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Treatment of Dementia with bosutinib: An open-label study of a tyrosine kinase inhibitor

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ABSTRACT

Objective: The pursuit of an effective therapeutic intervention for dementia has inspired interest in the class of medications known as tyrosine kinase inhibitors (TKIs) such as bosutinib.

Methods: 31 patients with probable Alzheimer's dementia (AD) or Parkinson's spectrum disorder with dementia (PDD) completed 12 months of bosutinib therapy and an additional 12-months of follow-up. The Clinical Dementia Rating scale (as estimated by the Quick Dementia Rating System (QDRS)) was the primary cognitive status outcome measure. Secondary outcome measures included the Repeatable Battery Assessment of Neuropsychological Status (RBANS) and the Montreal Cognitive Assessment (MoCA). Cox regression methods were used to compare results with population-based estimates of cognitive decline.

Results: The present paper reports on cognitive outcomes obtained at 12 months for 31 participants and up to 24 months for a 16-participant subset. Safety and tolerability of bosutinib were confirmed among the study population (M_{age} = 73.7 years, SD_{age} = 14 years). Bosutinib was associated with less worsening in CDR scores (HR = -0.62, $p < 0.001$, 95% CI: -1.02 - -0.30) and less decline in RBANS performance (HR = -3.42, $p < 0.001$, 95% CI: -3.59 - -3.72) during the year of treatment than population-based estimates of decline. In the 24-month follow up, wherein 16 patients were observed after 1 year post-intervention, 31.2% of participants exhibited worsened CDR levels compared to their 12-month performances.

Conclusions: Results support an overall positive outcome after one year of bosutinib. Future studies should explore the relationship between tyrosine kinases and neurodegenerative pathology as well as related avenues of treatment.

I. Introduction

To date, no therapy has proven to significantly halt clinical deterioration among patients with neurodegenerative conditions, including Alzheimer's and Parkinson's spectrum diseases.[1] Existing literature demonstrates conversion rates from amnestic mild cognitive impairment (MCI) to dementia ranging from 15-29% annually, with expected progression to more advanced stages cited at 22%-36% each year.[4-11] As many as 5.6% of patients with MCI have been reported to revert to normal cognition.[10] Sustained improvement among patients with dementia is unexpected, although transient periods of lucidity may be observed.[11]

The pursuit of an effective intervention has inspired interest in tyrosine kinase inhibitors (TKIs). Tyrosine kinases such as Abl and Src have been associated with the neuronal destabilization seen in neurodegenerative conditions.[12, 14] Several preclinical studies have shown that TKIs can facilitate autophagy, promoting the elimination of abnormal protein deposits.[12-13, 15-16] Additionally, TKI medications appear to reduce inflammation and apoptosis, possibly promoting

facilitatory microglial responses.[13, 17] These effects may not require a crossing of the blood brain barrier, as there appears to be reciprocal communication between neuroinflammation and systemic inflammatory factors.[17-19] Bosutinib (Bosulif) is a dual Src/Abl kinase inhibitor with a record of safety and efficacy for treatment of chronic myeloid leukemia.[20-23] The present paper reports on an ongoing, open-label clinical trial using bosutinib for the investigational treatment of degenerative dementias. We hypothesize that one year of bosutinib therapy will yield reduced rates of clinical deterioration compared to population-based estimates of decline in neurodegenerative disease.

II. Methods

2.1 Standard Protocol Approvals, Registrations, & Patient Consents

This study (Clinical Trial identifier # NCT02921477) was initially reviewed and approved by Quorum IRB. This study has since been transferred to Advarra IRB and is listed under the protocol number Pro00036231. The most recent approval number is CR00173276.

Potential participants were recruited from Los Angeles neurology clinics. If potential participants endorsed interest, study staff provided overview information to those patients and their caregivers. Screening was then completed (as detailed below), and once candidacy was established, study staff briefed participants and their caregivers on the protocol, possible risks and benefits, follow-up procedures, costs, and examinations. Informed consent was reviewed in full with participants and caregivers and allowed time for any and all questions. Caregivers were included in the consenting process to verify commitment and adherence to follow-up procedures. All participants provided written, signed informed consent. Each participant was given a copy of his or her signed consent.

