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CLINICAL STUDY PROTOCOL

Title: A Randomized Pivotal Study of Renew™ NCP-5 for the Treatment of Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type

Protocol Number: Renew™ NCP-5 -1001

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Sponsor: Renew Research, LLC, Renew Health Ltd., Renew Group Private Ltd.

Sponsor Signature: _____

Date: 6/23/2021

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APPROVAL SIGNATURE

A Randomized Pivotal Study of Renew™ NCP-5 for the Treatment of Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type (Renew™ NCP-5-1001)

The signature below represents my review and approval of:

Protocol Version 3.1

Site Principal Investigator: _____

Date: _____

LIST OF ABBREVIATIONS

The following abbreviations are used in this study protocol.

Abbreviation or specialist term	Explanation
AD	Alzheimer's Disease
ADAS-Cog	Alzheimer's Disease Assessment Scale Cognitive
ADCS-ADL	Alzheimer's Disease Co-op Study-Activities and Daily Living
ADCS-CGIC	Alzheimer's Disease Co-op Study-Clinical Global Impression of Change
ADR	Adaptive Design Report
APOE	Apolipoprotein E
BPM	Beats per Minute
CBF	Cerebral Blood Flow
CBFV	Cerebral Blood Flow Velocity
CHF	Congestive Health Failure
CRP	C-reactive protein
CVR	Cerebrovascular reactivity
DD	Device Deficiency
DSM IV	Diagnostic & Statistical Manual of Mental Disorders, 4th ed.
ECG	Electrocardiography
ECP	External Counterpulsation
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRU	Health Resource Utilization
ICH	International Conference on Harmonisation
IDE	Investigational Device Exemption
INR	International normalized ratio
LDL-C	Low Density Lipoprotein Cholesterol
LM	Logical Memory
LP-PLA2	Lipoprotein-associated phospholipase A2
MCI	Mild Cognitive Impairment
MMSE2	Mini Mental State Examination – Second Edition
MOCA	Montreal Cognitive Assessment
MPO	Myeloperoxidase Enzyme
MRI	Magnetic Resonance Imaging
NIA	National Institute of Aging
NPI	Neuropsychiatric Inventory
NSR	Non-significant Risk
PSI	Pounds per Square Inch
SPECT Scan	Single Photon Emission Computed Tomography
TUG	Timed Up and Go Test
vADAS-Cog	Vascular Dementia Assessment Scale Cognitive Subscale
VD	Vascular Dementia
WMH	White Matter Hyperintensities

1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1 Background

Alzheimer's Disease (AD) is an acquired cognitive and behavioral impairment of sufficient severity that it markedly interferes with social and occupational functioning and is the most common cause of dementia (Sun, Zhu, et al., 2007). Specifically, AD is a progressive neurodegenerative disorder characterized by the gradual onset of dementia. AD is well established to be degenerative, progressive, and irreversible, as the disease interferes with the neuron-to-neuron communication at synapses and contributes to cell death (Sun, Zhu, et al., 2007). No currently available treatment for AD slows or stops the damage to neurons that causes AD symptoms and eventually makes the disease fatal (Sabayan, Jansen, et al., 2012).

There is a strong correlation between AD and poor Cerebral Blood Flow (CBF) (Sun, Zhu, et al., 2007). Cognitive decline occurs naturally with age; however, a more severe decline, as in Mild Cognitive Impairment (MCI), is a precursor to AD. Observational studies have shown that the treatment of vascular risk factors including hypertension, diabetes, cerebrovascular diseases, and hypercholesterolemia, decrease the risk of dementia progression (Li, Wang, et al., 2011; Daulatzai, 2017).

Currently, FDA has not cleared or approved any medical devices for the treatment of AD or MCI. Non-pharmacological strategies for delaying the progression of cognitive deficits and resulting functional impairment in AD, have produced limited results and only include activities such as art therapy, activity-based therapy and memory training. Given the lack of a highly effective and safe treatment for AD, there is a strong unmet medical need for additional treatment options.

Evidence suggests that there may be a significant cerebral vascular component to cognitive impairment associated with AD and therefore, treatments targeting cerebral perfusion and vascular health are worth pursuing (Paillard, 2015). External counterpulsation (ECP) treatment improves coronary and peripheral vascular health and may improve cerebral vascular health. Physical exercise is the most basic and efficient way to improve blood flow (Erickson, Voss, et al., 2011) and has been shown to increase cardiac output, which in turn leads to an increase in CBF (Paillard, 2015). Wang, Karp, et al. (2002) and Verghese, Lipton, et al. (2003) have shown that elderly patients who partake in physical activity are less likely to develop dementia and experience cognitive decline. However, due to cognitive or physical decline, patients with signs of dementia are not always able to exercise. Renew™ NCP-5 is designed to simulate the effects of sustained vigorous exercise, which otherwise may not be feasible for patients with MCI/AD.

Renew™ NCP-5, an External Counterpulsation (ECP) device, has a well-established safety profile and may increase cerebral perfusion that could be beneficial in the treatment of MCI due to AD and mild

dementia of the Alzheimer's type (mild AD). Therefore, Renew Research, LLC, the sponsor, plans to conduct a clinical trial to establish safety and effectiveness for the proposed indications.

1.2 Renew™ NCP-5

Renew™ NCP-5, an ECP device, is a non-invasive treatment that improves coronary and peripheral vascular health and may improve cerebral vascular health. It enhances circulation and stimulates endothelial production of trophic factors such as nitric oxide, resulting in peripheral vasodilation, reduction in vascular inflammation and improved vascular compliance. These and other factors result in increased coronary artery blood flow, reduced cardiac afterload and reduced systemic blood pressure. Thus, Renew™ NCP-5 has been used to treat patients with chronic angina and Congestive Heart Failure (CHF) by increasing cardiac output and reducing the workload of the heart. ECP increases cardiac output by improving systolic unloading and venous return (Barsness, 2001). Patients with CHF have an increased risk of cognitive dysfunction presumably because of decreased CBF. In a study done by Kozdag, Iseri, et al. (2013), ECP therapy resulted in improvement in all cognitive domains except visual and verbal memory tests in patients with CHF. Thus, Renew™ NCP-5 may be used as an exercise alternative to increase CBF. The effects of Renew™ NCP-5 may act similarly to exercise therapy and are explored for patients with mild AD and MCI in this study.

Counterpulsation is a term that describes balloon inflation, when internal, or synchronized pressure during diastole and deflation in early systole, when external. During the Renew™ NCP-5 session, the patient's lower extremities are wrapped in three compressive pneumatic cuffs applied to the calves, lower thighs, and buttocks. Electrocardiogram (ECG)-gated, sequential leg compression occurs as these cuffs are inflated from distal to proximal in early diastole and then rapidly deflated at the onset of systole. The rapid inflation increases diastolic pressure (diastolic augmentation), increasing coronary perfusion pressure and myocardial perfusion. The rapid cuff deflation promotes lower extremity arterial "runoff" and leads to a decrease in systolic pressure (systolic unloading), thereby reducing cardiac afterload. The Renew™ NCP-5 session also increases venous return, promoting an increase in cardiac output.

The pressure causes 'volume displacement' of blood within the aorta, both proximally and distally. This leads to a potential increase in coronary blood flow and potential improvements in systemic perfusion by augmentation of the intrinsic 'Windkessel effect' (Catanho, Sinha, & Vijayan, 2012) whereby potential energy stored in the aortic root during systole is converted to kinetic energy with the elastic recoil of the aortic root (Belz, 1995). This effect produces diastolic augmentation by forcing freshly oxygenated blood back toward the heart and coronary arteries at the beginning of diastole. Additionally, the volume of venous blood returned to the heart under pressure increases both oxygen supply and perfusion pressure in the myocardium. This effect increases heart preload (giving the heart greater volume to pump) and reduces heart afterload as the vascular beds in the lower extremities are emptied by the pressure. Thus, work and oxygen demand on the heart muscle is decreased. As a result, the patient's

peak diastolic pressure is significantly increased, benefiting the heart muscle and other organs, such as the kidneys, due to increased circulation. At the same time, the patient's systolic pressure is also reduced to the general benefit of the vascular system (Campbell, Satran, et al., 2008). This effect has been shown to produce measurable and reproducible beneficial cardiovascular effects in healthy individuals (Hilz, Werner, et al., 2004) as well as individuals with cardiac compromise such as angina, heart failure or coronary artery disease (Shechter, Matetzky, et al., 2003; Braith, Conti, et al., 2010).

1.3 Mechanism of Action

The physiologic effect of Renew™ NCP-5 is comparable to mild/moderate exercise, which is beneficial in normal and sick persons. Both exercise and ECP improve endothelial function, and account for the action of ECP (Gurovich & Braith, 2013; Bonetti, Barsness, et al., 2003). The results of the hemodynamic effects are proliferation of collateral circulation in the heart, vasodilatation due to enhanced endothelial functioning, and peripheral conditioning. All these effects produce clinical benefits including improvements in the cardiovascular system and other organs.

Low shear stress, the frictional force per area that is exerted by blood flow on the vessel wall, is found in MCI and AD (van Es, van der Flier, et al., 2009). A key physiological outcome that connects proliferation of collateral arteries to endothelial function is the increase in shear stress resulting from the increase in flow velocity due to the diastolic augmentation created by ECP (Zhang, He, et al., 2007). First, the action of the sequential (legs to thighs to buttocks) compression at the onset of diastole pushes blood from the peripheral vessels up to the heart. This action is known as diastolic augmentation. As the heart enters systole, the pressure is released, thereby decreasing the work of the heart resulting in decreased oxygen consumption, adaptive proliferation of coronary collateral arteries (arteriogenesis), and improved cardiovascular functioning (Buschmann, Utz, et al, 2009; Pagonas, 2011). Additional coronary effects include improved endothelial function and decreased peripheral resistance due to increased shear stress as flow velocity increases, which activates the nitric oxide cycle and produces vasodilatation (Bonetti, Barsness, et al., 2003; Jerca, Jerca, et al., 2002; Michel & Feron, 1997). This phenomenon has also been referred to as a decrease in arterial stiffness (increase in elasticity) (Hui, Lawson & Barness, 2010; Casey, Beck, et al., 2011). The increase in elasticity promotes the Windkessel function within the aorta as it serves as a buffering chamber behind the heart to forward blood from the left ventricle into the peripheral circulation (Belz, 1995). It was demonstrated that shear stress can promote improved endothelial functioning by stimulating growth factors and activating the nitric oxide cycle and endothelin-1 cycle (Papaioannou & Stefanadis, 2005), which results in vasodilatation. In addition to these improvements in coronary function and the cardiovascular system, there is the effect of passive exercise leading to conditioning of the peripheral vasculature. This is accomplished through sequential compression on the lower extremities that leads to increased blood flow in a similar manner to physical activity.

1.4 Implications for Cerebral Blood Flow

Age related neurodegenerative and vascular associated pathologies exist in patients with MCI and AD. Increased atherosclerosis/arteriosclerosis of the intracranial arteries are found in AD leading to ischemia and cognitive dysfunction. Studies indicate that pulse pressure (systolic blood pressure-diastolic blood pressure) reflects the elasticity of large arteries and is an increased risk for dementia (Peters, Beckett, et al., 2013). One study confirmed that CBF 20% lower in AD than age-matched normal was correlated with decrease pulse pressure and compromised cognitive performance. CVD and brain hypoperfusion may participate in the pathogenesis of neurodegenerative disease (Rohrer, Debbins, et al., 2012).

Studies have shown a positive effect on CBF from ECP with a subsequent change in cognitive scores. ECP has undergone a preliminary investigation in patients with senile dementia of the Alzheimer type. Li, Yao, et al. (1994) treated 10 patients (mean age 74.5 years) with ECP for one hour a day for a total of 48 hours in eight weeks and all 10 patients completed the ECP treatments with no adverse events. Following ECP treatment, patients showed a mean increase in their Hasegawa's Dementia Scale score of 1.9, although the mean change was not statistically significant. In addition, pre- and post-treatment SPECT scans were completed in six of the 10 patients. The SPECT scan results demonstrated that cortical perfusion was significantly increased post-ECP compared to pre-ECP.

Moriarty, Badawi, et al. (2016) studied ECP treatment in four MCI patients. All four patients completed 35 one- hour treatments over seven weeks. CBF was assessed at baseline and post-ECP treatment by arterial spin labeling perfusion MRI. At baseline, blood flow in MCI patients was significantly less compared to healthy controls in the hippocampus ($p=0.007$) and inferior parietal lobe ($p=0.013$). While suggestive, perfusion increases were observed in the MCI patients post-ECP but did not reach significance in the hippocampus ($p = 0.064$) and precuneus ($p = 0.057$) in this small study of four patients.

Acute ECP effects on CBF have not been studied in AD patients, but a number of studies have examined the effects in both healthy subjects and stroke patients. Studies have shown different effects in healthy subjects versus stroke patients. Researchers have hypothesized that healthy subjects exhibit cerebral autoregulation that is observed as an augmented diastolic CBFV during ECP, balanced by a corresponding drop in systolic CBFV for a net zero or small negative change in mean CBFV (measured in the middle cerebral artery) (Folstein, Folstein & McHugh, 1975, Marthol et al 2005, Jungehuelsing et al, 2010). Since acute ECP studies have not yet been conducted for MCI or AD patients, it is unknown if augmented mean CBFV will be observed in addition to augmented diastolic CBFV. ECP could affect cerebral vascular health and cognition through indirect effects on the cardiovascular system or through acute effects on CBF (diastolic augmentation or mean CBFV).

In summary, ECP has been shown to produce significant positive health benefits and the potential for enhanced coronary functioning in chronic stable angina, among other conditions. The same mechanisms

by which ECP provides benefit in angina may also extend to brain perfusion. These benefits of ECP occur by similar mechanisms to vigorous exercise, as demonstrated in multiple published studies.

2. DETERMINATION OF ELIGIBILITY

This research study will test the safety and efficacy of the Renew™ NCP-5 System (Renew™ NCP-5) for the treatment of Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. Specifically, this study will evaluate how the Renew™ NCP-5 device works in relation to changes in cognition.

For any clinical study, it is important to ensure the eligibility of participating subjects and to understand the diversity of that population. Thus, similar studies of MCI and AD have used the Mini- Mental State Examination 2 (MMSE2), the Logical Memory Sub-Scale II of the Wechsler Memory test (LMII), and the Montreal Cognitive Assessment (MOCA) to assess cognition and the Cardiovascular Risk (CVR) scale to assess appropriateness to participate in a study.

The MMSE2 is a brief assessment instrument used to assess cognitive function in geriatric patients. The MMSE2 can be used to screen for cognitive impairment and as a measurement of cognitive change over time. The instrument is divided into two sections. The first section measures orientation, and attention, while the second section tests the ability of the patient to name objects, follow verbal and written commands, write a sentence, and copy figures. Folstein, Folstein, et al. (1975) demonstrated the MMSE2 to be both reliable and valid in a group of elderly subjects: including those with dementia, depression with cognitive impairment, depression and "normal" elderly patients. The validity of the MMSE2 is demonstrated by a positive correlation between the patients' MMSE2 scores and their scores on both the verbal and performance sections of the Wechsler Adult Intelligence Scale. The MMSE2 has been shown to possess sensitivity and specificity in various populations. Although the MMSE2 alone is unable to provide diagnostic information, the data on its sensitivity and specificity in cognitively impaired patients demonstrates its utility as a screening instrument. The Logical Memory Sub-test of the Wechsler Memory Scale is a standardized assessment of narrative episodic memory, assessing immediate recall and delayed recall.

