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RESEARCH ARTICLE

Rasagiline effects on glucose metabolism, cognition, and tau in Alzheimer's dementia

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Abstract

Background: A Phase II proof of concept (POC) randomized clinical trial was conducted to evaluate the effects of rasagiline, a monoamine oxidase B (MAO-B) inhibitor approved for Parkinson disease, in mild to moderate Alzheimer's disease (AD). The primary objective was to determine if 1 mg of rasagiline daily for 24 weeks is associated with improved regional brain metabolism (fluorodeoxyglucose-positron emission tomography [FDG-PET]) compared to placebo. Secondary objectives included measurement of effects on tau PET and evaluation of directional consistency of clinical end points.

Methods: This was a double-blind, parallel group, placebo-controlled, community-based, three-site trial of 50 participants randomized 1:1 to receive oral rasagiline or placebo (NCT02359552). FDG-PET was analyzed for the presence of an AD-like pattern as an inclusion criterion and as a longitudinal outcome using prespecified regions of interest and voxel-based analyses. Tau PET was evaluated at baseline and longitudinally. Clinical outcomes were analyzed using an intention-to-treat (ITT) model.

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Results: Fifty patients were randomized and 43 completed treatment. The study met its primary end point, demonstrating favorable change in FDG-PET differences in rasagiline versus placebo in middle frontal ($P < 0.025$), anterior cingulate ($P < 0.041$), and striatal ($P < 0.023$) regions. Clinical measures showed benefit in quality of life ($P < 0.04$). Digit Span, verbal fluency, and Neuropsychiatric Inventory (NPI) showed non-significant directional favoring of rasagiline; no effects were observed in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) or activities of daily living. Rasagiline was generally well tolerated with low rates of adverse events and notably fewer neuropsychiatric symptoms in the active treatment group.

Discussion: These outcomes illustrate the potential benefits of rasagiline on clinical and neuroimaging measures in patients with mild to moderate AD. Rasagiline appears to affect neuronal activity in frontostriatal pathways, with associated clinical benefit potential warranting a more fully powered trial. This study illustrated the potential benefit of therapeutic repurposing and an experimental medicine proof-of-concept design with biomarkers to characterize patient and detect treatment response.

KEYWORDS

Alzheimer's disease, dopamine, FDG-PET, flortaucipir, glucose metabolism, MAO-B, QoL-AD, rasagiline, tau PET

1 | INTRODUCTION

The need for effective therapeutics for patients with mild to moderate Alzheimer's disease (AD) is urgent, given limitations of currently approved medications and a high rate of negative clinical trial outcomes.¹ We conducted a Phase II "proof of concept" (POC) randomized clinical trial to evaluate the potential benefit of rasagiline in patients with mild to moderate AD. Rasagiline is a selective monoamine oxidase B (MAO-B) inhibitor approved for treatment of Parkinson disease (PD) that has been shown to be safe and well-tolerated. MAO-B inhibition increases the availability of dopamine, which mediates cognitive functions including executive abilities, working memory, attention, and reward as well as motor function.² In nonclinical AD models, rasagiline has demonstrated potential neuroprotection, with reductions in amyloid accumulation, tau hyperphosphorylation, and neurofibrillary tangle formation.^{3,4}

Studies of rasagiline in patients with PD and schizophrenia suggest that the agent produces cognitive and other clinical benefits.⁵⁻⁷ Selegiline, a related MAO-B inhibitor, has shown cognitive benefit in AD and PD,⁸⁻¹⁰ and phase II and III trials of the MAO-B inhibitor lazabemide in AD patients demonstrated benefit in several cognitive and behavioral endpoints.¹¹ However, some clinical studies of MAO-B inhibitors have shown mixed or negative results. For example, sembragiline did not meet cognitive or functional end points in AD patients over 52 weeks, but neuropsychiatric and functional benefit was noted in the more impaired subgroup. Ladostigil showed potential atrophy-slowness effects but did not significantly alter clinical

progression in mild cognitive impairment patients.^{12,13} No trial has examined the effects of rasagiline on functional brain networks and relationship to clinical benefit. The present study sought to understand the rasagiline as a potential treatment for patients with mild to moderate AD, supported by imaging of neuronal function and tau pathology.

The primary end point was change in cerebral glucose metabolism measured using fluoro-2-deoxyglucose (FDG) positron emission tomography (PET), demonstrated to correspond to disease progression and functional treatment effects.^{14,15} Based on prior studies,¹⁶ we hypothesized that FDG changes would be measurable with greater power over a shorter duration than clinical effects and could aid in understanding the biological basis for potential clinical outcomes. FDG-PET was also used to evaluate the presence of an AD-like pattern of glucose metabolism as an enrollment prerequisite, increasing confidence in a diagnosis of AD. A progressive pattern of temporoparietal hypometabolism has been reported to differentiate AD from other dementias, correlate with clinical status,¹⁷ and to be consistent with brain amyloidopathy.¹⁸ Clinical end points were evaluated as secondary outcomes to verify directional consistency with FDG.

This trial also included longitudinal measurement of tau with flortaucipir (Tauvid; Avid Radiopharmaceuticals) as a measure of AD pathology. Tau aggregation is observed early in AD in medial temporal regions, spreading to lateral temporal, posterior, and frontal neocortex as AD progresses.¹⁹⁻²¹ Tau increases have been detected over periods as short as 9 months.²² This trial expanded on prior studies by measuring tau changes over a shorter period of 24 weeks and a broad range of AD severity, concurrent with FDG-PET.

HIGHLIGHTS

- Rasagiline is a monoamine oxidase B inhibitor approved in Parkinson disease.
- Rasagiline was evaluated in patients with mild to moderate Alzheimer's disease.
- A beneficial effect on frontostriatal glucose metabolism was observed versus placebo.
- Directional changes in quality of life and cognition supported clinical benefit.
- Relationships were observed between tau, other biomarkers, and treatment effect.

