Effects of azeliragon on ADAS-cog and CDR domains and individual items in patients with mild Alzheimer's disease and type 2 diabetes (T2D)

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Introduction

Azeliragon, an orally bioavailable inhibitor of the receptor for advanced glycation endproducts (RAGE), was evaluated in an 18-month Phase 3 study as a treatment for patients with mild Alzheimer's disease (AD) (the STEADFAST Study). Post-hoc analyses in a subgroup of patients with type 2 diabetes (T2D) (HbA1c ≥ 6.5%) found that azeliragon-treated patients exhibited less cognitive decline (ADAS-cog11, 5.5 unit difference between active and placebo at 18 months, nominal p<0.01), less whole brain atrophy, less hippocampal atrophy, less ventricular enlargement, and reduced plasma inflammatory cytokine concentrations compared to patients treated with placebo (presented at ADPD 2019).

The current retrospective exploratory analysis on data from the STEADFAST A-Study diabetes subgroup was performed to evaluate ADAS-cog and CDR symptom domains and individual test items to ascertain which were sensitive to treatment effects.

Objective

The objectives of this exploratory post-hoc analysis were:

- To describe the effects of azeliragon on the 3 symptom ADAS-cog domains (memory, language and praxis) and individual items.
- To describe the effects of azeliragon on the 2 symptom CDR domains (cognition and function) and individual items.

Methods

- Retrospective, post-hoc analysis of data from the diabetes (HbA1c ≥ 6.5%) subgroup in the azeliragon Phase 3 STEADFAST A-study in patients with mild AD (MMSE 21-26 and CDR-global 0.5 or 1)
  - N=47 individuals
- Treatments: azeliragon 5 mg/day or placebo x 18 months
- Mean ADAS-cog11 changes from baseline at Month 18 were calculated for total score, domain score (memory, language and praxis) and individual item scores
- Mean CDR changes from baseline at Month 18 were calculated for sum of boxes, domain score (cognition and function) and individual items scores
- ADAS-cog total score and CDR-sb were analyzed using MMRM.
- ADAS-cog and CDR symptom domain and individual item change form baseline to Month 18 were assessed using Student's t-test. Tests were not corrected for multiple comparisons
- Standard effects sizes calculated as Cohen d values
  - $d = \frac{mean_{azeliragon\ change\ baseline} - meanpl_{acebo\ change\ baseline}}{SD_{pooled}}$

Methods

ADAS-cog11 Individual Items and Symptom Domains Defined

Domain	Item	Score Range*
Memory	Word Recall	0-10
	Naming	0-5
	Orientation	0-8
	Word Recognition	0-12
	Remembering Test Instructions	0-5
Language	Commands	0-5
	Language	0-5
	Comprehension	0-5
	Word Finding	0-5
Praxis	Constructional Praxis	0-5
	Ideational Praxis	0-5

*Higher scores indicate greater cognitive impairment

CDR Individual Items and Symptom Domains Defined

Domain	Item	Score Range*
Cognition	Memory	0-3
	Orientation	0-3
	Judgment and problem solving	0-3
Function	Community affairs	0-3
	Home and hobbies	0-3
	Personal care	0-3

