

# Botanical Mixture Stabilizes Cognitive Function in Patients with Mild and Moderate Alzheimer's Disease

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## Abstract

**Context:** Currently, there is no treatment that can stop the progression of Alzheimer's disease. We have used transgenic *Drosophila melanogaster* models and machine learning to develop an eight component botanical mixture (Geneaire™ ReBuilder™) that targets multiple genetic pathways involved in brain aging and dementia that are homologous between *Drosophila* and humans.

**Objective:** To test the effects of ReBuilder on the cognitive function of subjects diagnosed with mild or moderate Alzheimer's disease.

**Methods:** We recruited 50 subjects with mild to moderate AD to participate in a double-blind, placebo-controlled clinical study. During the 12-month pilot study, the subjects were evaluated quarterly on the Mini Mental State Exam (MMSE), Alzheimer's Disease Cooperative Study's Activities of Daily Living (ADCS-ADL), and the Clinical Dementia Rating Sum of Boxes (CDR-SB).

**Results:** The addition of ReBuilder to subjects' existing Namenda and Exelon regimens stabilized cognitive decline in patients with mild AD and slowed cognitive decline in patients with moderate AD.

**Conclusions:** These results were observed in both sexes and in all ages tested. Importantly, no adverse side effects attributable to ReBuilder were reported. The results of this clinical pilot warrant further study of ReBuilder in AD.

**Keywords:** Alzheimer's disease; Dementia; Aging; Neurology; APOE; Genetics; Cognition

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## Introduction

Alzheimer's Disease (AD) is the 6<sup>th</sup> leading cause of death in the United States [1]. Today, more than 5 million Americans are living with Alzheimer's disease (AD), and 1 in 3 seniors' dies with AD or another form of dementia [2]. By 2050, the number of people expected to be living with AD will rise to 14 million and cost an estimated \$1.1 trillion dollars [2]. Deaths of those with AD were about 600,000 in 2010 and are projected to rise to 1.6 million by 2050, which is expected to be some 43% of all older adult deaths [3]. Beta-amyloid (A $\beta$ ) plaques and hyperphosphorylated Tau (pTau) neurofibrillary tangles have been the dominant focus of research on AD pathophysiology since the disease was first recognized by Alois Alzheimer in 1906 [4,5]. While plaques and tangles are diagnostic for AD [5-7], the cause(s) of their soluble precursors that kill neurons has not been determined. The majority of AD patients are diagnosed after 60 years of age. Many studies point to aging related processes like inflammation [8-14],

neural vascular damage [15-21], neural stress [9,22-32], altered cell metabolism [33-37], cellular autophagy [38-45], microglial dysfunction [46-48], mitochondrial dysfunction [49-52], astrocyte function [53-59] and dietary factors [60-65] as potential causal factors in the decline of brain function over the decades that precede an actual AD diagnosis. AD is a multifaceted pathology involving many biochemical pathways and thus a multifaceted therapeutic approach may prove beneficial.

*Drosophila melanogaster*, the common fruit fly, has been extensively studied and is a highly tractable genetic model

organism for understanding molecular mechanisms of human diseases. Many basic biological, physiological, and neurological properties are conserved between mammals and *D. melanogaster*, and nearly 75% of human disease-causing genes are believed to have a functional homolog in the fly [66,67]. Therefore we used genetic and machine learning approaches on age-related data bases for humans and flies to identify many homologous CNS-specific genetic and biochemical pathways involved in longevity. We targeted genes known to be important in AD and screened botanical products known to interact with the pathways we identified using transgenic *Drosophila* models [68]. The result is ReBuilder, a 7-component botanical supplement that is effective in reducing neural dysfunction in our *Drosophila* model of AD. For this human pilot study, we added an eighth component, bioperine, to improve absorption of ReBuilder.

## Materials and Methods

Fifty human subjects of mixed gender between the ages of 60 and 90 were recruited and enrolled in this double-blind, placebo-controlled, IRB-approved pilot clinical study. The subjects had been on stable maximum tolerated doses of Memantine and/or Rivastigmine for at least 2 months, and nothing was changed in their standard therapy for the duration of our pilot study. The subjects were randomly assigned to either the active or placebo arm of the study. The subjects were evaluated approximately every three months (quarterly) from October 2013 to December 2015. The subjects were referred to Genescent Corporation by William R. Shankle, MD, and evaluated in the office of Cristina Rizza, MD in Fountain Valley, CA.

