7 ± 11.1
Degree of Fluctuation[c]	2.61 ± 0.39	2.69 ± 0.60	2.78 ± 0.85
Dose-normalized C_{max} ([ng/mL]/mg)	4.26 ± 0.550	4.07 ± 1.30	3.69 ± 1.56
Dose-normalized AUC_{24} ([ng•h/mL]/mg)	36.2 ± 7.90	34.6 ± 14.3	30.0 ± 9.65

AUC_{24} = area under the plasma concentration-time curve from time zero to 24 hours post dose; C_{24} = observed plasma concentration 24 hour post dose; C_{max} = maximum observed plasma concentration; C_{min} = minimum observed plasma concentration; QD = once daily; T_{max} = time to maximum observed plasma concentration

a. Median (minimum through maximum).

b. C_{min} and fluctuation index were not calculated for two subjects (one subject was randomized to Group 4; placebo to 7.5 mg group and the other to Group 5; placebo to 15 mg group) because the intensive pharmacokinetic samples were collected for the subjects at Week 12 after they received the first dose of upadacitinib (C_{min} and fluctuation index are not meaningful after first dose).

c. Calculated as $((C_{max} - C_{min})/C_{average})$

(Source: Table 19 of Study M140663 CSR)

Conclusions

- Results showed a dose-response relationship in the primary endpoint ACR20.

4.2 Appendix – Summary of Bioanalytical Method Validation

4.2.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The bioanalytical methods used for upadacitinib measurement in human plasma and urine are listed in the table below:

Table 4.2-1. Summary of validated analytical method reports

Compound(s)	Validation Report	Matrix	Report Site
Compound: Upadacitinib	c-da-rd12654-val-lcms-pla c-da-rd160683-update-lcms-plasma c-da-rd181039-update-val-lcms-pla	plasma	AbbVie

Study	Analytical Report	Study	Analytical Report	Study	Analytical Report
M13-401	m13401-analytical-plasma	M13-549	m13549-analytical-plasma	M14-680	m146801-analytical-plasma m146802-analytical-plasma m146804-analytical-plasma
M13-537	m13537-analytical-plasma	M13-550	m13550-analytical-plasma		
M13-539	m13539-analytical-plasma	M13-551	m13551-analytical-plasma		
M13-540	m13540-analytical-plasma	M13-845	m13845-analytical-plasma	M15-555	m15555-analytical-plasma
M13-541	m13541-analytical-plasma	M14-174	m14174-analytical-plasma	M15-558	m15558-analytical-plasma-wuxi
M13-542	m13542-analytical-plasma	M14-465	m14465-analytical-plasma-interim	M15-868	m15868-analytical-plasma
M13-543	m13543-analytical-plasma	M14-663	m14663-analytical-plasma	M15-878	m15878-analytical-plasma
M13-545	m13545-analytical-plasma m13545-analytical-plasma-wuxi	M14-677	m14677-analytical-plasma	M16-094	m16094-analytical-plasma
M13-547	m13547-analytical-plasma	M14-678	m14678-analytical-plasma	M16-552	m16552-analytical-plasma
M13-548	m13548-analytical-plasma	M14-679	m14679-analytical-plasma	M17-221	m17221-analytical-plasma

Compound(s)	Validation Report	Matrix	Report Site	Studies	Bioanalytical Study Report
Upadacitinib	c-da-rd12773-val-lcms-urn c-da-rd140745-update-lcms-urine	urine	AbbVie	M13-401	m13401-analytical-urine
				M13-543	m13543-analytical-urine
				M13-551	m13551-analytical-urine
				M13-845	m13845-analytical-urine
				M15-558	m15558-analytical-urine-wuxi

(Source: Table 25 of Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Quantification of upadacitinib in human plasma

A 96-well salt-assisted liquid/liquid extraction HPLC tandem mass spectrometric method was used for the determination of upadacitinib in human plasma. The key descriptive parameters for the assay (Validation Report 12654) are summarized in Table 4.4-2. The same method has been updated with additional interference and stability assessment as reported in Reports 160683 and 181039 (Table 4.4-3). In general, the bioanalytical method was fully validated and found to be sensitive and accurate for the determination of upadacitinib in human plasma. All samples were analyzed within the demonstrated stability window.

Table 4.2-2 Summary of the bioanalytical method validation for the determination of upadacitinib in human plasma (Validation report 12654)

LIMS Project ID	A1293543
LIMS study ID	A1293543MPLAVal
Validation Report	July 2012 or R&D/12/654
Critical Method Information	None
Analyte/Metabolite Name(s)	A-1293543 (ABT-494)
Internal Standard Name(s)	A-1293543-d4 (ABT494 IS)
Species/Matrix	Human Plasma
Anticoagulant	K_2 EDTA
Sample Volume	50 µL
Curve Range(s):	0.0503 ng/mL to 102 ng/mL for A-1293543
Extraction Type	Salt-Assisted Liquid/Liquid Extraction
Automation (if applicable)	96-Deep Well Format, Pipetting Robot (e.g., Starlet, Nimbus), Automation Station
Instrumentation/Detection	LC-MS/MS (API 5000, 5500 or 6500)
Run Time	Approximately 1.5 minutes
Freeze/Thaw Matrix Stability	5 cycles in polypropylene tubes at ~ -70°C 6 cycles in polypropylene tubes at ~ -20°C
Room Temperature Matrix Stability	29 hours at room temperature in polypropylene tubes stored at ~ -70°C 22 hours at room temperature in polypropylene tubes stored at ~ -20°C
Autosampler Stability	260 hours in a cold autosampler (set point of 4°C) in a polypropylene plate
Run Storage Stability	167 hours in a cold autosampler (set point of 4°C) in a polypropylene plate
Frozen Matrix Stability	244 days stored at ~ -70°C in polypropylene cryogenic vials 1209 days stored at ~ -20°C in polypropylene cryogenic vials
Whole Blood (Sample Collection) Stability	Upto 4 hours in whole blood in polypropylene tubes at room temperature
Hemolyzed Matrix Test	Evaluation of 5% lysed blood had no impact on assay performance.
Lipemic Matrix Test	No impact on assay performance
Room Temperature Analyte Stock Solution Stability	A-1293543: 6 hours in 50/50 (*v/v*) Acetonitrile/Water in an amber glass bottle at room temperature from ~ 100 µg/mL to ~ 4 mg/mL
Refrigerated Analyte Stock Solution Stability	A-1293543: 5 days in 50/50 (*v/v*) Acetonitrile/Water in an amber glass bottle at room temperature from ~ 100 µg/mL to ~ 4 mg/mL
IS Stock Solution Stability at Room Temperature	A-1293543-d4: 6 hours in 50/50 (*v/v*) Acetonitrile/Water in an amber glass bottle at room temperature from ~ 80 µg/mL to ~ 300 µg/mL

*Note that samples with concentrations above the upper limit of quantitation for any given run were diluted and assayed with a set of QC samples with the same dilution factor. The dilution factor of 20 was reported.
(Table source: Appendix C of Report 160683)

Table 4.2-3 Updates of the bioanalytical assay validation for the determination of upadacitinib in human plasma in Reports 160683 and 181039

Update	Conclusions
Interference evaluation in presence of other drugs (Report 160683)	non-interference was established from methotrexate, ketoconazole, rifampicin, atorvastatin, dextromethorphan, levonorgestrel (Norgestrel), midazolam, caffeine, S-warfarin, R-warfarin, omeprazole, rosuvastatin, and ethinylestradiol.
Freeze-thaw stability (Report 181039)	Freeze thaw evaluation samples were stable for at least 7 freeze/thaw cycles in polypropylene cryogenic vials at -20^{0}C.
Frozen storage stability (Report 181039)	1615 days stored at ~ -20°C in polypropylene cryogenic vials.

Quantification of upadacitinib in human urine

A 96-well salt-assisted liquid/liquid extraction HPLC tandem mass spectrometric method was used for the determination of upadacitinib in human urine. The assay (Validation Report 12773) has been updated with additional stability assessment (Reports 140745). The key descriptive parameters for the assay are summarized in Table 4.4-4. In general, the bioanalytical method was fully validated and found to be sensitive and accurate for the determination of upadacitinib in human urine. All samples were analyzed within the demonstrated stability window.

Table 4.2-4 Summary of the bioanalytical method validation for the determination of upadacitinib in human plasma (Validation Reports 12773 and 140745)

LIMS Project ID	ABT494
LIMS Study ID	A1293543MURNVal
Validation Report	R&D/12/773
Validation Stability and Update Report	R&D/14/0745
Critical Method Information	Make sure the stock solutions are stored in glass bottles and are protected from light.
Analyte Name(s)	A-1293543 (ABT494)
Internal Standard Name(s)	A-1293543-d4 (ABT494 SLIS)
Species/Matrix	Human Urine
Anticoagulant	N/A
Sample Volume	35 µL
Curve Range(s):	1.01 ng/mL to 1000 ng/mL
Extraction Type	Dilution of Human Urine for analysis using LC-MS/MS
Automation (if applicable)	96-Deep Well Format, Starlet
Instrumentation/Detection	LC-MS/MS (API 5000)
Run Time	2.0 minutes (MS acquisition time: 1 min)
Freeze/Thaw Matrix Stability	At least 6 cycles in polypropylene tubes at ~ -20°C
Accumulated Room Temperature Matrix Stability	At least 19 hours at room temperature in polypropylene tubes
Autosampler Stability	At least 74 hours in a polypropylene plate in an autosampler (set point 4°C)
Run Storage Stability	At least 76 hours in a polypropylene plate in an autosampler (set point 4°C)
Frozen Matrix Stability	At least 518 days in polypropylene tubes at ~ -20°C
Room Temperature Analyte Stock Solution Stability	ABT-494: At least 6 hours in 1:1 acetonitrile:water in an glass bottle covered with aluminum foil at room temperature
Refrigerated Analyte Stock Solution Stability	At least 5 days in 1:1 acetonitrile:water in an glass bottle covered with aluminum foil when refrigerated
IS Stock Solution Stability at Room Temperature	A-1293543-d4: At least 6 hours in 1:1 (v/v) acentonitrile:water in an glass bottle at room temperature

(Source: Appendix C of Reports 140745)

4.3 Appendix – Pharmacometrics Review

4.3.1 Population Pharmacokinetic Analyses of Upadacitinib Phase 1 Through Phase 3 Studies in Healthy Subjects and RA Patients

4.3.1.1 Introduction

The objectives of this analysis were to:

- Characterize the population pharmacokinetics of upadacitinib for both the immediate-release (IR) and extended-release (ER) formulations in healthy subjects and in subjects with moderate to severe RA using data across Phase 1, 2, and 3 clinical trials
- Explore factors influencing upadacitinib pharmacokinetics (patient demographics, impact of renal impairment renal impairment, combination with Methotrexate, concomitant intake of antacids or proton pump inhibitors, etc.)

4.3.1.2 Model development

- Data

The population pharmacokinetics of upadacitinib in RA subjects and healthy subjects were characterized using the data from five global Phase 3 studies (M13-542, M13-549, M15-555, M14-465, and M13-545), one regional Phase 2b/3 study in Japan (M14-663), two Phase 2 studies (M13-537 and M13-550), and four Phase 1 studies (M13-401, M13-543, M13-845, and M14-680). In total, PK data from 4170 subjects (96% with RA, and 4% healthy) were included in the analyses. Refer to the Clinical Pharmacology review for brief descriptions of the studies included in the population PK analyses. Table 4.3-1 provides summary statistics of the baseline demographics, and other intrinsic or extrinsic factors for subjects included in the population pharmacokinetic analyses.