2 | METHODS**2.1 | Study design**

This was a double-blinded, randomized, placebo-controlled study of the effects of 0.5 mg of rasagiline daily followed by 5 months of 1 mg of oral rasagiline daily in 50 patients with mild to moderate AD (clinicaltrials.gov NCT02359552). The study was conducted after institutional review board approval with informed consent. Key inclusion criteria were a clinical diagnosis of probable AD (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINDS-ADRDA) criteria), age 50 to 90 years, Mini-Mental State Exam (MMSE) 12-26, and Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) pattern of hypometabolism consistent with AD.²³ Exclusion factors included neurologic, radiologic, or laboratory indications of non-AD dementia; medications that might interact with rasagiline; and factors that might lead to inability to complete the study. Patients on stable doses of cholinesterase inhibitors and memantine for at least 3 months prior to randomization were permitted. No dose changes were permitted during the study.

The primary outcome measure of this exploratory trial was the change from baseline to week 24 in FDG-PET in pre-specified AD-relevant regions including medial and lateral temporal, posterior cingulate-precuneus, inferior parietal, and middle frontal cortices. The anterior cingulate and striatum, relatively preserved in late AD, were prespecified given their glucose metabolic correlation with dopamine²⁴ and a reported increase in striatal glucose metabolism with associated neuropsychiatric benefit following selegiline administration.²⁵ A voxel-based data-driven pattern derived from a multivariate machine learning analysis of baseline and 24-week scans was evaluated. This approach measures multi-region response as a single end point, taking into account relationships between regions.

Secondary outcome measures included change in tau measured by flortaucipir PET over 24 weeks; safety and tolerability; and the following clinical end points: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog), MMSE, Digit Span (DS), Controlled

RESEARCH IN CONTEXT

1. Systematic review: The authors reviewed the literature using PubMed, meeting abstracts and presentations, and other on-line searches. Relevant publications regarding studies of monoamine oxidase B (MAO-B) inhibitors and imaging biomarkers used in the study were cited.
2. Interpretation: This double-blind, placebo-controlled experimental medicine study of the effects of rasagiline in Alzheimer's disease (AD) met its primary outcome of improved or mitigated decline of glucose metabolism in the treatment group compared to placebo. Directional changes consistent with treatment benefit were observed in some measures of cognition, including those mediated by frontal subcortical systems sensitive to dopaminergic effects, and quality of life.
3. Future Directions: Improved treatments for patients with mild-to-moderate AD are needed. Repurposed agents offer a means of developing new therapies while shortening development times and reducing cost. This study suggests that rasagiline warrants further evaluation as a repurposed therapy for AD, and illustrates a proof-of-concept (POC) study design as a model for other studies.

Oral Word Association Test (COWAT), Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC), ADCS Activities of Daily Living (ADL) scale, Quality of Life-AD (QoL-AD, with study partner), and Neuropsychiatric Inventory (NPI).

2.2 | Randomization

The study was conducted by the Cleveland Clinic Lou Ruvo Center for Brain Health at three sites (Las Vegas NV, Cleveland OH, Lakewood OH). Randomization was stratified by site, performed by the research pharmacist using a predetermined randomization schedule in which participants were assigned to rasagiline or placebo in a 1:1 ratio using randomly generated blocks of four or six participants.

2.3 | Statistical power

Prior FDG-PET studies showed that metabolic changes associated with cognitive effects in AD can be detected in an unpaired design with less than 20 participants per arm.¹⁴ Disease-related decline can be detected, although powered measurement of mitigation requires additional participants or time.¹⁶ The study was not powered for clinical significance, but—as an experimental medicine approach—was designed to assess directionality for consistency with FDG findings and to determine the number of participants required to show a rasagiline-placebo difference in a powered trial.