At the initial enrollment office visit, we administered the Mini Mental State Examination (MMSE) and the Clinical Dementia Rating Sum of Boxes (CDR-SB) to each subject. Each subject's caregiver was interviewed using the Alzheimer's disease Cooperative Study's Activities of Daily Living (ADCS-ADL) Inventory to assess the subject's current self-care capabilities. After this initial visit, the subjects were instructed to begin taking one capsule of ReBuilder in the morning and one capsule in the evening daily. Each subject had a caregiver who ensured compliance in taking all their medications. The subjects and their caregivers returned to our office approximately every three months to have the aforementioned tests repeated. ReBuilder is currently distributed by Geneaire.

The components of the ReBuilder treatment used in the clinical

study and their known actives and targets are given in **Table 1**. The formulation is protected by US Patent 9744204.

## Ethics

The subjects signed informed consent forms upon enrollment. This study protocol was approved by the Institute of Regenerative and Cellular Medicine Institutional Review Board (approval number: ICSS-2013-007). This study is registered on the Clinical Trails website of the United States government (NCT03611439).

## Statistics

Throughout the 12-month period, the subjects' scores on the MMSE, ADCS-ADL, and CDR-SB were recorded and compared to their initial baseline scores. The subjects' mean test scores and changes in their mean test score were plotted in relation to their average baseline scores and presented with 95% confidence intervals. Only the subjects for whom we had data for the initial visit and all 4 subsequent quarters were included in the analysis presented here.

To maximize the number of subjects that would be assigned the active botanical compound, 43 subjects were given ReBuilder and only 7 patients were assigned to the placebo arm of the study. To make up for the small number of subjects in the placebo arm (only 5 completed the trial), we compared the data from our active subjects to previously published data from 471 AD subjects of matched demographics and AD symptoms from the study by Bernick et al. The subjects in this previously published study were treated and tested in the same manner as our placebo arm. Our 5 placebo subjects experienced similar loss of cognitive function as measured by MMSE, ADCS-ADL, and CDR-SB as the 471 placebo subjects in the Bernick study. Moreover, with the large clinical study from Bernick et al. we were able to match all the active subjects in our pilot with large numbers of age and condition matched surrogate placebo controls.

## Results

Thirty out of the 43 subjects receiving ReBuilder successfully completed our 12-month pilot study. Of those 30, 17 were categorized as "mild" in disease severity based on an initial score at enrollment of 21 to 30 points out of a possible 30 points on the Mini Mental Status Exam (MMSE), a widely used test for dementia. The remaining 13 subjects were categorized as "moderate" in disease severity based on an initial MMSE score

**Table 1** Composition, known actives, and targets of treatment (US Patent 9744204).

Component	Known Active (s)	Targets	References
<i>Astragalus membranaceus</i> (extract)	Astrogalosides I-VII Flavenoids, HDTICs	Telomerase, Mitochondria, ptau, mTOR, TNF- $\alpha$ , ERK, AMPK	[69-75]
Berberine HCL	Berberine (98%)	Acetylcholinesterase, AMPK, $\alpha$ -adrenergic receptors, $\beta$ -Amyloid	[76-81]
<i>Vaccinium uliginosum</i> or <i>Pterocarpus marsupium</i> (extracts)	Resveratrol Analogs	PPAR $\alpha$ , PGE2, AMPK, phosphodiesterase, Mitochondria	[82-86]
L-Theanine	L-Theanine (98%)	NMDA receptors, EAATs, GABA receptors, eNOS, mitochondria	[87-93]
Genistein	Genistein (98%)	ER $\alpha$ , AMPK, p450c21, PRPF8	[94-96]
Lithium Orotate	Lithium	NCS-1/Frequenin, Abeta, NMDA, GSK3B, ptau	[97-105]
Selenium Glycinate	Selenium	PRPF8, ERCC1, Selenoproteins	[106-108]

of 11 to 20 points.

During the course of the 12-month pilot study, the mild and moderate subjects taking ReBuilder maintained MMSE scores close to their initial baseline scores. The ReBuilder subjects did not experience the rate of decline seen in the subjects from the Bernick study [109], which we used as our benchmark control for the expected rate of decline during the same study (Figure 1A).

Looking at the 17 mild subjects who completed the pilot, there appears to be a pronounced preservation of the baseline MMSE scores after 12 months of treatment (Figure 1B).

Looking at the 13 subjects with moderate AD who received ReBuilder and completed the pilot study, there is also a pronounced preservation of baseline MMSE score. The moderate AD subjects taking ReBuilder, as with the mild AD subjects, continued to score much closer to their baseline than the subjects in the Bernick study (Figure 1C).

