Safety and Efficacy Results From the Phase 2 Elevage Study of Azeliragon in Mild Alzheimer's Disease and Type 2 Diabetes

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Disclosures

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- Employees of vTv Therapeutics LLC

Suzanne Hendrix, PhD, Jessie Nicodemus-Johnson, PhD

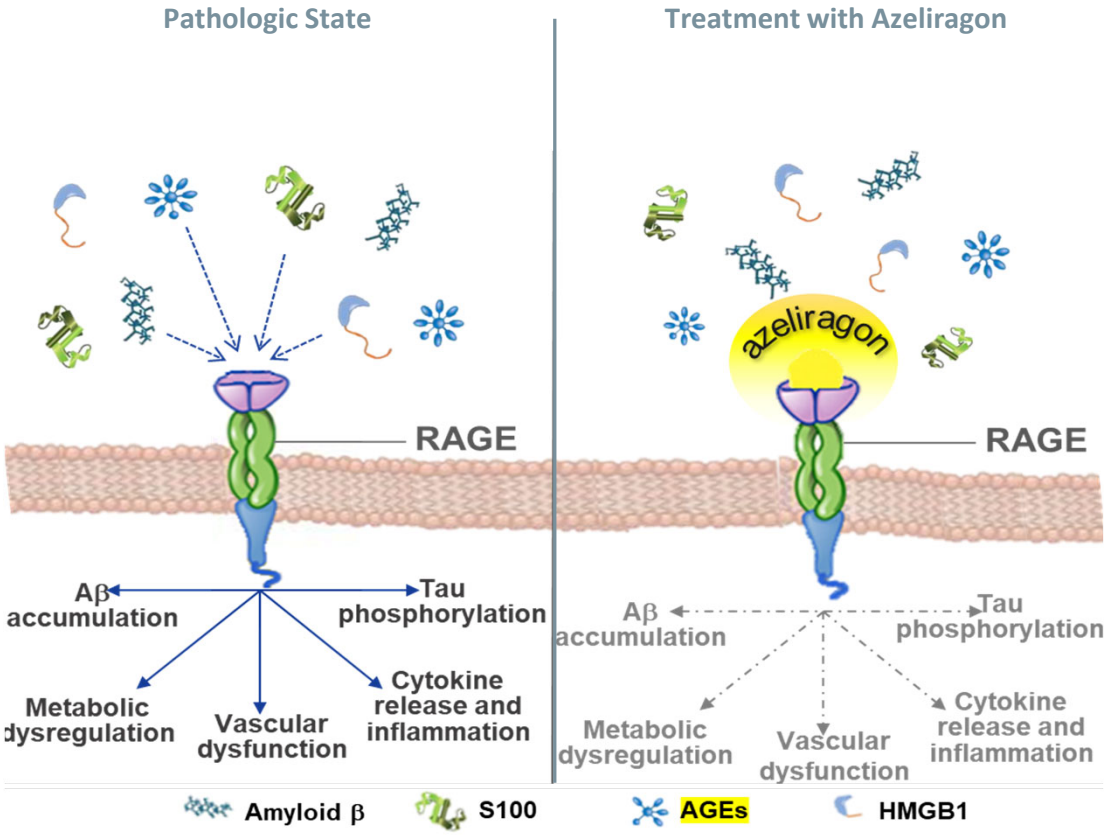
- Employees of Pentara Corporation (contracted by vTv Therapeutics)

Louis Kirby

- Paid consultant for vTv Therapeutics LLC

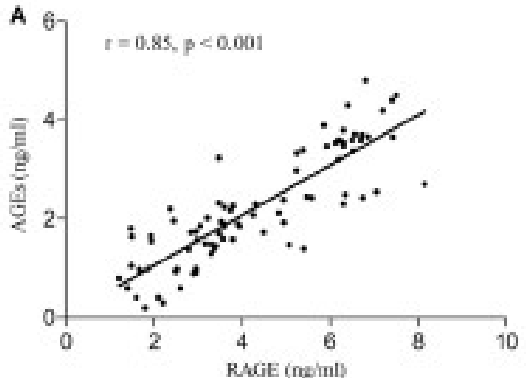
Receptor for Advanced Glycation Endproducts (RAGE) and Azeliragon

