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

NCT03710642

Protocol Version 11.0
06 DEC 2021

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Sponsor: Alzheimer's Disease Cooperative Study
at University of California, San Diego,

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PROTOCOL VERSION	**VERSION DATE**
Protocol Version 11.0	06DEC2021

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LIST OF ABBREVIATIONS

AD	Alzheimer’s disease
ADCS	Alzheimer's Disease Cooperative Study
ADCS-ADL-Severe	ADCS Activities of Daily Living–Severe Dementia version
ADCS-CGIC	ADCS-Clinical Global Impression of Change
ADCS-CGIC-A	ADCS-Clinical Global Impression of Change in Agitation
ADL	Activities of Daily Living
AE	Adverse Event
AR	Adrenoreceptor
BID	Twice Per Day
BL	Baseline
BP	Blood Pressure
BPRS	Brief Psychiatric Rating Scale
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CGIC	Clinical Global Impression of Change
CGIC-A	Clinical Global Impression of Change in Agitation
CMAI	Cohen Mansfield Agitation Inventory
CNS	Central Nervous System
CRA	Clinical Research Associate
CSF	Cerebrospinal Fluid
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCl	Hydrochlorate
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology

ITT	Intent-to-Treat
LAR	Legally Authorized Representative
LC	Locus Ceruleus
LOCF	Last Observation Carried Forward
LTC	Long-Term Care
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Effects Model for Repeated Measures
MMSE	Mini Mental State Exam
NE	Norepinephrine
NIA	National Institute on Aging
NIH	National Institutes of Health
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory-Nursing Home version
OHRP	Office for Human Research Protections
PEACE-AD	Prazosin for Disruptive Agitation in Alzheimer’s Disease
PI	Principal Investigator
PHI	Protected Health Information
PK	Pharmacokinetics
PO	By Mouth
PT	Preferred Term
PTSD	Posttraumatic Stress Disorder
QAM	Every Day at Mid-Morning
QHS	At Bedtime
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDD	Total Daily Dose
TEAE	Treatment-Emergent Adverse Event
VA	Veterans Affairs

PROTOCOL AGREEMENT

(SIGNATURES ON FILE AT ADCS)

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1 PROTOCOL SYNOPSIS

Protocol Title	Prazosin for Disruptive Agitation in Alzheimer's Disease (AD) (PEACE-AD)
Project Co-Directors	Elaine Peskind, MD, Murray Raskind, MD
Coordinating Center	Alzheimer's Disease Cooperative Study (ADCS)
Participating Sites	Approximately 12-18 ADCS PIs will participate in this trial. PIs will enroll participants residing in either a long-term care (LTC) facility associated with the site or at home with full-time caregiving. An LTC is defined as either an assisted living or skilled nursing facility. Full time caregiving is defined as having continuous daily caregiving.
Study Design	This is a Phase IIb multicenter, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of prazosin in 35 participants with Alzheimer's disease (AD) complicated by disruptive agitation residing in an LTC or in the home with full-time caregiving.
Duration of Study Participation	The total active study duration is approximately 3 years, including start-up, recruitment of all participants and follow-up periods. The total duration of individual study participation is approximately 16 weeks. Individual study participation consists of the following: • Screening period up to 28 days. • Duration of treatment of 12 weeks.
Randomization Schedule	Participants on this study will be randomized 2:1 (prazosin:placebo), for approximately 23 participants in the active group and 12 in the placebo control group.
Summary of Investigational (Intervention) Product	Oral prazosin HCl capsules will be administered twice daily, with individualized doses up to a maximum of 4 mg mid-morning (QAM) and 6 mg at bedtime (QHS), or matching placebo capsules
Inclusion Criteria	1. Males and females with probable or possible AD by NINCDS-ADRDA criteria utilizing medical history; medical records review; and documented physical, neurological, and other examinations and laboratory tests. At Screening, physical, neurological and other examinations; and laboratory tests will be performed as possible and tolerated by the agitated participants. Brain imaging is not a requirement. 2. Participants must reside in either a participating LTC or at home with full-time caregiving.

	3. Participants must have disruptive agitation significant enough to disrupt caregiving and, in the opinion of the Site Principal Investigator, to justify further treatment. Disruptive agitation, defined as having any combination of the following target behaviors, a) irritability, b) physically and/or verbally aggressive behavior, c) physically resistive to necessary care, and/or d) pressured motor activity (e.g., pressured pacing), must have occurred nearly daily during the previous week and at least intermittently for 4 weeks prior to screening, documented on the Behavioral Inclusion Criteria Checklist at Screening. Target behaviors may be any combination of the listed domains as long as they meet the above-described criteria for frequency and severity. 4. Psychotropic medication, if used, should be stable for at least 2 weeks prior to randomization. 5. If taking cholinesterase inhibitor and/or memantine, must be on stable dose(s) for 3 months prior to randomization. 6. During the week before randomization, the above-described behaviors must be rated as of at least “moderate” severity. These behaviors must be problematic in that they cause participant and caregiver distress and/or interfere with essential care or disrupt their living environment.
Exclusion Criteria	1. History of schizophrenia, schizoaffective disorder, or bipolar disorder according to the criteria of the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM). 2. Other neurodegenerative diseases, including Parkinson’s disease and Huntington’s disease, or cerebral tumor. 3. Dementia other than probable or possible AD per NINCDS-ADRDA criteria, such as human immunodeficiency virus (HIV) dementia, Creutzfeldt-Jakob disease, frontotemporal dementia, multiple cerebral infarctions, or normal pressure hydrocephalus. 4. Current treatment for seizure disorder. (Note: anticonvulsants prescribed for disruptive agitation are acceptable). 5. Abnormal laboratory values with clinical significance in the opinion of the site Principal Investigator. 6. Current unstable medical illness including delirium, worsening congestive heart failure, unstable angina, recent myocardial infarction (within the past 3 months), acute infectious disease, severe renal or hepatic failure, severe respiratory disease, metastatic cancer, or other conditions that, in the Site Principal Investigator’s opinion, could interfere with the analyses of safety and efficacy in this study. 7. Bedbound; participants may be ambulatory or use a wheelchair. 8. Absence of any comprehensible language. 9. Participation in another clinical trial for an investigational agent and took at least one dose of study drug (unless unblinded to placebo) within 12 weeks prior to screening. (The end of a previous investigational trial is defined as the date of the last dose of an investigational agent).

	10. Preexisting recurrent hypotension (systolic blood pressure [BP] <110). 11. Preexisting orthostatic hypotension (>20 mmHg drop in systolic BP following 2 minutes of standing posture [or sitting if unable to stand], accompanied by dizziness, lightheadedness, or syncope). 12. A 2-week washout is required prior to BL for the following exclusionary medications: prazosin or other alpha-1 blocker, sildenafil, vardenafil, tadalafil, and avanafil. 13. Women of childbearing potential (must be at least 2 years post-menopausal or surgically sterile for inclusion). 14. The participant may not be an immediate family member of personnel directly affiliated with this study, the study site or study funding agency. Immediate family member is defined as a spouse, parent, child, or sibling, any of whom may be related by blood, adoption, or marriage. 15. Participants whom the Site Principal Investigator deems to be otherwise unsuitable for participation.
Primary Outcome Measure	The primary outcome measure for this study is the ADCS-Clinical Global Impression of Change in Agitation (ADCS-CGIC-A) targeting disruptive agitated behaviors.
Key Secondary Outcome Measure	The key secondary outcome measure is the: • Neuropsychiatric Inventory (home based) (NPI) / Neuropsychiatric Inventory-Nursing Home version (NPI-NH)
Other Secondary Outcome Measures	Other secondary outcome measures are: ADCS Activities of Daily Living–Severe Dementia version (ADCS-ADL-Severe) • Number of study days completed • Total mg of rescue lorazepam administered
Exploratory Outcome Measures	The exploratory outcome measures are: • Analysis of the Cohen-Mansfield Agitation Inventory[12], which will be administered at Baseline and Week 12 to assess specific symptoms of agitation. • Analysis of a subset of NPI/NPI-NH Agitation/Aggression, Anxiety, Disinhibition, Irritability/Lability, and Aberrant Motor Behavior domains that likely are related to increased central nervous system (CNS) noradrenergic activity is planned. • At a subset of participating ADCS sites, locomotor activity and nighttime sleep continuity as measured by wrist actigraphy (e.g., accelerometry) will be collected. This will be referred to hereafter as the “actigraphy sub-study”.
Safety Endpoints	Incidence and severity of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and withdrawals due to adverse events (AEs); changes from baseline (BL) in the following safety assessments: supine and orthostatic BP and heart rate (HR) measurements.

2 INTRODUCTION

2.1 Overview

Prazosin for Disruptive Agitation in Alzheimer's Disease (PEACE-AD) is a Phase IIb multicenter, randomized, double-blind, placebo-controlled trial of 12-weeks treatment with the brain active alpha-1 adrenoreceptor (AR) antagonist prazosin for disruptive agitation in 35 Alzheimer's disease (AD) residents in either a long-term care (LTC) setting or at home with full-time caregiving allowing remote (telephone or video) or home visits. Disruptive agitation is defined as having any combination of the following target behaviors: a) irritability, b) physically and/or verbally aggressive behavior, c) physically resistive to necessary care, and/or d) pressured motor activity (e.g., pressured pacing). LTC is defined as assisted living or skilled nursing facility. A previous single site pilot study addressing disruptive agitation in 22 predominantly LTC-residing AD participants demonstrated efficacy of prazosin on all three primary outcome measures.[1] The current multicenter study is funded by the National Institute on Aging (NIA), and coordinated through the NIA-funded Alzheimer's Disease Cooperative Study (ADCS) with supplemental funding from the Alzheimer's Association.

Rationale for inclusion of AD outpatients with disruptive agitation residing at home with full-time caregiving, including the impact of the COVID-19 pandemic. The current COVID-19 pandemic has had its greatest mortality and morbidity in residents of LTC facilities. In response, LTCs across the nation are in "lockdown" with severe restrictions on visitors, including PEACE-AD study personnel. Furthermore, many facilities have reduced availability for new admissions and many families providing home caregiving for AD patients with disruptive agitation are reluctant to seek LTC placement for fear of exposing their loved one to the deadly coronavirus. In fact, the loss of dementia day care, respite care, and similar caregiver-supportive programs, as well as isolation at home of both AD patients and caregivers, has led to caregivers struggling to manage even more severe disruptive agitated behaviors at home. These COVID-19 related problems provide strong rationale and even necessity for including home-dwelling AD patients in PEACE-AD.

Rationale for flexibility in using remote technology for visits. Recommended COVID-19 safety measures for high risk elderly persons severely limit access of study personnel to LTC settings and argue for performing as many study procedures as possible remotely in both LTC and home caregiving settings to optimize safety for participants, caregivers, and study personnel. Where possible, the screening visit should be conducted in person. However, depending on local restrictions and safety recommendations, sites will have the flexibility to perform screening visits in the LTC, clinic, or through a home visit. Although it is preferable, if possible, to have the screening visit done in person, any of these three options can be done via remote technology, if necessary. All subsequent visits will be performed either in-person or via remote technology.

2.1.1 Rationale for Studying Prazosin

Prazosin is a generically available alpha-1 AR antagonist that crosses the blood brain barrier[18] and blocks central nervous system (CNS) alpha-1 AR activation when administered orally.[19] In a placebo-controlled pilot trial in predominantly LTC-residing AD patients, prazosin was significantly and substantially superior to placebo for disruptive agitation (see Section 3 Preliminary Studies).

2.1.2 Rationale for Study Design

Data from AD clinical and *postmortem* brain tissue studies[15-17] suggest that noradrenergic stimulation via the CNS alpha-1 AR contributes to the pathophysiology of agitation in AD. Thus, blockade of excessive CNS noradrenergic activation with the brain active alpha-1 AR antagonist, prazosin, is a rational approach to the treatment of disruptive agitation in AD.

2.1.3 Rationale for the Dose

Although the successful pilot study of prazosin for disruptive agitation in AD used a total daily dose (TDD) of 6 mg, there were participants who did not fully respond to the maximum dose and there were very few adverse events. It was determined that a higher maximum TDD of 10 mg/day using a flexible dose titration based on response and tolerability to optimum maintenance dose will provide greater benefit without appreciably increasing risk.

2.1.4 Rationale for Length of Trial

A 12-week participant treatment (prazosin or placebo) duration was chosen to allow adequate time for the 29-day study drug titration (necessary for safety) while providing a sufficient 8-week observation period at optimum achieved maintenance dose. Because agitated dementia patients are themselves distressed as well as highly difficult for caregivers and disruptive in their living environment, a longer treatment trial would be impractical.

2.1.5 Rationale for Actigraphy Sub-Study

Agitation and aggression, particularly during the afternoon to nighttime hours, present a significant problem in patients with AD who reside in long-term care and home caregiving settings. Prazosin has shown promise in treating disruptive agitation in AD in both an open label feasibility study as well as a small placebo-controlled pilot study. However, primary outcomes in these small studies have relied on subjective caregiver-based questionnaires, which may be subjective and dependent upon personnel and resources. The effect of prazosin on objective outcome measures of nighttime agitation, including locomotor activity, would add valuable information to the clinical trial.

A small European placebo-controlled study used wrist actigraphy as the primary outcome to assess the effect of melatonin or dronabinol on agitation in participants with AD[35]. In this inpatient study, 24 participants with probable AD and 20 control participants wore a wrist Actiwatch for 14-16 days, including a 2-day period of baseline assessment prior to pharmacological intervention. A treatment: baseline ratio of motor activity as detected by wrist actigraphy was calculated for each participant, and means across participants were compared between active study drug and placebo groups (lower ratio = less agitation). This ratio was significantly decreased during the 12-hour nighttime period in the active study drug compared to the placebo condition ($P<0.05$, Kruskal Wallis test). Exact effect sizes could not be inferred from this publication due to missing data.