The trend of baseline score maintenance in subjects taking ReBuilder continues if we separate the subjects by gender. Generally, Alzheimer’s disease affects more women than men due to women having longer average lifespans, and possibly because of hormonal differences between the genders. In our pilot study, we had nearly equal numbers of each gender, with 16 women and 14 men. Both genders saw positive effects when ReBuilder was added to their standard therapy (Figures 1D and 1E).

The E4 variant of the *Apolipoprotein E (APOE)* gene puts an individual at an increased risk of developing Alzheimer’s disease. The risk increase is present in an individual with one copy of the E4 allele, and greater still if the individual has 2 copies. The *APOE4* gene variant is associated with an increased number of amyloid protein plaques in the brain tissue of affected individuals and earlier onset of AD symptoms [110]. In our pilot study, we had 14 subjects taking ReBuilder who carried at least one E4 allele. While it took 6 months for these subjects to see an effect from taking ReBuilder, the overall changes in their MMSE scores were positive by Q4 (Figure 1F).

The Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) is a questionnaire widely used to assess the

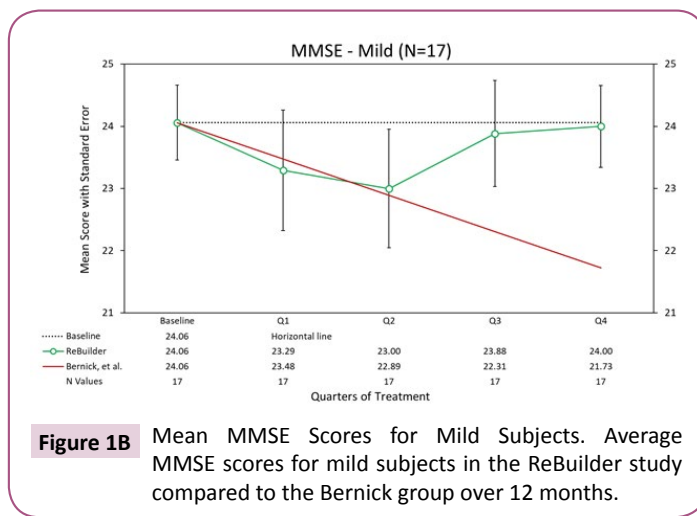


Figure 1B Mean MMSE Scores for Mild Subjects. Average MMSE scores for mild subjects in the ReBuilder study compared to the Bernick group over 12 months.

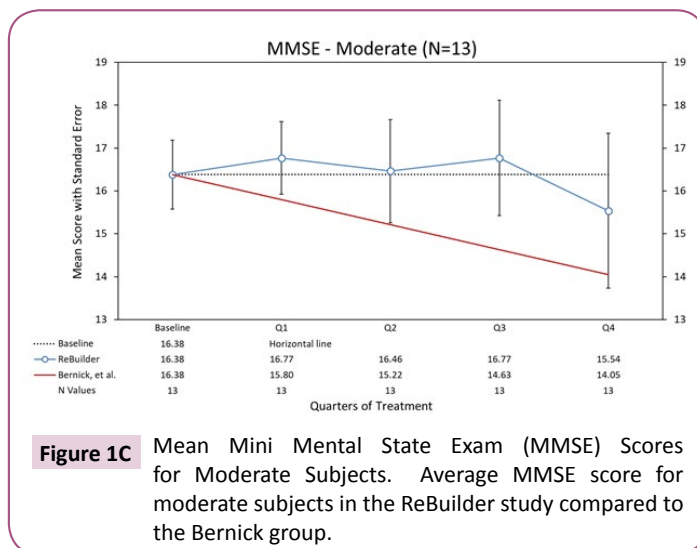


Figure 1C Mean Mini Mental State Exam (MMSE) Scores for Moderate Subjects. Average MMSE score for moderate subjects in the ReBuilder study compared to the Bernick group.

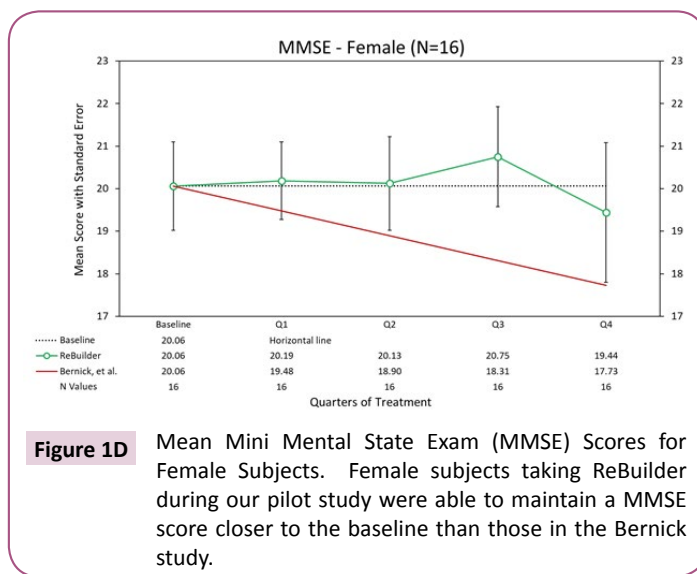


Figure 1D Mean Mini Mental State Exam (MMSE) Scores for Female Subjects. Female subjects taking ReBuilder during our pilot study were able to maintain a MMSE score closer to the baseline than those in the Bernick study.

