Effect of mild or moderate hepatic impairment on the clearance of azeliragon

Ann Gooch, Aaron H Burstein, Scott J Brantley, Michael J Lamson, Imogene Dunn, Larry D Altstiel
vTv Therapeutics LLC, High Point, NC; Nuventra Pharma Sciences, Inc., Durham, NC

Introduction

Azeliragon is an oral antagonist of the Receptor for Advanced Glycation Endproducts (RAGE) currently being evaluated in a pivotal Phase 3 study for mild Alzheimer's disease (AD). Azeliragon is metabolized by hepatic enzymes prior to elimination. The present study evaluated the pharmacokinetics (PK), safety and tolerability of azeliragon in subjects with mild or moderate hepatic impairment compared to healthy subjects.

Objectives

The primary objective of this study was to:

- Evaluate the effect of hepatic impairment on the pharmacokinetics of azeliragon and its metabolites of interest (M1, M2, and M3) by comparing subjects with mild or moderate hepatic impairment to healthy volunteers.

The secondary objective of this study was to:

- Evaluate the safety and tolerability of azeliragon in subjects with mild or moderate hepatic impairment compared to healthy volunteers.

Study Design

- Non-randomized, open-label, single-dose trial using a "reduced" design in which 8 subjects with mild hepatic impairment (Child-Pugh category A), 8 subjects with moderate hepatic impairment (Child-Pugh category B) and 8 age, weight, and gender-matched healthy volunteers received a single 15 mg oral dose of azeliragon.
- Subjects were admitted to the Clinical Research Unit on Day -1, received a single 15 mg dose of azeliragon on the morning of Day 1 under fasted conditions, and remained confined until Day 5.
- Blood (approximately 3 mL) for quantitating the concentrations of azeliragon and metabolites of interest in plasma were taken at:
  - 0 (pre-dose), 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 (Day 3), 72 (Day 4), 96 (Day 5), 120 (Day 6), 144 (Day 7), 216 (Day 10), 312 (Day 14), 480 (Day 21), 648 (Day 28), 816 (Day 35), and 984 hours (Day 42) following azeliragon dosing.
- Plasma samples were analyzed for azeliragon, M1, M2, and M3 concentrations by validated LCMS/MS methods. The calibration range of the assays was 0.2 – 50 ng/mL using a plasma sample volume of 50 µL. The lower limit of quantification (LLOQ) was 0.2 ng/mL.

Pharmacokinetic Analysis

Noncompartmental Analysis

Primary Endpoints

- Cmax, AUClast, AUCinf, CL/F, Vz/F, and t½ of azeliragon following a single dose.
- Cmax, AUClast, AUCinf , and t½ of azeliragon metabolites of interest (M1, M2, and M3) following a single dose of azeliragon

Secondary Endpoints

- Clast, Tmax, and AUC0-24 for azeliragon and azeliragon metabolites of interest
- Unbound fraction of azeliragon and azeliragon metabolites at 12 hours and 96 hours
- Cmax, AUClast, and AUCinf metabolite to parent ratios for azeliragon metabolites of interest

Statistical Analysis

- Exposure parameters (i.e., Cmax, AUClast, and AUCinf) were analyzed using a mixed effects ANOVA, with treatment as a fixed effect and subject as a random effect.
- The geometric mean ratio and 90% confidence intervals for the ratio (test/reference) of the exposure parameters were used to estimate the effect of mild and moderate hepatic impairment on the PK of azeliragon and metabolites of interest.

Demographic / Baseline Characteristics

Characteristic	Healthy (n=8)	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)
Age (years)	57.0 (6.85)	55.5 (3.82)	55.4 (8.16)
Weight (kg)	90.5 (10.8)	101 (24.0)	83.6 (19.7)
Sex: male, n (%) female, n (%)	 7 (87.5%) 1 (12.5%)	 8 (100%) 0 (0%)	 6 (75.0%) 2 (25.0%)
Race: White, n (%) Black, n (%)	 5 (62.5%) 3 (37.5%)	 8 (100%) 0 (0%)	 7 (87.5%) 1 (12.5%)
Ethnicity: Not Hispanic or Latino	 8 (100%)	 8 (100%)	 8 (100%)

- There were no important demographic or baseline characteristics differences between groups.

Classification of Hepatic Impairment: Child-Pugh Scale

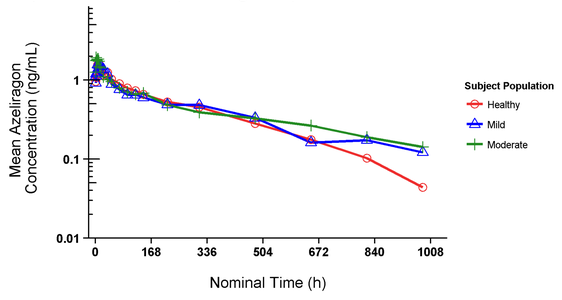
Assessment	Assigned Score for Observed Finding		
	1 point	2 points	3 points
Encephalopathy Grade[a]	0	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Prothrombin time (seconds prolonged)	<4	4 to 6	>6

[a] Grade 0: normal consciousness, personality, neurological examination, electroencephalogram
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves
Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves
Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity

Classification of clinical severity:
Mild (Group A): Total score 5-6 points
Moderate (Group B): Total score 7-9 points

NCA Results

Mean Plasma Azeliragon Concentration vs Time Plot with Subject Populations Overlaid (Semi-log Scale)

