A 24-week, Three-site, Randomized, Double Blind, Placebo Controlled, Parallel Group, Proof-of-concept Study to evaluate the effect of Rasagiline in the regional brain metabolism on FDG PET in Patients with Mild to Moderate Alzheimer's Disease

(*Rasagiline Rescue in Alzheimer's Disease Clinical Trial*)

Amendment #5

Compound: Rasagiline

Protocol number: R2-001

Phase: II

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PROTOCOL SYNOPSIS

TITLE	A 24-week, Three-site, Randomized, Double Blind, Placebo Controlled, Parallel Group, Proof-of-concept Study to evaluate the effect of Rasagiline in the regional brain metabolism on FDG PET in Patients with Mild to Moderate Alzheimer's Disease (*Rasagiline Rescue in Alzheimer's Disease Clinical Trial*)
STUDY NAME	R2 Trial
NAME OF ACTIVE INGREDIENT	Rasagiline mesylate
NAME OF INVESTIGATIONAL PRODUCT	Azilect® (rasagiline)
STUDY PHASE	Phase II
INDICATION	Mild to Moderate Alzheimer's Disease
PRIMARY OBJECTIVE	To determine if exposure to 1 mg of Rasagiline daily is associated with improved regional brain metabolism in the treatment group compared to the placebo group in Alzheimer's Disease patients
SECONDARY OBJECTIVES	• To evaluate the efficacy of Rasagiline 1 mg once daily compared to placebo after a 24-week treatment on cognition (ADAS-Cog 11), activities of daily living (ADCS-ADL), global function (CGIC), and neuropsychiatric symptoms (NPI) • To evaluate the efficacy of Rasagiline 1 mg once daily compared to placebo after 24 week treatment on measures of executive function (mazes and cancellation of the ADAS-Cog, Digit Span test, and Controlled Oral Word Association Test [COWAT] for verbal fluency)To evaluate the safety and tolerability of rasagiline as measured by incidence of adverse events/serious adverse events (AEs/SAEs), clinical laboratory test data, vital signs, 12 lead EKG data, brain MRI findings • To correlate the relationship of changes in **^{18}F-AV-1451** Tau imaging to clinical measures
STUDY DESIGN	This is a Phase II, randomized, double blind, placebo controlled, parallel group, proof-of-concept three-site study, to evaluate the effect of rasagiline in the regional brain metabolism on FDG PET. The study consists of two phases: a 24-week double blind placebo controlled treatment period and a 4-week follow-up period. Patients will be randomized to a 1:1 ratio at Baseline to receive either rasagiline or matching placebo.

	The study drug will be given as 0.5 mg dose once daily for the first 4 weeks; it will be increased to 1 mg daily for the next 20 weeks. A total of 50 subjects will be enrolled: 25 will receive rasagiline and 25 will receive matching placebo for the 24-week treatment period.
STUDY ENDPOINTS	**Primary Endpoint** The primary study endpoint is the change from Baseline to Week 24 in regional glucose metabolism as measured by standard uptake units regional (SUVr) obtained through the FDG-PET. **Secondary Endpoints** • Change from Baseline to Week 24 in **^{18}F-AV-1451** Tau PET imaging SUVr • Change from Baseline to Week 24 on the scores of MMSE, ADAS-Cog 11 and CGIC • Change from Baseline to Week 24 on the scores of NPI and ADCS-ADL • Change from Baseline to Week 24 on the scores of Digit Span test, COWAT and QoL–AD/Study Partner • Correlation between changes in clinical measures (rasagiline vs. placebo change from baseline) and SUVr for FDG PET and SUVr for **^{18}F-AV-1451** Tau PET • Correlation between SUVr for FDG PET and SUVr for **^{18}F-AV-1451** Tau PET • Safety and tolerability as measured by incidence of adverse events/serious adverse events (AEs/SAEs), clinical laboratory test data, vital signs, 12-lead EKG data • Proportion of subjects with adverse events, serious adverse events and adverse events leading to discontinuation over the 24-week double blind treatment period • Proportion of subjects with laboratory abnormalities • Proportion of subjects with EKG abnormalities
SAMPLE SIZE	Target enrollment is 50 subjects and will be recruited from three sites of the Cleveland Clinic Lou Ruvo Center for Brain Health – Las Vegas, Cleveland Main Campus and Lakewood sites
KEY INCLUSION CRITERIA	• Males or females 50 to 90 of age inclusive • Diagnosis of probable AD (NINCDS-ADRDA criteria) • Positive fluorodeoxyglucose PET ([18F]-FDG PET) scan compatible with AD as determined by the ADM Diagnostics LLC (ADMdx) criteria at screening • Must be willing to undergo **^{18}F-AV-1451** Tau PET scan at Baseline and Week 24 visits • MMSE = 12-26 (inclusive) • Must have a study partner who is able and willing to comply with all required study procedures

	• Have at least eight years of education and should have previously (in pre-AD condition) been capable of reading, writing, and communicating effectively with others in English • If receiving therapy with a cholinesterase inhibitor and/or memantine, the dose of these agents has been stable for at least 60 days prior to screening
KEY EXCLUSION CRITERIA	• Any non-AD neurological disease • MRI findings indication of a non-AD diagnosis • Screening laboratory studies that are 1.5 times above or below the highest and lowest range of normal for each test, respectively • **History of melanoma; history of malignancy within the past five years with the exception of basal cell or squamous cell carcinoma, in-situ cervical carcinoma, or localized prostate cancer**
DISALLOWED MEDICATIONS	• Meperidine (Demerol) • Ciprofloxacin • MAO inhibitors such as but not limited to the following: Isocarboxazid, Phenelzine, Selegiline, and Tranylcypromine. • Dextromethorphan and Nuedexta • **Hydroxyzine** • **Diphenhydramine** • **Scopolamine** • **Cyproheptadine** • **Oxybutynin** • **Fesoterodine** • **Solifenacin** • **Darifenacin** • **Dicyclomine** • **Glycopyrrolate** • **Antipsychotics such as but not limited to the following most commonly used antipsychotic medications: Haloperidol, Quetiapine, Ziprasidone, and Risperidone**
MEDICATIONS WITH LIMITED DOSES	**<u>Antidepressants are excluded</u>** with the following exceptions: • Amitriptyline ≤ 50 md/d • Trazodone ≤ 100 mg/d • Citalopram ≤ 20 mg/d • Escitalopram ≤ 10mg/d • Sertraline ≤ 100 mg/d • Paroxetine ≤ 30 mg/d • Mirtazapine ≤ 30 mg/d • Buspirone ≤ 30mg/d • Fluoxetine ≤40 mg/d • Bupropion ≤150 mg/d • Duloxetine ≤60 mg/d • Venlafaxine ≤125 mg/d • No hypnotic the night prior to or day of PET scan preceding the scan