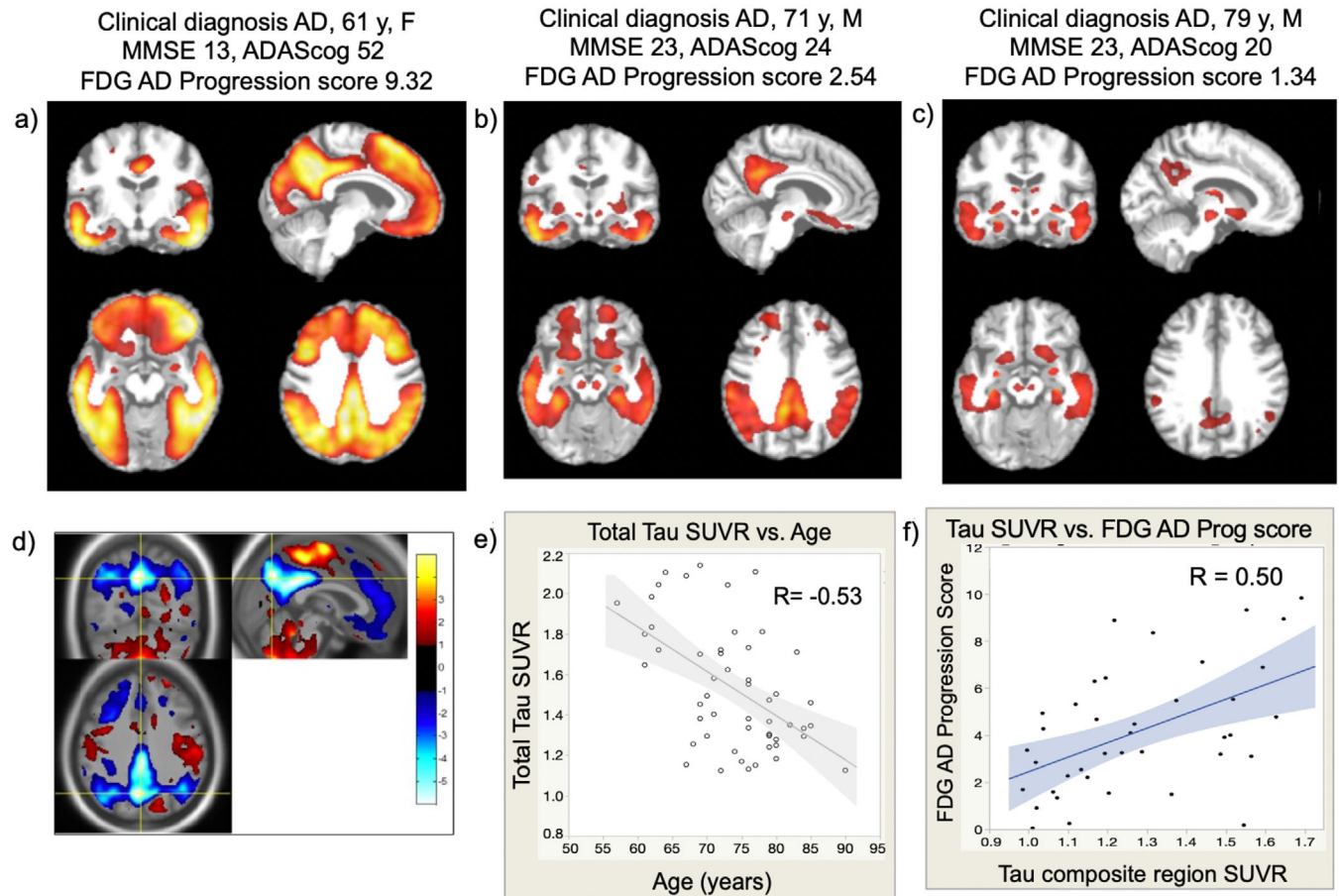


FIGURE 1 Baseline FDG and Tau burden. a-c, Tau burden for three participants age 61, 72, and 79 years shown with baseline clinical and FDG scores. d, Pattern of hypometabolism and preservation relative to whole brain that is quantified by the AD Progression score. e, Relationship between participant age and total tau SUVR. f, Relationship between tau burden in a composite of temporal and parietal regions involved in the pattern of (d) versus FDG-AD Progression score

2.4 | Procedures

2.4.1 | Medication

Rasagiline was initiated at 0.5 mg once daily for 4 weeks, increased to a 1 mg dose once daily at week 5, and maintained at this dose until the end of week 24. Active and placebo tablets were provided by Teva, re-coated identically, and repackaged by randomization ID in a blinded manner.

2.4.2 | Image acquisition and measurement

MRI was acquired at screening, and FDG and flortaucipir PET imaging were performed at baseline and at week 24. Images were acquired using protocols based upon the Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni-info.org) and processed as described in the Supplemental Material.

Each participant's baseline FDG-PET scan was evaluated using two previously developed image classifiers that use a single time point. The first was trained to differentiate scans of persons having status of

amyloid negative and cognitively normal, amyloid positive with various stages of MCI and AD, frontotemporal dementia, and dementia with Lewy bodies (DLB). The second quantifies the degree to which a scan expresses a pattern of hypometabolism and preservation relative to whole brain that reflects the progression of AD from amyloid negative, cognitively normal status through amyloid-positive AD dementia. This pattern (Figure 1d) is characterized by hypometabolism in posterior cingulate, precuneus, inferior parietal, and temporal cortices, and correlates with subsequent rate of cognitive decline.²³ Participants were included if their highest probability class was on the AD spectrum, with or without indication of secondary disease such as DLB.

FDG Standardized Uptake Value ratios (SUVRs) were measured and compared using different reference regions to confirm that changes were not driven by a single reference. Data-driven multivariate machine learning was applied to identify voxel intensity patterns characterizing differences between treatment arms. Scans were grouped into classes based upon visit (baseline, 24 weeks), study arm, and age (younger, older), and input to the classifier software. The software used Principal Component Analysis (PCA), Canonical Variate Analysis (mathematical combinations of PCs), and intensive iterative split-half data resampling to determine the pattern(s) that best discrim-

inated groups while minimizing data overfitting.²⁶ Pattern expression was quantified as a numeric score for each participant.

Tau SUVRs were measured in cortical tissue excluding cerebellum; a composite temporal region, the regions measured for FDG-PET; and using an adaptive approach that measured the change in subject-specific set of voxels that were suprathreshold at baseline or 24 weeks to avoid directional bias, standardized to a common total volume. White matter and cerebellar cortex reference regions were defined using a Gaussian decomposition approach (PERSI) (Supplement).²⁷

2.4.3 | Clinical end points

The ADAS-cog, NPI, ADCS-ADL, DS, and COWAT were administered at baseline, and at weeks 4, 8, 24, and 28. MMSE was administered at screening, baseline, and 24 weeks. The CGIC was collected at 4, 8, 24, and 28 weeks. QoL-AD was administered at baseline and 24 weeks. Safety was monitored through weekly review of adverse events throughout the study.

2.4.4 | Statistical analysis

Participants who completed both PET visits and passed image quality control were evaluated longitudinally. Six-month changes in SUVR values and classifier scores were compared between treatment arms by ANOVA adjusted for age, baseline values, and interaction terms when applicable (JMP v14 (SAS); G:Power software). Comparisons were also made within younger and older age strata given reports of greater tau and more rapid progression in younger AD participants²⁰ and potential comorbidities that may influence outcomes in older participants. Statistical comparisons were based on absolute change values.

Mixed-model repeated-measures analyses were used to assess between-group clinical end point differences in modeled change over 24 weeks. The dependent variable was the change from baseline score. Fixed effects were baseline outcome measure scores, treatment arm, visit, and treatment-by-visit interaction. Study visit was treated as a continuous variable; an unstructured variance-covariance matrix was used. The primary efficacy analysis was based on the modified intention-to-treat (mITT) population, including all randomly assigned participants with at least one post-baseline observation. Testing for treatment differences was conducted by assessing the statistical significance of the treatment-by-visit regression coefficient. Relationships between clinical and imaging end points were explored using correlation (Pearson R). Because this was a preliminary POC study, no adjustments for multiple comparisons were made and a two-sided *P*-value of 0.05 was considered significant.

