The effects of rasagiline on cerebral glucose metabolism, cognition, and tau in a double-blind, placebo-controlled Phase II clinical trial 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 MAO-B inhibitor, 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 (fluoro-2-deoxyglucose positron emission tomography (FDG PET)) compared to placebo. Secondary objectives included use of flortaucipir PET to assess effects on tau pathology and determination of directional consistency of clinical endpoints.

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 at screening for the presence of an AD-like pattern as an inclusion criterion and as an outcome using prespecified regions of interest and image classification for longitudinal data. Participants who completed baseline and 24-week FDG PET scans and passed quality control were included in the primary analysis; secondary clinical outcomes were analyzed using an Intention-to-Treat (ITT) model.

Findings

Between May 19, 2015 and January 26, 2018, 96 participants were screened, 50 randomized, and 43 completed treatment. The study met its primary endpoint, demonstrating favorable change in FDG PET differences in rasagiline vs. placebo in middle frontal (2.5%,95%CI 0.3–4.7%,$p<0.025$), anterior cingulate (2.2%,0.1–4.3%,$p<0.041$), and striatal (2.4%,0.2–4.3%,$p<0.023$) regions. Tau PET cortical region secondary endpoints did not differ between study arms. Clinical secondary endpoint measures of Quality of Life ($p<0.04$) and Controlled Word Association Test ($p<0.08$) favored rasagiline. Rasagiline treatment was generally well tolerated with low rates of both serious and other adverse events and notably less neuropsychiatric symptoms reported with rasagiline.

Conclusions

These study outcomes illustrate the potential benefits of rasagiline on clinical and neuroimaging measures in mild to moderate AD patients. Rasagiline appears to affect neuronal activity in frontostriatal pathways, as observed through changes in glucose metabolism. This study illustrated the benefit of a POC design using biomarkers to characterize a diverse patient population and treatment response. Limitations include the study size and duration. Further investigation of rasagiline as a repurposed treatment in AD is warranted.

Trial Registration

Clinicaltrials.gov number NCT02359552, February 10, 2015.

Introduction

The need for effective therapeutics for patients with mild to moderate Alzheimer's disease (AD) is urgent, given the limitations of currently approved medications and the high rate of clinical trial failures[1]. We conducted a Phase II "Proof of Concept" (POC) randomized clinical trial (RCT) 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 the treatment of Parkinson's disease (PD) that has been shown to be safe and well-tolerated. MAO-B inhibitory properties

increase the availability of dopamine, which mediates cognitive functions including executive abilities, working memory, attentional processes, and reward[2] as well as motor function. MAO-B inhibition may increase synaptic function on a short-term basis by suppressing astrocytic gamma-amino butyric acid (GABA) production[3].

In nonclinical research using AD models, rasagiline has demonstrated potential neuroprotective effects with reductions in amyloid accumulation, tau hyperphosphorylation, and neurofibrillary tangle formation[4,5]. Results of prior clinical studies of rasagiline in patients with PD and schizophrenia have suggested that beyond motor improvement there are cognitive and other clinical benefits[6–8]. Selegiline, a related MAO-B inhibitor, has shown cognitive benefit in AD and PD[9–11], and Phase II and III trials of the MAO-B inhibitor lazabemide have demonstrated benefit in several cognitive and behavioral endpoints in AD patients[12]. Some clinical studies of MAO-B inhibitors, however, have shown mixed results or had negative outcomes, making it uncertain as to how, and when, a therapeutic such as rasagiline may produce benefit. For example, sembragiline did not meet cognitive or functional endpoints in AD patients over 52 weeks, but neuropsychiatric and functional benefit were noted in the more impaired subgroup. Ladostigil showed potential atrophy-slowing effects but did not reach significance in slowing clinical progression in mild cognitive impairment (MCI) patients.[13,14]. Further, no trial has examined the effects of these compounds, specifically rasagiline, on functional brain networks that may contribute to clinical benefit. The present study sought to understand the potential for rasagiline to provide benefit in the mild to moderate AD population as supported by functional and molecular imagng.

An important aspect of this POC RCT was the use of positron emission tomography (PET) imaging biomarkers to measure effects on disease-relevant biomarkers including glucose metabolism and tau pathology. Abnormal glucose metabolism with fluoro-2-deoxyglucose (FDG) PET was used to evaluate the presence of an AD-like pattern as a prerequisite to enrollment, increasing diagnostic confidence in the presence of AD. A progressive pattern of temporoparietal hypometabolism on FDG PET (particularly in posterior cingulate, precuneus, inferior parietal and lateral temporal, and medial temporal regions) has been reported to differentiate AD from other dementias, correlate with clinical status[15], and to be consistent with the presence of brain amyloidopathy[16]. Changes in glucose metabolism have been demonstrated to correspond to clinical effects of symptomatic treatments[17,18]. The primary endpoint of the present study was change in cerebral glucose metabolism, reflecting potential benefit on neuronal activity. As demonstrated in other studies[19], we hypothesized that FDG changes would be measurable with greater power over a shorter duration than the clinical effects and would aid in understanding the biological basis for any potential clinical effect. Clinical effects were evaluated as secondary outcomes to verify their directional consistency with FDG outcomes. Together, if positive, these outcomes would provide information regarding effect sizes, sample sizes, and relevant endpoints suitable for larger, more adequately powered trials with primary clinical outcomes.

This trial included longitudinal measurement of tau protein with the PET tracer flortaucipir (AV-1451; Avid Radiopharmaceuticals) as a measure of AD pathology that correlates with the extent of clinical and cognitive impairment. Tau aggregation is observed early in AD in medial temporal regions, spreading to lateral temporal, posterior, and frontal neocortex as AD progresses[20,21]. Tau burden correlates with clinical status and progressive worsening with regional increases detectable over periods as short as 9 months[22,23]. The current trial expanded on prior studies by using a shorter period of 24 weeks with a mild-to-moderate AD study population. It allowed evaluation of inter-modality relationships acquired at the same time points in the same patients and provided information on effects of rasagiline on tau pathology in humans. The trial included a broad age and clinical severity range.

Methods

This was a 24-week, double blind, placebo controlled, parallel group, randomized phase II POC study.

Participants

A total of fifty patients were enrolled in the study. Key inclusion criteria were a clinical diagnosis of probable AD (using the National Institute of Neurological Disease and Stroke - Alzheimer's Disease and Related Disorders criteria; references for clinical criteria and measures in supplementary material), age 50–90, Mini-Mental Status Examination (MMSE) score of 12–26 inclusive, and FDG PET pattern of hypometabolism consistent with AD[24]. Exclusion factors included neurologic, radiologic, or laboratory indications of non-AD dementia; medications that might interact with rasagiline; and factors that might lead to an inability to complete the study. Questionable cases were reviewed by adjudication among the study physicians, resulting in exclusion of two potential participants. Patients on stable doses of cholinesterase inhibitors and memantine for at least 3 months prior to randomization were permitted. The only protocol change during the conduct of the trial was an increase of the allowable doses of concomitant antidepressant medications, if the dose was stable prior to entry. This increase was allowed due to new safety data indicating that higher doses of antidepressants would not increase the chance of a tyrosine reaction. No dose changes were permitted during the course of the study. Participants or legal guardians as applicable provided written informed consent.

Randomization and Masking

The study took place at the Cleveland Clinic Lou Ruvo Center for Brain Health at three locations: Las Vegas, NV, Cleveland, OH, and Lakewood, OH. Within each site, randomization was determined by the Cleveland Clinic research pharmacist using a predetermined randomization schedule in which participants were assigned to rasagiline or placebo in a 1:1 ratio. No stratification factors were used in generating the randomization schedule.