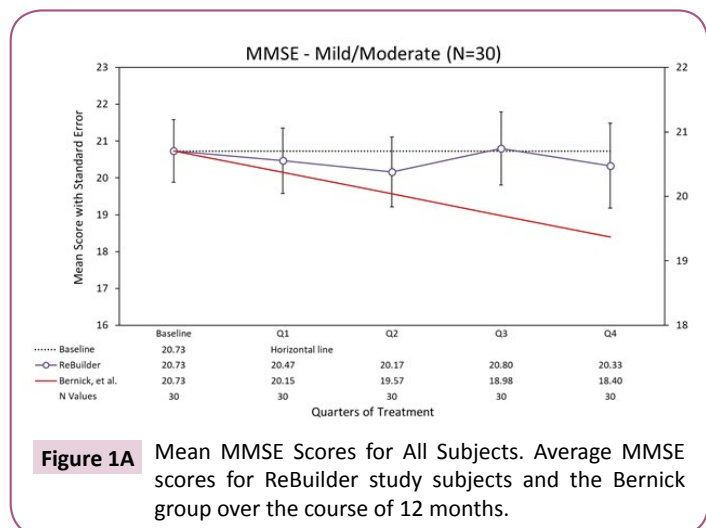
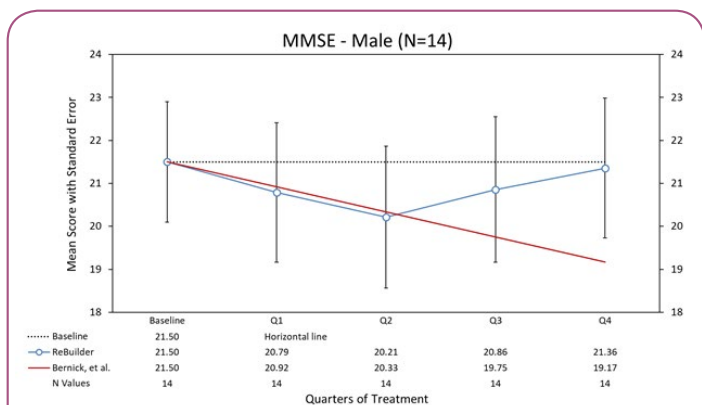
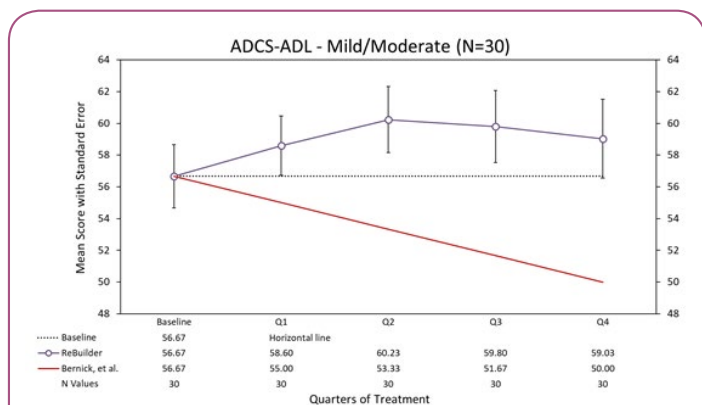


Figure 1A Mean MMSE Scores for All Subjects. Average MMSE scores for ReBuilder study subjects and the Bernick group over the course of 12 months.