Table 4.3-1 Summary of Demographics, Other Intrinsic or Extrinsic Factors of Interest for Subjects Included in the Population Pharmacokinetic Analyses

CHARACTERISTICS		Phase 1 (N = 188)	Phase 2 (N = 456)	Phase 2b/3 in Japan (N = 147)	Phase 3[c] (N = 3379)	All Subjects (N = 4170)
Age (years)	Mean (SD)	36.0 (11.50)	56.0 (12.33)	55.5 (11.90)	54.5 (12.13)	53.9 (12.73)
	Median	33.50	56.00	58.00	56.00	55.00
	Min - Max	19.0 - 70.0	19.0 - 85.0	19.0 - 78.0	18.0 - 87.0	18.0 - 87.0
Body Weight (kg)	Mean (SD)	75.4 (11.09)	76.4 (15.98)	58.3 (11.31)	77.2 (19.98)	76.4 (19.33)
	Median	74.00	75.00	55.00	74.00	74.00
	Min - Max	52.0 - 101.0	42.0 - 134.0	40.0 - 93.0	36.0 - 196.0	36.0 - 196.0
Body Height (cm)	Mean (SD)	172.6 (7.91)	163.9 (9.08)	158.6 (8.25)	163.2 (9.33)	163.5 (9.45)
	Median	173.00	163.00	157.00	163.00	163.00
	Min - Max	151.0 - 191.0	137.0 - 192.0	138.0 - 182.0	135.0 - 198.0	135.0 - 198.0
Body Mass Index (kg/m^2)	Mean (SD)	25.3 (3.07)	28.4 (5.30)	23.1 (3.85)	28.9 (6.84)	28.5 (6.60)
	Median	25.50	27.75	22.80	27.80	27.40
	Min - Max	18.5 - 33.4	18.8 - 44.3	16.2 - 41.5	13.3 - 71.9	13.3 - 71.9
Body Surface Area (m^2)	Mean (SD)	1.9 (0.16)	1.8 (0.21)	1.6 (0.17)	1.8 (0.24)	1.8 (0.23)
	Median	1.87	1.81	1.55	1.79	1.79
	Min - Max	1.5 - 2.3	1.3 - 2.5	1.3 - 2.0	1.2 - 2.9	1.2 - 2.9
Sex	Male N, (%)	164 (87%)	95 (21%)	35 (24%)	697 (21%)	991 (24%)
	Female N, (%)	24 (13%)	361 (79%)	112 (76%)	2682 (79%)	3179 (76%)

CHARACTERISTICS		Phase 1 (N = 188)	Phase 2 (N = 456)	Phase 2b/3 in Japan (N = 147)	Phase 3[c] (N = 3379)	All Subjects (N = 4170)
Race	White N, (%)	83 (44%)	426 (93%)	--	2827 (84%)	3336 (80%)
	Black N, (%)	52 (28%)	21 (5%)	--	183 (5%)	256 (6%)
	Asian N, (%)	34 (18%)	3 (1%)	147 (100%)	290 (9%)	474 (11%)
	Multiple Races N, (%)	18 (10%)	5 (1%)	--	--	23 (1%)
	Other N, (%)	1 (1%)	1 (0%)	--	79 (2%)	81 (2%)
Hispanic Subject	No N, (%)	165 (88%)	353 (77%)	147 (100%)	2490 (74%)	3155 (76%)
	Yes N, (%)	23 (12%)	103 (23%)	--	889 (26%)	1015 (24%)
Tobacco Use	Non-User N, (%)	153 (81%)	355 (78%)	73 (50%)	2041 (60%)	2622 (63%)
	User N, (%)	35 (19%)	101 (22%)	30 (20%)	646 (19%)	812 (19%)
	Ex-User N, (%)	--	--	44 (30%)	688 (20%)	732 (18%)
	Missing N, (%)	--	--	--	4 (0%)	4 (0%)
Alcohol Use	Non-User N, (%)	96 (51%)	339 (74%)	39 (27%)	2026 (60%)	2500 (60%)
	User N, (%)	92 (49%)	117 (26%)	73 (50%)	1044 (31%)	1326 (32%)
	Ex-User N, (%)	--	--	35 (24%)	284 (8%)	319 (8%)
	Missing N, (%)	--	--	--	25 (1%)	25 (1%)
Subject Population	Healthy Subject N, (%)	178 (95%)	--	--	--	178 (4%)
	Subject with RA N, (%)	10 (5%)	456 (100%)	147 (100%)	3379 (100%)	3992 (96%)

CHARACTERISTICS		Phase 1 (N = 188)	Phase 2 (N = 456)	Phase 2b/3 in Japan (N = 147)	Phase 3[c] (N = 3379)	All Subjects (N = 4170)
High Sensitivity C-Reactive Protein (mg/L)[a]	Mean (SD)	2.5 (4.21)	13.6 (18.11)	13.9 (15.09)	17.9 (21.88)	17.1 (21.25)
	Median	1.10	6.37	7.51	9.63	9.28
	Min - Max	0.1 - 28.0	0.1 - 135.3	0.8 - 84.6	0.2 - 207.0	0.1 - 207.0
DAS28 C-Reactive Protein[b]	Mean (SD)	Not collected	5.7 (0.95)	5.1 (0.91)	5.8 (0.97)	5.7 (0.97)
	Median	Not collected	5.71	5.06	5.77	5.73
	Min - Max	Not collected	3.0 - 8.0	3.4 - 7.8	1.8 - 8.4	1.8 - 8.4
Methotrexate Use	No N, (%)	178 (95%)	--	24 (16%)	1270 (38%)	1472 (35%)
	Yes N, (%)	10 (5%)	456 (100%)	123 (84%)	2109 (62%)	2698 (65%)
ALT (U/L)	Mean (SD)	19.3 (9.86)	23.4 (16.18)	19.2 (19.84)	20.6 (13.10)	20.8 (13.67)
	Median	17.00	20.00	14.00	17.00	17.00
	Min - Max	7.0 - 76.0	4.0 - 185.0	6.0 - 220.0	5.0 - 257.0	4.0 - 257.0
AST (U/L)	Mean (SD)	19.2 (6.37)	22.4 (9.39)	22.5 (12.53)	19.8 (8.93)	20.1 (9.08)
	Median	18.00	20.00	20.00	18.00	18.00
	Min - Max	10.0 - 59.0	5.0 - 95.0	11.0 - 132.0	6.0 - 195.0	5.0 - 195.0
Creatinine Clearance (mL/min)	Mean (SD)	111.7 (21.86)	109.6 (36.25)	96.3 (28.14)	115.1 (38.98)	113.7 (37.92)
	Median	109.55	105.90	94.17	109.60	108.70
	Min - Max	64.1 - 184.7	41.2 - 241.1	38.3 - 173.1	30.2 - 390.9	30.2 - 390.9

CHARACTERISTICS		Phase 1 (N = 188)	Phase 2 (N = 456)	Phase 2b/3 in Japan (N = 147)	Phase 3[c] (N = 3379)	All Subjects (N = 4170)
Creatinine Concentration (mg/dL)	Mean (SD)	1.0 (0.16)	0.8 (0.19)	0.7 (0.17)	0.7 (0.17)	0.7 (0.18)
	Median	0.98	0.71	0.60	0.70	0.70
	Min - Max	0.6 - 1.4	0.4 - 1.6	0.4 - 1.7	0.3 - 1.8	0.3 - 1.8
Albumin (g/dL)	Mean (SD)	4.7 (0.32)	4.3 (0.29)	4.2 (0.29)	4.2 (0.30)	4.2 (0.31)
	Median	4.70	4.30	4.20	4.20	4.20
	Min - Max	3.6 - 5.4	3.2 - 5.0	3.5 - 4.9	2.6 - 5.8	2.6 - 5.8
Total Bilirubin (mg/dL)	Mean (SD)	0.8 (0.30)	0.4 (0.23)	0.4 (0.18)	0.4 (0.19)	0.4 (0.21)
	Median	0.70	0.40	0.40	0.35	0.40
	Min - Max	0.1 - 1.6	0.1 - 2.6	0.2 - 1.1	0.2 - 1.9	0.1 - 2.6
Anti-Acid Drugs	No N, (%)	188 (100%)	432 (95%)	137 (93%)	3157 (93%)	3914 (94%)
	Yes N, (%)	--	24 (5%)	10 (7%)	222 (7%)	256 (6%)
CYP3A Inhibitors	None/Weak N, (%)	188 (100%)	436 (96%)	144 (98%)	3248 (96%)	4016 (96%)
	Moderate N, (%)	--	16 (4%)	2 (1%)	118 (3%)	136 (3%)
	Strong N, (%)	--	4 (1%)	1 (1%)	13 (0%)	18 (0%)
CYP3A Inducers	None/Weak/Moderate N, (%)	188 (100%)	453 (99%)	147 (100%)	3371 (100%)	4159 (100%)
	Strong N, (%)	--	3 (1%)	--	8 (0%)	11 (0%)
H_2 Receptor Antagonists	No N, (%)	188 (100%)	440 (96%)	134 (91%)	3238 (96%)	4000 (96%)
	Yes N, (%)		16 (4%)	13 (9%)	141 (4%)	170 (4%)
Proton-Pump Inhibitors	No N, (%)	188 (100%)	305 (67%)	86 (59%)	2165 (64%)	2744 (66%)
	Yes N, (%)	--	151 (33%)	61 (41%)	1214 (36%)	1426 (34%)
pH Modifying Drugs	No N, (%)	188 (100%)	278 (61%)	70 (48%)	1946 (58%)	2482 (60%)
	Yes N, (%)	--	178 (39%)	77 (52%)	1433 (42%)	1688 (40%)

RA = rheumatoid arthritis; SD = standard deviation; Min = minimum; Max = maximum

a. High sensitivity C-reactive protein was collected for 52 of the Phase 1 subjects and 4034 subjects overall.

b. DAS28 C-reactive protein was not collected in Phase 1 studies resulting in 3982 subjects overall.

c. Not including Phase2b/3 Study in Japan.

(Source: Applicant's Population Pharmacokinetic Report R&D/18/0165, Table 5)

- Model building process

A nonlinear mixed-effects model (NONMEM) was developed to characterize the population pharmacokinetics of upadacitinib after oral administration of doses ranging from 1 to 48 mg using the IR formulation and 7.5 mg to 30 mg using the ER formulation.

Intrinsic and extrinsic factors that may contribute to variability in upadacitinib pharmacokinetics were tested using a stepwise forward inclusion, backward elimination covariate model building procedure. Forward inclusion and backward elimination steps were conducted at $\alpha = 0.01$ and $\alpha = 0.001$ significance levels, respectively, based on the likelihood ratio test. Continuous covariates were included in the model using power functions centered on the median value of each covariate in the dataset. Categorical covariates were tested with a multiplicative model.