A second study used wrist activity to assess the effect of dronabinol on nighttime agitation in participants with AD and dementia[36]. Six participants, five with AD and one with vascular dementia, wore wrist actigraphy devices while receiving 2.5mg dronabinol for two weeks. Nocturnal activity was compared used repeated-measures, comparing baseline levels to those after two weeks of treatment. Treatment with dronabinol significantly decreased nocturnal activity compared to baseline ($P<0.05$, Wilcoxon signed rank test, corresponding to a Cohen's d effect size of ~0.9). Furthermore, participants' agitation symptoms as assessed using the NPI

before and after treatment showed significant improvement in NPI scores in the treatment group (P<0.05, Wilcoxon signed rank test, again corresponding to a Cohen's *d* effect size of ~0.9).

2.2 Background and Significance

Disruptive agitation is a common distressing problem for AD patients, their caregivers, and families, whether they reside in LTC or at home..[2-7] This group of behaviors in AD patients residing at home is the most common precipitant of LTC placement.[8] Prior to the COVID-19 pandemic, LTC placement helped reduce the burden on the frequently exhausted family caregiver. With COVID-19, the option of LTC placement is now less readily available. Even when AD patients with disruptive agitation are able to be admitted to LTC, the burden of managing disruptive agitation is only shifted to the LTC staff, but remains a very difficult and challenging care issue in LTC facilities. In this protocol, the term "disruptive agitation" includes a group of behaviors that are highly prevalent in the later stages of AD and that often cluster together: irritability and anger outbursts, physical resistiveness to necessary care, verbal and/or physical aggression, and pressured motor hyperactivity (e.g., pressured pacing). These behaviors become more frequent as dementia progresses and are eventually expressed for at least some period of time by the majority of AD patients.[7,9] Disruptive agitation in later stage AD patients is arguably the most serious and difficult to treat behavioral problem in both the LTC or at home.[10,11] Effective treatments for disruptive agitation in later stage AD patients remains an important unmet need. In this protocol, whether residing in LTC facilities or continuing to be cared for at home, the patient population with AD complicated by disruptive agitation does not differ.

3 PRELIMINARY STUDIES

3.1 Neurobiologic Rationale for the Alpha-1 AR Antagonist, Prazosin, as a Potential Therapeutic for Disruptive Agitation in AD

Norepinephrine (NE) released from pontine locus ceruleus (LC) neurons that project to postsynaptic AR in neocortical and limbic brain areas has long been recognized to increase arousal and activation.[20,21] Excessive activation by NE of these postsynaptic AR (predominantly alpha-1 AR and beta AR) produces hyperarousal, agitation, irritability, and the "fight-or-flight" response. Although LC neuronal number is reduced in AD,[22] brain NE release remains normal or even increased in AD as indicated by normal or increased cerebrospinal fluid (CSF) NE concentrations.[23] This apparently paradoxical finding likely reflects compensatory upregulation of NE production in surviving LC neurons as demonstrated in *postmortem* human brain tissue studies by Drs. Peskind's and Raskind's group and other laboratories[24, 25] and *not* decreased clearance of NE from brain in AD.[26] The *postmortem* brain tissue studies also demonstrated increased expression of alpha-1 AR in brain areas mediating arousal and activation in AD patients, especially those with an *antemortem* history of disruptive agitation.[16] Others similarly have demonstrated increased alpha-1 AR expression in AD patients with *antemortem* aggressive behavior.[17] Finally, Drs. Peskind and Raskind demonstrated that equivalent CSF NE increases following yohimbine administration produced agitated behaviors only in persons with AD and not in cognitively normal older persons.[15]

The studies described above support excessive activation of brain alpha-1 AR by NE contributing to the pathobiology of disruptive agitation in AD. If so, an alpha-1 AR antagonist that crosses from blood into brain is a rational choice as a pharmacologic treatment for this major clinical problem. Prazosin, the most lipophilic and thus most brain-penetrant, of clinically

available alpha-1 AR antagonists has been demonstrated selectively to antagonize neuronal responses mediated by alpha-1 AR in brain when administered peripherally.[19] Given the clinical availability of prazosin as an inexpensive generic drug, its good safety record (including rarely producing sedation), and the demonstration of prazosin efficacy for severe hyperarousal symptoms in posttraumatic stress disorder (PTSD),[27, 28] a placebo-controlled pilot study of prazosin for moderate to severe disruptive agitation in persons with advanced AD participants both residing in LTC facilities and at home was conducted.[1]

3.2 Placebo-Controlled Pilot Study of Prazosin for Disruptive Agitation in AD

This was a double-blind, placebo-controlled trial of prazosin for disruptive agitation in AD. Twenty-two male and female participants with probable or possible AD (mean [± standard deviation (SD)] age 80 ± 11.2 years, age range 59 to 95 years) and severe disruptive agitation of at least one-month duration were randomized to prazosin (n=11) or placebo (n=11) for 8 weeks. The participants were nursing home residents (N=14) and participants residing at home (N=8). Prazosin was initiated at 1 mg at bedtime (QHS) and titrated using a flexible dose algorithm to optimal dose (maximum dose 2 mg every morning at mid-morning [QAM] plus 4 mg at bedtime [QHS]). Maintenance psychotropic and cognitive acting drugs were held constant during the trial. Outcome measures were the ADCS-Clinical Global Impression of Change (CGIC), Neuropsychiatric Inventory (NPI) total score, and Brief Psychiatric Rating Scale (BPRS). NPI and BPRS were obtained at baseline (BL) and then every two weeks; CGIC was obtained every 2 weeks post-BL.

Participants assigned to prazosin (mean dose 5.7 ± 0.9 mg/day) had significantly greater improvements in behavioral outcome measures compared to those assigned to placebo (mean dose 5.6 ± 1.2 mg/day). For the CGIC, end-point scores were 2.6 ± 1.0 vs. 4.5 ± 1.6, p=0.011. For the Neuropsychiatric Inventory (NPI) total score, the change from BL was 19 ± 21 vs. -2 ± 15, p=0.01. The five disruptive agitation-relevant NPI domains all favored prazosin (Table 1).

Table 1. Change from BL in agitation-relevant NPI domains in prazosin and placebo groups

	NPI Items (LOCF: change from BL [mean ± SD])				
	Agitation/ Aggression	Anxiety	Disinhibition	Irritability/ Lability	Aberrant Motor Behavior
Prazosin (n=11)	-3.6 ± 4.5	-2.6 ± 3.5	-2.4 ± 3.1	-1.7 ± 4.6	-1.9 ± 4.6
Placebo (n=11)	-0.8 ± 3.1	0.4 ± 3.6	1.5 ± 2.9	-1.0 ± 3.4	1.5 ± 3.0

3.3 Safety and Compliance

Prazosin was generally well-tolerated and adverse effects were similar between prazosin and placebo groups (Table 2). Mean change from BL in Mini Mental State Exam (MMSE) scores in the testable participants was -1 ± 1.2 in the prazosin group and -2 ± 2.1 in the placebo group. There were no deleterious effects of prazosin on cognition or activities of daily living (ADL) in this pilot study.

Table 2. Adverse effects

	Prazosin	Placebo
Sedation	3	3
Confusion	1	4
Lower extremity edema[a]	1	2
Hypotension[b]	2	1
Headache	0	2
Cough	2	0
Hallucinations	1	1
Dizziness on standing	2	0
Rash[c]	0	2

[a] One participant in each group terminated from the study early due to peripheral edema.

[b] One participant in each group terminated from the study early due to orthostatic hypotension; the other prazosin participant's hypotension resolved when concomitant antihypertensive medications were adjusted.

[c] One participant in the placebo group terminated from the study early due to rash.

In summary, there were statistically and clinically significant differences favoring prazosin over placebo in behavioral outcome measures of disruptive agitation and prazosin was well tolerated. Patterns of improvement were similar between LTC and home-dwelling participants. Several of the home-dwelling AD participants whose families were actively considering LTC placement because of disruptive agitation opted to continue care at home with maintenance prazosin. These preliminary data support the need for a larger placebo-controlled study to establish efficacy and safety of prazosin for disruptive agitation in individuals with AD, in both LTC and home caregiving settings.

4 SPECIFIC AIMS

Specific Aim 1 (Primary Aim): To evaluate the efficacy and safety of the alpha-1 AR antagonist, prazosin, in the treatment of disruptive agitation as defined in this protocol in participants with probable or possible AD residing either in an LTC or at home with full-time caregiving.

Hypothesis 1a: Participants randomized to prazosin will manifest greater benefit on the primary outcome measure – the ADCS-Clinical Global Impression of Change-Agitation (ADCS-CGIC-A) anchored to disruptive agitation.

Hypothesis 1b: Participants randomized to prazosin will manifest greater benefit on the key secondary outcome measure – the Neuropsychiatry Inventory.

Hypothesis 1c: Participants randomized to prazosin will receive a lower total dose of lorazepam "rescue medication" administered during the trial.

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.

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.

Hypothesis 1f: The incidence of adverse events (AEs) will not differ between participants randomized to prazosin and those randomized to placebo.

Specific Aim 2 (Secondary Aim): To evaluate the impact of prazosin treatment for disruptive agitation on participants' function.

Hypothesis 2: Participants randomized to prazosin will manifest greater benefit on the ADCS-Activities of Daily Living-Severe Dementia version (ADCS-ADL-Severe).

Specific Aim 3 (Secondary Aim): To evaluate the impact of prazosin treatment for disruptive agitation on the LTC environment or home caregiver distress in the home caregiving environment

Hypothesis 3: Participants randomized to prazosin will have a greater reduction in the NPI-NH "occupational disruptiveness"/NPI "caregiver distress" items.

Specific Aim 4 (Exploratory Aim): To evaluate the ability of the CMAI to detect prazosin effects on signs and symptoms of disruptive agitation in AD. The CMAI was developed to provide a detailed frequency assessment of 29 signs and symptoms of agitation in persons with dementia. It has been sensitive to treatment effects in other agitation randomized controlled trials.

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 will compare active vs placebo at 12 weeks.

Specific Aim 5 (Exploratory Aim): To evaluate the ability of five noradrenergic activity-relevant NPI/NPI-NH behavioral domains (Agitation/Aggression, Anxiety, Disinhibition, Irritability/Lability, and Aberrant Motor Behavior) to detect prazosin effects on disruptive agitation in AD.

Hypothesis 5: Improvement in the five domain NPI/NPI-NH subset score will have a greater effect size in response to prazosin treatment than the 12-domain NPI-NH total score.

Specific Aim 6 (Exploratory Aim): To examine locomotor activity and nighttime sleep continuity as measured by wrist actigraphy (e.g., accelerometry) in a subset of study participants over the 24-hour period and the 12-hour nighttime period for each week during the 12-week study duration.

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.

5 STUDY DESIGN

5.1 Study Population

The trial as initially designed included up to 186 participants with probable or possible AD and disruptive agitation. Before the COVID 19 pandemic in March 2020, it was intended that the trial be conducted in the LTC setting exclusively. However, following the COVID 19 pandemic the trial was redesigned to allow participants to be recruited from either the LTC setting or at home with full-time caregiving. (protocol amendment v8). Furthermore, with the impact of the pandemic the feasibility of enrolling this study sample was reviewed and a redesignation of the trial as a pilot study with a revised sample size of between 25-80 participants was made (see section 13.1 below).

5.2 Participating Sites

ADCS site PIs will collaborate with one or several local LTC facilities where study participants reside and will also identify participants who reside at home with full-time caregiving. The ADCS will serve as the Coordinating Center for the study. Approximately 12-18 ADCS sites will participate in this trial, each of which may have an associated 1-4 long-term care (LTC) facilities and/or serve a population of AD patients with disruptive agitation still residing at home with full-time caregiving. LTC is defined as assisted living or skilled nursing facility. Home-dwelling participants must have a primary caregiver who supports and lives with them at home, and who will act as the Study Partner. The Study Partner may or may not be the LAR. They may have additional assistance from paid or unpaid caregivers. The Study Partner must agree to and in the opinion of the site PI be able to provide information for study assessments, measure participant blood pressure and heart rate, oversee administration of study medication and rescue lorazepam under direction of the site PI, maintain regular contact with study team, participate in study visits, and report adverse events.

5.3 Inclusion Criteria

Participants must meet all of the following criteria be included in the study:

1. Men and women with probable or possible AD by NINCDS-ADRDA criteria utilizing history; medical records review; physical and neurological exam; and laboratory tests (as applicable). Brain neuroimaging is not a requirement.
2. Participants must either reside in an LTC that is associated with the study site or at home with full-time caregiving.
3. Participants must have disruptive agitation significant enough to disrupt caregiving and, in the opinion of the Site Principal Investigator, to justify treatment. Disruptive agitation, defined as having any combination of the following target behaviors, must have occurred nearly daily during the previous week and at least intermittently for 4 weeks prior to screening:
    a) irritability,
    b) physically and/or verbally aggressive behavior,
    c) physical resistiveness to necessary care
    d) pressured motor activity (e.g., pressured pacing)

    These behaviors must be problematic in that they cause participant and caregiver distress and/or interfere with essential care or disrupt their living environment. Target behaviors may be any combination of the listed domains. Disruptive agitation must meet this threshold at Screening, documented on the Behavioral Inclusion Criteria Checklist.
4. Psychotropic medication, if used, should be stable for at least 2 weeks prior to randomization.
5. If taking cholinesterase inhibitor and/or memantine, must be on stable dose for 3 months prior to randomization.
6. During the week before randomization, the above-described behaviors of eligible participants must be rated as of at least “moderate” severity.