The MOCA is a widely used cognitive assessment for patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. It includes a memory recall test, visuospatial abilities, executive function, attention, concentration, working memory, naming and orientation to time and place. Subjects with a MOCA score of greater than or equal to 11 will be included in the study. In a validation study by the developer of the MOCA (Nasreddine, Z Phillips, NA 2005), 94 patients diagnosed with MCI and 93 patients diagnosed with mild AD were assessed by the MMSE2 and MOCA. The MOCA was significantly more sensitive in detecting MCI (90%) vs MMSE2 (18%). Further, the MOCA detected mild AD more reliably (100%) than the MMSE2 (78%). These

findings were confirmed by other investigators (Luis CA, Keegan AP, Mullan M, 2009). MOCA has been used extensively in studies of MCI and mild AD. (Ciesielska N, Sokolowski R, Mazur E, et al 2016).

The study checklists were developed based on the following 2011 National Institute on Aging (NIA) - Alzheimer's Association (AA) "core clinical criteria" guidelines: (i) The diagnosis of dementia due to Alzheimer's disease & (ii) The diagnosis of mild cognitive impairment due to Alzheimer's disease, which will be used in conjunction with the MMSE2, LM, and MOCA tests. All required checkboxes within the study checklist for "The diagnosis of probable AD dementia" must be "yes" to qualify for inclusion into the study as a subject with mild AD. If the patient does not meet all the required criteria in the study checklist for "The diagnosis of probable AD dementia," the site will proceed with completing the study checklist for "The diagnosis of mild cognitive impairment due to Alzheimer's disease," and all required checkboxes must be "yes" to qualify for inclusion into the study as a subject with MCI due to AD.

Understanding the importance of vascular status, the Cardiovascular Risk Assessment (CVR) will be used to assess the subject's cardiovascular risk. The CVR score will be calculated based on the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk, which will be used to stratify subjects at baseline into a 10-year low/medium risk vs. high/very high risk, based on CVR score (Goff, Lloyd-Jones, et al., 2013).

2.1 Assessment of Cognition

The objective of the study is to determine the efficacy of Renew™ NCP-5 System for the treatment of Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type as measured by changes in cognition. Thus, various assessments of cognition used in similar studies will be implemented.

The vADAS-Cog (Vascular Dementia Assessment Scale) is an expanded version of the Alzheimer's Disease Assessment Scale (ADAS-Cog14), that is being used in the National Institute on Aging Alzheimer's Disease Research Centers (National Institute on Aging, 2018). The ADAS-Cog is an instrument devised to assess the severity of cognitive impairment in patients with AD. The scale includes short neuropsychological tests in which the patient performs simple tasks such as word recall, word recognition, and constructional praxis. The cognitive section of the ADAS-Cog consists of two items that assess the following: language (aphasia) and motor skills (praxis). Rosen, Mohs, et al. (1984) evaluated the test-retest and interrater reliabilities of the individual scale items and the entire scale in patients with dementia of the Alzheimer's type. The ADAS-Cog was shown to be valid in the ability to detect patients with clinically diagnosed AD from matched non-demented controls. Kramer-Ginzberg, Mohs, et al. (1988) demonstrated at I2 month and 24 month retesting that higher scores on the ADAS-Cog correlated with disease progression. Because both of the above cognitive and non-cognitive parameters are assessed, the ADAS-Cog is a reliable instrument for use in psychopharmacologic trials involving patients with AD.

The vADAS-Cog has been shown to be a more sensitive measure of cognition than ADAS-Cog in subjects with vascular burden in the brain (Ylikoski, Jokinen, et al., 2007). The vADAS-Cog is made up of ADAS-Cog14 plus three additional tests: the symbol digit test (the number of correct responses in 90 s); the digit span backward test (the number of digits recalled backwards); and the verbal fluency test (animal category in one minute).

Additional neuropsychological assessments used in other studies show changes over time and assess the importance of change to the clinician and caregiver (ADCS-CGIC) and the ability of the subject to carry out activities of daily living (ADCS-ADL). The Trail Making Test B is used in many studies to assess executive function, a key to continued functioning for the patient.

2.2 Imaging and Physiological Assessment

2.2.1 Imaging Studies

Imaging studies may be important in understanding the mechanism by which treatment results in change in cognition or delays the progression of the disease. Both structural/clinical imaging and functional/vascular physiology will be assessed.

Changes in hippocampal volume over time, measured by MRI, have been extensively used as a biomarker for MCI and AD. The European Medicines Agency (EMA) has qualified hippocampal volume as a biomarker for selecting patients for trials in early AD (Hill et al, 2014). FDA has cleared software for MRIs to measure hippocampal volume (Ahdidan et al, 2016).

A vascular component is seen in the great majority of cases of MCI and mild AD (Snyder et al, 2015, Di Marco et al, 2015, Strickland, 2018). Assessing changes in cerebral blood flow can inform the mechanism of change in the vascular contribution to MCI and AD (Bron et all, 2014). It should be noted that no known AD biomarkers have yet been qualified by the Food and Drug Administration (FDA) as a valid surrogate marker of clinical decline that can be used as a substitute for clinical measures.

2.2.2 Hippocampal Volume as a Biomarker of Disease Modification

Hippocampal volume is one of the best-established biomarkers used in research to stage the progression of AD (Trzepacz et al, 2016). The hippocampus is a key structure in mediating memory processes (Pohlack et al, 2014, Hebscher et al, 2017, Longoni et al, 2015) and is affected early in AD (Vecchio et al, 2017, Zhao et al, 2017). Hippocampal volume correlates with AD neuropathological burden, particularly neurofibrillary tangles (Thaker et al, 2017). Hippocampal volume changes are widely used as clinical trial endpoints to provide evidence in support of disease modification (Bredesen et al 2016, Pini et al, 2016). A recent meta-analysis found hippocampal atrophy in AD to be 4.66% (3.92-5.4), significantly higher than the 1.41% (0.52-2.30) in older normal adults (Barnes et al, 2009). Additionally, Schuff et al (Schuff et al, 2009) evaluated 112 cognitive normal elderly individuals, 226 MCI and 96 AD

patients, and found that MCI and AD patients showed significantly more hippocampal volume loss over six months and accelerated loss over 12 months. Therefore, a reduction in hippocampal atrophy compared to placebo could support disease-modification if corresponding clinical benefit is also observed. These factors have led to widespread efforts to utilize hippocampal volume as a surrogate marker of AD, including as noted above, by the EMA.

2.2.3 Regional Cerebral Blood Flow and White Matter Hyperintensities as Potential Biomarkers of Disease

Blood flow is reduced in AD and is known to lead to brain tissue damage, which in turn accelerates the course of the disease. Vascular risk/disease is highly comorbid with AD (Gottesman et al, 2017, Rabinovici et al, 2017) and is linked to conversion from cognitively healthy to MCI (Bangen, Preis, et al., 2018), with increased risk for an AD diagnosis (Arvanitakis, Capuano, et al., 2016; Brickman, Zahodne, et al., 2015). Decreased blood flow thus influences the clinical progression of the disease (Bhargava, Weiner, et al., 2006). In fact, it has been suggested that a 'two hit' process of vascular and classical AD pathology is necessary for the full expression of AD dementia (Nelson, Sweeney, et al., 2016).

Vascular disease can be expressed in many forms. In the brain, cerebral blood flow is reduced in AD and MCI (Alsop, Detre, et al., 2000; Dai, Lopez, et al., 2009), and has been shown to be associated with neurovascular dysfunction that affects the brain's ability to auto-regulate blood flow (Kisler et al, 2017). Reductions in CBF are linked to more rapid conversion from MCI to AD (Hirao, Ohnishi, et al, 2005;) and regional CBF tracks with cognitive symptoms in patients with AD. Alterations in CBF are strong in regions known to exhibit early and high classical AD pathology (Dai, Lopez, et al., 2009; Hirao, Ohnisi, et al., 2009). Reduced CBF is also found in individuals who are not impaired but are at risk for AD, for example in carriers of the APOE4 gene allele (Van der Lee, et al, 2018). The utility of CBF as a biomarker for early AD has been justified (Hays, Zlatar, & Wierenga, 2016). Specifically, as a biomarker, CBF has diagnostic utility for prediction of individuals with MCI that will progress and/or convert to AD as well as in tracking progression of AD. In this regard, CBF is considered a mechanism of disease that should be targeted through novel therapeutics and may provide an important indicator of disease modification for slowing the progression of AD.

Regional CBF can be assessed and quantified by MRI (Zhang et al, 2017). High quality anatomic images demonstrated decreased flow in the temporal, parietal, frontal, posterior and cingulate cortices. Severe cognitive dysfunction as measured by MMSE2 correlated with decreased CBF in the post parietal and post cingulate cortices. In another study (Roher, Debbins, et al., 2012), age related neurodegeneration and vascular associated pathologies, such as arteriosclerosis, may increase brain hypoperfusion and lead to increased risk of AD.

A second way that vascular disease is expressed in the brain is through secondary vascular-associated brain tissue damage. Vascular disease can be expressed in many forms. In the brain, white matter hyper

intensities (WMH) of presumed vascular origin (Wardlaw, Valdes Hernandez & Munoz-Maniega, 2015) seen on magnetic resonance imaging (MRI) are in part due to cerebral hypoperfusion (reduced cerebral blood flow) resulting in hypoxic, ischemic tissue damage to the white matter connections in the brain (Fernando, Simpson, et al., 2006; Black, Gao & Bilbao, 2009). WMH are therefore related to alterations in brain function and cognition generally and not specific to AD. However, WMH are much more highly prevalent in AD compared to cognitively healthy older adults (Coutu, Goldblattt, et al., 2016) and may be more predictive of decline than traditional imaging markers of AD pathology (Coutu, Lindemer, et al., 2017). Enhancement of vascular processes that increase CBF and reduce WMH burden therefore may represent an important disease-modifying target for dementia.

Similar to primary affected structures such as the hippocampus which are affected long before a diagnosis of AD, the rate of WMH increase also accelerates several years before a diagnosis of MCI (Silbert, Dodge, et al., 2012). Dynamic tissue changes within WMH occur just prior to the conversion from MCI to AD (Lindemer, Salat, et al., 2015), suggesting that prevention of such damage may slow the conversion from an independent to dependent clinical state. Additionally, WMH are highly correlated with primary imaging markers of AD pathology such as hippocampal and ventricular volumes (Coutu, Goldblatt, et al., 2016), suggesting that vascular disease may exacerbate the primary pathology of AD. The annual increase in WMH volume is reported to be between 12.5% and 25% in community dwelling individuals with early confluent lesions or greater at baseline (Schmidt, Enzinger, et al., 2003). WMH have been explored as surrogate clinical trial endpoints for small vessel disease (Schmidt, Scheltens, et al., 2004). A therapeutic increase or preservation in CBF and/or a decrease or preservation of WMH volume could support disease-modification. This hypothesis would be strengthened if corresponding clinical benefits were also observed.

2.2.4 Physiological Assessments

Falls in older people with dementia or cognitive impairments increases rates of hospitalization, dependence, depression and caregiver burden.

The Timed Up & Go Test is a common clinical screening tool used to assess a patient's mobility, balance, gait speed, and fall risk. The patient is timed while they rise from an arm chair, walk to a line on the floor three meters away, turn around and walk back to the chair and sit down again. The subject wears his regular footwear and uses his customary walking aid (cane or walker) if necessary (Barry, Galvin, et al., 2014).

The Functional Reach Test is a valid and reliable measure used to identify deficits in dynamic balance and fall risk. It is a single-task, dynamic measure of the difference in arm's length and maximal forward reach using a fixed base of support in the standing position (Duncan, Weiner, et al., 1990).

2.3 Blood studies

Exploring the changes in blood factors in MCI and AD patients may lead to a better understanding of how they may contribute to the development of dementia.

Alterations in quantity and quality of blood cells may be involved in the pathogenesis of AD and may contribute to disease progression (Turcato, Serafini, et al., 2016). In a recent study (Chen, Bu, et al., 2017), AD patients were found to have increased levels of mean corpuscular hemoglobin, mean corpuscular volume, red cell distribution width-standard deviation, mean platelet volume and decreased levels of platelet distribution width, red blood cell, hematocrit, hemoglobin, lymphocyte, and basophil compared to normal controls.

Serum markers of hypercoagulability and markers of inflammation lead to thrombosis, accelerated atherogenesis and dementia (Gupta, Watkins & Thomas, 2005). A 2009 study (Smith, Chen, et al., 2009) suggests that vessel diameter, flow velocity, and whole blood viscosity are altered in AD subjects compared to controls. AD patients had significantly increased whole blood viscosity, which was correlated with disease severity (Smith, Chen, et al., 2009). In another study (Chang, Liang, et al., 2007), fibrinogen concentration and mean corpuscular cell volume levels of erythrocytes were significantly higher in AD patients.

Oxidative stress-induced elevation of fibrinogen concentration could lead to accelerated erythrocyte aggregation as a result of blood viscosity and blood viscoelasticity leading to impaired oxygen transport efficiency in the blood of AD patients.

Inflammatory markers such as C-reactive protein and Lp-PLA2 and MPO are implicated in the pathogenesis of AD and VD. C-reactive protein (CRP) is a strong marker of VD in early stages of the disease (Androsova, Mikhailova, et al., 2013).

Lipid levels may be related to development of MCI and AD and significantly lower lipid levels have been found in patients with AD than controls. Late phases of AD show significantly lower entire lipid profile and significantly lower cholesterol and LDL-C. Lipid profile may be connected to the etiology and progression of AD. An association between low serum cholesterol and LDL-C levels and cognitive decline in AD have been shown (Persecki, Muck-Seler, et al., 2011).

3. RATIONALE

Understanding the impact of Renew™ NCP-5 on increasing cardiac perfusion and its similarity to exercise in increasing blood flow to not only the heart but to other organs in the body, this study assumes that the Renew™ NCP-5 will increase cerebral blood flow. Renew Research, LLC anticipates that Renew™ NCP-5 session intervention may effectively treat or delay cognitive impairment from Mild

Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. Studies show that ECP improves cardiac output and arterial stiffness, and may have the potential to improve cerebral blood flow. These effects could have a positive effect on cognitive impairment. Please see Figure 1 below.

Figure 1.