- RAGE is a pattern recognition receptor with diverse ligands
- RAGE expression is usually low in the majority of healthy adult tissues
- Upregulated under pathologic conditions (e.g., AD, Diabetes)
- Azeliragon antagonizes RAGE, blocking ligands from binding to the receptor and blunting resultant downstream pathological events

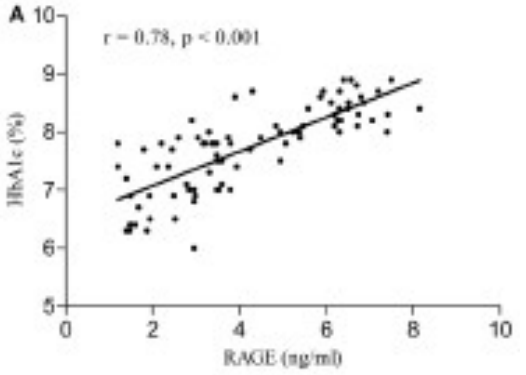


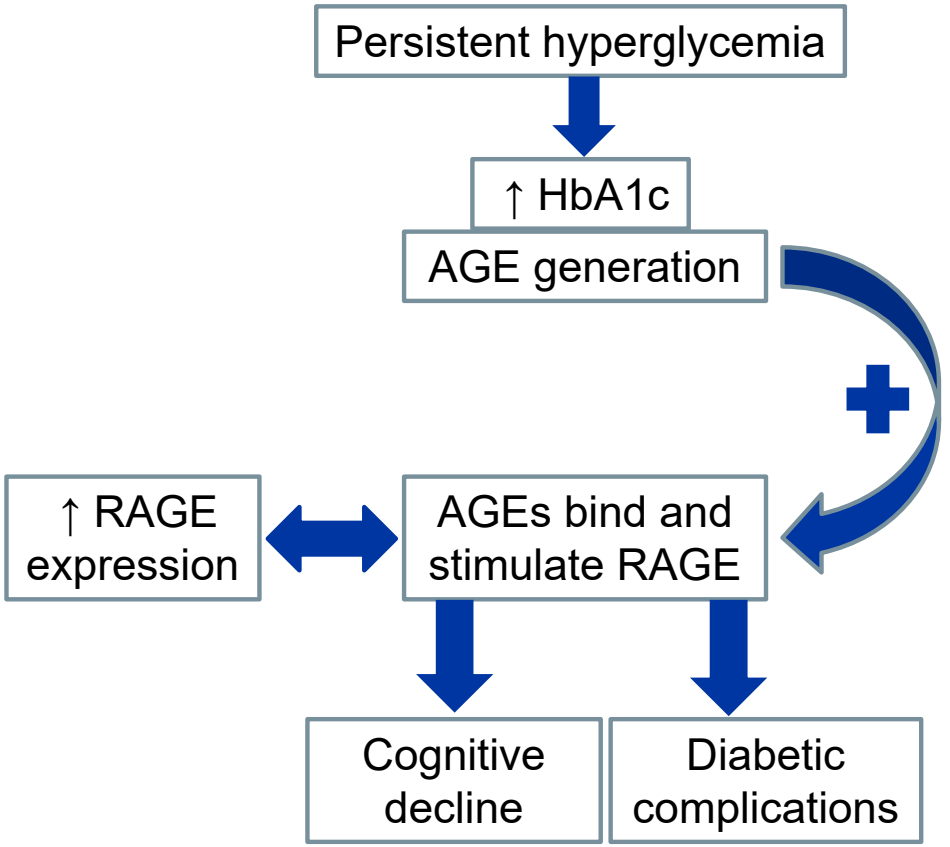
HbA1c: a surrogate for increased RAGE expression