5.4 Exclusion Criteria

Participants meeting any of the following criteria must <u>not</u> be included in the study:

1. History of schizophrenia, schizoaffective disorder, or bipolar disorder according to the criteria of the most current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM).
2. Other neurodegenerative diseases, including Parkinson's disease and Huntington's disease, or cerebral tumor.
3. Dementia other than probable or possible AD per NINCDS-ADRDA criteria, such as human immunodeficiency virus (HIV) dementia, Creutzfeldt-Jakob disease, frontotemporal dementia, multiple cerebral infarctions, or normal pressure hydrocephalus.
4. Current treatment for seizure disorder (Note: anticonvulsants prescribed for disruptive agitation in the absence of seizure disorder will be allowed).
5. Abnormal laboratory values with clinical significance in the opinion of the site Principal Investigator.
6. Current unstable medical illness including delirium, worsening congestive heart failure, unstable angina, recent myocardial infarction (within the past 3 months), acute infectious disease, severe renal or hepatic failure, severe respiratory disease, metastatic cancer, or other conditions that, in the Site Principal Investigator's opinion, could interfere with the analyses of safety and efficacy in this study.
7. Bedbound; participants may be ambulatory or use a wheelchair.
8. Absence of any comprehensible language.
9. Participation in another clinical trial for an investigational agent and took at least one dose of study drug (unless unblinded on placebo) within 12 weeks prior to screening. (The end of a previous investigational trial is defined as the date of the last dose of an investigational agent).
10. Preexisting recurrent hypotension (systolic BP <110).
    - If a reading of <110 systolic is measured at screening,
      - If the individual is taking antihypertensive medication: The Site PI should reassess the need for such medication and consider medication adjustments in consultation with the participant's physician. One week following adjustment of antihypertensive(s), screening BP will be repeated for reassessment of eligibility. Further adjustment of antihypertensive medication regimen by the participant's health care prescriber, may be indicated if systolic pressure remains <110. For inclusion, new systolic measurement following medication adjustment must be ≥110.
      - If the individual is not taking antihypertensive medication: repeat at least 3 BP measures over the course of 7-14 days. For inclusion, all three follow-up systolic measurements must be ≥110.
      - Any systolic reading <100 is exclusionary.
11. Preexisting orthostatic hypotension (>20 mmHg drop in systolic BP following 2 minutes of standing posture [or sitting if unable to stand] and accompanied by dizziness, lightheadedness, or syncope).
12. A 2-week washout is required prior to BL for the following exclusionary medications: prazosin or other alpha-1 blocker, sildenafil, vardenafil, tadalafil, and avanafil.
13. Women of childbearing potential are not included in this study. Women of non-childbearing potential are defined as any of the following:
    - have been postmenopausal (no menstrual cycle for past 24 months)
    - do not have a uterus,

- have bilateral tubal ligation,
- have undergone bilateral salpingectomy, and/or bilateral oophorectomy

14. The participant may not be an immediate family member of personnel directly affiliated with this study, the study site or funding agency. Immediate family is defined as a spouse, parent, child, or sibling, any of whom may be related by blood, adoption, or marriage.
15. Participants whom the Site Principal Investigator deems to be otherwise unsuitable for participation.

5.5 End of Study/Participant Withdrawal/Early Study Termination

A study participant will be considered to have completed this study at the end of 12 weeks of treatment (i.e., Week 12 or end of study). In the event of withdrawal or early study termination, participants will complete the Week 12 or end of study assessments as defined in Appendix 2. Withdrawal/early termination assessments will be completed as soon as possible; if safety is a concern, withdrawal/early termination assessments can be omitted. Caregivers will be instructed to report any newly occurring or changes in previously reported AEs and SAEs that occur between the early termination visit and 30 days after the last dose to the ADCS Site Study Coordinator or designee. Withdrawn participants will not be replaced in the study population.

5.5.1 Reasons for Early Termination

Participants may be terminated from study participation for reasons such as:

1. Death
2. AEs. The participant has experienced an intolerable AE that, in the opinion of the Site Principal Investigator, requires early study discontinuation or participant cannot tolerate a minimum of 1 mg BID of study drug.
3. Protocol violation. The participant fails to meet protocol entry criteria or did not adhere to protocol requirements.
4. Non-compliance. The participant is non-compliant with intake of study drugs. i.e., does not take any study drug for more than 7 consecutive days.
5. Consent is withdrawn. The participant wishes to withdraw from the study, or the LAR wishes the participant to be withdrawn.
6. Withdrawal by Site Principal Investigator. Consult the Medical Monitor for withdrawal for other reasons.
7. Coordinating Center request. The ADCS Coordinating Center determines it is in the participant's best interest to discontinue participation from the study.
8. Study termination. The PEACE-AD study is terminated by the ADCS, alone or at the recommendation of the Project Co-Directors, Data Safety Monitoring Board (DSMB), NIA or NIA Program Official.

6 STUDY DRUG AND COMPARATOR

6.1 Name and Description of Investigational Product (IP) and Comparator

Commercially available prazosin HCl 1 mg and 2 mg capsules and inactive matching placebo capsules will be used in this study.

6.1.1 Formulation Packaging and Labeling

Prazosin or placebo ("study drug") is provided as 1 mg and 2 mg capsules. Dispensing will allow for 7 days of dosing at QAM and QHS from BL up to Week 6 and then 14 days of dosing at QAM and QHS from Week 6 until Week 12 completion (or early termination). The supplies will be labeled in accordance with all applicable guidelines and/or regulations and will be blinded as to participant treatment assignment.

6.1.2 Mode of Administration

Study drug will be orally administered (PO) and is ideally intended to be swallowed whole. Study drug administration may be assisted by applesauce or similar food if that allows the drug to be swallowed whole. However, if a participant cannot swallow the capsules whole, an alternative is to open the capsules and administer with food. In the LTC setting, this will be done by an unblinded study team member. In the home setting, the blind is maintained even if the capsule is opened, because the caregiver will not be exposed to both the active and placebo forms of study drug.

In the LTC setting, each site will create and document procedures to protect the study blind with the designation of an unblinded individual who will administer study drug that has been opened and mixed with food (e.g., applesauce or pudding) to participants. This method of study drug administration will only be followed when participants are unable to swallow the capsules whole. Unblinded individuals involved in opening the capsules and mixing with food will not provide information for any blinded ratings.

6.1.3 Shipping, Storage and Handling of IP

Study drug will be shipped directly from the study drug warehouse to the ADCS site investigational or research pharmacist once the site has been granted ADCS approval to enroll. Upon receipt of the study drug shipment at the ADCS site, the pharmacist or delegated site staff will verify the condition of the study drug supplies, register the study drug via the Oracle Interactive Response Technology (IRT) system, and document receipt per instructions in the Procedures Manual.

Once a new study participant has been randomized, the ADCS site pharmacist will prepare the individual participant prescription based on designated treatment arm assignment at the lowest dose level per protocol, 1mg QHS (see Section 6.2.1). Study drug supply will be dispensed per the number of dosing days as described in Section 6.1.5. Study drug will be packaged and labeled in accordance with local pharmacy standard procedure.

The prepared initial study drug prescription will be dispensed to the ADCS Site Study Coordinator or delegated site staff for either transport or secure mailing to the LTC facility or home caregiver. For participants residing in an LTC, responsible research team member at the LTC will be designated to receive participant study drug from ADCS Site Study Coordinator or delegated site staff upon arrival at the LTC facility. LTC facility staff will document their receipt of the study drug for each participant as it is received. LTC facility staff or home caregiver will be responsible for individual participant dose administration.

At each weekly or bi-weekly study drug dispensing interval, the site pharmacist will prepare subsequent prescriptions for each participant based on the current dose titration level determined by the prescribing clinician and in accordance with the dose titration schedule

described in Section 6.2.1. Subsequent prescriptions for each participant will be prepared, transported or mailed and documented in the same manner as the initial study drug prescription.

At the time of each study visit, the ADCS Site Study Coordinator or delegated site staff will return unused study drug from the previous dispensing interval to the ADCS site pharmacy. For participants residing in an LTC, the ADCS Site Study Coordinator or delegated site staff will receive any unused study drug from the LTC or home caregiver from the previous dispensing interval for return to the ADCS site pharmacy.

All study drug-related transactions at the ADCS site and LTC facility or home caregiver will be documented by delegated study team staff on Drug Accountability Logs provided by the ADCS.

Further instructions related to the chain of custody for study drug are detailed in the study Procedures Manual.

Study drug must be stored in a limited access area at LTC facilities or safely in the home caregiving setting at room temperature (15-30 °C; 59-86 °F). Only authorized site study personnel or the home caregiver may access study drug.

Based on local differences in the logistical relationships between ADCS sites and LTC facilities or home caregivers, alternative scenarios for the study drug chain of custody may be considered on a case-by-case basis with Project Directors and ADCS Coordinating Center.

6.1.4 Replacement Procedures for IP

Instructions for resupply shipments or replacement of study drug are referenced in the Procedures Manual.

6.1.5 Study Drug Dispensing

One week of study drug will be dispensed at the at the in-person or remote BL Visit (Day 1). The study staff, either at the site clinic or LTC, either in person or via remote visit, will follow the dosing titration procedures as outlined in Section 6.2 of this protocol. To allow a window for study visits, 7 days of study drug plus a 1-day extra supply will be provided at the BL, Day 8, and Day 15 titration visits. From Day 22 through Week 5, 7 days of study drug plus a 2-day extra supply will be provided at each visit. From Week 6 until Week 12 (or early termination), 14 days of study drug plus a 2-day extra supply will be provided at each visit either in person or by mail. For participants residing in an LTC, LTC staff will maintain the study drug supply and administer study drug to the participant. For home-dwelling participants, their caregiver will administer study drug to the participant. Each participant's drug supply will be dispensed according to the randomization ID assigned by the ADCS Electronic Data Capture (EDC) system.

6.1.6 Accountability and Return of IP

It is the responsibility of the ADCS Site Principal Investigator to oversee accurate monitoring of the receipt, storage, dispensing, and accounting of all study drug according to accepted medical and pharmaceutical practice. Copies of all invoices of study drug shipments must be retained. Accurate, original records of study drug inventory and dispensing must be maintained using drug accountability logs provided by ADCS.

All study drug receipt, dispensing, return and destruction documentation related to Site Drug Accountability must be kept in investigational or research pharmacy records at the ADCS site. For participants residing in an LTC, the LTC facility will maintain medication dispensing records. For home-dwelling participants, the Study Partner will document medication doses dispensed in

a medication log. All study drug receipt and return documentation related to LTC Facility Drug Accountability will be retained by the ADCS Site Study Coordinator or delegated site staff. All disposition records must be made available for inspection by ADCS or its representatives upon request. Drug Accountability Logs will be provided by ADCS for the accounting of study drug for each study participant and for maintaining the overall balance. A reason(s) must be given for any capsules that are not accounted for. Any unused study drug assigned to participants for the previous 7-day dosing period from BL to Week 6 or 14-day dosing period from Weeks 6-12 (or early termination) will be collected, and a new supply of study drug will be dispensed. The ADCS Site Study Coordinator or delegated site staff will inspect all returned study drug and will record the number of used and unused capsules on the electronic case report form (eCRF) and the Drug Accountability Logs. Each ADCS site must keep all used and unused study drug in their original containers for inspection by the Study Coordinator and until the ADCS monitor performs drug accountability during a site visit. If any unused capsules remain at the end of the study, they will be accounted for at the site close-out visit in the presence of the ADCS monitor. Once authorized by the ADCS monitor, during an interim monitoring visit or close-out visit, unused study drug may be destroyed at the ADCS site according to the site drug destruction policy.

6.2 Dosing Administration and Schedule

6.2.1 Study Drug Dose Escalation

The dose titration schedule is divided into a fixed dose titration phase from Day 1-14 and a flexible dose titration phase from Day 15-29, followed by a maintenance dose period for the remainder of the 12-week study. An algorithm-based dose titration procedure to optimum dose prazosin or placebo (maximum dose 4 mg QAM and 6 mg QHS for 10 mg TDD) will be employed. The Project Directors may be contacted (see contact information on Page 2 of this protocol) at any point throughout the trial for any questions or cases in need of additional support on dosing decisions.

Table 3. Dose titration schedule

Day(s)	AM Dose (QAM)	Bedtime Dose (QHS)
1-3	**none**	**1 mg**
4-7	**1 mg**	**1 mg**
8-10	**1 mg**	**2 mg**
11-14	**2 mg**	**2 mg**
15-21	**3 mg**	**3 mg**
22-28	**4 mg**	**4 mg**
29	**4 mg**	**6 mg**

Dose increases will be allowed only during the fixed and flexible dosing period (Days 1-29). No further dose escalation will be allowed throughout the maintenance period (Day 30 through study completion or early termination). Dose escalation must occur in a step-wise manner, increasing a single-dose level at a time.

The first dose of study drug (1 mg QHS) must be administered to the study participant only after all assessments are performed for the BL Visit. Study drug will be administered QHS on study

Days 1-3. On study Day 4 and for the remainder of the 12-week study (study completion) or until early termination, study drug will be administered twice daily (at approximately mid-morning and QHS). The time and date of each study drug administration will be recorded in the LTC medication records by LTC staff for LTC-dwelling participants and on the medication log by the Study Partner for home-dwelling participants. Study drug can be taken without regard to food consumption.

6.2.1.1 Fixed Dose Titration

A starting dose of prazosin 1 mg QHS will be administered for three days (Days 1-3). During fixed dose titration, the dose will be gradually increased to 1 mg QAM and 1 mg QHS (Days 4-7), then to 1 mg QAM and 2 mg QHS (Days 8-10), and then to 2 mg QAM and 2 mg QHS (Days 11-14) in the absence of unacceptable AEs. When the end of the fixed dose titration phase is completed, the participant may begin the flexible dose phase. Note: LTC staff for LTC-dwelling participants and Study Partners for home-dwelling participants will be instructed in safety precautions for administration of initial dose and up-titrated doses of study drug.

