2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: ABT-494 (Upadacitinib)		
Name of Active Ingredient: ABT-494 (Upadacitinib)		

Title of Study: 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

Coordinating Investigator: [redacted]

Study Sites: 3 sites in the US

Publications: None

Studied Period (Years):
First Subject First Visit: 24 August 2016
Last Subject Last Visit: 16 August 2017

Phase of Development: 1

Objective:

The objective of this study was to assess the pharmacokinetics and safety of a single upadacitinib dose in subjects with normal renal function, and in subjects with mild, moderate and severe renal impairment.

Methodology:

Single-dose, open-label, multicenter study designed to assess the pharmacokinetics and safety of a single upadacitinib 15 mg dose in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.

Enrolled subjects were assigned to one of the 4 groups based on their renal function as follows.

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

Serial blood and urine samples for upadacitinib assays were collected for 120 hours after dosing in each group.

Number of Subjects (Planned and Analyzed):

Planned: 24, Entered: 24, Completed: 24, Evaluated for Safety: 24, Evaluated for Pharmacokinetics: 24

Diagnosis and Main Criteria for Inclusion:

All Subjects

- Male or female between 18 and 75 years old, inclusive at date of consent.
- Subject's Body Mass Index (BMI) was ≥ 18.0 to ≤ 38.0 kg/m^2.

Subjects with Normal Renal Function (Group 1)

- A condition of general good health based upon the results of a medical history, physical examination, vital signs, laboratory profile and 12-lead electrocardiogram (ECG).
- At screening, eGFR ≥ 90 mL/min/1.73 m^2.

Subjects with Renal Impairment (Groups 2, 3 and 4)

- Judged to be in stable condition and acceptable for study participation based upon the results of a medical history, physical examination, laboratory profile and ECG.
- Presence of clinically significant renal impairment as indicated by a screening eGFR < 90 mL/min/1.73 m^2, to assign subjects to renal function groups (Group 2 [mild], Group 3 [moderate] and Group 4 [severe]).

Test Product, Dose/Strength/Concentration, Mode of Administration:

Upadacitinib 15 mg extended-release tablet was orally administered.

Duration of Treatment:

Subjects received a single dose of upadacitinib.

Criteria for Evaluation

Pharmacokinetic:

C_{max}, T_{max}, AUC_t, AUC_{inf}, $t_{1/2}$, fraction of upadacitinib dose excreted unchanged in urine (f_e) and renal clearance (CL_R)

Safety:

Adverse events, vital signs, ECGs, and clinical laboratory tests.

Statistical Methods

Pharmacokinetic:

A regression analysis was performed on the logarithms of C_{max} and AUC against the eGFR and creatinine clearance (CL_{cr}). The factor of primary interest was eGFR. In addition, an analysis of covariance (ANCOVA) was performed for C_{max}, AUC_t, AUC_{inf}, CL/F, T_{max}, and β. Age, sex, body weight and smoking status were evaluated as possible covariates in both the regression and ANCOVA analyses.

It was noted that one subject with moderate renal impairment (Subject [redacted] had 77% lower upadacitinib AUC than subjects with normal renal function group (Group 1). The subject's C_{max} and AUC were also noticeably lower than all other subjects with moderate renal impairment (Group 3). Subgroup analyses were performed excluding Subject [redacted] to ensure a conservative estimate of the effect of renal impairment on upadacitinib exposures.

Summary/Conclusions

Pharmacokinetic Results:

The point estimates and the corresponding 90% confidence intervals of relative bioavailability using the different analyses:

All Subjects:

		Regression Analysis of eGFR		Regression Analysis of CL_{cr}		ANCOVA	
Group Test vs. Reference	**Parameter**	**Point Estimate**	**90% CI**	**Point Estimate**	**90% CI**	**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

Summary/Conclusions (Continued)

Pharmacokinetic Results (Continued):

Sensitivity Analysis Excluding Outlier with Low Exposure in Moderate Renal Impairment Group:

		Regression Analysis of eGFR		Regression Analysis of CL_{cr}		ANCOVA	
Group Test vs. Reference	**Parameter**	**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

CI = Confidence Interval

Safety Results:

Upadacitinib 15 mg was well tolerated by subjects at all stages of renal impairment, as well as subjects with normal renal function. There was no pattern to the adverse events reported, and no new safety issues were identified in this study.

Conclusions:

Upadacitinib AUC_{inf} central values were 18%, 33% and 44% higher in subjects with mild, moderate, and severe renal impairment, respectively, compared to subjects with normal renal function (based on a conservative analysis excluding one outlier with low exposures in the moderate renal impairment group). Upadacitinib C_{max} central values were similar in subjects with mild, moderate, and severe renal impairment compared to subjects with normal renal function.