The covariates investigated for influence on upadacitinib pharmacokinetic parameters included:

- For apparent oral clearance (CL/F): baseline serum bilirubin concentration, baseline creatinine clearance, baseline total bodyweight, baseline age, baseline AST, baseline ALT, baseline DAS28-CRP, baseline hsCRP, sex, race (white, black, Hispanic, Asian), country (Taiwan, Japan, China, Korea), concomitant use of methotrexate (MTX), concomitant use of pH-modifying medications (antacids, H2 receptor antagonists, proton-pump inhibitors), concomitant use of moderate or strong CYP3A inhibitors, concomitant use of strong CYP3A inducers.
- For apparent volume of distribution of the central compartment (Vc/F): Sex, race (white, black, Hispanic, Asian), baseline total bodyweight and country (Taiwan, Japan, China, Korea).
- For bioavailability of the extended-release formulation: upadacitinib dose, concomitant use of antacids, concomitant used of H2 receptor antagonists, concomitant use of proton pump inhibitors,

concomitant use of any pH-modifying agents, concomitant use of moderate or strong CYP3A inhibitors, and concomitant use of strong CYP3A inducers.

The final model was evaluated based on goodness-of-fit plots, visual predictive checks, and nonparametric bootstrap. The non-linear mixed-effects modeling software NONMEM was used for all data analyses and simulation-based model evaluations.

4.3.1.3 Results

- Final model

A two-compartment model with first-order absorption for the IR formulation, mixed zero and first order absorption with lag time for the ER formulation, and linear elimination was used to describe upadacitinib plasma concentration-time profiles.

Statistically significant covariates were patient population (RA versus healthy), creatinine clearance, and baseline bodyweight on CL/F; and body weight on Vc/F. The oral bioavailability of the ER formulation relative to IR formulation was estimated to be 76%.

Visual predictive check indicated that the final model incorporating these covariates described the central tendency and variability of the data reasonably well. The estimated pharmacokinetic parameter values based on the original dataset were in good agreement with the medians of the parameter values estimated from the bootstrap replicates. The fixed and random effects parameter estimates for the final population pharmacokinetic model are listed in Table 4.3-2. The goodness-of-fit plots for the final model for all data are shown in Figure 4.3-1. The Visual Predictive Check (VPC) plot for the final model with all data is shown in Figure 4.3-2.

Table 4.3-2 Parameter Estimates and Bootstrap Analysis Results for the Final Model

	Population Analysis	Bootstrap Analysis[a]	
Parameter	**Estimate (%RSE)**	**Median**	**95% Confidence Interval**
CL/F (L/h)[b]	40.9 (1.6)	41.3	39.6 - 42.5
Vc/F (L)[b]	156 (1.7)	156	150 - 161
Q/F (L/h)[b]	3.22 (5.8)	3.22	2.86 - 3.63
Vp/F (L)[b]	68.0 (7.2)	67.4	59.7 - 78.3
Immediate-Release KA (1/h)	2.77 (7.4)	2.77	2.35 - 3.25
Immediate-Release Absorption Lag Time (h)	0.200 (3.9)	0.202	0.176 - 0.225
Bioavailability of the Extended-Release Formulation Relative to the Immediate-Release Formulation (%)	76.2 (1.4)	76.3	73.0 - 79.7
Extended-Release KA (1/h)	0.0523 (6.0)	0.0523	0.0460 - 0.0590
Extended-Release Absorption Lag Time (h)	0.154 (7.7)	0.155	0.110 - 0.186
Fraction of Extended-Release Dose Absorbed through Zero-Order Process (%)	74.5 (1.7)	74.3	71.3 - 77.0
Zero-Order Infusion duration (h)	3.29 (1.7)	3.29	2.77 - 3.63
CL/F Ratio of RA Subjects Compared to Healthy Subjects[c]	0.754 (1.7)	0.754	0.727 - 0.777
Covariate Exponent of Creatinine Clearance on CL/F[c]	0.256 (10.0)	0.256	0.205 - 0.305
Covariate Exponent of Weight on Vc/F[c]	0.804 (8.0)	0.789	0.656 - 0.921
Covariate Exponent of Weight on CL/F[c]	0.132 (28.7)	0.127	0.0595 - 0.206
ISV on CL/F in Phase 1 (%)	21 (22)	20	18 - 22
ISV on CL/F in Phase 2/3 (%)	37 (16)	37	35 - 39
ISV on Vc/F in Phase 1 (%)	24 (27)	24	21 - 28
ISV on Vc/F in Phase 2/3 (%)	53 (26)	53	45 - 62
ISV on Extended Release KA (%)	67 (25)	66	58 - 75
Proportional Error SD in Phase 1	0.344 (16.9)	0.344	0.324 - 0.370
Proportional Error SD in Phase 2/3	0.543 (9.9)	0.543	0.533 - 0.555
Additive Error SD (ng/mL)	0.0858 (38.6)	0.0858	0.0467 - 0.109

CL/F = apparent oral clearance; ISV = inter-subject variability; KA = absorption rate constant; Q/F = apparent inter-compartmental clearance; RSE = relative standard error; SD = standard deviation; Vc/F = apparent volume of distribution of central compartment; Vp/F = apparent volume of distribution of peripheral compartment; ISV was calculated as SQRT(ω^2)*100.

a. 456 successful runs out of 500.

b. Estimates are for the immediate-release (based on immediate-release bioavailability).

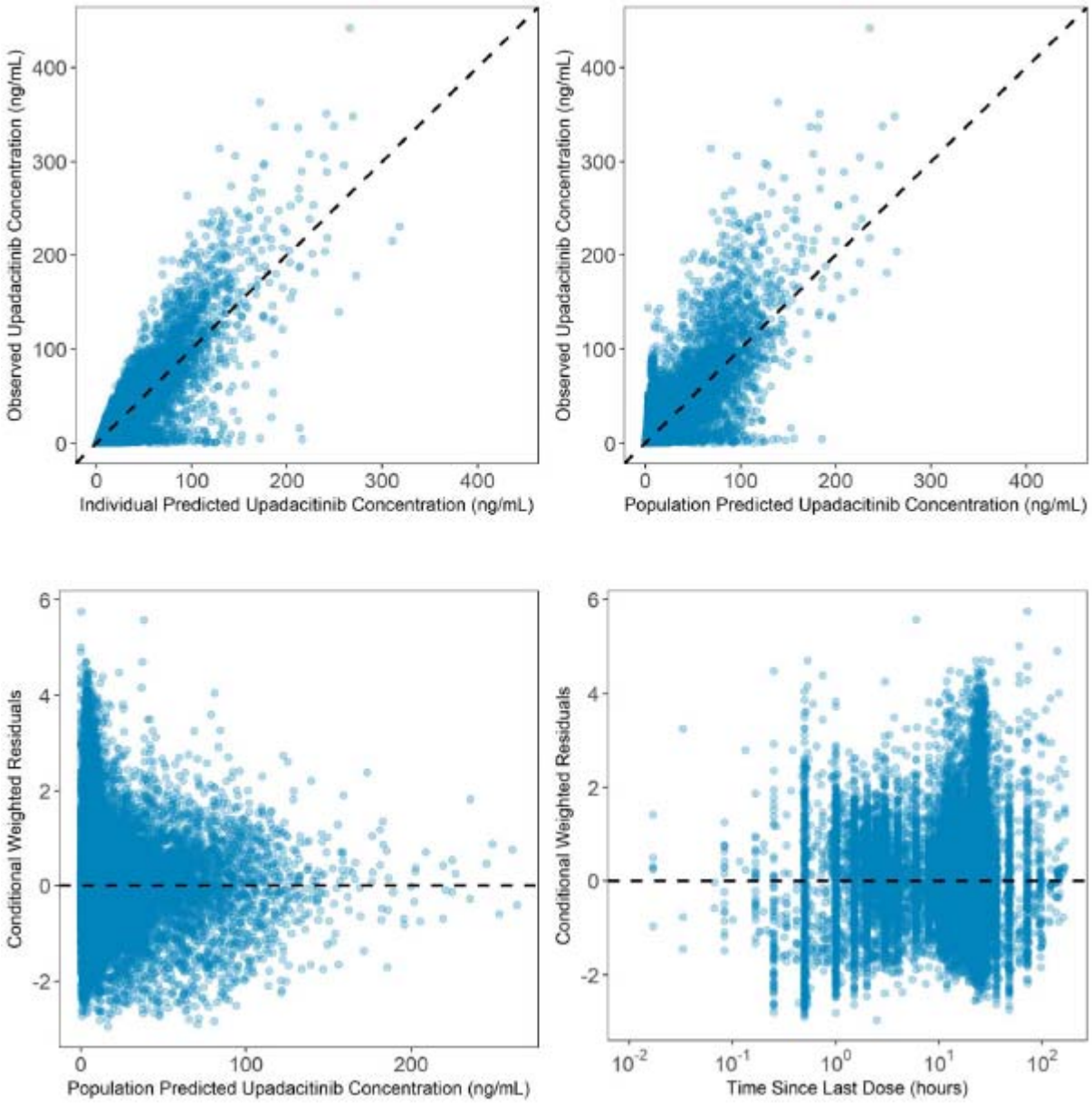
c. Typical clearance and volume of central compartment with particular covariate combination:

$$CL/F = \begin{cases} 40.9 * \left(\frac{CRCL[mL/min]}{108.7\ mL/min}\right)^{0.256} * \left(\frac{WTKG[kg]}{74\ kg}\right)^{0.132} \frac{L}{h} & \text{for healthy subjects} \\ 40.9 * \left(\frac{CRCL[mL/min]}{108.7\ mL/min}\right)^{0.256} * \left(\frac{WTKG[kg]}{74\ kg}\right)^{0.132} * 0.754\ \frac{L}{h} & \text{for RA subjects} \end{cases}$$

$$V_c/F = 156 * \left(\frac{WTKG[kg]}{74\ kg}\right)^{0.804} L$$

(Source: Applicant's Population Pharmacokinetic Report R&D/18/0165, Table 8)

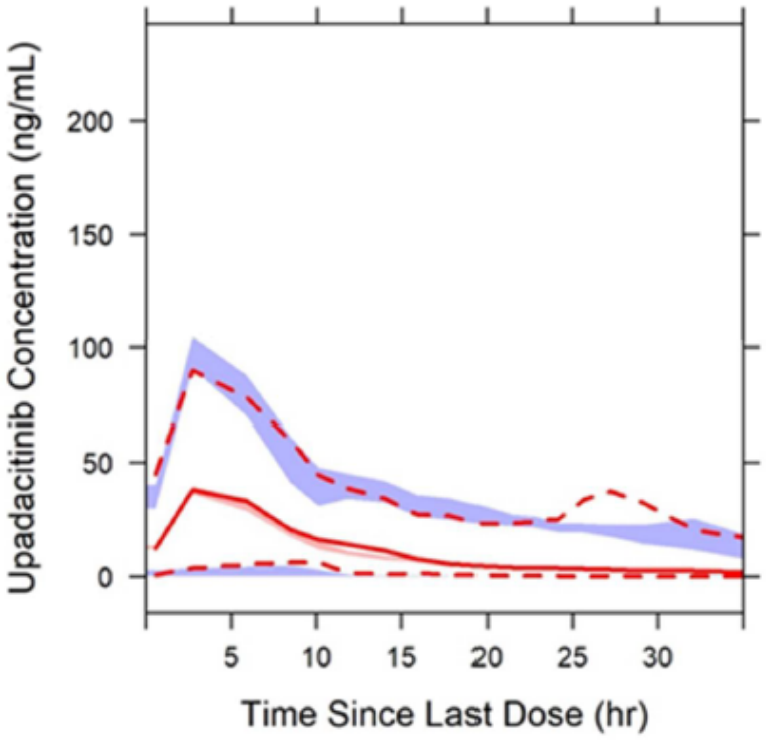
Figure 4.3-1 Goodness-of-fit plots for the final model



Goodness-of-fit plots for the individual-predicted and population-predicted versus observed concentrations (upper left and right, respectively) and conditional weighted residuals versus population-predicted concentration and time since last dose (bottom left and right, respectively).