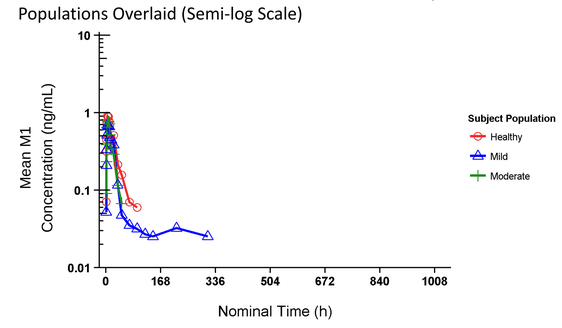


Results from Mixed-Effects ANOVA based on Azeliragon Pharmacokinetic Parameters

Comparison	Parameter	Geometric LSM [a] (Test)	Geometric LSM [a] (Reference)	Test/Reference (%)	90% Confidence Interval
Mild vs. Healthy[b]	Cmax (ng/mL)	1.77	1.72	103	(74.78, 142.59)
	AUClast (h*ng/mL)	304	302	101	(52.37, 193.66)
	AUCinf (h*ng/mL)	451	474	95.2	(51.32, 176.53)
Moderate vs. Healthy[c]	Cmax (ng/mL)	2.29	1.72	133	(96.48, 183.96)
	AUClast (h*ng/mL)	262	302	86.5	(44.99, 166.35)
	AUCinf (h*ng/mL)	500	474	105	(53.6, 207.42)

[a]LSM = Least Squares Mean
[b]Test = Mild; Reference = Healthy
[c]Test = Moderate; Reference = Healthy

Mean Plasma M1 Concentration vs Time Plot with Subject Populations Overlaid (Semi-log Scale)

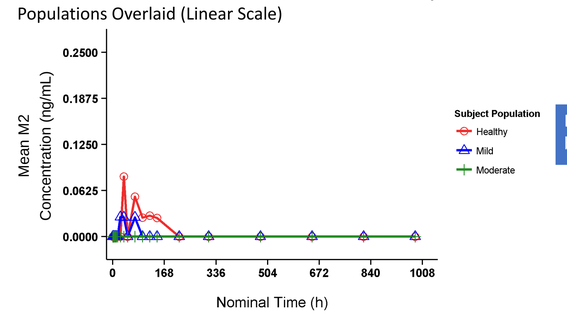


Results from Mixed-Effects ANOVA based on M1 Pharmacokinetic Parameters

Comparison	Parameter	Geometric LSM [a] (Test)	Geometric LSM [a] (Reference)	Test/Reference (%)	90% Confidence Interval
Mild vs. Healthy[b]	Cmax (ng/mL)	0.69	0.899	76.7	(45.36, 129.78)
	AUClast (h*ng/mL)	12.1	14.5	83.5	(30.83, 226.42)
	AUCinf (h*ng/mL)	NA	78.7	NA	(NA, NA)
Moderate vs. Healthy[c]	Cmax (ng/mL)	0.727	0.899	80.9	(47.82, 136.82)
	AUClast (h*ng/mL)	8.88	14.5	61.3	(22.63, 166.19)
	AUCinf (h*ng/mL)	NA	78.7	NA	(NA, NA)

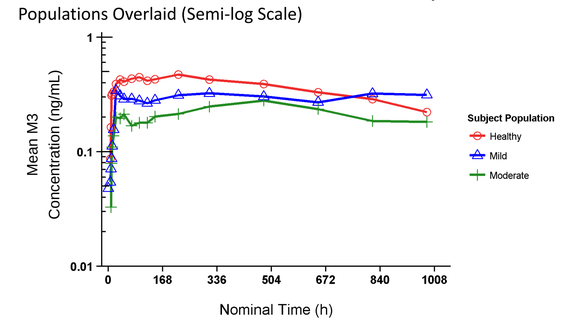
[a]LSM = Least Squares Mean
[b]Test = Mild; Reference = Healthy
[c]Test = Moderate; Reference = Healthy

Mean Plasma M2 Concentration vs Time Plot with Subject Populations Overlaid (Linear Scale)



Due to the small number of quantifiable samples, comparisons between populations were not feasible for M2.

Mean Plasma M3 Concentration vs Time Plot with Subject Populations Overlaid (Semi-log Scale)



Results from Mixed-Effects ANOVA based on M3 Pharmacokinetic Parameters

Comparison	Parameter	Geometric LSM [a] (Test)	Geometric LSM [a] (Reference)	Test/Reference (%)	90% Confidence Interval
Mild vs. Healthy[b]	Cmax (ng/mL)	0.530	0.498	106	(67.33, 168.4)
	AUClast (h*ng/mL)	313	307	102	(47.43, 291.7)
	AUCinf (h*ng/mL)	638	625	102	(65.5, 158.9)
Moderate vs. Healthy[c]	Cmax (ng/mL)	0.424	0.498	85.1	(52.56, 137.94)
	AUClast (h*ng/mL)	263	307	85.8	(38.29, 192.22)
	AUCinf (h*ng/mL)	NA	625	NA	(NA, NA)

[a]LSM = Least Squares Mean
[b]Test = Mild; Reference = Healthy
[c]Test = Moderate; Reference = Healthy

Conclusions

Azeliragon

- The results from the ANOVA indicated that moderate hepatic impairment is associated with a 33% increase in Cmax and 13.5% decrease in AUClast compared to healthy subjects.
- There were only minor differences between healthy subjects and those with mild hepatic impairment.

Metabolites of Interest

- Hepatic impairment (mild and moderate) is associated with a decrease in M1 exposures.
- Moderate hepatic impairment is associated with a decrease in M3 exposure. Exposure to M3 in subjects with mild hepatic impairment is consistent with the healthy subjects.

Overall

- There was no clinically important effect of hepatic impairment on the Cmax, AUClast, or AUCinf for any analyte.
- Therefore, it is expected that no dose adjustments will be required when administering azeliragon to patients with mild or moderate hepatic impairment.