Analysis of treatment emergent adverse event incidences in phase 2 study of azeliragon reveal potential attenuation of psychiatric system organ class (SOC) adverse events and expected drug effects in gastrointestinal SOC

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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). A phase 2 study evaluated the efficacy and routine safety and tolerability of azeliragon in subjects with mild-to-moderate AD (baseline MMSE 14 through 26). The ongoing azeliragon phase 3 study in mild AD includes patients with entry MMSE of 21 through 26. Routine statistical methodologies for the analysis of treatment-emergent adverse events (TEAEs) includes incidence comparisons based on proportions of patients reporting at least one TEAE and also survival methodologies applied to time to first report of a TEAE. Native MedDRA hierarchy levels, including the system organ class (SOC) and high level group terms (HLGT), are used.

Objectives

The objectives of this analysis were to :

- Evaluate the relative profiles of TEAEs by SOC for the Phase 2b placebo group and the group treated with azeliragon 5 mg/d for delineation.
- For those SOCs with statistical delineation ($p < 0.1$), evaluate the relative profiles of TEAEs by HLGTs

Study Design

- The phase 2 study was a randomized, double-blind, placebo-controlled, 18-month study in mild-to-moderate AD investigating effects of once daily oral treatment with azeliragon.
- Adverse events were collected at each visit on a single AE page, regardless of how the AE was identified (e.g., clinical observation, subject report, laboratory test).

Methods

- Statistical analysis (Fisher's exact test, FET) of all reported TEAEs included the initial comparison of TEAE incidence overall (any TEAE) followed by analysis of TEAEs by SOC, and, where nominal significance is observed, analysis proceeded to HLGTs of interest.
- Populations of analysis included all randomized patients (mild-to-moderate; baseline MMSE 14 through 26) and the subpopulation of mild AD (baseline MMSE of 21 or more).
- Kaplan-Meier curves were generated for TEAEs identified with nominal significance observed focused on time to first report.

Results

Comparisons of placebo-treated patients with patients treated with 5 mg/d azeliragon revealed two SOCs with nominal p-values less than 5% in either population of analysis:

- GI disorders (p=0.04) in Mild
- Psychiatric disorders (p=0.04) in Mild to Moderate

All other SOCs showed no remarkable disparity between treatment groups in incidences of reported TEAEs in both populations of analysis.

Table 1. TEAEs occurrence in ≥5% of subjects in any Treatment Group

System Organ Class	Population: Mild to Moderate (MMSE 14-26)			Population: Mild (MMSE 21 or more)		
	Treatment Group		FET p-value	Treatment Group		FET p-value
	5 mg azeliragon (n=131)	Placebo (n=133)		5 mg azeliragon (n=73)	Placebo (n=68)	
Any SOC	114 (89%)	120 (90%)	ns	60 (82%)	61 (90%)	ns
Nervous system disorders	54 (41%)	54 (41%)	ns	33 (45%)	27 (40%)	ns
Psychiatric disorders	35 (27%)	52 (39%)	**0.037**	17 (32%)	26 (38%)	**0.06**
HLGT: Anxiety	*8 (6%)*	*21 (16%)*	***0.017***	*3 (4%)*	*11 (16%)*	***0.023***
Gastrointestinal disorders	44 (34%)	30 (23%)	**.055**	27 (37%)	14 (21%)	**0.04**
Infections and infestations	35 (27%)	41 (31%)	ns	16 (22%)	17 (25%)	ns
Injury, poisoning and procedural complications	36 (28%)	36 (27%)	ns	19 (26%)	18 (27%)	ns
General disorders and administrative site conditions	36 (28%)	28 (21%)	ns	22 (30%)	13 (19%)	ns
Musculoskeletal and connective tissue disorders	30 (23%)	34 (26%)	ns	20 (27%)	16 (24%)	ns
Investigations	32 (24%)	27 (20%)	ns	14 (19%)	15 (22%)	ns
Respiratory, thoracic and mediastinal disorders	22 (17%)	23 (17%)	ns	12 (16%)	9 (13%)	ns
Skin and subcutaneous tissue disorders	17 (13%)	22 (17%)	ns	7 (10%)	14 (21%)	0.10
Renal and urinary disorders	17 (13%)	16 (12%)	ns	9 (12%)	8 (12%)	ns
Metabolism and nutrition disorders	14 (11%)	11 (8%)	ns	10 (14%)	4 (6%)	ns
Cardiac disorders	14 (11%)	12 (9%)	ns	11 (15%)	9 (13%)	ns
Vascular disorders	9 (7%)	13 (10%)	ns	5 (7%)	8 (12%)	ns
Surgical and medical procedures	8 (6%)	10 (8%)	ns	3 (4%)	5 (7%)	ns
Neoplasms benign, malignant and unspecified	7 (5%)	4 (3%)	ns	4 (6%)	4 (6%)	ns
Eye disorders	4 (3%)	8 (6%)	ns	2 (3%)	5 (7%)	ns
Reproductive system and breast disorders	4 (3%)	6 (5%)	ns	3 (4%)	3 (4%)	ns