6.2.1.2 Flexible Dose Titration

During the flexible dose titration phase (Days 15-29), **two** conditions must be met for the study drug dose to be increased:

1. The participant does NOT have “marked improvement” in agitation/aggression behaviors as determined by the Clinician-Rated Change in Behavioral Symptoms Assessment. Marked improvement is defined as complete or almost complete resolution of symptoms of disruptive agitation.
2. The participant does NOT have unacceptable AEs on the Adverse Symptom Checklist and does not have hypotension or orthostatic hypotension as defined above.

If both conditions are met, dose increases will occur on Day 15 to 3 mg QAM and 3 mg QHS, on Day 22 to 4 mg QAM and 4 mg QHS, and finally on Day 29 to a maximum of 4 mg QAM and 6 mg QHS for a TDD of 10 mg.

Participants who are rated as having “marked improvement” prior to achieving the maximum allowed dose per the titration schedule and who then have reemergence of agitation symptoms will be allowed to increase the dose during the titration period following the specific dose increments in Table 3 until Day 29. No further dose increases will be allowed after Day 29.

Lorazepam exception: If the participant received a dose of lorazepam within 48 hours of the dose titration visit, the study drug dose will be increased unless the participant is experiencing an unacceptable AE on the Adverse Symptom checklist or has hypotension or orthostatic hypotension. The dose will increase regardless of rating as “marked improvement” or any other rating.

6.2.2 Dose Reductions and Re-Challenges

If the participant experiences an unacceptable or intolerable AE during the dose titration period, the dose will be reduced to the last tolerated dose (dose reduction per Table 4) until the side effects remit, or are acceptable/tolerable. For safety purposes, the dose may be decreased at any time throughout the study.

Specifically, in the event of orthostatic hypotension, a dose increase cannot occur if the orthostatic blood pressure measurement reveals a 20 mm Hg or greater drop in systolic blood

pressure after two minutes of upright posture (or after two minutes of sitting if unable to stand). The Clinician Prescriber and ADCS Site PI (if different from Clinician Prescriber) must be informed by LTC staff or Study Partner of any drop in systolic blood pressure by 20 mm Hg or more. The dose will either be maintained at the current level or decreased to the last tolerated dose based on clinical judgment of the Clinician Prescriber. The Clinician Prescriber will assess associated factors (such as intercurrent illness, hot weather, dehydration) in response to the orthostatic hypotension and utilize clinical judgment in determining best course of action, such as temporarily not administering a dose of study drug, reducing the dose, or possible dose re-challenge following symptom resolution.

If the AE resolves at the lower dose, the Site Principal Investigator utilizing clinical judgment may choose to re-challenge with the higher dose. A re-challenge is permitted only during the dose titration period (Days 1-29), according to the dose titration steps described in Table 3 above. A maximum of two dose re-challenges is allowed. Requests for additional dose re-challenge (more than two times during dose titration period) may be submitted to the ADCS Coordinator Center, and will be reviewed on a case-by-case in consultation with the Project Directors.

Dose reductions and re-challenges must occur in a step-wise manner, with doses as outlined in Tables 3 and 4.

Table 4: Dose reductions

Current Dose		Dose Reduction	
Midmorning	QHS	Midmorning	QHS
	1 mg	Study Discontinuation	Study Discontinuation
1 mg	1 mg		1 mg
1 mg	2 mg	1 mg	1 mg
2 mg	2 mg	1 mg	2 mg
3 mg	3 mg	2 mg	2 mg
4 mg	4 mg	3 mg	3 mg
4 mg	6 mg	4 mg	4 mg

If the participant is not able to tolerate a minimum of 1 mg twice per day (BID) of study drug, he or she will undergo early termination procedures.

6.2.3 Overdose

For the purposes of this study, an overdose of study drug is defined as ingestion by a study participant of more than the daily dose prescribed per 24-hour period. Any overdose event must be reported on the Protocol Deviation eCRF. Any AEs related to the overdose must be reported on the AE and/or SAE eCRF. An overdose that is associated with an AE will be analyzed as an AE. Refer to the eCRF Completion Guidelines for details.

6.2.4 Study Drug Orders

Study drug orders will be written per the Titration Schedule. To allow a window for study visits, 7 days of study drug plus a 1-day extra supply will be provided at the BL, Day 8, and Day 15 titration visits. From Day 22 through Week 5, 7 days of study drug plus a 2-day extra supply will be provided at each titration visit. From Week 6 until Week 12 (or early termination), 14 days of study drug plus a 2-day extra supply will be provided at each titration visit. Study drug orders will include mid-week dose changes per the titration schedule above. See Procedures Manual for details regarding study drug orders.

7 METHODS OF ASSIGNING PARTICIPANTS TO TREATMENT GROUPS

7.1 Randomization

Eligible participants per site will be randomized using a 2:1 schedule to prazosin or placebo and stratified by site and gender.

7.2 Blinding/Masking

7.2.1 Blinding at the Study Site

This study is a double-blind, randomized, placebo-controlled trial. Study treatment group information (prazosin or placebo) will remain blinded to the participant, family members, family or paid or unpaid home caregivers, and all members of the study team (e.g., Site Principal Investigators, Study Coordinators, Research Nurses, and LTC facility staff) until participant study completion (completion at week 12 or early termination). ADCS periodic safety reviews will be performed in a blinded manner unless the data warrant unblinding due to safety concerns. The treatment code may be broken (unblinded) between randomization and study termination if that knowledge, i.e., knowing exactly which study drug the participant is taking, is essential to the medical management of the participant. Procedures for emergency unblinding are described below. These procedures ensure that neither ADCS monitoring staff nor the Site Principal Investigator(s), other site and/or LTC facility staff or home caregivers have premature access to the study participants' treatment assignments.

7.2.2 Premature Unblinding of Study Participants in the Event of a Medical Emergency

Only in the case of an emergency, when knowledge of whether the participant has received the investigational product is essential for the clinical management or welfare of the participant, may the investigator request to unblind a participant's treatment assignment. If the investigator needs the blind to be unmasked for a participant for any reason, the investigator must contact the ADCS Medical Monitor (and/or Project Directors) to obtain an approval. The blind will need to be broken centrally at the ADCS Coordinating Center. If the blind is broken, whether it be by accident or for the welfare of the participant, the investigator MUST contact the ADCS Medical Monitor. The Site Principal Investigator or designee must report every instance of unblinding to ADCS within 24 hours. When premature breaking of the blind occurs, whether accidental or for participant safety, the Blind Break Notification Form must be completed and submitted to ADCS by fax. Refer to the Procedures Manual for more detailed procedures related to breaking the blind and reporting requirements. The Site Principal Investigator or designee is responsible for ensuring that the instructions on how to perform a blind break are stored safely, that their location is known, and that access is readily available to the relevant staff in case of an emergency. **Breaking the blind for medical necessity is extremely rare.**

Any other reason to reveal a participant's treatment identity prior to the participant's study completion or early termination must be approved by ADCS. If unblinding is necessary, an early termination visit should be completed prior to blind breaking whenever possible. All instances of premature unblinding by the study site must be documented on the eCRF.

7.2.3 Breaking the Blind for Individual Participants at Study Completion or Early Termination

At the participant's study completion, the study drug assignment for each participant will be unblinded by the Site Principal Investigator or designee. Breaking of the blind for an individual

study participant will occur after completion of the end of study visit (Week 12) or after completion of early termination visit procedures. A participant may early terminate from the study according to the reasons listed in Section 5.5 of this protocol only.

The necessity for breaking the blind is based on patient care and safety requirements related to discontinuation of active study drug, prazosin, and to provide for optimal follow-up management by the participant's health care provider/LTC facility. The pilot study found that important clinical factors in the treatment of these difficult to manage patients argues for breaking the blind to provide optimal post-study management. Treatment with prazosin in individual participants following completion of study requirements is at the discretion of the participant's treating clinician. There are no provisions for open-label extension use of prazosin within this protocol.

It should be emphasized that the Clinician Rater, who will perform all outcome assessment measures, will be kept blind to all participants' study drug assignments, rescue lorazepam, adverse effects, and vital signs throughout the study.

8 PARTICIPANT COMPLIANCE

8.1 Compliance

Study drug compliance will be reviewed by the Study Coordinator weekly by two means: review of the medication dispensing records and by capsule counts. Any drug lost will also be recorded by the site. Percent compliance will be calculated. Less than 80% compliance at each study visit will be documented as a protocol deviation.

If a participant has taken no study drug for 3 or more consecutive days, the Clinician Prescriber or designee must contact the Project Directors or designee for re-titration instructions. If the participant has taken no study drug for more than 7 consecutive days, the participant will be early terminated from the study.

8.2 Allowed Concomitant Psychoactive Medications

Participants may continue on stable dose of psychotropic medications at the dose the participant is receiving at enrollment. The dose must be stable for 2 weeks prior to randomization. For cholinesterase inhibitors (donepezil [Aricept], rivastigmine [Exelon], or galantamine [Razadyne], memantine [Namenda], and/or donepezil/memantine [Namzaric]) a stable dose for 3 months prior to randomization is required.

8.3 Rescue Lorazepam

Lorazepam is the only medication allowed as a "rescue" medication during the 12-week study treatment period. In the LTC setting, lorazepam to be provided by the participant's primary care provider, who will be responsible for any necessary discussion of lorazepam use and possible benefits versus risks with the participant and legally authorized representative (LAR). In the outpatient home setting, lorazepam will be prescribed by the site PI and dispensed by the caregiver. This exact approach has been successfully and safely used as a "rescue strategy" in the CitAD outpatient study of the antidepressant citalopram for agitation in Alzheimer's disease[13]. No other rescue medications to treat agitation will be allowed during the 12-week treatment period.

Rescue lorazepam 0.5 mg PO (may be taken twice for a total dose of 1.0 mg/day) is allowed as a rescue medication for moderate to severe disruptive agitation for a maximum of 21 days during the 12-week treatment period. In the LTC setting, rescue lorazepam use will be

documented per medication dispensing records as per usual care. Doses of lorazepam will be recorded on the Lorazepam Source Document Worksheet for both LTC and home-dwelling participants.

8.4 Prohibited Concomitant Medications

Use of any prohibited concomitant medication will result in early termination.

Prohibited concomitant medications include:

- Prazosin or other alpha-1 blocker
- Sildenafil, vardenafil, tadalafil or avanafil is prohibited starting 2 weeks prior to BL. Any of these drugs combined with prazosin may increase risk of hypotension and/or priapism
- Current or past enrollment in an investigational drug trial with at least one dose of study drug taken within 12 weeks of screening

Note that the initiation, dose increase, or dose decrease of any psychoactive medication other than allowed rescue lorazepam (for a maximum of 21 days) after BL is prohibited and will result in early termination from the study.

9 PHARMACOKINETICS (PK) OF PRAZOSIN

Absorption: Prazosin is well absorbed from the gastrointestinal tract with an average of 60% (43 -82%). Prazosin is not affected by food. After oral administration, the time to peak plasma concentration is 1-3 hours. Prazosin plasma concentrations usually do not correlate with therapeutic effect.

Distribution: Protein binding is very high at 92% to 97%. Volume of distribution is approximately 0.5 – 0.9 L/kg.

Metabolism: Prazosin in metabolized extensively in the liver. The major pathways are demethylation and conjugation, and it is excreted unchanged or as metabolites. The major metabolite O-demethylated metabolite accounts for 75% to 80% of elimination; minor metabolites account for about 2% to 10% of elimination. The active metabolite is the major metabolite; all metabolites are less active than prazosin in lowering blood pressure. CYP450 is unknown. The plasma half-life has been reported to be 2-4 hours after oral ingestion.

Excretion: Prazosin is mostly excreted in bile and feces (< 90%) with 6% to 10% in urine. 5% to 11% is excreted as unchanged drug and the remainder as metabolites. Elimination is slower in congestive heart failure patients.

10 STUDY ASSESSMENTS AND PROCEDURES

A skilled and experienced Clinician Rater who is blinded to treatment assignment, adverse events, vital signs, and doses of rescue lorazepam administered will conduct interview-based and cognitive assessments using the ADCS-CGIC-A, NPI/NPI-NH, and ADCS-ADL. Results of all study assessments described below will be captured on the eCRF through the ADCS EDC system. Note: Because of COVID-19 access restrictions and/or safety precautions, interviews for ratings may be performed by remote visit.

10.1 ADCS-Clinical Global Impression of Change in Agitation (CGIC-A)

The ADCS-CGIC-A is the primary outcome measure. It will be anchored to disruptive agitation, the target behaviors in this study. It measures whether the effects of active treatment are substantial enough to be detected by a skilled and experienced clinician on the basis of both observation of the participant and an interview of the participant's primary caregiver, and for participants residing in an LTC, other facility staff. The participant is rated on a 7-point Likert scale, ranging from 1 (marked improvement) to 4 (no change) to 7 (marked worsening). The ADCS-CGIC has demonstrated clinical utility in assessing change in AD clinical trials, and is considered a test for clinically meaningful change.[31] It is a highly reliable measure that provides a clinically meaningful overall assessment of improvement (or worsening) of the target behavioral problems.

At the BL visit, the Clinician Rater will fill out the ADCS-CGIC-A Baseline Worksheet which will provide detailed information on the target symptoms of irritability, physical and/or verbal aggressive behavior, physical resistiveness to necessary care, and pressured motor activity. Information from the primary caregiver, and for LTC residents, the LTC primary informant and other staff, as well as observation of the participant, will be used to provide detailed information on frequency and severity of symptoms and impact on caregiver(s). Subsequent outcome assessment visit ratings on the ADCS-CGIC-A will use this information to make comparisons to symptoms at BL.

10.2 Neuropsychiatric Inventory (NPI, home care setting) and Neuropsychiatric Inventory–Nursing Home version (NPI-NH, LTC setting)

The NPI/NPI-NH is the key secondary outcome measure. The NPI was designed to characterize the neuropsychiatric symptoms and psychopathology of patients with AD and other dementias residing in the community about which information was obtained from family caregivers. The content of the questions and their scoring in the NPI-NH are identical to those of the NPI except for some slight rephrasing to be consistent with the LTC environment where information is gathered from professional caregivers.[32] Assessment of the impact of behavioral disturbances on family and professional caregivers, is assessed by a "caregiver distress" scale in the NPI and an "occupational disruptiveness" scale in the NPI-NH; scoring of this component remains identical.

