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Effect of Hepatic Impairment on Eluxadoline Pharmacokinetics

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Keywords

eluxadoline, pharmacokinetics, hepatic impairment, irritable bowel syndrome, safety

Irritable bowel syndrome (IBS) is a chronic gastrointestinal disorder characterized by recurrent abdominal pain and altered bowel movements that is subtyped as predominantly diarrheal (IBS-D), constipating, or mixed/alternating between diarrhea and constipation.[1] The global presence of IBS is approximately 11%, with one-third of all IBS cases being IBS-D.[2,3] Patients with IBS-D commonly experience multiple symptoms, including bloating, abdominal pain, urgency, and diarrhea, ranging in levels of severity from mild and intermittent to severe and continuous.[4] The burden of symptoms experienced by patients with IBS-D is associated with significant reductions in quality of life and increased use of healthcare resources.[5,6] These burdens emphasize the need for pharmacological treatments to more effectively manage IBS-D symptoms.

FDA-approved therapies for adults with IBS-D include eluxadoline, rifaximin, and alosetron (specifically for women with severe IBS-D).[7] Eluxadoline (Viberzi; Furiex Pharmaceuticals, Inc, a subsidiary of Allergan plc, Parsippany, New Jersey) is a mixed μ-opioid receptor and κ-opioid receptor agonist and δ-opioid receptor antagonist that is locally active in the gastrointestinal tract.[8] In 2 phase 3 clinical trials, eluxadoline 75 mg and 100 mg twice daily demonstrated efficacy in improving the abdominal pain and stool consistency associated with IBS-D, measured by a composite efficacy end point combining stool consistency and abdominal pain responses.[9] Eluxadoline was well tolerated; clinical trials have shown that incidence rates of adverse events (AEs) and serious AEs were similar between eluxadoline-treated groups (at 75-mg and 100-mg doses) compared with those receiving placebo.[10] The most common yet infrequent AE was constipation; discontinuation due to constipation was low. Treatment-emergent AEs tended to occur within the first few weeks after initiation of treatment.

In nonclinical studies of cannulated rats low levels of eluxadoline were detectable in the hepatic portal vein after oral administration, although concentrations in the jugular vein were mostly below detectable levels.[11] Additional evidence demonstrated that eluxadoline has poor oral bioavailability in humans (1.02%), primarily due to low gastrointestinal permeability (2.3%) but also resulting from hepatic first-pass extraction (55.8%).[12] These results suggest that the liver plays an important role in the clearance of eluxadoline. The aim of this study, which was completed prior to the approval of eluxadoline, was therefore to determine whether hepatic impairment has any clinically relevant effect on exposure to eluxadoline by assessment of the pharmacokinetic (PK), safety, and tolerability profile of a single oral dose of eluxadoline.

Methods

Study Design

Investigational review boards (Schulman Associates IRB, Sunrise, Florida, and Independent IRB, Inc, Plantation, Florida) approved the study protocol. All

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volunteers provided written, informed consent, which was reviewed and approved by the institutional review boards before the start of the study. This was a phase 1, open-label, parallel-group, multicenter clinical trial that assessed the effect of mild, moderate, and severe hepatic impairment on the PK, safety, and tolerability profile of eluxadoline 100 mg. Volunteers were stratified across 4 groups of hepatic impairment using the Child-Pugh classification system based on scores of serum bilirubin, serum albumin, prothrombin time, ascites, and hepatic encephalopathy[13]: mild hepatic impairment (Child-Pugh class A), moderate hepatic impairment (Child-Pugh class B), severe hepatic impairment (Child-Pugh class C), and volunteers with normal hepatic function (healthy volunteers) matched to the hepatically impaired volunteers with respect to sex and age (±10 years).

Study Volunteers

Male and female volunteers aged 18 to 85 years with a body mass index of 18 to 40 kg/m^2 were included in the study. Key exclusion criteria included a functioning liver transplant, hemoglobin <10 g/dL, QTc >480 milliseconds, elevated serum lipase >2 × upper limit of normal, and a history of any of the following: abnormal 12-lead electrocardiogram, pancreatitis, sphincter of Oddi dysfunction, biliary duct disease (excluding gallstones), cholecystitis in the past 6 months, abdominal surgery in the past 3 months, or any major gastric, hepatic, pancreatic, or intestinal surgery. Hepatically impaired volunteers on medication must have received stable doses for ≥14 days before starting the study and were excluded if they had a clinical exacerbation of liver disease within the past 14 days, acute viral hepatitis within the past month, massive tense ascites, or severe or acute renal failure. Healthy volunteers were required to be in good health on physical examination and to have normal vital sign measurements and were excluded if they had a positive test result for hepatitis B surface antigen or hepatitis C virus antibody.