Correlation of RAGE with AGEs in group of diabetic elderly patients with MCI



Correlation of HbA1c with RAGE in group of diabetic elderly patients with MCI

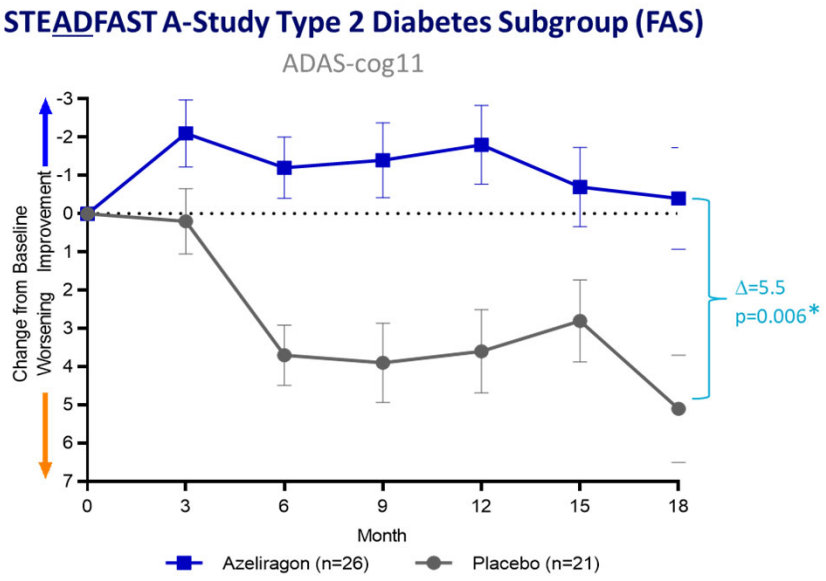




1. Gorska-Ciebiada M, Saryusz-Wolska M, Borkowska A, Ciebiada M and Loba J (2015) C-reactive protein, advanced glycation end products, and their receptor in type 2 diabetic, elderly patients with mild cognitive impairment. Front. Aging Neurosci. 7:209. doi: 10.3389/fnagi.2015.00209
2. Zheng, F., Yan, L., Yang, Z. et al. HbA1c, diabetes and cognitive decline: the English Longitudinal Study of Ageing. Diabetologia 61, 839–848 (2018). https://doi.org/10.1007/s00125-017-4541-7

STEADFAST Study in Mild Alzheimer's Disease

- Two Phase 3 randomized, double-blind, placebo-controlled, parallel group, 18-month trials (A-Study and B-Study)
- 880 subjects with probable mild AD
  - 2011 NIA-AA criteria, Screening MMSE 21-26, CDR-global 0.5-1
- Successfully demonstrated safety and tolerability of azeliragon 5 mg/day
- Failed to demonstrate statistically significant benefit of azeliragon on co-primary endpoints of ADAS-cog and CDR-sb in mild AD
- Post hoc subgroup analysis showed cognitive benefits in diabetes subgroup of A-Study



Type 2 Diabetes: Patients with diabetes (HbA1c ≥ 6.5% at anytime during the study)
Results are LSMeans ± SE based on MMRM model.
*All p values are nominal. FAS =Full Analysis Set

Data presented on March 30, 2019 at the 14th International Conference on Alzheimer's & Parkinson's Diseases held in Lisbon, Portugal
[1]Thomas et al. Alzheimer's & Dementia 2016:12;598-603.

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Elevage Study Objectives

- Strategic Objective
  - Replicate STEADFAST post-hoc subgroup analysis in Phase 2 POC study before embarking on Phase 3 part of the study

- Part 1 Study Objectives
  - Primary - Evaluate effect of 6 months of treatment with oral azeliragon on cognitive performance in subjects with mild AD and impaired glucose tolerance
  - Secondary
    - Evaluate efficacy of azeliragon treatment on measures of function and activities of daily living
    - Evaluate the efficacy of azeliragon treatment on complications of diabetes
    - Evaluate the safety and tolerability of 6 months of azeliragon treatment
    - Evaluate effect of azeliragon on biomarkers and markers of inflammation

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Elevage 2-Part Study Design

Studies	Part 1 – Phase 2 Proof of concept	Part 2 – Phase 3 confirmatory
Design	6-month, randomized, double-blind, placebo-controlled Phase 2 study	18-month, randomized, double-blind, placebo-controlled Phase 2 study
Sample Size **Geography**	100 (Planned); 43 (Actual) United States and Canada	200 TBD
Population	Mild Alzheimer's disease • Clinical diagnosis of probable AD (2011 NIA-AA criteria) • MMSE 21-26, CDR global 0.5 or 1, ADAScog14 ≥ 10 Impaired glucose tolerance • HbA1c 6.5-9.5%	
Dose Regimen	• Azeliragon 5 mg or placebo once daily; randomized 1:1	
Primary Endpoint	• Change from Baseline in ADAScog14 at Month 6	• Change from Baseline in ADAScog14 at Month 18 • Change from Baseline in CDR-sb at Month 18
Secondary Endpoints	• CDR-sb, FAQ, Amsterdam-IADL, eGFR	• FAQ, Amsterdam-IADL, MMSE, eGFR, whole brain volume