In addition to including baseline values as model covariates, methods were implemented to further assess the impact of baseline differences on outcomes. The software package “designmatch”²⁸ was used to match treatment and placebo groups for MMSE, ADL, ADAS, and QoL-AD at baseline. T-test and Analyses of Covariance (ANCOVAs) were run on the reduced set. A Cochran-Mantel-Haenszel test

was performed on the full data set, splitting the sample at the median for the MMSE (score of 20). Pre-defined exploratory analyses evaluated treatment effects for all clinical end points by baseline clinical severity measured by MMSE.

3 | RESULTS

3.1 | Participants

Between May 19, 2015 and January 26, 2018, 96 participants were screened, of whom 50 were randomized to rasagiline or placebo and 43 completed treatment. Of the 25 placebo participants, 3 were lost to follow-up (delusions, stroke, worsening pseudobulbar/other effects), and one did not have a week-24 FDG PET scan, resulting in 21 placebo participants for image analysis. Of the 25 participants in the rasagiline arm, 4 were lost to follow-up (broken hip/rib, atrial fibrillation, other non-adverse event factors) (Figure S1).

Table 1 shows the demographic and baseline clinical characteristics of enrolled patients by treatment arm. Age, sex, education, genotype, and baseline NPI, DSPAN, and COWAT scores did not differ between groups. MMSE and ADAS-cog baseline scores were more impaired (by chance) in the placebo arm than the rasagiline arm ($P < 0.06$), whereas the rasagiline arm had worse baseline QoL-AD scores ($P < 0.02$). Of the 43 participants who completed the study, one did not have a week-24 FDG PET scan and 3 were excluded from analysis due to pre-specified behavioral or motion confounds during image acquisition. Among the 39 participants included in longitudinal image analysis, baseline MMSE and ADAS-cog scores did not differ between groups and QoL-AD scores were worse in the rasagiline-treated group ($P < 0.05$).

3.2 | Baseline PET and ApoE characterization

Of the 59 participants whose screening FDG scans were analyzed using the Dementia Classifier, 57 exhibited a pattern of hypometabolism classified as AD-like and were included for potential enrollment. Seventy-one percent of participants were apolipoprotein E gene (APOE) $\epsilon 4$ variant carriers, consistent with trials where positive amyloid imaging is used as an entry criterion.²⁹ Participants were diverse in FDG AD Progression Classifier scores (Figure 1f), which correlated with baseline MMSE ($R = -0.44$, $P < 0.001$) and ADAS-cog scores ($R = 0.42$, $P < 0.003$). AD Progression score and baseline MMSE did not differ significantly between study arms in the PET analysis population.

Tau burden varied widely across participants (Figures 1a-c) but did not differ between treatment arms. Tau was associated with age (Figure 1e), as younger participants (age 57 to 69 years) exhibited pervasive burden while oldest participants (late 70s to 90) had lower, primarily temporal burden with smaller posterior clusters, and patients in their 70s showed a wide range. Spatial patterns varied in asymmetry and occipital involvement. Forty-seven of the 50 participants (94%) had readily visualized elevated flortaucipir and positive regional SUVRs,

TABLE 1 Baseline demographic and clinical characteristics of the study population

Mean (std dev)	Placebo (N = 25)	Rasagiline (N = 25)	All (N = 50)	P-value (Placebo vs Rasagiline)
Age (range)	73.4 (7.1) (57 - 84)	74.7 (7.4) (62 - 90)	74 (7.2) (57 - 90)	0.53
Gender (F/M)%	44 / 56	56 / 44	50 / 50	0.60
Education	14 (2)	14 (3)	14 (3)	0.83
ADAS-Cog	28 (11)	23 (6)	26 (9)	0.06
MMSE	19 (5)	21 (4)	20 (4)	0.06
ADL	58 (11)	62 (8)	60 (10)	0.20
NPI	8 (9)	8 (8)	8 (8)	0.78
DSPAN	12 (3)	13 (3)	12 (3)	0.13
COWAT	21 (13)	27 (13)	24 (13)	0.13
QOL-AD	40 (5)	36 (6)	38 (6)	0.02
APOE 2/3	4%	4%	4%	0.50
2/4	0%	4%	2%	
3/3	16%	29%	22%	
3/4	60%	38%	49%	
4/4	20%	25%	22%	
AChEI(s)	84%	84%	84%	1.00
Memantine	44%	40%	42%	0.78
Antidepressant(s)	36%	56%	46%	0.16
Anxiolytic(s)	4%	4%	4%	1.00
Antipsychotic(s)	8%	4%	6%	0.56
site id 1	48%	52%	50%	1.00
site id 2	36%	36%	36%	
site id 3	16%	12%	14%	

while three had threshold cortical SUVR values (1.3). Total tau correlated with FDG AD Progression classifier score ($R = -0.41$, $P < 0.003$).

3.3 | Trial outcomes

3.3.1 | Primary end point

The study met its primary end point of improvement in longitudinal glucose metabolism in rasagiline-treated participants versus placebo in one or more prespecified regions and in the pattern determined through voxel-based analysis (Figure 2a,b). Rasagiline-treated participants decreased less than placebo-treated participants in middle frontal cortex (left $P < 0.012$, E.S. 0.82; bilateral $P < 0.025$, E.S. 0.75), anterior cingulate cortex ($P < 0.043$, E.S. 0.68), striatum ($P < 0.02$, E.S. 0.83) (Table 2) and in the voxel-based classifier-derived pattern ($P < 0.02$, Figure 2b), which was consistent with regional effects. Treatment effects remained significant when including age, baseline SUVR, and baseline MMSE as covariates. Age was a significant covariate for middle frontal cortex and striatum. Results using whole brain, subcortical white matter, and pons as alternate reference regions were in agreement regarding affected regions and directionality.

