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(–)-Phenserine and Inhibiting Apoptosis: In Pursuit of a Novel Intervention for Alzheimer's Disease

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1. Introduction

The identification of a nucleus basalis of Meynert lesion in Alzheimer's disease (AD) brains in 1983 provided a target for drug development.¹ A series of cholinergic interventions that proved unable to arrest the disease led Zaven Kachaturian to call for a five-years delay in symptom expression or disease onset.² His goal was a broadly based public health approach to disease prevention and modification. This policy and the time-limited efficacy of cholinesterase inhibitors shifted over 200 subsequent drug developments to pursue a new

goal in AD, disease course modification. Unfortunately, to date, no drug intervention has proven successful evidencing clinically significant modifications in AD outcomes for patients. Because of reliabilities of measurements, cognitive symptoms have become the most commonly quantified symptoms associated with AD disease progression.³ An early study by Sano et al. pursued a different strategy using the onset of functional impairments to show statistically significant differences between Vitamin E and selegiline.⁴ This study confirmed preliminary findings that activities of daily living (ADL) in AD patients over two years of followup show up to one third of all patients losing f six out of seven ADL skills.⁵ The initially most impaired subjects experience the highest losses.

These data reflect commonsense impressions of the importance of different outcome factors for AD patients. Cognitive losses of abilities to remember names, dates, day of the week are clearly less impairing than inability to dress oneself, getting lost outside the home, leaving the stove burners on after being distracted, or inappropriately accusing neighbors of stealing. As a result, along with other modifications to methods of drug evaluation, we find a need to specifically define medicine's targeted disease modification in terms directly relevant for the wellbeing of AD patients as reflected by ADL.

In this paper, to inform our pending testing of (–)-phenersine tartrate ((–)-pheneserine), we address issues of AD clinical trial methods and mechanisms. In large part, we selected (–)-pheneserine for possible disease course moderation based on its preclinical ability to protect neurons from self-imposed preprogrammed cell death (apoptosis) evidenced in recent preclinical studies.⁶

2. Background

AD researchers have long sought to increase the reliability and relevance of AD clinical trials (CT) for clinicians.^{7–9} Similar to clinical trials that address other disease conditions, AD clinical trials provide only limited guidance to the clinician. For example, the implications of a clinical trial for an individual patient are uncertain, because the trial predicts only a number of patients on average who will need to be treated in order to provide the trial's benefits to one individual. Errors in methods have plagued AD drug developments, a problem highly prevalent in other areas of medical research and clinical practice.^{10, 11} Investigators publish but fail to replicate many studies.¹² AD clinical trials with primarily cognitive outcomes can have questionable relevance for the everyday wellbeing of patients. The potential for bias is widespread amongst academic, commercial, and not for profit interest groups.^{13, 14} As a result, with the aim of optimizing our clinical trial methods for testing possible neuroprotection against self-induced preprogrammed (apoptotic) neuronal cell death, we have identified seven issues that may have unnecessarily limited the validity of earlier AD research efforts and the information content of clinical trials for clinicians.

3. Methods

We searched PubMed/Medline and identified articles for background on the neuropathological progression of AD and its implications for drug target identification, for AD clinical trial criteria to assess disease modification outcomes, for plasma biomarkers

associated with AD neuropathologies and especially apoptosis, and for methodological critiques of AD CT methods. As a result we identified and addressed seven issues and, in response to these issues, reviewed the Thal-Sano AD Prevention Design^{4, 5} for possible applications in our proposed CT.

4. Results

1. When does the person become a patient with AD?

Up to three decades have been reported to separate first detectable amyloid accumulations in human brains at 45 years of age and younger from the onset of sporadic AD after age 65.¹⁵ In these intervening decades no clinical evidence of AD neuropathology appears until shortly before the onset of AD with mild cognitive impairment. Under these conditions investigational treatment is confounded by the lack of induced cognitive deficit to be remedied as evidence for a drug's clinical efficacy. This early neuropathology currently limits interventions against AD to diagnosed MCI and AD patients.¹⁶ Consequently any intervention against AD must be effective in the presence of possibly well-established and irreversibly active pathologies.

