Does an Audio Wearable lead to Agitation Reduction in Dementia: The Memesto AWARD Proof-of-Principle Clinical Research Study

Protocol Number: ESS-MEM-001

Principal Investigator: Raj C. Shah, MD

Sponsor: Edgewater Safety Systems, Inc.

Grant Title: Development of Memesto, a wearable repetitive message and music therapy device that senses and reduces agitation in persons with AD/ADRD

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CONFIDENTIALITY STATEMENT

This document is confidential communication. Acceptance of this document constitutes agreement by the recipient that no unpublished information contained herein will be published or disclosed without prior approval of the Principal Investigator or other participating study leadership and as consistent with the NIH terms of award.

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Council on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812).

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to an Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form(s) will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator:

Signed: _____ Date: _____

Name: Raj C. Shah, MD

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title: *Does an Audio Wearable lead to Agitation Reduction in Dementia: The Memesto AWARD Proof-of-Principle Clinical Research Study*

Grant Number: *1R43AG074725-01*

Study Description: *This is a 12-week proof-of-concept study to evaluate the efficacy of Memesto in reducing agitation in persons with Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD) currently living in a residential care facility. It is hypothesized that Memesto use will result in a reduction in agitation.*

Study Objectives and Endpoints:

Primary Objective	***Primary Endpoint***
To evaluate the efficacy of Memesto in reducing agitation	*Change in average score on the Neuropsychiatric Inventory (NPI) agitation domain subscale from baseline to Week 10*
Secondary Objective	***Secondary Endpoint***
To evaluate the clinical benefit of Memesto in reducing agitation	*Change in average score on the Clinical Global Impressions – Severity (CGI-S) scale from baseline to Week 10*

Study Population: *Participants will include 20 persons with AD/ADRD living in a residential care facility. Each participant will have two study partners: (1) a spouse, sibling, or adult child, and (2) a professional caregiver from the care facility (e.g., nurse, activity director, certified assistant).*

Phase or Stage: *Proof-of-Concept*

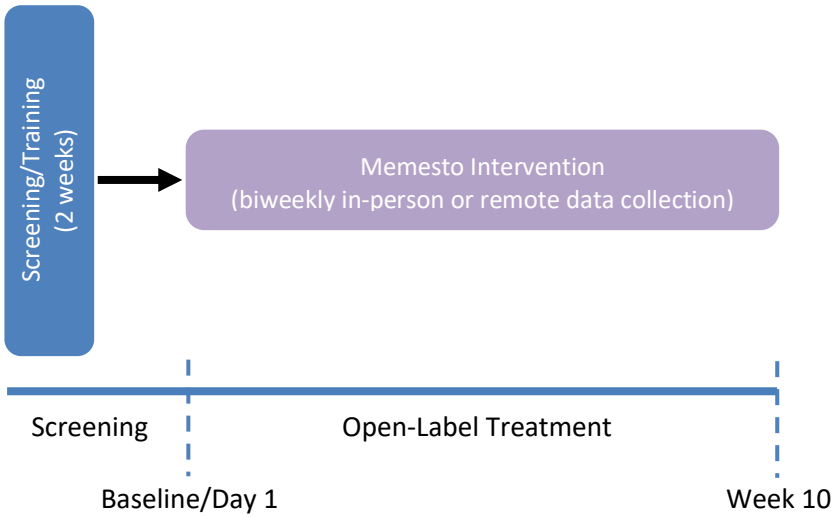
Description of Sites/Facilities Enrolling Participants: *This study is to be conducted in one or more residential care facilities in the United States.*

Description of Study Intervention/Experimental Manipulation: *After informed consent is obtained and preliminary eligibility established, participants will be trained and issued the Memesto device for use over a 2-week screening/training phase. Participants successfully completing this phase will proceed into a 10-week open-label treatment phase (via telephone and/or in-person data collection).*

Study Duration: *The entire study (opening of enrollment through completion of data collection) is anticipated to last approximately 7 months.*

Participant Duration: *Study participation will consist of a 2-week screening/training phase followed by a 10-week data collection phase.*

