Is RAGE the missing link between diabetes and dementia? Results from a subgroup analysis of the STEADFAST trial

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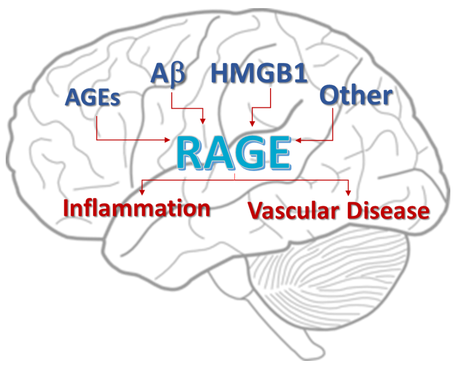
Introduction

The association between diabetes and dementia is well documented, and numerous studies have suggested a link between type 2 diabetes (T2D) and Alzheimer's disease (AD). Recently, a linear correlation between circulating glycosylated hemoglobin A1c (HbA1c) levels and cognitive decline has been demonstrated in the English Longitudinal Study of Ageing. The Receptor for Advanced Glycation End-products (RAGE) is a multiligand receptor of the immunoglobulin superfamily. The multiligand nature of RAGE is highlighted by its ability to bind diverse ligands such as advanced glycation end-products (AGEs). AGEs have been linked to diabetic complications and β-amyloid fibrils, a hallmark of AD. The pathogenic role of RAGE in chronic inflammation is well-documented. RAGE is sharply upregulated in numerous cell types under pathological conditions, and RAGE-ligands upregulate the receptor's expression establishing a vicious cycle that perpetuates inflammation, induces vascular damage and prevents tissue repair.



The role of inflammation and RAGE expression/signaling associated with AD and T2D raises the question of whether RAGE could be a common denominator between AD and T2D and whether treatment with azeliragon, an oral RAGE-inhibitor or antagonist could have a distinct effect in patients presenting with both T2D and AD. This hypothesis was supported by the observation, in the phase 2b study of azeliragon, that AD patients with high fasting plasma glucose or prediabetes (diabetic subjects were excluded from this study) responded better to treatment with azeliragon.

Objectives

To determine if a differential response to azeliragon was observed in patients presenting both T2D and AD in the STEADFAST trial.

Rationale Supporting Subgroup Selection

Phase 2B

- "Faster progressors" (Placebo decline 10.5 points in ADAS-cog$_{11}$ /18 months)
- Potential higher concentrations of RAGE ligands
- Potentially higher degree of inflammation and cell death ongoing
- Higher glucose predicted better ADAS-cog$_{11}$ response

Phase 3

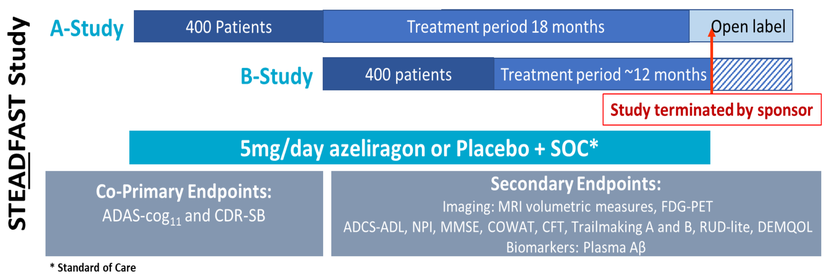
- More "Non/slow progressors" (Placebo decline 3.3 points in ADAS-cog$_{11}$/ 18 months)
- Potential lower concentrations of RAGE-ligands
- Potentially lower degree of inflammation and cell death ongoing

Could we use RAGE ligand concentrations in plasma as indicators of RAGE activation to identify and select a population that will respond to azeliragon in the phase 3 study?

HbA1$_c$ chosen as a surrogate marker for AGEs

Study Design

The STEADFAST study was a randomized, double-blind, placebo-controlled trial in approximately 800 patients with probable mild AD, MMSE 21-26, CDR global 0.5-1, receiving stable standard of care therapy (acetylcholinesterase inhibitor and/or memantine; SoC) evaluating the efficacy and safety of 18 months of treatment with azeliragon 5 mg/day relative to placebo.