(Source: Applicant's Population Pharmacokinetic Report R&D/18/0165, Figure 11)

Figure 4.3-2 Prediction-Corrected Visual Predictive Check Plotted Versus Time Since Last Dose Using All Extended-Release Formulation Data



The shaded blue areas represent the 95% confidence interval of the 2.5th and 97.5th percentiles of prediction-corrected simulated concentrations, the shaded red area represent the 95% confidence interval of the 50th percentile of prediction-corrected simulated concentrations, the solid red line represents median of prediction-corrected observed concentrations, and dashed red lines represent the 2.5th and 97.5th percentile of the prediction-corrected observed concentrations.

(Source: Applicant's Population Pharmacokinetic Report R&D/18/0165, Figure 14)

4.3.1.4 Assessment of the effect of covariates on upadacitinib pharmacokinetics

After identifying the statistically significant covariates for upadacitinib pharmacokinetic parameters, simulations were performed to explore their clinical relevance or impact on upadacitinib AUC_{24} and Cmax at steady state for the clinical regimen of 15 mg QD extended-release.

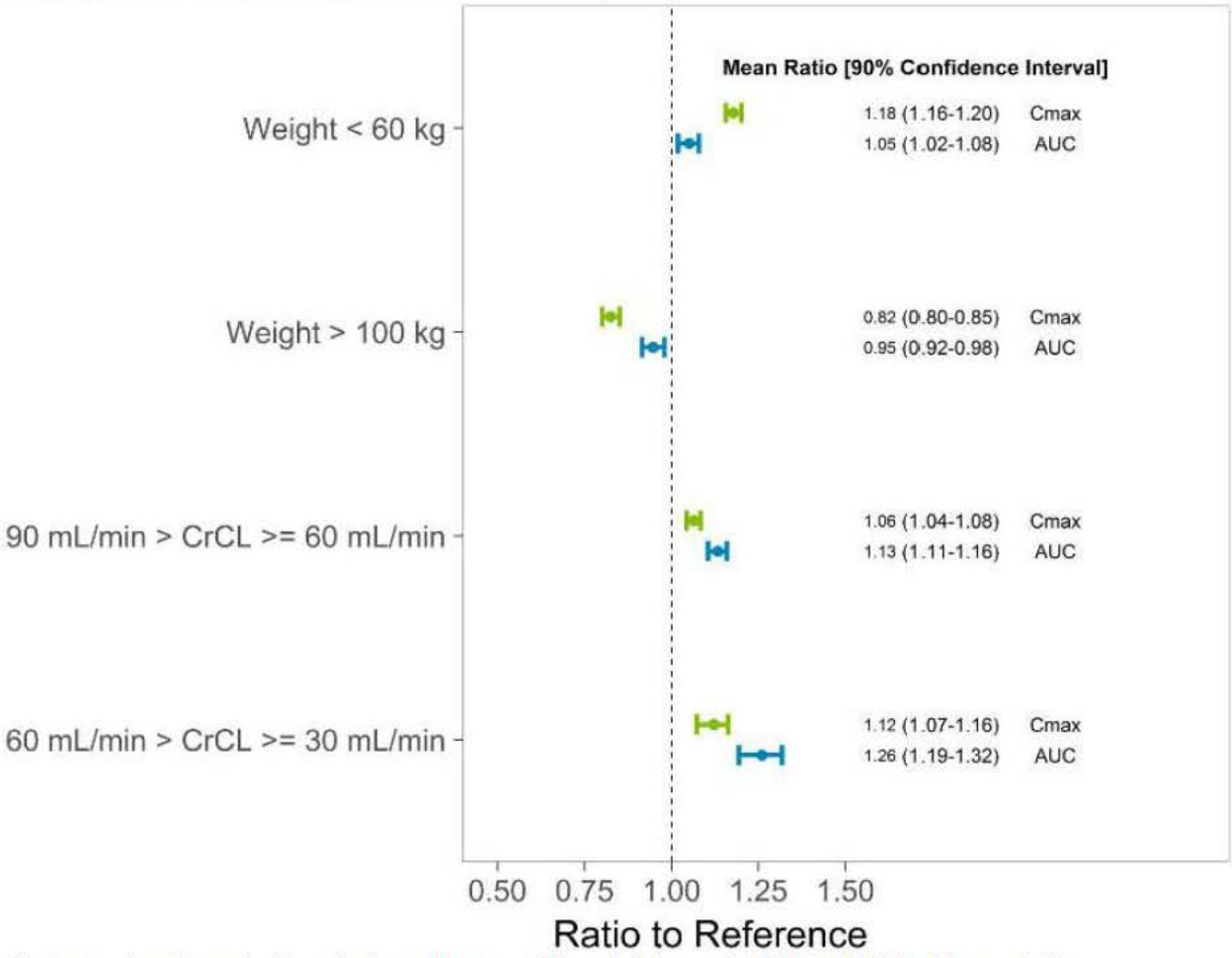
Simulations with 200 replicates of the dataset using the demographics of RA patient population from the Phase 2 and 3 studies were performed. Simulations for each of the statistically significant covariates of interest were carried out separately while fixing the other covariates to the reference value. Predicted upadacitinib AUC and Cmax from the simulations in each subset of subjects based on the covariate of interest (test group) were compared to the corresponding reference group to calculate the ratio of exposures in the test relative to the reference groups. The mean of the ratios across the replicates and the 90% confidence interval for the mean (5th and the 95th percentiles of the ratios) were calculated and summarized graphically using a forest plot in Figure 4.3-3. The test and reference groups for the assessment of covariate effects were as follows:

- Body Weight:
  - Test groups: < 60 kg and > 100 kg
  - Reference group: 60 - 100 kg
- Creatinine clearance:
  - Test groups: 60 to < 90 mL/min and 30 to < 60 mL/min

- Reference group: ≥ 90 mL/min

The vertical dashed line shows the exposure ratio of 1 relative to the reference group (Figure 4.3-3). Based on the simulations, subjects with RA with bodyweight < 60 or >100 kg were predicted to have 5% higher or lower AUC on average, and 18% higher or lower Cmax, on average, respectively, compared to subjects with bodyweight 60 - 100 kg. Subjects with mild (CrCl 60 to < 90 mL/min) or moderate (30 to < 60 mL/min) renal impairment are predicted to have approximately 13 and 26% higher AUC, respectively, compared to subjects with normal renal function.

Figure 4.3-3 Model-Predicted Covariate Effect on Upadacitinib Cmax and AUC24 for Different RA Subpopulations Relative to the Reference RA Population



(Source: Applicant's Population Pharmacokinetic Report R&D/18/0165, Figure 16)

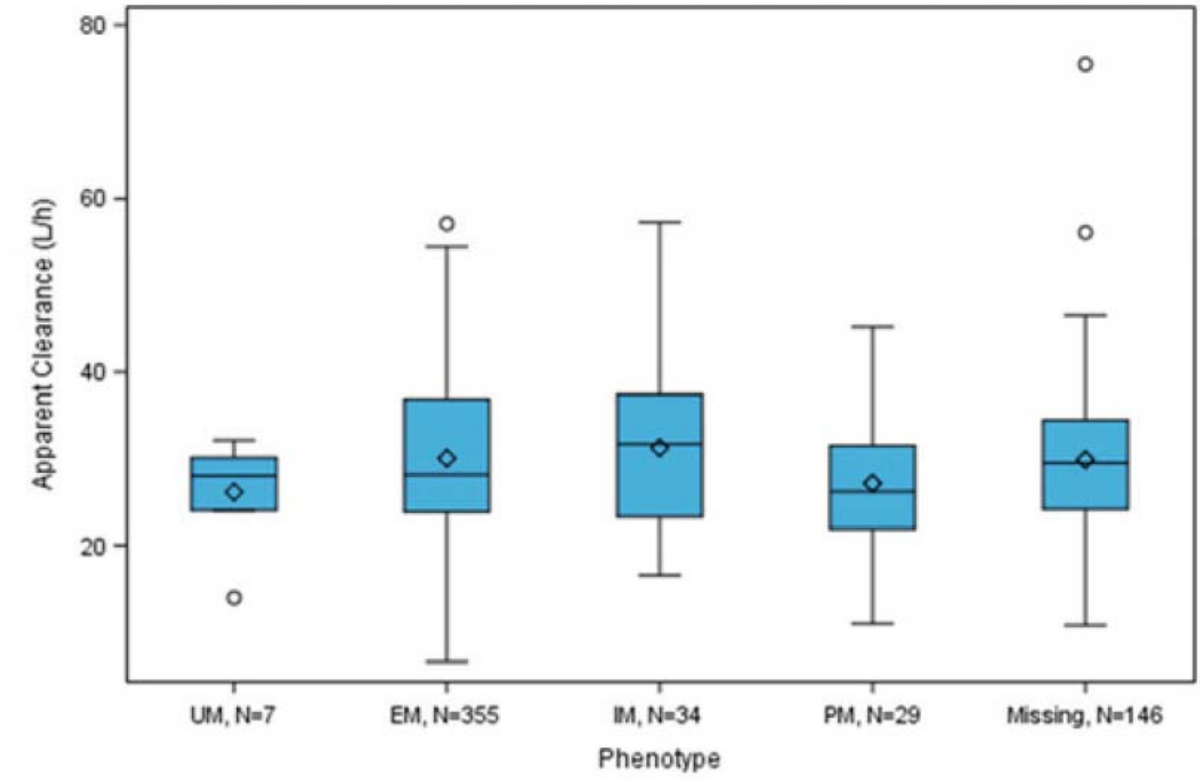
Reviewer's comments: *The applicant's population PK analysis is acceptable. The goodness-of-fit plots and the visual predictive check indicate that the population PK model can characterize the PK profiles of upadacitinib for the ER formulation in healthy volunteers and RA patients. Even though the reviewer experienced rounding error while replicating the applicant's analyses, the applicant's conclusion appears reasonable,* (b) (4)

4.3.2 Population Pharmacokinetic Analyses of Upadacitinib Phase 1 and RA Phase 2 Studies

Before the availability of the Phase 3 data, the sponsor conducted a population pharmacokinetic analyses (R&D/17/0334) using data from three Phase 1 studies (Studies M13-401, M13-543 and M13-845) and two Phase 2 studies (Studies M13-537 and M13-550). The analyses included data from 573 subjects (81% with RA and 19% healthy). The final pharmacokinetic model was re-fitted to include data from Phase 1 Study M14-680 to estimate the absorption parameters for upadacitinib extended-release formulation. This analysis characterized upadacitinib population pharmacokinetics in healthy volunteers and subjects with RA using data from Phase 1 and 2 studies and was used to generate the individual empirical Bayesian parameter estimates which were used in upadacitinib Phase 2 exposure-response analyses.

Similar model structure was used as descripted previously: upadacitinib pharmacokinetics were adequately characterized using a two-compartment model with a first-order absorption process, absorption lag time, and a linear elimination process. Upadacitinib absorption from the extended-release formulation was adequately described by a mixed zero- and first-order absorption process. CYP2D6 genotype-inferred phenotypes were determined for a total of 573 subjects in the combined dataset: there were 355 (62%) normal metabolizers, 36 (6%) intermediate metabolizers, 29 poor metabolizers (5%), and 7 (1%) ultra-rapid metabolizers. CYP2D6 metabolic phenotype had no effect on upadacitinib apparent oral clearance (CL/F). Upadacitinib CL/F individual estimates were similar for subjects with different CYP2D6 metabolic phenotypes (Figure 4.3-4).