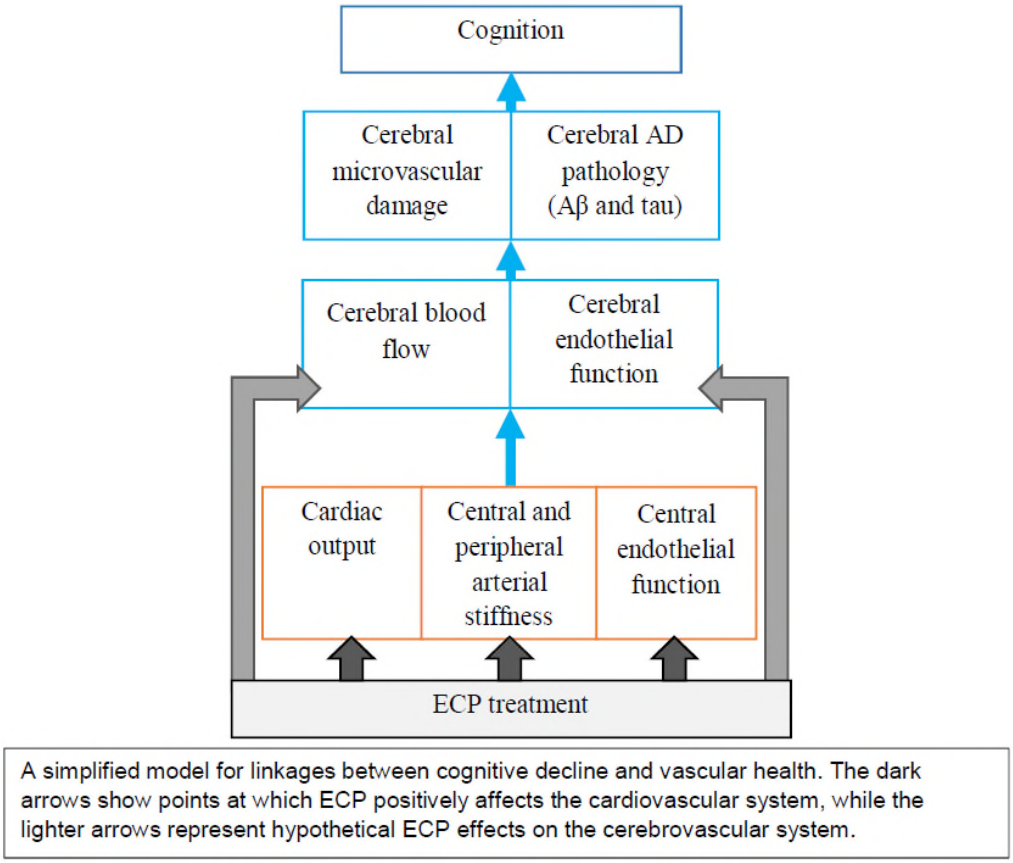

Figure 1: A model for cognitive impairment, cerebral vascular health, and potential points at which Renew™ NCP-5 could play a positive role.

3.1 Potential Risks

In accordance with 21 C.F.R. Part 812 and FDA's guidance document entitled "Significant Risk and Nonsignificant Risk Medical Device Studies" (Jan. 2006), FDA concurred with Renew Research LLC's conclusion that its proposed clinical study poses nonsignificant risk (NSR) and therefore is subject to the abbreviated IDE requirements found in 21 C.F.R. 812.2(b). The Renew™ NCP-5 System does not qualify as significant risk for purposes of an IDE because: (1) the device is not an implant; (2) the device is proposed to be used as a treatment for MCI and mild AD, and is not intended for a use in supporting or sustaining human life; and (3) while the device is of substantial importance in diagnosing, curing,

mitigating, or treating disease, including mild AD, or otherwise preventing impairment of human health, (4) the device does not present a potential for serious risk to the health, safety, or welfare of a subject.

Renew™ NCP-5 therapy is safe in healthy patients, as well as in patients with atherosclerosis, coronary artery disease, cerebrovascular diseases and other comorbidities that may exist in the AD population. Only minor adverse events have been recorded during treatment with Renew™ NCP-5. Moreover, Renew™ NCP-5 has been used in patients who suffered from ischemic stroke, including in cases where the drug dextran was being used (Han & Wong, 2008), and subjects suffering from AD (Li, Yao, et al., 1994) without serious complications. Lastly, Renew™ NCP-5 has previously been used in older patient populations in multiple studies (e.g., average age: 63 years (Applebaum, Kasliwal, et al., 1997), 64 years (Werner, Marthol, et al., 2003), and 74.5 years (Han & Wong, 2008)) without complications.

AD presents as neurological degeneration that disrupts neuron-to-neuron communication and leads to cell death. Neurological degeneration and cell death, however, will not place AD patients at a greater risk than other populations undergoing Renew™ NCP-5 treatment. While patients with AD often have several comorbidities, primarily due to the more advanced age of the AD population, the study screening process will effectively exclude conditions that may place a subject at a higher risk during Renew™ NCP-5 treatment. This will include subjects with congestive heart failure, deep vein thrombosis, elevated heart rate, heart valve disease, and untreated high blood pressure, among others. Study subjects with these conditions, who are at a greater risk during Renew™ NCP-5 treatment, will be excluded from the study. Moreover, study subjects will not need to terminate their current treatment regimen in order to participate in the study, except under limited circumstances. Subjects will thus not be subject to heightened risk that may be associated with the termination of their current treatment regimen.

The conclusion that treatment with the Renew™ NCP-5 External Counterpulsation System does not present a serious risk to health is supported by the academic literature and historical safe use of Renew™ NCP-5 therapy. The physical symptoms of mild AD, neurological degeneration and cell death, will not place subjects at a heightened risk. In addition, comorbidities found in the AD population that would subject a patient to heightened risk during Renew™ NCP-5 will be excluded during the screening process. Given that Renew™ NCP-5 has been used in medical treatment for over 50 years, the conditions that heighten patient risk during Renew™ NCP-5 treatment are well established and are reflected in the study protocol. Moreover, patients will be required to maintain their current treatment regimen during participation in the proposed study.

Specifically, minor adverse events reported from the use of the Renew™ NCP-5 External Counterpulsation System and approaches to mitigating the risks are as follows:

- Skin irritation, abrasions, bruising and breakdown around the areas on which the device is placed has been reported but are transient. Fabric sleeves can be used under the

compression cuffs to minimize the chance of skin irritation. Subjects can also use topical creams after treatments to reduce irritation.

- Mild headaches and musculoskeletal pain, including leg and low back pain have been reported. Patients with a history of either of these chronic problems may be excluded from study participation or withdrawn from treatment if symptoms become unmanageable. The use of over the counter analgesics will help alleviate the discomfort.
- Edema in the legs may occur but is generally transient. If it persists, support hose can be used between treatments.
- Toothache is generally transient and can be treated with over the counter analgesics.
- Fatigue

There are potential risks from other assessments that will be performed:

- Some subjects may experience anxiety or feelings of claustrophobia from the MRI. Study staff will explain the MRI procedure and answer any questions. Earplugs/headphones will be given to the participant to decrease the noise associated with the MRI. If necessary, an anxiolytic may also be prescribed. Study staff will explain that there will be no exposure to radiation and will exclude anyone who has metallic parts in their bodies.
- When blood is drawn, the participant may feel discomfort or experience some bruising, both of which are transient. Skilled phlebotomists will explain the procedure and ensure there is minimal trauma and anxiety.
- There are no reported risks associated with performing ultrasound Doppler. Patient anxiety with these assessments will be addressed by the study staff and operator.

3.2 Potential Benefits

The clinical research study team cannot and does not guarantee or promise that subjects will receive any benefits from this study. However, it is anticipated that treatment with Renew™ NCP-5 will improve cognition and may slow the progression of MCI or AD. At the very least, subjects will have access to this device, Renew™ NCP-5, which would otherwise not be available to them.

4. STUDY OBJECTIVES AND PURPOSE

The purpose of the study is to identify a safe and effective approach to treatment for Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type as measured by changes in cognition and identify a biomarker to measure disease progression.

The primary objective of the study is to determine the efficacy of Renew™ NCP-5 treatment for Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type as measured by changes in cognition.

The secondary objectives of this study are to:

- Evaluate the safety of Renew™ NCP-5 therapy in treatment for MCI due to AD and mild dementia of the Alzheimer's type.
- Confirm the effectiveness of Renew™ NCP-5 treatment through additional neuropsychological testing.

In addition, exploratory objectives of this study are to:

- Evaluate the physiological mechanism of action of Renew™ NCP-5 treatment related to cognition as measured by cognitive and neuro-behavioral assessments, biological markers, ultrasound and laboratory assessments.
- Understand the relationship of hippocampal volume change over time to changes in cognition.
- Compare ADAS-Cog12 scores at 12, 24, 36, and 48 weeks between an external control arm of digital twins and each of the actual treatment and active sham groups.

5. STUDY DESIGN AND ENDPOINTS

5.1 Study Design

This pivotal, single blind, parallel design, multi-site study intends to examine the efficacy and safety of Renew™ NCP-5 therapy in the treatment of Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. Subjects will be prospectively randomized to treatment or active sham (in a 1:1 ratio) using stratification for Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type, and CVR score at multiple sites. Subjects will be assessed for stratification and then randomized within strata to either the treatment group or active sham group with one treated subject for one active sham subject. Randomization assignments will be made using permuted blocks. Investigators shall receive the assignments from an Interactive Web Response System (IWRS). The following factors will be used for stratification prior to randomization: cognitive decline (MCI due to AD vs. mild AD) and CVR score (low/medium vs. high/very high).

Additional pre-specified subgroup analyses of the primary efficacy outcome will be conducted using the same method as the primary analysis. The subgroup includes cognitive decline (MCI due to AD vs. mild AD) and CVR score (low/medium vs. high/very high). These subgroup analyses results will not be used to draw conclusions of efficacy. The subgroup analyses will serve as a supportive purpose to the primary analysis; therefore, Type I error will not be adjusted for the subgroup analyses.

Prior to randomization, subjects will be diagnosed with either Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type, based on the study checklist developed, which follows the 2011 National Institute on Aging (NIA)-Alzheimer's Association (AA) "core clinical criteria" guidelines. After the subject completes the MMSE2, LMII and the MOCA, the investigator will review the

results and complete the 2011 NIA-AA study checklist, which identifies the "core clinical criteria" for diagnosis of probable AD dementia as indicated by the presence of cognitive and/or behavioral symptoms. Positive responses to the first five questions are required for inclusion in the mild AD cohort. If the responses to the first five questions within the checklist for the diagnosis of probable AD dementia are not positive, the investigator will then complete the 2011 NIA-AA "core clinical criteria" study checklist for MCI due to AD. Responses to the first four questions of that study checklist for the diagnosis of MCI due to AD must be positive, and the clinical impression must conform with typical presentation of individuals for whom there is an intermediate level of certainty that they have MCI due to AD, in order for subjects to be included in the MCI due to AD cohort.

The MOCA, LM, MMSE2, and the complaint of memory loss by the subject and/or caregiver will be used to assess the subject; however, eligibility for the study will be determined by a MOCA score of greater than or equal to 11. The efficacy of Renew™ NCP-5 treatments to influence cognitive symptoms will be evaluated through performance on the vADAS-Cog compared to the active sham treatment group.

Subjects, ages 55-85, will be consented for 13 months study participation, and will receive thirty-five 60-minute Renew™ NCP-5 treatment sessions during a 7-to-12-week initial treatment period, and then transition to a lower frequency maintenance period (twice a week) for a total treatment period of 24 weeks. During the initial treatment period (~1-12 weeks) subjects should be treated five days per week but at a minimum receive treatments three days per week. For subjects who are unable to complete 5 treatment days per week, the treatments should be spread-out as much as possible. In order to complete 5 treatments per week, it is permissible for those subjects to have 2 treatments per day as long as there are no more than 3 days between treatments. If two treatments are conducted on the same day, subjects will need to wait a minimum of one-hour between treatments. Treatments should be completed per the above schedule. The schedule may be adjusted due to holidays or extenuating circumstances. If subjects need to miss visits during any particular week, then treatments should be added to the week prior to or after the missed visits. A total of 35 treatments must be completed within the 12-week period. More than 7 days between treatments would be considered a protocol violation.

Once the first 35 treatments have been administered, subjects will start the maintenance period. During the maintenance period, subjects should be treated two days per week, one session per day with a minimum of two full days between each treatment. Subjects may be rescheduled on an as needed basis as long as 6 treatments are maintained within a 3-week period. Rescheduling should be kept to a minimum and all efforts should be made to have treatments every week.

Assessment visits should occur the day following the last treatment session but no later than 2 days (48 hours) after the last treatment. If necessary, on an as-needed basis, a treatment session of 30 minutes or more (≥ 30 minutes) will be considered as a completed session.

The investigator will assess vADAS-Cog at baseline, 6, 12, 18, 24 weeks, 9 and 12 months, or upon termination of treatment. Testing sessions will include additional secondary psychological assessments including the National Institute on Aging's Alzheimer's Disease Cooperative Study-Clinical Global Impression Scale (ADCS-CGIC) by the clinician and patient/caregiver and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL), Trail Making Test B, and ADAS-Cog. The ADCS-ADL, ADCS-CGIC, Logical Memory and Trail Making will be completed by blinded psychometricians.

Subjects will receive MRI brain scans at screening to ensure there is no existing exclusionary brain pathology. Brain pathology would include evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions. Central Reading of the MRIs will be conducted at Massachusetts General Hospital (MGH). Subjects who are re-screened for this study may utilize their initial screening MRI scan to determine eligibility if the initial screening MRI was completed within 90 days of re-screening. At 24 weeks and end of study (12 month), an MRI will assess changes in hippocampal volume, a biologic marker for AD. A repeat scan may be obtained if necessary. Additionally, as exploratory endpoints, subjects treated at selected sites will receive Transcranial Doppler or the Moor deep tissue oxygenation to evaluate cerebral blood flow at study start and periodically throughout the trial period.

Safety evaluation, including ongoing review of adverse events and vital signs will occur at every visit throughout the study. This trial will have frequent interim analyses to stop accrual early for expected success or for futility as outlined in more detail below.

For exploratory endpoints, blood samples will be drawn at screening, 12 weeks, 24 weeks and 12 months, or upon termination of treatment. A repeat lab draw may be obtained at any time if needed. Polymorphism of the apolipoprotein (ApoE) gene and its effect in modulating hippocampal change will be assessed at baseline. Additional exploratory lab endpoints include assessment of blood viscosity, inflammatory markers, and blood fibrinogen at baseline, 12 weeks, 24 weeks and 12 months, or upon termination of treatment. Exploratory endpoints of balance, functional mobility, and fall-risk will be measured via the Timed Up & Go (TUG) test and the Functional Reach Test at baseline, weeks 6, 12, 18, 24, 9 and 12 months, or upon termination of treatment. Neuro-behavioral symptoms will be assessed using the Neuropsychiatric Inventory (NPI) at baseline, weeks 6, 12, 18, 24, 9 and 12 months, or upon termination of treatment.

5.2 Endpoints

5.2.1 Primary Endpoint

The primary endpoint for this study is the **average of the change from baseline in vADAS-Cog score at 12, 18 and 24 weeks after initiation of treatment**. vADAS-Cog is an expanded version of the ADAS-Cog assessment, and the former has been shown to be a more sensitive measure of cognition than ADAS-Cog in subjects with vascular burden in the brain.

The vADAS-Cog represents a collection of tests of different domains of brain function.