Additional Measures for Proof of Concept

- Additional measures derived from prior study data to potentially demonstrate proof of concept if ADAS cog 14 was not significant.
  - Cognitive Composite
    - Prior study data suggested ADAScog signal was driven by a subset of individual items.
    - Score = ADAS-cog comprehension, word finding difficulty, remembering test instructions items
  - Modified Cognitive Composite
    - Prior study data suggested additional aspects of cognitive decline consistent with age-related cognitive decline.
    - Score = Cognitive composite + ADAS-cog orientation and word recognition items
  - Global Statistical Test
    - Combination of 3 z-scores (ADAS-cog, CDR-sb, A-IADL)

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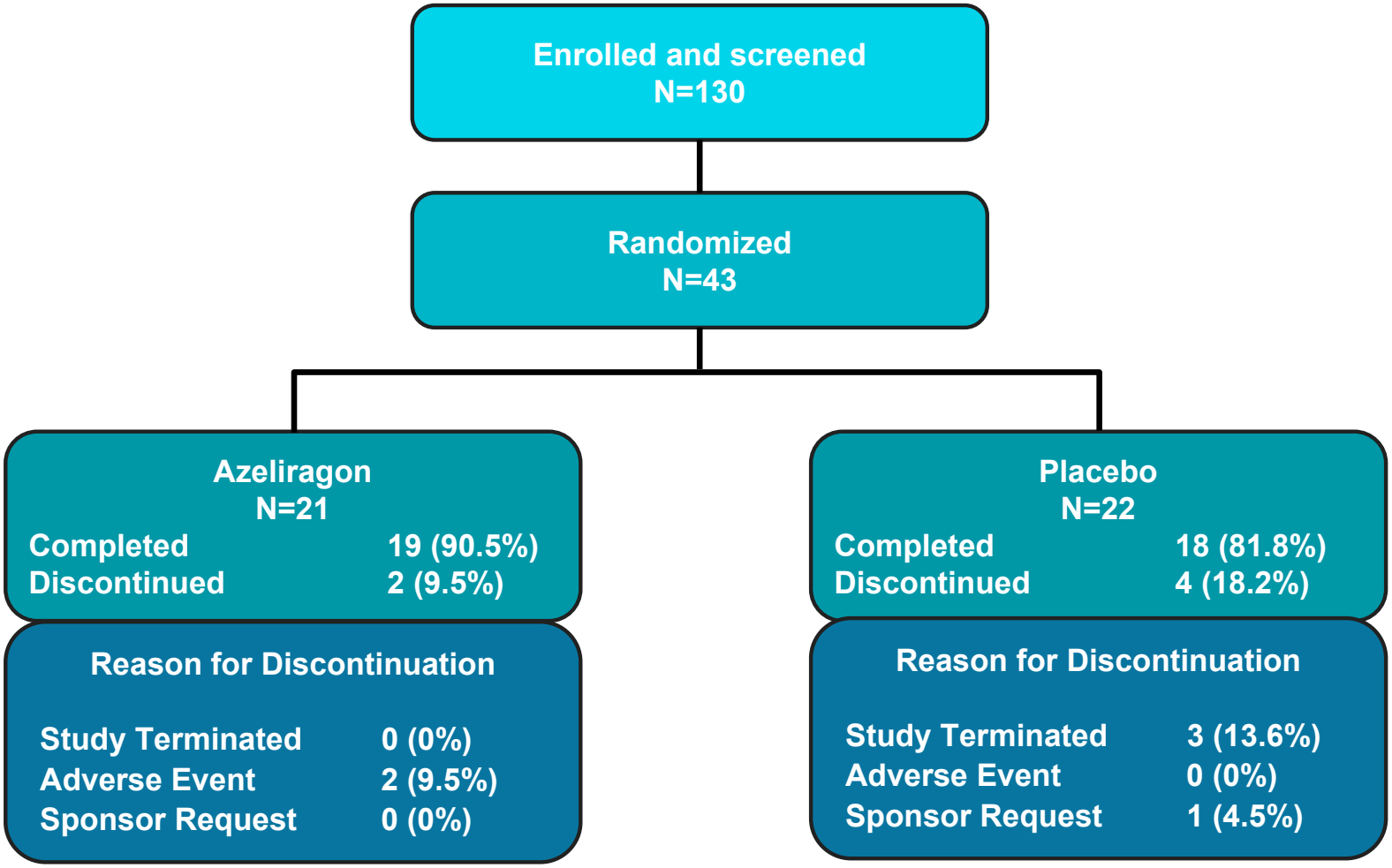
Disposition