Figure 4.3-4 Distribution of Upadacitinib Model-Estimated Apparent Oral Clearance by CYP2D6 Metabolic Phenotype



UM = ultra-rapid metabolizer, EM = extensive metabolizer, IM = intermediate metabolizer, PM = poor metabolizer

(Source: Applicant's Population Pharmacokinetic Report R&D/17/0334, Figure 9)

Reviewer's comments: *The applicant conducted population PK analysis using data from Phase 1 and RA Phase 2 Studies. The impact of CYP2D6 genotype-inferred phenotype on upadacitinib CL/F was assessed*

in the analysis. The conclusion that CYP2D6 genotype-inferred phenotype did not correlate with upadacitinib CL/F is acceptable.

Table 4.3-3 Specific Comments on Applicant's Final Population PK model

Utility of the final model			**Reviewer's Comments**
Support labeling statements about intrinsic and extrinsic factors in Section 12.3 of the label:	**Intrinsic factor**	• "Body weight, gender, race, ethnicity, and age did not have a clinically meaningful effect on upadacitinib exposure [See Use in Specific Populations (8.5)]." • "Renal impairment has no clinically relevant effect on upadacitinib exposure. Upadacitinib AUC was 18%, 33%, and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function. Upadacitinib Cmax was similar in subjects with normal and impaired renal function." • "CYP2D6 metabolic phenotype had no effect on upadacitinib pharmacokinetics."	• The statement is acceptable. Covariate analysis using the sponsor's final PK model demonstrates that no evident effect on PK exists for body weight, gender, race, ethnicity, and age. • The statement regarding renal impairment is mainly supported by a dedicated study, and effect of creatine clearance on upadacitinib PK is also evaluated in the population PK analysis. Creatine clearance is a significant covariate in the final population PK model and the results are consistent to the dedicated study: 13% and 26% higher AUC in subjects with mild and moderate renal impairment, respectively, compared to normal renal function. • the conclusion regarding the effect of CYP2D6 metabolic phenotype on upadacitinib PK is acceptable.
	Extrinsic factor	• (b) (4)	The conclusion (b) (4) is not adequately supported (b) (4) The

			statement regarding methotrexate is acceptable.
Derive exposure metrics for Exposure-response analyses	N.A.		N.A.
Predict exposures at alternative dosing regimen	N.A.		N.A.

4.3.3 Exposure Response Analysis

4.3.3.1 Exposure-efficacy relationship

- Sponsor's analysis

The data for the full time course of ACR20, ACR50, ACR70, low disease activity (LDA) [based on DAS28 (CRP)], CR [based on DAS28 (CRP)] and dropout status for each subject in Studies M13-537, M13-550, M13-542, M13-549, M15-555 and M14-465 were used to develop continuous-time Markov exposure-response models of ACR scores as well as LDA/CR. Upadacitinib individual predicted plasma concentration versus profiles (based on population pharmacokinetic model including the same studies; R&D/18/0165) were used as input for the Markov models.

The efficacy of upadacitinib was exposure-dependent. Exposure-efficacy Markov Chain models for ACR responses as well as for LDA/CR [based on DAS28 (CRP)] described placebo responses as well as response to upadacitinib treatment in subjects with RA reasonably well. Simulations were performed using the final efficacy models to predict the efficacy responses following dosing with upadacitinib 15 mg QD, and 30 mg QD regimens (Table 4.3-4). Results of the exposure-efficacy simulations demonstrate that upadacitinib at the 30 mg QD dose provide only a small incremental efficacy benefit compared to 15 mg QD, indicating that the 15 mg QD dose achieved the plateau of the response.

Table 4.3-4 Model-Simulated Clinical Efficacy Responses Following Placebo and Upadacitinib 15 mg and 30 mg QD Dosing Regimens (Based on Exposure-Response Analyses of Phase 2 and 3 Studies)

Population	Clinical Efficacy Response Variable[a]	Upadacitinib Dosing Regimen		
		Placebo	15 mg QD	30 mg QD
MTX-IR on Background MTX	ACR20	40 (34, 47)	66 (60, 71)	68 (62, 74)
	ACR50	17 (12, 22)	41 (35, 48)	45 (39, 52)
	ACR70	6 (3, 11)	23 (18, 29)	26 (21, 33)
	LDA	19 (13, 24)	45 (40, 52)	50 (44, 57)
	CR	11 (8, 16)	31 (25, 36)	34 (29, 41)
bDMARD-IR on Background MTX	ACR20	36 (30, 43)	58 (52, 65)	61 (54, 67)
	ACR50	14 (8, 19)	34 (27, 42)	38 (32, 45)
	ACR70	5 (2, 9)	18 (13, 24)	21 (16, 26)
	LDA	18 (14, 24)	40 (34, 47)	45 (39, 51)
	CR	11 (7, 15)	27 (21, 33)	31 (25, 36)
MTX-IR on Upadacitinib Monotherapy	ACR20	36 (29, 44)	65 (58, 72)	68 (61, 75)
	ACR50	12 (8, 16)	42 (36, 49)	45 (38, 52)
	ACR70	3 (1, 7)	24 (18, 30)	27 (20, 33)
	LDA	17 (12, 23)	50 (44, 58)	55 (48, 62)
	CR	11 (7, 16)	36 (31, 44)	40 (34, 47)

MTX-IR = Methotrexate inadequate responder; bDMARD-IR = Biologic disease-modifying anti-rheumatic drug inadequate responder

a. Data are presented as median (5^{th}, 95^{th} percentiles).

(Source: Summary of Clinical Pharmacology Studies, Module 2.7.2)

4.3.3.2 Exposure-safety relationship

- Sponsor's analysis

For the exposure-safety analyses, upadacitinib individual Cavg values based on the empirical Bayesian individual pharmacokinetic parameter estimates from the population pharmacokinetic model were used as the exposure measure. The adverse events and laboratory parameters evaluated for relationships with upadacitinib exposures included serious infection, pneumonia, herpes zoster infection, changes in platelet count, changes in hemoglobin, lymphopenia (Grade 3 or higher, Grade 4 or higher), and neutropenia at Week 12/14 and at Week 24/26. Exploratory quartile plots were first evaluated using a pooled dataset across all studies (Studies M13-537, M13-550, M13-542, M13-549, M15-555, M14-465, and M13-545) to identify key safety variables at Week12/14 and Week 24/26 that appear to be related to upadacitinib exposure.

No trends for exposure-response relationships were observed for pneumonia, herpes zoster infection, changes in platelet count, lymphopenia (Grade 4 or higher), and neutropenia. A trend for possible exposure-response relationship based on the exploratory quartile plots was observed for hemoglobin, lymphopenia (Grade 3 or higher at Week 12/14), and serious infections (at Week 24/26). These parameters which showed a trend for relationship with exposure were assessed further. Logistic regression models were used to describe the relationships between upadacitinib exposures and these efficacy parameter changes at Week 12/14 as well as with serious infections up to Week 24/26. Increased upadacitinib exposures were associated with higher incidence of hemoglobin decrease from baseline (> 1 g/dL and > 2 g/dL) for both Week 12/14 and Week 24/26 and with increased incidence of serious infections up to Week 24/26. On the other hand, upadacitinib exposures were only associated with higher

incidence of lymphopenia Grade 3 or higher at Week 12/14; while the relationship with exposure was not statistically significant at Week 26.

Reviewer's comments: *The applicant's exposure response analyses, which are generally consistent with the observed efficacy and safety data, appear reasonable.*

4.4 Appendix – Physiological-based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK report (No. RD171073) titled "Development and Application of Physiologically-Based Pharmacokinetic Model of Upadacitinib" to support the PK bridge of the drug-drug interactions studies using the immediate-release (IR) formulation to the extended-release (ER) to-be-marketed formulation. Specifically, PBPK modeling approach was applied to assess the effects of ketoconazole (a strong CYP3A4 inhibitor), and rifampin (a strong CYP3A4 inducer) on the PK of upadacitinib when administered as ER formulation.

The Division of Pharmacometrics has reviewed the PBPK report, modeling and simulation files, and the Applicant's responses to our request for information dated 25 February 2019 and 28 March 2019, and concluded the following:

- PBPK analyses were considered adequate to evaluate the effect of the CYP3A4 modulators, ketoconazole and rifampin, on upadacitinib IR and ER formulations.
- PBPK analyses estimated that the effects of strong CYP3A4 inhibition or induction, including potential modulation of intestinal efflux transporters P-gp/BCRP, are expected to be comparable (<25% difference) for the IR and the ER formulations of upadacitinib.

Background

Upadacitinib to-be-marketed formulation is a 15 mg extended-release (ER) tablet for oral administration. The proposed recommended dose is 15 mg once daily (QD) with or without food. Upadacitinib was administered as immediate-release (IR) capsule formulation in some Phase 1 and 2 studies; while the ER tablet formulation in later Phase 1 and Phase 3 studies. The bioavailability of upadacitinib ER formulation is estimated to be 76% relative to the IR formulation. After single dose (SD) administration of the IR formulation, median Tmax was 1-2 hours and terminal elimination half-life (t1/2) was 6 to 16 hours; while for the ER formulation, median Tmax was 2-4 hours and t1/2 ranged from 9 to 14 hours. Upadacitinib exposure (Cmax and AUC) were approximately dose-proportional over single and multiple dose ranges for both IR and ER formulations (i.e., 3 to 24 mg following SD and twice-daily administration of the IR formulation, and 7.5 to 45 mg SD and 15-30 mg QD administration of ER formulation). Multiple QD dosing of the ER formulation showed minimal accumulation in plasma and steady-state concentrations were achieved within 4 days (M14-680).

Upadacitinib is cleared via multiple pathways. Upadacitinib is primarily metabolized by cytochrome P450 (CYP) CYP3A4 with a minor contribution of CYP2D6. In the ADME study using a single dose of upadacitinib IR formulation, unchanged upadacitinib was the major drug-related moiety in plasma (79%) with no major circulating metabolites (<13%). About 24% and 38% of total dose of upadacitinib was excreted unchanged in urine and feces, respectively. The amount of unchanged upadacitinib in the feces in first 24 -48 hours were minor (around 1% and 14%, respectively), suggesting upadacitinib is well absorbed.

In vitro, upadacitinib is a substrate for the efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) (RD160380), but it is not a substrate for the hepatic uptake transporters organic anion transporting polypeptide (OATP) 1B1 and 1B3 (RD160380). Clinically, no significant interaction with rifampin, a CYP3A4 and OATP1B inhibitor (postulated P-gp and BCRP inhibitor), following a single-dose administration, was observed with upadacitinib IR formulation (M13-540).

Upadacitinib was determined to be a CYP3A4 inducer in vitro (RD16-1011); although, clinically, there was no significant effect on the PK of the index CYP3A4 substrate midazolam (M14-624). The effect of upadacitinib on itself as a CYP3A4 inducer is expected to be not relevant considering the linear and time-independent PK (RD18-0165, M13-845), and minor effect on midazolam

Methods

PBPK model structure and development

The PBPK analyses were performed using the population-based PBPK software Simcyp® (V17, Simcyp Ltd., a Certara Company, Sheffield, United Kingdom).

