

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: Upadacitinib		
Title of Study: 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		
Coordinating Investigator: ██████████		
Study Site: Two United States sites		
Publications: None		
Studied Period (Years): First Subject First Visit: 30 August 2016 Last Subject Last Visit: 31 May 2017	Phase of Development: 1	
Objective: The objective of this study was to assess the pharmacokinetics and safety of upadacitinib following oral administration of a single dose of upadacitinib in subjects with hepatic impairment.		
Methodology: Single-dose, open-label, multicenter study to assess the safety and pharmacokinetics of upadacitinib following oral administration of a single 15 mg dose of upadacitinib in subjects with mild and moderate hepatic impairment relative to healthy subjects. Serial blood samples for assay of upadacitinib were collected for 120 hours after dosing.		
Number of Subjects (Planned and Analyzed): Planned: 18, Entered: 18, Completed: 18, Evaluated for Safety: 18, Evaluated for Pharmacokinetics: 18.		
Diagnosis and Main Criteria for Inclusion: Male and female subjects whose ages were between 18 and 75 years. Six subjects with normal hepatic function, six subjects with mild hepatic impairment and six subjects with moderate hepatic impairment.		
Test Product, Dose/Strength/Concentration and Mode of Administration: Upadacitinib 15 mg film-coated tablet (ER7) was orally administered.		

Duration of Treatment:

A single 15 mg dose of upadacitinib was administered in the morning of Study Day 1.

Criteria for Evaluation

Pharmacokinetic:

C_{max} , T_{max} , β , $t_{1/2}$, AUC_t , AUC_{inf} and CL/F .

Safety:

Vital signs, physical examinations, ECGs, laboratory tests and adverse events.

Statistical Methods

Pharmacokinetic:

Plasma concentrations and pharmacokinetic parameter values of upadacitinib were tabulated for each subject and each hepatic function group, and summary statistics were computed for each sampling time and each parameter.

For upadacitinib, an analysis of covariance (ANCOVA) was performed for T_{max} , the terminal phase elimination rate constant (β), and the natural logarithms of C_{max} and AUC. Body weight, age, sex, and smoking status were considered as possible covariates. A necessary condition for such variable candidates included in the final model was that the regression coefficient be significant at level 0.10. Within the framework of the ANCOVA, the effect of each hepatic impairment group was estimated and compared to the normal hepatic function group at significant level of 0.05. For C_{max} and AUC, estimates and 90% confidence intervals were provided for the mean ratio of each impaired hepatic function group to that of the normal hepatic function group.

One subject with moderate hepatic impairment (Subject ██████) showed 72% lower upadacitinib AUC than subjects with normal hepatic functions. Additionally, the subject's C_{max} and AUC were noticeably lower than all other subjects with moderate hepatic impairment (Group 3). A subgroup sensitivity analysis was performed excluding Subject ██████ from the moderate hepatic impairment group (Group 3) relative to subjects with normal hepatic function (Group 1), to ensure a conservative estimate for the effect of hepatic impairment on upadacitinib exposure. For the sensitivity analysis, ANCOVA was conducted to estimate the effect of hepatic impairment in the same way as it was conducted for the full analysis dataset.

Summary/Conclusions						
Pharmacokinetic Results:						
All Subjects:						
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
<p>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).</p> <p>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).</p>						
Sensitivity Analysis Excluding Outlier with Low Exposure in Moderate 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
<p>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).</p> <p>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).</p>						

Summary/Conclusions (Continued)

Safety Results:

Upadacitinib was generally well tolerated by the subjects. No clinically significant vital signs or hematology measurements were observed during the course of the study. There was no pattern to the adverse events reported, and no new safety issues were identified from this study.

Conclusions:

There was no statistically significant difference in upadacitinib C_{max} and AUC in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function. Upadacitinib AUC central value was 28% and 24% higher in subjects with mild and moderate hepatic impairment, respectively, compared to subjects with normal hepatic function (based on a conservative analysis excluding one outlier with low exposures in the moderate hepatic impairment group). Upadacitinib C_{max} central value was similar in subjects with mild hepatic impairment and 43% higher in subjects with moderate hepatic impairment compared to subjects with normal hepatic function.