DIETARY ADJUSTMENT	High tyramine-containing foods will be **avoided**: • Sausages, salami, pickled herring • Fava beans • Tap beers, non-pasteurized beers • Sauerkraut, yeast extract, soybean products including soy sauce • Aged cheeses
DRUG DOSAGE AND FORMULATION	Subjects will take one 0.5 mg dosage Rasagiline tablet or the matching placebo once a day orally from Baseline visit to Week 4 visit. The dose will be titrated to one 1 mg dosage tablet or the matching placebo once a day starting on Week 5 through Week 24.
DURATION OF PARTICIPATION	This is a 34-week study comprised of 7 in-clinic visits
PLACEBO	A matching oral placebo will be used
ROUTE OF ADMINISTRATION	Oral
PROCEDURES	Physical and neurological exam, MRI, [18F]-FDG PET, **^{18}F-AV—1451** Tau PET, ECG, vitals, clinical laboratory tests, MMSE, ADAS-Cog 11, CGIC, NPI, ADCS-ADL, Digit Span, COWAT, QoL–AD/Study Partner
STATISTICAL CONSIDERATION	Intent-to-Treat (ITT) - The primary FDG analysis will include all patients who received both a screening and end of study scan of acceptable quality. Modified Intent-to-Treat (mITT) – All randomized subjects who have been dispensed study medication and have one post-baseline visit during the blinded phase of the study. Per-protocol (PP) population – All ITT subjects who complete the study (Week 24) and have ingested between 80%to 120% of the prescribed study medication as measured by pill count. Observed case – An observed case analysis of all patients completing the study will be conducted. Last Observation Carried Forward (LOCF) – Clinical data imputation will use the LOCF approach for missing patients. Responder analysis – Responders will be defined as those that have a significant improvement on brain metabolism on FDG for the whole brain or for any of the pre-specified regions. A secondary analysis will compare the changes in FDG at 24 weeks compared to the projected expected metabolism based on the Baseline FDG findings.
ADVERSE EVENTS	<u>SAFETY</u> Orthostatic vital signs, ECG, hematology, chemistry, TSH, B12 and urinalysis (UA) collected at Screening and at end of study

	TOLERABILITY Side effects data will be collected and converted to systems data using a data dictionary. DSMB No Independent DSMB is required.

1. PROTOCOL AMENDMENT #5 SUMMARY OF CHANGES**Change made to inclusion criteria: MMSE 12-26 (inclusive); previously 12-22 (inclusive)**

PROTOCOL AMENDMENT #4 SUMMARY OF CHANGES

1. Addition of other allowed medications

2. Change made to inclusion criteria #8 stable dose changed from 3 months to 60 days.

PROTOCOL AMENDMENT # 3 SUMMARY OF CHANGES

1. Clarification on allowed antidepressants
2. Cyclobenzaprine changed from disallowed medications to allowed medications
3. Addition of other allowed medications
4. Addition of other disallowed medications

PROTOCOL AMENDMENT # 2 SUMMARY OF CHANGES

Addition of the language "T1 sequencing" at Section 7.1 Screening Visit bullet MRI part

PROTOCOL AMENDMENT # 1 SUMMARY OF CHANGES

1. Addition of ^{18}F-AV-1451 Tau imaging in Screening visit as a non-optional sub-study

2. Addition of ^{18}F-AV-1451 Tau imaging Companion Protocol

3. Change from the use of the CIBIS+ and CIBIC+ to CGIC for the visit assessments

4. Change from QoL–Treatment/Patient to QoL–AD/Caregiver

5. Change from ADAS-Cog 13 to ADAS-Cog 11 rating scale

6. Addition of OSU-TBI-ID

7. Change in Brain MRI Sequence

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ABBREVIATIONS

AD	Alzheimer's disease
ADAGIO	Attenuation of Disease Progression with Azilect® Given Once Daily
ADAS-cog 11	Alzheimer's Disease Assessment Scale, 11 item version
ADCS-ADL	Alzheimer's Disease Cooperative Study, Activities of Daily Living
ADDF	Alzheimer's Drug Discovery Foundation
ADMdx	ADM Diagnostics LLC
ADNI	Alzheimer's Disease Neuroimaging Initiative
CBC	Complete blood count
CC	Cleveland Clinic
CDR	Clinical Dementia Rating
CGIC	Clinician Global Impression of Change
COWAT	Controlled oral word association test
CRF	Case Report Form
CT	Computed tomography
DBS	Deep Brain Stimulation
DICOM	Digital Imaging and Communications in Medicine
ECG	Electrocardiogram
FDA	Food and Drug Administration
FDG PET	Fluorodeoxyglucose positron emission tomography
FTD	Frontotemporal dementia
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intent-to-Treat
LBD	Lewy Body Dementia
LOCF	Last Observation Carried Forward
LOO	Leave-one-out independent testing approach
LRCBH	Lou Ruvo Center for Brain Health
MAO-A	Selective monoamine oxidase A
MAO-B	Selective monoamine oxidase B
MAPK	Mitogen-activated protein kinase
MCI	Mild cognitive impairment
mITT	Modified Intent-To-Treat
MMSE	Mini Mental State Examination
MRI	Magnetic Resonance Imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association
NPI	Neuropsychiatric Inventory
OSU TBI-ID	Ohio State University Traumatic Brain Injury Identification Method
QoL	Quality of life
PKC	Protein kinase C
PP	Per-protocol
SUVr	Standardized Uptake Ratio