10.3 ADCS-Activities of Daily Living–Severe Dementia version (ADCS-ADL-Severe)

The ADCS-ADL-Severe questionnaire is a secondary outcome measure aimed at detecting functional decline in people with severe AD. It was developed as a result of a research project funded by the NIA and conducted by the ADCS to develop cognitive and functional instruments for the assessment of participants with AD with relevance to clinical trials.[33] This scale is best suited for evaluating people with MMSE scores below 15/30, or equivalent. Questions are administered to a qualified caregiver informant about a set of 19 basic and instrumental ADL. Instrumental ADL are selected to be relevant to this level of severity of dementia, e.g., obtaining a beverage, turning lights on and off, turning a faucet on and off. Performance of each of these activities during the past 4 weeks, as well as the level of performance, are rated. A total score is derived by summing scores across items, and ranges from 0 (maximal impairment) to 54 (maximally independent function).

10.4 Cohen Mansfield Agitation Inventory (CMAI)

The CMAI is an exploratory outcome measure for estimating frequency of agitated behaviors. The CMAI assesses the frequency of agitated behaviors in elderly persons and was developed for use in the LTC facility. The CMAI will be administered by the Clinician Rater who interviews LTC staff for LTC residents and the Study Partner for home-dwelling participants. The CMAI rates 29 agitated behaviors, each on a 7-point scale of frequency ranging from “never” to “several times per hour.” Ratings pertain to the 2-week period preceding the rating[37]. The CMAI will be completed at baseline and study termination.

10.5 Total mg Lorazepam Administered and Study Days Completed.

Information on the total mg rescue lorazepam administered and number of study days completed will be collected as additional secondary outcome measures. If prazosin is more effective than placebo, it is predicted that participants randomized to prazosin will be prescribed lower cumulative mg of rescue lorazepam for management of persistent or worsening disruptive agitation. Similarly, given that dropout from the study is an option if disruptive agitation remains unmanageable or worsens at the highest tolerated dose of study drug, it is reasonable that if prazosin is more effective than placebo, that participant dropout for persistent/increased disruptive agitation will occur sooner in the placebo group than in the prazosin group.

10.6 Treatment Blinding Questionnaire

The Treatment Blinding Questionnaire was created by the ADCS to assess the perception of blind being maintained until the end of the study. The questionnaire is to be completed by the Site Principal Investigator, Clinician Prescriber, Clinician Rater, and Caregiver at the end of study.

10.7 Physical and Neurological Examination

A medically qualified professional (may be MD, DO, ARNP, or PA-C) will perform a brief physical examination that addresses the major body systems (i.e., head/ears/eyes/nose/throat, cardiovascular, pulmonary, abdomen, musculoskeletal, and extremities). Neurological examination will include an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor, and gait. Because many agitated AD participants may not be cooperative with the physical exam, a recent documented physical exam (within the previous 12 months), together with observation of the participant at the screening visit, can be used to determine eligibility by the Site Principal Investigator.

Height and weight will be recorded at screening. If participant is unable to stand for height and/or weight measurement, it will be obtained from medical records. Weight measurement will be repeated at 12 weeks.

10.8 Electrocardiogram (ECG)

A 12-lead ECG performed within one year prior to screening may be used for eligibility determination if available. The ECG must be reviewed, signed, and dated by the Site Principal Investigator (or a qualified designee). Those with clinically significant ECG findings will be referred for follow-up as deemed appropriate by the Site Principal Investigator and may, if clinically indicated, be excluded from the study. If a prior reading is not available, an appropriately qualified individual will conduct a standard 12-lead resting ECG. If the participant refuses an ECG at screening, the Site Principal Investigator will use their clinical judgement to

consider medical history, examination, and overall health to determine eligibility without an ECG.

10.9 Clinical Laboratory Evaluations

Laboratory values obtained within the year prior to screening may be used for eligibility determination if available. Laboratory reports will be reviewed, signed and dated by the Site Principal Investigator (or a qualified designee). If a value is outside of the laboratory's reference range, the reviewer will indicate whether or not it is clinically significant. Those results that are deemed clinically significant shall be provided to the participant's primary care provider for follow-up as needed. If laboratories have not been collected within the past year, collection of specimens for the following laboratory tests will be attempted: complete blood count, routine blood chemistries (sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose). Routine urinalysis will be performed at screening if indicated by clinical symptoms (e.g., urinary frequency). Laboratory samples will be analyzed by the local laboratory using local standard laboratory supplies. Laboratory evaluations may be repeated if necessary. Because many agitated AD participants are not cooperative, CBC, documented blood chemistries within the past year can be used to determine eligibility. If the participant refuses a blood draw or urine collection at screening, and blood chemistry results within the past year are not available, the Site Principal Investigator will use clinical judgement to consider medical history, examination, and overall health to determine eligibility without labs.

10.10 Vital Signs

10.10.1 Blood Pressure (BP) and Heart Rate (HR) Measurements

Supine and orthostatic BP and HR measurements will be performed. Systolic and diastolic BP and HR will be obtained following at least 10 minutes of supine posture and then repeated immediately following 2 minutes of standing (or sitting if unable to stand). Supine and orthostatic BP and HR measurements will be performed at least daily during the titration period (up to Day 35). For the 24-hour period following the first dose and each dose increase, supine and orthostatic BP and HR measurements will be taken both morning and evening. Beginning on Day 36 (Week 6), supine and orthostatic BP and HR measurements will be performed every 3 days.

For BP and HR parameters, unacceptable side effects will include supine hypotension (supine systolic BP <100), clinically meaningful orthostatic hypotension (> 20 mmHg drop in systolic BP accompanied by dizziness, lightheadedness or syncope), or clinically meaningful HR increase (20 beats per minute or more).

For home-dwelling participants, the Study Partner will be provided an automated blood pressure/heart rate machine and trained in its use at the Screening visit. Training will include demonstration the cuff by the trainer, followed by observation of the study partner demonstrating the correct procedure including supine and standing measurements. The Study Partner will be trained on correct positioning of the cuff, how to read the display, and what to record in the diary. The Study Partner will be instructed to call study personnel if blood pressure measurements fall below levels in the paragraph above or if the participant experiences lightheadedness or dizziness. Study Partners will be instructed in cautions for orthostatic hypotension and will be given information on symptoms and precautions to prevent orthostatic hypotension.

10.11 Adverse Symptoms Checklist

The Adverse Symptoms Checklist (targeting anticipated adverse effects of prazosin) will be completed at BL, each step of the prazosin dose titration phase, and at all subsequent visits. Occurrence of lightheadedness, dizziness on standing (if able to stand), palpitations, drowsiness, headache, nausea, lack of energy, weakness, depressed mood, and other adverse effects will be rated by the Clinician Prescriber. To be considered an AE, the symptom must be new or clinically meaningfully worse compared to BL assessment.

10.12 Open-ended AE Reporting

New and clinically meaningfully worse symptoms on the Adverse Symptom Checklist as well as all other AEs will be reported via open-ended AE reporting on the eCRF.

10.13 Locomotor Activity and Nighttime Sleep Continuity (Actigraphy Sub-Study)

Locomotor activity will be measured over the 24-hour period and the 12-hour nighttime period for each week during the 12-week study of prazosin dosing to efficacy. Sleep continuity will be extrapolated from total activity counts during the 12-hour nighttime period and compared at each week during the 12-week study duration.

Activity levels will be monitored continuously during the entirety of the 12-week study using wrist actigraphy (Actiwatch, Philips Respironics). Wrist actigraphy includes an accelerometer, which produces voltage that reflects the amount of motion of the device. Within the sensor, the degree and force of all movements are calculated into activity counts, which are then recorded to the device. Activity counts will be exported manually after the study period via USB transfer of data from the device to a secure database residing on a password-protected computer. No PHI will be stored in this database. Activity counts will be calculated for every two minutes for the entire length of the trial. Continuous monitoring will be critical as the study design employs a flexible dose titration schedule as well as the use of rescue medications for agitation (e.g., lorazepam).

11 SAFETY

11.1 Adverse Events (AEs), Serious Adverse Events (SAEs), and Reporting

Timely collection and assessment of AEs and SAE reports are critical for protecting the safety of clinical investigation participants. SAE reporting is a regulatory responsibility of ADCS under the Code of Federal Regulations (Title 21, Subpart B, Section 312.32) and the European Union Clinical Trials Directive 2001/20/EC. 9.1.

11.2 Adverse Events (AEs)

CRF Title 21 Food and Drugs, Chapter 1 FDA, Subchapter D Drugs for Human Use, Part 312 Investigational New Drug Application, Section 32 IND safety reporting:

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfCFR/CFRSearch.cfm?fr=312.32

An AE is defined as any untoward (not favorable, unpleasant, bad) medical occurrence associated with the use of a drug, whether or not considered drug related. An AE can be any unfavorable and/or unintended sign, symptom, syndrome, or disease temporally associated with the use of an IP, whether or not considered related to the IP. Examples include:

- All treatment-emergent signs and symptoms (change from the participant's baseline status), e.g., an increase in severity or frequency of pre-existing disorder;

- Exacerbations of the underlying disease;
- Extensions or exacerbations or symptomatology, subjective events reported by the study participant, new clinically significant abnormalities in clinical laboratory, physiological testing, or physical examination.
- Any reactions from the IP, abuse of the IP, withdrawal phenomena, sensitivity, or toxicity to the IP;
- Apparent unrelated illnesses;
- Injury and/or accidents;
- Minor skin irritation caused by actigraphy device (actigraphy sub-study only)

Treatment-emergent AEs (TEAEs) are those AEs that occur after the first dose of study drug until 30 days after the last dose.

Caregivers will be instructed to report any newly occurring or changes in previously reported AEs and SAEs that occur between the Final Study Visit (Week 12) and 30 days after the last dose to the ADCS Site Study Coordinator or designee.

AEs will be collected from the time of informed consent until 30 days after the final dose of study drug. Additional information regarding AE definitions and documentation is located in the Procedures Manual.

11.2.1 Adverse Events of Special Interest

Orthostatic Hypotension: Per the Physicians' Desk Reference (PDR), the risk for first dose hypotension is increased with initial doses over 2 mg. In the PEACE-AD study, the risk of first dose hypotension is minimized by using the starting dose of 1 mg at bedtime administered after the participant is in bed for the night. Caregivers must be available to assist participants to the bathroom in the night following first dose.

ADCS Site PI and staff, as well as caregivers, will be trained in the appropriate process for performing supine and standing (or sitting if participant unable to stand) and orthostatic blood pressure measurements per protocol. Completion of training will be documented via certifications procedures as described in the Procedures Manual.

For outpatient participants still residing at home, the caregiver will be provided an Omron (or similar) automated BP and HR measurement machine. The caregiver will be trained in the use of the device at the Screening Visit for those participants meeting study entrance criteria. The caregiver will be instructed to notify ADCS Site team member if the BP falls below level described below or participant experiences dizziness, lightheadedness or syncope.

It is recognized that a sample of study participants with moderate to severe dementia and disruptive agitation may not be able to fully comply with 10 minutes of supine position followed by exactly two minutes of upright posture. Best efforts will be made, consistent with participant assent, to perform these measurements as outlined. Training procedures will include a discussion of how to handle such cases. Documentation on compliance will be retained in participant medical records.

Supine and orthostatic BP and HR measurements will be performed at least daily during the titration period (up to Day 35). For the 24-hour period following the first dose and each dose increase, supine and orthostatic BP and HR measurements will be taken both morning and night. Beginning on Day 36 (Week 6), supine and orthostatic BP and HR measurements will be

performed every 3 days. Any abnormalities noted in these measurements will be reported to the Clinician Prescriber and ADCS Site PI (if different from the Clinician Prescriber) by the caregivers or ADCS site staff.

Falls: All participants in PEACE-AD will be at some risk for falls. This risk for falls will be evaluated in all participants prior to randomization. The LTC facilities will assess fall risk, per Medicaid/Medicare and OBRA regulations. Home-dwelling participants will be similarly assessed for fall risk using a fall risk factors checklist. Risk factors for falls include fall history, unsteady gait, age, assistance for balance, transfer, walking, wandering, denial of physical limitation, orthostatic hypotension, urinary frequency or incontinence, infection, medications, sensory impairments, footwear, confusion/dementia, delirium or sedation, sleep disorders and impulsive behavior or poor judgment. Participant care plans will be developed for LTC resident and home-dwelling participants to prevent falls with interventions that may include (but are not limited to) assistive devices such as walker, cane, or wheelchair; assistance with ambulation; non-skid footwear; strength-building exercises; eyeglasses; pain management; adequate fluids; and toileting schedule and recommendations for any necessary alterations in the home environment (e.g., removal of throw rugs, clearing traffic pattern).

During the screening period, each potential participant will have their fall risk formally reviewed and updated by a member of the LTC facility staff or the ADCS Site Principal Investigator for home-dwelling participants. This will include an assessment of balance and gait as part of the screening neurological examination. Where this study assessment identifies a fall risk of particular concern, this risk will be discussed with the legally authorized representative at the time of informed consent with a decision taken around suitability to continue screening for the trial. As part of a management plan for those with a fall risk of particular concern, there will be increased attention and awareness of significant postural blood pressure changes and monitoring of falls. Study Partners of home-dwelling participants will be provided information about prevention of falls.

Falls will be recorded as an AE in the ADCS EDC and flagged for medical safety review to allow for real-time monitoring of any significant negative outcomes and reporting to the DSMB per standard procedure of reporting adverse events.