2. Disease prevention, arrest, or disease course modification?

A disease modification aim for AD potentially involves practical interplays amongst interventions able to prevent, arrest, and control AD pathologies. No intervention has slowed or arrested the natural progression of clinical AD. At present, exercise, mental activity, and diet have been proposed as possibly relevant. For example, recent prospective studies have associated higher adherence to a Mediterranean-type diet with slower cognitive decline, reduced risk of progression from MCI to AD, reduced risk of AD and a decreased all-cause mortality in AD patients.^{17, 18}

For the AD patient in their eighth decade with a mean life expectancy of five years, a five-year delay in experiencing disabilities from AD could provide a remaining life in which the disease progression has been effectively arrested. For the AD patient in their early seventh decade with a mean life expectancy of twenty years, a five-year delay in disabilities from AD would provide only a delay during which hopefully newly developed interventions would further put off the onset of disabilities. It may be the case that only time limited delays in disease progression will be possible for drug interventions with clinically diagnosable patients and that primary prevention will be required to delay clinical onset and render some drugs most useful. We expect that (–)-phenserine, should it effectively inhibit neuronal self-induced preprogrammed cell death, will do so only for a time limited period, and will delay, not prevent, deterioration into increased impairments and disabilities. Its or other drugs similarly successful would only intensify the search for primary preventive interventions.

3. Time to move beyond the Amyloid Hypothesis?

Investigators have increasingly emphasized a loss of utility for the “Amyloid Hypothesis”, which posits the accumulation of potentially toxic amyloid-beta peptide (A β) comprising short 40–43 amino acid (A β ₄₀, A β ₄₂). This loss reveals the lack of sufficiently deep

understanding of the basic mechanisms of AD that investigators have chosen to target in CTs. Peter Davies puts the matter bluntly: “We’re flogging a dead horse.”¹⁹ “There’s no sign of anybody getting better, even for a short period, and that suggests to me that you have the wrong mechanism.” George Perry agrees “The amyloid hypothesis is dead” “It is not a reasonable hypothesis any longer.”¹⁹ Even major champions of the amyloid hypothesis, like John Hardy and Bart De Strooper, have modified their views by indicating that “Dementia may not be a direct consequence of amyloid- β toxicity but instead as the result of a decade long disease process called the ‘cellular phase’ of Alzheimer’s disease”²⁰

This pessimism cautions us about the utilities to be expected from (–)-phenserine’s inhibitory effects in animal models on multiple AD neuropathologies at doses equivalent to those that can be achieved in humans.^{6, 21, 22} Consequently, citing prior drug failures intervening against inflammation, A β ₄₂, A β ₄₂ amyloid, and other AD neuropathologies, we conclude that the mechanism of a new drug may well be independent of the Amyloid Hypothesis. In preclinical testing (–)-phenserine inhibited the initiation of neuronal preprogrammed cell death, increased anti-apoptotic Bcl-2 and BDNF expression, and attenuated rises in GFAP and pro-apoptotic activated caspase-3.^{21, 22}

4. Molecular probes, disease biomarkers, and evidencing drug-induced brain changes in CTs

Two biochemical methodological factors complicate our proposed ascription of any clinical benefits to a (–)-phenserine induced inhibition of neuronal preprogrammed cell death. A lack of readily available biological markers of target engagement has confounded new drug development. Molecular probes of the apoptotic biochemical cascade have not been previously used in AD CTs. Biochemical measurements meant to reflect brain states in humans are limited to blood and CSF samples. As a result we have developed methods for quantifying the contents of plasma extracellular vesicles (exosomes: 30 to 150 nm in spherical diameter extracellular vesicles) enriched for neuronal origin to assay traditionally studied AD neuropathological states and to identify activities in the apoptotic cascade. The isolation of such exosomes enriched for neuronal origin from peripheral blood provides a new diagnostic platform with the potential to time-dependently track neuropathological changes *in vivo*.²³ As a window to follow neuronal apoptosis we plan to assay, obtained from clinical trial subjects’ blood, neuronal marked exosome levels of Bcl-2, BAX, and activated Caspase 3. These same exosome methods have already been used successfully with the AD biomarkers A β ₄₂, Tau, and others.^{23–30} Similarly, Bcl-2/BAX ratios and activated Caspase 3 assays have had wide use assessing apoptotic activities in cancer and other disorders³¹, and are widely evaluated in preclinical drug development models.³²

5. For disease course modification, what molecular or clinical outcomes must drug interventions ameliorate? Can neuronal cell death be averted?