A 24-WEEK, THREE-SITE, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PARALLEL GROUP, PROOF-OF-CONCEPT STUDY TO EVALUATE THE EFFECT OF RASAGILINE IN THE REGIONAL BRAIN METABOLISM ON FDG PET IN PATIENTS WITH MILD TO MODERATE ALZHEIMER'S DISEASE

Rasagiline Rescue in Alzheimer's Disease Clinical Trial (R2 Trial)

1. Novelty and Relevance

1.1 Introduction

Rasagiline is a selective monoamine oxidase B (MAO-B) inhibitor. Rasagiline has been used extensively for the treatment of Parkinson's disease (PD) where it is approved for signs and symptoms of idiopathic PD as initial monotherapy and as adjunct therapy to levodopa (package insert). Rasagiline is currently being studied in a 24-week, multi-center, randomized, double-blind, placebo-controlled, add-on parallel group study to assess the efficacy of rasagiline on cognition in patients with Parkinson's disease (Study TBT-1012-PM106). Pre-clinical observations (summarized below) document neuroprotective activities of rasagiline beyond those of MAO-B inhibition. The pre-clinical evidence, utility in PD, and the history of benefit of selegiline---a related MAO-B inhibitor---in Alzheimer's disease (AD), provide the rational for a clinical trial of rasagiline in AD. This proposal outlines a clinical trial based on a partnership between the Alzheimer's Drug Discovery Foundation (ADDF), Cleveland Clinic Lou Ruvo Center for Brain Health and ADM Diagnostics LLC (ADMdx) to conduct a clinical trial in mild to moderate AD.

Several novel aspects are incorporated in the clinical trial design presented. Rasagiline is a repurposed agent and repurposing has many benefits in terms of accelerating development of AD therapies (1,2). The use of a biomarker as a primary outcome --- fluorodeoxyglucose positron emission tomography (FDG PET) --- is also a novel approach and allows a smaller number of patients to be recruited into the trial. The incorporation of Tau imaging with the novel ligand T807 (Avid Radiopharmaceuticals) is also innovative and has the opportunity to advance understanding of neuroprotection, neurofibrillary tangles, and tau imaging. This is the first clinical trial in which positive tau imaging will be required at baseline. Tau imaging will be secondary outcome of the trial, and there will be opportunities to understand the information provided by tau imaging as a complement to FDG imaging. The use of the Cleveland Clinic Lou Ruvo Center for Brain Health's distributed clinical trial infrastructure is also a trial innovation. Recruitment sites will include the Lou Ruvo Center for Brain Health in Las Vegas, Nevada (led by Jeffrey Cummings, MD, ScD and Kate Zhong, MD) and the Lou Ruvo Center for Brain Health in Cleveland, Ohio (led by James Leverenz, MD with referrals from the Lakewood Campus site led by Babak Tousi, MD). In addition, we will add novel, clinical trial outcomes sensitive to executive function and relevant to dopamine D1 receptor activation anticipated with MAO-B inhibition. Together, these novel trial design aspects promise to advance an understanding of rasagiline as well as to enhance clinical trial methodologies for AD drug development.

1.2. Preclinical Data

Rasagiline is a selective MAO-B inhibitor (3). Rasagiline has been shown to have neuroprotective, antiapoptotic action dependent on BCL-2, protein kinase C (PKC), and the proteasome-ubiquitin complex (4). Importantly, the S-Isomer of rasagiline (TBT1022) is more than 1,000 times less potent as a MAO inhibitor and exhibits comparable neuroprotective activity. In pre-clinical experiments, TBT1022 protects mitochondrial viability by activating BCL-2 and PKC and by down- regulating the proapopotic FAS Bax protein families (5). Importantly, from an AD therapeutic perspective,

propargylamine-containing compounds such as rasagiline modulate proteolytic cleavage of the amyloid beta precursor protein (APP), decreasing beta amyloid production by activation of the non-amyloid genic alpha-secretase pathway. This effect involves activation of mitogen-activated protein kinase (MAPK) and PKC (6, 7).

These kinases are deregulated in AD and they contribute to tau hyperphosphorylation and the formation of neurofibrillary tangles (31, 32). These observations link rasagiline to tau hyperphosphorylation, neurofibrillary tangle formation, and possibly detectable effects on tau imaging (33, 34)

1.3. Pharmacology of Rasagiline

Rasagiline is a selective, potent and irreversible MAO-B inhibitor. It is well absorbed from the gastrointestinal tract and is highly blood-brain barrier penetrant. Unlike selegiline, it is not metabolized to amphetamine-like derivatives (8). Rasagiline has a molecular weight of 267.34 Daltons. It has a 100-fold selectivity for MAO-B compared to MAO-A. Rasagiline is metabolized through the CYP1A2 cytochrome P450 enzyme system and 1A2 inhibitors should be avoided in patients receiving treatment with rasagiline (3). The major metabolite of rasagiline is 1(R)-aminoindan which at doses used in humans is unlikely to function as a MAO inhibitor. The T-max of Rasagiline is 1 hour. High fat meals impair the absorption of the drug reducing the Cmax and area under the curve (AUC) by 60% and 20% respectively. The Tmax of rasagiline is not affected by food and the reduction in AUC is not statistically significant. Plasma protein binding ranges from 88% - 94% and the mean volume of distribution at steady state is 87 liters. There is virtually complete biotransformation before excretion with dealkylation and hydroxylation followed by glucuronidation and conjugation (3). The principal side effects observed in clinical trials in patients with PD include dyskinesia, nausea, falls, weight loss, constipation, postural hypertension, arthralgia, vomiting, abdominal pain, anorexia, and abnormal dreams.