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Demographics, Baseline Characteristics

Statistic	Placebo (n=22)	Azeliragon 5 mg (n=21)
Country		
Canada, n (%)	6 (27.3%)	5 (23.8%)
USA, n (%)	16 (72.7%)	16 (76.2%)
Race, White, n (%)	22 (100.0%)	19 (90.5%)
Ethnicity, Not Hispanic or Latino	21 (95.5%)	20 (95.2%)
Sex, Female, n (%)	11 (50.0%)	9 (42.9%)
Age, Mean (SD)	77.0 (6.56)	76.3 (5.82)
ApoE4 Carrier, n (%)	10 (45.5%)	12 (57.1%)
Years since AD Dx, Mean (SD)	2.3 (0.90)	2.2 (1.03)
AD Treatment, n (%)		
AchEI	19 (86.4%)	18 (85.7%)
Memantine	7 (31.8%)	10 (47.6%)
Both	4 (18.2%)	7 (33.3%)
HbA1c, Mean (SD)	7.2 (0.67)	7.3 (0.60)

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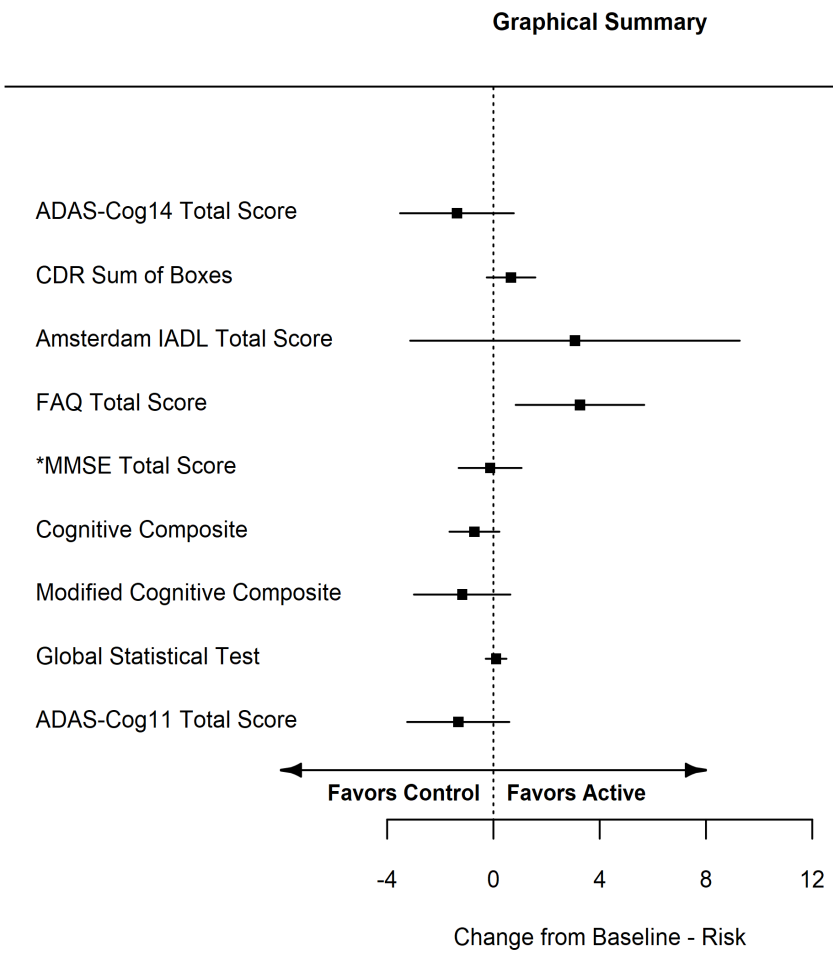
Baseline Characteristics

