Escitalopram for Agitation in Alzheimer's Disease Research Group
(S-CitAD)

Protocol: Appendix A

Design Summary

Version 1.2
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S-CitAD Design Summary

Title

- Escitalopram for Agitation in Alzheimer's Disease (S-CitAD)

Primary objective

- To examine in a masked, randomized trial the efficacy and safety of escitalopram in combination with a psychosocial intervention (PSI) for the treatment of agitation in participants with Alzheimer's Disease (AD) who fail to improve with a PSI, by comparing escitalopram and placebo treatment groups

Secondary objectives

- To examine the predictors of response to escitalopram therapy on AD participants with agitation who fail to show improvement on a PSI alone
- To examine the predictors of relapse, the duration of response, and time-course of any subsequent relapse, in AD participants with agitation who improve on a PSI, with extended follow-up in parallel with the randomized participants

Type of trial

- Phase III, parallel group, superiority, placebo-controlled, double-masked randomized trial
- Multicenter
- Two parallel treatment groups with simultaneous cohort
- Enrichment design: following 3 weeks of PSI alone, only participants not showing a response move on to randomization
- Cohort arm: following 3 weeks of PSI alone, participants who DO SHOW a response are monitored on usual care

Randomization

- 1:1 allocation ratio
- Stratification by clinic

Study population

- Enroll: 588 participants who meet S-CitAD criteria for AD and clinically significant agitation
- Randomize: 392 participants will be randomized, expecting 196 in each of the two treatment groups (escitalopram + PSI and placebo + PSI)
    - Only randomizing participants not showing a response to 3 weeks of PSI

Sample size and power calculations

- Two-sided alpha = 0.05 for the primary outcome
- Power between 80% and 90% with 10% loss to follow-up

Intervention

- Escitalopram for 12 weeks, target dose 15 mg/day (range 5-15 mg per day) taken orally, plus standardized PSI
- Placebo for 12 weeks, taken orally, plus standardized PSI
- Simultaneous cohort receiving standardized PSI only (showed response after 3 weeks)

Duration of follow-up

- 24 weeks (with treatment and assessments for 12 weeks, and an additional 12 weeks of safety and efficacy follow-up)

Data collection schedule

- Scheduled in-person visits at weeks 3, 6, 9, and 12 after randomization for treatment and assessment administration
- Telephone contacts at weeks 1 and 2 after randomization for medication titration and dose adjustments
- Telephone contacts at weeks 4.5, 7.5, and 10.5 after randomization for safety and efficacy
- Telephone contacts at weeks 18 and 24 after randomization for safety and efficacy

Masking

- Double-masked (treatment assignment masked to participants and all study staff, including physicians, nurses, and neuropsychologists) for 12 weeks after randomization

Primary outcome measure

- Clinically significant improvement in agitation over 12 weeks as measured by 'moderate' or 'marked' improvement in agitation on the modified Alzheimer's Disease Cooperative Study Clinical Global Impression of Change (mADCS-CGIC) among participants not showing clinically significant improvement during a preceding 3-week run-in period of the PSI alone
  - *We hypothesize that a higher proportion of escitalopram + PSI participants, compared to participants receiving placebo + PSI, will experience clinically significant improvement*

Other outcome measures

Efficacy

- Agitation over 12 weeks as measured by the Neuropsychiatric Inventory – Clinician Rating Scale sum of the Agitation and Aggression Domains (NPI-C/AA)
  - *We hypothesize that participants on escitalopram + PSI will have lower sums of agitation and aggression NPI-C scores compared to those on placebo + PSI*
- Changes in behavior and psychological disturbances over 12 weeks as measured by an abbreviated Neuropsychiatric Inventory (NPI)
  - *We hypothesize that participants on escitalopram + PSI will have lower abbreviated NPI scores compared to those on placebo + PSI*
- Functional performance over 12 weeks, assessed by the ADCS-Activities of Daily Living (ADCS-ADL)
  - *We hypothesize that participants on escitalopram + PSI will have better ADL outcomes compared to those on placebo + PSI*
- Cogitative function over 12 weeks as assessed by the Mini-Metal-State Examination (MMSE)
  - *We hypothesize that participants on escitalopram + PSI will have higher cognitive function compared to those on placebo + PSI*
- Caregiver burden over 12 weeks as assessed by the Zarit Caregiver Burden Inventory (ZBI)
  - *We hypothesize that participants on escitalopram + PSI will have lower caregiver burden compared to those on placebo + PSI*