Drug-drug interactions are historically a concern with MAO inhibitors, particularly tyramine-rich foods and beverages. Although such interactions have not been problematic in patients with selective MAO-B inhibitors, foods with particularly high concentrations of tyramine (aged cheese, sauerkraut, sausage, pickled herring) will be avoided in the course of the study. Similarly, sympathomimetic agents will also be avoided in trial participants.

As a repurposed agent, rasagiline has substantial advantages since there is extensive study of the pharmacokinetics and pharmacodynamics of the compound in both healthy volunteers and patients with PD.

1.4. Clinical Data

Rasagiline has been extensively studied in the treatment of PD (9). Among the most important studies was the Attenuation of Disease Progression with Azilect® Given Once Daily (ADAGIO) study (10, 11). A secondary analysis of the ADAGIO study (12) provided additional insight into the trial outcomes. Of particular importance is the attention to non-motor outcomes including cognition presented in the secondary analysis. Both the 1mg and 2mg doses were associated with an improvement in the activities of daily living subscore as well as the UPDRS mentation subscore and the Parkinson Fatigue Scale (12). The ADAGIO study suggests that cognitive impairment in PD was improved through treatment with rasagiline. Many of the mechanisms of rasagiline relevant to its activity in PD are also relevant to the treatment of AD.

Further support for pursuing a clinical trial of rasagiline in AD is provided by the double-blind, placebo controlled trial of selegiline, alpha-tocopherol and a combination of both of these agents compared to placebo in treatments with AD (13). In this study of patients with moderate AD, there were significant

delays in the time to primary outcome for treatment with selegiline, alpha-tocopherol or combination therapy. Primary outcomes included death, institutionalization, and loss of the ability to perform activities of daily living or severe dementia (defined as a Clinical Dementia Rating score of 3).

1.5. Application to Alzheimer's disease

The data available for PD and for AD suggest a pharmacologic profile of rasagiline compatible with either disease modification or symptomatic improvement or both. Enhanced mitochondrial function and improved dopamine neurotransmitter function would be anticipated to provide symptomatic benefit whereas the antiapoptotic neuroprotective activity of Rasagiline would be expected to provide disease modification. The proposed clinical trial will not resolve whether one or both of these important therapeutic modalities are predominant. The clinical trial is designed to demonstrate if there is enhanced metabolism in a treatment group compared to a placebo-control. The mechanism of rasagiline is highly supportive of an effect on AD with aspects such as modulation of APP metabolism uniquely relevant to AD.

2. Supporting Data

FDG PET analyses and interpretation as well as site qualification will be done by ADMdx. This section provides background information on the analytic methodology to be used in this study. Technical aspects of site qualification, scanner variables, and PET and magnetic resonance imaging (MRI) acquisition are presented in the appendix.

^{18}F-AV-1451 Tau imaging data will be analyzed by ADMdx.

All clinical and imaging data will be integrated through a database constructed by the Alzheimer's Disease Cooperative Study (ADCS) and clinical-imaging integration analyses will be conducted in conjunction with ADCS statisticians (http://ADCS.org).

2.1. Glucose Metabolism as a Biomarker of Neuronal Function

The loss of synaptic activity and neuronal function is closely associated with reductions in glucose metabolism, a primary energy source that is measurable using FDG PET (14, 15). AD is characterized by a specific, progressive pattern of hypometabolism that begins in medial temporal and posterior cingulate cortices, extends to temporo-parietal cortices and eventually affects most cortical regions. Different types of dementia are characterized by distinctive patterns of decline (16), which in turn correlate with the domains of cognition and function that become impaired (17). Representative patterns from two different types of dementia are shown in Figure 1 below, where blue represents significant declines in glucose metabolism relative to normal controls.

ADMdx has focused on the use of FDG PET, amyloid PET, and other markers to differentiate dementia types, predict cognitive trajectory, measure longitudinal change, and assess pharmacologic effects on brain glucose metabolism. This has included the application of advanced machine learning approaches, optimized image quality control and processing, and collection of extensive reference data for the detection of disease, longitudinal change, and drug effect.

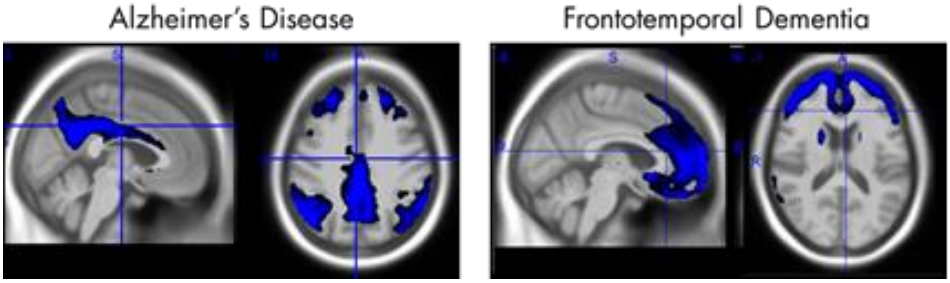


Figure 1. Metabolic patterns on FDG PET distinguishing AD and FTD

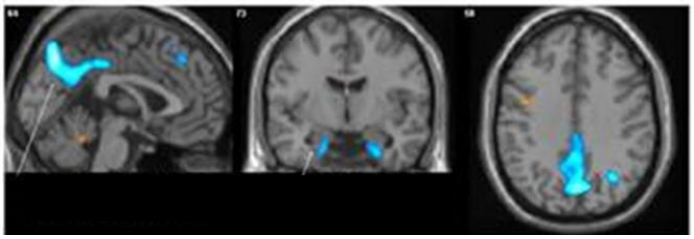
2.2 Dementia Classifier

The ADMdx Dementia Classifier is a machine learning-based software tool that has been trained to differentiate different forms of dementia using the FDG PET scans of 133 subjects with clinical diagnoses including Normal, AD, Frontotemporal Dementia (FTD), and Lewy Body Disease (LBD) (with pathology or autopsy confirmation where available). The classifier compares the voxels of an independent test subject scan to a series of image patterns (canonical variables) that uniquely combine to characterize each type of dementia. The probability of a match with each dementia is determined. Validation was performed using a Leave-One-Out (LOO) approach and with completely independent test subjects. Accuracies achieved in the LOO analysis were: AD vs. FTD 96%, AD vs. Semantic Dementia 97%, and AD vs. LBD 100%. The classifier was subsequently applied to other scans including those of subjects participating in studies of bapineuzumab. It was found that subjects with amyloid plaque were more likely to show hypometabolic FDG patterns as identified using ADMdx's dementia classification software, and that patients without AD pathology were less likely to show an AD pattern (18). ADMdx is continuing to refine its classification approaches.