Placebo arm FDG AD Progression scores increased in severity ($P < 0.01$), and regional SUVRs likewise decreased in posterior cingulate-precuneus ($P < 0.03$, E.S. 0.74), inferior parietal ($P < 0.01$, E.S. 0.86), and middle frontal ($P < 0.001$, E.S. 1.74) regions, with decline greater in younger participants.

3.3.2 | Secondary end points

Longitudinal clinical end points for the rasagiline and placebo arms over 24 weeks are presented in Figure 3. A favorable outcome for rasagiline compared to placebo was observed for QoL-AD ($P < 0.04$ all participants, adjusted for baseline QoL; $P < 0.07$ with a reduced set of matched baseline participants and adjusted for baseline QoL and MMSE; $P < 0.07$ Mantel-Haenszel chi-square). In particular, uniform improvements were observed in rasagiline-treated participants compared to decline in placebo participants with similar baseline values (Figure 3b,c), and trajectories were clearly separated in the matched baseline analysis of all ages (Figure 3d). Directionally favorable outcomes were observed in Digit Span, CGIC, COWAT, and NPI. No significant differences were observed in ADL and ADAS-cog (Figure 3a, Table S1). Mean values for each time point and results for pre-specified

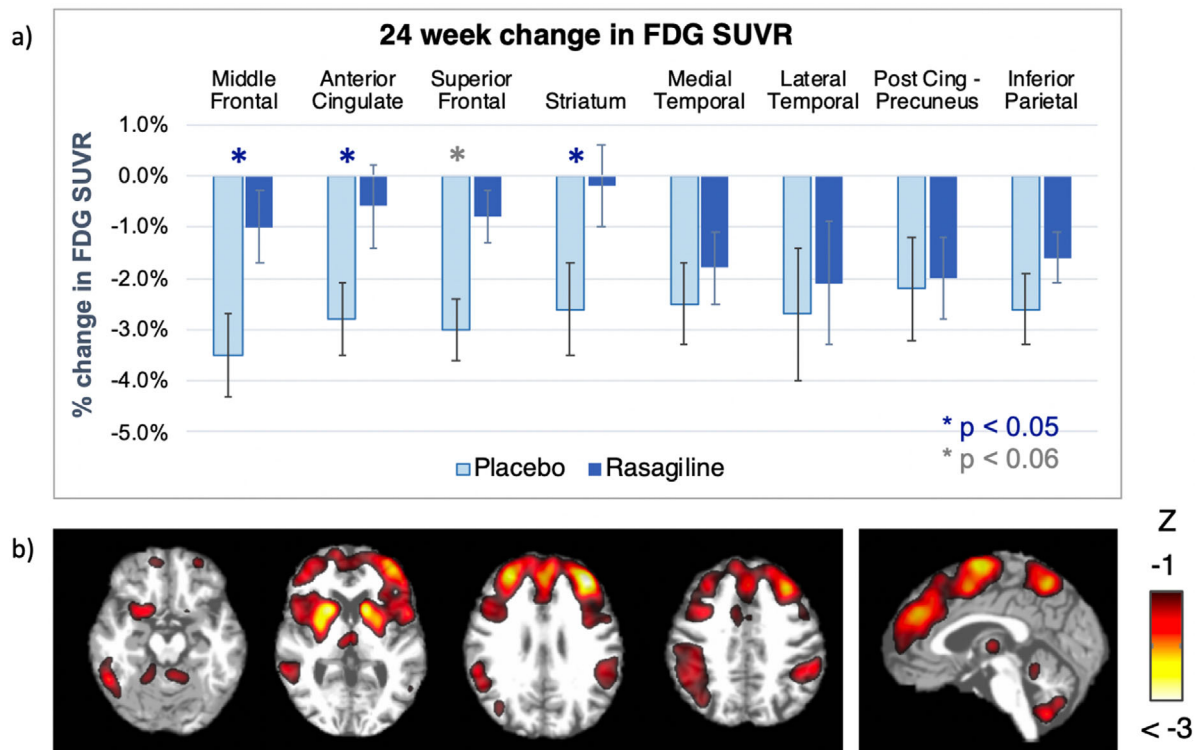


FIGURE 2 a, Twenty-four-week change in FDG SUVR in placebo- versus rasagiline-treated patients. b, Longitudinal voxel-based classifier results showing regions where rasagiline-treated participants declined less in glucose metabolism than placebo-treated participants

MMSE strata are shown in the Supplementary Material. There were no side effects.

Increases in tau PET were observed in some participants over 24 weeks, particularly those with higher baseline values (Figure 4a,b). Greater slopes and statistical power were observed when using the adaptive method that defined the region of interest according to combined pre- or post-suprathreshold voxels (Figure 4b). No treatment differences in change in flortaucipir were observed in cortical regions having suprathreshold values at baseline. Uniform longitudinal decreases were observed in the rasagiline but not placebo arm in subcortical regions, particularly accumbens ($P < 0.0001$) and putamen ($P < 0.003$) (Supplement).

3.3.3 | Relationships between imaging and clinical end points

Higher tau burden, lower glucose metabolism, and lower cortical thickness in temporal regions at baseline correlated with greater decline in MMSE score in placebo participants ($P < 0.008$, $P < 0.05$, $P < 0.004$, respectively). These relationships (Figure S2a) were not seen in rasagiline trajectories, which were relatively stable or improved independent of these baseline values. Longitudinal differences between rasagiline and placebo arms were most pronounced in participants having greater tau, lower metabolism, and lower volumes in temporal regions at baseline. Change in QoL-AD score, which differed between placebo and rasagiline arms, correlated with a pattern of increased metabolism

in anterior cingulate, frontal, and striatal regions (Figure S2b,c) and with FDG SUVR increases in these regions (anterior cingulate $R = 0.47$, $P < 0.002$, caudate $R = 0.47$, $P < 0.002$) (Figure S2d).