PK Evaluation

Eluxadoline plasma concentrations were determined from samples collected at 0 hours (before dosing) and at the following time points after a single 100-mg oral dose of eluxadoline: 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 24, and 48 hours, continuing once every 24 hours for 5 more days. Quantitation of eluxadoline concentrations in plasma samples was performed using a validated, specific, and sensitive liquid chromatography-tandem mass spectrometry assay with a lower limit of quantitation of 0.100 ng/mL. Individual plasma concentration versus actual data time profiles for eluxadoline were used to derive PK parameters using noncompartmental analyses and WinNonlin (Phoenix) Version 6.2 (Pharsight Corporation, St. Louis, Missouri). PK parameters, including total exposure by area under the plasma concentration versus time curve to last measurable concentration ($AUC_{0\text{-}t}$), peak exposure (C_{max}), and time to reach peak plasma concentration, were calculated. AUC from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$), terminal half-life ($t_{1/2}$), apparent oral clearance (CL/F), and apparent volume of distribution based on terminal phase (V/F) were calculated for volunteer subsets with available data.

Safety Assessments

Safety was evaluated through physical examinations, clinical laboratory results (serum chemistry, hematology, and urinalysis), vital sign measurements (blood pressure and pulse rate), and electrocardiogram measurements. Concomitant medications, pregnancy test results for female volunteers, and AEs and serious AEs were also documented. Volunteer baseline was defined as the last assessment before the first dose of eluxadoline.

Statistical Analyses

Descriptive statistics for the PK parameters, including mean, standard deviation, coefficient of variation, median, minimum, and maximum, were calculated. An analysis of variance was performed on the natural log–transformed PK parameters with the hepatic function group as a fixed effect. The outputs of the analyses included geometric least-squares mean ratios and corresponding 90%CIs.

Results

Volunteer Demographics and Disease Characteristics

A total of 30 volunteers were included, with equal numbers having normal (n = 15) and impaired (n = 15) hepatic function. Volunteers in the impaired hepatic function group were classified as having either mild (n = 6), moderate (n = 6), or severe (n = 3) hepatic impairment. Recruitment of volunteers with severe hepatic impairment was stopped after 3 patients because the data gathered from these 3 volunteers were sufficient to assess the PK of eluxadoline and to observe demonstrably increased systemic exposure. The baseline demographics and disease characteristics for the enrolled population were comparable between groups (Table 1); the recruited volunteers were aged 45 to 68 years; other than in the severe hepatic impairment group, the majority of volunteers in each group were male.

PK Analysis

Mean eluxadoline plasma concentrations for hepatically impaired volunteers were consistently higher than those in healthy volunteers over 24 hours, with the severe hepatic impairment group having higher mean

Table 1. Baseline Demographics and Disease Characteristics

	Normal Hepatic Function (n = 15)	Mild Hepatic Impairment (n = 6)	Moderate Hepatic Impairment (n = 6)	Severe Hepatic Impairment (n = 3)
Age, y				
Mean (SD)	56.1 (6.3)	53.8 (5.7)	56.5 (5.0)	58.3 (3.8)
Min, max	45, 68	46, 62	52, 64	54, 61
Male, n (%)	12 (80.0)	6 (100)	5 (83.3)	1 (33.3)
Race, n (%)[a]				
White	13 (86.7)	3 (50.0)	6 (100)	3 (100)
Black	2 (13.3)	2 (33.3)	0	0
Ethnicity, n (%)				
Hispanic or Latino	0	1 (16.7)	0	0
Not Hispanic or Latino	15 (100)	5 (83.3)	6 (100)	3 (100)
Height, cm				
Mean (SD)	172.8 (8.4)	173.4 (4.4)	174.5 (7.0)	165.3 (3.5)
Min, max	156.0, 184.3	168.1, 180.4	161.8, 183.4	162.8, 169.3
Weight, kg				
Mean (SD)	85.3 (14.4)	87.2 (12.6)	88.6 (13.5)	72.4 (15.6)
Min, max	55.6, 101.8	64.3, 98.9	63.9, 99.5	55.0, 85.1
BMI, kg/m^2				
Mean (SD)	28.4 (3.4)	29.0 (4.3)	29.4 (6.0)	26.4 (4.9)
Min, max	21.4, 33.8	21.2, 33.3	20.9, 38.0	20.8, 29.7

BMI indicates body mass index; SD, standard deviation.