2.3. AD Progression Classifier

ADMdx has also developed a classifier trained on subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database with clinical diagnoses of Normal (negative for AD), Normal-declined, mild cognitive impairment (MCI), MCI who converted to AD, and AD. This classifier assigns a numeric score to each independent test subject that reflects the degree to which the subject expresses a pattern of decline within regions including those shown in Figure 2 (19).

Figure 2. A portion of the pattern of glucose metabolism decline characterizing progression from NL to AD dementia



As a further illustration of the AD Progression Classifier, Figure 3 shows the mean (and S.E.M.) progression scores for Normal (NL), Early MCI (EMCI), Late MCI (LMCI), and AD subjects from ADNI, all amyloid positive as measured using amyloid PET scans (20). For each diagnostic class, the score at baseline and at 24 months post-baseline are shown. It can be seen that the score captures the progression of hypometabolism across diagnostic classes, as well as the 24-month progression within those classes. Rate of decline is greatest in AD subjects.

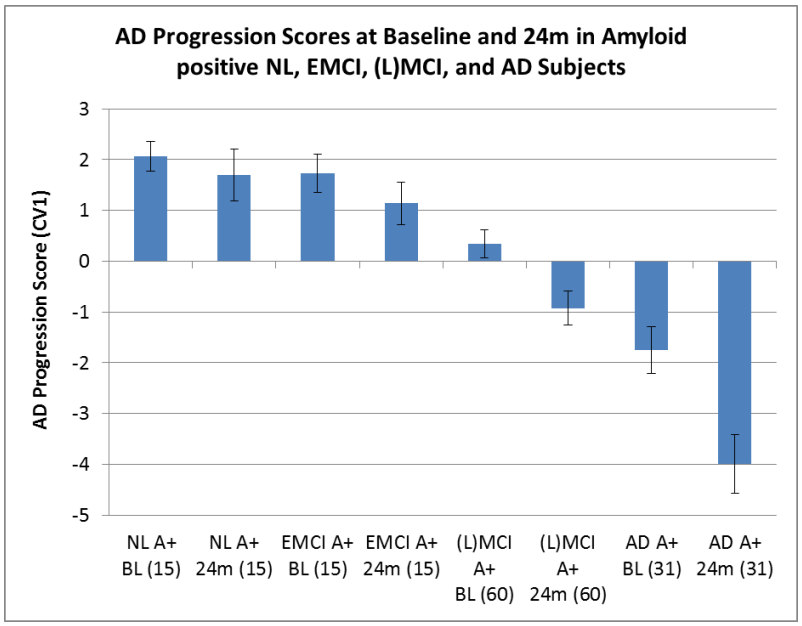


Figure 3. AD Progression scores of amyloid positive NL, EMCI, (L)MCI, and AD subjects at baseline and 24 months (same subjects) (mean, S.E.M. bars)

2.4. Predicting Cognitive Trajectories

We have applied the AD Progression Classifier to 72 NL (40 with amyloid data available), 173 MCI (87 with amyloid data available), and 50 AD subjects from the ADNI database, comparing the classifier score as a predictor of decline in MMSE, CDR-sum of boxes (CDR-sb), and ADAS-Cog 11 to other predictors (baseline MMSE, baseline CDR-sb, baseline ADAS-Cog 11, and amyloid cortical average Standardized Uptake Value Ratio (SUVr)). Results indicated that the AD Progression score was a significant predictor of decline in these measures and a better predictor than the other variables tested[6]. The classifier was also applied to patients in a trial of bapineuzumab, with the result that more severe hypometabolism at baseline as identified by ADMdx's AD Progression Classifier was a strong predictor of subsequent clinical decline over the course of the trials (18).

2.5 Glucose Metabolism as a Measure of Drug Effects

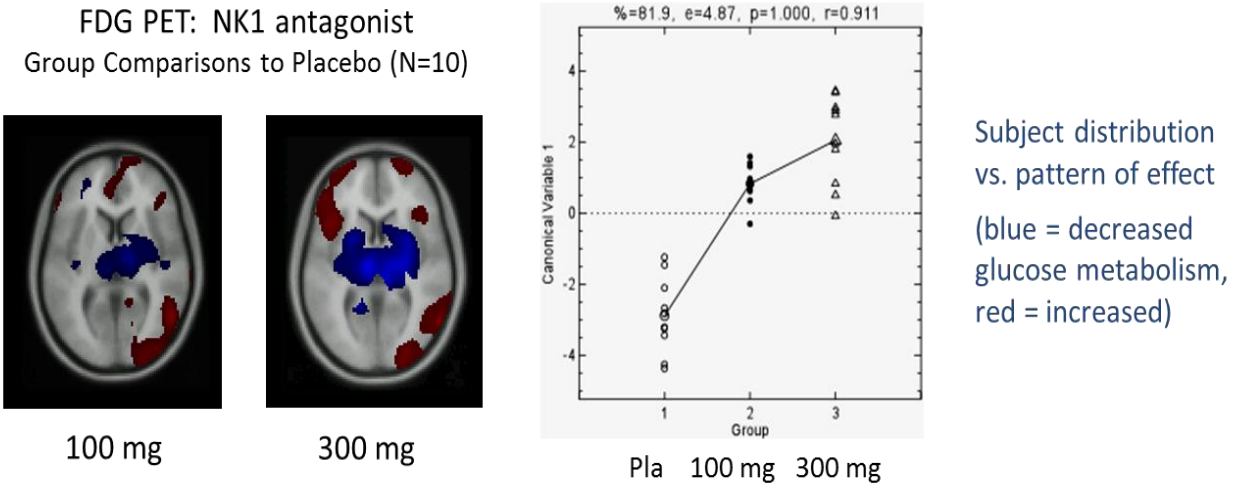


Figure 4. Increases (red) and decreases (blue) in glucose metabolism relative to placebo at a lower and higher dose of an NK1 antagonist. Eigenplot at right shows individual subject expression of the primary pattern of change relative to placebo, and relative to one another, for each treatment dose.