2.2 Participants

Currently, 60 participants between the ages of 45-89 are enrolled in this study. This paper reports on (1) the 31 participants who have completed the first year of study involvement and (2) the 16 participants who have completed the second year. Of the 31 participants, 16 were diagnosed with Parkinson's disease spectrum disorders with dementia (PDD) (M_{age} = 71.8 years, SD_{age} = 10.94 years; 4 females, 12 males), while the remaining 15 met criteria for probable Alzheimer's dementia with evidence of pathophysiological process (AD) (M_{age} = 74.63 years, SD_{age} = 9.59; 8 females, 7 males).[8, 10] Of the 16 participants who completed the second year, 8 were diagnosed with PDD (M_{age} = 75.66 years, SD_{age} = 7.25 years; 1 female, 7 males) and 8 were diagnosed with AD (M_{age} = 79.75, SD_{age} = 6.02 years; 4 females, 4 males).

2.3 Neurocognitive and Behavioral Performance Measures

The following measures were used to evaluate participant neurocognitive status throughout study involvement: the Quick Dementia Rating Scale (QDRS) used to estimate the Clinical Dementia

Rating (CDR); Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; versions A-D); Montreal Cognitive Assessment (MoCA; 7.1-7.3); Smell Test (Brief Smell Identification Test); 9-Hole Pegboard Task; 25-foot Timed Gait Task; and Beck Depression Inventory (BDI-II).

The Quick Dementia Rating Scale (QDRS) form consists of 10 categorical questions (5 cognitive, 5 functional), each with 5 detailed options depicting the level of impairment as either 0 (normal), 0.5 (mild/inconsistent impairment), 1 (mild/consistent impairment), 2 (moderate impairment), or 3 (severe impairment). To ensure consistency, the individual identified as the caregiver agreed to complete the QDRS interview at each follow-up milestone. Based on Dr. Galvin's conversion table, total QDRS scores were converted to Clinical Dementia Rating (CDR) scores ranging from 0 (normal aging), 0.5 (mild cognitive impairment), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia).[25]

The Repeatable Battery for Assessment of Neuropsychological Status (RBANS) versions A, B, C, and D were administered at each follow-up timepoint to assess immediate memory, visuospatial skill, language, attention, and delayed memory.[22] The four versions (A-D) were rotated after each testing session to minimize practice effects.

The Montreal Cognitive Assessment (MoCA) was used to evaluate gross cognitive status.[27-28] The MoCA tests frontal-executive functions, language, orientation to time and place, visuospatial construction, attention, and immediate and delayed memory. MoCA scores range from 0-30 possible points; 26 or greater is considered to reflect normal cognitive status.[29] Different versions of the MoCA were utilized to mitigate practice effects.

The Timed 25-Foot Walk Test (T25-FW) and the Rolyan ® Nine-Hole Pegboard Test (9-HPT) were used to evaluate gross motor functioning and fine motor dexterity, respectively. Both tests were particularly relevant for participants with PD.[30] The Brief Smell Identification Test (B-SIT), which has also been shown as a valid and reliable measure, was used to assess olfactory function prior to study entry.[31]

2.4 Advanced MRI Techniques

Each prospective subject underwent advanced magnetic resonance (MR) neuroimaging as part of the inclusion criteria. The multimodal MRI included volumetric measurement of the hippocampus, arterial spin labeling (ASL) perfusion scans, blood oxygen level dependent (BOLD) sequences, and diffusion tensor imaging (DTI). These modalities have been shown to yield clinical indicators for various neurodegenerative subgroups and show sensitivity to disease progression.[32-35]

Participant scans were done at one of three imaging centers in the Los Angeles/Santa Monica area. Imaging sequences were standardized and data was harmonized among the locations. All

MR images were quality controlled prior to being processed and analyzed. Post-processing was done using FSL with identical parameters (www.fmrib.ox.ac.uk.fsl).[36]

Participants were required to do follow-up imaging at the same center where baseline scans were conducted. For each participant, the clinical information and imaging data was reviewed by a panel consisting of board-certified neurologists, board-certified psychiatrists, a neuropsychologist, and a neuroradiologist; diagnosis and clinical classification was determined by expert consensus.