[a]Race was missing for 1 volunteer with mild hepatic impairment.

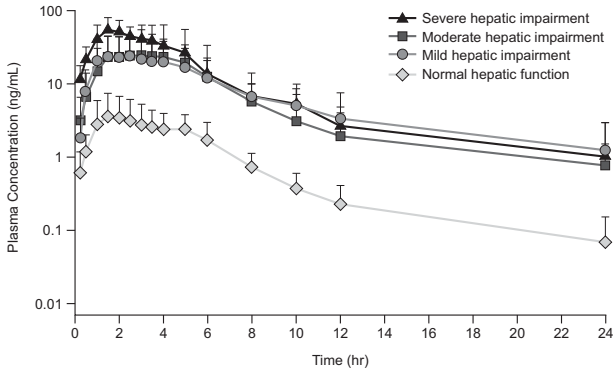

Figure 1. Plasma concentration–time profile after a single 100-mg dose of eluxadoline. Data values and error bars represent mean and standard deviation, respectively.

concentrations compared with other groups (Figure 1). The terminal-phase concentrations appeared to decline multiexponentially.

Calculations of PK parameters showed that the $AUC_{0\text{-}t}$ of eluxadoline was higher in volunteers with mild (187.5 ng·h/mL), moderate (166.2 ng·h/mL), and severe (286.5 ng·h/mL) hepatic impairment compared with healthy volunteers (20.9 ng·h/mL) (Table 2). Results were similar for C_{max}, with higher mean values for volunteers with mild (27.6 ng/mL), moderate (29.9 ng/mL), and severe (58.8 ng/mL) hepatic impairment compared with healthy volunteers (4.1 ng/mL).

Statistical analyses of $AUC_{0\text{-}t}$ and C_{max} comparing healthy volunteers with the hepatically impaired volunteers demonstrated that the ratio of geometric least-squares means was similar between these PK parameters. There were 6-fold and 4-fold increases in both $AUC_{0\text{-}t}$ and C_{max} in volunteers with mild and moderate hepatic impairment compared with healthy volunteers, respectively. In volunteers with severe hepatic impairment there were 16-fold and 18-fold greater average increases in $AUC_{0\text{-}t}$ and C_{max}, respectively.

In addition, mean oral clearance of eluxadoline was markedly decreased in hepatically impaired volunteers compared with healthy volunteers, with decreases of 94.4%, 78.4%, and 95.2% in volunteers with mild, moderate, and severe hepatic impairment, respectively. Terminal half-life was increased for volunteers with hepatic impairment compared with healthy volunteers.

Safety

Overall, 14 volunteers (46.7%) reported 35 AEs, occurring in 5 (83.3%), 4 (66.7%), and 2 (66.7%) volunteers in the mild, moderate, and severe hepatic impairment groups, respectively, and in 3 (20.0%) healthy volunteers (Table 3). The most common AE was dizziness, in 4 volunteers overall: 2 with mild hepatic impairment, 1 with moderate hepatic impairment, and 1 with severe hepatic impairment. Gastrointestinal disorder AEs were reported by 5 volunteers: 2 (33.3%) in the moderate hepatic impairment group, 2 (66.7%) in the severe hepatic impairment group, and 1 (6.7%) in the normal hepatic function group. The majority of AEs were mild in severity, with no deaths or AEs leading to study drug discontinuation. Two serious AEs were reported: 1 volunteer with moderate hepatic impairment experienced acute myocardial infarction 13 days after dosing and while levels of eluxadoline