GI disorders SOC showed greater incidence in the group treated with 5 mg/d azeliragon relative to placebo.

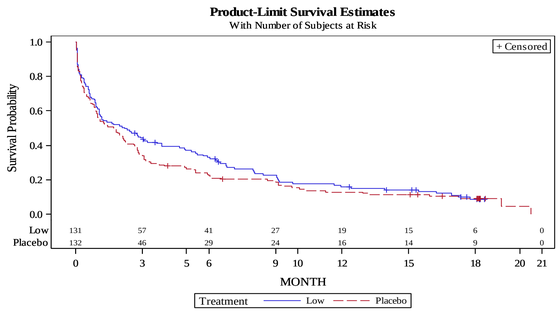
- This result is supported by time-to-event analysis,
- MedDRA HLGTs, in decreasing order of frequency, were gastrointestinal motility and defecation conditions (17% azeliragon; 9% placebo), gastrointestinal signs and symptoms (17% azeliragon; 9% placebo), and salivary gland conditions (16% azeliragon; 14% placebo).

Psychiatric disorders SOC showed decreased incidence from the group treated with 5mg/d azeliragon relative to placebo (p=0.04)

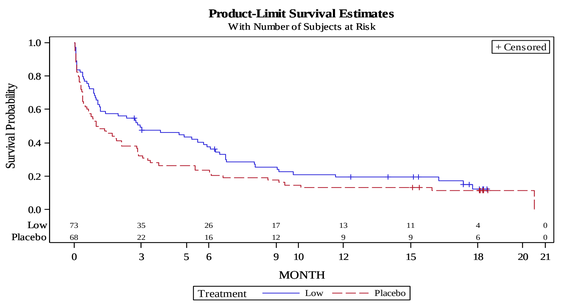
- Result is supported by time-to-event analysis, consistent with attenuation of signs and symptoms of AD for TEAEs classified by MedDRA in this SOC.
- MedDRA HLGTs, in decreasing order of frequency, were anxiety disorders and symptoms (6% azeliragon; 15% placebo; p=0.02) and depressed mood disorders and disturbances (9% azeliragon; 13% placebo; ns).

Kaplan-Meier Curves: ANY TEAE

Mild-to-Moderate: 5 mg/d azeliragon (n=131) vs placebo (n=132) for time to first [any] TEAE (Logrank p=0.3; Wilcoxon p=0.3; FET p=0.4 with any TEAE)

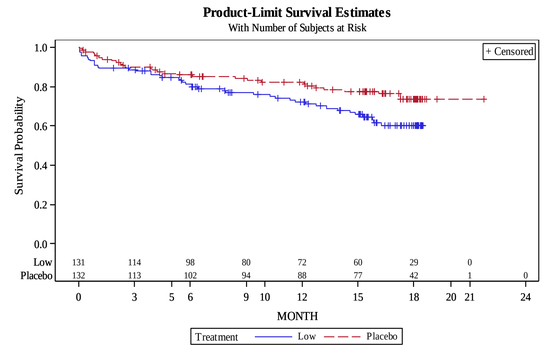


Mild: 5 mg/d azeliragon (n=73) vs placebo (n=68) for time to first [any] TEAE (Logrank p=0.1; Wilcoxon p=0.04; FET p=0.2 on proportions with any TEAE)

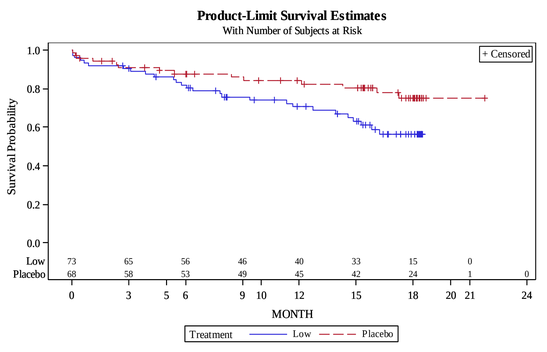


Kaplan-Meier Curves: GI SOC

Mild-to-Moderate: 5 mg/d azeliragon (n=131) vs placebo (n=132) for time to first gastrointestinal disorders TEAE (Logrank p=0.04; Wilcoxon p=0.057; FET p=0.056 on proportions with GI TEAE)