Outcome Measures

The primary outcome measure was the change from baseline to week 24 in FDG PET in one or more prespecified brain regions, based on centralized processing and analysis of the data. The following regions were selected due to their established progressive hypometabolism in AD: medial temporal, lateral temporal, posterior cingulate-precuneus, inferior parietal, and middle frontal cortices. The anterior cingulate and the striatum, which are typically preserved in AD, were also prespecified. These regions were included because of prior reports of correlations between dopamine and glucose metabolism in both areas[25] as well as a case report of increased striatal glucose metabolism (FDG) and an associated neuropsychiatric benefit following selegiline administration[26]. A data-driven region derived from a multivariate machine learning pattern analysis of baseline and 24-week scans for placebo vs. treatment groups was also specified.

Secondary outcome measures included the change in tau over 24 weeks as measured using flortaucipir PET imaging, safety and tolerability as measured by adverse events, and the following clinical endpoints: Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog), MMSE, Digit Span (DS), Controlled Oral Word Association Test (COWAT), The 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), and Neuropsychiatric Inventory (NPI). The study was not powered to achieve statistical significance in clinical measures, but rather to assess directionality for consistency with FDG PET findings and to provide information regarding the number of participants that would be required to show a drug-placebo difference on primary outcomes in the design of a more definitive fully powered

trial. Relationships between changes in clinical measures and FDG PET and flortaucipir PET and correlations between FDG PET and flortaucipir PET were explored.

Statistical Power

Prior studies using FDG PET showed that regional metabolic changes associated with cognitive effects in AD can be detected in an unpaired study design with group sizes of less than 20 per arm[17]. Detection of reductions in disease-related clinical decline would require additional participants and/or a longer timeframe depending on the effect size and required power[19]. However, a preliminary comparison of directionality could be made. This POC trial was not powered for significance in clinical outcomes but rather for a preliminary assessment of directional consistency and relationship to FDG outcomes.

Procedures

Rasagiline was initiated at 0.5 mg once daily for the first four weeks, increased using a fixed titration schedule to a 1 mg dose once daily starting from week five, and maintained at the same dose until the end of week 24. Active and placebo tablets were provided by Teva, and re-coated in an identical manner. Drug supply was then repackaged by randomization ID, blinded with regard to active or placebo treatment.

FDG and flortaucipir PET imaging were performed at screening or baseline respectively and at week 24. MRI was acquired at screening. 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 (with study partner) was administered at baseline and 24 weeks. Safety was monitored through weekly review of adverse events throughout the study.

Image acquisition and measurement

FDG PET, flortaucipir PET, and MRI images were acquired using protocols based upon the Alzheimer's Disease Neuroimaging Initiative (ADNI, www.adni-info.org) protocol and quality controlled and processed as described in the Supplemental Material.

The first application of FDG PET was as an inclusion measure at baseline, whereby an AD-like pattern of hypometabolism was required. To evaluate this, each participant's baseline scan was spatially normalized (warped) to a template and evaluated using a combination of two previously developed, complementary image classifiers. The first of these ("Dementia Differentiation") was trained to differentiate the scans of persons characterized as amyloid negative and cognitively normal, amyloid positive with various stages of MCI and AD, frontotemporal dementia, and dementia with Lewy bodies (DLB). This classifier assigns probabilities of belonging to each of these disease classes. The second "AD Progression" classifier 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 preclinical, prodromal, and dementia stages. This pattern, illustrated in Fig. 2d, is characterized by worsening glucose hypometabolism in posterior cingulate, precuneus, inferior parietal, and temporal cortices, and has been shown to correlate with subsequent rate of cognitive decline[24]. Both of these classifiers use a scan from a single time point. The AD Progression score can be compared between time points to assess longitudinal progression. Prospective participants were included if they scored along the MCI to AD spectrum, with or without an indication of a secondary disease such as DLB.

At baseline and at 24 weeks, FDG Standardized Uptake Value ratios (SUVRs, the ratio of the signal intensity in a target region of interest to that in a reference region) were measured in the prespecified regions of interest. SUVRs were compared using multiple different reference regions to confirm that directionality was not driven solely by the values in a single reference region. Data-driven multivariate machine learning was also applied to the scans to compare treatment groups at baseline and to assess longitudinal change. This classification used the voxel-based FDG scans as inputs and produced voxel intensity patterns that characterized group differences. Scans were grouped into classes based upon visit (baseline or 24 weeks), study arm (placebo or rasagiline), and age (younger and older strata), and input to the classifier software with their group number. The classifier software then used a combination of Principal Component Analysis (PCA), Canonical Variate Analysis (mathematical combinations of the PCs), and data resampling to determine the pattern(s) that best discriminated groups while minimizing data overfitting. The expression of each pattern identified in classification was quantified as a numeric score for each participant.

Tau SUVRs were measured in several exploratory regions: total cortical gray tissue excluding cerebellum, a composite temporal region (CTR), the regions measured for FDG PET, and additional cortical and subcortical regions defined on MRI using Freesurfer 6.0 as well as an adaptive approach. The adaptive approach defined a subject specific mask (region defined by spatial boundaries) of suprathreshold voxels at baseline and 24 weeks, “OR’ing” these masks to allow measurement of changes in either direction in order to avoid directional bias. The measured volumes were standardized for comparison across participants to a common total volume. White matter and cerebellar cortex reference regions were defined using a Gaussian decomposition approach (PERSI)[27] and compared in cross-sectional and longitudinal measurement. Given research supporting the association of an amyloid burden with tau spread to neocortical regions beyond medial temporal structures[28] the tau assessment provided a further, post-hoc confirmation of likely AD pathology. Methods are described in further detail in the Supplemental Material.

Statistical Analysis

Participants who completed both PET visits and met image quality control were evaluated for longitudinal change. SUVR values and classifier scores were evaluated using a difference of differences (24 weeks minus baseline, placebo vs. rasagiline) model adjusted for age, education, baseline values, and interaction terms when applicable (JMP v14 statistical software; G*Power software). Treatment groups were compared between study arms overall and by prespecified subgroups based upon participant age (pre-specified) and sex (post-hoc). Relationships to patient age were evaluated given reports of greater tau burden in younger AD participants[25] and the potential for comorbidities that may influence outcomes in older participants.

Mixed-model repeated-measures analyses were used to assess between-group differences in the modeled change in scores from baseline to week 24. The dependent variable in each analysis was the change from the baseline score. Fixed effects were baseline scores on outcome measures, study-drug assignment (rasagiline or placebo), 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 population, which included all randomly assigned participants for whom there was at least one postbaseline observation. Since this was a preliminary POC efficacy study, no adjustments for multiple comparisons were made and a two-sided p-value of 0·05 was considered statistically significant. Testing for treatment differences was conducted by assessing the statistical significance of the treatment-by-visit regression coefficient. Exploratory analyses were undertaken to evaluate treatment effects by baseline clinical severity as measured by MMSE and by sex. Clinical endpoints were examined in relationship to imaging endpoints using correlation analysis (Pearson’s R).