1.2 SCHEMA



1.3 SCHEDULE OF ACTIVITIES

Visit / Study Activity	Screening	Treatment					
	1 Week -2 to 0	**2** Baseline Day 1	**3** Week 2 *(±3 days)*	**4** Week 4 *(±3 days)*	**5** Week 6 *(±3 days)*	**6** Week 8 *(±3 days)*	**7/ET** Week 10/ET* *(±3 days)*
Informed Consent	X						
Personal/Demographic Information	X						
Brief Medical History	X						
Device Allocation/Training	X						
Device Use Accountability		X	X	X	X	X	X
Device Return							X
CGI-S	X	X	X	X	X	X	X
NPI agitation domain		X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X

***ET = Early Termination**

2 INTRODUCTION

2.1 STUDY RATIONALE

Alzheimer's disease and Alzheimer's disease related dementias (AD/ADRD) represent the most common forms of dementia, with an estimated 7.2+ million Americans living with Alzheimer's disease or Lewy body dementia.[1-2] As many as 70% of persons with AD/ADRD experience reduced quality of life due to agitation,[3] with behavioral disruptions such as aggression, combativeness, shouting, exit-seeking, and disinhibition. Agitated individuals with dementia make up a significant portion of those living in residential care facilities, because family/home caregivers can no longer manage the burden alone.

Based on studies on the effectiveness of simulated presence therapy, repetitive messaging, and reminiscence therapy,[4-5] Edgewater Safety Systems developed a smart media player (Memesto) worn by the AD/ADRD patient that delivers personalized music and pre-recorded messages to reduce agitation.

The current study will confirm proof-of-concept by generating quantitative data that audio therapy of family/caregiver voice and music delivered by the Memesto reduces agitation in AD/ADRD persons living in a residential care facility.

2.2 BACKGROUND

An unprecedented need exists for rigorous, transformative solutions to improve health outcomes for the 7.2+ million people in the United States (US) who suffer with AD/ADRD. [1-2] AD/ADRD are age-related neurodegenerative diseases characterized by losses in memory, orientation, independent decision-making capacity, and self-care. Lack of effective care approaches and technologies leads to premature institutionalization for AD/ADRD sufferers and poor quality of life for themselves and their caregivers.[6-7]

Up to 70% of AD/ADRD sufferers experience acute agitation,[3] which worsens as the disease advances. To reduce agitation, caregivers regularly administer anti-psychotic drugs, which can have serious side effects that include risk of fall, heart problems, stroke, and possibly even death. A 2018 *Human Rights Watch* report states that every week, US care facilities provide anti-psychotic drugs to over 179,000 people who do not have diagnoses for the drug's intended use, using them instead to 'mentally subdue' distressed patients.[8] AD/ADRD patients displaying agitation, especially once it has reached crisis level, require significant stressful intervention from caregivers, contributing to caregiver burn-out.

Typically, caregivers detect building agitation in AD/ADRD persons from experience. Two key problems with this approach are that: 1) caregivers are often overwhelmed with direct patient care and intervention, reducing patient monitoring time; and 2) rising agitation isn't always obvious until it reaches crisis mode and severe behavioral problems arise. Therapies (Behavior-Based Ergonomic Therapy, for example) are used which aim to calm patients by keeping them busy with activities they like and hoping for the best. Such therapies work some of the time, but require staff resources, and can neither predict nor stop rising agitation.

A means of detecting agitation in patients as it increases and automatically delivering an effective, calming intervention would have benefit. Edgewater Safety Systems created the Memesto, a wearable smart audio player that delivers time-settable and/or repeating voice/music therapy to reduce patient agitation. The device was informally piloted on AD/ADRD persons in care facilities, with 11 of 11 caregivers rating the unit 4.5 of 5 for "usefulness in lowering agitation". Caregiver feedback indicated patients were calmer,

quality of life increased, and less anxiety medication was required. Positive testimonials from caregivers on the effectiveness of the device spawned the idea that an *automated wearable* device with sensors that could detect rising agitation and proactively intervene would substantially aid patient *and* caregiver.