A 2-point average change from baseline in vADAS-Cog at 12, 18 and 24 weeks after initiation of treatment will be used to determine effectiveness. Examples of the typical functional changes associated with a 2-point change in vADAS-Cog include:

- Improvement in orientation – subject can now remember current date and day of week;
- Less errors in naming – 50% reduction in mistakes naming a real object;
- Improvement in following commands – subjects fail to follow 1/5 simple commands instead of 3/5 commands previously failed;
- Improvements in spoken language – misunderstanding decreases from moderately severe to mild (3-5 errors mean mild);
- Better constructional praxis – 40% improvement in number of figures copied correctly;
- Better word recall – 20% improvement in ability to remember words immediately after hearing them 3 times.

It is expected that the effect of the treatment will be demonstrated first at 12 weeks but will maintain or improve through to 24 weeks of treatment. Accordingly, since the 12 week (the completion of initial phase of treatment), 18 week and 24 week (end of maintenance phase) vADAS-Cog scores represent the entire expected period of the treatment duration, it is appropriate to measure the average of 12, 18 and 24 week vADAS-Cog scores as the primary endpoint for this study. The primary endpoint is the average of the change assessed at each of these three time points, referred to as an integrated primary endpoint.

Sponsor will repeat the analysis of the primary endpoint using 9-month and 12-month data.

As described in the Adaptive Design Report (ADR), included in Appendix A, the primary endpoint will be evaluated during interim analyses (after 100 subjects have been randomized and after every additional 25 subjects are randomized), up to a total of 250 subjects.

5.2.2 Secondary safety and effectiveness endpoints

Because there is no gold standard to measure the changes from treatment in cognition for MCI or mild AD, secondary endpoints will include assessments performed in other similar studies. While cognitive and imaging assessments may show changes over time, it is important to assess the importance of change to the clinician and caregiver (ADCS-CGIC) and the ability of the subject to carry out activities of daily living (ADCS-ADL). The Trail Making Test B is used in many studies to assess executive function, a key to continued functioning for the patient. Because the vADAS-Cog includes the ADAS-Cog14 that has been used to assess changes in cognition in pharmaceutical studies, it is important to compare it to the findings from the vADAS-Cog.

The secondary effectiveness endpoints of the study include:

- The safety of Renew™ NCP-5 treatments as reflected in adverse events, labs and vital signs;
- The average of the change from baseline in Alzheimer's Disease Cooperative Study-Activities of Daily Living (**ADCS-ADL**) Total Score at 12, 18 and 24 weeks after initiation of treatment;
- The answers to the NIA's Disease Cooperative Study-Clinical Global Impression of Change Scale (**ADCS-CGIC**) at 12, 18 and 24 weeks after initiation of treatment;
- The average of the change from baseline in executive function, assessed by the **Trail Making Test B** at 12, 18 and 24 weeks after initiation of treatment;
- The average of the change from baseline in **ADAS-Cog14** at 12, 18 and 24 weeks after initiation of treatment. ADAS-Cog14 score will be calculated using the subtests from the vADAS-Cog test and will not be conducted as a separate test.

Sponsor will repeat the analysis and conduct the battery of secondary endpoints on the 9 and 12 month data.

5.2.3 Payor-based endpoints

The payor-based endpoints, described below, will be used to assess the clinical and cost effectiveness of the Renew™ NCP-5 external counter-pulsation (ECP) for patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. Effectiveness of ECP on cognitive impairment, compared to active sham group, measured by the clinical effectiveness endpoints identified, will be key in communicating the value and benefits of adding ECP as a treatment option for this patient population. In order for physicians to widely access ECP as a treatment option for their patients, reimbursement from commercial payers will be required. To facilitate reimbursement, the study is measuring the impact of ECP on health related quality of life (HRQoL), reduction in disease burden, and health resource ustilization (HRU) to help assess the cost effectiveness of ECP, and potential cost savings for health systems and payers. Results from this study will be presented to Centers for Medicare and Medicaid Services (CMS) and commercial insurers to initiate reimbursement approval of ECP.

- A comparative analysis between treatment and active sham groups on **Health Resource Utilization (HRU) data** will be conducted using the following analysis and time points:
  - The difference in change from baseline analyzed at:
    - 24 weeks
    - 9 months
    - 12 months
  - An average of 24 weeks, 9 months, and 12 months

- A comparative analysis between treatment and active sham groups in their change of ability to drive based on a self-rated answer to a question
- A comparative analysis between treatment and active sham groups in **vADAS Cog Scores** will be conducted using the following analysis and time points:
  - The difference in change from baseline analyzed at:
    - 24 weeks,
    - 9 months,
    - 12 months;
  - An average of 24 weeks, 9 months, and 12 months
- A comparative analysis between treatment and active sham groups in **ADCS-ADL Scores** will be conducted using the following analysis and time points:
  - The difference in change from baseline analyzed at:
    - 24 weeks
    - 9 months
    - 12 months
  - An average of 24 weeks, 9 months, and 12 months
- A comparative analysis between treatment and active sham groups in **Fall Risk Assessment/Functional Reach Test/TUG Test Scores** will be conducted using the following analysis and time points:
  - The difference in change from baseline analyzed at:
    - 24 weeks
    - 9 months
    - 12 months
  - An average of 24 weeks, 9 months, and 12 months
- A comparative analysis between treatment and active sham groups in **NPI Aggression Index Scores** will be conducted using the following analysis and time points:
  - The difference in change from baseline analyzed at:
    - 24 weeks
    - 9 months
    - 12 months
  - An average of 24 weeks, 9 months, and 12 months
- The answers to the **QOL/Patient Survey** at 12 months after initiation of treatment.

5.2.4 Exploratory endpoints

Imaging studies may be important in understanding the mechanism by which treatment results in change in cognition or delays the progression of the disease. Understanding that there is a vascular component to MCI and mild AD, assessing changes in cerebral blood flow can inform the mechanism of change. Research indicates that hippocampal volume change over time, measured by MRI, has potential as a marker for MCI and AD. MRI will be conducted at screening after all other assessments have found

the subject to be eligible to participate in the study. This will allow results confirming no brain pathology, which would include evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions to be available for review at the baseline visit. If a history of cerebral aneurysm is suspected, the subject will be referred to their primary physician and/or neurologist.

The exploratory endpoints for this study include:

- Evidence of altered peripheral or cerebrovascular physiology including:
    - The observed value and change from baseline in hippocampal volume measured by MRI at 24 weeks and 12 months after initiation of treatment
    - Changes from baseline to 24 weeks after initiation of treatment or active sham in:
        - **Cerebral blood flow (CBF) in multiple regions (hippocampus, precuneus, parietal, inferior frontal lobe) measured by arterial spin labeling** between the treatment and active sham groups from screening, to 24 weeks and 12 months (selected sites only);
        - **Global cerebral blood flow as measured via MRI**
        - White matter hyperintensities as **measured via MRI**
        - **CBF velocity in cerebral arteries as measured by Transcranial Doppler at baseline, 12 and 24 weeks (selected sites only)**
        - **Endothelial function via flow-mediated dilation (FMD) (brachial or femoral), as measured by ultrasound at baseline, 12 and 24 weeks (selected sites only)**
        - **Arterial stiffness via pulse wave velocity (PWV)** measured by arterial tomography or ultrasound at baseline, 12 and 24 weeks (selected sites only)
        - **Arterial stiffness via augmentation index** measured by arterial tomography at baseline, 12 and 24 weeks
        - **Deep tissue oxygenation** (hemoglobin concentration and SO2) via near infrared spectroscopy at baseline, 12 and 24 weeks
        - **Blood viscosity** at baseline, 12 and 24 weeks (selected sites only)
        - **Lipid panel**: total cholesterol, LDL-C, HDL-C, triglycerides, Blood fibrinogen at baseline, 12 and 24 weeks
        - **Inflammatory markers**: C-Reactive Protein (CRP), Lp-PLA2 and MPOS at baseline, 12 and 24 weeks
        - **CBC**: including Red Cell Distribution Width (RDW) & Hemoglobin at baseline, 12 and 24 weeks
        - ~~Presence~~
- **Difference in change from baseline** at 12 and 24 weeks in the **Behavioral Assessment** measured via Neuropsychiatric Inventory (NPI) Agitation/Aggression.

- **Difference in change from baseline** at 12 and 24 weeks in **balance, functional mobility, and fall-risk assessment measured via Timed Up & Go (TUG) test and the Functional Reach Test**.

- **Time course comparative analysis** between treatment and active sham groups in **ADAS Delayed Word Recall** (a sub-test of the vADAS cog) at baseline, 12 and 24 weeks.

- **Time course comparative analysis** between treatment and active sham groups in **ADAS Word Recognition** (a sub-test of the vADAS-cog) at baseline, 12 and 24 weeks.

- **Comparison of ADAS-Cog12 scores at 12 weeks, 24 weeks, 9 months, and 12 months between an external control arm of digital twins and each of the actual treatment and active sham groups**. An external control arm of digital twins (digital subjects with the same baseline characteristics as actual study participants) simulates, at a subject level, clinical trajectories of actual study subjects under the counterfactual scenario of no treatment. Ten digital twins will be created for each subject enrolled in the study. The digital twins will be generated by a model of AD progression developed by Unlearn.AI Inc., based on data from the control arms of 18 AD and MCI phase II and III clinical trials (4897 subjects) (Neville, et al., 2015). This model was shown to generate digital controls which are statistically indistinguishable from those of actual control subjects across a wide variety of clinical measures included in the model (Fisher, et al., 2019; Walsh, et al., 2020). The treatment effect vs. external control group will be estimated for each of the actual study arms (treatment and active sham), including testing the hypothesis that there is no treatment effect in the active sham arm vs. external control arm.

6. STUDY ENROLLMENT AND WITHDRAWAL

6.1 Inclusion Criteria

Subjects will meet all inclusion criteria and none of the exclusion criterion. The study is open to both genders and members of all minority groups. Subjects enrolled into the study will:

1. Be 55-85 years of age at the time of signing the informed consent
2. Be able to provide consent or have legally authorized representative/caregiver who can provide consent
3. Be able to read and write in English or Spanish
4. Have a clinical diagnosis consistent with 2011 NIA-AA “core clinical criteria” guidelines for: (i) The diagnosis of dementia due to Alzheimer’s disease or (ii) The diagnosis of mild cognitive impairment due to Alzheimer’s disease:
    - MOCA score of greater than or equal to 11
    - All required checkboxes within the study checklist for “The diagnosis of probable AD dementia” must be “yes” or

- All required checkboxes within the study checklist for "The diagnosis of mild cognitive impairment due to Alzheimer's disease" must be "yes"

5. Stable medications for past 30 days and plan to remain on stable medications for the first 24 weeks of study participation for treatment of chronic conditions
6. Subject should have a caregiver, study partner or companion (which can be a domestic party) who can complete the study assessments. The assessments may be conducted over the phone if they don't accompany the participant
7. Must have the potential to improve by at least 2 points or more in the vADAS-COG

6.2 Exclusion criteria

Subjects who meet any of the exclusion criteria will be excluded from study participation. The investigator shall exclude subjects with the following conditions:

1. Unwilling or unable to participate in study procedures
2. Weight >297 lbs. or >135 kg at screening
3. Major confounding neurodegenerative or psychiatric disorder unrelated to the condition under study, including:
    a. History of clinically-evident stroke
    b. Current uncontrolled epileptic seizures or epilepsy
    c. Multiple Sclerosis or Parkinson's Disease
    d. Current clinically significant major psychiatric disorder (e.g., Major Depressive Disorder) according to DSM-V criteria or significant psychiatric symptoms (e.g., hallucinations) that could impair the completion of the study
4. Anyone with active or history of cerebral hemorrhage including subdural & subarachnoid or cerebral aneurysm
5. Evidence of any of the following (based on Section 4.1.1(D) of the 2011 NIA-AA guidelines on The diagnosis of dementia due to Alzheimer's disease):
    a. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden
    b. Core features of Dementia with Lewy bodies other than dementia itself
    c. Prominent features of behavioral variant frontotemporal dementia
    d. Prominent features of semantic variant primary progressive aphasia or nonfluent/agrammatic variant primary progressive aphasia
    e. Evidence for another concurrent, active neurological disease, non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition
6. In the opinion of the investigator, any current clinically-significant systemic illness or medical condition that is likely to result in deterioration of the subject's condition, affect the subject's safety during the study, or to be incompatible with performance of the study procedures, including:

a. History of head trauma with a diagnosis of moderate to severe traumatic brain injury
b. Known current substantially elevated intracranial pressure
c. Known current significant sleep deprivation
d. Known history (within five years) or current significant drug abuse or alcoholism

7. Any contraindication for MRI such as insulin pumps or pacemakers, including dual chamber pacemakers where atrial pacing may interfere with Renew™ NCP-5 inflation timing sequence
8. Hypotension as defined as <80/50 blood pressure at the time of screening
9. Ongoing uncontrolled severe hypertension (≥ 180 mmHg systolic or ≥ 110 mmHg diastolic
10. Heart rates < 35 or >125 beats per minute (BPM) at screening
11. Current uncontrolled arrhythmia. Controlled arrhythmia should have beat-to-beat, cycle-length variability less than ±25% at rest.
12. Current congestive heart failure
13. Cardiac catheterization within two weeks, any surgical intervention within six weeks before Renew™ NCP-5 treatment or a hip or knee replacement within 3 months as long as rehab is complete and symptoms have resolved
14. Known presence of abdominal aortic aneurysm
15. Existing aortic insufficiency grade II or higher (regurgitation can prevent diastolic augmentation)
16. Current or past venous thrombosis or thromboembolism
17. Current limiting peripheral vascular disease with history strongly suggestive of lower extremity ischemia or claudication, arterial occlusive disease (aortoiliac, ileofemoral, or femoral popliteal)
18. Demonstrable deficiency in sensation in lower extremities as a result of diabetes or other medical condition
19. Current bleeding disorders
20. Current use of major anti-coagulation therapy (such as Heparin therapy or Coumadin® therapy) with INR > 1.5
21. Current severe pulmonary disease that prevents the subject from lying supine
22. Presence of local infection, vasculitis , burn, open wound, or bone fracture on any limb which would prevent the ability to perform the Renew™ NCP-5 treatment
23. Current use of medications that in the investigator's judgement are incompatible with the study goals
24. Significant changes in existing medical plans for treatment of cognitive impairment or dementia in last three months and/or or planned changes during the trial
25. Presence of any of the contraindications for using the Renew™ NCP-5 device
26. Athletic injuries, including Charley horses, pulled muscles and/or edematous muscles; necrotizing cellulitis in the past 30 days which would prevent the ability to perform the Renew™ NCP-5 treatment (evaluate and treat prior to Renew™ NCP-5 treatment)
27. Unwilling or unable to maintain stable exercise regimen throughout the trial
28. Participation in any clinical drug trial 30 days or five half-lives, whichever is longer, prior to screening visit

29. Use of any device to increase cerebral blood flow in the past 30 days
30. History of claustrophobia
31. Subject unable to lay supine for 90 minutes

6.3 Recruitment and Retention

The study will enroll 100-250 subjects. Up to 16 sites will enroll at least one subject, and up to two will be international sites. A maximum of 50 subjects will be enrolled at a single site. Subjects will participate in the study for up to 13 months (up to 28 days screening, 24 weeks treatment and 6 months follow-up) and the study will continue for approximately 36 months.