In addition to measuring disease-related changes in neuronal activity, FDG PET can capture drug-related effects, even in small group sizes and at acute doses, depending upon effect. Figure 4 shows the acute effects of a lower and higher dose of an NK1 antagonist compound as measured in a double-blinded randomized crossover study of 10 normal healthy volunteers. Acute changes observed in glucose metabolism were consistent with clinical effects observed in a separate chronic dosing study. The graph in Figure 4 shows each subject's expression of the primary pattern of change for placebo and each treatment dose. These results were obtained using ADMdx's multivariate pattern analysis software (NPAIRS), which uses Principal Component Analysis (PCA) and Canonical Variate Analysis (CVA) to segregate signal from noise, identify the component patterns contributing to overall effect, determine the relative contribution of each pattern, measure each subject's relative expression of the pattern, and provide metrics regarding the reproducibility and predictive power of the group results, and identify patterns of effect. It provides a powerful tool to gain insight into treatment effects (21, 22).

2.6 Tau Imaging as a Measure of Drug Effect

Several kinases (e.g., MAPK PCK) are deregulated in AD and they contribute to tau hyperphosphorylation and the formation of neurofibrillary tangles (31, 32). These observations link rasagiline to tau hyperphosphorylation, neurofibrillary tangle formation, and possibly detectable effects on tau imaging (33, 34)

The incorporation of Tau imaging with the novel ligand **^{18}F-AV-1451** (Avid Radiopharmaceuticals) provides the opportunity to advance understanding of neuroprotection, neurofibrillary tangles, and tau imaging. This is the first clinical trial in which tau imaging will be required at baseline. Tau imaging will be secondary outcome of the trial, and there will be opportunities to understand the information provided by tau imaging as a complement to FDG imaging.

3. STUDY OBJECTIVES and ENDPOINTS

3.1 Primary Objective

To determine if exposure to 1 mg of rasagiline once daily is associated with improved regional brain metabolism in the treatment group compared to the placebo group after a 24-week double blind study treatment in Patients with Mild to Moderate Alzheimer's Disease

3.2 Secondary Objectives

- To evaluate the efficacy of rasagiline 1 mg once daily compared to placebo after a 24-week treatment on cognition (ADAS-Cog 11), activities of daily living (ADCS-ADL), global function (CGIC), and neuropsychiatric symptoms (NPI)
- To evaluate the efficacy of rasagiline 1 mg once daily compared to placebo after a 24-week treatment on measures of executive function (Digit Span test, and Controlled Oral Word Association Test [COWAT] for verbal fluency)
- To evaluate the safety and tolerability of rasagiline as measured by incidence of adverse events/serious adverse events (AEs/SAEs) clinical laboratory test data, vital signs, 12-lead EKG data,
- To evaluate the correlation of FDG-PET results to **^{18}F-AV-1451 (**T807) Tau PET results
- To correlate the relationship of **^{18}F-AV-1451 (**T807) Tau imaging to clinical measures

3.3 Primary Endpoint

The primary study endpoint is the change from screening visit (baseline FDG) to Week 24 in regional glucose metabolism as measured by standardized uptake value ratio (SUVr) obtained through the FDG-PET.

3.4 Secondary Endpoints

- Change from Baseline**^{18}F-AV-1451** Tau PET imaging SUVr results to Week 24 results
- Change from Baseline to Week 24 on the scores of MMSE, ADAS-Cog 11, CGIC
- Change from Baseline to Week 24 on the scores of NPI and ADCS-ADL
- Change from Baseline to Week 24 on the scores of Digit Span test, COWAT and QoL–AD/Study Partner
- Safety and tolerability as measured by incidence of adverse events/serious adverse events (AEs/SAEs) clinical lab test data, vital signs, 12-lead EKG data
- Proportion of subjects with adverse events, serious adverse events and adverse events leading to discontinuation over the 24-week double blind treatment period
- Proportion of subjects with laboratory abnormalities
- Proportion of subjects with ECG abnormalities