Safety

- Vital signs (blood pressure, pulse, respiratory rate), and weight
- Balance and gait stability as measured by the Get up and Go Test
- Standardized electrocardiogram (ECG) monitoring, with special attention to the QTc interval
- Adverse events (AE) and serious AEs (SAEs)
- *We hypothesize that escitalopram will be as well as tolerated as placebo on these safety outcomes*

Data analysis

- Primary analysis by assigned treatment group (intention-to-treat)
- Initial descriptive analyses
- Regression methods for effect estimates
- Assessment of baseline variables for interaction or confounding

Inclusion criteria

1. Alzheimer's dementia diagnosed clinically by the National Institute on Aging (NIA) and the Alzheimer's Association (2011 NIA/AA criteria)
2. Mini-Mental State Examination (MMSE) score of 5-28 inclusive
3. Meets the International Psychogeriatric Association (IPA) provisional criteria for agitation in cognitive disorders
4. Clinically significant agitation/aggression as assessed by the Neuropsychiatric Inventory (NPI) for which either
    - The frequency is 'Very frequently,' or
    - The frequency is 'Frequently' AND the severity is 'Moderate' or 'Marked'
5. Provision of informed consent for participation in the study by both caregiver and participant (or, if participant is unable to provide informed consent, with surrogate consent and participant assent)
6. Availability of a caregiver who spends at least several hours per week with the participant, supervises his/her care, is willing to accompany the participant to study visits, and is willing to participate in the study
7. Stable (for ≥ 7 days) dosing of antipsychotics for agitation or psychosis, if being used at all
8. A medication for agitation is appropriate, in the opinion of the study physician

Exclusion criteria

1. Has major depressive episode (MDE) in the past 90 days (meeting the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-V) criteria)
2. Presence of another brain disease that ***fully*** explains the dementia, (e.g., extensive brain vascular disease, Parkinson's disease, dementia with Lewy bodies, traumatic brain injury, or multiple sclerosis)
3. Residence in a skilled nursing or Long-Term Acute Care (LTAC) facility
4. Contraindication to treatment with escitalopram as determined by a study physician, such as recent (30 days) use of Monoamine oxidase inhibitors (MAOIs) or potential participant is hypersensitive to escitalopram or citalopram or any inactive ingredients
5. Prior failed treatment attempt with citalopram or escitalopram for agitation after adequate trial, at minimally accepted dose
6. Indication for psychiatric hospitalization or acute suicidality, in the opinion of the study physician
7. Recent (< 7 days) changes in antipsychotics (including brexpiprazole), or psychosis (delusions or hallucinations) requiring a new or change in antipsychotic treatment (in the opinion of the study physician)
8. Abnormal corrected QT interval using Bazett's formula (QTcB) as determined on enrollment ECG (defined as > 450 ms for men and > 470 ms for women)
9. Recent (30 days) presence of severely reduced renal function (as identified by a Glomerular filtration rate (GFR) clearance < 30 mL/min) or reduced hepatic function
10. Current treatment (within 7 days) with any of the following:
    - anticonvulsants (other than Dilantin for seizures)
    - antidepressants (other than trazodone, ≤ 50 mg per day at bedtime)
    - benzodiazepines (other than lorazepam), or
    - psychostimulants
11. Recent (< 14 days) changes in Dextromethorphan/quinidine, prazosin, and pimavanserin
12. Recent (< 14 days) use of medical marijuana
13. Current participation in a clinical trial or in any study that may add a significant burden or affect neuropsychological or other study outcomes
14. Significant communicative impairments that would affect participation in a clinical trial
15. Any condition that, in the opinion of the study physician, makes it medically inappropriate or risky for the potential participant to enroll in the trial