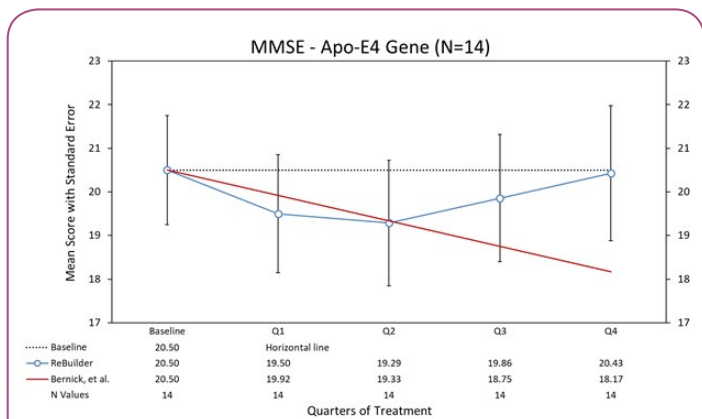
competence of patients with Alzheimer’s Disease (AD) in basic and instrumental activities of daily living (ADL). The ADCS-ADL scores competence in daily activities on a 78-point scale. Slight score changes in this assessment can indicate that a subject is,



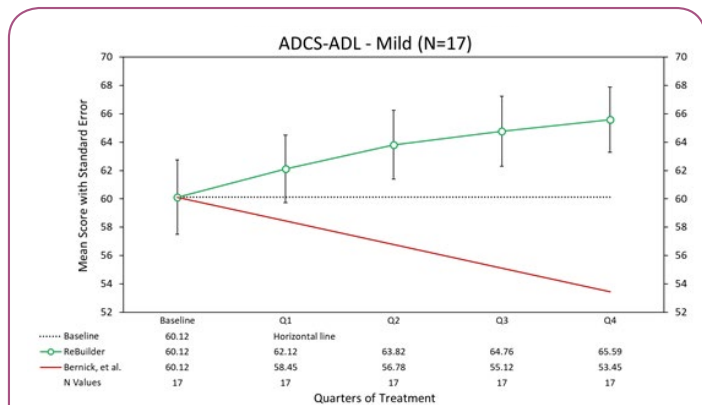
**Figure 1E** Mean Mini Mental State Exam (MMSE) Scores for Male Subjects. Male subjects taking ReBuilder during our pilot study took 6 months to see an improvement in their MMSE score. BY Q4 the men rebounded back to their baseline score.



**Figure 2A** Mean Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Scores for All Subjects. The mean score for all subjects taking ReBuilder rises above their initial baseline average score and maintains that improvement for the duration of the pilot study.



**Figure 1F** Mean Mini Mental State Exam (MMSE) Scores for APOE4 Subjects. Average MMSE scores of the ReBuilder subjects eventually rebounded to baseline by the end of 12 months.



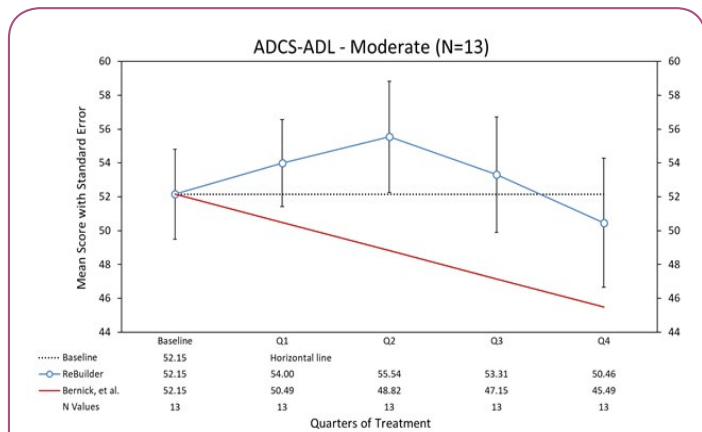
**Figure 2B** Mean Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Scores for Mild Subjects. On average, the Mild AD subjects taking ReBuilder improved in Activities of Daily Living and remained above baseline for the duration of the study.

or is not, able to choose appropriate clothing or prepare a simple meal.

On average, our subjects taking ReBuilder gained 2.34 points on this measure after 12 months of treatment. The control group is expected to have lost 6.67 points during the same amount of time (**Figure 2A**).

The 17 mild subjects who completed the pilot appear to display an improvement, on average, of ADCS-ADL scores after 12 months of treatment (**Figure 2B**).

The ADCS-ADL scores of the 13 subjects with moderate AD who completed the pilot study did not see an overall improvement compared to their mean baseline scores after 12 months of treatment. However, the mean point loss of 1.69 still falls quite short of the projected point loss of 6.67 based on the Bernick study (**Figure 2C**).