Subjects will be recruited from the clinics and outpatient practices of the investigators participating in the study, referrals from community-based practices and from recruitment efforts. Study staff will be trained in approaches to recruitment and will be provided with flyers and brochures with patient information. Announcements will be placed on relevant websites. Research staff will provide support and education to the family/caregivers and ensure they understand the study and its potential benefits. A pre-screening questionnaire may be used to identify potential subjects who will be invited for an in-person screening visit. Eligible subjects will be randomized at multiple sites into the study.

Ongoing contact with the subject and caregiver during the treatment phase will be maintained, as the subject will receive treatments up to five days per week. Missed appointments will be followed up by phone calls to understand reasons for missing the treatment and support will be provided in the form of transportation, or other needs. After the intense initial phase, the subjects will be seen less frequently, but the sites will maintain contact with the subject through mail, email, text message and phone calls as needed.

6.4 Withdrawal or Termination

After randomization, all treatment subjects will have an initial four treatments (which are part of the planned 35 treatments) in which the PSI will be gradually increased to maximum tolerability with the goal of reaching 3-6 PSI by the fifth treatment. Subjects are not to be terminated if they cannot reach 3-6 PSI. Each treatment session will last for 60-minutes and a treatment session 30 minutes or more (≥ 30 minutes) will be considered as a completed session.

The investigator can decide to withdraw a subject if any clinical adverse event, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject. Further, if a subject meets an exclusion criterion that precludes further study participation, she/he will be withdrawn from the study.

Subjects are free to withdraw consent and discontinue participation at any time. Their decision to do so will not affect their ability to receive medical care or lose any benefits to which they are otherwise entitled.

All withdrawn subjects will be encouraged to complete study assessments at 6, 12, 18, 24 weeks, 9 and 12 months/end of study assessments and final MRI. Safety follow up procedures to capture adverse events, SAE or unanticipated problems will be initiated.

If the study is temporarily suspended or terminated early, written notification documenting the reason for study suspension or termination will be provided by the terminating party. The PI will inform the IRB and sponsor and provide the reason for termination or suspension. Determination of unexpected or significant risks to subjects, demonstration of efficacy, insufficient compliance to protocol requirements, determination of futility or incomplete data are some of the potential reasons for termination or suspension of the study. Enrolled subjects will be followed up to week 24 if the trial is terminated early.

7. DEVICE

Details about the description, operation, preparation and use of the Renew™ NCP-5 device are found in a separate Training Manual.

7.1 Device Description

The Renew™ NCP-5 device used in the study has been FDA cleared under K152115. The Renew™ NCP-5 device has the following major components: a switch panel, a foldable treatment bed, main unit, and a set of patient cuffs. During Renew™ NCP-5 treatments, the patient's lower extremities are wrapped in compressive pneumatic cuffs applied to the calves, lower thighs, and buttocks. The device is a microprocessor-controlled system that sequentially inflates then deflates three pairs of air cuffs, which compress vascular beds in the muscles of the calves, thighs, and buttocks in synchrony with the heart cycle to achieve the desired therapy. The attached computer provides real time monitoring of: heart rate; Inflation and deflation time; treatment time; treatment pressure; and peak diastolic/peak systolic ratio (P/P). The PC provides synchronous display of the ECG signal, the inflation/deflation signal, and the pulse wave (Renew Group Private, Ltd., 2017).

Input and data from the ECG, plethysmograph, and the pressure/vacuum transducers are processed by the microprocessor to control the valve timing and air pressure in the tank that is delivered to the cuffs. Treatment pressure is monitored with an internal pressure sensor and the operator-selected set point maintained by a closed-loop control system. Valve inflation and deflation timing is also set by the operator based on the relative position of the R-wave of the patient's ECG. Detailed description of the device is also shown in Appendix D, the Investigator Brochure.

7.2 Acquisition of Device

The Renew™ NCP-5 system arrives in a wooden crate as a single shipment consisting of: NCP-5 unit, Laptop PC, and Accessories (cables, hoses, supplies). The unit is also the patient treatment platform. Delivery includes factory installation and set-up. Before the technician departs from the installation site, s/he completes a checklist and the site manager signs confirmation of the quality control/assurance steps taken by the technician.

7.3 Storage and Stability

The Renew™ NCP-5 system should be stored at room temperature in a secure location. It does not require calibration and can be serviced by an approved technician, as needed.

7.4 Preparation

The technicians will follow the preparation and treatment instructions as outlined in the Renew™ NCP-5 training manual.

7.5 Dosing and Administration

The subject is positioned lying flat on the foldable treatment bed and pneumatic, blood pressure like cuffs, are placed on his/her legs: calf, lower thigh and buttocks. They are connected to monitors that record heart rate and rhythm. The cuffs will be inflated and deflated based on the actions of the subject's heart (between heartbeats). Compression pressure will be given at different levels depending on whether the subject is assigned to the treatment group or the active sham group. The subject's overall ability to tolerate the treatment may impact the pressure applied. The operator of the device will increase pressure progressively and assess the subject's level of discomfort.

For all treatment subjects, the first four sessions represent the escalation phase. There will be a 5-minute ramp up period where the pressure is increased 1PSI / min until the desired pressure is reached. The goal for the treatment group will be at least 2.5 PSI (pounds per square inch) for the first treatment, and then escalate the pressure gradually through the fourth session at which time the goal for the subject should be at least an average of 3 PSI/session. For all sessions, the subject should reach the highest tolerable pressure. Patients are not to be terminated if they can't reach 3-6 PSI. Each treatment session is 60 minutes however, if necessary, on an as-needed basis, a treatment session of 30 minutes or more (≥ 30 minutes) will be considered as a completed session.

After the fourth session, the operator shall continue to slowly increase the pressure to give the subject time to adapt to the rising pressure in order to reach the maximum level that the subject finds comfortable with a goal of reaching 3-6 PSI or the highest tolerable pressure. The operator may alter the pressure in the event that a subject becomes uncomfortable after the start of treatment. For both treatment arms, the Renew™ NCP-5 operator should record the average compression pressure and

maximum diastolic augmentation (the ratio of diastolic peak height to systolic peak height – P/P) during each treatment session just before (1-2 minutes) reducing the pressure at the end of treatment.

Active sham control subjects will receive the same initial and maintenance treatment regimens as treated subjects except that the pressure will not exceed an average of 0.5 PSI over all treatments. Active sham subjects will undergo cognitive testing and imaging at the same time points as treated subjects. The purpose of the active sham Renew™ NCP-5 treatments is to give the subject an experience that seems to be an authentic treatment but, instead, provides minimal or no therapeutic benefit.

For a active sham treatment, the subject is handled exactly as in a typical therapeutic treatment (vitals, wrapping of cuffs, etc.), but with two important differences:

- The treatment pressure is set to a maximum of 0.5 psi and is kept there for the duration of the active sham treatment. Note that it may be difficult to maintain the pressure at exactly 0.5 psi. Although all attempts should be made to use a maximum of 0.5 psi, occasional, transient excursions as high as 1.0 psi are permissible.
- Although the subject will have ECG electrodes attached to his/her chest as per usual Renew™ NCP-5 protocol, the cable from those leads will not be connected to the Renew™ NCP-5 machine. Instead, the Renew™ NCP-5 machine will be connected to an ECG simulator hidden under the plastic “skirt” of the machine.

The ECG simulator is used to drive the Renew™ NCP-5 machine, rather that the subject’s actual ECG. This causes the "squeezes" applied by the machine to be out of sync with the patient’s heartbeat, thus minimizing any possible therapeutic effect.

ECG simulator settings are as follows:

- Normal sinus rhythm (NSR)
- Heart rate = 70 bpm
- Amplitude – 4 mV
- Sleep – No

Each treatment session will last for 60-minutes. During the initial treatment period (~1-12 weeks) subjects should be treated five days per week but at a minimum receive treatments three days per week. A maximum of 35 treatments may be administered in the initial 12-week treatment period. Once the first 35 treatments have been administered, the subjects will start the maintenance period where subjects will receive two treatments per week. For subjects who are unable to complete 5 treatment days per week, the treatments should be spread-out as much as possible. In order to complete 5 treatments per week, it is permissible for those subjects to have 2 treatments per day as long as there are no more than 3 days between treatments. If two treatments are conducted on the same day, subjects will need to wait a minimum of one-hour between treatments. Treatments should be

completed per the above schedule. The schedule may be adjusted due to holidays or extenuating circumstances. If subjects need to miss visits during any particular week, then treatments should be added to the week prior to or after the missed visits. A total of 35 treatments must be completed within the 12-week period. More than 7 days between treatments would be considered a protocol violation.

Once the first 35 treatments have been administered, subjects will start the maintenance period where. During the maintenance period, subjects should be treated two days per week, one session per day with a minimum of two full days between each treatment. Subjects may be rescheduled on an as needed basis as long as 6 treatments are maintained within 3-week period. Rescheduling should be kept to a minimum and all efforts should be made to have treatments every week.

Assessment visits should occur the day following the last treatment session but no later than 2 days (48 hours) after the last treatment.

If necessary, on an as-needed basis, a treatment session of 30 minutes or more (≥ 30 minutes) will be considered as a completed session.

Subjects should not eat 60 minutes prior to treatment but if necessary, a light snack is acceptable. Cognitive testing will occur at baseline, weeks 6, 12, 18, 24, 9 and 12 months after baseline. Assessments should be performed the day after the last treatment but no more than 48 hours after the last treatment. For all cognitive testing days, the vADAS-Cog will be administered first and all assessments should be done before 3:00 PM.

If assessment occurs on the same day as treatment, the following must be observed:

- Assessments must occur **after** treatment
- vADAS-Cog must be the first assessment performed
- Assessments must occur **prior** to labs and imaging
- Assessments must be completed before 3:00 PM

7.6 Duration of Therapy

Subjects will receive thirty-five 60-minute Renew™ NCP-5 sessions during the 7-to-12-week initial treatment period, and then transition to a lower frequency maintenance period (twice a week) for a total treatment period of 24 weeks.

7.7 Tracking of Therapy

The operator uses the PC to enter patient demographics, record pre and post-treatment data, and process data acquired by the microprocessor module to display user feedback for the Renew™ NCP-5 treatment on the LCD showing treatment parameters and patient waveforms during use.

8. STUDY PROCEDURES AND SCHEDULE

The investigator brochure (IB) will be supplied to sites as a separate document and is attached to this protocol as Appendix D.

8.1 Study Specific Procedures

- **Medical and Treatment History –** The subject's medical and treatment history including past procedures will be obtained by interview and review of medical records. The investigator will review body systems, identify start/stop dates, and determine if the condition is ongoing. Exclusion criteria identify conditions and timeframes that will exclude the subject from participation.

- **Medication history –** Medications and supplements are expected to have been stable for 30 days prior to study start and remain stable over the first 24 weeks of the study for chronic conditions. All medications and supplements will be recorded and their impact on the study will be assessed**.**

- **Physical examination –** A physical examination, including a brief neurological exam, will be performed to ensure subjects do not exhibit any exclusion criteria and are healthy enough to participate in the study. A second physical exam will take place at end of study.

- **Exercise history and Mobility Assessments –** Subjects will confirm their level of exercise, including cognitive exercises such as language exercises, Sudoku puzzles or online brain training programs (e.g. Lumosity), number of times per week, and length of each exercise session. The aim is to maintain the same level of exercise over the course of the study. Mobility assessments will be performed to assess the participant's balance, functional mobility, and fall risk.

    - **Timed Up & Go (TUG) Test –** A common clinical screening tool used to assess a patient's mobility, balance, gait speed, and fall risk. The patient is timed while they rise from an arm chair, walk to a line on the floor three meters away, turn around and walk back to the chair and sit down again. The subject wears his regular footwear and uses his customary walking aid (cane or walker) if necessary.

    - **Functional Reach Test –** A valid and reliable measure used to identify deficits in dynamic balance and fall risk. It is a single-task, dynamic measure of the difference in arm's length and maximal forward reach using a fixed base of support in the standing position.

- **Patient questionnaire –** Patient self-evaluation questionnaire

- **Health Resource Utilization Questionnaire – RUI – (Resource Use Inventory)-** Patient self-reported questionnaire designed to assess health related services the patient has used during the course of the study.

- **Vital signs –** An electrocardiogram will be performed at screening to ensure the subject is healthy enough to participate in the study and does not demonstrate any cardiovascular problems. Blood pressure, heart rate and respirations will be recorded before and after each Renew™ NCP-5 treatment and at every visit.

- **Radiographic and imaging assessments –** Magnetic resonance imaging (MRI) will be performed to rule out other brain pathology including evidence of infection, infarction (including multiple lacunas in a critical memory structure), or other focal lesions. If a history of cerebral aneurysm is suspected, the subject will be referred to their primary physician and/or neurologist. Central Reading of the MRI's will be conducted at MGH. In addition, MRI will be performed at screening and at 12 weeks, 24 weeks and 12 months to assess hippocampal volume and regional cerebral blood flow changes over time. Freesurfer software will be used to measure volume (Schmidt, Storrs, et al., 2018). Studies show that Hippocampal atrophy associated with episodic memory declines over time as observed for word fluency, fluid IQ (block design) and processing speed. These changes are significant in subjects 65-80 years old and noted in 55- 60-year-old subjects (Gorbach, Pudas, et al., 2016).

  At select sites, MRI will be used to assess global cerebral blood flow and white matter hyperintensities (WMH) at initial screening, 24 weeks, and 12 months. WMH reflects cerebral hypoperfusion and small vessel disease and is a covariate for vascular disease. WMH lesions are tied to disease progression and decreased cerebral blood flow.

  At select sites, Doppler ultrasound will be performed to assess Pulse Wave velocity, flow mediated dilation, endothelial function, and arterial stiffness. KU uses the Moor imaging product to monitor deep tissue oxygenation including SO_2, deoxygenated hemoglobin, and oxygenated hemoglobin.

  Central reading of all MRI images will be performed at MGH, based on an imaging protocol which will be provided as a separate document. They propose the use of a Siemens Skyra as the platform for imaging to ensure reproducibility and comparability and have developed an automated protocol to ensure standardization across sites. If other platforms are used, MGH will adapt the protocol for their use. It is imperative that, at the very least, the subject's imaging will be performed on the same machine.

- **Eligibility Checks and Cognitive Assessments –** Cognitive assessments should be performed as early in the day as possible (before 3:00 PM) and at approximately the same time every assessment. The vADAS-Cog will always be the first assessment performed. Assessments can be performed on the same day as Renew™ NCP-5 treatment as long as they are performed after treatment is completed. If assessments are not performed on the same day as treatment, it is recommended that subjects come in the day following treatment for all assessment testing but no later than 2 days (48 hours) post last Renew™ NCP-5 treatment. Psychometricians/designees will be blinded to treatment.

    - **MMSE2 –** The MMSE2 is a brief assessment instrument used to assess cognitive function in geriatric patients. The MMSE2 is used to screen for cognitive impairment and as a measurement of cognitive change over time. It is described in detail in Section 2.