2.5 Procedure

All participants received a neurocognitive examination, lumbar puncture, multimodal MRI, EKG, BDI and bloodwork to evaluate their eligibility for this study. To qualify for inclusion, participants were required to show pathophysiological evidence of AD or meet criteria for PDD. Estimated Clinical Dementia Rating (CDR) scores were required to fall between 0.5 and 2, a range equivalent to Mild Cognitive Impairment (MCI) and Moderate Dementia, respectively.[25-38]

The lumbar puncture, which assessed for Aß-42 and Tau protein levels in cerebrospinal fluid, has been shown to demonstrate sensitivity and specificity in identifying AD pathophysiology.[37] The advanced MRI obtained prior to study entry was required to show evidence of a neurodegenerative process for study inclusion: disproportionate atrophy of mesial temporal structures including the hippocampus, decreased signal on ASL in the temporal and parietal regions, and/or reduced signal in the putamen. Other pathological findings (e.g., stroke, cortical dysplasia, neoplasm) that could be related to the patient's dementia presentation were exclusionary.

Patients with cognitive decline due to acute illness or vascular pathologies were excluded. Other exclusionary criteria included advanced terminal illness, advanced kidney, pulmonary, cardiac, or liver failure, definite or probable pregnancy, breastfeeding, and Major Depressive Disorder (MDD). The Beck Depression Inventory-II (BDI-II), which has been demonstrated as a statistically valid and reliable measure of MDD, was administered as a screening method for depression.[39-40] Inability to give informed consent was also a basis for exclusion.

Concurrent interventions and therapies were not considered exclusionary unless the study doctor deemed them a threat to patient safety when used in conjunction with the study protocol. Study participants were allowed to participate in additional therapies at the same site and under the purview of the study doctor. Concurrent interventions were recorded and are included in the discussion section of this paper. Attempts were made to harmonize concurrent treatments, which included a list of nutraceuticals (see Table 1). Future publications from this study group will focus on distinguishing effect sizes between different treatment modalities.

Once enrolled, participants were given the study medication (at no cost) and instructed to take 1 pill each morning with breakfast. All participants started at 100mg daily for the first month. The dosage titration regimen was set to increase by 1 pill (100mg) each month until a maximum daily dosage of 300mg was achieved. Participants whose labs (detailed in the following paragraph) were within study guidelines with minimal-to-no side effects were cleared to increase to 200mg daily by the second month. After 2 months, based on the same criteria, participants were permitted to increase to the maximum 300mg daily dose. This dose was maintained for the duration of the first year unless labs or side effects necessitated a dose reduction. Participants whose transaminase levels or other tolerability issues precluded them from achieving the maximum study dose maintained the highest dose that was safe and tolerable for them. Upon achieving dose stabilization, participants were also allowed to use nutritional supplements according to a list (Table 1). Compliance with nutritional supplementation was discussed at each visit, but there was no attempt to perform pill counts or other means of monitoring.

Participants obtained bloodwork semi-weekly during the first three months of medication to verify safety and tolerability. After reaching the maximum dose, participants were cleared to decrease the bloodwork frequency to monthly for the duration of the year. Each lab order included tests for vitamin B12, thyroid hormone (TSH, T4, T3), bilirubin (direct and total), alkaline phosphatase, ALT, AST, potassium, magnesium, creatinine/creatinine clearance, and hemoglobin, as well as total counts of white blood cells, platelets, and absolute neutrophils. Additional labs were ordered at the discretion of study doctors based on tolerability, reported side effects, and patient history.

In addition, participants met routinely with study staff and doctors to assess tolerability and monitor for any potential side effects. Throughout the two years of study involvement, participants met with the doctor every month. Participants living out of state were permitted to meet this criterion through telemedicine visits so long as they tolerated the medication without side effects and had access to a local physician familiar with the study. All study participants were required to report to the primary study site for neuropsychological testing appointments.

Neuropsychological exams, including the RBANS, MoCA, 9-HPT, and T25-FW tests, were repeated at 6, 12, 18, and 24 months. Functional neuroimaging was repeated twice after baseline scans; once upon completion of study medication and again at the 2-year mark.

Participants were not paid or reimbursed for participation. Consultation and follow-up visits were provided free of charge. Pfizer served as the study sponsor and provided medication at no cost to participants. Most other study-related costs were absorbed by the principle investigator, any costs that fell to the responsibility of the participant were clarified prior to and as a part of informed consent.

