Alzheimer's Disease Cooperative Study
UC San Diego

Prazosin for Disruptive Agitation in Alzheimer's Disease (AD) (PEACE-AD)
Short Title: Prazosin for Agitation in AD
Protocol Number: ADC-042-PRAZ

Statistical Analysis Plan (SAP)

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Document Version/Date:	V2 - 08 February 2022
Author:	Ronald G. Thomas, Ph.D., Professor Herbert Wertheim School of Public Health and Human Longevity Science University of California, San Diego Signature: _____ Date: 2/8/22

Investigator Approval

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol.

I have discussed any questions I have regarding the contents of this document with the biostatistical author.

I also understand that any subsequent changes to the planned statistical analyses, as described herein, will be updated within any publications related to the study.

Project Director Signatories:

Elaine Peskind, MD, co-PD

Signature: _____

Date: _____

Murray Raskind, MD, co-PD

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ADCS Principal Investigator Signatory:

Howard Feldman, MD, Director, Alzheimer's Disease Cooperative Study

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Elaine Peskind, MD, co-PD

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ALZHEIMER'S DISEASE COOPERATIVE STUDY (ADCS)

Prazosin for Disruptive Agitation in Alzheimer's Disease

Statistical Analysis Plan

Date: 08 February 2022
Version: 2
ADCS Biostatistics Core

Table of Contents

1. Introduction

This study is a multisite, randomized, double-blind, placebo-controlled trial comparing efficacy and safety of prazosin versus placebo in AD patients with disruptive agitation either in long-term care or home-dwelling with a caregiver.

1.1 Randomization / Study Design

In this randomized, double-blind study design, eligible participants per site will be randomized using a 2:1 schedule to either the prazosin or placebo groups, and stratified by gender.

2. Power and Sample Size Determination

Power calculations for PEACE-AD were based on two-sample t-tests. Sample sizes were initially estimated targeting a power=80%, assuming a 2-sided alpha=5%, a standardized effect size of .44 SDs, and a dropout rate of 10%. This is a reasonable estimate of attrition given the study population and the relatively short follow-up period. Based on these considerations, 186 total participants are required: 124 in the prazosin group, and 62 in the control group.

Following COVID-19 in March 2020, it became clear that it would not be possible to successfully recruit this sample size to this protocol. In turn, a decision was made to change the focus to being a pilot trial of between 25-80 participants, a target number that was considered feasible in the aftermath of the pandemic. The range of sample sizes were then considered as a function of the standardized effect size delta; for delta = .71 the required sample size is 80 (53 in the prazosin group, and 27 in the control group), for delta = .79 the required sample size is 65 (43 in the prazosin group, and 22 in the control group), for delta = .91 the required sample size is 50 (33 in the prazosin group, and 17 in the control group), for delta = 1.0 the required sample size is 40 (27 in the prazosin group, and 13 in the control group), for delta = 1.2 the required sample size is 30 (20 in the prazosin group, and 10 in the control group).

The statistical analyses at study conclusion will be based on longitudinal regression data analysis that is expected to increase statistical power over the initial estimates with two-sample t-tests.

3. Selection of Participants to Be Used in Analysis

The intent-to-treat (ITT) data set will include all eligible individuals who are randomized. The modified ITT data set will include all eligible individuals who are randomized and reached the minimum allowed dose of 1mg BID). This definition has been adjusted from the protocol to allow the largest representation of treated participants who achieved a potentially therapeutic dose.

The per-protocol data set will include all eligible participants who: 1) complete the 12-week assessments for the primary analysis, and demonstrate 80% drug compliance as documented in medication administration records.

The modified ITT data set (mITT) will serve as the primary efficacy analysis. The ITT and per protocol analyses will also be performed as part of the secondary analytic plan.

3.1 Safety Analysis Population

The safety analysis population is defined as those subjects that are randomized and took at least one dose of study drug. Categorical safety data will be analyzed, compared between treatment arms, using the exact contingency table method, Fisher's Exact Test.

4. Efficacy Analysis

4.1 Analysis of the Primary Outcome

Hypothesis 1a: Participants randomized to prazosin will manifest greater benefit on the primary outcome measure – the ADCS-Clinical Global Impression of Change in Agitation (ADCS-CGIC-A) anchored to disruptive agitation. The ADCS-CGIC-A is a 7-point scale that is structured as the clinician's assessment of change from baseline compared to the ADCS-CGIC-A Baseline Worksheet. A score of 1-2 indicates clinically meaningful improvement; a score of 3-5 indicates no clinically meaningful change; a score of 6-7 indicates clinically meaningful worsening.

The mITT data set will be used for primary analysis in this study. To address the aims for the primary efficacy analysis (Hypothesis 1a), longitudinal ADCS-CGIC-A scores from first post-baseline visit through 12 weeks will be analyzed using a mixed effects model for repeated measures (MMRM) to assess differences in ADCS-CGIC-A. The MMRM will include terms for time, intervention, intervention-by-time interaction plus covariates gender and severity of agitation at baseline defined as CMAI score. Time will be treated as categorical.

Differences in the primary outcome, ADCS-CGIC-A, between intervention groups will be tested at the two-sided 5% significance level. No adjustment to the type 1 error level will be made for secondary analyses.