Basically, with the limitation of the Amyloid Hypothesis, there is no known pathology that has been identified as a target essential to success of any form of AD disease modification. One potential target with intuitive, if not face validity, is the clinically indicated direct cause of AD symptoms and functional impairments, the death of neurons and loss of synaptic connections. To modify the disease course of AD, the death rate of neurons must be

lowered or the functionality of existing neurons must be at least temporarily prolonged and hopefully increased. Anatomically, neurons mediate all the functional impairments and disabilities associated with AD. Strategies in CTs to date have implicitly assumed that the targeted neuropathology would either result in an improved neuronal functioning or a reduction in the rate of neuronal loss in AD brains. These hopes have not been realized.^{19, 20}

As a consequence of neuronal and synaptic loss being the final common pathway evident in AD and other neurodegenerations, as confirmed with post mortem studies, we proposed to supplement transgenic (tg) mouse models of AD neuropathologies with a weight drop mouse model for concussion and traumatic brain injury (TBI).⁶ This latter model and an anoxia model also result in significant losses of neurons.²¹ In weight drop-induced concussion, (–)-phenserine dramatically reduced neuronal death when measured at 72 hours after injury by Fluoro-Jade C; a stain specific for late stage cells committed to degeneration. Likewise, (–)-phenserine mitigated ischemia-induced neuronal death as evaluated by Tunel staining consistent with measures of Bcl-2 and activated caspase-3.^{21, 22} To document the presence of other AD pathologies and (–)-phenserine acute activities, using specific immunohistochemistry antibodies, we evaluated the development of neuroinflammation by probing for activated microglial cell ionizing calcium-binding adaptor molecule 1 (IBA1) and then for TNF-alpha; demonstrating their presence following injury and mitigation by (–)-phenserine. Currently we have in process additional studies attempting to disconfirm our evidence that at present is consistent with an anti-preprogrammed cell death mechanism of (–)-phenserine's activities in animal anoxia and TBI models.

Without claiming anti-preprogrammed cell death activity for (–)-phenserine we regard further studies as useful as guidance for studies of other drugs with such novel mechanistic properties. In earlier studies we have shown that the inactivation of p53, the gatekeeper to apoptosis, fully abated cognitive deficits 7 days or hr ? following injury in a mouse weight drop model.³³ This action was reconfirmed in a moderate to severe rodent model of head injury in which p53 inactivation, similar to (–)-phenserine, blocked TBI-induced neuronal cell death, elevations in p53 and down-stream target levels as well as behavioral impairments (all evaluated at 24 hr following TBI).³⁴ Since prominent inflammatory, anti-amyloid, and other drug interventions have each failed in AD clinical trials to date, a method able to protect and preserve neurons functionally in the presence of the harsh if not toxic AD brain environment seems potentially of scientific and possible therapeutic importance.

6. Is there a more economical clinical trial model for use with early human trials?

Many AD clinical trials might have been compromised by human errors. In addition to being vigilant against these errors, we have sought ways to reduce the number of subjects required to assure adequate power in our CTs. Becker et al. found a mean of multiple ratings necessary to overcome unreliability that interferes with the power in clinical trials (CT).^{33–37} Five common sources of variance can compromise the validity of an otherwise apparently successful or unsuccessful CT. These include variance among subjects; variance within a research site; variance occurring across different clinical research sites; variance over time, and variance due to random measurement error.^{36, 37} Investigators must tolerate some variance sources. Investigators cannot practically reduce two sources of variance:

variance among subjects due to different levels of disease severity and variance over time as well as genetic variants (SNPs). Other sources of variance affecting CT validities are potentially under the control of investigators.

Consequently, we will statistically intervene in our CT design to reduce measurement variance.³⁶ The standard error of measurement (SEM) benefits investigators by two factors: the use of mean rather than raw data as numerators in data to be analyzed. This increases, with possible effects from systematic error, the likelihood that the numerator value approximates the mean or actual true score. The SEM reduces the denominator standard deviation by the square root of one minus the observed reliability of repeated measurements using the method of assessment. We reduced Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADCS-Cog)³⁸ and Mini Mental State Examination (MMSE)³⁹ variance in two CTs^{33, 34} to 83% of that present without SEM data points obtained by using the mean of three observations. Without this reduction in variance using SEMs from three repeated observations, the study N would have had to be increased by 145% to obtain equivalent power.⁴⁰ This innovation requires only three separate assessments of each subject at each evaluation used in a statistical comparison. One advantage from this is that, combining consecutive longitudinal assessments made over time, a clinical course can be established for each individual in a CT. Using confidence intervals of measurement (CIm) for the SEMs data analysis identifies individuals as responders and nonresponders.