2.6 Statistical Analyses

Bootstrapped Cox proportional hazards regression analyses were performed to assess the impact of bosutinib on participants' cognitive performance compared to the expected rate of cognitive decline in neurodegenerative disease. The expected rate of decline was calculated as the average of reported values in existing literature, yielding a 22% conversion rate from MCI to dementia and a 29% progression rate to a more advanced stage of dementia.[4-13] The expected rate of improvement for MCI was set at 5.6% while the expected rate of improvement for dementia was set at 0%.[9-10] All statistical analyses had an alpha value of 0.05 and were performed with IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

2.7 Data Availability

Data from this study will not be made publicly available due to ethical and privacy concerns. Anonymized data will be available upon reasonable request from any qualified investigator.

III. Results

3.1 Tolerability and Feasibility

All participants were able to tolerate the drug without notable side effects. 4 participants left the study for personal reasons unrelated to tolerability or medical justification. See Figure 1 for a delineation of maximum dosage achieved among the 31 participants who have completed the year of bosutinib treatment. BMI did not appear to be a primary limiting factor for maximum dose, as only 2 of the 9 participants who took 300mg or less had a BMI less than the normal cutoff of 18.5. Per the study protocol, participants whose labwork indicated elevated transaminase levels required a reduction in dose.

The only reported side effects were upset stomach, fatigue, and diarrhea, which occurred among less than 10% of participants. Overall, study participants tolerated the medication well. Bosutinib, therefore, has been confirmed as a safe agent among this population of older adults.

3.2 Cognitive Faculties at 12 Months of Bosutinib

Estimated CDR (Clinical Dementia Rating) scores were the primary cognitive outcome measure used in this study. Bosutinib was associated with less decline in CDR scale level (HR = -3.5, $p < 0.001$, 95% CI: -3.64 - -3.3) than the population-based estimate of expected cognitive deterioration. Bosutinib was also associated with an increased likelihood of maintaining a stable CDR scale level throughout the year of active treatment (HR = -0.62, $p < 0.001$, 95% CI: -1.02 - -0.30). Of the 31 participants who completed the year of bosutinib, 45.16% had an improved CDR score by at least one level from baseline at 12 months. An additional 45.16% had a stable CDR score at 12 months from baseline. Only 3 of 31 participants (9.68%) had a declined CDR scale level from baseline at 12 months (see Tables 2 and 3 for a breakdown of results stratified by neurodegenerative condition-type). There were no notable differences between groups stratified according to baseline CDR scores (Table 4).

MoCA (Montreal Cognitive Assessment) scores were used to assess for changes in gross cognitive status (MCID $\geq$ 2 points).[41] 22.6% of participants demonstrated clinically meaningful improvement on MoCA scores at 12 months. An additional 25.8% yielded stable MoCA scores from baseline at 12 months. 51.6% had reduced performance on the MoCA at 12 months. Bosutinib was associated with less decline in RBANS performance than the population-based estimate of decline (HR = -3.42, $p < 0.001$, 95% CI: -3.59 - -3.72). Assessments based on RBANS Total Index scores revealed clinically meaningful improvement in 22.6% of participants, clinically stable scores in 58.1%, and clinically meaningful decline in 19.4% (MCID $\geq$ 8 points).[42]

3.3 Absolute Risk Reduction & Numbers Needed to Treat at 12 Month Study Mark

Using population-based estimates of decline among patients with neurodegenerative disease, absolute risk reduction and numbers needed to treat were calculated for: 1) conversion of MCI to dementia and 2) progression to a more advanced stage of dementia.[4-7, 10-11] Absolute risk reduction was calculated to be 34.5–167% for participants enrolled with a baseline CDR equivalent to MCI; for participants enrolled with a baseline CDR equivalent to mild or moderate dementia, absolute risk reduction was calculated to be 27.8-245%. Numbers needed to treat were calculated to be 5.27-20 for participants enrolled with MCI. Numbers needed to treat for participants enrolled with mild to moderate dementia were calculated to be 3.85-8.33.

Based on reports of spontaneous recovery among 5.6% of patients with MCI who do not receive bosutinib therapy compared to participants in this study with MCI who did receive bosutinib therapy, absolute risk reduction was calculated to be 35.4% with a corresponding number needed to treat of 2.83.[10]

3.4 Cognitive Faculties at 6 Months Post Bosutinib (18-Month Mark)

At the time of this publication, 26 participants have exceeded the 18-month mark and 16 have surpassed the 24-months of study involvement. Of the 26 participants measured at 18-months, 30.8% yielded improved CDR scores compared to their performance at the 12-month mark. 38.4% exhibited stable CDR scores, and 30.8% showed worsened CDR scores. When comparing baseline CDR score to CDR score at the 18 month-mark, there was no longer a difference (statistical trend that did not withstand correction for multiple comparisons) in likelihood of dementia worsening between study participants and the population-based estimate of decline without intervention (HR = -0.53, $p = 0.1$, 95% CI: -1.15 - 0.31). However, participants were more likely to be at an improved CDR at the 24-month mark from their baseline CDR than was expected based on the population-based estimate of decline (HR = -2.05, $p < 0.001$, 95% CI: -3.62 - -1.04).

