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Combination Treatment of a Novel β_2 Adrenoceptor Agonist, CST-2032, and Nadolol Improves Cognitive Measures in Participants with Alzheimer's Disease

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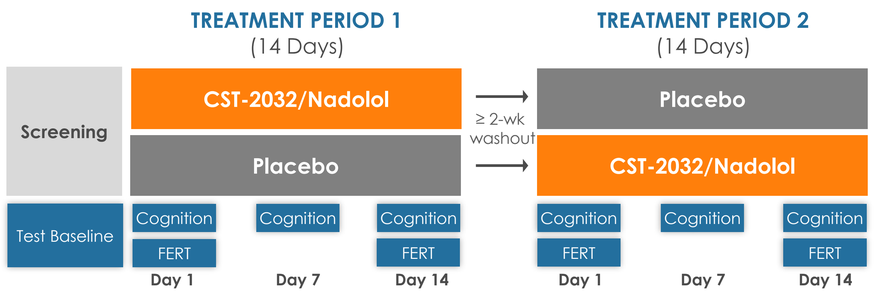
Aims

The locus coeruleus (LC), the primary source of forebrain noradrenaline, is among the earliest sites of neuronal loss and pathology in Alzheimer's disease (AD) and Parkinson's disease (PD). Deteriorating LC signaling could be therapeutically replaced using exogenous selective adrenoceptor (AR) agonists to reactivate the adrenergic stimulus of cortical and limbic structures. Prior studies established that β_2-ARs agonists increase regional cerebral blood flow in hippocampus, thalamus and amygdala, areas associated with cognition, attention, alertness and emotional salience, and may offer benefit for treatment of cognitive and emotional impairment in AD or PD. This abstract describes the safety and efficacy of the novel selective β_2-AR agonist, CST-2032, when administered with low-dose nadolol, in participants with MCI_{AD} or early AD dementia.

Methods



Blinded oral CST-2032 (3mg) + nadolol (3mg), or placebo was administered once-daily for 2 weeks in a 2-period crossover design to participants with MCI (MCI_{AD}) or mild dementia due to probable AD, and Montreal Cognitive Assessment (MoCA) scores between 14-26, across 16 sites in the USA and New Zealand. Multiple measures of cognition were evaluated, including the Digit Symbol Substitution Test (DSST) and the Facial Expression Recognition Test (FERT) at baseline and during each treatment period.

To eliminate peripheral side effects of CST-2032, 3 mg nadolol, a CNS impermeant & selective β_2-blocker was administered once-daily.

Results

36 participants with AD were enrolled, 58% male, average 67 years old, with mean MoCA score of 20.9 and MoCA Memory Index of 7.8. An additional 18 participants were enrolled with PD who are included in the evaluation of safety.

Conclusions

- AD participants had impaired cognition at enrollment.
- Treatment with the β_2-AR agonist, CST-2032, when administered with the peripherally restricted antagonist nadolol, significantly improved performance on the DSST, a cognitive test requiring attention, processing speed and executive function, as well as on measures of social cognition, in less than 2 weeks.
- Combination therapy with CST-2032+nadolol was well-tolerated, with no significant peripheral β_2-AR safety findings.
- The effects of 14-day treatment with CST-2032+nadolol support further studies to explore the breadth, magnitude and duration of clinical benefit achievable in MCI_{AD} / AD patients with cognitive impairment following longer durations of treatment.

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Table 1. Demographics & Baseline Disease Characteristics

	AD Participants (N=36)
Age (years) [mean (SD)]	66.6 (7.86)
Male / Female (%)	58.3% / 41.7%
Ethnicity: Hispanic or Latino / Other (%)	47.2% 52.8%
Race: Black or African American/White (%)	13.9% / 86.1%
Years of Education [mean (SD)]	14.9 (2.20)
MoCA [mean (SD)]	20.9 (2.98)
MoCA-Memory Index [mean (SD)]	7.8 (3.72)
DSST Score [mean (SD)]	14.4 (7.60)

Figure 1. CST-2032+Nadolol Increases Correct & Reduces Incorrect Responses in DSST