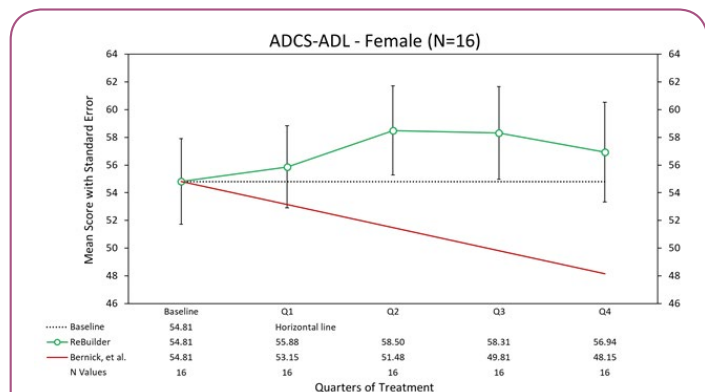


**Figure 2C** Mean Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Scores for Moderate Subjects. Moderate subjects taking ReBuilder remained close to their baseline score for the duration of the study.

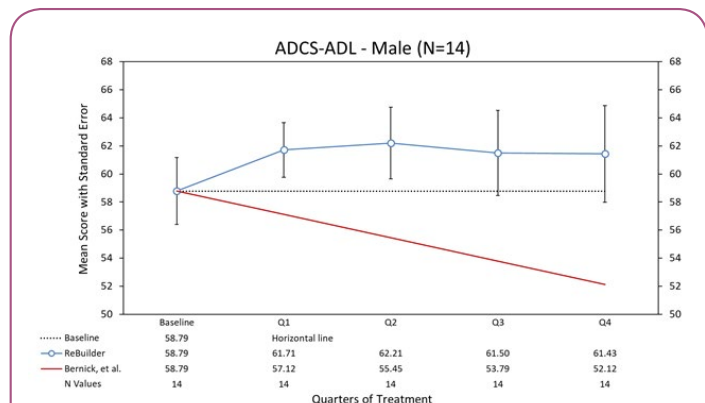
When the subjects in our pilot study are separated by gender, the overall improvement in activities of daily living remains. The subjects taking ReBuilder achieve and maintain a clinically meaningful improvement in the ADCS-ADL assessment that is

above their average baseline scores, and far above the score projected based on the Bernick study at the end of 12 months, regardless of gender (Figures 2D and 2E).

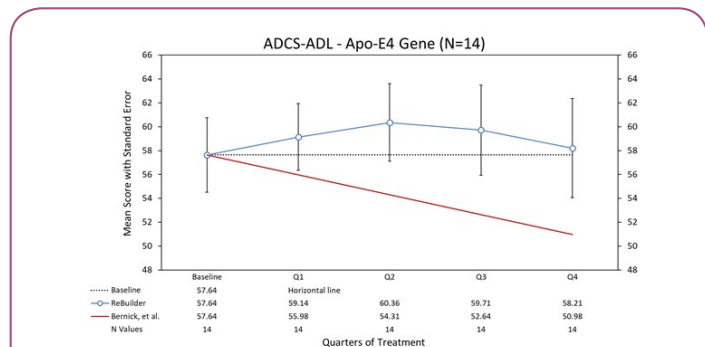
Separating out the subjects with the *APOE4* genetic variant, a clinically meaningful improvement in the ADCS-ADL assessment is still observed at the end of 12 months (Figure 2F).



**Figure 2D** Mean Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Scores for Female Subjects. Female subjects taking ReBuilder maintained scores above their baseline for the duration of the study.



**Figure 2E** Mean Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Scores for Male Subjects. Male subjects taking ReBuilder maintained ADL scores above their baseline for the duration of the study.



**Figure 2F** Mean Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) Scores for *APOE4* Subjects. Subjects genetically predisposed to Alzheimer’s taking ReBuilder maintained ADL scores close to their baseline for the duration of the study.

The Clinical Dementia Rating (CDR-SB) is used to quantify the severity of symptoms of dementia. This measure assesses a subject’s cognitive and functional performance in six areas: memory, orientation, judgment & problem solving, community affairs, home and hobbies, and personal care. Scores in each of these are combined to obtain a composite score, with a higher score indicating greater severity of dementia symptoms.

Overall, the subjects taking ReBuilder in our pilot study maintained a CDR-SB score close to their baseline. This suggests that the subjects’ severity of dementia symptoms did not increase as expected over the 12-month pilot study and that they experienced better stability in their symptoms (Figure 3A).

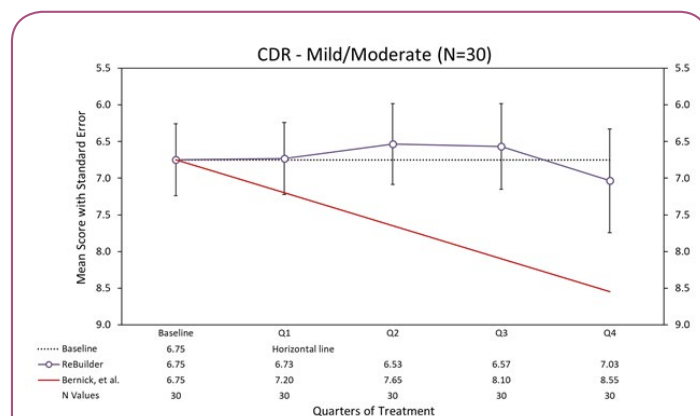
For our mild subjects, the mean CDR-SB scores stayed above baseline for the latter portion of the pilot, possibly indicating a reduction in dementia symptoms (Figure 3B).