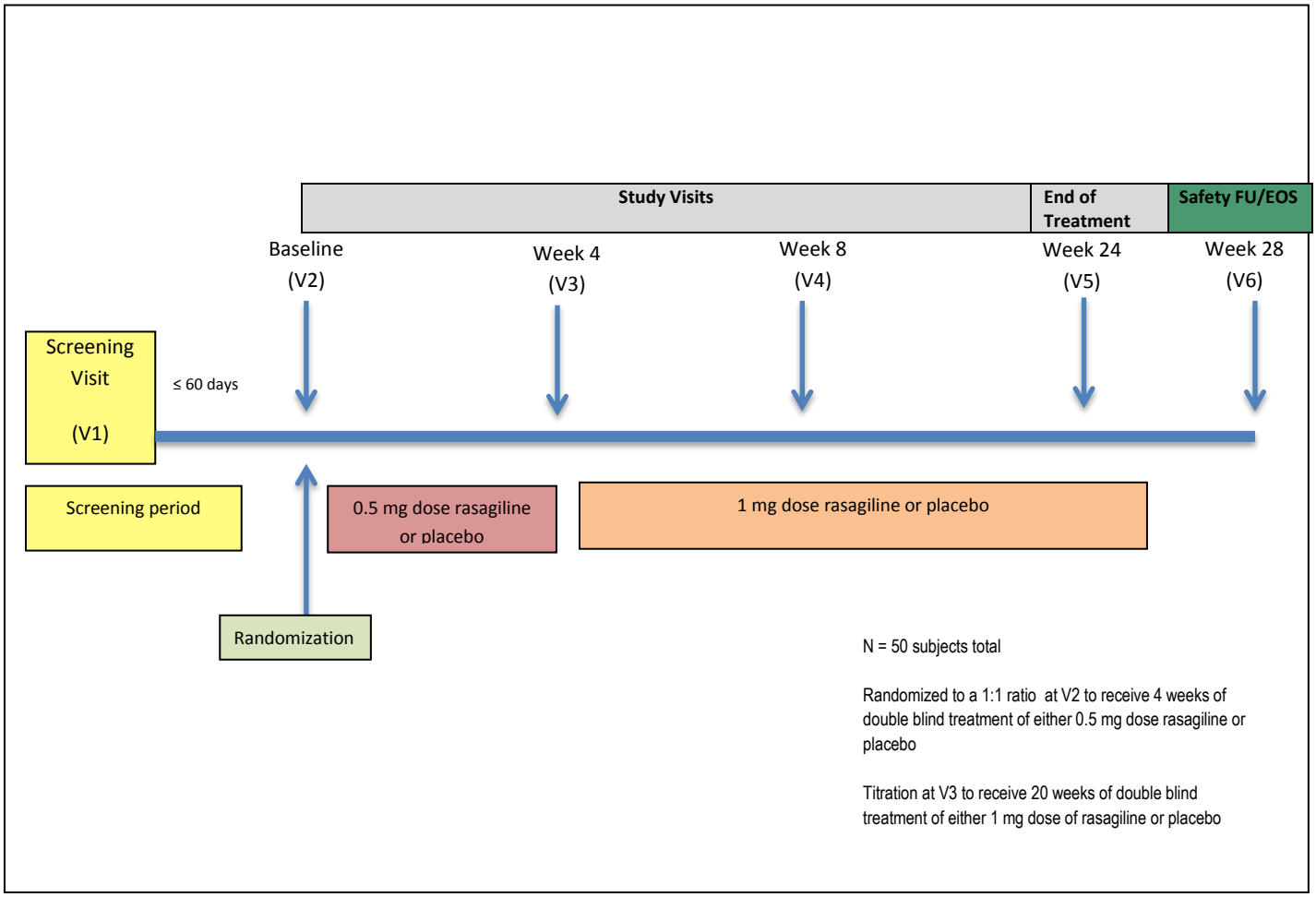
4. STUDY DESIGN

This is a 24 week, Phase II, randomized, double blind, placebo controlled, parallel group, proof-of-concept three-site study, to evaluate the effect of rasagiline in the regional brain metabolism on FDG PET in patients with mild to moderate Alzheimer's disease.

The study consists of two phases: a 24-week double blind placebo controlled treatment period with a 4-week follow-up period. Patients will be randomized to a 1:1 ratio at Baseline to receive rasagiline or matching placebo treatment.

The study drug will be given as 0.5 mg dose once daily for the first 4 weeks then increased to 1 mg dose daily tablet for the next 20 weeks. A total of 50 subjects will be enrolled and will be randomized to a 1:1 ratio. Twenty-five participants will receive rasagiline and the other 25 will receive matching placebo for the 24-week treatment period.

Figure 5. **Research Schematic**



Visit 1 – Screening visit (within a 60-day period); MRI, FDG PET and **^{18}F-AV-1451** Tau imaging

Visit 2 – Baseline (Week 1)

Visit 3 Week 4; increase dose from 0.5 mg QD to 1 mg QD

Visit 4 Week 8

Visit 5 –Week 24; blood draws, FDG PET & **^{18}F-AV-1451** Tau imaging, end of treatment

Visit 6 – Follow-up Visit/ Week 28; end of study/early discontinuation

5. SUBJECT SELECTION AND WITHDRAWAL

5.1 Inclusion Criteria

1. Males or females 50 to 90 years of age inclusive
2. Diagnosis of probable AD according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria
3. Positive fluorodeoxyglucose PET ([18F]-FDG PET) scan compatible with AD as determined by the ADM Diagnostics LLC (ADMdx) criteria
4. Must be willing to undergo **^{18}F-AV-1451** Tau imaging at Screening and Week 24 visits
5. Mini-Mental State Examination (MMSE) score between 12-26 inclusive
6. Must have a study partner who is able and willing to comply with all required study procedures
7. Have at least eight years of education and should have previously (in pre-AD condition) been capable of reading, writing, and communicating effectively with others in English
8. If receiving therapy with a cholinesterase inhibitor and/or memantine, the dose of these agents has been stable for at least 60 days prior to screening
9. Willing and able to provide informed consent by either the subject or subject's legal representative
10. Willing and able to comply with study visits, treatment plan, laboratory tests, brain imaging and other procedures
11. Females must be postmenopausal

5.2 Exclusion Criteria

1. Any clinically relevant neurological disorder capable of producing a dementia syndrome including Parkinson's disease, stroke, vascular dementia, dementia with Lewy bodies, frontotemporal dementia and others
2. Psychosis or is receiving antipsychotic treatment
3. MRI findings indication of a non-Alzheimer's disease diagnosis
4. History of melanoma; history of malignancy within the past five years with the exception of basal cell or squamous cell cancer, in-situ cervical cancer, or localized prostate cancer
5. History of Deep Brain Stimulation (DBS)
6. History of seizure in the past three years prior to randomization
7. Any contraindication of having brain MRI
8. Any contraindication of having PET (inability to lie flat and still for the duration of the scan, intolerance to previous PET such as hypersensitivity reaction to PET ligand or imaging agent)
9. The subject has any unstable medical illness including hypertension, congestive heart failure, chronic obstructive pulmonary disease, renal failure, liver failure or other organ compromise

10. Uncontrolled hypertension (systolic blood pressure [BP] ≥ 160 mmHg, or diastolic BP ≥ 100 mmHg; US National Institutes of Health [NIH] Seventh Report of the Joint National Committee [JNC 7] criteria). Hypertensive patients whose BP is controlled with medication to systolic BP < 160 mmHg and diastolic BP < 100 mmHg are eligible.