Priapism: The risk of priapism in this participant population of elderly LTC residents is extremely low. Caregivers will be educated in the risk of priapism and instructed to observe participants for persistent erection and potential signs of distress related to persistent erection in the course of providing routine daily care. In the event of priapism, the ADCS Site PI will be contacted by the caregiver for further instruction and additional appropriate medical management.

11.3 Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

Each AE shall be classified by the Site Investigator as “serious” or “not serious.” The seriousness of an event is defined according to the applicable regulations and generally refers to the outcome of an event. An SAE is one that meets one or more of the following:

- Is fatal,
- Is life threatening,
- Requires inpatient hospitalization,
- Prolongs existing hospitalization,

- Is persistently or substantially disabling (significant disruption of normal life functions),
- Is a congenital anomaly or birth defect (in an offspring),
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs if they have the potential to jeopardize participant safety or to require medical or surgical intervention to prevent one of the outcomes listed in this definition, e.g., allergic bronchospasm requiring intensive treatment in an emergency room, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All study participants experiencing an SAE will be seen by the Site Principal Investigator (or designee) as soon as feasible upon learning of the SAE.

SAEs will be collected from the time of informed consent until 30 days after the final dose of study drug. Additional information regarding SAE definitions and documentation is located in the Procedures Manual.

11.3.1 Definition of Life Threatening

A life-threatening SAE is defined as an SAE that places the study participant at immediate risk of death from the event as it occurred. This does not include AEs, which, had they occurred in more severe forms, may have caused death.

11.3.2 Definition of Hospitalization

Hospitalization is defined by ADCS as a full admission to the hospital for diagnosis and treatment. This includes any prolongation of an existing inpatient hospitalization. Examples of visits to a medical facility that do not meet the study criteria for hospitalization include:

- Emergency room visits (that do not result in a full hospital admission)
- Outpatient surgery
- Preplanned or elective procedures

These events would not be reported as SAEs unless:

- The event triggering the hospital visit is an SAE as defined by other SAE criteria such as life threatening, results in persistent or substantial disability/incapacity, or per medical judgment of the Site Principal Investigator.
- Any other event fulfilling the definition of serious that develops as a result of the in-hospital procedure or extends the hospital stay is an SAE.

11.3.3 Definition of Disability

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

11.3.4 Definition of Important Medical Events

AEs that do not result in death, are not life threatening, or do not require hospitalization may be considered an SAE when the event jeopardizes the study participant or require medical or surgical intervention to prevent one of the outcomes listed in this definition. An SAE may also include any event that the Site Principal Investigator or ADCS Medical Monitor judges to be serious or that suggests a significant hazard, contraindication, side effect, or precaution.

11.3.5 Reporting Serious Adverse Events (SAEs)

For sites in the United States, the reporting of SAEs by ADCS to regulatory authorities is required. For sites in Canada, reporting of SUSARs will follow national requirements. In the event of any SAE, the caregiver will be instructed to contact the Site Principal Investigator (or designee) using the contact information provided in the Informed Consent Form.

An SAE or overdose of study drug which occurs during the course of the investigation (i.e., any time after informed consent, regardless of study drug exposure) or within 30 days of receiving the last dose of study drug must be entered into the ADCS EDC by the Site Principal Investigator within 24 hours of learning of the event (refer to the Procedures Manual for further instruction). This entry will trigger an alert to the appropriate ADCS personnel and Project Co-Directors. A notification will be sent to all participating sites and the DSMB once the report is available.

At a minimum, events identified as serious, unexpected, possibly related to study drug must be immediately reported to the responsible Institutional Review Board (IRB)/Independent Ethics Committee (IEC). Local IRB policy for reporting of SAEs must be followed as well.

Expected adverse events are those listed on the Adverse Effects Checklist. Unexpected events are those not listed in the protocol, package insert or informed consent document.

Open/unresolved SAEs will be followed for 30 days following the last dose of study drug or until the SAE is resolved – whichever occurs first.

12 SCHEDULE OF EVALUATIONS AND PROCEDURES

The protocol schedule of events is located in Appendix 2.

The screening period may last up to 28-days followed by a maximum 12 weeks of treatment.

12.1 Pre-screening

During the prescreen phase, sites will identify potential participants through a variety of sources (i.e., reviewing potential participants residing at the LTC facility, in their outpatient practices, and referrals from other providers) and assess if they may potentially qualify for the study following the site's standard practice for recruitment.

Potential participants will be identified through multiple sources. Home-dwelling participants may be identified from the site's known list of patients, from referrals from outside physicians, and through community outreach. Participants residing in an LTC may be identified by the LTC facility staff based on knowledge of the study eligibility criteria. Once a potential candidate is identified, LTC facility staff will contact the ADCS Site PI and Study Coordinator (or delegated site staff) for further review of participant details and assessment of eligibility.

Following this initial identification, if deemed appropriate to proceed with informed consent and screening procedures, the ADCS site study staff will contact participant family members and/or LAR either directly (home-dwelling participants) or through the LTC staff (LTC residents) to schedule a meeting with ADCS site study team and all relevant parties to review the informed consent and study details. A copy of the informed consent will be provided to participant family members and/or LAR during the meeting. The ADCS Site Study Coordinator or delegated site staff will complete the informed consent process and proceed with formal screening procedures as described in section 12.2 if consent is signed.

12.2 Screening (within 28 days prior to randomization)

For both LTC and home-dwelling potential participants, the participant's LAR must sign an informed consent form (ICF) and Health Insurance Portability and Accountability Act (HIPAA) authorization prior to performance of any study procedures. For home-dwelling participants, the Study Partner will participate in the Informed consent process and will sign a separate "Study Partner Responsibilities Consent" to attest they will follow the required protocol procedures, under the PI's oversight. The Study Partner is identified as a person living with the potential participant who will not be the subject of research, but rather the informant on behalf of the participant. The Study Partner's role for the home-dwelling participants is pivotal in ensuring compliance to the protocol-required procedures. The Study Partner may also be the LAR for the participant and in this case will be expected to sign the ICF and HIPAA on behalf of the participant and also sign the Study Partner Responsibilities Consent.

The screening assessment will determine eligibility to proceed to randomization, and may be conducted within 28 days of BL (Day 1). Screening procedures will include the following:

- ICF/HIPAA: participant's LAR for LTC participants and for home-dwelling participants,
- For home-dwelling participants, the Study Partner must sign the Study Partner Responsibilities Consent.
- Review of inclusion/exclusion criteria (including the Behavioral Inclusion Criteria Checklist)
- Demographics review
- Medical and psychiatric history
- Record concomitant medications
- Physical examination
- Neurological examination
- Obtain weight (if able to stand)
- Supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR
- Blood and urine collection for clinical labs, if not performed within a year of screening (refer to protocol section 10.9)
    - Complete blood count (CBC)
    - Blood chemistry: sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, and glucose,
    - Routine urinalysis (if indicated by clinical symptoms)
- 12-lead resting ECG, if not performed within a year of screening (refer to protocol section 10.8)

12.2.1 Confirmation of Eligibility

The participant may proceed to the BL visit if:

- all inclusion/exclusion criteria are met
- results from all required screening procedures have been reviewed
- eligibility has been approved by:
    - Site Principal Investigator
    - Project Directors
    - ADCS Medical Safety

12.3 Baseline/Randomization (Titration - Day 1)

The following will be performed at the BL visit:

- Supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR
- Review and record concomitant medications
- Baseline Symptoms Checklist and open-ended AEs
- Outcome assessments:
  - ADCS-CGIC-A Baseline Worksheet
  - NPI/NPI-NH
  - ADCS-ADL-Severe
  - CMAI
- Initiate wrist actigraphy with Respironics Actiwatch device (actigraphy sub-study only).
- Randomization: Each eligible participant will be assigned a randomization ID and will receive blinded study drug as assigned (placebo or prazosin). Randomization may occur up to 3 days prior to first dose of study drug.
- Dispense 1-week study drug supply per randomization schedule. The starting dose will be 1 mg QHS (TDD=1 mg). Study drug will be dispensed at one week intervals from BL until Week 6 and then at 2 week intervals from Week 6 until Week 12 completion (or early termination). Additional information regarding drug orders is located in the Procedures Manual.

12.4 Titration Visits - Days 8, 15, 22, and 29 *(± 1 Day until Day 15, then ± 2 Days)*

The following will be performed at the Titration visits:

- Supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR
- Review and record concomitant medications
- Adverse Symptoms Checklist and open-ended AEs
- Clinician Prescriber rated change in behavioral symptoms
- Dosing decision per Table 3, Dose Titration Schedule
- Dispense and/or collect study drug
- Study drug accountability
- Check Respironics Actiwatch device is being worn continuously by participant (actigraphy sub-study only)

For additional titration information, see Section 6.2, Dosing Administration and Schedule

12.5 Maintenance Visits

12.5.1 Safety Assessments – Weeks 5, 6, and 10 (± 2 Days)

Safety assessments will be done at Weeks 5, 6 and 10.

- Supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR
- Review and record concomitant medications
- Adverse Symptoms Checklist and open-ended AEs
- Dispense and/or collect study drug
- Study drug accountability

- Check Respironics Actiwatch device is being worn continuously by participant (actigraphy sub-study only)

No dose increases are allowed following Day 29. Dose may be decreased at any time due to intolerable adverse events.

12.5.2 Outcome Assessment – Week 8 (± 2 Days)

This visit collects outcome data; the following assessments will be performed:

- Supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR
- Review and record concomitant medications
- Adverse Symptoms Checklist and open-ended AEs
- Dispense and/or collect study drug
- Study drug accountability
- Outcome assessments:
    - ADCS-GCIC-A
    - NPI/NPI-NH
    - ADCS-ADL-Severe
- Check Respironics Actiwatch device is being worn continuously by participant (actigraphy sub-study only)
- No dose increases are allowed following Day 29. Dose may be decreased at any time due to intolerable adverse events.

12.6 End of Study - Week 12 (± 2 Days) or Early Termination

The following procedures will be performed at this visit:

- Supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR
- Weight (if participant able to stand)
- Review and record concomitant medications
- Adverse Symptoms Checklist and closure of open-ended AEs as appropriate
- Collect unused study drug
- Study drug accountability
- Outcome assessments:
    - ADCS-GCIC-A
    - NPI/NPI-NH
    - ADCS-ADL-Severe
    - CMAI
- Removal of Respironics Actiwatch device for return to analyzing site (actigraphy sub-study only)
- Administer Treatment Blinding Questionnaires (Site PI, Clinician Prescriber, Clinician Rater and Caregiver)
- Break the blind after all study procedures completed
- Develop, discuss, and document follow-up care plan

12.7 Between Visits

LTC or home caregivers will be responsible for performing supine and orthostatic (standing or sitting if unable to stand) systolic and diastolic BP and HR at least daily during the titration period (up to Day 35). For the 24-hour period following the first dose and each dose increase, supine and orthostatic BP and HR measurements will be taken both morning and evening. Beginning on Day 36 (Week 6), supine and orthostatic BP and HR measurements will be performed every 3 days. These recordings will be maintained in a log that is completed either at the participant's home residence or at the LTC facility. In addition, BP and HR measurements will be performed by caregiver, or if an in-person visit can take place, by the ADCS Site Study Coordinator, or Clinician Prescriber on study visit days for recording in the eCRF. If it is necessary to conduct the visit remotely, the LTC or home caregiver-provided BP and HR measurements will be entered into the eCRF.

For those sites participating in the wrist actigraphy sub-study, caregivers will be responsible for ensuring that the Actiwatch device is worn by the participant continuously during the entirety of the 12-week study. ADCS Site personnel will assist with receipt of the watch by mail, putting the watch on the non-dominant wrist of the participant, and removing/mailing the watch back to the analyzing site every four weeks for the duration of the 12 week trial.

13 STATISTICAL METHODS

This study is a multicenter, randomized, double-blind, placebo-controlled trial comparing efficacy and safety of prazosin versus placebo in AD patients with disruptive agitation.

13.1 Power and Sample Size Determination

Power calculations for PEACE-AD were based on two-sample t-tests. Sample sizes were 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 active group, and 62 in the control group

Following COVID-19 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 data analysis that is expected to increase statistical power.

13.2 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 completed the fixed dose titration period at Day 14. The per-protocol data set will include all eligible participants who: 1) complete the 12-week assessments for the primary analysis, and 2)

demonstrate 80% drug compliance as documented in medication administration records. The safety analysis population is defined as those subjects that are randomized and took at least one dose of study drug.

13.3 Efficacy Analysis

13.3.1 Analysis of the Primary Outcome(s)

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 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-BL visit through 12 weeks will be analyzed using a mixed effects model for repeated measures (MMRM) to assess differences in ADCS-CGIC-A. The ADCS-CGIC-A is a 7-point scale that is structured as the clinician's assessment of change from BL 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 MMRM will include terms for time, intervention, intervention-by-time interaction plus covariates site and gender. Time will be treated as categorical.

Categorical safety data will be analyzed, compared between treatment arms, using the exact contingency table method, Fisher's Exact Test.

Differences in the primary outcome of change in 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.

A secondary sensitivity analysis of the primary outcome measure will also be performed to address the aims for Hypothesis 1a. The details of this analysis are further described in the Statistical Analysis Plan (SAP).

13.3.2 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 NPI/NPI-NH. An MMRM analysis will compare active vs placebo at 12 weeks.

Hypothesis 1c: Participants randomized to prazosin will receive a lower 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. An MMRM analysis will compare active vs placebo at 12 weeks.

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 potential confounding factors.

Hypothesis 1e: There will be larger proportion of responders to prazosin (defined as moderate or marked improvement) vs nonresponders (defined as minimal improvement; no change; or minimal, moderate, or marked worsening) on the ADCS-CGIC-A. A logistic regression model

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 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 will compare active 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 will compare active vs placebo at 12 weeks.

13.3.3 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 will compare active vs placebo at 12 weeks.