3.3.4 | Safety and tolerability

Rasagiline was generally well tolerated, with neuropsychiatric adverse events (AEs) in 5 (20%) placebo and 0 (0%) rasagiline patients, non-neuropsychiatric AEs in 10 (40%) placebo and 13 (52%) rasagiline patients, and no treatment-related deaths (Table S2). No rasagiline-treated participants experienced neuropsychiatric symptoms of agitation/irritability or psychosis compared to five placebo participants (t test not significant).

4 | DISCUSSION

4.1 | Rasagiline effects

This investigation of rasagiline as a treatment for AD met its primary outcome of demonstrating improvements or less decline in glucose metabolism changes in prespecified regions compared to placebo over 24 weeks. FDG-PET findings suggested that rasagiline supports metabolic function in frontostriatal networks. Rasagiline prolongs dopamine availability through MAO-B inhibition, and results were consistent with previous studies that have established dopaminergic

TABLE 2 Region of interest results: difference (24 weeks minus baseline) mean, S.D. and difference between arms with 95% confidence interval

SUVRs	Middle frontal	Anterior cingulate	Superior frontal	Striatum	Medial temporal	Lateral temporal	Post cing - precuneus	Inferior parietal
Placebo	-0.032 (0.030)	-0.020 (0.021)	-0.016 (0.022)	-0.024 (0.029)	-0.015 (0.034)	-0.020 (0.029)	-0.017 (0.023)	-0.025 (0.029)
Rasagiline	-0.011 (0.030)	-0.003 (0.026)	-0.003 (0.018)	-0.002 (0.028)	-0.010 (0.034)	-0.016 (0.024)	-0.016 (0.018)	-0.018 (0.022)
Difference (95% CI)	0.020 (0.00-0.04)	0.016 (-0.00-0.03)	0.013 (0.00-0.04)	0.022 (0.00-0.04)	0.005 (-0.02-0.03)	0.005 (-0.01-0.02)	-0.001 (-0.01-0.01)	0.007 (-0.01-0.02)
Percentages								
Placebo	-3.5%	-2.8%	-2.0%	-2.6%	-2.5%	-2.7%	-2.2%	-2.6%
	(3.5%)	(3.1%)	(2.7%)	(3.1%)	(5.7%)	(4.4%)	(3.1%)	(3.5%)
Rasagiline	-1.0%	-0.6%	-0.4%	-0.2%	-1.8%	-2.1%	-2.0%	-1.6%
	(3.5%)	(3.1%)	(2.1%)	(3.1%)	(5.7%)	(4.4%)	(3.1%)	(3.5%)
Difference (95% CI)	2.5% (0.3-4.7%)	2.2% (0.1-4.3%)	1.6% (0.0-3.2%)	2.4% (0.2-4.3%)	0.8% (-2.4-4.0%)	0.6% (-1.8-3.0%)	0.2% (-1.5-1.9%)	0.9% (-1.5-3.3%)
P-values ^a	0.025	0.041	0.054	0.023	n.s.	n.s.	n.s.	n.s.

^abased on the SUVR values and comparison of differences from baseline. Abbreviation: ns, not significant.

effects on frontostriatal neuronal function, with benefits on working memory and other cognitive function.^{30,31} Because 84% of participants in each arm of the present study were taking acetylcholinesterase inhibitors and/or medications such as memantine, rasagiline effects were incremental to the action of these medications.

The favorable effect in QoL observed for rasagiline was consistent with benefits on QoL reported with rasagiline in PD patients.^{5,6} QoL has been associated in other studies with dopaminergic function.³¹ Changes in DS, CGIC, COWAT, and NPI were directionally consistent with FDG results. The lack of ADAS-cog effect was similar to some studies of MAO-B inhibitors and rotigotine,³² illustrating that a POC approach may efficiently identify end points for larger trials relevant to the cognitive signature of the treatment. The lower number of rasagiline-treated participants who spontaneously reported neuropsychiatric events compared to the placebo group suggests an additional effect worthy of further study. This observation supports the finding of a potential MAO-B inhibition effect on neuropsychiatric symptoms in AD patients reported in a phase 2 trial of sebragiline.¹²

Our findings indicate that differences associated with rasagiline treatment may be most detectable in participants exceeding baseline thresholds of temporal tau burden, hypometabolism, and atrophy (Figure S2). Prospective biomarker stratification may help focus analyses on subgroups in which benefit is greatest.

The longitudinal progression in AD classifier pattern in placebo group and the 2% to 3% differences between study arms in frontostriatal regions were similar to the magnitude of change observed in other FDG-PET studies of AD and central nervous system drugs.^{14,15} The placebo group decreases in striatum, which is relatively preserved in late-onset AD, was driven by decreases in left caudate in younger patients. Caudate glucose metabolism has been identified as significantly reduced in early onset versus Late-onset AD.³³

4.2 | Tau

This study illustrated the diverse distribution of tau in AD as well as its relationships to age, FDG-PET, and clinical status. Results suggest that tau accumulation is observable over periods as short as 24 weeks, with higher accumulation rates associated with higher baseline tau burden. Adaptive region definition increased change detection likely because it captured the diverse spatial distribution of tau across participants without diluting to entire cortex, and may minimize impact of head motion-induced tissue shifts by "ORing" pre- and post-suprathreshold boundaries.

Because rasagiline is a highly selective MAO-B inhibitor, this study provided a stringent test of possible MAO-B binding of flortaucipir. The uniform flortaucipir signal reductions observed in subcortical regions in rasagiline-treated but not placebo-treated participants may suggest binding to MAO-B. However, effects were very weak compared to MAO-B-binding reductions caused by a rasagiline dose equal to that in the present study³⁴ and to the signal depletion of [18F]THK5351, a tracer with strong MAO-B affinity, following rasagiline treatment³⁵ (further discussion in Supplement).