There are two key knowledge gaps to close in proving feasibility of an automated, agitation-sensing next-generation Memesto device. First, quantitative evidence must be used to demonstrate that Memesto-delivered audio therapy reduces agitation. Second, the feasibility of an automated agitation-sensing and audio intervention system must be established by building a prototype and testing it to validate real-time operation. This study aims to generate the quantitative data needed to show Memesto-delivered audio therapy reduces agitation.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Risks to study participation are minimal. The Memesto exists in the form of an off-the-shelf, commercially available wi-fi enabled cellular phone coupled with a mobile operating system- and web-based application that enables recording and loading of audio media via the internet. The device will not be used as a cellular phone nor will it have cellular service. Per guidance issued by the US Food and Drug Administration (FDA) on software device functions and mobile medical applications,[9] the Memesto is not considered a medical device and is therefore not regulated by the FDA.

There is potential that using the device (e.g., wearing the device, listening to repeated music/voice messages) as well as answering study-related questions about the participant's mood and behavior may become upsetting, frustrating, and/or tiring to either the participant and/or study partners.

2.3.2 KNOWN POTENTIAL BENEFITS

Participants with AD/ADRD may see modest benefit if agitation is improved. Study partners also may find some relief and/or feel more engaged in caring for a person living with AD/ADRD experiencing agitation through use of the device. Finally, study-related questions may serve to help study partners recognize agitation symptoms more reliably and with greater precision.

In contrast, societal benefits may be substantial. Problems associated with dementia and agitation are common and create significant distress for persons living with AD/ADRD and their family and professional caregivers. Knowledge gained from the study has direct implications for efforts to advance a non-pharmacological approach to reducing the morbidity associated with agitation in persons living with AD/ADRD.

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

This is a minimal risk study. While it could not otherwise be carried out without the involvement of persons with AD/ADRD and their caregivers, study-related questions may be refused and further participation may be declined at any time. Potential study benefits, while modest to the participant, may be of critical importance to providing family and professional caregivers with more tools for improving agitation in persons living with AD/ADRD. Thus, the anticipated benefit-risk profile of this study is favorable.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS
Primary	
To evaluate the efficacy of Memesto in reducing agitation	Change in average score on the Neuropsychiatric Inventory (NPI) agitation domain subscale from baseline to Week 10
Secondary	
To evaluate the clinical benefit of Memesto in reducing agitation	Change in average score on the Clinical Global Impressions – Severity (CGI-S) scale from baseline to Week 10

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is an open-label, proof-of-concept study evaluating the efficacy of Memesto in reducing agitation in persons with AD/ADRD currently living in a residential care facility. Approximately 20 persons with AD/ADRD will take part in the study. Each participant will have two study partners: a family caregiver and a professional caregiver (from the residential care facility) willing to participate in the study along with the person with AD/ADRD.

Participants will be adults with a dementia diagnosis who have clinically significant agitation, defined as a state of poorly organized and purposeless psychomotor activity characterized by at least one of the following: aggressive verbal (screaming, cursing), aggressive physical (destroying objects, grabbing, fighting), or non-aggressive physical (restlessness, pacing) behaviors.

After informed consent is obtained from both the participant and respective study partners, participants will complete a preliminary screening for eligibility and trained on the Memesto to use over a two-week screening/training phase. Once satisfactorily completing this phase, participants will be followed for 10 weeks of data collection with visits (either in-person or via telephone) occurring at baseline and at Weeks 2, 4, 6, 8, and 10.

The primary study endpoint is the NPI agitation domain subscale with a secondary study endpoint of the CGI-S scale; both assessed as the average change from baseline to the end of treatment (Week 10).

The study will be approved and overseen by an Institutional Review Board (IRB). Safety will be monitored by the principal investigator (PI) and study staff via adverse event reporting in accordance with all IRB and funding agency requirements.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As this is a proof-of-concept study designed to provide initial data to determine whether Memesto use quantitatively reduces agitation in persons with AD/ADRD, study design consists of a single open-label treatment arm. While the open-label design has some risk for reporting bias, it is expected that "triangulation" with ratings from two separate study partners will reduce some of the bias while still enabling a clear signal for further device development in the form of a future randomized trial involving a sham device.