For moderate subjects, the severity of their dementia symptoms does increase by the end of the pilot study, but not to the same degree that is seen in the Bernick group over the same time period (Figure 3C).

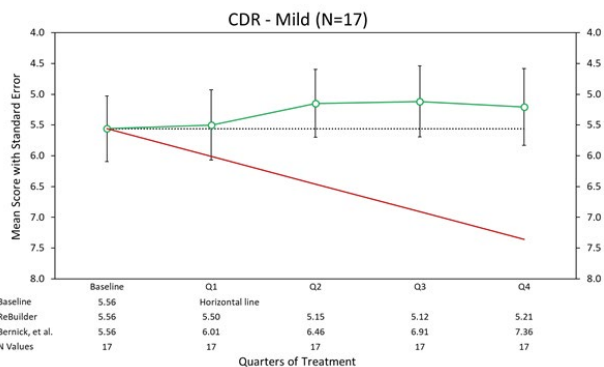
When the subjects taking ReBuilder are separated by gender, we still see a reduction in dementia severity as indicated by the average CDR-SB scores (Figures 3D and 3E).

Looking at the subjects with the *APOE4* genetic variant [110], we also see a reduction in dementia symptoms. This suggests that ReBuilder can improve the symptoms of those genetically predisposed to Alzheimer’s disease (Figure 3F).

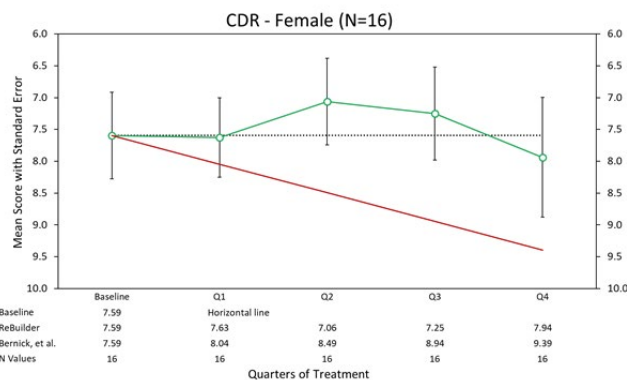
On the whole, the above results show that subjects taking ReBuilder during our 12-month pilot at least slowed in their AD progression as indicated by the MMSE, ADCS-ADL, and CDR-SB. In some measures, the subjects appear to stabilize and even reduce their AD symptoms. No adverse side effects such as changes in mood, sleeping habits, balance issues, or digestive disturbances were observed in the subjects treated with ReBuilder.



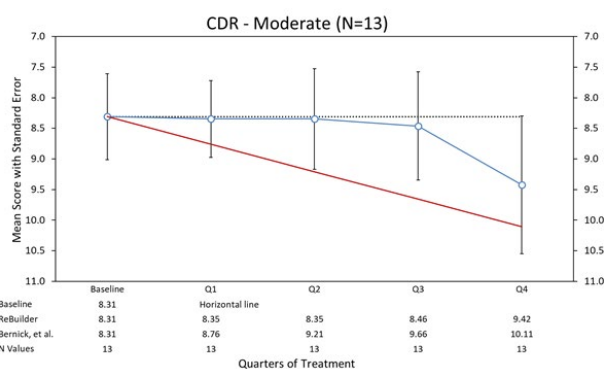
**Figure 3A** Mean Clinical Dementia Rating Sum of Boxes (CDR-SB) Scores for All Subjects. On average, CDR-SB scores stayed very close to baseline for subjects taking ReBuilder. Note that the score scale on the Y-axis is inverted to show that a decreasing CDR-SB score indicates improvement of symptoms.