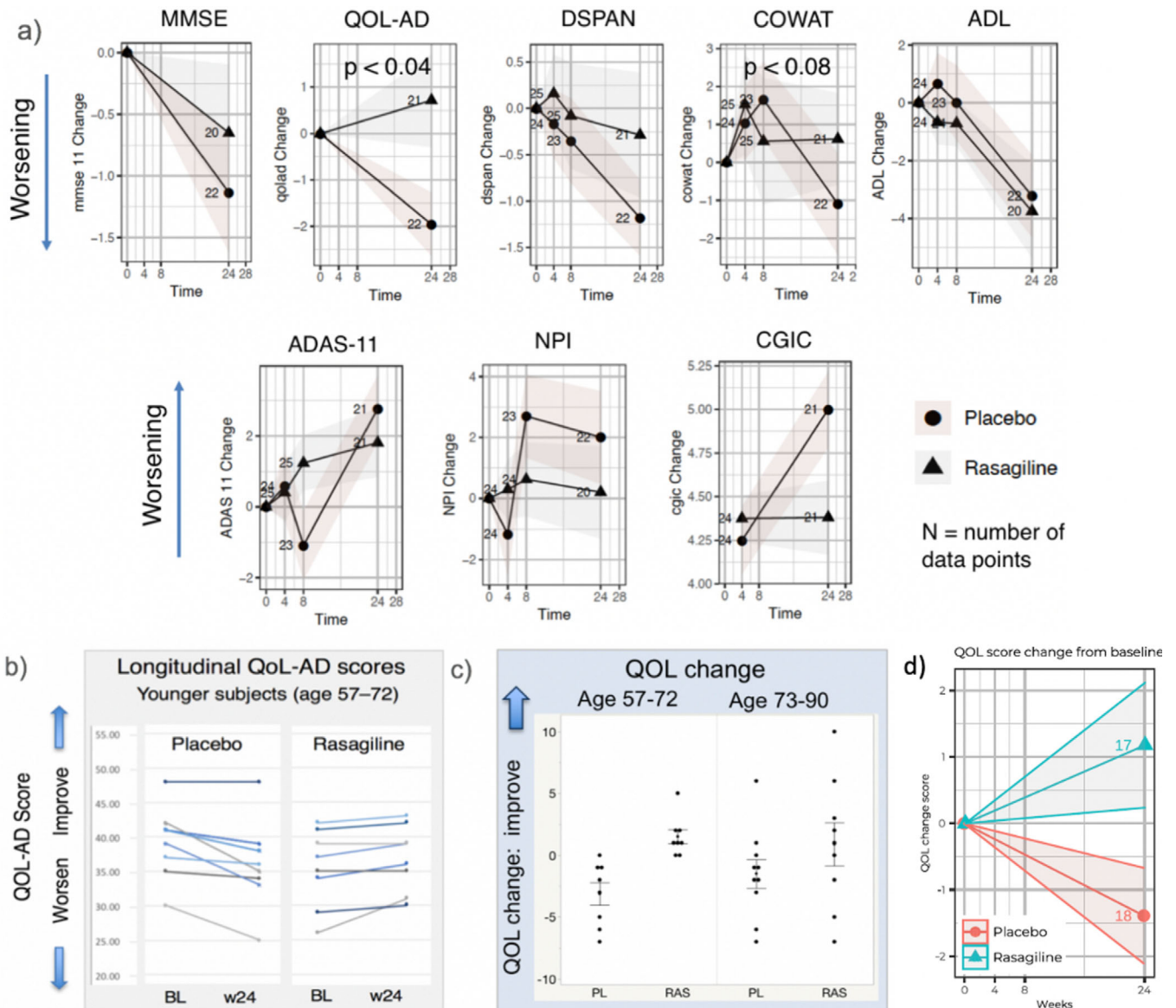


FIGURE 3 a, Longitudinal change in clinical end points by study arm. b, Individual participant longitudinal QoL-AD scores in the Younger subgroup. c, Change in QoL by study arm, younger, and older subgroups (PL = placebo, RAS = rasagiline treated). d, Change in QoL-AD from baseline in placebo and rasagiline group after matching for baseline clinical characteristics; decreases reflect worsening and increases represent improvement

4.3 | Study limitations

Limitations of the study include its small sample size and 24-week duration, intended for POC. The lack of amyloid measurement was a diagnostic limitation. However, flortaucipir, selective for AD variant tau, provided evidence of AD pathology and may serve as a surrogate indicator of amyloid given the observed relationship between neocortical tau and positive amyloid burden.^{36,37} The high number of APOE $\epsilon 4$ carriers (71%) in the study is consistent with a trial population comprised primarily of AD patients.

The by-chance imbalance in baseline MMSE, ADAS-cog, and QoL scores between treatment arms posed a challenge also seen in other studies.^{38,39} The multiple approaches applied to adjust for and/or

balance these variables all supported the baseline-adjusted model results. However, imbalances impact analysis complexity and interpretation, and prospective approaches to balancing arms could aid in other trials.