*Higher scores indicate greater impairment

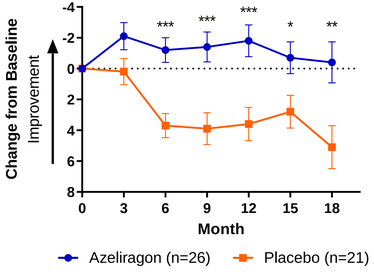
Demography / Baseline Characteristics

Characteristic	A-Study	
	Placebo (N=21)	Azeliragon (N=26)
Age, yr	76.6 ± 7.0	77.0 ± 7.9
Sex, n (%)		
Female	1 (4.8)	8 (30.8)
Male	20 (95.2)	18 (69.2)
Race, n (%)		
White	17(81.0)	25 (96.2)
Black	2 (9.5)	1 (3.8)
Asian	1 (4.8)	0
American Indian or Alaska Native	1 (4.85)	0
Ethnicity, Non-hispanic or Latino, n (%)	17 (81)	20 (76.9)
Education level below undergraduate college degree, n (%)	11 (52.4)	18 (69.1)
Years since diagnosis	2.8 ± 2.6	2.5 ± 1.7
APO ε4 allele carrier, n(%)	12 (57.1)	11 (42.3)
Background AD medication		
Acetylcholinesterase inhibitor, n (%)	21 (100)	24 (92.3)
Memantine, n (%)	4 (19.0)	12 (46.2)
Both, n (%)	4 (19.0)	10 (38.5)
Baseline MMSE	23.5 ± 2.6	23.9 ± 2.7
Baseline ADAS-cog11	16.1 ± 6.0	15.0 ± 4.4
Baseline CDR-sb	4.2 ± 1.9	4.0 ± 1.7
Baseline ADCS-ADL	60.5 ± 12.0	67.7 ± 6.9

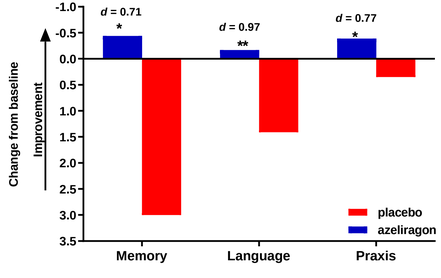
* Plus minus values are reported as mean ± SD.

Results

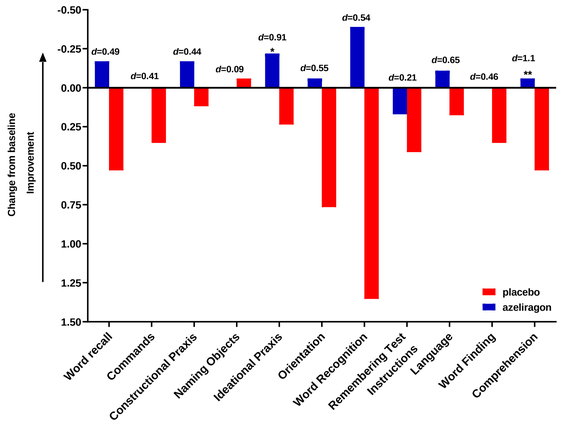
ADAS-cog total LSmean +/- SE



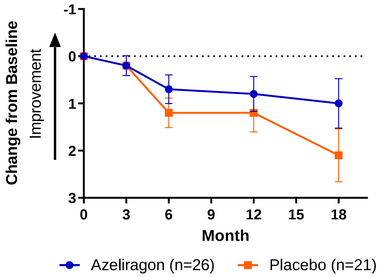
Month 18 Mean Change from Baseline for ADAS-cog Symptom Domains



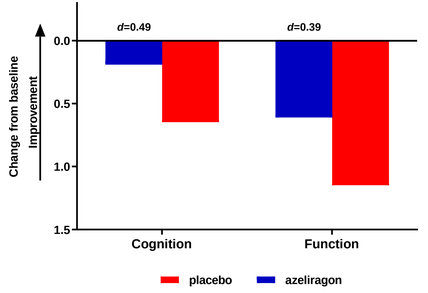
Month 18 Mean Change from Baseline for ADAS-cog Individual Items



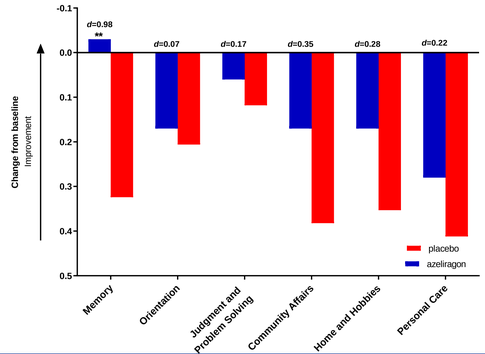
CDR-sb LSmean +/- SE



Month 18 Mean Change from Baseline for CDR Symptom Domains



Month 18 Mean Change from Baseline for CDR Individual Items



*p<0.05; **p<0.01, ***p<0.001

Conclusions

- Results suggest that beneficial effects of less decline in memory, language and praxis contribute to the nominally statistically significant beneficial effect of azeliragon on ADAS-cog11 in patients with AD and type 2 diabetes