Regarding MoCA scores, at 18 months, 20% participants showed clinical improvement compared to scores at 12 months, 36% demonstrated clinically stable scores from 12 months, and the remaining 44% showed clinical decline from 12 months. RBANS Total Index Score results at the 18-month mark revealed 32% of participants had clinically meaningful improvement from 12 months, 36% who yielded clinically stable scores from 12 months, and the remaining 32% exhibited clinically meaningful reduction in scores from 12 months. When comparing RBANS score at 18 months to baseline scores, both participants and population-based estimates were equally likely to show decline (HR = -0.38, $p = 0.28$, 95% CI: -1.02 - 0.5); however, study participants were more likely to continue to show cognitive benefits than population-based estimates (HR = -1.82, $p < 0.001$, 95% CI: -3.34 - -0.66).

3.5 Cognitive Faculties at 1 Year Post Bosutinib (24-Month Mark)

At the time of this publication, 16 participants have completed the 24-months of study involvement. CDR scores among this patient subset show 18.8% with clinically meaningful improvement from 12 months, 50% with clinical stability, and 31.2% with clinically meaningful decline. When comparing baseline CDR score to CDR score at 24 months, there was no longer a difference in likelihood of dementia worsening between participants and the population-based estimate of decline (HR = 0.1, $p = 0.88$, 95% CI: -3.13 - 0.97). However, study participants were more likely to earn an improved CDR score at the 24-month mark compared to baseline than population-based estimates of expected decline (HR = -0.69, $p < 0.002$, 95% CI: -3.1 - -0.14).

24-month MoCA scores showed clinically meaningful improvement among 50% of participants from the 12-month mark, clinical stability among 43.8%, and a clinically meaningful decline in 1 subject (6.2%). RBANS Total Index scores at 24 months revealed 31.2% of participants with clinically meaningful improvement, 37.5% with clinically stable scores, and 31.2% with clinically meaningful worsening from 12 months. When comparing baseline RBANS scores to RBANS scores at the 24-month mark, study participants were equally likely to show decline as population-based estimates (HR = -0.24, $p = 0.6$, 95% CI: -1.02 - 1.58); however, participants were more likely to continue to show cognitive benefits (HR = -1.90, $p < 0.001$, 95% CI: -3.53 - -0.61).

IV. Discussion

These results bolster findings from previously reported studies and justify further investigation of bosutinib as a therapeutic agent for dementia.[13, 28] The data suggest an overall positive outcome among participants after a year of bosutinib, with a worsening in condition following treatment discontinuation. By 6 months post-bosutinib, patient deterioration more than tripled and continued to decline by the 24-month mark (gauged by the CDR scale). Moreover, this observation was consistent among all participants, regardless of how severe the dementia was at baseline (Table 4). Even so, study participants demonstrated increased likelihood of maintaining

stable or improved cognitive performance (gauged by the CDR and total RBANS scores) than would be expected based on population-based estimates of decline in neurodegenerative disease.

Future studies should include a larger study population and extended follow-up to assess durability beyond 2 years, as this study demonstrates a well-documented positive response among participants thus far. The open-label nature of this study did not preclude participants from pursuing other treatments, including nutraceuticals, dietary adjustments, focused ultrasound therapy, and/or regenerative approaches (e.g., exosomes).[43-44] 27 participants also underwent focused transcranial ultrasound as part of a separate study.[45] Preliminary comparative analyses of groups suggest that transcranial ultrasound did not yield the same degree of therapeutic benefit unless it was paired with bosutinib treatment.[43] Co-occurring interventions make it challenging to interpret direct relationships between the study medication and outcome results. However, given the likelihood of multi-system involvement in degenerative dementia, studies designed with a multi-modal approach may yield improved clinical efficacy. The multi-faceted treatment approach enacted in this study clinic was built around the intention to address the multi-system failures associated with Alzheimer's and Parkinson's spectrum diseases.[45-47] Results from combined interventions will be addressed in future publications. An extension of this open-label study will delay any co-occurring interventions for six months in order to better clarify the independent contribution of bosutinib to the overall effect. Additional review of outcome measures obtained for this study, including neuroimaging and motor functioning, will also be included in future publications.