    - **Logical Memory Sub-test of the Wechsler Memory Scale –** is a standardized assessment of narrative episodic memory. A short story is orally presented and the subject is asked to recall the story verbatim (immediate recall). Both Logical Memory I and Memory II will be administered.

    - **MOCA –** The Montreal Cognitive Assessment is a widely used cognitive assessment for patients with Mild Cognitive Impairment due to Alzheimer's Disease or Mild Dementia of the Alzheimer's Type. It includes a memory recall test, visuospatial abilities, executive function, attention, concentration, working memory, naming and orientation to time and place.

    - **Cardiovascular Risk Assessment** (CVR) **–** is a tool to assess the subject's cardiovascular risk which will be used to stratify subjects at baseline into low/medium risk (< 20% 10 year risk) vs. high/very high risk (>≥20% 10 year risk).

    - **Hachinski Scale –** is a tool used to identify a likely vascular component once a dementia diagnosis has been established. Vascular changes more commonly coexist with Alzheimer's plaques. Scores reflect attention and executive function.

    - **vADAS-Cog –** The vADAS-Cog is made up of ADAS-Cog14 plus three additional tests: the symbol digit test (the number of correct responses in 90 s); the digit span backward test (the number of digits recalled backwards); and the verbal fluency test (animal category in one min). The ADAS-Cog is an instrument devised to assess the severity of cognitive impairment in patients with AD. The scale includes short neuropsychological tests in which the patient performs simple tasks such as word recall, word recognition, and constructional praxis. The cognitive section of the ADAS consists of II items, which assess

the following: language (aphasia), and motor skills (praxis). Rosen, Mohs, et al. (1984) evaluated the test-retest and interrater reliabilities of the individual scale items and the entire scale in patients with dementia of the Alzheimer's type. The ADAS was shown to be valid in the ability to detect patients with clinically diagnosed AD from matched non-demented controls. Because both of the above cognitive and non-cognitive parameters are assessed, the ADAS is a reliable instrument for use in psychopharmacologic trials involving patients with AD.

- **ADCS-CGIC –** assesses clinic global impression of change over time by patient/caregivers and clinicians as indicators of meaningful change and reflects observable changes. Subject should have a caregiver, study partner or companion (which can be a domestic party) and may conduct the assessment over the phone if they do not accompany the participant).

- **ADCS-ADL –** The ADCS-ADL is a set of informant-based items describing performance of activities of daily living assesses the subjects ability to eat, walk, bathe, groom, dress, and other activities of daily living independently by patients with AD. Questions are asked of the caregiver and are given in the form of an interview. Subject should have a caregiver, study partner or companion (which can be a domestic party) and may conduct the assessment over the phone if they do not accompany the participant).

- **Trail Making TEST A & B –** Neuropsychological test of visual attention and task switching that assesses visual search speed, scanning, speed of processing, mental flexibility, and executive functioning. It is the most commonly used test in clinical practice to evaluate patients for MCI or mild AD.

- **2011 NIA-AA criteria –** In 2011, the National Institute on Aging (NIA) at National Institutes of Health (NIH) and the Alzheimer's Association published revised guidelines (NIA-AA) for modernization of the diagnosis of Alzheimer's disease. In these guidelines, the workgroups identified Alzheimer's disease as a continuum with three distinct stages: Preclinical, Mild Cognitive Impairment and Dementia. Checklists to assist in standardizing assessments across sites used to differentiate MCI and dementia will be implemented in this study.

- **Neuropsychiatric Inventory** (NPI) **–** A behavioral assessment used to assess dementia-related behavioral problems. The NPI is administered to caregivers of dementia patients. Screening questions are used to assess sub-domains of behavioral functioning such as, but not limited to, agitation/aggression, dysphoria, anxiety, irritability/lability, and appetite and eating abnormalities. Positive responses to these screening questions identify problems in the

associated sub-domain. The caregiver is then asked to rate frequency, severity, and distress of symptoms in the related sub-domain. Higher scores are correlated to patients with dementia.

8.2 Laboratory Evaluations

- **Comprehensive Metabolic Panel (CMP) –** Blood test to assess levels of electrolytes, how well the kidneys and liver are working, and blood glucose. Includes 14 blood tests that provide information about the current health status of the patient. Performed at baseline to assess whether the subject is healthy enough to participate in the study. Performed at intervals during the study to confirm no change in subject's health. Vitamin B12 and TSH will also be assessed.

- **ApoE –** Polymorphism of the apolipoprotein (ApoE) gene and its effect in modulating hippocampal change will be assessed.

- **Lipid Panel –** Provide a profile of cholesterol, HDL, LDL, and triglycerides to assess cardiac risk and general health of the subject

- **Complete blood count (CBC) –** Gives information about the cells in a patient's blood, including hemoglobin, hematocrit, and white blood cells to assess patient's general health.

- **C-reactive protein (CRP) and Lp-PLA2 and MPOS –** Blood markers for inflammation in the body. These inflammatory markers are implicated in the pathogenesis of AD and VD. CRP is a strong marker of vascular disease in early stages of the disease.

- **Blood viscosity –** AD patients have significantly increased whole blood viscosity which is correlated with disease severity.

8.3 Study Schedule

Table 1: Renew™ NCP-5 Treatment Schedule

Treatment Schedule	
Renew™ NCP-5 initial treatment visits	3-5 treatments per week to 35 treatments
Renew™ NCP-5 maintenance treatments	2 treatments per week as maintenance up to week 24

Table 2: Renew™ NCP-5 Visit Schedule

Evaluation/ Procedure	Screening	Baseline	Randomization / T1	Weeks 1-6	Week 6 Assessment	Weeks 7-12	Week 12 Assessment	Weeks 13-18	Week 18 Assessment	Week 19-24	Week 24 Assessment	9 Month Assessment	12 Month / Early Termination
Procedure Window by Study Day or Treatment Day	**Day -35 to Day -7**	**Day -14 to Day -1**	**Day 1**		**Day 42 (+/- 2 Days)**		**Day 84 (+/- 2 Days)**		**Day 126 (+/- 2 Days)**		**Day 168 (+/- 2 Days)**	**Day 252 (+/- 7 Days)**	**Day 365 (+/- 7 Days)**
Informed Consent	X												
MOCA	X										X	X	X
Demographics	X												
Medical, Treatment & Procedure History	X											X*******	
Vitals**	X	X	X	X	X	X	X	X	X	X	X	X	X
EKG	X												
Labs	X						X				X		X
Physical Exam (including Neuro)	X												X
Hachinski Scale Assessment		X									X	X	X
2011 NIA Checklist Administration (MCI or AD checklist to be administered)	X												
CVR Calculation		X											
Exercise Regimen		X			X		X		X		X	X	X
TUG Test		X			X		X		X		X	X	X

Evaluation/ Procedure	Screening	Baseline	Randomization / T1	Weeks 1-6	Week 6 Assessment	Weeks 7-12	Week 12 Assessment	Weeks 13-18	Week 18 Assessment	Week 19-24	Week 24 Assessment	9 Month Assessment	12 Month / Early Termination
Procedure Window by Study Day or Treatment Day	**(Day -35 to Day -7)**	**Day -14 to Day -1**	**Day 1**		**Day 42 (+/- 2 Days)**		**Day 84 (+/- 2 Days)**		**Day 126 (+/- 2 Days)**		**Day 168 (+/- 2 Days)**	**Day 252 (+/- 7 Days)**	**Day 365 (+/- 7 Days)**
Functional Reach Test		X			X		X		X		X	X	X
Patient Questionnaire		X			X		X		X		X	X	X
vADAS-Cog****		X			X		X		X		X	X	X
ADCS-CGIC****		X			X		X		X		X	X	X
ADCS-ADL****		X			X		X		X		X	X	X
Trail Making Test A & B ****		X			X		X		X		X	X	X
Logical Memory I & II****	X										X	X	X
MMSE2	X										X	X	X
NPI		X			X		X		X		X	X	X
Health Resource Utilization Survey (RUI)		X					X				X	X	X
Patient Satisfaction Survey													X
Inclusion and Exclusion Eligibility Checks	X	X	X										
Randomization			X										
NCP-5 Treatment			X	X		X		X		X			
MRI (including hippocampal volume)***	X										X*****		X******
Ultrasound/MOOR deep tissue oxygenation***			X								X		
AE		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Con-Treatments	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Disposition													X

*Day 1 = first treatment day. All visit windows are based on the 1st treatment date

**Vitals are pre & post treatment except for screening and Month 12/ET

***The initial MRI will be performed after the participant meets the initial screening criteria. Only designated sites will perform MRI to assess regional CBF, regional brain volume, resting state connectivity and/or Ultrasound to assess Flow Mediated dilation, pulse wave velocity, AI, Transcranial Doppler, Cerebral artery blood flow, Moor deep tissue oxygenation.

********vADAS-Cog assessment **MUST** be the first cognitive test administered, and all cognitive assessments **MUST** be completed before labs and imaging. Cognitive tests can be administered on the same day as treatment visit but must be done before 3:00 PM and **after** treatment is completed.

***** MRI must be done after last treatment but may take place on or before the Week 24 assessment visit

******MRI must be completed within 14 Days prior to the Month 12 Visit

*******If not collected at screening visit

8.4 Study Visits

8.4.1 Screening (-35 to -7 days prior to baseline)

Screening assessments ascertain whether the patient is eligible to participate in the study. Assessments that require the least imposition on the patient and the staff will be performed first to exclude patients before they are subjected to more demanding assessments. As necessary, screening may be performed on multiple visits. The MRI will be performed after the screening inclusion/exclusion criteria have been met. Assessments will be performed in the order noted on the time and events schedule:

- Obtain informed consent verified by signature on written informed consent
- Administer the MOCA
- Review demographics, medical/treatment history to determine eligibility based on inclusion/exclusion criteria
- Concomitant Medications and Treatments
- Perform vital sign check and EKG
- Draw blood for:
    - ApoE
    - Blood CBC, CMP, lipid panel, fibrinogen, CRP, LP-PLA2, MPOS, lipoprotein particles, Blood viscosity, B12, TSH
- Perform physical (including neurological) examination to determine eligibility based on inclusion/exclusion criteria
- Completion of “core clinical criteria” checklist(s) for the 2011 National Institute on Aging (NIA)-Alzheimer’s Association (AA) Guidelines on: (i) The diagnosis of dementia due to Alzheimer’s disease or (ii) The diagnosis of mild cognitive impairment due to Alzheimer’s disease
- Complete the Logical Memory I & II
- Administer the MMSE2
- Review inclusion/exclusion screening eligibility
- Perform MRI to rule out brain pathology, measure hippocampal volume and to assess exploratory endpoints (selected sites only). Brain pathology will include tumors, current or past bleeding, current or past aneurysms. The MRI should be done after the subject has been determined eligible to participate in the study. Initial screening MRI scan can be utilized if $\leq$ 90 days for subjects being re-screened.

8.4.2 Baseline Visit (Day -14 – Day -1)

- Vital Signs
- Administer Hachinski
- CVR calculation
- Review exercise regimen
- Patient questionnaire
- Administer baseline cognitive assessments including:

- vADAS-Cog (must always be administered first and before 3:00 PM)
- ADCS-CGIC for clinician and patient/caregiver
- ADCS-ADL
- Trail Making A&B

- TUG Test
- Functional Reach Test
- Health Resource Utilization Survey - RUI
- NPI
- Review concomitant medication and treatments
- Collect adverse events
- Schedule study visits for eligible subjects
- Verify inclusion/exclusion criteria

8.4.3 Randomization/First Treatment Day (Day 1)

Randomization must occur after eligibility confirmation and prior to first treatment. The following assessments should be performed during this visit:

- Verify inclusion/exclusion criteria
- Randomize subject
- Review concomitant medications and treatments
- Collect adverse events
- Record vital signs (Pre & Post)
- Administer treatment (All treatment subjects will have an initial four treatments (which are part of the planned 35 treatments) in which the PSI will be gradually increased to maximum tolerability with the goal of reaching 3-6 PSI by the fifth treatment).

For sites collecting data for exploratory endpoints, complete the following assessments:

- Ultrasound: Transcranial Doppler; cerebral artery blood flow
- Moor deep tissue oxygenation (selected sites only)

8.4.4 Weeks 1-6

- Record vital signs (Pre & Post)
- Review concomitant medications and treatments
- Collect adverse events
- During the treatment phase, administer treatments 5 days per week but at a minimum 3 days per week up to a maximum of 35 treatments total. (All treatment subjects will have an initial four treatments (which are part of the planned 35 treatments) in which the PSI will be gradually increased to maximum tolerability with the goal of reaching 3-6 PSI by the fifth treatment).

8.4.5 Week 6 – Day 42 (+/- 2 days)

- Cognitive assessments: It is recommended that subjects come in the day following treatment for all assessment testing but no later than 2 days (48 hours) post last treatment. Administer cognitive assessments including:
    - vADAS-Cog (must be administered first and before 3:00 PM; should be administered at the same time of day)
    - ADCS-CGIC
    - ADCS-ADL
    - Trail Making A & B
- Record vital signs (If non-treatment day)
- TUG Test
- Functional Reach Test
- NPI
- Exercise regimen
- Patient Questionnaire
- Review concomitant medications and treatments,
- Collect adverse events
- If treatment occurs on same day as assessments complete the treatment first
    - Vitals (Pre & Post)
    - During the treatment phase, administer treatments 5 days per week but at a minimum 3 days per week up to a maximum of 35 treatments total

8.4.6 Weeks 7-12

- Record vital signs (Pre & Post)
- Review concomitant medications and treatments
- Collect adverse events
- During the treatment phase, administer treatments 5 days per week but at a minimum 3 days per week up to a maximum of 35 treatments total (or during maintenance, administer two treatments per week separated by at least 2 days up to 24 weeks)

8.4.7 Week 12 – Day 84 (+/- 2 days)

- Cognitive assessments: It is recommended that subjects come in the day following treatment for all assessment testing but no later than 2 days (48 hours) post last treatment. Administer cognitive assessments including:
    - vADAS-Cog (must be administered first and before 3:00 PM; should be administered at the same time of day)
    - ADCS-CGIC
    - ADCS-ADL

  - Trail Making A & B
- Record vital signs (If non-treatment day)
- TUG Test
- Functional Reach Test
- Health Resource Utilization Survey - RUI
- NPI
- Exercise regimen
- Patient Questionnaire
- Review concomitant medications and treatments,
- Collect adverse events
- If treatment occurs on same day as assessments administer treatment first
  - Vitals (Pre & Post)
  - During the treatment phase, administer treatments 5 days per week but at a minimum 3 days per week up to a maximum of 35 treatments total (or during maintenance, administer two treatments per week separated by at least 2 days up to 24 weeks)
- Draw blood for:
  - Blood lipid panel, CBC, fibrinogen, CRP, LP-PLA2, MPO, lipoprotein particles to include: LDL-P, Lp(a)-P, VLDL-P, IDL-P, ApoB, B12, TSH
  - Blood viscosity

8.4.8 Weeks 13-18

- Record vital signs (Pre & Post)
- Review concomitant medications and treatments
- Collect adverse events
- Administer two treatments per week separated by at least 2 days as maintenance up to 24 weeks