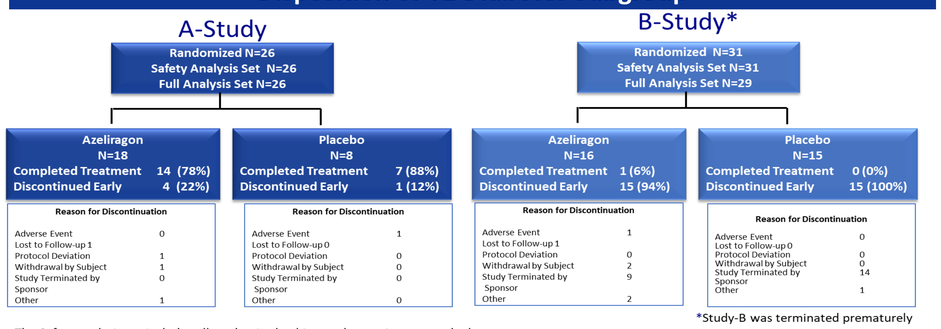
The clinical trial design included two separate studies (A-Study and B-Study) operationally conducted under a single protocol. Each study was randomized separately and independently powered to evaluate efficacy with respect to the co-primary endpoints of ADAS-cog and CDR-sb. **Entry criteria excluded patients with HbA1c >7.7%.**

Statistical Analysis

Following protocol-planned primary analysis, post-hoc analyses were done including this subgroup analysis in which **T2D was defined by HbA1c of 6.5% or more at baseline.**
Primary methodology presented is the protocol-planned statistical model: the primary analysis uses MMRM methodology with baseline as covariate, baseline stratum as a covariate, and subject as a random effect. The analysis population selection follows ICH E9 recommendations for randomization support (criteria are based on pre-randomization data and are applied to all patients in the study).
All p-values presented are nominal, since the primary analysis of this study was negative.

STEADFAST Study T2 Diabetes Subgroup

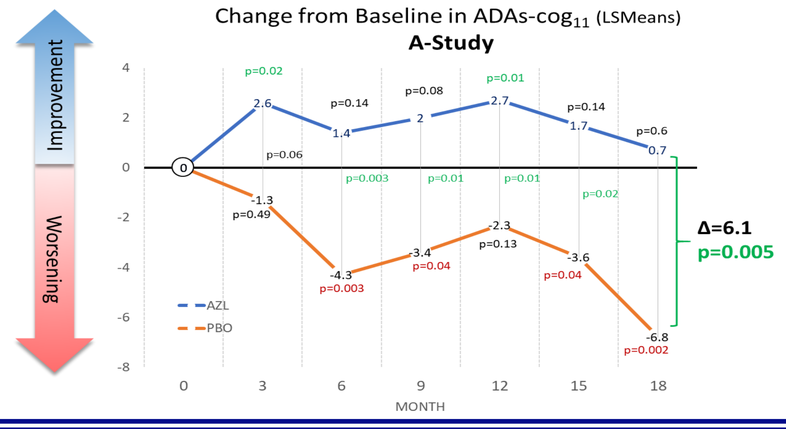
Disposition of T2 Diabetes Subgroup



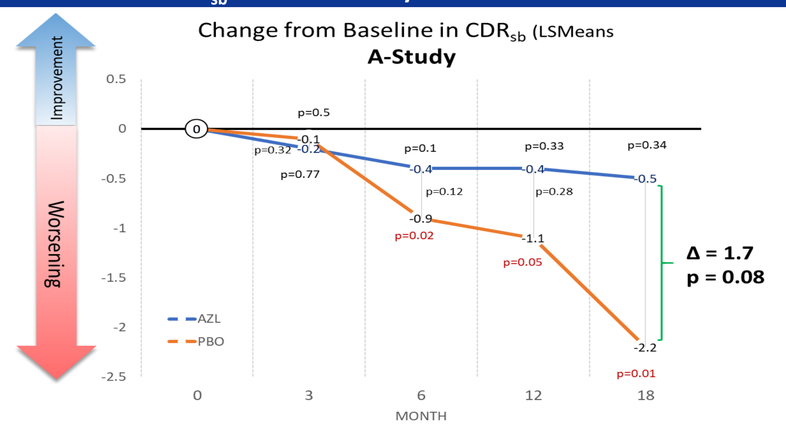
The Safety analysis set includes all randomized subjects who receive any study drug
The full analysis set includes all randomized mild AD subjects who receive any study medication and have any assessment.