Role of the funding source

The funder of the study had no role in study design or data collection, other than assisting in obtaining flortaucipir PET for the study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Participants

Between May 19, 2015 and January 26, 2018, ninety-six participants were screened, of whom fifty were randomized to the treatment of either rasagiline or matching placebo and forty-three completed treatment. Of the twenty-five participants allocated to the placebo arm, three were lost to follow up (associated with delusions (1), stroke (1), and worsening pseudobulbar/other effects (1, discontinued at baseline)), and one participant did not have a week-24 FDG PET scan but had clinical data, resulting in twenty-one placebo participants for image analysis. Of the twenty-five participants allocated to the rasagiline arm, four were lost to follow-up (associated with broken hip/rib (1), atrial fibrillation (1), and factors other than adverse events (2)). (Fig. 1. Trial profile)

Table 1 shows the demographic and baseline clinical characteristics of the enrolled patients by study arm. Age, sex, education, genotype, and baseline NPI, DSPAN, and COWAT scores did not differ between groups. Ninety-four percent of participants were Caucasian (non-Hispanic). Mean MMSE and ADAS-cog scores at baseline were more impaired in the placebo group than the rasagiline group ($p < 0{\cdot}06$), while the rasagiline group had worse baseline QoL-AD scores ($p < 0{\cdot}02$). Baseline values were included as covariates in statistical comparisons of longitudinal change for these endpoints. Pre-specified subgroup analyses stratified by baseline MMSE were also performed. Of the forty-three participants who completed the study, one did not have a week-24 FDG PET scan and three were excluded from longitudinal image analysis due to pre-specified behavioral or motion confounds during image acquisition. Among the thirty-nine participants included in longitudinal image analysis, baseline MMSE and ADAS-cog scores did not differ between groups and QoL-AD scores were lower (worse) in the rasagiline-treated group ($p < 0{\cdot}05$).

Table 1
Baseline demographic and clinical characteristics of the study population

	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)	0.055
MMSE	19 (5)	21 (4)	20 (4)	0.064
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)	0.018
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%	1.0
Memantine	44%	40%	42%	0.78
Antidepressant(s)	36%	56%	46%	0.16
Anxiolytic(s)	4%	4%	4%	1.0
Antipsychotic(s)	8%	4%	6%	0.56
site id 1	48%	52%	50%	1.0
site id 2	36%	36%	36%	
site id 3	16%	12%	14%	

Baseline PET and ApoE Characterization

Of the fifty-nine participants who had screening FDG scans analyzed using the Dementia Classifier, fifty-seven exhibited a pattern of hypometabolism classified as AD-like and were included for potential enrollment. Seventy-one percent of participants were ApoE-4 carriers, consistent with trials where positive amyloid imaging is used as an entry criterion[29]. Participants were diverse in FDG AD Progression Classifier scores (Fig. 2a), which correlated with the

range of baseline MMSE ($R = -0.44$, $p < 0.001$, Fig. 2d) 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. Younger participants had lower metabolism in inferior parietal ($p < 0.008$) and precuneus ($p < 0.04$) regions as compared to older participants at baseline.

Total tau burden varied greatly across participants (Figs. 2b,c,d) but did not differ between study arms. Tau was associated with age (Fig. 2e); younger participants (age 57 to 69) had pervasive tau distribution inclusive of frontal and parietal cortices while oldest participants (late 70 s to 90) had low total burden consisting primarily of temporal tau with smaller posterior clusters. Participants in their 70 s showed a broad range from low to moderate total tau. Spatial patterns varied, with hemispheric asymmetries in some participants and a dominant occipital burden observed in several participants. Forty-seven of the fifty participants enrolled in the study had readily visualized elevated flortaucipir signal and positive regional SUVRs. Three (of whom two completed the study) had threshold cortical SUVR values (1.3). Total tau burden correlated with FDG AD Progression classifier score ($R = -0.41$, $p < 0.003$).

Trial Outcomes

Primary end point

The study met its primary endpoint of improvement in longitudinal glucose metabolism in rasagiline-treated participants versus those on placebo in one or more prespecified regions (Fig. 3a). Table 2 shows percentage changes and the SUVR values, which were used for the statistical comparisons. Rasagiline-treated participants decreased to a lesser magnitude than placebo-treated participants in the pre-specified regions of 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), and in superior frontal cortex ($p < 0.05$, not pre-specified). Results using whole brain, subcortical white matter, and pons as alternate reference regions were in agreement regarding affected regions and directionality.

A voxel-based classifier comparison of change in placebo- and rasagiline-treated groups (an additional primary outcome measure) identified a spatial pattern in which rasagiline-treated participants had lesser decline in glucose metabolism than those on placebo ($p < 0.02$). This pattern, illustrated in Fig. 3b, is consistent with the pre-specified region of interest results and includes middle frontal, anterior cingulate, superior frontal, striatal, and insular regions, and less prominently, inferior parietal cortex.

Table 2
Region of interest results: Difference (24 weeks minus baseline) Mean, S.D. and Difference between Arms with 95% Confidence Interval

	Middle Frontal	Anterior Cingulate	Superior Frontal	Striatum	Medial Temporal	Lateral Temporal	Post Cing - Precuneus	Inferior Parietal
SUVRs								
Placebo	-0.032	-0.020	-0.016	-0.024	-0.015	-0.020	-0.017	-0.025
	(0.030)	(0.021)	(0.022)	(0.029)	(0.034)	(0.029)	(0.023)	(0.029)
Rasagiline	-0.011	-0.003	-0.003	-0.002	-0.010	-0.016	-0.016	-0.018
	(0.030)	(0.026)	(0.018)	(0.028)	(0.034)	(0.024)	(0.018)	(0.022)
Difference	0.020	0.016	0.013	0.022	0.005	0.005	-0.001	0.007
(95% CI)	(0.00–0.04)	(-0.00–0.03)	(0.00–0.04)	(0.00–0.04)	(-0.02–0.03)	(-0.01–0.02)	(-0.01–0.01)	(-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	2.5%	2.2%	1.6%	2.4%	0.8%	0.6%	0.2%	0.9%
(95% CI)	(0.3–4.7%)	(0.1–4.3%)	(0.0·3.2%)	(0.2·4.3%)	(-2.4·4.0%)	(-1.8–3.0%)	(-1.5–1.9%)	(-1.5–3.3%)
p-values*	0.025	0.041	0.054	0.023	n.s.	n.s.	n.s.	n.s.
*based on the SUVR values and comparison of differences from baseline; n.s. = not significant								

The decline in glucose metabolism in the placebo arm was consistent with expected changes in severity of AD over the 24-week period. FDG AD Progression scores increased in severity ($p < 0.01$ at 80% power), and regional SUVRs 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) (p-values at 80% power) regions consistent with the change in Progression scores. Mean decreases in glucose metabolism in younger placebo-treated participants were more than twice those of older placebo-treated participants in middle frontal ($p < 0.07$, left $p < 0.05$) and caudate ($p < 0.05$) regions.

Secondary Endpoints

Longitudinal clinical endpoints for the rasagiline and placebo treatment arms over 24 weeks showed a favorable outcome for the rasagiline group compared to the placebo group for QoL-AD ($p < 0.04$), with directional trends on COWAT ($p < 0.08$) and MMSE ($p < 0.07$) (Table 3). Results suggested that clinical endpoint differences at baseline, included as covariates in the statistical models and tested for impact in additional subanalyses, did not impact longitudinal comparisons between arms. There were no significant site effects.

In the pre-specified moderate subgroup (MMSE 10 to 18, N = 14), rasagiline-treated participants showed less decline than placebo treated participants in 6 of 8 clinical endpoints, at trend level in QoL-AD ($p < 0.06$) and COWAT ($p < 0.09$);. In the pre-specified mild subgroup (baseline MMSE 19 to 28, N = 36), rasagiline-treated participants had less decline, not significant, in 5 of 8 clinical endpoints (results in Table 3).