Statistic Mean (SD)	Placebo (n=22)	Azeliragon 5 mg (n=21)	P-value T-Test vs. Placebo
A-IADL Total Score	30.8 (21.47)	38.1 (22.20)	0.2801
ADAS-Cog11 Total Score	16.5 (5.70)	17.8 (5.75)	0.4532
ADAS-Cog14 Total Score	29.4 (8.87)	30.8 (7.53)	0.5958
CDR Global Score, n (%)			0.3175 *
0.5	11 (61%)	7 (39%)	
1.0	7 (39%)	11 (61%)	
CDR Sum of Boxes	4.2 (2.22)	4.7 (1.37)	0.3939
FAQ Total Score	12.0 (6.43)	16.2 (6.64)	0.0416
MMSE Total Score	23.5 (2.24)	23.7 (1.48)	0.7158

* Fisher's exact test

Summary of Mean Differences in Change from Baseline



	Graphical Summary	Azeliragon LS Mean (SE)	Placebo LS Mean (SE)	p-value	Estimate [95% CI]
ADAS-Cog14 Total Score		1.78 (0.82)	0.41 (0.69)	0.2055	-1.37 [-3.51 , 0.77]
CDR Sum of Boxes		0.58 (0.29)	1.25 (0.35)	0.1524	0.66 [-0.25 , 1.58]
Amsterdam IADL Total Score		6.24 (1.99)	9.31 (2.37)	0.3280	3.07 [-3.13 , 9.27]
FAQ Total Score		-0.49 (0.84)	2.77 (0.84)	**0.0089**	3.26 [0.84 , 5.68]
*MMSE Total Score		1.83 (0.41)	1.71 (0.43)	0.8340	-0.13 [-1.31 , 1.06]
Cognitive Composite		0.48 (0.37)	-0.23 (0.29)	0.1342	-0.71 [-1.65 , 0.23]
Modified Cognitive Composite		1.39 (0.74)	0.21 (0.52)	0.2003	-1.18 [-2.99 , 0.64]
Global Statistical Test		0.05 (0.13)	0.15 (0.14)	0.6075	0.10 [-0.29 , 0.49]
ADAS-Cog11 Total Score		1.76 (0.76)	0.43 (0.58)	0.1742	-1.32 [-3.25 , 0.60]

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* MMSE Change from Baseline direction inverted so positive change favors active

Safety Overview

No notable differences between azeliragon and placebo in Number of AEs, Treatment-related AEs, SAEs, Withdrawals due to AE, Deaths

Statistic	Placebo (N=22)	Azeliragon 5 mg (N=21)
Total Number of Adverse Events	37	33
Subjects with at least 1 AE	14 (63.6%)	14 (66.7%)
Subjects with at least 1 Related AE	1 (4.5%)	2 (9.5%)
Total Number of Serious Adverse Events	0	1
Subjects with at least 1 SAE	0 (0%)	1 (4.8%)
Subjects who had Drug Withdrawn due to an Adverse Event	0 (0%)	2 (9.5%)
Subjects with at least 1 AE leading to death	0 (0%)	0 (0%)

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Summary of Safety

All AEs reported by 2 or more subjects overall

Dictionary-Derived Term	Placebo (N=22)	Azeliragon 5 mg (N=21)	Overall (N=43)
Fall	3 (13.6%)	2 (9.5%)	5 (11.6%)
Diabetes mellitus	3 (13.6%)	1 (4.8%)	4 (9.3%)
Rotator cuff syndrome	0 (0.0%)	2 (9.5%)	2 (4.7%)
Upper respiratory tract infection	1 (4.5%)	1 (4.8%)	2 (4.7%)
Urinary tract infection	1 (4.5%)	1 (4.8%)	2 (4.7%)
Back pain	1 (4.5%)	1 (4.8%)	2 (4.7%)
Diarrhoea	1 (4.5%)	1 (4.8%)	2 (4.7%)
Cough	1 (4.5%)	1 (4.8%)	2 (4.7%)

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Conclusions

- The Elevage study failed to meet its primary objective with no statistically significant treatment differences on the ADAS-cog14 primary endpoint.

- The Change from Baseline in FAQ favored azeliragon, while the other secondaries measuring cognition and function did not show any significant treatment differences.

- Azeliragon 5 mg / day was well-tolerated with similar incidences of treatment-emergent adverse events overall and by system organ class (SOC) across both treatment groups.

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We sincerely appreciate all the patients, families, investigators and staff for their participation in the Elevage study.

elevage
Alzheimer's Disease study

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