Effects of angiotensin receptor blockade on renin angiotensin system and vascular outcomes in Black adults at risk for Alzheimer's disease

Brittany Butts
Scott Miners
Henrik Zetterberg
Pat Kehoe
Lynn Marie Trotti
Karima Benameur
Whitney Wharton

Background
The renin angiotensin system (RAS) regulates blood pressure in the body and the brain and may directly influence Alzheimer's disease (AD) biomarkers, including Aβ and tau neuropathology, and inflammatory markers. This hypothesis is supported by studies, including ours, showing that antihypertensives targeting the RAS reduce AD risk and progression in Black and White Americans. While mounting evidence supports a protective role of RAS medications, the mechanism has not been fully explained, and clinical trials investigating RAS medications in Black Americans are sparse. Mechanisms including both the classical and the regulatory RAS pathways require clarification in diverse cohorts. The purpose of this randomized clinical trial was to test the effects of an angiotensin receptor blocker on RAS and vascular outcomes in middle age Black adults with a parental history of AD.

Methods
Cognitively unimpaired Black adults (N=58) with a parental history of AD were enrolled in a Phase 1B randomized, placebo-controlled trial testing the effects of an angiotensin receptor blocker on brain RAS and vascular outcomes. Participants were randomized by sex and antihypertensive use to placebo (n=21), 20mg telmisartan (n=19), or 40mg telmisartan (n=18) for eight months. ANCOVA was performed for the 8 month measures adjusting for baseline measures and age. Post hoc testing for differences between groups was performed using Bonferroni correction.

Results
Participants were 59 ± 8 years of age and 86% female. Common comorbidities included hypercholesterolemia (45%) and hypertension (29%). In preliminary analyses, a one-way ANOVA revealed that there was a statistically significant difference in CSF ACE2 levels at 8 months between placebo and combined treatment groups ($F(2,28)=7.58$, $p=.003$, $eta^2=.397$). Adjustments for multiple comparisons (Bonferonni) found that the mean ACE2 values vs placebo was significantly lower than the 20 mg telmisartan group ($p=.011$, 95% CI=[-0.749, -.084]) and the 40 mg telmisartan group ($p=.010$, 95% CI=[-0.596, -.070]). No other significant differences at 8 months were found.

Discussion
Preliminary findings suggest a significant difference in CSF ACE2 levels among the treatment groups at trial completion, with the placebo group showing lower levels compared to both doses of telmisartan. However, no other significant differences were observed in the measured outcomes at this point. These results highlight a potential avenue for further exploration into the RAS and its modulation in the context of AD biomarkers among Black individuals with a familial AD risk. Additional analyses of vascular and AD risk markers are ongoing.