Table 3
Clinical endpoint longitudinal results

Endpoint	24 week mean change (S.D.)		p-value
	Placebo	Rasagiline	
MMSE	1.14 (2.27)	0.65 (2.48)	n.s.
ADAS-cog	2.76 (4.30)	1.81 (4.43)	n.s.
ADL	3.23 (6.71)	3.75 (7.27)	n.s.
COWAT	1.09 (6.31)	-0.62 (5.55)	0.08
CGIC	n/a	n/a	n.s.
Digit Span	1.18 (1.92)	0.29 (3.08)	n.s.
NPI	2.00 (7.18)	0.20 (6.79)	n.s.
QoL-AD	1·95 (3·28)	-1·11 (3·77)	0.04
S.D. = standard deviation; Mod = moderate; n.s. = non-significant			

Relationships between baseline imaging characteristics and changes in clinical endpoints

Higher tau burden, lower glucose metabolism, and lower cortical thickness in temporal regions at baseline correlated with greater decline in MMSE score in placebo treated participants (blue line) over the 24-week period ($p < 0.008$, $p < 0.05$, and $p < 0.004$ respectively). These relationships, shown in Fig. 5a, were not seen in the rasagiline trajectories (red lines), which were relatively stable or improved independent of their tau burden, glucose metabolism, or cortical thickness values at baseline. Longitudinal differences between the rasagiline and placebo arms were most pronounced in participants having greater tau, lower metabolism, and lower volumes in temporal regions at baseline.

Relationships between change in clinical endpoints and change in imaging biomarkers

The metabolic pattern resulting from the voxel-based classifier relating change in QoL-AD to changes in FDG PET showed increases (or mitigated decreases) in anterior cingulate, medial orbitofrontal, anterior superior frontal, and caudate regions associated with increasing QoL-AD score (Fig. 5b,c). Consistent with this, QoL-AD score was positively correlated with region of interest FDG SUVR changes in anterior cingulate ($R = 0.47$, $p < 0.002$, Fig. 7c) and caudate ($R = 0.47$, $p < 0.002$) (Fig. 5d). Longitudinal changes in COWAT and DS were positively correlated with change in middle frontal glucose metabolism ($R = 0.52$, $p < 0.02$ and 0.55, $p < 0.01$, respectively).

Longitudinal Tau PET

Increases in tau (flotaucipir) were observed in some participants over the 24 weeks, particularly in those with higher baseline values (Fig. 6a,b). Greater slopes and statistical power were observed when using the adaptive method that defined the region of interest according to pre- or post- suprathreshold voxels (Fig. 6b).

No differences in the change in flortaucipir were observed between study arms in cortical regions except for slight decreases noted in rasagiline subjects having subthreshold values in anterior cingulate and insula. Uniform longitudinal decreases were observed in the rasagiline arm but not the the placebo arm in the following subcortical regions: accumbens ($p < 0.0001$), putamen ($p < 0.003$), thalamus ($p < 0.05$), brainstem ($p < 0.03$) (p-values are for the comparison of 24 week flortaucipir SUVR change between rasagiline and placebo arms).

Safety and Tolerability

Rasagiline was generally well tolerated, with neuropsychiatric adverse events (AEs) in 5 (20%) placebo, 0 (0%) rasagiline, non-neuropsychiatric AEs in 10 (40%) placebo patients, 13 (52%) rasagiline, and no treatment-related deaths. Adverse events (AEs) with frequency of > 5% are presented by treatment group in Table 4, with those classified as severe identified in brackets. There were no rasagiline-treated participants who experienced neuropsychiatric symptoms of agitation/irritability or psychosis compared to 5 participants in the placebo group, (t-test NS). As seen in Table 4, there were higher rates of hypertension, increased thyroid stimulating hormone (TSH), falls and skin rashes with rasagiline treatment though treatment arm differences were small and most were not severe. Serious adverse events were observed in two rasagiline treated participants (1 fall, 1 disorientation) as compared to seven placebo treated patients.

Table 4
Adverse Events

Adverse Event	Placebo (n = 25)		Rasagiline (n = 25)	
	Number	Percent	Number	Percent
Abnormal Urinary Analysis	1	4%	2	8%
Agitation	2	8%	0	0%
Confusion	2	8%	2	8%
Delusions	3	12%	0	0%
Elevated blood pressure or cardiac related	2	8%	3	12%
Elevated thyroid stimulating hormone	1	4%	2	8%
Fall	1	4%	2	8%
Insomnia	2	8%	0	0%
Rash / skin lesion	1	4%	2	8%

Number and percent of subjects with adverse events who received 1 or more doses of study drug (occurring in 5% or more in either treatment group).

Discussion

Rasagiline effects

This Phase 2 POC RCT investigation of rasagiline as a treatment for AD met its primary outcome of demonstrating improvements/less decline in longitudinal changes in glucose metabolism in prespecified regions with rasagiline compared to placebo over 24 weeks. Results showed a favorable safety profile, and a reduced number of

neuropsychiatric side effects was noted in the rasagiline arm compared to placebo. Clinical endpoints favored rasagiline. Of particular note was QoL ($p < 0.04$, uncorrected), in which uniform improvements were observed in younger rasagiline treated participants compared to the decline observed in placebo participants (Fig. 5).

The FDG PET findings suggested that rasagiline acts on frontostriatal networks. Rasagiline prolongs dopamine availability through MAO-B inhibition, and results of this study were consistent with previous studies that have established positive effects on frontostriatal neuronal function associated with dopamine. Those studies have shown associated benefits on working memory and other cognitive function[31]. While dopamine is not reported to be affected in AD to the extent of some other neurotransmitters such as acetylcholine, it decreases with aging[31] and its deficits have been linked to AD with a possible role in cognitive decline[32]. Since 84% of participants in each study arm were taking acetylcholinesterase inhibitors and/or additional medications such as memantine, which support frontal function, the effects of rasagiline are incremental to the action of these medications.

The findings of this trial were consistent with results published from other studies of MAO-B inhibitors in AD. The favorable cognitive and quality of life effects observed in this study are similar to benefits previously reported for rasagiline in PD patients.[6,7] In our study, improvement in QoL-AD was correlated with glucose metabolism in anterior cingulate, a region found to be associated with quality of life in other studies[33]. The lower number of rasagiline-treated participants (0) who spontaneously reported neuropsychiatric events (agitation, psychosis) compared to the placebo group (5) suggests an additional treatment effect that is worthy of further study. This observation supports the findings of a potential effect of MAO-B inhibition on neuropsychiatric symptoms in AD patients reported in a Phase 2 trial of sembragiline, an MAO-B inhibitor[13].

In the present overall study population, the lack of benefit in ADAS-cog and ADL are consistent with other studies of MAO-B inhibitors that did not meet their ADAS-cog and ADL endpoints. ADAS-cog score has been observed to correlate with glucose metabolism in parietal, posterior cingulate, and precuneus regions in the ADNI population[35]. The frontostriatal effects of rasagiline may align best with other clinical endpoints.

The relationship between baseline biomarkers (tau, FDG, volumetric) and subsequent clinical decline observed in the placebo group was mitigated in the rasagiline treated group. Our data suggest that differences associated with rasagiline treatment may be most detectable in participants exceeding certain baseline biomarker thresholds of tau burden, hypometabolism, and atrophy (as shown in Fig. 6). Prospective biomarker stratification at baseline may help to focus analyses on subgroups in which benefit is greatest. Our results suggest that treatment response may be affected by participant age. For example, QoL treatment effect was observed in both age groups, but statistical power was greater in younger patients in whom this measure had less variability. Younger participants showed more rapid cognitive decline, consistent with previous reports[34] and had greater tau burdens.

Biomarker value and feasibility

Consistent with prior results that used data from ADNI and other studies, FDG PET as measured using disease-relevant image classifiers reflected the likelihood and clinical severity of AD[24]. Even in this multi-site trial of mild to moderate AD patients with a broad severity range, it was feasible to use FDG PET to detect group-related differences at baseline and over the 24-week period. The group differences in 24-week change, on the order of 2 to 3%, were similar to the magnitude of change observed in other FDG PET studies of central nervous system drugs[17,18]. Detection of these effects required careful control during image acquisition, selection of optimal reference regions for

SUVR measurement, and use of multivariate classification approaches; parameters achieved in this randomized controlled trial.