The upadacitinib PBPK model was developed based on in vitro, human ADME (M13-548) and PK data (M13-401 and M13-845). Briefly, an Advanced Dissolution, Absorption and Metabolism (ADAM) model and a minimal PBPK model were utilized to describe upadacitinib PK. The human intestinal effective permeability (Peff human 10.2 x 10^{-4} cm/s) was predicted using Mech Peff model. The unbound fraction in plasma (fup=0.48) and blood:plasma ratio (B/P=1) values were determined in vitro (RD17-0325). The distribution parameters (Vss, Vsac, Kin, and Kout) were estimated based on clinical data (M13-401). The enzyme kinetics (CLint) for CYP3A4 and CYP2D6 were derived from the in vitro study (A-1293543 Memo No. 09) and optimized based on the DDI study with ketoconazole and CYP2D6 phenotype population PK analysis (RD17-0334). The renal clearance contribution was determined based on the ADME (M13-548) and single dose PK (M13-401) studies. Because upadacitinib was well absorbed (M13-458), the unchanged drug in the feces was considered due to systemic clearance, assigned as non-specific clearance in the model. The contribution of each pathway to the total systemic clearance consisted of approximately 35% for CYP3A4, 5% for CYP2D6, 20% for renal clearance and 40% additional systemic clearance. The hepatic uptake of upadacitinib was assumed to occur via passive diffusion based on in vitro transporter data (RD160380). The kinetic parameters for P-gp and BCRP were based from in vitro studies (RD160380) and optimized based on in vivo PK (M13-401).

The absorption of the ER formulation was determined by assuming the in vivo dissolution profile of upadacitinib followed a Weibull distribution and the systemic disposition was consistent with the IR formulation. Weibull function parameters alpha (α=0.45) and beta (β=0.115) were estimated to recover the observed PK of upadacitinib after administration of the ER formulation (M15-868).

All simulations were performed using the default healthy volunteer population model (software's library, V17), and in the fasted state as food had no significant effect on the exposure of upadacitinib administered as ER formulation (M14-680).

The perpetrator models for ketoconazole "Sim-Ketoconazole-400mg QD", and rifampin single-dose "SV-Rifampicin-SD", and multiple-dose "SV-Rifampicin-MD" (software's compound library, V17) were used in the PBPK simulations for the respective DDIs.

As exploratory, the Applicant modified the compound files for ketoconazole and rifampin-MD to include P-gp interaction parameters to investigate the potential DDI effect on the efflux transporter on disposition of upadacitinib administered as IR or ER formulations. The default ketoconazole model was modified by incorporating a P-gp competitive inhibition constant (Ki) value of 2.53 µM based on collection of published in vitro data[1]. To represent rifampin MD-upadacitinib DDI, the Applicant modified upadacitinib model by increasing the intestinal P-gp relative expression factor (REF) value by 3.2-fold. A similar approach was previously proposed to predict digoxin-rifampin DDI[2]. The Applicant assumption was that rifampin has been reported to induce P-gp expression by approximately 3-fold in vitro[3] and in vivo[4]. The default rifampin-SD compound file (V17) proposed rifampin as a competitive inhibitor of both intestinal and liver P-gp and BCRP at single-dose.

PBPK model verification

The performance of upadacitinib PBPK model to predict upadacitinib PK profile after administration of the IR or ER formulations in healthy volunteers was verified by comparison of simulated and observed clinical PK data (M13-845, M14-680, M15-878, M15-539-Control, M15-551-Control). The DDI study between multiple-dose rifampin with upadacitinib administered as single-dose IR formulation (M13-540) was used to verify the contribution of CYP3A4 to the disposition of upadacitinib.

The PBPK simulations and respective study designs conducted for upadacitinib model verification and application are listed in Table 4.4-1.

Table 4.4-1 PBPK simulations (N) and respective study design used for upadacitinib model

#	Trials x N	Study	Upadacitinib Formulation: Dosing Regimen	Perpetrator	Dosing Regimen	Simulation Duration	PBPK Model Objective
1	10x10	M13-401	IR: 3, 6, 12, 24, 36 mg SD	NA	NA	3 days	Development
2	10x10	M13-401	IR: 3 mg SD on day 4	ketoconazole	400 mg QD for 6 days	7 days	Development
3	10x10	M13-845	IR: 3, 6, 12, 24 mg BID for 14 days	NA	NA	15 days	Verification
4	10x10	M14-680	IR: 6 and 12 mg BID for 7 days ER: 15 and 30 mg SD ER: 15 and 30 mg QD for 7 days	NA	NA	10 days	Verification
5	10x10	M15-878	ER: 30 mg SD, fasted	NA	NA	3 days	Verification
6	10x10	M13-539 M13-551	ER: 15 mg SD	NA	NA	5 days	Verification
7	10x16	M13-540	IR: 12 mg SD on days 1 and 8	rifampin	600 mg QD for 9 days	10 days	Verification
8	10x10	NA	ER: 15 mg QD on Days 4-8	ketoconazole	400 mg QD for 8 days	9 days	Application
9	10x10	NA	ER: 15 mg QD on Days 8-14	rifampin	600 mg QD for 14 days	15 days	Application

[1] University of Washington DDI Database

[2] Neuhoff S, Yeo KR, Barter Z, et al. Application of permeability-limited physiologically-based pharmacokinetic models: part II -prediction of p-glycoprotein mediated drug-drug interactions with digoxin. J Pharm Sci. 2013;102(9):3161-73.

[3] Greiner B, Eichelbaum M, Fritz P, et al. The role of intestinal p-glycoprotein in the interaction of digoxin and rifampin. J Clin Invest. 1999;104(2):147-53.

[4] Westphal K, Weinbrenner A, Zschiesche M, et al. Induction of p-glycoprotein by rifampin increases intestinal secretion of talinolol in human beings: a new type of drug/drug interaction. Clin Pharmacol Ther. 2000;68(4):345-55.

NA: Not applicable. Software's virtual healthy volunteer population was used for all simulations. (Source: Table 3 from the PBPK report, and Applicant's Response to Clin Pharm IR dated 3/28/19).

PBPK model application

The upadacitinib PBPK model was used to predict the following:

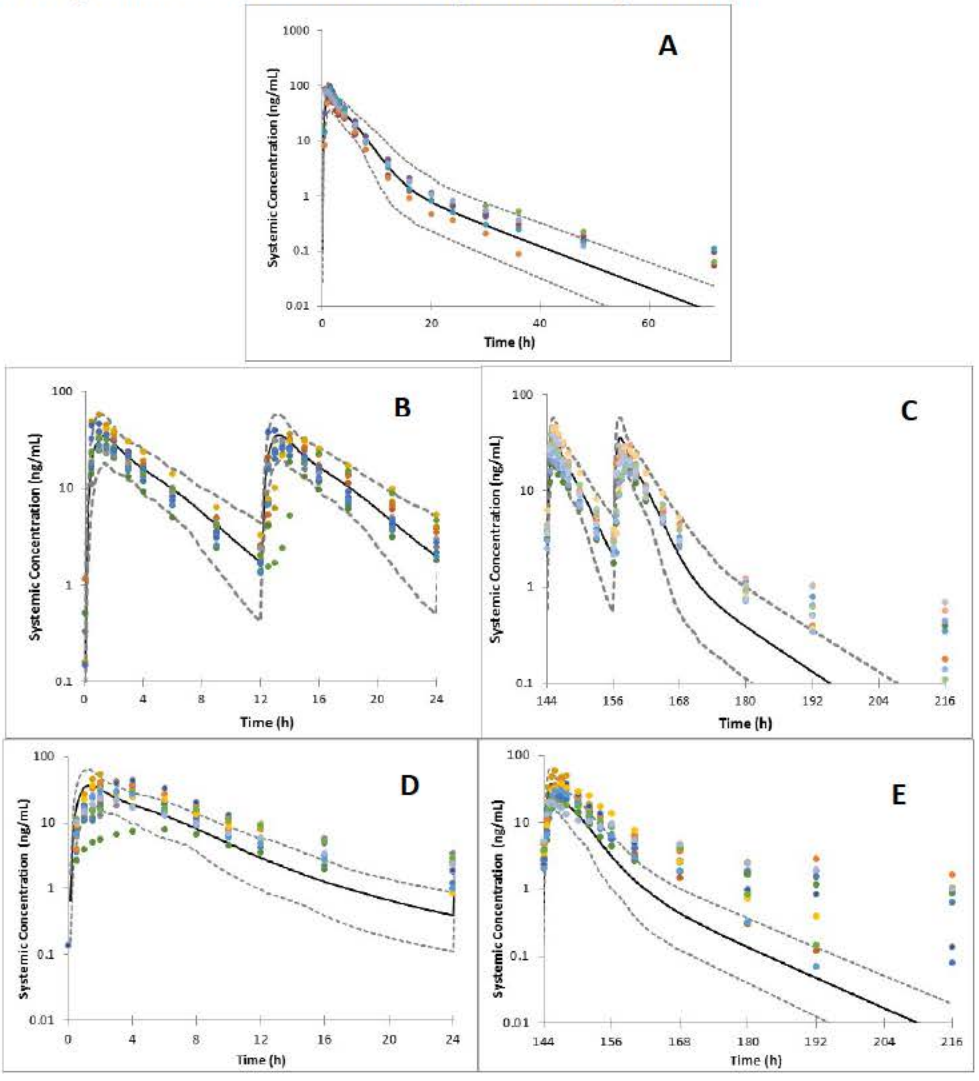
- Effect of ketoconazole as a CYP3A4 inhibitor (and potential P-gp inhibitor) on the PK of upadacitinib administered as ER formulation
- Effect of rifampin-SD as a CYP3A4 inhibitor (and potential P-gp and BCRP inhibitor) on the PK of upadacitinib administered as ER formulation
- Effect of rifampin-MD as a CYP3A4 inducer (and potential P-gp inducer) on the PK of upadacitinib administered as ER formulation

Results

Model performance

PBPK analyses were able to describe upadacitinib PK following a single dose or multiple doses of upadacitinib administered as IR or ER formulations in healthy subjects (Table 4.4-1, simulations #1, 3-6). The predicted versus observed PK profiles are shown in Figure 4.4-1.

Figure 4.4-1 PBPK predicted and observed PK profiles of upadacitinib



PBPK predicted mean (lines) and observed individual (circles) plasma concentration (log-scale) -time profiles of upadacitinib following (A) 12 mg SD of upadacitinib IR (Study M13-401); (B) 6 mg BID dose of upadacitinib IR Day 1; (C) 6 mg BID dose of upadacitinib IR Day 7 (Study M14-680-part 5); (D) 15 mg QD dose of upadacitinib ER Day 1; and (E) 15 mg QD dose of upadacitinib ER Day 7 (Study M14-680-part 5). The solid lines are the mean data for the simulated population and the dashed lines are the 5th and 95th percentiles. (Source: Reviewer's Analysis-simulation output files).