4.3 JUSTIFICATION FOR INTERVENTION

This study is designed to demonstrate the efficacy of Memesto in reducing agitation in persons with AD/ADRD. Data collected across the 10-week treatment phase is intended to establish device feasibility for further development.

4.4 END-OF-STUDY DEFINITION

The end of the study is defined as completion of Visit 7 (Week 10) or Early Termination (ET) as shown in ***Section 1.3, Schedule of Activities***.

5 STUDY POPULATION

Approximately 20 participants will be enrolled in the study. Each participant will have two study partners: (1) a spouse, sibling, or adult child; and (2) a professional caregiver from the care facility (e.g., nurse, activity director, certified assistant).

All participants must meet all the inclusion criteria and none of the exclusion criteria.

In order to provide a broader understanding of the Memesto's use in diverse populations of persons living with AD/ADRD, we plan on 50% of the participants living with AD/ADRD being non-White and anticipate 20% being Latino. Additionally, approximately 67% of the participant cohort will be women and 33% will be men.

5.1 INCLUSION CRITERIA

1. Age 18 years or older at time of informed consent.
2. Diagnosis of AD/ADRD as confirmed by study partner.
3. Significant agitation characterized by at least one of the following behaviors that are severe enough to warrant pharmacological treatment:
    a. Verbal aggression (e.g., screaming, cursing);
    b. Physical aggression (e.g., destroying objects, grabbing, fighting); or
    c. Non-aggressive physical behavior (e.g., restlessness, pacing).
4. CGI-S score ≥ 4 at Screening.
5. Availability of (1) a spouse, sibling, or adult child AND (2) a professional caregiver from the care facility (e.g., nurse, activity director, certified assistant) willing to serve as study partners who can:
    a. Provide study staff accurate information regarding the participant's personal and health information, mood, behavior, medications, and device use throughout the course of the study; and
    b. Record personalized messages and/or help identify music for audio therapy and program the Memesto's therapy schedule.
6. Signed informed consent obtained from (a) the participant or the participant's legally authorized representative (if the participant is incapable of providing consent for him or herself), and (b) both study partners.

5.2 EXCLUSION CRITERIA

1. Inability to demonstrate compliance using the Memesto during the screening/training phase as evidenced by continued inability to schedule audio therapies within the application or inconsistent use (i.e., wearing) of the device as reported by study partner(s).

5.3 LIFESTYLE CONSIDERATIONS

N/A

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but do not proceed into the 10-week treatment phase.

Individuals who do not meet the criteria for participation in this trial (screen failure) because of meeting the exclusionary criteria may be rescreened. Rescreened participants will be assigned the same participant number as for the initial screening.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

Working with dementia unit directors, nurse managers, and activity directors at given residential care facility (i.e., formal study partner), family caregivers of persons with AD/ADRD and agitation will be identified and approached. The recruitment process involves a presentation about AD/ADRD and agitation, the need for the study, and what is involved in study participation. Written materials on dementia, agitation, and the Memesto will be made available. Study staff will then engage individually with each potential participant and family caregiver (i.e., informal study partner) who expresses interest in the study. All study procedures, risks and benefits, and the option to withdraw without penalty will be reviewed.

Since this study is most likely to involve persons with moderate to severe dementia based on who typically have agitation with AD/ADRD in residential care facilities, most if not all participants will likely not have capacity to consent at the time of enrollment. Therefore, the power of attorney/authorized decision maker for the person living with AD/ADRD will be approached to provide consent for participation. After all parties have had as much time as needed to consider participation and all their questions answered, signed consents will be obtained with copies provided for their records.

Study retention is supported by having a two-week training period built into the protocol. Also, close follow-up with the participant triad (person with AD/ADRD, family caregiver, professional caregiver) will be maintained by study staff.

6 STUDY INTERVENTION

6.1 STUDY INTERVENTION ADMINISTRATION

6.1.1 STUDY INTERVENTION DESCRIPTION

Study intervention is 10-week use of the Memesto. The device exists in the form of an off-the-shelf, commercially available wi-fi enabled cellular phone coupled with a mobile operating system- and web-

based application that enables recording and loading of audio media via the internet. The device will not be used as a cellular phone nor will it have cellular phone service.