7. Is it time to move drug development beyond statistical significance of a disease marker modification, i.e., the current clinical research perspective, to clinically significant functional disability reduction, i.e., a more clinically informative public health perspective

Since CTs are tools used by medicine to best achieve its aims of disease treatment and promotion of patient health and wellbeing, we propose to use as outcome measures in our clinical trial, clinical functional impairment and disability measures with significance for the wellbeing of AD patients.

In this overview of AD and clinical trial practices we have identified seven issues that influence assessments of AD in clinical trials. We found in vitro and in vivo evidence of potential (–)-phenserine activities, at concentrations achievable in human brains, against a range of prominent AD pathologies and (–) phenserine neuronal protection in anoxia and traumatic brain injury animal models. Staining for markers of apoptotic cell death 72 hours following weight drop injury to mice and anoxia injury to rats revealed (–)-phenserine protection of neurons compared to drug untreated control injured rodents. As a result we proposed a clinical trial designed to address the problematic issues identified in our overview of current AD research practices.

The Thal-Sano AD Prevention Design—In an effort to assess the possible prevention of AD progression, researchers at the Alzheimer Disease Cooperative Study (ADCS), designed and successfully executed a clinical trial test of Vitamin E and deprenyl.^{4, 5} A total of 341 patients received the selective monoamine oxidase inhibitor selegiline (10 mg a day), alfatocopherol (vitamin E, 2000 IU a day), both selegiline and alpha-tocopherol, or placebo for two years. Unique to this clinical trial, the primary outcome was the time to the

occurrence of any of the following: death, institutionalization, loss of the ability to perform basic activities of daily living, or severe dementia (defined as a Clinical Dementia Rating of 3 for the initially Clinical Dementia Rated 2 subjects). Placebo treated subjects showed a greater than 30% decline in event free survival at one year and greater than 70% at two years. A significant delay in this primary outcome was found with each drug and their combination with estimated increases in median survivals of 145 to 230 days.

In preparations for this clinical trial, the ADCS investigators had analyzed Consortium to Establish a Registry for Alzheimer's Disease (CERAD) data on one and two year outcomes, using the above occurrences, for Clinical Dementia Rating (CDR) Scale rated 1 and 2 subjects.⁴ These data showed one and two year progressions for the selected occurrences for both CDR 1 and 2 rated groups of AD patients; however, because of the higher rates of decline for CDR 2 subjects this group was selected for the clinical trial to reduce sample size.

We view these data as demonstrating the utility of selected event occurrences as indicators of disease course progression and possible drug effects on disease course modification. Consequently we propose to index disease decline with time to onset of functional impairments, including cognitive outcomes,³ and disabilities affecting the wellbeing of AD patients. Following the Kachaturian criteria for a fully successful mitigation of disabilities from AD, in our proposed trial, for clinical significance, a 50% reduction in progression into disability would be needed, projected to or measured at five years.

4. Discussion

We propose for efficacy studies a (–)-phenserine clinical trial disease course amelioration design.

Protocol design (See Protocol Design Table 1)

To contextualize the onset of functional impairments both within and across individual subjects, we will adopt a five-year three phase study. During Phase I, to be completed during Year 1, subjects will be recruited, placed on donepezil, and evaluated for baseline and at two-month intervals for the functional impairments to be used as outcome variables.

In Phase 2, initiated with the onset of study Year 2, patients will be randomly and blindly assigned to (–)-phenserine extended release dosing (see Investigational drug dosing below) or continued on donepezil. Following optimization of dosing for subjects assigned to (–)-phenserine extended release dosing, these subjects will be evaluated on three weekly intervals during a one month period and then randomly assigned blindly to either continued optimized (–)-phenserine extended release dosing or “optimized” (blindly randomly ordered for selective subjects on donepezil) on donepezil dosing using placebo tablets. All subjects will continue on the assigned treatment until either leaving the study prior to completion or until the end of Year 4, a potential 2 ½ year double blind duration of treatment. At termination each subject will have three assessments at weekly intervals during the final month. For subjects unwilling or unable to complete the one month of repeated assessments

the last three in progress assessments will be used for the outcome analysis. (See Outcome Analysis).

Sample selection

Subjects will be individuals diagnosed with AD and with mild or moderate disease severities.

Recruitment

The study will be conducted at multiple academic medical center sites with faculty and staff who have already completed participation in a federally funded AD CT. Subjects will be patients with diagnosed mild to moderate AD and currently under care at the site such that team support for patient subjects and caregivers will be available to volunteers throughout their participation in the research.