Our results suggest that tau accumulation is measurable over periods as short as 24 weeks, with higher accumulation rates associated with greater baseline tau burden. Methods used, including choice of reference region and target region definition, impact detection of change. The adaptive region definition likely provided increased detection in participants with moderate to high tau burden for two reasons: (1) it captured the diverse spatial distribution of tau across participants without diluting to include the entire cortex region, and (2) it may have been less impacted by head motion, in that the “ORing” of pre and post suprathreshold boundaries would allow capture of tissue of interest even if there was some shifting between scans and would nclude a somewhat more permissive boundary than pre-defined cortical segments.

Since rasagiline is a highly selective MAO-B inhibitor, this study provided a stringent test regarding possible (off-target) MAO-B binding properties of flortaucipir. The uniform flortaucipir signal reductions observed in subcortical regions and in limited cortical regions in rasagiline but not placebo treated participants may suggest weak binding to MAO-B. However, these effects were weak when compared to the complete MAO-B binding reductions caused by a dose of rasagiline equal to that used in the present study[36] and to the depletion of signal associated with [18F]THK5351, a tracer with strong affinity for MAO-B, following rasagiline treatment[37]. The observed reductions did not significantly impact cortical interpretation where tau was likely present. Other off-target binding, potentially related to entites including iron deposits, neuromelanin, and MAO-A[38,39], was observed but did not appear to impact overall findings.

Study limitations

Limitations of the study include its small sample size and its 24-week duration, intended for POC. The lack of amyloid imaging or CSF molecular signature of amyloid was a diagnostic limitation. However, the tau PET tracer, selective for AD variant tau, provided evidence of hallmark AD pathology and may serve as an indicator of amyloid given the observed relationship between neocortical tau and a positive amyloid burden[28,40]. Although age-related tau, weak binding to TAR DNA-binding protein-43[39], and off-target binding must be considered, it is likely that participants with suprathreshold neocortical tau accumulation were amyloid positive. The high number of ApoE-4 carriers (71%) in the study suggests that the trial population was comprised primarily of AD patients. Recent clinical trial reports have also shown that in mild to moderate AD trials, clinical diagnosis is associated with greater than 90% cerebrospinal fluid or amyloid PET diagnostic confirmation[29,41].

Given the advanced disease stage of some participants, motion during image acquisition and behavior deviation during FDG uptake were encountered; these factors were controlled through monitoring, multi-frame acquisition, and exclusion. The parallel arm design of the study was more limited in power than a within-participant crossover study but avoided disease progression confounds that could arise from a sequential crossover design. Ethnic diversity was limited. The significance levels achieved in this study were modest and uncorrected for multiple comparisons. However, the classifier comparisons distilled multiple region comparisons into a single measure, and as a POC study, the design was intended to identify directional outcomes for clinical measures.

Conclusion

The findings of a beneficial effect of rasagiline upon longitudinal FDG metabolism over 24 weeks of treatments and directional benefit on clinical outcome measures support the potential for further development of rasagiline as an AD

therapeutic. Given that this is an available, generic treatment with substantial safety data, it would be a cost- and time-effective addition to the currently sparse selection of available treatments for AD. A larger, fully powered Phase 3 clinical trial of rasagiline that incorporates learnings from this POC trial is warranted.

FDG PET findings suggest that rasagiline may act on cognitive outcomes through effects on frontostriatal pathways. Findings point toward consideration of QoL, executive function, and behavioral endpoints that have not served as primary endpoints in other trials of MAO-B inhibitors. Findings show the importance of stratification, which can be achieved using biomarkers, of these heterogeneous patient populations to better detect treatment effect. Evaluation could include assessment of long-term neuroprotective effects that were beyond the scope of this POC trial. More broadly, this study demonstrated the utility of a POC design using imaging biomarkers for participant inclusion and evaluation as a path to increase the probability of success of larger AD trials.

Abbreviations

AD
Azheimer's disease
ADAS-cog
Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCS
Alzheimer's Disease Cooperative Study
ADL
Activities of Daily Living
ADNI
Alzheimer's Disease Neuroimaging Initiative
CGIC
Clinical Global Impression of Change
COWAT
Controlled Oral Word Association Test
CTR
composite temporal region
DLB
Dementia with Lewy bodies
DS
Digit Span
FDG PET
flurorodeoxyglucose positron emission tomography
GABA
gamma-amino butyric acid
ITT
intention-to-treat
MAO-B
monoamine oxidase B
MCI
mild cognitive impairment
MMSE

Mini-Mental Status Examination
NPI
Neuropsychiatric Inventory
PCA
Principal Component Analysis
PD
Parkinson's Disease
POC
Proof of Concept
QoL-AD
Quality of Life – Alzheimer's Disease
RCT
randomized clinical trial
SUVR
Standardized Uptake Value ratio
TSH
thyroid stimulating hormone

Declarations

Ethics approval and consent to participate

The study was conducted under the Cleveland Clinic's Institutional Review Board approval with informed patient consent.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

DM, RA, and AL are employees of ADM Diagnostics, Inc., which provided the image data management and analysis for this study through a service contract.

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HF is Executive Director of the Alzheimer's Drug Discovery Foundation, which provided funding for the study.

CR reports grants from Toyama Pharmaceuticals, Biohaven Pharmaceuticals, and Vivoryon (Probiodrug) during the conduct of the study.

Other authors have nothing to disclose.

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Authors Contributions

JC was the principal investigator of the trial, led the protocol design, and participated in manuscript writing and editing. DM was the imaging lead for the study and the principal author of the manuscript. AR was a lead clinical investigator for the trial and provided review and input to the protocol design and the manuscript. RT provided the clinical endpoint statistical analysis and review of the manuscript. RA and AM provided image data quality control, processing, and analysis. CR contributed to data management, team coordination, and manuscript review. JK provided ApoE genotyping for the study. BT and JL were clinical investigators for the trial and provided manuscript review and input. HF assisted in obtaining the flortaucipir PET tracer and study funding and provided manuscript review. KZ provided input to study design, support in the conduct of the trial, and review and input for the manuscript. HF led the ADCS in providing clinical endpoint statistical analyses and overall study data management and provided editing and review of the manuscript.