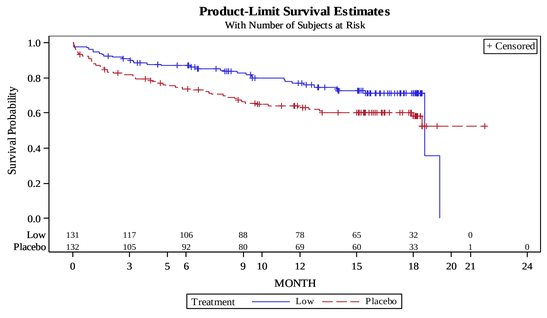


Mild: 5 mg/d azeliragon (n=73) vs placebo (n=68) for time to first gastrointestinal disorders TEAE (Logrank p=0.037; Wilcoxon p=0.057; FET p=0.04 on proportions with GI TEAE)

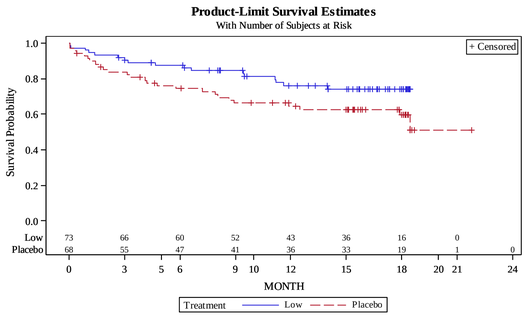


Kaplan-Meier Curves: Psychiatric Disorders SOC

Mild-to-Moderate: 5 mg/d azeliragon (n=131) vs placebo (n=132) for time to first psychiatric disorders TEAE (Logrank p=0.03; Wilcoxon p=0.01; FET p=0.037 on proportions with psychiatric TEAE; HLGT anxiety disorders p=0.017)

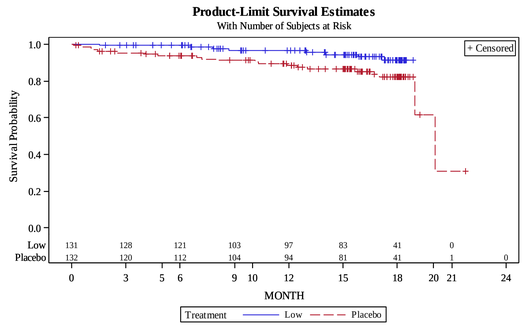


Mild: 5 mg/d azeliragon (n=73) vs placebo (n=68) for time to first psychiatric disorders TEAE (Logrank p=0.07; Wilcoxon p=0.07; FET p=0.07 on proportions with psychiatric TEAE; HLGT anxiety disorders p=0.022)

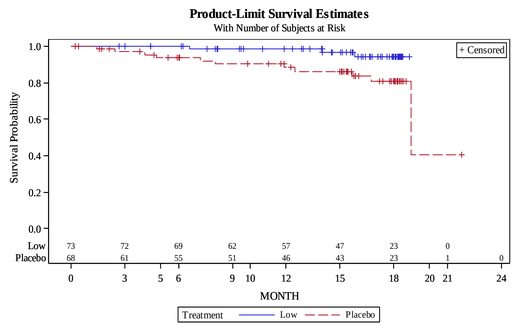


Kaplan-Meier Curves: Anxiety Disorders (HLGT)

Mild-to-Moderate: 5 mg/d azeliragon (n=131) vs placebo (n=132) for time to first TEAE of anxiety disorders (p=0.017)



Mild: 5 mg/d azeliragon (n=73) vs placebo (n=68) for time to first TEAE of anxiety disorders (p=0.022)



Conclusions

- Statistical analysis of TEAEs reveal results consistent with attenuation of TEAEs associated with AD that are classified by MedDRA in the psychiatric disorders SOC.
- Statistical analysis of TEAEs also show expected association of tolerability TEAEs classified in the GI Disorders SOC.
- Comparison of TEAEs in other SOCs revealed no remarkable delineation.