Future research should explore the usefulness of TKIs such as bosutinib in treating other degenerative conditions, such as dementia with Lewy bodies (CTI: NCT03888222). Other studies may be organized to evaluate the density of protein aggregates with Tau PET scans before and after bosutinib treatment. Inflammatory serological markers evaluated before and after bosutinib treatment may help clarify the mechanism(s) of action. It will also be important to further elucidate the optimal dosage and duration of a treatment plan involving bosutinib for neurodegenerative conditions. TKI agents with better blood brain barrier penetration may also be considered. Depending on FDA licensing requirements for new indications of bosutinib, phase II and III study designs may be expedited to improve the accessibility of this medicine for all those seeking a therapeutic option for dementia.

Appendix 1: Authors

Name	Location	Contribution
Kennedy Mahdavi, B.S.	Neurology Management Associates	Data collection and analysis, site management, drafting of the manuscript
Sheldon Jordan, M.D.	Synaptec Network	Study design and conceptualization; revision of manuscript
Hannah Barrows, B.A.	Neurology Management Associates	Data collection and analysis, site management

Maša Pravdic, B.A.	Neurological Associates of West Los Angeles	Data collection and site management
Barshen Habelhah, M.A.	Neurology Management Associates	Data collection and analysis
Natalie Nicodemus, B.A.	Neurology Management Associates	Data analysis
Robin Blades, B.A.	Neurological Associates of West Los Angeles	Data collection
Jessica Iovine, M.A.	Neurological Associates of West Los Angeles	Data collection
Sergio Becerra, B.S.	Synaptec Network	Data analysis
Rachel Steiner, B.A.	Neurology Management Associates	Revision of the manuscript
Marisa Chang, M.D.	Neurology Management Associates	Conceptualization of the study, data acquisition
Santosh Kesari, M.D.	Pacific Neuroscience Institute	Data collection and analysis, revision of the manuscript
Alexander Bystritsky, M.D.	University of California, Los Angeles	Revision of the manuscript
Ed O'Connor, M.D.	Neurological Associates of West Los Angeles	Data acquisition, site management
Hyman Gross, M.D.	University of Southern California	Data acquisition, site management
F. Scott Pereles, M.D.	RAD Alliance	Data acquisition, revision of the manuscript
Mike Whitney, A.A.	RAD Alliance	Data acquisition
Taylor Kuhn, Ph.D.	Synaptec Network	Data analysis, statistical analysis, revision of the manuscript

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Figure 1: Maximum Bosulif Dosage Achieved Among Study Participants
A breakdown of maximum Bosulif dosages among all participants. Total N = 31.

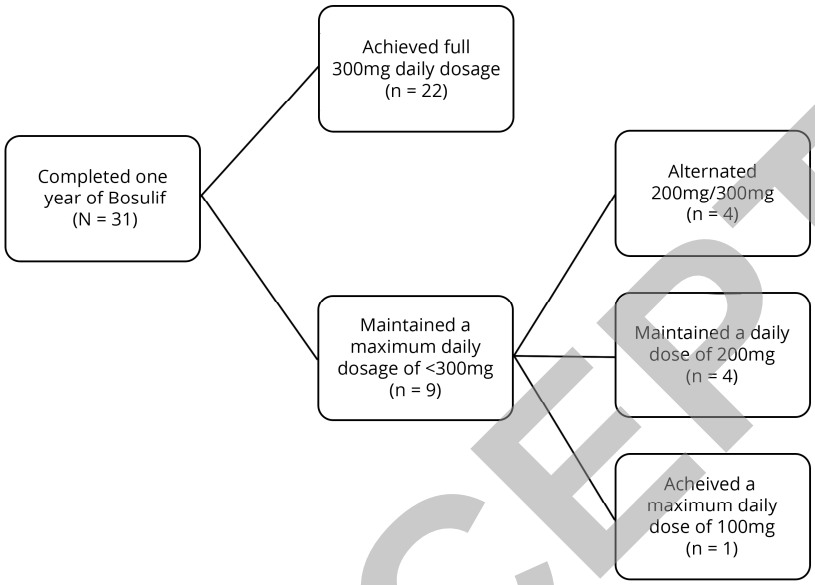

Table 1: List of Recommended Supplements
This list was reviewed with study participants as an additional treatment approach.