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Figures

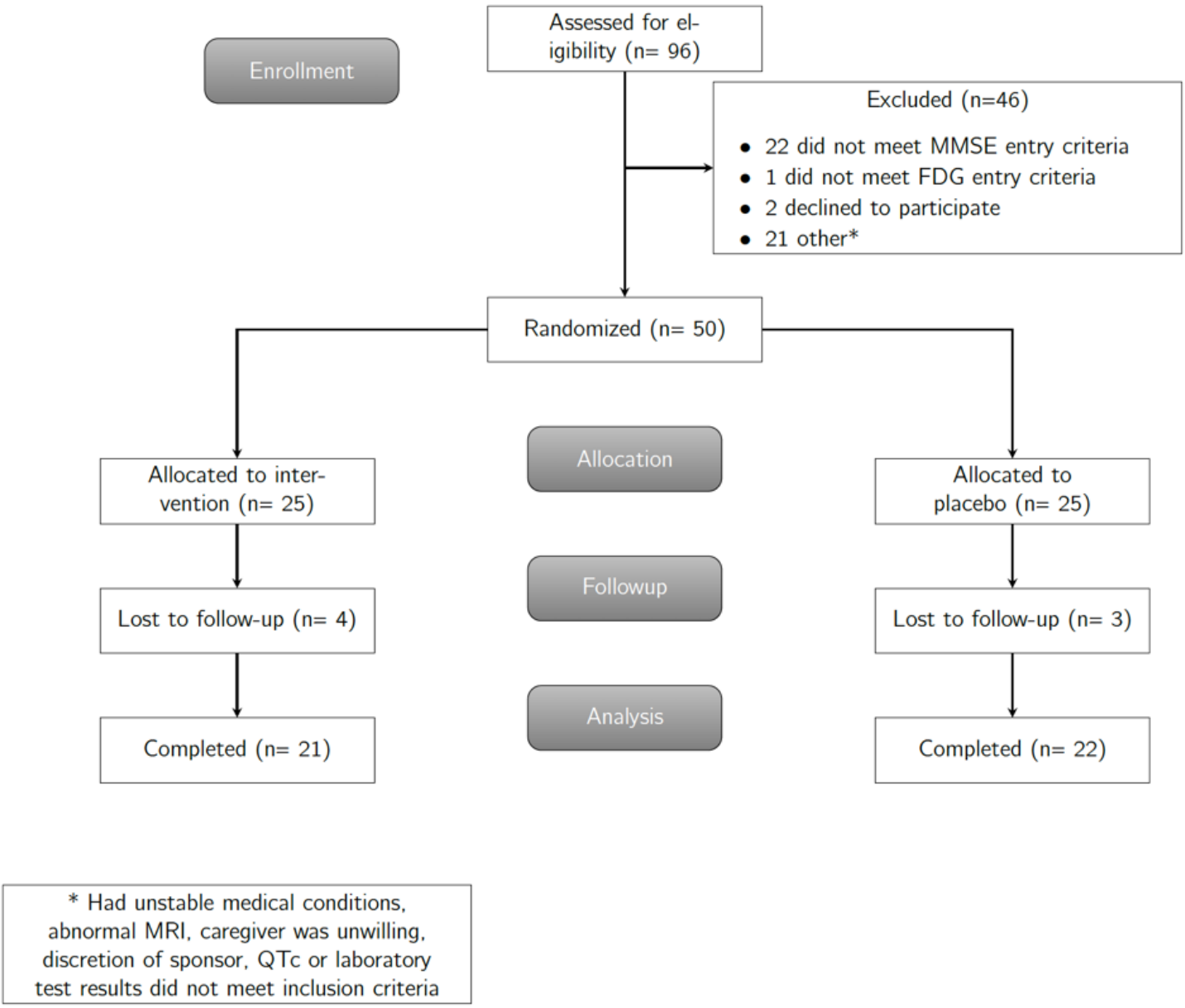

Figure 1

Flow of Patients through the Trial

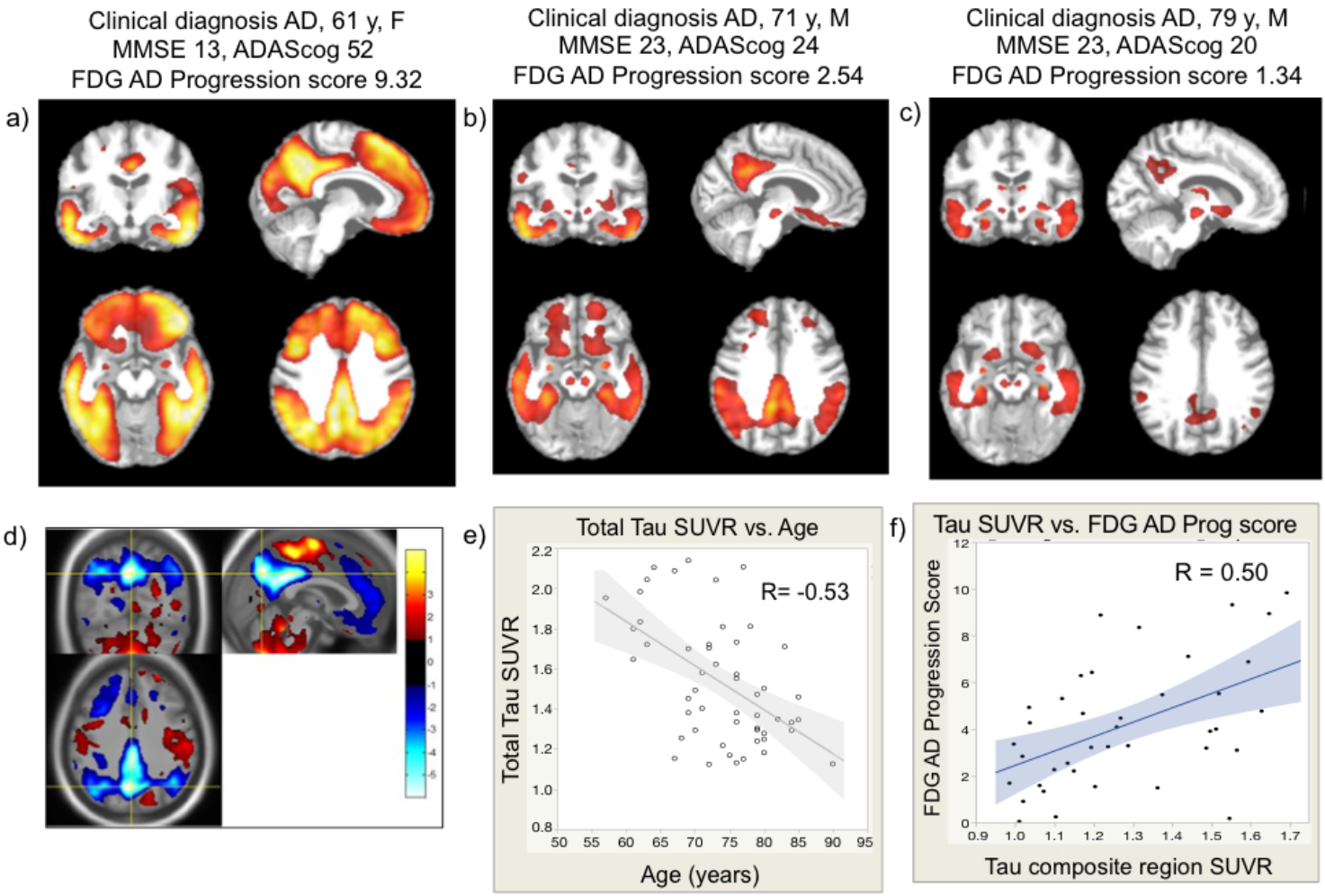

Figure 2

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) vs. FDG AD Progression score.