4.4 | Conclusion

The findings of a favorable effect of rasagiline on longitudinal FDG over 24 weeks of treatment and directional benefit on clinical outcomes support a potential benefit of rasagiline for AD patients. Given that this is an available, generic treatment with substantial safety data, it would be a cost- and time-effective addition to available treatments. A

- a) Image: Increases in flortaucipir SUVR values from baseline to 24 weeks in participant with high tau burden

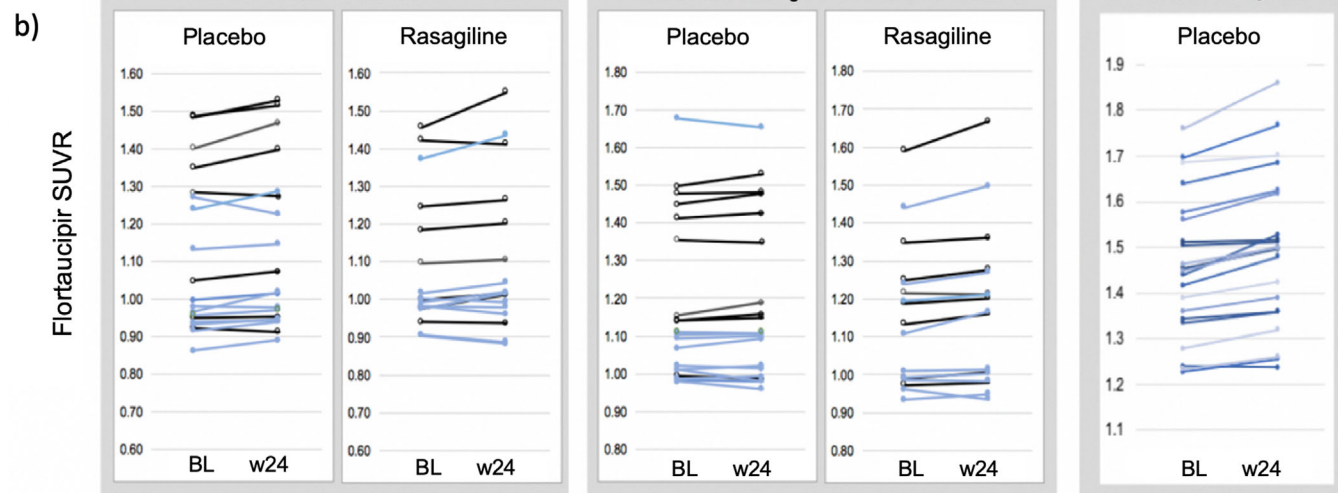
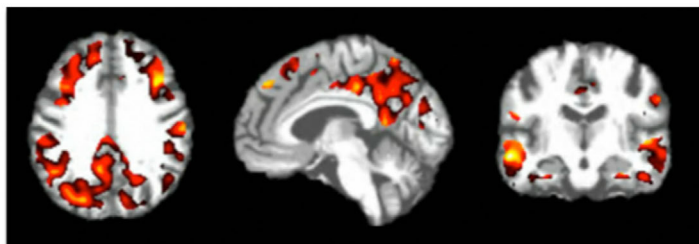


FIGURE 4 a, Example of increases in tau burden in a high tau imaging participant over 24 weeks. b, Twenty-four-week changes in flortaucipir SUVRs for middle frontal, posterior cingulate-precuneus, and an adaptive region determined by baseline and week 24 suprathreshold voxels, by study arm

powered clinical trial with assessment of QoL-AD, executive function, and neuropsychiatric aspects is warranted. More broadly, this study demonstrated the utility of a POC/experimental medicine design incorporating imaging biomarkers for participant inclusion, evaluation, and stratification as a path to increase the probability of success of larger AD trials.

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CONFLICTS OF INTEREST

Dawn C. Matthews, Randolph D. Andrews, and Ana S. Lukic are employees of ADM Diagnostics, Inc., which provides clinical trial imaging services and image analysis products. Carolyn Revta has received grants from Toyama Pharmaceuticals, Biohaven Pharmaceuticals, and Vivoryon (Probiobdrug) during the conduct of the study. Babak Tousi has received a grant from the Alzheimer's Drug Discovery Foundation during the study. James B. Leverenz has received research support from the Alzheimer's Association, Avid Radiopharmaceuticals, Department of Defense, GE Healthcare, Lewy Body Dementia Association, Michael J Fox Foundation, National Institutes of Health, and Sanofi/Genzyme. Howard Fillit is founding Executive Director and Chief Science Officer of the Alzheimer's Drug Discovery Foundation, which funded the rasagiline clinical trial, and has provided consulting to the following pharmaceutical companies: Axovant, vTv, Lundbeck, Otsuka, Lilly, Biogen (RTI), Roche, Genentech, Merck, Samus, Pfizer, and Alector. Howard H. Feldman reports a service agreement through UCSD with the Cleveland Clinic for data management and biostatistics during the conduct of this study; grants from Toyama Pharmaceuticals, Biohaven Pharmaceuticals, and Vivoryon (Probiobdrug); service agreements through UCSD for consulting with Eisai Pharmaceuticals, Merck Pharmaceuticals, Tau RX, Samus Therapeutics, Arkuda Therapeutics, Samumed, and Axon Neurosciences Roche/Genentech Pharmaceuticals for DMC and DSMB activities; Tau Consortium for Scientific Advisory Board; and Novo Nordisk for Advisory Board.

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AUTHOR CONTRIBUTIONS

Jeffrey Cummings was the principal investigator of the trial, led the protocol design, and participated in article writing and editing. Dawn C. Matthews was the imaging lead for the study and the principal author of the article. Aaron Ritter was a lead clinical investigator for the trial and provided review and input to the protocol design and the article. Ronald G. Thomas provided the clinical end point statistical analysis and review of the article. Randolph D. Andrews and Ana S. Lukic provided image data quality control, processing, and analysis. Carolyn Revta contributed to data management, team coordination, and manuscript review. Jefferson W. Kinney provided APOE genotyping for the study. Babak Tousi and James B. Leverenz were clinical investigators for the trial and provided article review and input. Howard Fillit assisted in obtaining the flortaucipir PET tracer and study funding and provided article review. Kate Zhong provided input to study design, support in the conduct of the trial, and review and input for the article. Howard H. Feldman led the ADCS in providing clinical end point statistical analyses and overall study data management and provided editing and review of the article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted under institutional review board approval with informed patient consent.

CONSENT FOR PUBLICATION

All appropriate author consents have been obtained. Other consent is not applicable.

AVAILABILITY OF DATA AND MATERIALS

Data have been published in clinicaltrials.gov and are being made available on-line by the Alzheimer's Disease Coordinating Study (ADCS).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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