A neck lanyard with waterproof case will be provided with the device to facilitate use and accountability.

6.1.2 ADMINISTRATION AND/OR DOSING

Participants will be provided the Memesto at Screening for a two-week screening/training phase of use. Participants successfully completing this phase will continue use for 10 weeks of bi-weekly data collection.

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

All study staff responsible for providing device training will be instructed on device use by Edgewater Safety Systems. Training will be documented and filed in the Investigator Site File (ISF). Further, representatives from Edgewater Safety Systems will be available throughout the duration of the study for device- or application-related questions or troubleshooting.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

N/A

6.4 STUDY INTERVENTION ADHERENCE

Adherence to study treatment will be recorded in the form of a device accountability log completed by the formal study partner in-between study visits as well as review of scheduled voice/music therapies within the Memesto application.

6.5 CONCOMITANT THERAPY

Use of prescription and non-prescription medications will be reviewed at each study visit and documented in the relevant electronic case report form (eCRF).

6.5.1 RESCUE THERAPY

N/A

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

All participants who permanently discontinue study treatment and do not agree to continued data collection through study completion (Week 10), for whatever reason, will be withdrawn from the study. Refer to ***Section 0, Schedule of Activities*** for data to be collected at the time of discontinuation (i.e., ET).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request. The PI may discontinue a participant from the study for any of the following reasons:

- Significant study intervention non-compliance;
- Inability to replace a study partner should a study partner's participation end early;
- Lost-to-follow up; unable to contact participant (see ***Section 7.3, Lost to Follow-Up***);
- Any event or medical condition or situation occurs such that continued collection of follow-up study data would not be in the best interest of the participant; or
- The study is cancelled.

The reason for participant discontinuation or withdrawal from the study will be documented in the relevant eCRF.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she repeatedly fails to participate in scheduled visits and is unable to be contacted by study staff after at least 3 documented attempts.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

8.1.1 NEUROPSCYHIATRIC INVENTORY

The Neuropsychiatric Inventory (NPI) is a widely used, well-established instrument that assesses behavioral changes in neurologic illnesses through a structured interview with a caregiver.[10] Behavioral domains are scored based on frequency and severity. The nursing home version of the inventory will be utilized in this study and administered (in-person or via telephone) to both the formal and informal study partners by qualified and trained study staff. Only the agitation domain of the NPI will be administered as part of this study.

8.1.2 CLINICAL GLOBAL IMPRESSIONS SCALE - SEVERITY

The Clinical Global Impressions Scale – Severity (CGI-S) is a brief observer-rated instrument that establishes a global rating of illness severity.[11] The scale responses range from 1 (normal) to 7 (amongst the most extremely ill). The CGI-S in relation to agitation will be administered (in-person or via telephone) to both the formal and informal study partners by qualified and trained study staff.

8.2 SAFETY ASSESSMENTS

Adverse event (AE) reporting will begin at Screening and will continue until the end of the study. The occurrence of AEs will be sought by non-directive questioning of the participant and/or study partners during each study visit. AEs may also be detected when volunteered through unsolicited contact by the participant and/or study partners between study visits. Refer to ***Section 8.3, Adverse Events and Serious***

Adverse Events and ***Section 8.4, Unanticipated Problems*** for further details regarding collection, documentation, and reporting requirements.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

This protocol uses the National Institute on Aging (NIA) guidelines for reviewing and reporting adverse events (AEs) and serious adverse events (SAEs). Definitions are from the January 2007 Office of Human Research Protections (OHRP) *Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events: OHRP Guidance.*[12]

8.3.1 DEFINITION OF ADVERSE EVENTS

An AE is defined as any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the participants' involvement in the research, whether or not considered related to participation in the research.

Given this is a minimal risk study, only AEs associated with use of the Memesto device or with study-related questioning will be recorded.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

An SAE is defined as any AE that:

- Results in death
- Is life threatening, or places the participant at immediate risk of death from the event as it occurred
- Requires or prolongs hospitalization
- Causes persistent or significant disability or incapacity
- Results in congenital anomalies or birth defects
- Is another condition which investigators judge to represent significant hazards

Hospitalizations/emergency room visits for worsening of agitation associated with the underlying AD/ADRD will not be considered SAEs.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

All recorded AEs will have their severity classified by an appropriately-trained clinician as follows:

- **Mild** – Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient.
- **Moderate** – Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning.
- **Severe** – Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed.