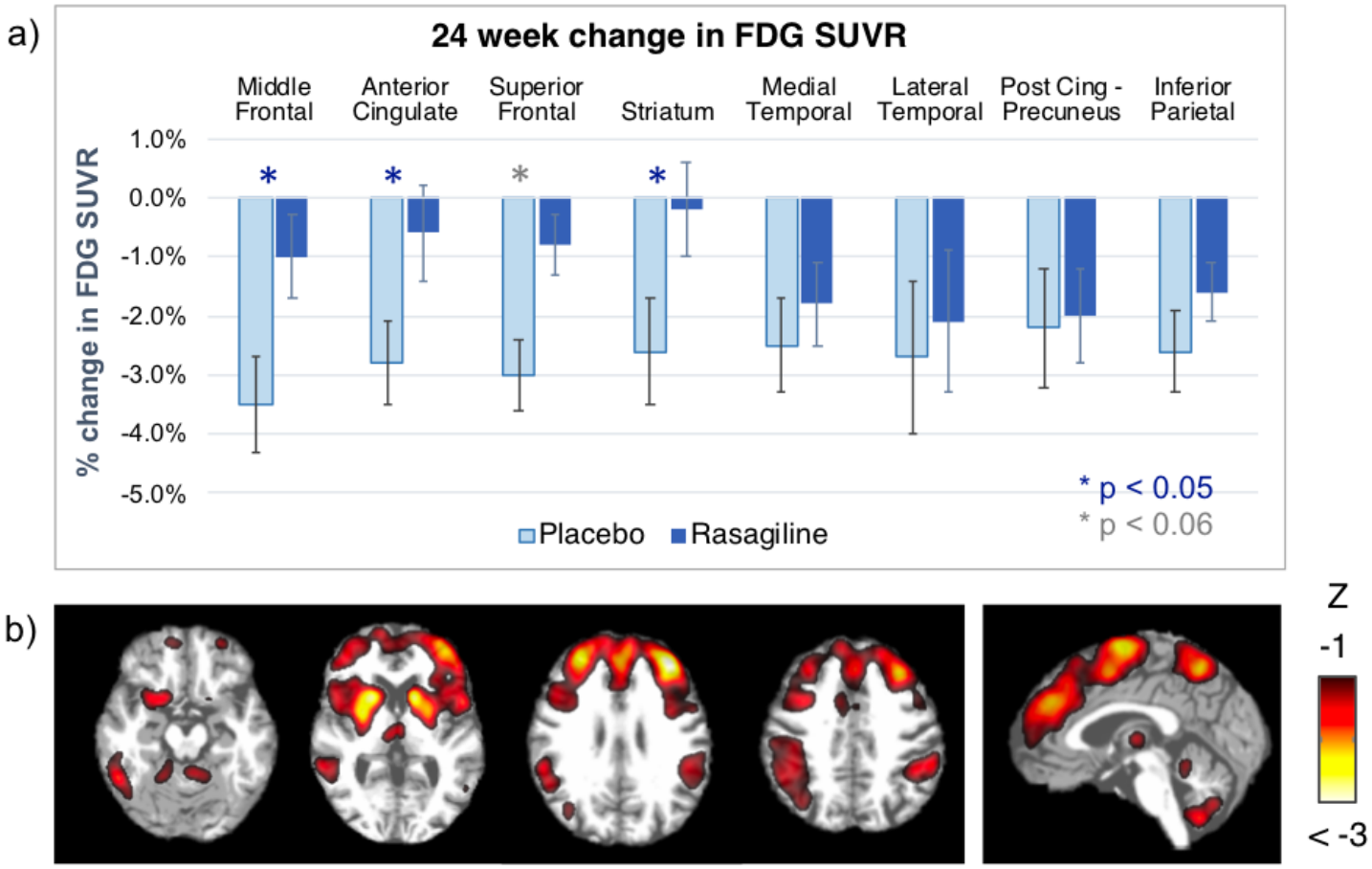

Figure 3

a) 24-week change in FDG SUVR in placebo- vs. rasagiline-treated patients; b) Longitudinal voxel-based classifier results showing regions where rasagiline-treated participants declined less in glucose metabolism than placebo-treated participants.

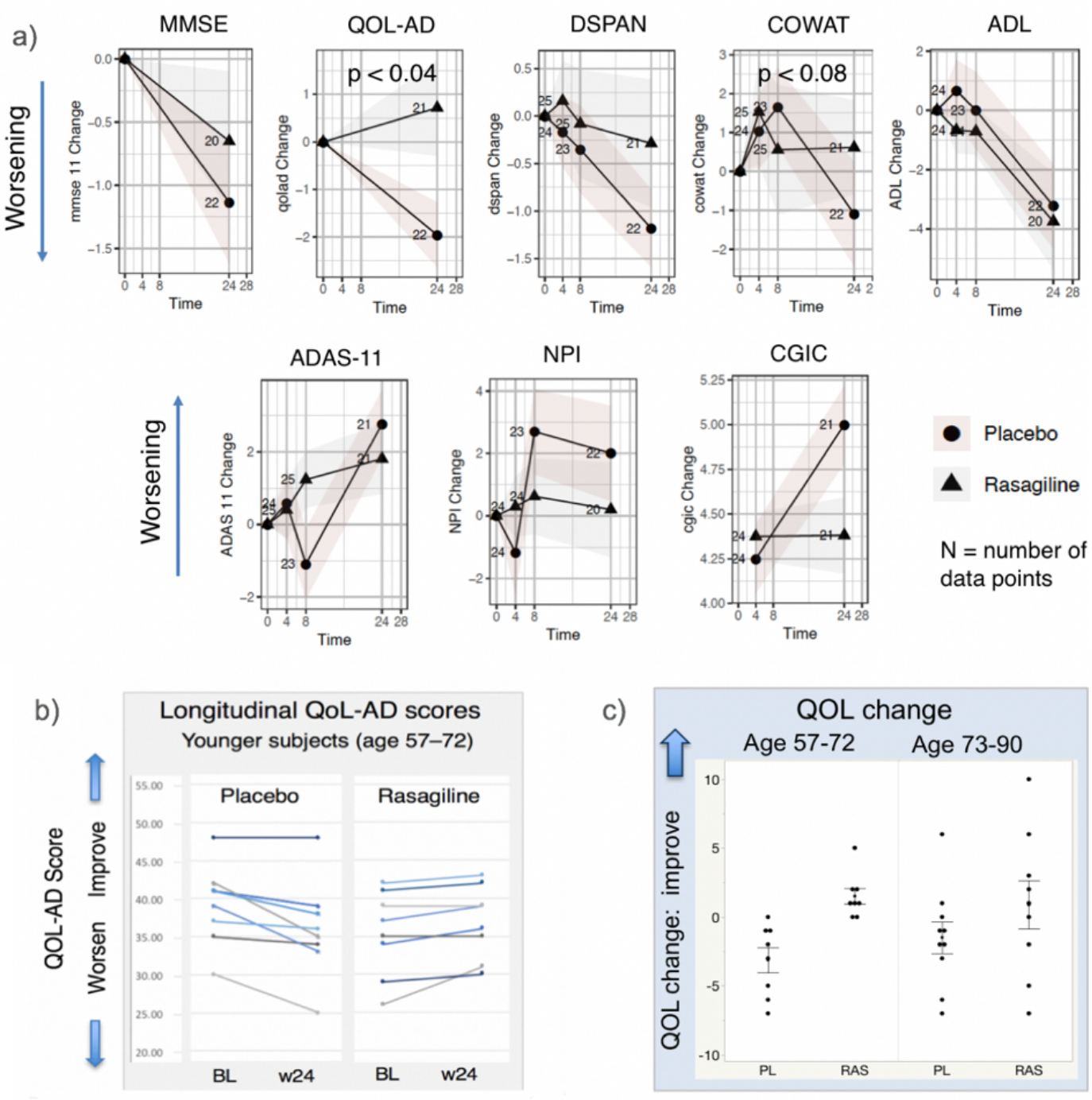

Figure 4

a) Longitudinal change in clinical endpoints 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)