Outcome variables

All subjects will be evaluated at baseline and during the final month of the study at three weekly intervals and at two month intervals throughout the study.

Clinical outcome variables will include the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog),³⁸ Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory,⁴¹ Mini Mental State Examination (MMSE),³⁹ Cambridge Cognition Battery,⁴² the Neuropsychiatric Inventory (NPI),⁴³ which surveys the severity and frequency of psychological and behavioral problems, the Caregiver Activity Survey (CAS),⁴⁴ which measures time caregivers spend assisting Alzheimer patients in 6 major areas of daily activities; and the Dependence Scale (DS),⁴⁵ which assesses 6 levels of a patient's functional dependence. For overall change we will use the Alzheimer's Disease Cooperative Study Clinical Impression of Global change (ADCS-CGIC CIBIC+).⁴⁶

An FDA compliant Clinician Rated Treatment Emergent Adverse Events Scale and vital signs will be administered at each visit. Each subject will receive a medical history, physical examination, electrocardiogram, vital signs, CBC, laboratory panel, and urinalysis. At the first and final visits and each intervening contact with the subject, treatment emergent events and serious adverse events will be actively elicited using

Biochemical outcome variables will include probes assessed using samples derived from plasma derived exosomes that are enriched for neuronal origin by cell surface markers.^{23–33} Primary outcome variables will be key mechanism-based proteins involved in apoptosis (Bcl-2, BAX, activated Caspase 3) and neuronal functionality (synaptophysin, synaptopodin, synaptotagmin).²⁷ Classical markers of AD (specifically, A β ₄₀, A β ₄₂, t-tau, p-tau)^{23–25} and neuroinflammation will be assessed with particular regard to possible provocation of these mechanisms by TBI. Since microglia possess the same markers as macrophages, exosomes are not a selective indicator of brain inflammation.

Drug dosing

(-)-Phenserine will be dosed using Extended Controlled Release Tablets (ECRT). Data from animal and in vitro kinetic studies indicate the use of b.i.d. dosing with 15 mg. (-)-phenserine to address immediate release estimates of a 3 ng/ml loss of (-)-phenserine to metabolism per hour at target concentration or 45% erythrocyte acetylcholinesterase (AChE) inhibition from drug and metabolites, and the need for absorption of 3 mg/hr from oral administration. In response, b.i.d. doses will be in an extended release formulation (ECRT) loaded to deliver 1.5 ng/ml/hr and comprised to release drug over 24 hours. Continued use of b.i.d. administration provides the advantage of averaging release that is modified by varied gastrointestinal conditions during 24 hour transits. An initial ECRT dose is increased weekly until, after completion of a week of dosing, the subject exhibits the target 45% $\pm$ 10% AChE erythrocyte membrane inhibition. This provides a drug plus metabolite activity in brain within the range Effective Concentration (EC)_{100 $\pm$ 50}. Subjects then will remain on that dosing for one additional week. If erythrocyte membrane AChE inhibition remains within the confidence range, the subject can then proceed into the double blind.

Data analyses

The analysis and presentation of the trial will be in accordance with CONSORT guidelines. We will compare three baseline and three on treatment ADAS-Cog and MMSE ratings and all other outcome variables to control intra-site variance with the SEM, and exclude other errors with an inter-site analyses, interdisciplinary case management of all subjects, monthly staff visits with subjects, phone availability of staff 24/7, trained raters, and so forth.

5. Implications

What will be accomplished?

We propose that these plans effectively address the seven problem areas we earlier identified as potential compromises to any successful AD CT, and we aim to test this hypothesis with an experimental drug with the potential to impact a target with strong face validity in AD, traumatic brain injury (TBI), and neurodegenerations: preprogrammed apoptotic neuronal death. Specifically, subjects, with mild to moderate AD, will test the investigational drug (-)-phenserine in the presence of well-established and irreversibly active AD pathologies. The investigational drug, (-)-phenserine, will have the opportunity to inhibit neuronal self-induced preprogrammed cell death, to do so for up to a 2 1/2 year time limited period and therefore will demonstrate or not an ability to delay deterioration into increased impairments and disabilities in persons with AD. Prior drug failures intervening against inflammation, A β ₄₀, A β ₄₂ amyloid, and other AD neuropathologies, in our view, almost assure that any efficacy demonstrated by (-)-phenserine will be associated with its abilities in preclinical studies to inhibit neuronal self induced preprogrammed cell death. Efficacy will be demonstrated by delays in the onset of clinical functional impairments. The mechanism of (-)-phenserine efficacy inhibiting the initiation of neuronal preprogrammed cell death will be supported by the profile of anti-apoptotic, Bcl-2, and pro-apoptotic brain marked exosome BAX and activated Capsase-3. Synaptophysin and other markers of neuronal functionality will indicate improved neuronal functioning compared to measures consistent with a reduced rate of neuronal loss in AD brains. We expect these outcomes to be achieved

economically with reduced numbers of subjects without losses of power by use of repeated measure comparisons for outcome variables.