Table 4.4-2 Comparison of PBPK predicted and observed mean (SD) Cmax and AUC values of upadacitinib

Upadacitinib Formulation: Dosing Regimen	Observed		Predicted		Predicted/observed	
	Cmax (ng/mL)	AUC (ng hr/mL)	Cmax (ng/mL)	AUC (ng hr/mL)	Cmax	AUC
IR 3 mg SD	25.0 (6.88)	102 (27.5)	17.7 (6.26)	78.2 (19.8)	0.7	0.8
IR 6 mg SD	38.9 (9.96)	159 (37.5)	35.4 (12.5)	156 (39.6)	0.9	1.0
IR 6 mg BID day 1	36.5 (9.03)	289 (61.7)	36.6 (12.3)	299 (74.3)	1.0	1.0
IR 6 mg BID day 7	33.9 (8.76)	288 (63.5)	36.8 (12.3)	312 (78.8)	1.1	1.1
IR 12 mg SD	64.6 (10.3)	231 (34.5)	70.7 (25.1)	312 (79.2)	1.1	1.3
	82.9 (12.1)	329 (48.9)	70.6 (24.8)	312 (79.2)	0.9	0.9
IR 12 mg BID day 1	80.8 (18.9)	497 (74.8)	72.9 (24.7)	597 (149)	0.9	1.2
IR 12 mg BID day 7	73.9 (14.2)	534 (97.8)	73.3 (24.6)	620 (157)	1.0	1.2
IR 24 mg SD	158 (18.4)	612 (78.6)	138 (46.9)	615 (158)	0.9	1.0
ER 15 mg SD	26.0 (9.65)	242 (63.6)	38.6 (16.7)	191 (52.1)	1.5	0.8
	26.6 (8.39)	215 (56.5)	36.6 (47.7)	185 (18.2)	1.4	0.9
	31.1 (11.8)	270 (77.7)	36.6 (47.7)	185 (18.2)	1.2	0.7
ER 15 mg QD day 1	31.7 (12.6)	249 (71.9)	38.6 (16.7)	187 (50.7)	1.2	0.8
ER 15 mg QD day 7	31.9 (11.2)	279 (71.4)	38.9 (16.7)	191 (52.1)	1.2	0.7
ER 30 mg SD	63.7 (21.1)	491 (133)	77.2 (33.4)	382 (104)	1.2	0.8
	58.2 (17.5)	486 (115)	77.2 (33.4)	382 (104)	1.3	0.8
ER 30 mg QD day 1	65.7 (14.2)	454 (102)	77.2 (33.5)	374 (101)	1.2	0.8
ER 30 mg QD day 7	68.2 (20.5)	525 (123)	77.7 (33.3)	381 (104)	1.1	0.7

Data are presented as mean (standard deviation). Predicted/observed ratio of mean values. SD: single dose; BID: twice daily; QD: once daily; AUC0-72h for SD, AUC0-24h for BID and QD. Trial design simulations: Table 4.4-1, simulations #1-6. (Source: Simulation output files, CSR M13-539, CSR M13-551, CSR M15-878, CSR M13-845, CSR M13-401, CSR M14-680).

PBPK analysis fairly predicted the PK parameters for upadacitinib. The predicted mean Cmax and AUC values were within ±50% of the observed data (Table 4.4-2).

It was noted, however, a systematic prediction bias. The PBPK model consistently under-predicted the terminal half-life after single or multiple dosing of the IR or ER formulations (Figure 4.4-1). For the ER formulation, the PBPK model consistently over-predicted Cmax values (prediction error around 20 to 50%), under-predicted AUCtau values (prediction error around -20 to -30%) (Table 4.4-2), and under-predicted Tmax values (prediction error around -25 to -50%) (see discussion on Model Limitations section).

Model verification

The DDI effect of ketoconazole was used to refine the contribution of CYP3A4 metabolism to upadacitinib administered as a single dose 3 mg IR (Table 4.4-1, simulation #2). The predicted ratio of geometric means for Cmax and AUC were within ±25% of the observed values (Table 4.4-3). The metabolic contribution of CYP3A4 (or fmCYP3A4) for upadacitinib was estimated to be around 35% in the PBPK model.

Table 4.4-3 Comparison of observed and predicted Mean (SD) Cmax and AUC values of upadacitinib (3 mg SD) in the absence and presence of ketoconazole (400 mg QD)

Treatment	Cmax (ng/mL)		AUCinf (ng h/mL)		Cmax Ratio (90%CI)		AUC Ratio (90%CI)	
	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Control	17.1 (6.18)	21.4 (4.18)	75.5 (18.5)	87.7 (12.6)	1.32 (1.29-1.36)	1.70 (1.55-1.89)	1.70 (1.63-1.76)	1.75 (1.62-1.88)
with ketoconazole	22.3 (7.15)	36.3 (6.34)	125.9 (22.7)	156 (31.8)				

PK data are presented as mean (SD). Ratio of geometric means for Cmax and AUC values expressed as with inhibitor/without inhibitor. Observed values (N=11-12) from study M13-401. Trial design parameters: Table 4.4-1, simulation #2. (Source: Simulation output files, CSR M13-401).

The DDI effect of multiple-dose rifampin was used to verify the contribution of CYP3A4 metabolism to upadacitinib administered as a single dose of 12 mg IR (Table 4.4-1, simulation #7). The predicted geometric mean of the ratios for Cmax and AUC were within 20% difference of the observed values (Table 4.4-4). The PBPK analysis suggested that upadacitinib PBPK model provided a reasonable estimate of the metabolic contribution of CYP3A4 in vivo.

Table 4.4-4 Comparison of observed and predicted Mean (SD) Cmax and AUC values of upadacitinib (12 mg SD) in the absence and presence of rifampin (600 mg SD and QD)

Treatment	Cmax (ng/mL)		AUC_{36h} (ng h/mL)		Cmax Ratio (90%CI)		AUC Ratio (90%CI)	
	Predicted	Observed	Predicted	Observed	Predicted	Observed	Predicted	Observed
Control	68.0 (23.7)	62.0 (10.9)	309 (78.6)	334 (76.1)	-	-	-	-
with rifampin SD	86.9 (30.5)	71.3 (15.5)	342 (83.7)	357 (80.9)	1.28 (1.26-1.30)	1.14 (1.02-1.28)	1.11 (1.10-1.12)	1.07 (1.01-1.14)
with rifampin QD	42.1 (19.9)	31.7 (11.5)	135 (63.3)	131 (27.9)	0.58 (0.56-0.60)	0.49 (0.44-0.55)	0.42 (0.40-0.44)	0.39 (0.37-0.42)

PK data are presented as mean (SD). Ratio of geometric means of Cmax and AUC values expressed as with inducer/without inducer. Observed values (N=12) from study M13-540. Trial design parameters: Table 4.4-1, simulation #7. (Source: Simulation output files, Reviewer's analysis, CSR M13-540).

To evaluate a possible effect of P-gp inhibition by a strong CYP3A4 inhibitor such as ketoconazole, the Applicant proposed a competitive inhibition constant (Ki) for P-gp in the ketoconazole model. The predicted upadacitinib Cmax ratio increased as a function of the selected Ki value (higher predicted Cmax ratio with lower Ki value), with lesser effect on upadacitinib AUC ratio. There was a <20% impact on the predicted interaction if the P-gp contribution is included in the DDI ketoconazole-upadacitinib IR simulations (Table 4.4-5).

Table 4.4-5 PBPK predicted changes in upadacitinib exposure (Cmax and AUC ratios) following concomitant administration of upadacitinib IR formulation (3 mg or 12 mg) with ketoconazole (400 mg QD) or rifampin (600 mg SD and QD)

DDI Scenario	Perpetrator Dosing Regimen	Perpetrator PBPK Model	[a] Predicted Cmax Ratio (90% CI)	[a] Predicted AUC Ratio (90%CI)
CYP3A4 inhibitor	KTZ 400 mg QD	Default	1.32 (1.29-1.36)	1.70 (1.63-1.76)
CYP3A4, P-gp inhibitor	KTZ 400 mg QD	Inclusion P-gp Ki=2.53 µM	1.38 (1.35-1.41)	1.71 (1.65-1.77)
CYP3A4, P-gp inhibitor	KTZ 400 mg QD	Inclusion P-gp Ki=0.16 µM	1.61 (1.56-1.67)	1.75 (1.68-1.83)
CYP3A4, P-gp, BCRP inhibitor	RIF 600 mg SD	Default	1.28 (1.26-1.30)	1.11 (1.10-1.12)

CYP3A4 inhibitor	RIF 600 mg SD	Exclusion Ki P-gp and BCRP	1.03 (1.03-1.03)	1.09 (1.09-1.10)
CYP3A4 inducer	RIF 600 mg QD	Default	0.58 (0.56-0.60)	0.42 (0.40-0.44)
CYP3A4, P-gp inducer	RIF 600 mg QD	Inclusion 3.2-fold induction P-gp	0.53 (0.50-0.56)	0.38 (0.36-0.41)

[a]Data are presented as ratio of geometric means of Cmax and AUClast values expressed as with perpetrator/without perpetrator. Trial design parameters: Table 4.4-1, simulations #2 and 7. (Source: Simulation output files- Reviewer's analysis, Tables 8 and 9 from Applicant's Response to IR dated 28 March 2019).

The upadacitinib exposure ratios in terms of Cmax were comparable (<10% difference) between the default rifampin model and the modified model that included a 3.2-fold induction for intestinal P-gp (Table 4.4-5). Therefore, accounting for intestinal P-gp induction by rifampin had minor affect in the predicted exposure ratios of upadacitinib IR when concomitantly administered with multiple-dose rifampin.

The reviewer conducted PBPK analysis evaluating the DDI effect of single dose rifampin to explore the relevance of intestinal P-gp and BCRP efflux (and CYP3A4 metabolism) on the disposition of upadacitinib administered as a single dose of 12 mg IR (Table 4.4-1, simulation #7). The PBPK model predicted an increase of AUC comparable with the observed values (1.11 vs 1.07, 3% prediction error) (Table 4.4-4), confirming a reasonable estimate of CYP3A4 metabolism in the model. However, the model over-predicted the interaction in terms of Cmax ratio (1.28 versus 1.14, 13% prediction error) (Table 4.4-4). Exploratory simulations without interaction towards the intestinal efflux transporters resulted in a 20% lower Cmax ratio (Table 4.4-5). These results suggested an overestimation of intestinal P-gp and BCRP contribution in upadacitinib PBPK model. Nonetheless, it would allow a conservative evaluation of the effect of P-gp/BCRP modulators and its potential impact on upadacitinib administered as ER formulation.

Model application

PBPK analysis was applied to bridge the clinical DDI effect of strong CYP3A4 modulators (and potential modulation of the intestinal efflux transporters P-gp and BCRP) observed with upadacitinib IR formulation to the ER formulation. PBPK analysis estimated the exposures of upadacitinib following concomitant administration of the therapeutic proposed dose of 15 mg QD ER formulation, with the strong CYP3A4 inhibitor ketoconazole (400 mg QD) and the strong CYP3A4 inducer rifampin (600 mg QD) (Table 4.4-1, simulations #8 and 9).

Using the default perpetrator models, the effects of strong CYP3A4 inhibition or induction on upadacitinib steady-state exposure with the ER formulation were predicted to be comparable to the effects previously observed in the clinical DDI studies conducted with upadacitinib IR formulation (Table 4.4-6 versus Tables 4.4-3 and 4.4-4).

There was a <25% impact on the predicted interaction if the P-gp involvement (P-gp inhibition by ketoconazole or induction by rifampin-MD) was considered in the DDI effect for the upadacitinib ER formulation (Table 4.4-6).

The predicted effect of single-dose rifampin (as a CYP3A4/P-gp/BCRP inhibitor) on upadacitinib ER formulation was also comparable to the observed with the IR formulation (CmaxR 1.27 vs 1.14).