8.4.9 Week 18 – Day 126 (+/- 2 days)

- Cognitive assessments: It is recommended that subjects come in the day following treatment for all assessment testing but no later than 2 days (48 hours) post last treatment. Administer cognitive assessments including:
  - vADAS-Cog (must be administered first and before 3:00 PM; should be administered at the same time of day)
  - ADCS-CGIC
  - ADCS-ADL
  - Trail Making A & B
- Record vital signs (If non-treatment day)
- TUG Test

- Functional Reach Test
- NPI
- Exercise regimen
- Patient Questionnaire
- Review concomitant medications and treatments
- Collect adverse events
- If treatment occurs on same day as assessments administer the treatment first
    - Vitals (Pre & Post)
    - Administer two treatments per week separated by at least 2 days as maintenance up to 24 weeks

8.4.10 Weeks 19-24

- Record vital signs (Pre & Post)
- Review concomitant medications and treatments
- Collect adverse events
- Administer two treatments per week separated by at least 2 days as maintenance up to 24 weeks

8.4.11 Week 24 – Day 168 (+/- 2 days)

- Cognitive assessments: It is recommended that subjects come in the day following treatment for all assessment testing but no later than 2 days (48 hours) post last treatment. Administer cognitive assessments including:
    - vADAS-Cog (must be administered first and before 3:00 PM; should be administered at the same time of day)
    - ADCS-CGIC
    - ADCS-ADL
    - Trail Making A & B
    - Logical Memory I & II
- MOCA
- Vital signs (If non-treatment day)
- Hachinski
- MMSE2
- TUG Test
- Functional Reach Test
- Health Resource Utilization Survey - RUI
- NPI
- Exercise regimen
- Patient questionnaire

- Review concomitant medications and treatments
- Collect adverse events
- If treatment occurs on same day as assessments administer the treatment first
    - Vitals (Pre & Post)
    - Administer two treatments per week separated by at least 2 days as maintenance up to 24 weeks
- Draw blood for:
    - Blood lipid panel, CBC, fibrinogen, CRP, LP-PLA2, MPO, lipoprotein particles to include: LDL-P, Lp(a)-P, VLDL-P, IDL-P, ApoB, B12, TSH
    - Blood viscosity
- MRI (Must be done after last treatment but may take place on or before the Week 24 Assessment Visit)

For sites collecting data for exploratory endpoints, complete the following assessments:

- Ultrasound: Transcranial Doppler; cerebral artery blood flow
- Moor deep tissue oxygenation

8.4.12 Month 9 (Week 36) – Day 252 (+/- 7 days)

- Administer cognitive assessments including:
    - vADAS-Cog (must be administered first and before 3:00 PM; should be administered at the same time of day)
    - ADCS-CGIC
    - ADCS-ADL
    - Trail Making A & B
    - Logical Memory I & II
- MOCA
- Record vital signs
- TUG Test
- Hachinski
- Functional Reach Test
- Health Resource Utilization Survey-RUI
- NPI
- Exercise regimen
- Patient Questionnaire
- Medical History, if not collected at screening visit
- Review concomitant medications and treatments
- Collect adverse events

8.4.13 Month 12/Study Termination – Day 365 (+/- 7 days)

- Administer cognitive assessments including:
  - vADAS-Cog (must be administered first and before 3:00 PM; should be administered at the same time of day)
  - ADCS-CGIC
  - ADCS-ADL
  - Trail Making A & B
  - Logical Memory I & II
- MOCA
- Vital signs
- Physical Exam including neuro
- Hachinski
- TUG Test
- Functional Reach Test
- Health Resource Utilization Survey - RUI
- NPI
- Exercise regimen
- Patient Questionnaire
- Patient Satisfaction Survey
- MMSE2
- Review concomitant meds and treatments
- Collect adverse events
- Draw blood for:
  - Blood lipid panel, CBC, fibrinogen, CRP, LP-PLA2, MPO, lipoprotein particles to include: LDL-P, Lp(a)-P, VLDL-P, IDL-P, ApoB, B12, TSH
  - Blood viscosity
- MRI (Must be completed within 14 Days prior to the Month 12 Visit)
- Complete Study Disposition Form

8.4.14 Early Termination Visit

All procedures scheduled for the 12 month/final visit should be performed in the event of an early termination visit. The subject should be encouraged to complete these assessments.

8.4.15 Study Disposition

Subjects will be discharged from the study to their pre-study routine. Ideally, subjects will continue in the study to complete the assessments and the 12 month visit. All subjects in the active sham arm will be eligible to participate in an active treatment follow up study after completion of the 12 month visit.

8.5 ONGOING ASSESSMENTS

8.5.1 Concomitant Medications, Treatments and Exercise

Subjects will be expected to be on stable medication for 30 days prior to study start and through the first 24 weeks of the study for chronic conditions. Changes in concomitant medications will be recorded. Treatment for adverse events will be recorded. The current use of medication that in the investigator's judgement are incompatible with study goals will be prohibited and may result in the subject's withdrawal from the study. Subjects should not begin any other treatments that, in the investigator's judgement may affect cerebral blood flow.

Subjects will be requested to maintain their pre study exercise regimen throughout the first 24 weeks of the study. Exercise level will be assessed at baseline, 6, 12, 18, and 24 weeks, 9 months and 12 months.

8.5.2 Laboratory Evaluations

Laboratory evaluations will occur at all the time points specified in the time and events schedule. The laboratory evaluations that will be performed are listed in **Figure 2**.

Blood Chemistry		
Sodium AST ALT Total cholesterol Triglycerides Total protein	Potassium Glucose Creatinine Serum calcium Chloride Bicarbonate	Blood urea nitrogen Total bilirubin Albumin Globulin B12 TSH
Hematology		
Hemoglobin Hematocrit Platelets	White blood cell count total and differential Red blood cell count	
Exploratory Labs		
ApoE Fibrinogen Lipid panel	CRP LP-PLA2 MPOS	Blood viscosity

Figure 2: Laboratory evaluations to be performed

Abnormal laboratory test results of a magnitude deemed clinically significant by the investigator will be repeated as soon as possible (preferably within 48 hours) to rule out laboratory error. For tests where there is a persistent abnormality, repeat analyses shall be performed until the cause is determined and return to baseline occurs or the investigator deems the abnormality to be of no clinical significance. If these values are deemed clinically significant then these tests should be discussed with the medical monitor. If these abnormalities are accompanied by clinical symptoms, then these should be captured as AEs.

A central laboratory will be used in this study. All details regarding the collection, shipment of samples, reporting of results and alerting extreme values will be provided by the central laboratory and compiled in a Laboratory Manual.

8.5.3 Vital signs

The following vital signs assessments should be performed at Screening, Baseline, and at all visits (including early discontinuation):

- Height- at screening visit only
- Weight
- Body temperature
- Respiratory rate
- Heart rate
- Blood pressure (sitting after 5 minutes on assessment visits, Supine after five minutes on treatment visits).

8.5.4 Physical examination

Information collected during the physical examination will be recorded in the source documentation and subsequently on the Case Report Forms (CRF).

8.5.5 Electrocardiogram

A 12-lead EKG will be performed and documented in the patient's medical chart at screening to ensure the patients does not have any contraindications for participation in the study. The investigator will review the ECG for eligibility criteria and sign/date the ECG report.

9. SAFETY ASSESSMENTS

Safety will be monitored throughout the trial as follows: monitoring and recording of anticipated adverse effects, unanticipated adverse effects (UAEs), serious adverse effects, unanticipated adverse device effects (UADEs), the assessment of laboratory parameters, and vital sign measurements.

9.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence experienced by a subject in conjunction with their participation in a clinical trial regardless of whether the event is related to the procedure or study device. An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational device whether or not it is related to the investigational device. This includes any condition that is new in onset (not present prior to study treatment) or aggravated in severity or frequency from the baseline condition, any condition resulting from concurrent illness,

reactions to concomitant medications, progression of disease states, and also includes abnormal lab test results if associated with clinical signs or symptoms judged by the investigator to be clinically significant.

All AEs that occur after the consent form is signed must be reported in the AE section of the CRF. Documentation for all AEs should contain the Adverse Event (medical condition), the date the AE started and if applicable, the stop date; the preliminary assessment of the relationship to study treatment; any action taken with regard to study treatment; the outcome of the event; whether the event was serious and if so, whether the event was anticipated or unanticipated; and whether treatment was required.

For purposes of this study, a Serious Adverse Event (SAE) is defined in accordance with ISO 14155-2011(en), Clinical Investigation of Medical Devices, as an adverse event that, in the view of the Investigator or the sponsor:

- Led to death
- Led to serious deterioration in the health of the subject that resulted in:
    i. Inpatient hospitalization or prolong hospitalizations
    ii. Life threatening illness or injury
    iii. Permanent impairment of a body structure or a body function
    iv. Medical/Surgical intervention to prevent one of the outcomes listed in line ii. or iii. above

The sponsor is using the above ISO-14155-2011(en) definition of a SAE as an extra safety precaution in this study since no definition of "serious adverse effect" exists in Federal regulations governing medical device clinical trials, 21 CFR Part 812, Investigational Device Exemptions.

An unanticipated adverse device effect (UADE) is defined, in 21 CFR Part 812.3(s) as any serious ["serious" as defined above and in ISO14155-2011(en)] adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the protocol or investigational plan (e.g., Investigators Brochure, Product Labeling, Informed Consent Document etc.) or any other serious problem associated with a device that relates to the rights, safety or welfare of the subject. Unanticipated adverse device effects will be collected in an ongoing fashion during the study and will be entered into a separate safety database.

All adverse events that do not meet any of the criteria for SAEs or UADEs should be regarded as non-serious adverse events and/or an anticipated AE and will be documented, and subsequently reported, at least annually to the IRB and Sponsor.

Progression of disease reflects lack of therapeutic efficacy and should not be treated as serious adverse events. However, other events or complications meeting the criteria for serious adverse events should be considered as a serious adverse event and should be reported to the IRB regardless of presumed relationship to the investigational treatment.

All subjects who have been exposed to study treatment will be evaluated for adverse effects. All adverse effects will be evaluated beginning with onset, and evaluation will continue until resolution or recovery is observed or until the Investigator determines that the participant's condition is stable, whichever is earlier. The Investigator will take all appropriate and necessary therapeutic measures required for resolution of the adverse effect. Any medication necessary for the treatment of an adverse effect must be recorded on the study Concomitant Medication form. If more than one distinct adverse effect occurs, each event will be recorded separately.

9.2 Adverse Event Assessment

All adverse events (AE), observed or reported, will be initially assessed by the Investigator or his/her medically qualified designee, and recorded on the study Adverse Effect Form according to the protocol and the Manual of Procedures. The need to capture AEs is not dependent upon whether or not the clinical event is associated with the use of the study treatment.

Severity will be assessed using the following definitions:

- Mild: Aware of sign or symptom, but easily tolerated
- Moderate: Discomfort sufficient to cause interference with usual activity
- Severe: Incapacitating, with inability to work or do usual activity

The relationship to Investigational Treatment will be assessed by the Investigator using the following criteria:

- Not Related: Evidence exists that the adverse event definitely has a cause other than the study treatment (e.g. pre-existing condition or underlying disease, intercurrent illness, or concomitant medication) and does not meet any other criteria listed.

- Suspected: There is a reasonable possibility that the treatment caused the adverse event. "Reasonable possibility" means there is evidence to suggest a causal relationship between the treatment and the adverse event. A causal relationship requires a temporal relationship to exist between the adverse event onset and administration of study treatment.

- Probably Related — Strong evidence exists that the study treatment caused the adverse event. There is a temporal relationship between the event onset and administration of the study treatment. There is strong therapeutic evidence that the event was caused by the study treatment. The participant's clinical state and concomitant therapies have been ruled out as a cause.

All subjects who have been exposed to study treatment will be evaluated for adverse effects. All adverse effects will be evaluated beginning with onset, and evaluation will continue until resolution or recovery is observed or until the Investigator determines that the participant's condition is stable, whichever is earlier. The Investigator will take all appropriate and necessary therapeutic measures required for resolution of the adverse effect. Any medication necessary for the treatment of an adverse effect must be recorded on the study Concomitant Medication form. If more than one distinct adverse effect occurs, each event will be recorded separately.

9.3 Adverse Event Reporting

9.3.1 Adverse Event Reporting

The study period during which adverse events must be reported is defined as the period from signing informed consent to the end of the study treatment follow-up (Month 12). If an adverse event is unresolved by the day of the 12-month data collection visit, and it is possible to follow the participant thereafter, this will be attempted for 30 days after the participant's last study treatment.

9.3.2 Reporting of Unanticipated (Serious) Adverse Device Effects, Serious Adverse Events, or Device Deficiencies

Device Deficiency (DD) is the inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance with or without patient involvement. This may include malfunctions, misuse or use error, or inadequacy in the information supplied by the manufacturer.

All DDs, Serious Adverse Events (SAE), whether Anticipated or Unanticipated, which occur during the study, including death, must be reported in writing within 3 working days of the site becoming aware of the event.

The local site Investigator must provide information on the SAE in a written narrative form, with as much information as possible. This should include a copy of the completed study Serious Adverse Effect form, and any other diagnostic information that will assist the understanding of the event. In the case of hospitalization, the de-identified admission report and if possible, the discharge summary should be obtained and submitted to the pharmacovigilance team (MVS and KAI) via email. Significant new information on ongoing serious adverse events should be provided promptly.

9.4 Emergency procedure for unblinding

For this study, the subject and the psychometrician/designee will be blinded. Neither the Renew™ NCP-5 operator nor the PI will be blinded. The psychometrician/designee administering all cognitive tests should be blinded. There does not seem to be any reason that the subject or psychometrician will be unblinded in the event of a serious adverse event. Only the investigator, who is unblinded, will need to assess what intervention the subject may need or whether the subject can continue in the study.

9.5 Instructions for completing adverse effect case report forms

Each AE is to be reported on the AE CRF provided. Refer to the CRF or to the CRF Completion Guidelines for details.

10. ADMINISTRATIVE PROCEDURES

10.1 Changes to the protocol

Any change to this protocol will be made by means of a protocol amendment approved by Renew Research, LLC. Any changes that affect patient safety or welfare must be submitted to the relevant IRB for approval before implementation.

If the investigator believes an immediate change to the protocol is necessary for safety reasons and the change is implemented by him/her, Renew Research, LLC should be notified immediately and the IRB should be informed within 10 working days.

10.2 Monitoring procedures

During the course of the study, remote and onsite monitoring may be used to obtain a reasonable assurance of data quality and proper study implementation. If the study monitor visits the clinical sites, they may review any or all relevant study records for completeness, protocol adherence, and compliance to investigational device Good Clinical Practice (GCP). The study monitor may also review CRF data against the source documents at the study sites. Therefore, the study monitor must be granted access to relevant clinic and hospital records in order to review consistency with the CRF.

All monitoring will be linked to a signal-based process using critical data points and other pertinent factors. Instances of missing or uninterpretable data may be discussed with the Investigator or site staff for resolution.