Table 2: Table of 12 Month CDR Score Conversions per Neurodegenerative Type
Reflects changes in CDR among each subject population, as indicated by an increase or decrease by at least one level.

Table 3: Table of CDR Scores from Baseline to 12 Months Per Condition
Top: Dementia without Parkinsonian Features; Bottom: Parkinson's Spectrum Disorders with Dementia

Table 4: CDR Conversion Patterns Stratified According to Baseline CDR Scale Level
Top: Dementia without Parkinsonian Features; Bottom: Parkinson's Spectrum Disorders with Dementia

Table 1

List of Recommended Supplements

Supplement Name	Dosage	Availability
Coenzyme Q10 (Ubinquinol)	300mg/day	Over-the-counter
Theracurmin HP	600mg/day	Over-the-counter
Resveratrol	1000-2000mg/day	Over-the-counter
Vitamin D3	1000-2000 units/day	Over-the-counter
Neo40	1 lozenge/day	Over-the-counter
Tru Niagen (nicotinimide riboside)	300mg/day	Over-the-counter
Metatrol (wheat germ extract)	2 capsules/day	Over-the-counter
Valtrex (valacyclovir)	500mg/day	Prescription required
Valcyte (valgancyclovir)	450mg/day	Prescription required; only if indicated by labwork

Table 2

Table of 12 Month CDR Score Conversions per Neurodegenerative Type

	Dementia without Parkinsonian Features		Parkinson's Spectrum Diseases with Dementia	
Improved CDR	53.3%	(8/15)	37.5%	(6/16)
Stable CDR	40%	(6/15)	43.8%	(8/16)
Declined CDR	6.7%	(1/15)	18.8%	(2/16)

**Reflects changes in CDR among each subject population, as indicated by an increase or decrease by at least one level.*

Table 3

Table of CDR Scores from Baseline to 12 Months Per Condition

Dementia Without Parkinsonian Features

Participant ID	Baseline CDR	6 Month CDR	12 Month CDR
0012	1	0.5	0.5
0014	1	0.5	0.5
0015	3	3	3
0005	0.5	0.5	0.5
0004	2	1	2
0006	0.5	0.5	0.5
0008	1	0.5	0.5
0009	1	0.5	0
0026	1	1	1
0025	1	2	0.5
0033	0.5	0	0.5
0027	0.5	0.5	0
0051	0.5	0.5	0
0032	0.5	1	1
0044	0.5	0.5	0

Parkinson's Spectrum Diseases with Dementia

Participant ID	Baseline CDR	6 Month CDR	12 Month CDR
0016	2	1	0.5
0003	2	1	1
0001	1	1	1
0036	0.5	0.5	1
0010	1	0.1	1
0018	1	1	1
0020	0.5	0.5	0.5
0019	0.5	0.5	0.5
0007	1	0	0.5
0022	0.5	0.5	0.5
0024	1	1	0.5
0043	1	0.5	0.5
0047	0.5	0.5	1
0031	0.5	0.5	0
0037	0.5	0.5	0.5
0002	1	1	1

Table 4

CDR Conversion Patterns Stratified According to Baseline CDR Scale Level

Dementia without Parkinsonian Features

	Baseline = 0.5 (7/15)		Baseline = 1 (6/15)		Baseline = 2 (1/15)		Baseline = 3 (1/15)	
Improved CDR	42.9%	(3/7)	83.3%	(5/6)	--	--	--	--
Stable CDR	42.9%	(3/7)	16.7%	(1/6)	100%	(1/1)	100%	(1/1)
Declined CDR	20.0%	(1/5)	--	--	--	--	--	--

Parkinson's Spectrum Diseases with Dementia

	Baseline = 0.5 (7/16)		Baseline = 1 (7/16)		Baseline = 2 (2/16)		Baseline = 3 (0/16)	
Improved CDR	14.3%	(1/7)	42.9%	(3/7)	100%	(2/2)	--	--
Stable CDR	57.1%	(4/7)	57.1%	(4/7)	--	--	--	--
Declined CDR	28.6%	(2/7)	--	--	--	--	--	--

Treatment of dementia with bosutinib: An open-label study of a tyrosine kinase inhibitor

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