Hypothesis 5: Improvement in the five domain NPI/NPI-NH subset score will have a greater effect size in response to prazosin treatment than the 12-domain NPI/NPI-NH total score. An MMRM analysis will compare active 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. Univariate means analysis will be performed to compare activity counts between participants on prazosin and participants on placebo for each time period. Secondary actigraphy outcome measures will include logistic regression of motor activity counts to changes in NPI/NPI-NH subscores for agitation for each participant.

13.3.4 Safety Analysis

Hypothesis 1f: The incidence of adverse events (AEs) will not differ between participants randomized to prazosin and those randomized to placebo. Fishers 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 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

13.3.5 Safety Endpoints

Safety results will be summarized by treatment group using descriptive statistics. No formal statistical testing will be performed for any of the safety endpoints; hence no p-values will be reported. All safety analyses will be performed using the Safety Set.

13.3.6 Blood Pressure (BP) and Heart Rate (HR)

Changes from BL in supine 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 active vs placebo at 12 weeks.

13.4 Criteria for the Termination of the Trial

The trial may be terminated early by the Data Safety Monitoring Board (DSMB) based on safety and feasibility, or by the Project Co-Directors, DSMB, NIA and NIA Program Official recommendations. The trial may be terminated early at an individual participating site based on site IRB recommendations as well.

14 DATA AND SAFETY MONITORING BOARD (DSMB)

The ADCS DSMB will review the safety of all participants enrolled in the trial on an ongoing basis. The initial task of the DSMB will be to review the protocol to identify any necessary modifications. If modifications are necessary, revisions will be reviewed by the DSMB prior to its recommendation on initiation of the project. The DSMB, based on its review of the protocol, will work with ADCS Medical and Safety Core personnel to identify the study-specific data parameters and format of the information to be regularly reported. The DSMB will meet regularly at approximately 3-month intervals. The DSMB will initially be provided with data blinded to treatment status, but they may request unblinded data if there is a safety concern. The DSMB and NIA representative will meet in person or by conference call on a quarterly basis.

Additionally, the DSMB will be informed of the occurrence of any SAEs within 7 days of being reported to the ADCS. The DSMB may at any time request additional information from the ADCS.

Based on the review of safety data, the DSMB will make recommendations regarding the conduct of the study. These may include amending safety monitoring procedures, modifying the protocol or consent, terminating the study or continuing the study as designed. Using the ADCS safety review process and the DSMB, there is substantial oversight and case review to alert the Site Principal Investigators, in a timely manner, to any safety issues that may arise. For further details, please refer to the DSMB charter.

15 RECORDING AND COLLECTION OF DATA

15.1 Source Documents and Electronic Case Report Forms (eCRF)

The Site Principal Investigator or designee will record all data collected (either written or electronic record). Written data will be entered on source documents. Electronic data will be entered on the eCRF through the ADCS EDC system. The site staff will be suitably trained on the use of the eCRF and appropriate site personnel will be authorized to provide electronic signatures. The Site Principal Investigator is responsible to verify the integrity of the data and acknowledge as such by signature.

All site entries will be made in a secured web site and the Site Principal Investigator or designee will review the record for completeness. If corrections are necessary to the eCRFs, the Site Principal Investigator or designee will update the eCRF and provide documentation of the reason for change.

Completed eCRFs will be submitted according to the eCRF Completion Guidelines, and reviewed by the ADCS to determine their acceptability. If necessary, data correction data queries will be generated by ADCS for resolution by the study site.

15.2 Study Files and Participant Source Documents

Participant confidentiality is strictly held in trust by the participating Site Principal Investigator, research staff, and the ADCS and/or participating institution and their agents. The study protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the ADCS or funding agency. Authorized representatives of the ADCS or funding agency may inspect all documents and records required to be maintained by the Site Investigator, including but not limited to, medical records (LTC facility, office, clinic or hospital) and pharmacy records for the participants in this study. The study site will permit access to such records. All records will be kept behind two locks (e.g., in a locked cabinet located in a locked office). Identifiable and coded data will be stored separately. Any transport of files that must occur between the study site and the participants' place of residence (in the home or an LTC facility) will occur in compliance with HIPAA of 1996. All computer entry and networking programs will be done using participant identification numbers only.

Information about study participants will be kept confidential and managed according to the requirements of the HIPAA of 1996. Those regulations require a signed participant HIPAA Authorization informing the participant of the following:

- What protected health information (PHI) will be collected from participants in this study
- Who will have access to that information and why
- Who will use or disclose that information

- The rights of a research participant or LAR to revoke their authorization for use of their PHI.

In the event that a participant/LAR revokes authorization to collect or use PHI, the Site Principal Investigator, by regulation, retains the ability to use all information collected prior to the revocation of participant/LAR authorization. Each Site Principal Investigator, under the guidance of his/her IRB, is responsible for ensuring that all applicable HIPAA regulations and State laws are met.

15.3 Release of Information

The following study information will be released as documented in the informed consent form and/or HIPAA authorization:

- Clinically meaningful abnormal laboratory values to the participant/LAR and participant's health care provider.
- Study condition (prazosin or placebo) and dose to participant/LAR and participant's health care provider at study termination (completion or early termination).
- Information necessary for safety and regulatory monitoring by IRB, the FDA, the NIA, the Office for Human Research Protections (OHRP), and others as required.

No other information will be released without written permission of the participant/LAR.

16 ADMINISTRATIVE PROCEDURES

16.1 Study Timeline

The approximate timeline for this study is projected as follows: (1) approximately 5 months for study startup activities that will include communication with the Food and Drug Administration (FDA) regarding Investigational New Drug (IND) application requirements, site IRB and regulatory approvals, and the Investigator training meeting; (2) recruitment will last for approximately 9 months; and (3) 4 months of follow up. The study will therefore be active for approximately 1.5 years.

It is anticipated that this study will require approximately 14 months for all participants to complete all visits from Screening through Week 12.

16.2 Ethics and Regulatory Considerations

16.2.1 Good Clinical Practice (GCP)

This study will be conducted in compliance with the protocol and accordance with GCP guidelines, as defined by the International Conference on Harmonisation (ICH) Guideline, Topic E6, the United States Code of Federal Regulations, Title 21, Part 50 (21CFR50) – Protection of Human Subjects and Part 56 – Institutional Review Boards (IRBs), HIPAA, Federal and State regulations and all other applicable local regulatory requirements and laws.

Study personnel involved in conducting this study will be qualified by education, training and experience to perform their respective task(s) in accordance with GCP. LTC facility personnel responsible for performing study activities on this trial will be required to undergo training on human research protections and Good Clinical Practice in line with NIH guidance, as well as training on the protocol. All training activity for LTC facility personnel will be documented, and training certifications maintained on file at the ADCS participating site and ADCS Coordinating Center.

For participants who reside at home, the study oversight remains the responsibility of the Investigator and his/her delegates and relies on training and providing resources to the Study Partners via close contact and documented communication. The responsibilities and expectations for the Study Partners are described in the document “Study Partner Responsibilities Consent” that requires the Study Partner’s signature before any study activity begins.

16.2.2 Institutional Review Board (IRB)

IRBs and Research Ethics Boards must be constituted and their authority delegated through the institution’s normal process of governance according to applicable State and Federal requirements for each participating location. Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the OHRP. The single IRB will follow Federal Policy or the “Common Rule” as described in HHS regulations, 45 CFR 46. Any amendments to the protocol or consent materials must also be approved before they are placed into use. In the United States, only institutions holding a current US Federal-wide Assurance issued by OHRP may participate. Refer to: http://www.hhs.gov/ohrp/assurances/.

The Site Principal Investigator must obtain approval from the IRB for all subsequent ADCS protocol amendments and, when warranted, changes to the informed consent document. Protocol and ICF amendments can be made only with the prior approval of the ADCS. The Site Principal Investigator may not implement any protocol deviation without prior notification to the ADCS and prior review and documented approval of the IRB of record, except where necessary to eliminate an immediate hazard to study participants, or when change(s) involve only logistical or administrative aspects of the trial (ICH 4.5.4). The Site Principal Investigator shall notify the IRB of deviations from the protocol or SAEs occurring at the site, in accordance with procedures as defined by the IRB of record.

16.2.3 Informed Consent and HIPAA Compliance

Informed consent will be obtained in accordance with US 21 CFR 50.25, the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and Health Canada requirements. Applicable HIPAA privacy notifications will be implemented and HIPAA authorizations signed before protocol procedures are carried out. Information should be given in both oral and written form as deemed appropriate by the Site’s IRB.

Prior to the beginning of the trial, the Site Principal Investigator must have the IRB’s written approval of the ICF and any other written information to be provided to participants and be approved by ADCS Regulatory Affairs. Consent forms must be in a language fully comprehensible to the prospective participants and/or their LAR. Participants, their relatives, guardians, or LAR will be given ample opportunity to inquire about the details of the study. Prior to a participant’s participation in the trial, the written ICF must be signed and personally dated by the participant’s LAR, the participant (if possible), and by the person who conducted the informed consent discussion. In cases where the LAR is unable to attend the consenting session on-site (e.g., lives in another state), remote consenting will be allowed by telephone or use of video conferencing (e.g., Skype or FaceTime). If telephone or video conferencing is used, the session may not be recorded for any reason. The blank ICF will be sent to the LAR via mail ahead of a pre-arranged consent meeting during which the consent process with the legally authorized representative will occur. Where appropriate, the participant may also be included in

this consent meeting and asked to provide assent at this time. After the consenting discussion, if he/she agrees, the LAR will send the completed signed consent form via facsimile, email or via telephone (using text or applications such as “Genius Scan”). In all cases, the LAR will be asked to return the original copy via mail as a follow up for the final informed consent record. Participants/LAR should be provided copies of the signed ICF and HIPAA authorization. For face to face or remote informed consent discussions, copies of the ICF and HIPAA authorization shall be placed in the participant’s medical record, either at the study site or at the LTC.

16.2.4 Inclusion of Children as Participants in Research Involving Human Subjects

Not applicable. No children will be enrolled in this study.

16.3 Study Monitoring

The ADCS monitor is responsible for inspecting the eCRFs and source documentation at regular intervals throughout the study to verify adherence to the protocol, completeness and accuracy of the data, and adherence to local regulations on the conduct of clinical research. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory requirements and continued adequacy of the investigational site and its facilities. The Site Principal Investigator will cooperate in the monitoring process by ensuring the availability of the eCRFs, source documents and other necessary documents at the time of the monitoring visits. The Site Investigator will promptly address any matters brought to his/her attention by the monitor. The Site Principal Investigator may also be asked to meet in-person with the site monitor during certain visits.

The CRAs assigned to the study are responsible for verifying the following with respect to IP:

- Storage time and condition is acceptable, and that supplies are sufficient throughout the trial
- IP is supplied only to participants who are eligible to receive it and at the protocol specified dose(s)
- LTC facilities, site staff, and home caregivers are provided with necessary instruction on properly receiving, using, handling, storing, and returning the IP
- Receipt, use, and return of the IP is controlled and documented adequately
- Destruction of unused IP at the ADCS sites complies with applicable regulatory requirement(s) and is performed in accordance with site drug destruction policy.

16.4 Audit

In accordance with ICH GCP, representatives of the ADCS and/or regulatory agency may select this study for audit. The Site Principal Investigator and study staff are responsible for maintaining the site investigator file containing all study-related regulatory documentation as outlined by ADCS Regulatory Affairs that will be suitable for inspection at any time by ADCS, its designees, and/or regulatory agencies. Inspection of site facilities (e.g., pharmacy, laboratories) to evaluate the trial conduct and compliance with the protocol may also occur.

16.5 Records Retention

No study document shall be destroyed without prior written agreement between the ADCS and the Site Principal Investigator. Should the Site Principal Investigator wish to assign study records to another party or move them to another location, he/she may do so only with the prior written consent of the ADCS.

Essential documents and study records must be retained for a minimum of seven years following primary publication of study results, or per the requirements of the local regulatory guidelines, whichever is longer. The ADCS Coordinating Center will notify sites when retention of such documents is no longer required.

16.6 Publication Policy

The results of this study will be published. To coordinate dissemination of data from this study, a publication committee will be formed. The committee will consist of the PEACE-AD Co-Directors, ADCS Publication Committee, interested Site Principal Investigators and appropriate ADCS personnel. The committee will solicit input and assistance from other Investigators as appropriate and adhere to all ADCS publication policies.

16.7 Sharing of Final Research Data

Data from this research will be shared with other researchers pursuant to the 02/26/2003 National Institutes of Health (NIH) Final Statement on Sharing Research Data. The ADCS grant contains a data sharing policy consistent with the goals of the NIH but which also respects the rights of commercial partners. The NIH policy can be found at: **http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-032.html**.

NIH believes that data sharing is important for further translation of research results into knowledge, products, and procedures to improve human health. The NIH endorses the sharing of final research data to serve these and other important scientific goals. To protect participants' rights and confidentiality, identifiers will be removed from the data before they are shared.

17 PERSONNEL REQUIREMENTS – ROLES AND RESPONSIBILITIES

The Site Principal Investigator is responsible for the overall conduct of the study at the site. The Site Principal Investigator will supervise study personnel, including sub-investigators, Study Coordinator, and Clinician Rater. The Site Principal Investigator will ensure that Clinician Rater(s) maintain a high level of skill and accuracy in conducting assessments. Additionally, the Site Principal Investigator or designee will perform or supervise clinical evaluation of all participants, assure that inclusion and exclusion criteria are met prior to study drug randomization, and ensure protocol adherence.

The Clinician Prescriber may be the Site Principal Investigator or a clinician designee and may be an MD, DO, ARNP, or PA-C. The Clinician Prescriber will perform physical and neurological exams, make dose titration decisions, and document and manage adverse events.