4.2 Analysis of Secondary Outcomes

Hypothesis 1b: Participants randomized to prazosin will manifest greater benefit on the key secondary outcome measure – the Neuropsychiatric Inventory (NPI)/Neuropsychiatry Inventory-Nursing Home version (NPI-NH). Similar analyses to that described for the primary analysis will be performed on the total scores of the NPI/NPI-NH. An MMRM analysis as described above for the primary outcome measure will compare prazosin vs placebo at 12 weeks.

Hypothesis 1c: Participants randomized to prazosin will receive a lower cumulative total dose of lorazepam "rescue medication" administered during the trial. Similar analyses to that described for the primary analysis will be performed on the total dose of rescue lorazepam. Multiple linear regression

analysis will compare prazosin vs placebo through at 12 weeks. Gender and severity of agitation at baseline as measured by the CMAI will be included as covariates.

Hypothesis 1d: Study discontinuation ("dropout") due to persistent or worsening intolerable disruptive agitation will occur sooner in the placebo group than in the prazosin group. A Cox proportional hazards model will be used to compare the median time to dropout between groups adjusting for covariates (i.e., gender and baseline CMAI score). Those individuals who dropout for drug intolerance will be censored within this analysis according to their time from randomization to their last observation on protocol.

Hypothesis 1e: There will be larger proportion of responders to prazosin (defined as moderate or marked improvement) vs non-responders (defined as minimal improvement; no change; or minimal, moderate, or marked worsening) on the ADCS-CGIC-A. A logistic regression model including covariates of gender and baseline severity on CMAI will be used to compare percent of responders (ADCS-CGIC-A scores of 1 and 2) vs minimal or no change (ADCS-CGIC-A scores of 3, 4, and 5) vs worsening (ADCS-CGIC-A scores of 6 and 7).

Hypothesis 2: Participants randomized to prazosin will manifest greater benefit on the modified ADCS-Activities of Daily Living-Severe Dementia version (ADCS-ADL-Severe). Similar analyses to that described for the primary analysis will be performed on the ADCS-ADL-Severe. An MMRM analysis using the model specified for the primary outcome measure above will compare prazosin vs placebo at 12 weeks.

Hypothesis 3: Participants randomized to prazosin will have a greater reduction in the NPI/NPI-NH "caregiver distress"/ "occupational disruptiveness" score. Similar analyses to that described for the primary analysis will be performed on the NPI/NPI-NH "caregiver distress"/ "occupational disruptiveness" score. An MMRM analysis using the model specified for the primary outcome measure above will compare prazosin vs placebo at 12 weeks.

4.3 Analysis of Exploratory Outcomes

Hypothesis 4: Participants randomized to prazosin will manifest greater benefit on the CMAI. Similar analyses to that described for the primary analysis will be performed on the CMAI. An MMRM analysis including gender as a covariate will compare prazosin vs placebo at 12 weeks.

Hypothesis 5: Improvement in the five domain NPI/NPI-NH subset score (Agitation/Aggression, Anxiety, Disinhibition, Irritability/Lability, and Aberrant Motor Behavior) will have a greater effect size in response to prazosin treatment than the 12-domain NPI/NPI-NH total score. An MMRM analysis using the model specified for the primary outcome measure above will compare prazosin vs placebo at 12 weeks.

Hypothesis 6: Participants randomized to prazosin will manifest greater improvement in sleep continuity during the 12-hour nighttime period and at each week during the 12-week study duration. Improvement in the primary actigraphy outcome measures will be defined as a decrease in locomotor

activity as assessed by total activity counts over the 24-hour period, specifically a decrease in the 12-hour period from 6 PM to 6 AM for each week of the 12 weeks of the study.

Due to small numbers, individual activity count time series and collection procedures will be reviewed by the Peace-AD actigraphy team (Drs. Jeff Kaye and Miranda Lim, OHSU) for practicability and hypothesis generation. No efficacy analyses will be performed.

5. Safety Analysis

Hypothesis 1f: The incidence of adverse events (AEs) will not differ between participants randomized to prazosin and those randomized to placebo. Fisher's exact test will be used to compare rates of dropout due to AEs between treatment groups.

Safety will be assessed by summarizing and analyzing AEs during the intervention period. AEs will be coded according to established Medical Dictionary for Regulatory Activities (MedDRA) terms and summarized by MedDRA System Organ Class (SOC) and Preferred Term (PT).

Treatment-emergent adverse events (TEAEs) will be defined as events that first occurred or worsened on or after randomization.

An overview of AEs, including the number and percentage of participants who died, suffered Serious Adverse Events (SAEs), discontinued due to AEs, and who suffered TEAEs, will be provided. A comparison between intervention arms will be performed.

The number and percentage of the following types of AEs will be reported:

- TEAEs
- All TEAEs
- TEAEs that led to study participant termination
- TEAEs related to study drug
- TEAEs by maximum severity
- SAEs
- All SAEs
- SAEs related to study drug
- AEs
- A listing of AEs will be reported

Summaries of AEs by within system organ class will be provided for the following:

- Preexisting conditions
- TEAEs
- SAEs
- Participant terminations due to AEs will also be listed

Blood Pressure (BP) and Heart Rate (HR)
Changes from baseline in supine (or sitting) and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR will be summarized using descriptive statistics. Similar analyses to that described for the primary analysis will be performed on supine and orthostatic systolic and diastolic BP and HR. An MMRM analysis will compare prazosin vs placebo at 12 weeks.

6. Software

Statistical software R (version 4.1.2) will be used *http:www.r-project.org.*

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