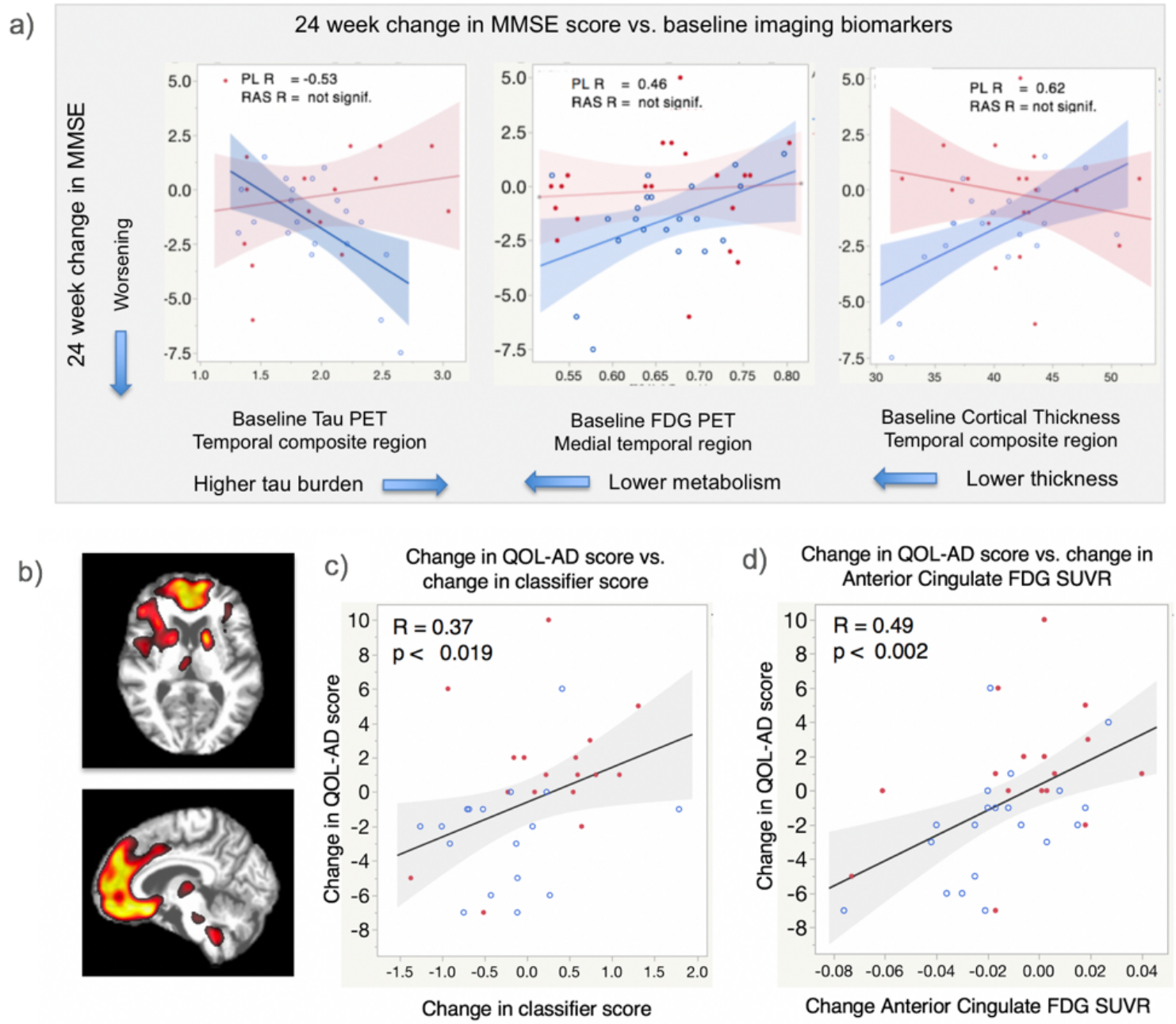

Figure 5

a) Twenty-four week change in MMSE scores vs. baseline temporal tau SUVRs, FDG PET SUVRs, and cortical thickness. Blue = placebo, Red = rasagiline. b) Classifier pattern of glucose metabolism increases (orange) associated with greater QoL-AD scores. c) Relationship between change in classifier score for pattern in (b) and change in QoL-AD score. Placebo = open blue circles, rasagiline-treated = solid red circles. d) Relationship between Anterior Cingulate FDG SUVR (pre-specified region of interest that is part of the classifier pattern) and change in QoL-AD score.

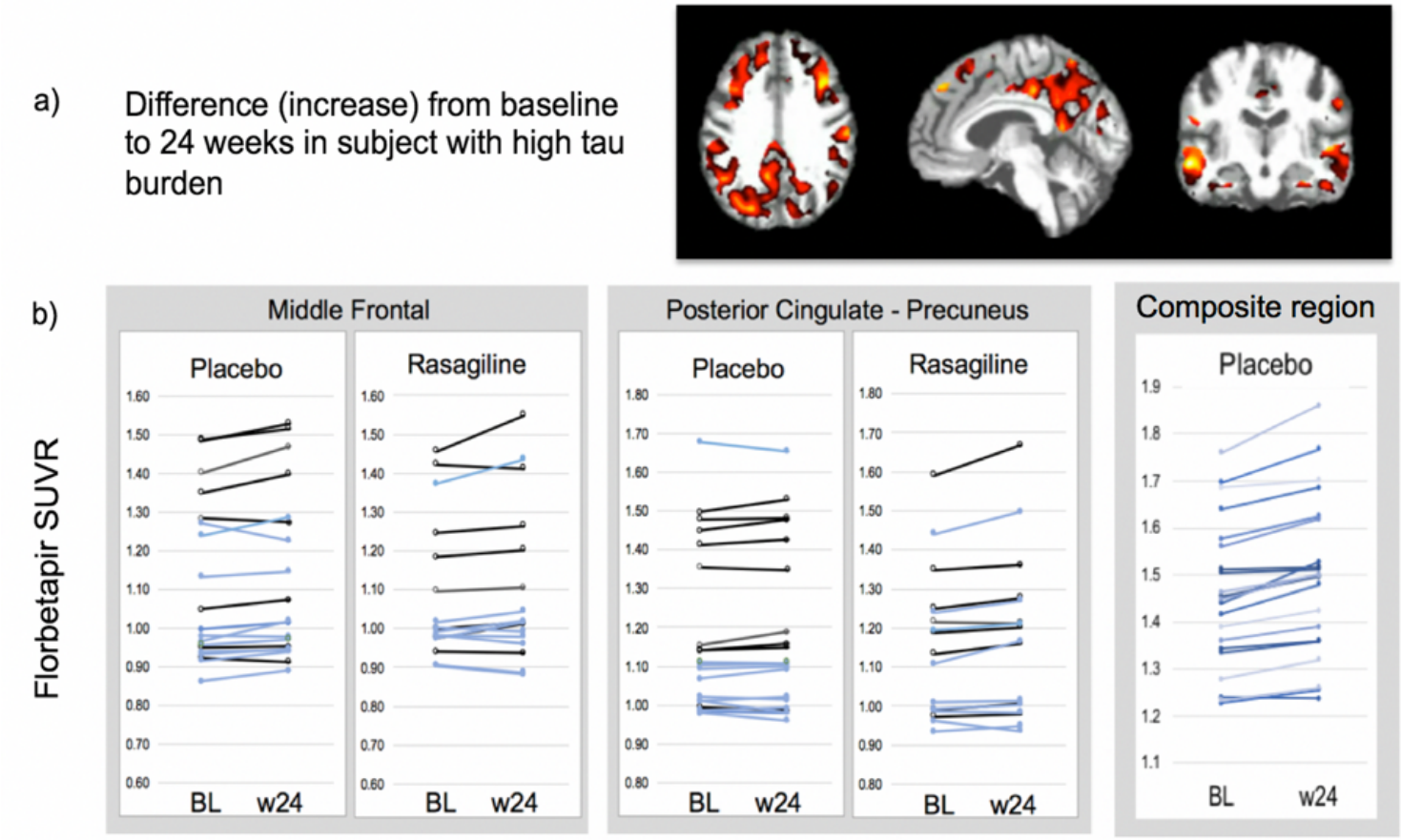

Figure 6

a) Example of increases in tau burden in a high tau imaging participant over 24 weeks. b) 24-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.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- POCtrialofrasasgilineSupplemental.docx