The Clinician Rater will perform the ADCS-CGIC-A, NPI/NPI-NH, ADCS-ADL-Severe, and CMAI. The Clinician Rater may be an MD, PhD clinical psychologist, ARNP, PA-C, MSW, or RN with the appropriate clinical experience and training to perform the outcome assessments. In the absence of clinical credentials, the Project Directors may accept a combination of education and experience on a case-by-case basis. The Clinician Rater will at all times remain blinded to treatment assignment, vital signs, adverse events, and concomitant medications. The Clinician Rater CANNOT also fulfill duties of the Clinician Prescriber or Study Coordinator.

The Study Coordinator will perform study visits, including scheduling visits, conducting the informed consent process, as well as ensuring availability of the Clinician Prescriber and Clinician Rater to perform their duties.

Participants who reside at home will ideally come to the study site for visits. When possible, the Screening visit should be performed in-person either at the study site or by home visit. If in-person screening is contraindicated due to safety concerns or local COVID-19 restrictions, screening may be conducted as a remote visit. If conducting screening as a remote visit, a combination of telephone and video conference can be used; at a minimum, the observational elements of the Physical and Neurological Exam including visual assessment of participant gait should be done via video conference.

Subsequent to the screening visit, if travel from home to the study site is precluded by participant agitation or COVID-19 restrictions and/or safety precautions, home visits will be performed when feasible. Alternatively, safety and outcome data may be obtained from the caregiver by remote visit. For home-based participants, the caregiver training on proper completion of BP and HR measurements must be done either in person or via video conference (not by telephone alone) in order to ensure correct placement of the blood pressure cuff and ability to record systolic and diastolic BP and HR recordings accurately both lying and standing. For participants who reside in an LTC, the Study Coordinator will serve as primary liaison to the LTC facility to ensure availability of the participant's LTC facility primary caregiver and other staff for interview by the Clinician Rater at BL and outcome visits. Similarly, COVID-19 restrictions and/or safety precautions may require that these visits take place by remote visit. The Study Coordinator will gather information as necessary from source documents and caregivers on BP and HR measurements (and may perform these measurements at study visits if LTC access is possible), doses of rescue lorazepam and other concomitant medications, and adverse events. The Study Coordinator will enter data into the eCRFs.

LTC and home-based caregivers will be available to the Clinician Rater for providing information to enable interview-based outcome assessments. Caregivers will also perform BP and HR measurements, record medication dosing per usual clinical requirements, and inform study personnel of adverse events. LTC Caregivers may also identify potentially eligible participants to Site Investigator and delegated ADCS site staff for further review and consideration. For those sites participating in the actigraphy sub-study, caregivers will ensure that the Actiwatch device is worn by the participant continuously during the entirety of the 12-week study.

Additional key personnel may be required, which is outlined in the Procedures Manual or depending on COVID-related restrictions and/or safety precautions

18 POTENTIAL RISKS AND BENEFITS

18.1 Potential Risks of Study Drug

Prazosin was first introduced in 1973 as Minipress (Pfizer) for clinical management of hypertension, and later became widely prescribed off label for urinary outflow obstruction secondary to benign prostatic hyperplasia. It has been prescribed safely to large numbers of middle-aged and older persons over the past four decades.

The following information regarding the side effect profile and safety record of prazosin is a synopsis from the Minipress "package insert"[29]: The most important adverse effect to be considered when prescribing prazosin is a "first dose effect" manifested by syncope with sudden loss of consciousness believed to be due to postural hypotension in approximately 1% of patients given an initial dose of 2 mg or greater. This rare adverse effect is self-limiting and in most cases does not recur after the initial period of therapy or during subsequent dose titration.

For safety, patients should always be started on 1 mg of prazosin. Additionally, for this study, the initial dose is administered at night in order to mitigate effects of any hypotensive response.

In clinical trials of prazosin, most frequent adverse reactions were: dizziness (10%), headaches (8%), drowsiness (8%), lack of energy (7%), weakness (7%), palpitations (5%), and nausea (5%). Less frequent adverse reactions (1-4%) were: vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, urinary frequency, and nasal congestion. Fewer than 1% of patients have reported the following (causal relations sometimes not established): abdominal discomfort or pain, tachycardia, paresthesias, hallucinations, pruritus, incontinence, impotence, and priapism.

Data from the placebo-controlled feasibility study of prazosin for disruptive agitation in AD support this safety record. Change in BP and HR from BL to last observation did not differ between prazosin and placebo groups. Of the 22 participants in the pilot placebo-controlled study, two participants (one assigned to prazosin and one to placebo) underwent early termination for orthostatic hypotension and two participants (one assigned to prazosin and one to placebo) underwent early termination for worsening peripheral edema, which readily reversed upon discontinuation of prazosin. In addition, many thousands of veterans with PTSD (including many elderly World War II and Korean War veterans) have now been treated with prazosin across the national Veterans Affairs (VA) system.[30] Prazosin for treatment of PTSD is generally well tolerated. Most common adverse effects have been transient orthostatic dizziness, nasal congestion, or headache.

Safety procedures in this study for the use of prazosin include exclusion of persons with unstable angina, recent myocardial infarction, preexisting recurrent hypotension (systolic <110) or orthostatic hypotension (> 20 mmHg drop in systolic BP accompanied by dizziness, lightheadedness or syncope); chronic severe renal failure; hepatic failure; or any unstable or severe medical disease. Screening procedures include 12-lead ECG, screening laboratory assessments, and physical/neurological examination; ECG and/or laboratory values obtained within the year prior to screening may be used for eligibility determination if available (refer to Protocol sections 10.8 and 10.9 for additional detail). Safety assessments during study participation include measurements of supine and orthostatic BP and HR performed at least daily during the titration period and one week after the last titration step in the flexible titration phase (up to Day 35). For the 24-hour period following the first dose and each dose increase, supine and orthostatic BP and HR measurements will be taken both morning and night. Thereafter, supine and orthostatic BP and HR measurements will be taken every 3 days. In addition, study participants will undergo assessment for adverse effects at each study visit.

During the course of the study, members of the Project Co-Directors team will be on-call to advise the Site Principal Investigator(s) or caregivers regarding eligibility, dosing decisions, and management of AEs. Any unexpected AE or SAE will be reported as described above.

18.2 Potential Risks of Actigraphy Sub Study

Participants may have mild skin irritation caused by the wrist band of the device, if this occurs, the device should be removed.

18.3 Potential Benefits

Participants in this trial who receive active prazosin may experience less disruptive agitation and/ or aggression which are common distressing problems in persons with AD.

18.4 Relationship of this Intervention to Current Treatment Practices in AD

Disruptive agitation is a common distressing problem in persons with AD residing in LTC facilities.[2-7] Current psychopharmacologic approaches to agitation in LTC residents in the advanced stages of AD are suboptimal. The widely prescribed antipsychotics often lack efficacy and the incidence of adverse effects is high.[10, 12] Although the antidepressant citalopram has been demonstrated modestly effective for mild/moderate agitation in earlier stage AD patients still at home, citalopram was actually inferior to placebo for agitation in more advanced AD patients in the LTC setting.[14] The development of well-tolerated pharmacologic treatments for moderate to severe agitation in later stage AD patients, including both those residing at home and in an LTC, remains an important unmet need.

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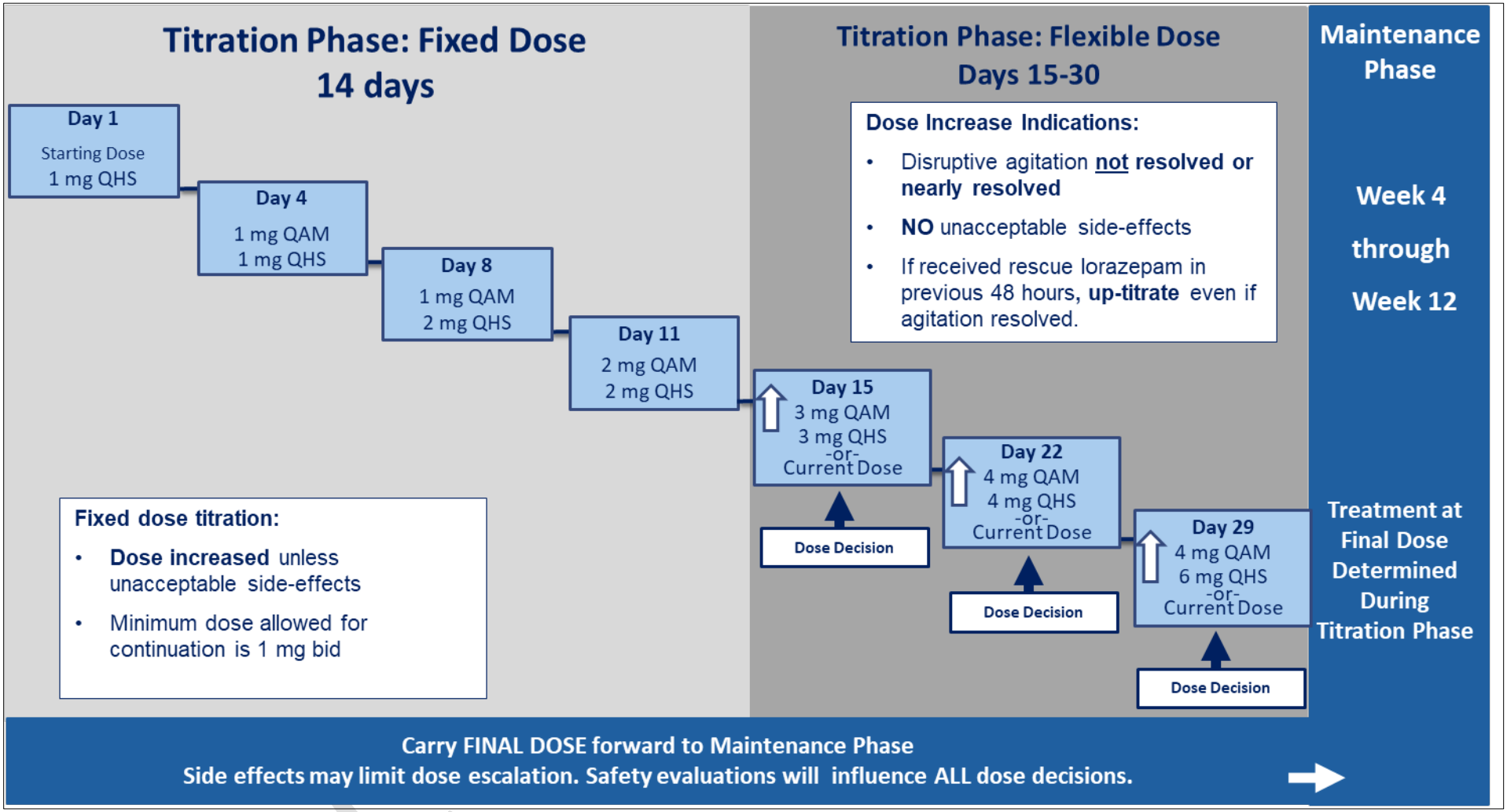
20 APPENDICES

APPENDIX 1 DOSE TITRATION DIAGRAM



APPENDIX 2 SCHEDULE OF EVENTS

Visit	Screening	Baseline	Titration	Titration	Titration	Titration	Titration	Titration	Safety	Safety	Outcome	Safety	Final / Early Term.
Study day/week number	D-28 to D0	D 1	D4 (±1d)	D8 (±1d)	D11 (±1d)	D15 (±1d)	D22 (±2d)	D29 (±2d)	Wk5 (±2d)	Wk 6 (±2d)	Wk 8 (±2d)	Wk 10 (±2d)	Wk 12 (±2d)
Obtain consent and HIPAA authorization (LAR and, if possible, participant)[1]	X												
Demographic Information	X												
Review of inclusion/exclusion criteria (incl. Behavioral Inclusion Criteria Checklist)	X												
Medical/Psychiatric History	X												
Physical/Neurological exam	X												
Assessment of Fall Risk	X												
Clinical Labs (CBC, blood chemistry, routine urinalysis)[2]	X												
12-lead resting ECG[3]	X												
Vital Signs (including supine & orthostatic BP, HR)[4]	X	X		X		X	X	X	X	X	X	X	X
Review LTC/Study Partner-recorded supine & orthostatic BP, HR (for day 4 & day 11 titration only)			X		X								
Clinician-Rated Change in Behavioral Symptoms (for dose titration purposes)[5]				X		X	X	X					
ADCS-CGIC-A Baseline Worksheet[5]		X											
ADCS-GCIC-A[5]											X		X
NPI / NPI-NH[5]		X									X		X
ADCS-ADL-Severe[5]		X									X		X
CMAI[5]		X											X
Record Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Symptoms Checklist		X	X	X	X	X	X	X	X	X	X	X	X
Dispense/Collect Study Drug /Drug Accountability		X		X		X	X	X	X	X	X	X	X
Place Actiwatch on Participant (Actigraphy Sub-Study Only)		X											
Check Actiwatch Device (Actigraphy Sub-Study Only)				X		X	X	X	X	X	X	X	
Remove Actiwatch Device and Return to Analysis Center (Actigraphy Sub-Study Only)													X
Break Study Drug Blind													X

[1] Consent may occur on a different day, before screening measures
[2] Existing laboratory values may be used if obtained within one year of Screening. If the participant refuses blood draw or urinalysis at screening, the clinical judgement of the Site PI will determine inclusion.
[3] Existing ECG results may be used if obtained within one year of Screening. If the participant refuses an ECG at screening, the clinical judgement of the Site PI will determine inclusion.
[4] Supine and orthostatic BP and HR measurements will be performed at least daily during the titration period (up to Day 35). For the 24-hour period following the first dose and each dose increase, supine and orthostatic BP and HR measurements will be taken both morning and night. Beginning on Day 36 (Week 6), supine and orthostatic BP and HR measurements will be performed every 3 days.
[5] Assessment involves study partner as an informant, or requires information recorded by study partner in the weekly diary

APPENDIX 3 LIST OF TABLES

APPENDIX 4 STUDY SCHEMATIC