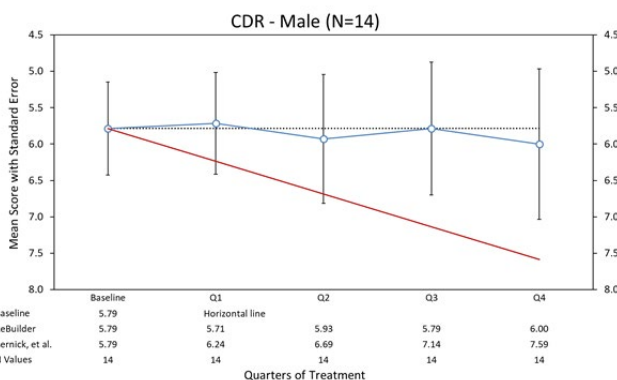
**Figure 3B** Mean Clinical Dementia Rating Sum of Boxes (CDR-SB) Scores for Mild Subjects. Mild subjects taking ReBuilder saw a reduced CDR-SB score by the end of the pilot study. Note that the score scale on the Y-axis is inverted to show that a decreasing CDR-SB score indicates improvement of symptoms.



**Figure 3D** Mean Clinical Dementia Rating Sum of Boxes (CDR-SB) Scores for Female Subjects. Female Subjects taking ReBuilder saw a reduction in dementia severity on the CDR-SB. Note that the score scale on the Y-axis is inverted to show that a decreasing CDR-SB score indicates improvement of symptoms.



**Figure 3C** Mean Clinical Dementia Rating Sum of Boxes (CDR-SB) Scores for Moderate Subjects. Moderate AD subjects taking ReBuilder had symptoms close to baseline until the last quarter of the study. Note that the score scale on the Y-axis is inverted to show that a decreasing CDR-SB score indicates improvement of symptoms.



**Figure 3E** Mean Clinical Dementia Rating Sum of Boxes (CDR-SB) Scores for Male Subjects. Male subjects taking ReBuilder reduced their dementia rating on the CDR-SB. Note that the score scale on the Y-axis is inverted to show that a decreasing CDR-SB score indicates improvement of symptoms.2015.

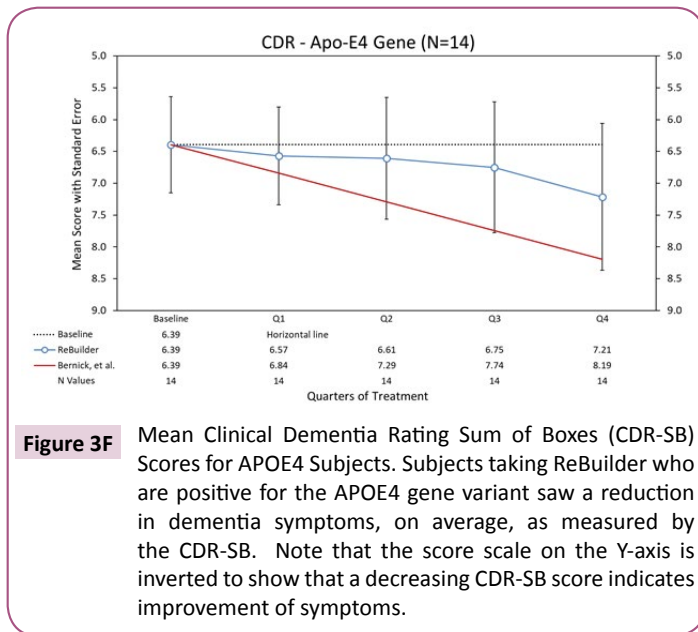
## Discussion

The subjects with mild and moderate AD in our pilot study experienced clinically meaningful stabilization in their disease progression over a 12 month period compared with the decline expected based on the Bernick study [109]. The results for mild and moderate AD subjects occurred regardless of the subjects' age, gender, or genetic status with respect to the *APOE4* genetic variant [111-114]. The benefit of reduced mental decline by all measures was greater in patients diagnosed with mild AD and less pronounced in moderate AD subjects. This suggests that treatment with ReBuilder is beneficial regardless of age, gender, *APOE4* status, or disease severity when added to standard AD treatment.

Though no quantitative biomarker studies were done during this pilot study, the positive effects seen in cognitive function suggest

that there are biological changes taking place that should be investigated further. ReBuilder is composed entirely of botanical substances that are generally regarded as safe (GRAS) by the FDA, and no deleterious side effects were reported or observed that were attributed to ReBuilder in this pilot study. Therefore, there is the potential for ReBuilder to not only be used as a supplemental AD treatment, but also prophylactically as a part of a normal individual's daily dietary supplement regimen.

While we cannot make definitive claims on the success of ReBuilder due to the small number of subjects in this pilot, we can say that the improvement in cognitive function that we have seen in subjects taking ReBuilder warrants further study in a larger AD cohort with biomarker assessment. In future clinical studies, advanced imaging technologies [33,115-120] should be used to verify that ReBuilder has effects on structural outcomes such as amyloid plaques, Tau tangles, and neuronal loss prevention with time.



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