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

All recorded AEs will have their relationship to study procedures, including the intervention, assessed by an appropriately-trained clinician based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the following categories:

- **Definitely Related** – The AE is clearly related to the investigational agent/procedure – i.e., an event that follows a reasonable temporal sequence from administration of the study intervention, follows a known or expected response pattern to the suspected intervention, that is confirmed by improvement on stopping and reappearance of the event on repeated exposure and that could not be reasonably explained by the known characteristics of the subject's clinical state.
- **Possibly Related** – An adverse event that follows a reasonable temporal sequence from administration of the study intervention follows a known or expected response pattern to the suspected intervention, but that could readily have been produced by a number of other factors.
- **Not Related** – The adverse event is clearly not related to the investigational agent/procedure - i.e. another cause of the event is most plausible; and/or a clinically plausible temporal sequence is inconsistent with the onset of the event and the study intervention and/or a causal relationship is considered biologically implausible.

8.3.3.3 EXPECTEDNESS

All recorded AEs will be assessed by an appropriately-trained clinician as to whether they were expected to occur or unexpected as follows:

- **Unexpected** – Nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol or consent form.
- **Expected** – Event is known to be associated with the intervention or condition under study.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The occurrence of an event may come to the attention of study staff during study visits or through unsolicited reporting by the participant and/or study partner outside of a study visit. All AEs occurring while on study, not otherwise precluded per the protocol, will be documented appropriately regardless of relationship. Events will be followed for outcome information until resolution or stabilization.

8.3.5 ADVERSE EVENT REPORTING

All events will be recorded on the relevant eCRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures, whether it was expected, and time of resolution/stabilization of the event. This study will utilize the NIA-approved flow sheets and forms to identify and track events.

Events will be assessed to determine if they meet criteria for an AE, SAE, or unanticipated problem (UP).

Events meeting criteria for an AE will be reported, as necessary, in accordance with IRB and funding agency requirements. Further details regarding AE reporting are outlined in the Data and Safety Monitoring Plan (DSMP).

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Events meeting criteria for an SAE will be assessed by the PI or delegated designee to determine if the event is unexpected, related to study procedures, or places participants or others at a greater risk of physical or psychological harm than was previously known or recognized. SAEs that are unanticipated in nature and deemed related to study procedures will be reported to the sponsor within 48 hours of knowledge of the SAE and to the IRB, when appropriate, in accordance with IRB requirements. Further details regarding SAE reporting are outlined in the DSMP.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

N/A

8.3.8 EVENTS OF SPECIAL INTEREST

N/A

8.3.9 REPORTING OF PREGNANCY

N/A

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

As defined by DHHS 45 CFR part 46, an unanticipated problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected, in terms of nature, severity, or frequency, given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the study population;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

Events meeting criteria for a UP will be reported to the sponsor within 48 hours of knowledge of the UP and to the IRB, when appropriate, in accordance with IRB requirements. Further details regarding UP reporting are outlined in the DSMP.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

N/A

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The primary hypothesis is that treatment with Memesto will result in a reduction in the average 10-week NPI agitation domain score compared to the average baseline score. The secondary hypothesis is that treatment with Memesto will result in a reduction in the average 10-week CGI-S score compared to the average baseline score.

Alternatively, the null hypotheses for both primary and secondary endpoints is that no change will be observed.

9.2 SAMPLE SIZE DETERMINATION

As a proof-of-concept study, no formal power calculation was utilized.

9.3 POPULATIONS FOR ANALYSES

The population for treatment and safety analyses will be participants who consented and successfully completed a baseline visit after going through a two-week training on the use of Memesto.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The general analytic approach is to compare outcome scores at 10 weeks of exposure to Memesto as compared to the baseline scores after the 2-week training period with Memesto. Missing data would be handled by the last observation carried forward method.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The pre-specified quantitative end point will be change from baseline in the NPI agitation domain score. The NPI agitation domain will be rated by each study partner (professional and family caregiver, respectively) for symptom frequency and severity. The domain score is a composite (frequency x severity) score of 1 to 12.