Table 2. Eluxadoline Plasma Pharmacokinetic Parameters and Statistical Analyses

Parameter	Normal Hepatic Function (n = 15)	Mild Hepatic Impairment (n = 6)	Moderate Hepatic Impairment (n = 6)	Severe Hepatic Impairment (n = 3)
$AUC_{0\text{-}t}$, ng·h/mL [mean (SD)]	20.9 (13.3)	187.5 (194.0)	166.2 (220.3)	286.5 (122.5)
Geometric LS means	16.8	105.1[a]	66.9[a]	270.9[a]
Ratio of geometric LS means (90%CI)[b]	-	6.3 (2.5-15.5)[a]	4.0 (1.6-9.9)[a]	16.1 (4.9-53.0)[a]
C_{max}, ng/mL [mean (SD)]	4.1 (3.6)	27.6 (20.6)	29.9 (37.7)	58.8 (19.1)
Geometric LS means	3.0	18.6[a]	12.0[a]	56.5[a]
Ratio of geometric LS means (90%CI)[b]	-	6.2 (2.5-15.4)[a]	4.0 (1.6-9.9)[a]	18.8 (5.7-61.9)[a]
Median T_{max}, h	2.0	2.3	1.3	1.5
Min, max	1.0, 6.0	1.0, 5.0	0.5, 5.0	1.5, 2.5
	(n = 9)	(n = 4)	(n = 4)	(n = 1)
$AUC_{0\text{-}inf}$, ng·h/mL [mean (SD)]	22.1 (17.5)	268.1 (195.7)	104.8 (77.1)	237.2 (NC)
$t_{1/2}$, h [mean (CV)]	4.4 (6.0)	14.4 (7.0)	21.8 (11.1)	5.9 (NC)
CL/F, L/h [mean (SD)]	8752 (7641)	490.4 (219.8)	1889 (1910)	422 (NC)
V/F, L [mean (CV)]	36,406 (31,073)	10,745 (8101)	54,851 (66,346)	3570 (NC)

$AUC_{0\text{-}inf}$ indicates area under the plasma concentration versus time curve from time 0 extrapolated to infinity; $AUC_{0\text{-}t}$, area under the plasma concentration versus time curve to last measurable concentration; CL/F, apparent oral clearance; C_{max}, peak exposure; CV, coefficient of variation; LS, least squares; NC, not calculable; $t_{1/2}$, terminal half-life; T_{max}, time to maximum plasma concentration; V/F, apparent volume of distribution based on terminal phase.

[a]Compared with the group with normal hepatic function.

[b]Analysis of variance was used to compare the natural log–transformed pharmacokinetic parameters of volunteers with hepatic impairment with those of healthy volunteers.

were undetectable, which was deemed unrelated to the study drug; 1 volunteer with severe hepatic impairment experienced reversible ileus with onset 4 days after eluxadoline administration, but it resolved fully approximately 3 days after onset. In the case of the reversible ileus, the volunteer's plasma eluxadoline was undetectable at the time of the reported event, and the AUC and C_{max} were below the maximum detected in this study. Although the investigator concluded that the ileus was related to the study drug, this event required no major intervention, and the volunteer was discharged from the hospital in less than 3 days.

Discussion

This study evaluated the PK, safety, and tolerability of eluxadoline in matched volunteers with and without varying degrees of hepatic impairment. Clinical studies in healthy volunteers found that a single oral dose of eluxadoline was poorly absorbed, with the drug being excreted primarily through the feces and with no identifiable metabolites in the urine.[14] Low levels of eluxadoline have also been found in the hepatic portal vein in nonclinical studies, and clinical data suggest that eluxadoline is cleared primarily by OATP1B1-mediated hepatic uptake and subsequent biliary excretion without significant hepatic metabolism.[8,12]

In healthy volunteers following oral administration of eluxadoline 100 mg, C_{max} and AUC were reported to be approximately 2 to 4 ng/mL and 12 to 22 ng·h/mL, respectively.[12,15] Results from the current study show that plasma concentrations of eluxadoline were within this reported range in healthy volunteers. However, mean eluxadoline plasma exposure was 6-fold, 4-fold, and 16-fold higher in volunteers with mild, moderate, and severe hepatic impairment (Child-Pugh classes A, B, and C), respectively.

Eluxadoline exposure was slightly lower in volunteers with moderate hepatic impairment compared to mild hepatic impairment. Although the reason for this finding is not entirely clear, it may be explained in part by the low number of volunteers within each group and the high PK variability of eluxadoline as well as the possibility that volunteers with mild and moderate hepatic impairment had similar degrees of impairment as it relates to hepatic uptake. However, volunteers with mild and moderate hepatic impairment had similarly increased levels of eluxadoline exposure compared to healthy volunteers (6-fold and 4-fold, respectively) and substantially lower exposures compared to those with severe hepatic impairment. Volunteers in the severe hepatic impairment group had drastically higher exposure compared to all other groups; the comparatively normal half-life in this group is most likely an anomaly because only 1 volunteer was included in the analysis.