11. STATISTICAL CONSIDERATIONS

A separate **Adaptive Design Report (ADR), presented in Appendix A1** details the primary outcome analysis and procedures. The ADR contains the plan for sample size consideration and the features of

the study design. The adaptive statistical analyses will be performed using commercial software acceptable to FDA. They describe how the primary outcome measure will be evaluated during interim analyses, which will begin when 100 patients have been randomized. Subsequent interim analyses are scheduled after every additional 25 subjects are randomized. In total, there are 7 analyses possible, which includes 6 interim analyses and the final analysis at 250 subjects, unless the study is stopped for success or futility before that.

Appendix A2 consists of the Adaptive Design report for the secondary outcome analysis of the ADL and ADAS-Cog14. As outlined above, a key secondary endpoint for this study is the change from baseline in the ADCS-ADL, also averaged across measurements taken at 12, 18, and 24 weeks after randomization. The purpose of this document is to pre-specify the Bayesian analysis of this endpoint.

Appendix B outlines **the Statistical Analysis Plan (SAP),** including the plans for analysis of the remaining secondary and exploratory endpoints selected for the study.

12. DOCUMENT RETENTION

The investigator must maintain source documents for each patient in the study. Source documents will include demographic and all medical information, including laboratory data, ECGs, and physical examinations. The investigator must also retain the original signed informed consent form for each patient.

The following documents related to the study must be retained by the investigator for as long as needed to comply with national and international regulations after discontinuing clinical development or after the last marketing approval: all source documents and laboratory records; CRF copies; patient informed consent forms; IRB approvals for the study protocol, informed consent forms, and all amendments; Investigator's Agreement; any other relevant study documentation.

Renew Research, LLC will notify the investigator(s) when the study-related records are no longer required. The investigator's signature on the protocol constitutes his/her agreement with these document retention procedures.

13. DATA FLOW

See **Figure 3**, below, for a summary diagram of data flow in this trial.

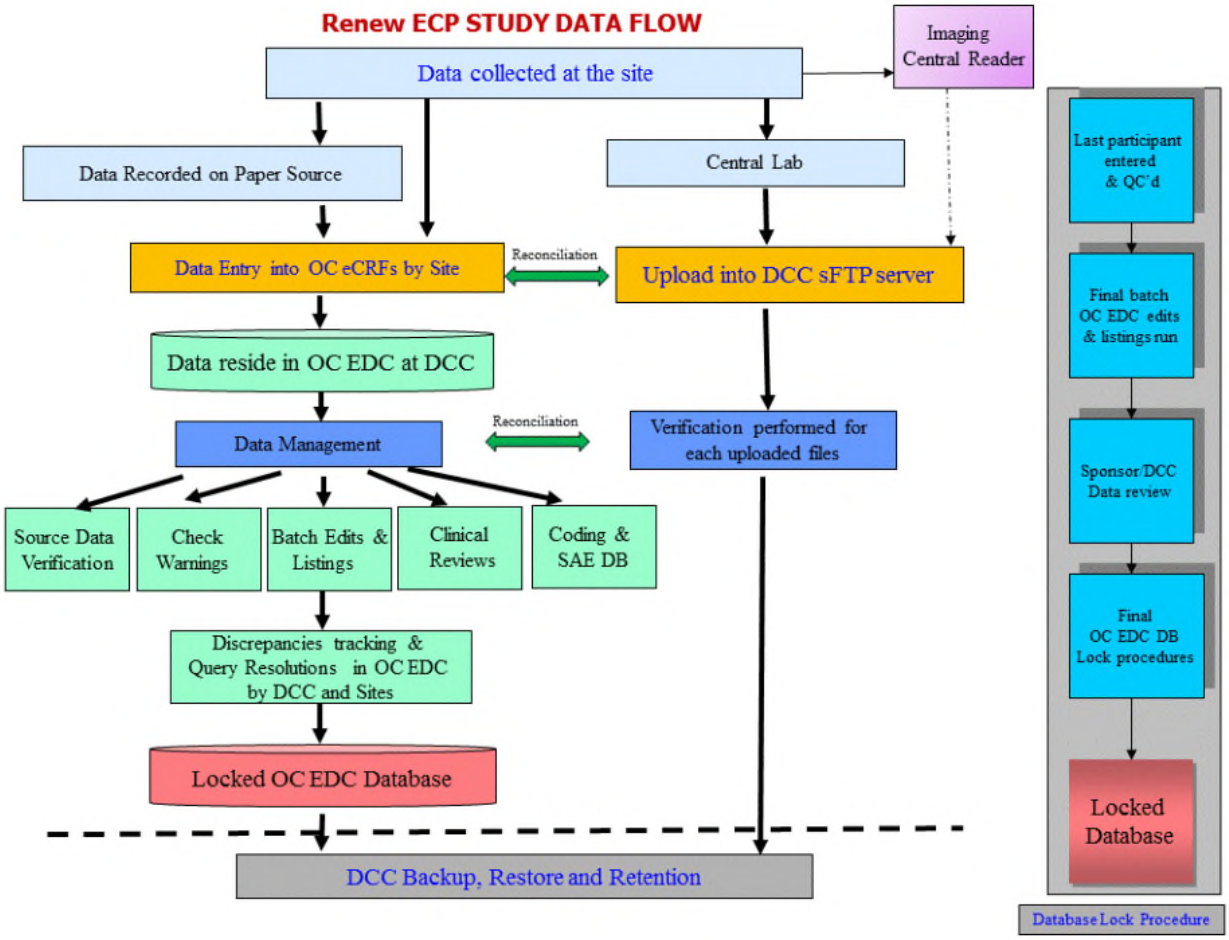

Figure 3: Renew™ NCP-5 - 1001 Data Flow

13.1 Source Data, Record Keeping, Handling, and Retention at the Sites

The source data for this study includes data collected at the site based on the protocol defined standardized assessments and CRFs, as well as electronic data for central labs and imaging. The investigators and authorized, trained site staff will maintain appropriate data to ensure adherence to the protocol, regulations, Manual of Procedures (MoP), and any other policies. Subjects at the site will be assigned a unique Participant ID that will be used to anonymize the subjects in the source data, record files and the commercial EDC System OpenClinica Enterprise™©(OC EDC) throughout the study. A clinical site master list with participant names, contact information, and study identifiers will be stored locally at each of the sites for that site only.

Site study staff may enter data obtained at the study visit directly into the eCRFs of the OC EDC system. For these data elements, the eCRF is the source. This direct entry of data can eliminate errors by not

using a paper transcription step before entry into the eCRF. In the event that immediate access to the OC EDC is not available or if the site prefers to record data on paper source, data recorded on paper source will be used and then will be transcribed into the eCRFs (see **Figure 3**). Authorized, uniquely credentialed study personnel will be given secure access to the OC EDC system to review data as necessary for proper decision-making, data management and signoffs.

The paper source data and records will be housed by the clinical site investigators as required by FDA IDE regulations 21 CFR 812.140. The investigators will be responsible for completeness and accuracy of documented data and records at their site to support study protocol adherence, review and audit. Enforcement will be carried out by regular internal audits and routine monitoring visits to verify that all processes are followed and required documentation is created and collected.

It is each clinical site Investigator's responsibility, by FDA regulation (21 CFR §812.140(d)), to retain essential study documents for at least two years after the study is completed. Study completion is defined as a time following final database closure and is to be determined by agreement between the Data Coordinating Center (DCC) and Renew.

13.2 Data Transmission, Data Handling, Storage, Retention and Archiving at DCC

Data transmission starts with the site study team review of the participant source documents, if used, to ensure data is accurate and complete. Site staff will enter data into the OC EDC (described in **Figure 3**). The lab electronic files will be uploaded by the central lab study team, with the proper user name and password assigned to each team member, to the sFTP server hosted at the DCC.

OpenClinica (OC) Enterprise™© EDC System

Data collected during a study visit will be directly entered onto eCRFs using OC EDC system. As a backup procedure, data recorded on the paper source by the site study staff will be transcribed by the site study staff onto eCRFs utilizing OC EDC for Web-based remote data entry and storage. OC EDC has a secure, robust and scalable technology infrastructure developed using the Java J2EE framework and relies on commercial database servers. It is validated according to 21 CFR 11, and is also CDISC compliant. OC EDC is an enhanced, fully validated build that is ideal for mission-critical settings. Study users will access OC EDC with password protection. In the OC EDC, Study Subjects will be identified only by the unique Participant ID assigned to them. OC EDC will not include personal identifiers, as required by HIPAA.

The OC EDC system offers modules to help the study team continuously review and monitor the data over the course of the clinical trial. When Investigator signoffs cannot be accomplished on source paper documents, Investigator signoffs will be executed electronically.

The Source Data Verification (SDV) feature helps study monitors track their evaluations to assess if the study data are complete, accurate, and verifiable. Rules for edit checks, logic errors and form navigation

are centered on key data fields such as dates, quantitative measures and other critical fields that can be corrected in real-time as data are entered. In addition, the DCC generated and Renew-approved queries can be entered and managed through the OC EDC Notes and Discrepancy module centrally. Data managers, monitors and site staff are able to manage data clarifications/queries regarding data entered into the EDC via the website. The embedded, real-time edits and queries result in time and cost efficiencies in data clean up and production of the final data sets. DCC will work with Renew to create and maintain user accounts for those who will require study EDC database access. The Manual of Procedures (MoP) and Data Management Plan (DMP) will outline data management activities and the details of data clarification and resolution.

After the last participant visit is entered, data is reviewed at DCC and/or by a Study Monitor, and eCRFs are set to complete, a final batch OCEDC system edit run will be done to ensure all queries and discrepancies have been addressed. Issues that cannot be resolved are described in a Memo To File and attached to any analyses. Renew and DCC will review data in tables and listings. The DCC will notify Renew that it considers the database ready for lock. An approval signature by Renew will be obtained prior to study database lock. The DCC will perform final database lock procedures per SOP. At the end of the study, all study data and materials requested by Renew will be sent, along with a packing document that identifies as specifically as possible, the contents of the shipment.

Secure File Transfer Protocol (sFTP) system

The DCC will set up a secure File Transfer Protocol (sFTP) system for data transmission for the study, provide the sites and central lab with access to upload data and files and other study components and resource centers with access to download data and files. Transmission specifications and schedules will be documented and approved by Renew. External data will be reviewed and reconciled to ensure file integrity, completeness, and correctness. The DCC team will document the data format, receipt process, and schedule for receipt in writing, and both the sites and DCC will sign off on this mutual Data Transmission Agreement. The process will be quality assured with test data prior to the first data transfer.

Secure sockets layer (SSL) certificates will be used to provide for encrypted and secure communications between the DCC, Sites, Central lab and other study components. This encryption minimizes the likelihood of interception or modification of data during transmission. DCC's network infrastructure (internal and external systems) is protected from the public Internet by various mechanisms including, but not limited to, firewalls (with restrictive policies in place), virtual private network (VPN) endpoints and software as well as antivirus and malware detection software. Certain aspects of the logs detailing action within the protection systems are collected and reviewed daily. For further protection against disaster or loss of data, all data will be backed up daily.

Anonymized site participant data will be received by the DCC through the sFTP. All original transmissions will be stored electronically in a secure server on the DCC network. Any problems identified during the upload and transmission process will be reported back to the sites for correction or clarification. The process for addressing data discrepancies with sites will be determined in coordination with other study components during study set-up. The data transmitted to and stored on DCC server will be automatically coded with the assigned participant identification number. No personal identifiers will be associated with these data.

Study Datasets
DCC will provide a SAS data set that integrates the final study data in the OCEDC system and the sFTP. The data set will conform to Renew specifications.

All records created by or received by DCC, will be retained for as long as they are required to meet the contractual, legal, regulatory, administrative, financial and operational requirements of DCC. The media used to transfer electronic files and study data will be discussed and documented in a study closeout plan that will be prepared as the study progresses. The necessary security measures will be taken for file/data security and integrity during preparation and transmission these files. A memo detailing the transfer of responsibility for study documentation will be prepared by the DCC and signed off by Renew prior to the shipment of material to Renew.

14. AUDITING PROCEDURES

In addition to routine monitoring, Renew Research, LLC or its designee may conduct audits of clinical research activities to assess regulatory compliance. A regulatory authority may also conduct an inspection. If a regulatory authority requests an inspection, the investigator must inform Renew Research, LLC immediately that this request has been made.

15. PUBLICATION OF RESULTS

As a multicenter study, the initial publications such as initial manuscripts, abstracts, and presentations reporting interim and final results for the study will be initiated per the prior agreed upon publication policy between Renew Research, LLC and the site's executed Clinical Trial Agreement. Manuscripts will be submitted to appropriate scientific journals, professional publications, and major medical meetings. All clinical sites and investigators contributing data to the study will be listed in an Appendix to the manuscript. Following release of the initial multicenter publication, investigators may prepare independent publications for publication review. Renew Research, LLC has the right to require any confidential information including chemical structures and chemical names to be excluded from publication.

15.1 Disclosure and Confidentiality

By signing the protocol, the investigator agrees to keep all information provided by Renew Research, LLC in strict confidence and to request similar confidentiality from his/her staff and the IRB. Study documents provided by Renew Research, LLC (protocols, investigators' brochures, CRFs, and other material) will be stored appropriately to ensure their confidentiality. The information provided by Renew Research, LLC to the investigator may not be disclosed to others without direct written authorization from Renew™ Research, LLC, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

16. DISCONTINUATION OF STUDY

Renew Research, LLC reserves the right to discontinue any study under the conditions specified in the clinical trial agreement.

17. ETHICS AND GOOD CLINICAL PRACTICE

For all sites located in the United States and its territories, this study must be carried out in compliance with the protocol and the principles of GCP, as described in: Title 21 Code of Federal Regulations (CFR) dealing with investigational device studies (including 21 CFR Parts 50 and 56 concerning informed consent and IRB regulations). For investigational sites located outside of the United States and its territories this study must be carried out in compliance with the protocol and the appropriate regulatory authority, such as ICH or MHRA; as well as any other International requirements or relevant mandates.

The investigator agrees when signing the protocol to adhere to the instructions and procedures described in it and thereby to adhere to the principles of GCP to which it conforms.

17.1 Institutional Review Board/Independent Ethics Committee

Before implementing this study, the protocol, the proposed informed consent form, other information provided to patients, and advertising must be reviewed by a properly constituted IRB. A signed and dated statement that the protocol and informed consent have been approved by the IRB must be given to Renew Research, LLC before study initiation. The name and occupation of the chairman and the members of the IRB must be supplied to Renew Research, LLC. Any amendments to the protocol, other than administrative ones, must be approved by this committee.

The investigator must explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail. Each patient must be informed that participation in the study

is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The patient should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the patient cannot read or sign the documents, oral presentation may be made or signature given by the patient's legally appointed representative, if witnessed by a person not involved in the study, mentioning that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained.

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APPENDIX A1: Adaptive Design Report (Primary Outcome)

APPENDIX A2: ADCS-ADL and ADAS-14 Secondary Outcome Analysis

APPENDIX B: Statistical Analysis Plan

APPENDIX C: Health Resource Utilization (HRU)

APPENDIX D: Investigator Brochure

This will be supplied as a separate attachment to sites.

APPENDIX E: Training Manual

This will be supplied as a separate attachment to sites.

APPENDIX F: Device Inspection Checklist

This will be supplied as a separate attachment to sites.