Effect of Food on the Pharmacokinetics of Azeliragon in Healthy Adult Subjects

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Introduction

Azeliragon is an orally bioavailable inhibitor of the receptor for advanced glycation endproducts (RAGE) being evaluated in a pivotal Phase 3 study for patients with mild Alzheimer's disease (AD). In transgenic mouse models, azeliragon reduces neuroinflammation, Aβ transport into the brain and Aβ deposition, and improves both regional cerebral blood flow and cognitive performance. Phase 2 results demonstrated that subjects with mild-to-moderate AD (MMSE14-26) treated with azeliragon 5 mg/day had a decreased decline in ADAS-cog11 at 18 months compared to placebo (Δ =3.1, p=0.008) and the mild AD subgroup (MMSE 21-26) had both decreased ADAS-cog decline compared to placebo (Δ = 4.0, p=0.02) and decreased decline in CDR-sb (Δ=1.0, p=0.02). In the Phase 2 study, azeliragon 5 mg/day delayed the time to cognitive deterioration (defined as a 7-point worsening in ADAS-cog) relative to placebo in patients with mild AD with a hazard ratio of 0.5 (logrank p=0.02).

Azeliragon is currently being evaluated in a pivotal Phase 3 study for efficacy and safety in patients with mild AD.

The present study evaluated the effect of an FDA high-fat meal on the pharmacokinetics (PK) of the 5 mg Phase 3 azeliragon capsule formulation.

Objective

The primary objective of this study was to characterize the relative bioavailability of the Phase 3 capsule formulation of azeliragon when administered in the fed and fasted states. Doses were administered as a single 5 mg oral capsule under fasted conditions or with a standard FDA high-fat breakfast.

Study Design

- Phase 1, randomized, parallel, single-dose study in healthy volunteers.
- Subjects (14 in each of 2 groups) were randomized to receive a single 5 mg dose of azeliragon under fasted or fed (FDA high-fat meal 30 minutes prior to dosing) conditions.
- Subjects were admitted to the clinical research unit (CRU) the morning of Day -1, received their randomly assigned treatments on the morning of Day 1, and remained domiciled until Day 2 (24 hours after dosing). Subjects were discharged from the CRU after completing all procedures on Day 2 and returned to the CRU on Days 3, 4, 6, 10, and 14 for study procedures.
- Pharmacokinetic (PK) blood samples were collected prior to dosing and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 48, 72, 120, 216, and 312 hours post-dosing.
- Vital signs, ECGs, physical examinations, clinical labs, and urinalysis were assessed pre-dose and at the final Day 14 visit; AEs and concomitant medications were monitored daily.

Pharmacokinetic and Statistical Analysis

- The following PK parameters derived using noncompartmental methods (Phoenix WinNonlin® version 6.3, Pharsight Corp; St. Louis, MO)
  - Cmax, Tmax, Tlag, Tlast, t1/2, AUClast, AUC0-72, AUCinf
- The point estimate and 90 percent confidence interval (90% CI) for the ratio of geometric least-squares means between test (fed) and reference (fasted) conditions were determined for AUClast, Cmax, and AUC0-72.
  - Natural log-transformed parameters were analyzed with a mixed-effects model with a fixed effect for treatment and a random effect for subject. Restricted Maximum Likelihood Estimates were utilized. Least squares means were calculated for each treatment, and comparisons of treatments were based on the 90% CIs for the ratio of the treatment means.
  - AUCinf was not included in the assessment of relative bioavailability, because no individual subject values met acceptance criteria for calculation of this parameter and were thus deemed not reportable.

Results

Figure 1. Mean overlay of azeliragon plasma concentrations over time following dosing in Fasted and Fed states. Left panel linear scale, Right panel semi-log scale.