Although eluxadoline exposures were higher for volunteers with hepatic impairment, the AE profile was similar between hepatically impaired volunteers

Table 3. Summary of Adverse Events

System Organ Class Preferred Term, n (%)	Normal Hepatic Function (n = 15)	Mild Hepatic Impairment (n = 6)	Moderate Hepatic Impairment (n = 6)	Severe Hepatic Impairment (n = 3)
Total number of adverse events	3	14	9	9
Number of volunteers with ≥1 adverse event	3 (20.0)	5 (83.3)	4 (66.7)	2 (66.7)
Nervous system disorders	0	3 (50.0)	2 (33.3)	1 (33.3)
Dizziness	0	2 (33.3)	1 (16.7)	1 (33.3)
Headache	0	1 (16.7)	1 (16.7)	1 (33.3)
Akathisia	0	1 (16.7)	0	0
Paresthesia	0	0	1 (16.7)	0
Gastrointestinal disorders	1 (6.7)	0	2 (33.3)	2 (66.7)
Abdominal discomfort	0	0	0	1 (33.3)
Abdominal tenderness	0	0	0	1 (33.3)
Constipation	0	0	0	1 (33.3)
Diarrhea	1 (6.7)	0	0	0
Dry mouth	0	0	0	1 (33.3)
Dyspepsia	0	0	1 (16.7)	0
Epigastric discomfort	0	0	1 (16.7)	0
Ileus	0	0	0	1 (33.3)
Nausea	0	0	0	1 (33.3)
General disorders and administration site conditions	0	2 (33.3)	1 (16.7)	0
Infusion site extravasation	0	0	1 (16.7)	0
Malaise	0	1 (16.7)	0	0
Sensation of foreign body	0	1 (16.7)	0	0
Vascular disorders	2 (13.3)	0	1 (16.7)	0
Flushing	0	0	1 (16.7)	0
Hematoma	1 (6.7)	0	0	0
Hypertension	1 (6.7)	0	0	0
Cardiac disorders	0	0	1 (16.7)	0
Acute myocardial infarction	0	0	1 (16.7)	0
Coronary artery disease	0	0	1 (16.7)	0
Eye disorders	0	1 (16.7)	0	0
Conjunctival hyperemia	0	1 (16.7)	0	0
Infections and infestations	0	1 (16.7)	0	0
Laryngitis	0	1 (16.7)	0	0
Pharyngitis	0	1 (16.7)	0	0
Upper respiratory tract infection	0	1 (16.7)	0	0
Renal and urinary disorders	0	1 (16.7)	0	0
Pollakiuria	0	1 (16.7)	0	0
Skin and subcutaneous tissue disorders	0	1 (16.7)	0	0
Pruritus	0	1 (16.7)	0	0

Adverse events were coded using the Medical Dictionary for Regulatory Activities version 11.0.

and healthy volunteers. The single dose of eluxadoline 100 mg was well tolerated by most study volunteers, including all mild and moderate hepatically impaired volunteers. Two serious AEs were noted. The case of myocardial infarction in the volunteer with moderate hepatic impairment was deemed unrelated to the study drug due to the lack of temporal relationship to study drug administration. The single case of reversible ileus in 1 out of the 3 severe hepatically impaired volunteers dosed was considered related to the study drug, but was managed during a 2½-day observational hospital stay with minimal interventions. A safety database search conducted at the time of the ileus event (when approximately 2100 individuals with IBS-D had been dosed with eluxadoline, including those in blinded studies) for the primary diagnosis of intestinal obstruction, fecal retention, pseudo-obstruction, decreased bowel motility, adynamic ileus, or opiate bowel dysfunction did not yield additional case reports.

The efficacy and safety of eluxadoline at doses of 75 mg and 100 mg were demonstrated in phase 3 clinical trials, and both doses are approved for use in adults with IBS-D.[9] Based on the results of this routine preapproval study, the eluxadoline US labeling indicates the use of the lower approved dose of 75 mg twice daily for individuals with mild and moderate hepatic impairment. Eluxadoline is contraindicated in individuals with severe hepatic impairment.[15]

Conclusion

Following a single 100-mg dose, systemic exposure of eluxadoline was higher in volunteers with hepatic impairment compared with healthy volunteers, especially in those with severe hepatic impairment. The lower approved dose of 75 mg is therefore recommended for patients with mild or moderate hepatic impairment, and eluxadoline is contraindicated in individuals with severe hepatic impairment.

Disclosures

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