Table 4.4-6 PBPK predicted changes in upadacitinib stead-state exposure (Cmax and AUC ratios) following concomitant administration of upadacitinib ER formulation (15 mg QD) with ketoconazole (400 mg QD) or rifampin (600 mg SD and QD)

DDI Scenario	Perpetrator Dosing Regimen	Perpetrator PBPK Model	[a] Predicted Cmax Ratio (90% CI)	[a] Predicted AUC Ratio (90%CI)
CYP3A4 inhibitor	KTZ 400 mg QD	Default	1.35 (1.32-1.38)	1.69 (1.64-1.75)
CYP3A4, P-gp inhibitor	KTZ 400 mg QD	Inclusion P-gp Ki=2.53 μM	1.40 (1.37-1.44)	1.70 (1.65-1.76)
CYP3A4, P-gp inhibitor	KTZ 400 mg QD	Inclusion P-gp Ki=0.16 μM	1.63 (1.58-1.68)	1.75 (1.69-1.81)
CYP3A4, P-gp, BCRP inhibitor	RIF 600 mg SD	Default	1.27 (1.25-1.29)	1.11 (1.10-1.12)
CYP3A4 inducer	RIF 600 mg QD	Default	0.54 (0.51-0.57)	0.39 (0.36-0.42)
CYP3A4, P-gp inducer	RIF 600 mg QD	Inclusion 3.2-fold induction P-gp	0.40 (0.39-0.43)	0.36 (0.34-0.37)

[a]Data are presented as ratio of geometric means of $Cmax_{ss}$ and $AUCtau_{ss}$ values expressed as with perpetrator/without perpetrator. Trial design parameters: Table 4.4-1, simulations #8 and 9. (Source: Simulation output files, Reviewer's analysis, Tables 8 and 9 from Applicant's Response to IR dated 28 March 2019).

Mechanistically, PBPK analysis suggested that upadacitinib is well absorbed and do not undergo an extensive first-pass elimination in the intestine. The fractions absorbed (fa) and escaping gut metabolism (fg) were 0.95 and 1 for the IR formulation, and 0.46 and 1 for the ER formulation, respectively. Based on in vivo dissolution data incorporated in the PBPK model, 90% of upadacitinib was dissolved overtime from the ER formulation. Clinically, 15 mg QD ER formulation provided equivalent $AUC_{0\text{-}24h}$ and comparable Cmax values to 6 mg BID IR formulation (M14-680). Based on PBPK predictions, along the segments of GI tract, there was a <25% difference in the total intestinal lumen concentration, enterocyte concentration and absorption rate between a single dose of 6 mg BID IR and 15 mg ER QD. For the doses used in the clinical DDI studies, single dose of 3 mg IR (DDI ketoconazole) or 12 mg IR (DDI rifampin), there were around 2-fold difference- lower and higher, respectively- in those concentrations/rates compared to 15 mg QD ER.

Decrease in apical efflux clearance via inhibition of intestinal transporters resulted in a decrease in the lumen concentration and absorption rate, and an increase in enterocyte concentration. Inversely, increase in apical efflux clearance via induction of transporters resulted in an increase in the lumen concentration and absorption rate, and a decrease in enterocyte concentration. For each interaction mechanism, the percentage changes in those concentrations/rates were equivalent between the IR and ER formulation, despite numerical differences. Ultimately, the net effect of modulation of intestinal efflux transporters (and interplay with modulation of CYP3A metabolism) was expected to be comparable for the IR and the ER formulations of upadacitinib as represented by the predicted interaction ratios (<25% difference).

Of note, in vitro assessment of upadacitinib transport in MDCK-MDR1 or -BCRP cells reported that the maximum efflux ratio (ERmax) for P-gp was around 2-fold higher than that of BCRP. The net P-gp efflux ratio was 15, which was reduced to 1.4 with a P-gp inhibitor; while the net BCRP efflux ratio was 14, which was reduced to 0.66 with a BCRP inhibitor (RD160380). The in vitro evidence may support the role of BCRP in the disposition of upadacitinib is expected to be similar or lower that of P-gp.

Model limitations

- The PBPK model development process excessively utilized optimization/refining of in vitro and system parameters to recover PK data from a limited number of clinical studies. Additionally, a systematic prediction bias on PK estimation was noted for both upadacitinib IR and ER formulations. It also appeared that the model overestimated the contribution of intestinal efflux transporters to the disposition of upadacitinib. The model was considered adequate for characterizing the DDI potential for the ER formulation with a strong CYP3A4 inhibitor and a strong CYP3A4 inducer, which have been previously characterized clinically using the IR formulation. Accordingly, the model is not considered adequate for quantitative predictions for untested DDI scenarios with new perpetrators.

- Upadacitinib was determined to be a P-gp and BCRP substrate in vitro (RD160380). Unchanged drug in feces may be due to systemic secretion and/or direct gut secretion/incomplete absorption. The mass balance data (RD150181) suggested that upadacitinib is well absorbed and a systemic secretion pathway seems plausible (amount of unchanged drug in the feces was minor in first 48 hours; while it was prolonged to 4-7 days after dosing). The current upadacitinib model did not mechanistically include P-gp or BCRP in the systemic secretion of upadacitinib.

  In the event of P-gp and/or BCRP be involved in active secretion of upadacitinib from systemic circulation, changes in systemic clearance may be expected with modulators of these transporters. Given the magnitude of interaction observed between upadacitinib and ketoconazole (as CYP3A4 and postulated P-gp inhibitor, AUCR 1.70), which could be attributed by CYP3A4 in the liver, the involvement of systemic clearance via P-gp pathway is probably low. Additionally, interaction with a single dose of rifampin (as a CYP3A4 and OATP1B inhibitor, and postulated P-gp and BCRP inhibitor at single dose) resulted in upadacitinib CmaxR of 1.14 and AUCR of 1.07, suggesting a low contribution of transporters to overall clearance of upadacitinib. Furthermore, it would be expected that changes in systemic clearance with modulators of P-gp/BCRP transporters affecting the elimination half-life of upadacitinib are comparable for both IR and ER formulations.

  Therefore, the involvement of systemic clearance via efflux transporter, while possible, would not be expected to impact the current conclusions for the PBPK model.

Conclusions

PBPK analyses was deemed adequate to evaluate the effect of ketoconazole and rifampin on upadacitinib PK following administration of IR or ER formulations. The model predicted the effects of strong CYP3A4 inhibition or induction, including potential modulation of intestinal efflux transporters P-gp/BCRP, are expected to be comparable (<25% difference) for the IR and the ER formulations of upadacitinib.

4.5 New Drug Application Filing Memo

CLINICAL PHARMACOLOGY FILING FORM

Application Information

NDA/BLA Number	211675	**SDN**	2
Applicant	Abbvie	**Submission Date**	12/18/2018
Generic Name	Upadacitinib	**Brand Name**	NA
Drug Class	JAK1 inhibitor		
Indications	(b) (4)		
Dosage Regimen	• The recommended oral dose is 15 mg once daily with or without food. • May be used as monotherapy or in combination with methotrexate or other conventional synthetic DMARDs		
Dosage Form	Extended-release tablets, 15 mg	**Route of Administration**	Oral
OCP Division	DCP2	**OND Division**	Pulmonary, Allergy and Rheumatology Prods

OCP Review Team	**Primary Reviewer(s)**	**Secondary Reviewer/ Team Leader**
Division	Lei He, PhD	Anshu Marathe, PhD
Pharmacometrics	Jing Niu, MD (DCP2)	Jingyu Yu, PhD
Genomics		

Review Classification	☐ Standard ☑ Priority ☐ Expedited		
Filing Date	2/15/2019	**74-Day Letter Date**	3/1/2019
Review Due Date	5/17/2019	**PDUFA Goal Date**	8/18/2019

Application Fileability

Is the Clinical Pharmacology section of the application fileable?

☑ Yes

☐ No

If no list reason(s)

Are there any potential review issues/ comments to be forwarded to the Applicant in the 74-day letter?

☐ Yes

☑ No

If yes list comment(s)

Is there a need for clinical trial(s) inspection?

☑ Yes

☐ No

If yes explain

Changes [redacted] (b) (4) have been made between the Phase 3 ER tablets and the proposed commercial ER tablets. Study M15-878 was conducted to demonstrate the bioequivalence between the ER tablets used in clinical studies and the proposed commercial ER tablets. This BE study will be used to support the bridging of PK, efficacy and safety data obtained from ER tablets used in Phase 3 clinical studies to the proposed commercial ER tablets. Therefore, we request that both the clinical site and bioanalytical site be inspected for this submission.

Tabular Listing of All Human Studies	☑ Yes ☐ No	Clinical Pharmacology Summary	☑ Yes ☐ No
Bioanalytical and Analytical Methods	☑ Yes ☐ No	Labeling	☑ Yes ☐ No

Clinical Pharmacology Studies			
Study Type		**Count**	**Comment(s)**
In Vitro Studies			
☑ Metabolism Characterization		3	
☑ Transporter Characterization		1	
☑ Distribution		1	
☑ Drug-Drug Interaction		3	
In Vivo Studies			
Biopharmaceutics			
☐ Absolute Bioavailability			
☑ Relative Bioavailability and Food effect		9	
☑ Bioequivalence		1	
☑ Other			Bioanalytical study reports
Human Pharmacokinetics			
Healthy Subjects	☑ Single Dose	1	
	☑ Multiple Dose	1	
Patients	☐ Single Dose		
	☑ Multiple Dose		
☑ Mass Balance Study		1	
☐ Other (e.g. dose proportionality)			
Intrinsic Factors			
☑ Race		2	
☐ Sex			
☐ Geriatrics			
☐ Pediatrics			
☑ Hepatic Impairment		1	
☑ Renal Impairment		1	

☐ Genetics					
Extrinsic Factors					
☑ Effects on Primary Drug	1				
☑ Effects of Primary Drug	4				
Pharmacodynamics					
☐ Healthy Subjects					
☐ Patients					
Pharmacokinetics/Pharmacodynamics					
☐ Healthy Subjects					
☑ Patients	3				
☑ QT	1				
Pharmacometrics					
☑ Population Pharmacokinetics	6				
☑ Exposure-Efficacy					
☑ Exposure-Safety					
Total Number of Studies		**In Vitro**	8	**In Vivo**	26
Total Number of Studies to be Reviewed			8		26

Criteria for Refusal to File (RTF)		
RTF Parameter	**Assessment**	**Comments**
1. Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	☑Yes ☐No ☐N/A	
2. Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	☑Yes ☐No ☐N/A	
3. Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	☑Yes ☐No ☐N/A	
4. Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?	☐Yes ☐No ☑N/A	
5. Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	☑Yes ☐No ☐N/A	
6. Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	☑Yes ☐No ☐N/A	
7. Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	☑Yes ☐No ☐N/A	
8. Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	☑Yes ☐No ☐N/A	
9. Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	☑Yes ☐No ☐N/A	
Complete Application **10.** Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the	☑Yes ☐No ☐N/A	

sponsor submitted a justification that was previously agreed to before the NDA submission?		
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality) Checklist		
Data		
1. Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	☑Yes ☐No ☐N/A	
2. If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	☐Yes ☐No ☑N/A	
Studies and Analysis		
3. Is the appropriate pharmacokinetic information submitted?	☑Yes ☐No ☐N/A	
4. Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	☑Yes ☐No ☐N/A	
5. Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	☑Yes ☐No ☐N/A	
6. Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	☑Yes ☐No ☐N/A	
7. Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?	☐Yes ☐No ☑N/A	
General		
8. Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	☑Yes ☐No ☐N/A	
9. Was the translation (of study reports or other study information) from another language needed and provided in this submission?	☐Yes ☑No ☐N/A	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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05/17/2019 01:32:49 PM

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