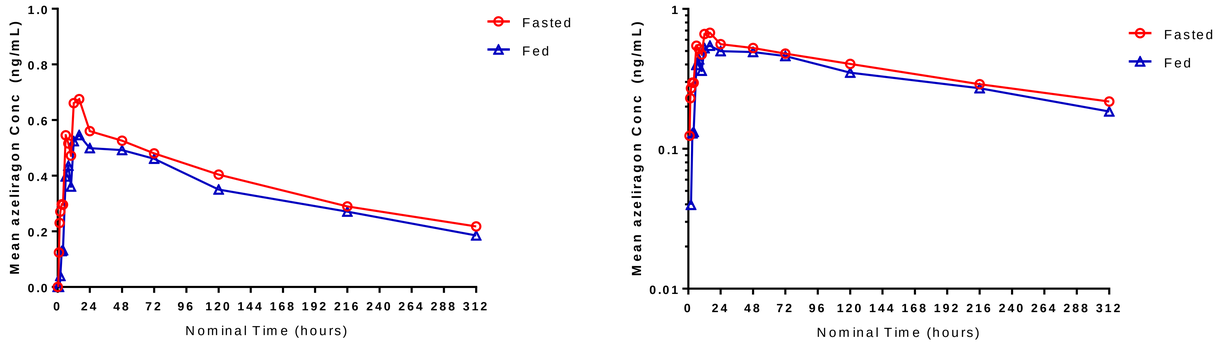

Table 1. Summary of Noncompartmental azeliragon Pharmacokinetic Parameters

Statistic	PK Parameter						
	Cmax (ng/mL)	Tmax (h)	Tlag (h)	AUClast (ng.h/mL)	Tlast (h)	AUC0-72 (ng.h/mL)	t1/2 (h)
Fasted							
N[a]	13	13	13	13	13	13	13
Mean	0.735	NC	NC	122	NC	40.0	276
SD	0.244	NC	NC	44.3	NC	12.6	82.6
GeoMean	0.703	NC	NC	113	NC	38.3	262
Median	0.693	16.00	1.00	118	312.00	36.5	282
Min	0.448	6.00	0.50	37.6	120.00	22.4	95.9
Max	1.38	48.00	4.00	196	312.00	70.2	394
Fed[b]							
N	14	14	14	14	14	14	14
Mean	0.601	NC	NC	101	NC	32.9	278
SD	0.151	NC	NC	38.2	NC	7.51	90.1
GeoMean	0.583	NC	NC	90.0	NC	32.0	264
Median	0.598	16.00	4.00	115	312.00	33.6	260
Min	0.357	6.00	1.50	22.8	72.00	20.4	121
Max	0.903	72.00	6.00	137	312.00	44.4	447

[a]13 subjects evaluable for fasted group; 1 subject excluded from PK parameter population due to insufficient number of quantifiable concentrations for reliable PK parameter estimation.
[b]Fed subjects received a standard FDA high fat breakfast 30 minutes prior to dosing.
NC = Not calculated; N = Number; SD = Standard deviation; Geo = Geometric; Min = minimum; Max = maximum

Table 2. Mixed-Effects ANOVA based on azeliragon Pharmacokinetic Parameters

Azeliragon PK Parameter	Fasted (Reference)			Fed (Test)			Fed / Fasted	
	N	GM[a]	90% CI[a]	N	GM[a]	90% CI[a]	GMR (%)	90% CI
AUClast (ng.h/mL)	13	113	88.2, 144	14	90.0	71.1, 114	79.9	57, 112
AUC0-72 (ng.h/mL)	13	38.3	33.6, 43.6	14	32.0	28.2, 36.3	83.5	69.7, 100
Cmax (ng/mL)	13	0.703	0.615, 0.802	14	0.583	0.513, 0.663	83.0	69.0, 99.8

[a]Back-transformed least-squares mean and confidence interval from linear mixed-effects model performed on natural log transformed values: GM = Geometric least-squares mean; CI = Confidence Interval; GMR = Geometric least-squares mean ratio between treatments (expressed as a percent of references)

Conclusions

- There was an approximately 16-20% reduction in exposure (AUC(0-last), AUC(0-72h), Cmax) when azeliragon 5 mg was administered following a high fat meal.
- At the Phase 3 dose of 5 mg/day, this magnitude of reduction is not anticipated to be clinically meaningful. Consequently, azeliragon may be given without regard to meals.