The average 10-week NPI agitation domain score from the reports of the two study partners will be compared to the baseline average agitation score. A positive finding would be that at least half of the participants would have a 30% reduction in the agitation domain score. The NPI manual (*http://npitest.net/faqs.html*) suggests that a 30% decrease in scores is generally clinically meaningful. Therefore, a positive finding would be that at least half of the study participants would have a 30% improvement after 10 weeks of treatment.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

A secondary endpoint will be a validated agitation measure (change in the average CGI-S score over the 10-weeks of data collection). The CGI-S is measured based on a 7-point Likert scale. The number of persons with a CGI-S score showing improvement will be calculated, defined as achieving a final Week 10 score (or if missing last observation, carried forward score) of 3 or less. A clinically meaningful signal will be if improvement is noted on 30% of the participants.

9.4.4 SAFETY ANALYSES

Safety outcomes will include adverse events as related to the device or with study procedures. A table of safety outcomes by frequency will be generated, if applicable.

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Participant baseline demographic (such as age, gender, race/ethnicity) and health characteristics (such as baseline scores on agitation measures) will be summarized using numbers and percentages for categorical variables and by means, medians, standard deviations, and ranges for continuous variables.

9.4.6 PLANNED INTERIM ANALYSES

N/A

9.4.7 SUB-GROUP ANALYSES

N/A

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

N/A

9.4.9 EXPLORATORY ANALYSES

An exploratory analysis will be the number of participants with a change in psychotropic medications (i.e., decrease) at 10-weeks of Memesto treatment as compared to baseline.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Written documentation of informed consent will be obtained from the participant (or power of attorney/authorized decision maker, when necessary) and both study partners prior to the start of the study. Informed consent forms and informational documents utilized in the conduct of this study will meet the requirements of 21 CFR 50, local regulations, ICH GCP guidelines, Health Insurance Portability and Accountability Act (HIPAA), and the IRB. All documents will be submitted and approved by the IRB prior to use; any revisions to the documents will be submitted and re-approved by the IRB prior to implementation.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Since this study is most likely to involve persons with moderate to severe dementia based on who typically have agitation with AD/ADRD in residential care facilities, most if not all participants will likely not have capacity to consent at the time of enrollment. Therefore, the power of attorney/authorized decision maker for the person living with AD/ADRD will most often be approached to provide consent for participation.

Before written consent is obtained, an appropriately trained and delegated study staff member will explain the purpose and requirements of the study, procedures involved, risks and benefits to participation, and the option to withdraw at any time without penalty. Ample opportunity will be given to consider study participation and to ask questions. After all parties have had as much time as needed to consider participation and all their questions answered, signed consents will be obtained with copies provided for their records.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Circumstances that may warrant termination or suspension by the PI, sponsor, and/or funding agency include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient compliance of study staff to the protocol (i.e., significant protocol violations)

The study may resume once concerns about safety and protocol compliance are addressed, and satisfy the funding agency, sponsor, and IRB requirements.

10.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the PI, study staff, the sponsor, and funding agency. This confidentiality is extended to the data being collected as part of this study. Data that could be used to identify a specific participant will be held in strict confidence within the research team. No personally-identifiable information from the study will be released to any unauthorized third party without prior written approval of the sponsor/funding agency.

All research activities will be conducted in as private a setting as possible.

The authorized representatives of the sponsor or funding agency and representatives of the IRB may inspect all source documentation collected as part of this study. The study site will permit access to such records.

The participant's and study partners' contact information will be securely stored for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by IRB, institutional, and sponsor/funding agency requirements.

Participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by the site will be secured and password protected.

It is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). The PI will ensure all mechanisms used to share data will include proper plans and safeguards for the protection of privacy, confidentiality, and security for data dissemination and reuse (e.g., all data will be thoroughly de-identified and will not be

traceable to a specific study participant). Plans for archiving and long-term preservation of the data will be implemented, as appropriate.