These plans and the problems identified in our review indicate will impact the proposed clinical trial and warrant preliminary studies. Therefore we will conduct selected initial studies to innovate as needed for a successful mechanistic-exploratory clinical trial. For patients meeting diagnostic criteria for concussion or TBI and AD, we will identify the profile of brain marked exosome plasma probes to be proposed as evidence for reduced apoptotic neuronal cell death and changes in the presence of an ECRT of (–)phenserine. Using these subjects we will explore candidate clinical outcomes for evidence of possible clinical significance that would justify the subsequent efficacy focused clinical trial. These steps will explore and develop the utility of brain marked exosome plasma probes as evidence of drug induced changes associated with neuronal apoptosis. As part of these steps we will optimize the formulation of our animal tested ECRT (–)phenserine to allow b.i.d. dosing individually optimized, using plasma drug concentration indicators, to provide a brain effect within the drug and metabolites predicted effective concentration. Finally, we will explore and develop specific criteria able to define medicine's often stated but unspecified target in neurodegenerations—disease modification—in terms directly relevant for the wellbeing of TBI and AD patients.

6. Conclusions

This promising test of drug-provoked inhibition of neuronal self-induced preprogrammed cell death offers two opportunities. First we will further study (–)phenserine and its potential novel mechanism for AD, TBI, and possibly other neurodegenerations, inhibition of neuronal self-induced apoptosis. Second, the feasibility of a study of this new approach to AD and TBI will hopefully inspire synthesis by others of other agents with similar anti-apoptotic potentials to interrupt the march of AD and other neuropathologies and their clinical consequences for patients.

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TABLE 1

Double-Blind, Donepezil Controlled, Randomized, Proof-of-Disease Modification-Concept (–) Phenserine Clinical Trial Total Trial will be comprised of Two 100 Subject Clinical Trials. One trial will be conducted at a single site in the UK and the second trial will be conducted at multiple sites in the US.

Group	Year 1	Year 2-2.5		Year 2.5-3	Intervening Analysis	Year 4	Final Analysis ** Outcome Criteria
Recruit * 200 Patient *** Subjects	Blinded Donepezil Treatment', Replacement ent of dropouts, Dose formulation studies, in twenty-subject to select (–)-phenserine, formulation for doubleblind.	100 Pt. Blindly randomized to Active Drug		Blind Phenserine Induction	Safety Committee Interim Analysis	Maintain Double-Blind for Investigators --- Contingent on Interim Analysis	Phenserine Statistically Significantly Better than Donepezil Controls on: Disability Event Avoidance: Cognitive: ADAS-Cog, MMSE, Cambridge Cognition Battery, time to occurrence of death, institutionalized, loss of activities of daily living, or dementia progression (defined as a Clinical Dementia Rating of +1 over baseline.)
		50 Pt. Blindly randomized to Continued Donepezil		Blind Donepezil Continued			
		50 Pt. Blindly randomized to Continued Donepezil		Blind Donepezil Continued			

* Assessments At baseline (Recruitment, Baseline Assessment and at least one week later at drug prescription prior to taking drug and to be repeated once very two months for four years and for 3 weeks during the last month at three and four years (At each rating investigators will be expected to provide quality Alzheimer's disease patient care (non-medication) to address any clinical progressions):

Cognitive: ADAS-Cog, MMSE, Cambridge Cognition Battery

Disability Event Avoidance: death, institutionalized, loss of activities of daily living (ADCS-IADL and Blessed Dementia Scale Part 2, Dependence Scale (rate level of care received: 1, limited home care; 2, care equivalent to that received in an adult care facility; and 3, care equivalent to that received in a skilled-nursing facility), Behavior Rating Scale for Dementia, Neuropsychiatric Index, and Clinical Dementia Rating Scale.

** Statistical Analyses will include progressive individual course predictions using as criteria of clinical change a maintained 5% change in predicted course.

*** Subjects will be mild to moderate AD subjects randomized separately.