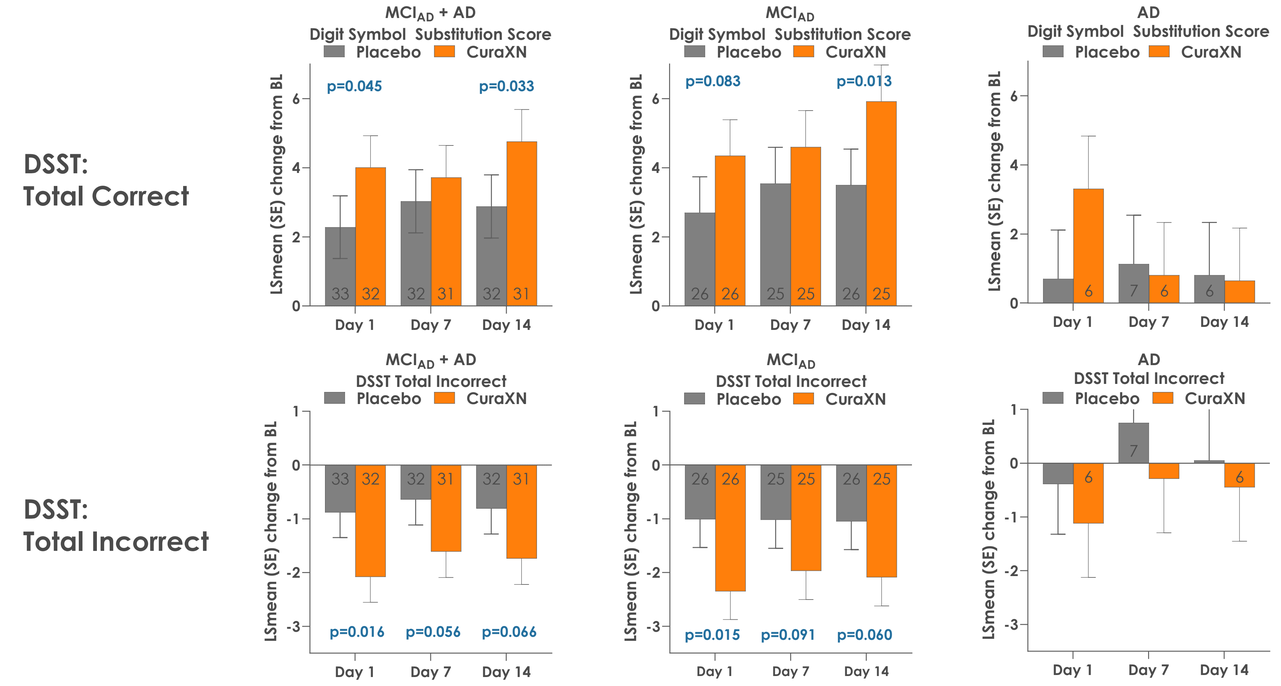

Figure 2. CST-2032+Nadolol Improves Reaction Speed and Other FERT Measures

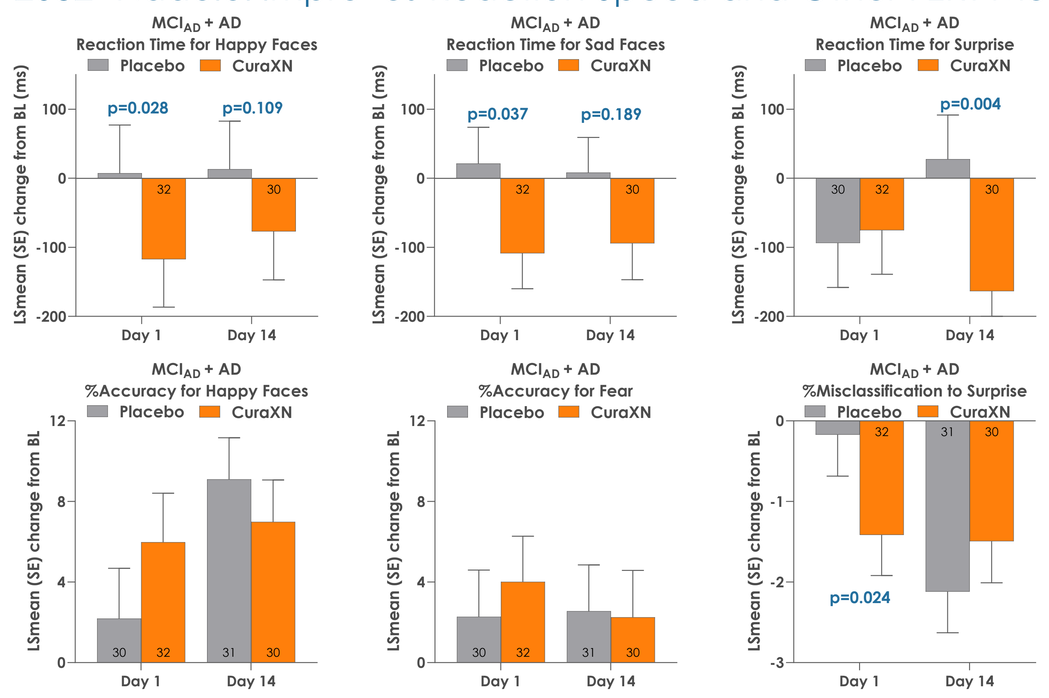

Table 2. Summary of Treatment Emergent Adverse Events in > 1 Participant

Adverse Event [n (%)]	Placebo (N=51)	CST-2032+Nadolol (N=46)
Participants with at least 1 TEAE	**13 (25.5)**	**15 (32.6)**
Lipase Increased	3 (5.9)	2 (4.3)
Amylase Increased	1 (2.0)	1 (2.2)
Urine Leukocyte Esterase Positive	2 (3.9)	0
Urinary Tract Infection	0	2 (4.3)
Nausea	0	2 (4.3)
Dry Mouth	1 (2.0)	1 (2.2)
Dizziness	2 (3.9)	1 (2.2)
Fatigue	0	2 (4.3)