Results T2 Diabetes Subgroup

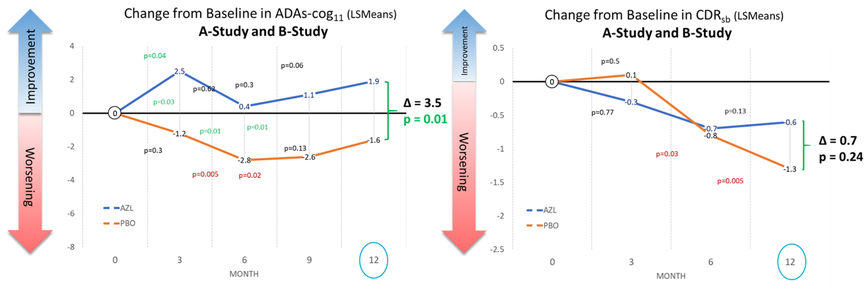
ADAS-cog$_{11}$: Potential Delay of Decline in Cognition



CDR$_{sb}$: Potential Delay of Decline in Function



Results of A-Study Confirmed by the Analysis of A+B* Studies Together



*B-Study was terminated prematurely with almost no data at M15 and M18, which resulted in B-Study data not suitable for independent interpretation

Demography – Baseline Characteristics

Full Analysis Set		Placebo (n=22)	Azeliragon 5 mg (n=33)
Age (years): Mean (Median)		78 (77)	76 (77)
Gender: males; females (% males)		18; 4 (82%)	22; 11 (67%)
Ethnicity: Not Hispanic or Latino, n (%)		17 (77%)	27 (82%)
Race: White, n (%)		19 (87%)	30 (91%)
Weight (kg): Mean (SD)		77 (13)	79 (17)
BMI (kg/m2): Mean (SD)		27 (3)	27 (4)
Baseline HbA1c: Mean (Median)		7.0 (6.9)	7.0 (6.9)
Baseline ADAS-Cog: Mean (Median)		16 (14)	16 (16)
Baseline MMSE: Mean (Median)		23 (24)	24 (24)
ApoE Status (% positive)		11 (50)	16 (49)
Years since diagnosis: Mean (Median)		2.6 (2.0)	2.6 (2.2)
Background SoC, n (%)	Memantine	8 (36)	12 (36)
	AChEI	21 (96)	30 (91)
	Both	7 (32)	9 (27)

Safety Overview: No Overall Safety Issues

Safety Analysis Set	Placebo (n=23)	Azeliragon 5 mg (n=34)
Subjects with any Treatment-emergent adverse event (TEAE), n (%)	14 (61%)	19 (56%)
Subjects with at least one related TEAE	0	4 (12%)
Subjects with any Serious AE[1] , n (%)	5 (22%)	7 (21%)
Subjects with TEAE leading to discontinuation of study[2], n (%)	1 (4%)	1 (3%)

[1]SAEs: All considered not related to study drug
[2]TEAEs leading to discontinuation of study: Increased HbA1c (n=1 azeliragon, mild and not serious) and pancreatic carcinoma (n=1 placebo, severe and serious)

No Significant Changes in HbA1c or Weight

		Mean (SD)					
		A-Study			B-Study		
Parameter	Treatment	Baseline	Month 18	Treatment	Baseline	Month 12
HbA1c (%)	PBO n=7	7.2 (0.7)	6.9 (0.6)	PBO n=9	6.8 (0.3)	6.94 (0.9)
	AZL n=14	6.9 (0.3)	6.7 (0.8)	AZL n=9	7.0 (0.5)	6.69 (0.5)
Glucose (mg/dL)	PBO n=7	142 (44)	130 (52)	PBO n=9	143 (36)	147 (73)
	AZL n=13	158 (42)	140 (57)	AZL n=9	135 (43)	143 (63)
Weight (kg)	PBO n=7	80 (12)	78 (12)	PBO n=9	78 (15)	77 (16)
	AZL n=14	85 (20)	83 (20)	AZL n=9	79 (17)	78 (14)

Supportive Analysis

The data presented here has been confirmed by supportive analysis using the Wilcoxon methodology (valid for small samples and without making parametric assumptions), ANCOVA by visit, and ANCOVA with multiple-imputations for coping with missing data. Other cognitive endpoints better suited for this population are currently being explored.

Conclusions

- Results of this analysis indicate a potential benefit of treatment with azeliragon for patients with T2D and AD.
- The improved cognition seems to be independent of changes in glycemic control, pointing to potential changes in inflammation/vascular dysfunction. Additional evaluation of MRI data and inflammatory markers is ongoing.
- Interpretation of these results is limited by the small number of subjects with both conditions participating in the STEADFAST study.
- Further studies are needed to confirm these promising results.