To further protect the privacy of study participants, the Secretary, Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (see *https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

N/A

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal Investigator:	Raj C. Shah, MD
Institution:	Rush Alzheimer's Disease Center, Rush University Medical Center
Address:	1653 West Congress Parkway, Chicago, IL 60612
Telephone:	1-312-563-2902 (o); 1-630-217-9959 (c)
Email:	Raj_C_Shah@rush.edu

10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of the PI.

10.1.7 CLINICAL MONITORING

N/A

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control (QC) procedures will be implemented as follows:

Informed Consent: Study staff will review both the documentation of the consenting process as well as the completed consent documents. This review will evaluate compliance with GCP, accuracy, and completeness. Feedback will be provided to the study team to ensure proper consenting procedures are followed.

Source Documents and the Electronic Data: Data will be initially captured on source documents (see ***Section 10.1.9, Data Handling and Record Keeping***) and will ultimately be entered into the study

database. To ensure accuracy, study staff will compare a representative sample of source data against the database, targeting key data points in that review.

Intervention Fidelity: Consistent delivery of the study interventions will be monitored throughout the intervention phase of the study. Procedures for ensuring fidelity of intervention delivery are described in ***Section 6.2.1, Interventionist Training and Tracking***.

Protocol Deviations: Study staff will review protocol deviations on an ongoing basis and will implement corrective actions when the quantity or nature of deviations are deemed to be at a level of concern.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of study staff under the supervision of the PI. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents will be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented/enrolled in the study. Data recorded in the eCRF derived from source documents will be consistent with the data recorded on the source documents.

Clinical data (including adverse events (AEs), concomitant medications, and expected adverse reactions data) will be entered into REDCap, a 21 CFR Part 11-compliant data capture system. Data will be entered directly from the source documents.

10.1.9.2 STUDY RECORDS RETENTION

Study documents will be retained for a minimum of 2 years after the last approval of a marketing application in an International Council on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor/funding agency, if applicable. It is the responsibility of the sponsor/funding agency to inform the PI when these documents no longer need to be retained.

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a protocol deviation as any noncompliance with the clinical trial protocol or International Council on Harmonisation Good Clinical Practice (ICH GCP) requirements. The noncompliance may be either on the part of the participant, the PI, or study staff. As a result of deviations, corrective actions will be developed by the site and implemented promptly.

It will be the responsibility of the PI to use continuous vigilance to identify and report deviations in accordance with all IRB and funding agency requirements. All deviations will be addressed in study source documents.

10.1.11 PUBLICATION AND DATA SHARING POLICY

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

- National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.
- This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial will be registered at ClinicalTrials.gov, and results information from this trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Data collected by Rush University will be accessible in a de-identified manner at the conclusion of the study, after the primary results are published in one or more peer-reviewed journals and otherwise as per NIH guidelines. In the meantime, data will be stored on secure Rush University servers and contact regarding data acquisition by interested parties can be made through ClinicalTrials.gov. Considerations for ensuring confidentiality of these shared data are described in ***Section 10.1.3, Confidentiality and Privacy***.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. This study will be conducted in accordance with all IRB and NIA policies, procedures, and guidelines for the disclosure and management of conflicts of interest.

10.2 ADDITIONAL CONSIDERATIONS

N/A

10.3 ABBREVIATIONS AND SPECIAL TERMS

AE	Adverse Event
AD/ADRD	Alzheimer's Disease and Alzheimer's Disease Related Dementias
CFR	Code of Federal Regulations
CGI-S	Clinical Global Impression - Severity
CoC	Certificate of Confidentiality
DHHS	Department of Health and Human Services
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic Case Report Form
ET	Early Termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council on Harmonisation
IRB	Institutional Review Board
NIA	National Institute on Aging

NIH	National Institutes of Health
NIHGPS	National Institutes of Health Grants Policy Statement
NPI	Neuropsychiatric Inventory
OHRP	Office for Human Research Protections
PI	Principal Investigator
SAE	Serious Adverse Event
UP	Unanticipated Problem
US	United States

10.4 PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

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