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 progression” (Placebo decline 10.5 points in ADAS-cog, 18 months)
• Potential higher concentrations of RAGE ligands
• Potentially higher degree of inflammation and cell death ongoing
• Higher glucose predicted better ADAS-cog, response

Phase 3
• More “Slow progression” (Placebo decline 3.3 points in ADAS-cog, 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? HbA1c 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 (acyethylcholinesterase inhibitor and/or memantine; SoC) evaluating the efficacy and safety of 18 months of treatment with azeliragon 5 mg/day relative to placebo.

A-Study 400 patients Treatment period 18 months Open label
B-Study 400 patients Treatment period 12 months Study terminated by sponsor

5mg/day azeliragon or Placebo + SOC

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 study 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.

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.

Results of this study are presented in an abstract form.

No Significant Changes in Hba1c or Weight

Safety Overview: No Overall Safety Issues

Results T2 Diabetes Subgroup

ADAS-cog11: Potential Delay of Decline in Cognition

Cognition

CDR-SB: Potential Delay of Decline in Function

Function

Conclusions

Supportive Analysis