11. Baseline laboratory studies that are 1.5 times above or below the highest and lowest range of normal values

12. Other clinically important abnormality on vital signs, physical examination, neurological examination or laboratory results, that could compromise the study or be detrimental to the subject

13. Have either: 1) Screening ECG with QTc > 450 msec if male or QTc > 470 msec if female; or 2) A history of additional risk factors for Torsades de Pointes (TdP) (e.g., hypokalemia, family history of Long QT Syndrome) or are taking drugs that are known to cause QT-prolongation; Patients with a prolonged QTc interval in the setting of intraventricular conduction block (e.g. right bundle branch block [RBBB] or left bundle branch block [LBBB], may be enrolled with sponsor approval; or 3) History of atrial fibrillation

14. The patient has taken rasagiline or any other MAOIs within 90 days prior to the Screening/Baseline Visit

15. The subject has an allergy to rasagiline

16. Other disallowed medications (taken within 30 days before the Screening/Baseline Visit and during the study) include anticholinergics, meperidine, dextromethorphan, tramadol, St. John's wort, methadone, cocaine, ciprofloxacin, or other CYP1A2 inhibitors

17. Has had a PET scan or radiotherapy within 6 months prior to the Screening visit

18. Has participated in an investigational drug or device study within 30 days prior to Screening

19. Unable to swallow uncrushed oral medication in tablet form

20. Has any condition or reason that, in the opinion of the investigator, could interfere with the ability of the patient to participate or complete the trial, or places the patient at undue risk or complicates the interpretation of safety or efficacy data

5.3 Subject Recruitment

Subjects will be recruited from three sites of the Cleveland Clinic, Lou Ruvo Center for Brain Health -- Las Vegas, Cleveland Main Campus and Lakewood site. Subjects may be referred directly to the clinical trial from community physicians. Advertising materials used for the trial will be approved by the Cleveland Clinic Institutional Review Board (IRB) prior to implementation.

5.4 Subject Withdrawal

Patients and caregivers are informed that they have the right to withdraw from the study at any time without prejudice or loss of benefit to which they are otherwise entitled.

The investigator or sponsor may withdraw a patient from the study in the event of an inter-current illness, adverse event, non-compliance, protocol violation and other reasons concerning the health or wellbeing of the patient.

Following are specific circumstances justifying withdrawal:

- Development of an inter-current medical condition or need for concomitant treatment that precludes further participation in the trial
- Unacceptable toxicity or any adverse event that precludes further participation in the trial
- The investigator removes the patient from the trial in the best interests of the patient
- Non-adherence to study regimen as determined by pill count
- Patient withdraws consent to continued participation in the trial

Patients who withdraw prior to study completion will be asked to return to the clinic to complete visit 6 (end of study) assessments.

5.5 Data Collection and Follow-up for Withdrawn Subjects

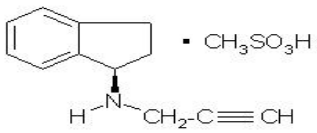
- All subjects who discontinue the trial prematurely will be followed.
- Every effort will be made to maintain contact with patients discontinuing treatment during the course of the trial.
- Reasons for withdrawal will be investigated and documented.
- All efforts should be made to document the outcome following the withdrawal.
- Patients who withdrew from the study will not be replaced.

6. STUDY TREATMENT

6.1 Study Drug

Azilect® tablets contain rasagiline (as the mesylate), a propargylamine-based drug indicated for the treatment of idiopathic Parkinson's disease. It is designated chemically as: 1H-Inden-1-amine, 2, 3-dihydro-N-2-propynyl-, (1R)-, methanesulfonate. The empirical formula of rasagiline mesylate is (C12H13N) CH4SO3 and its molecular weight is 267.34.

Its structural formula is:



Rasagiline mesylate is a white to off-white powder, freely soluble in water or ethanol and sparingly soluble in isopropanol. Each Azilect tablet for oral administration contains rasagiline mesylate equivalent to 0.5 mg or 1 mg of rasagiline base.

Each Azilect tablet also contains the following inactive ingredients mannitol, starch, pregelatinized starch, colloidal silicon dioxide, stearic acid and talc.The matching placebo will look exactly like the study medication to maintain the double blind design of the study.

6.2 Treatment Regimen

Subjects will be randomized to a 1:1 ratio to receive Rasagiline or the matching placebo 24-week double blind treatment.

Subjects will take one 0.5 mg rasagiline tablet or the matching placebo once a day on Baseline (Day 1) through Week 4. The dose will be titrated up to one 1 mg tablet or the matching placebo once a day starting **on Week 5** until the Week 28 (end of treatment visit).

6.3 Administration of Treatment

Study medication should be administered once daily, with or without food. Subjects will swallow all orally administered study medication as a whole and will not chew the medication before swallowing.

Patients will be given 1 month supply of 0.5 mg rasagiline or matching placebo tablets to take home on the day of randomization (Visit 2) with detailed instruction of taking one capsule once a day for 4 weeks. Patient is to return to clinic for Visit 3 (Week 4), when the dose will be increased to 1 tablet of 1 mg rasagiline or matching placebo once a day. Patients are to continue taking 1 tablet of 1 mg rasagiline or matching placebo once a day for the next 20 weeks of treatment.

Table 1 Group and Treatment Phases

Groups	**Treatment Phases**	
	Baseline to Week 4	Week 5 to Week 24
Active	1 x 0.5 mg rasagiline QD	1 x 1 mg rasagiline QD
Placebo	1 x matching placebo QD	1 x matching placebo QD

6.4 Subject Compliance Monitoring

Adherence to the study protocol will be judged by pill counts. Non-adherence of less than 80% of the anticipated dose will result in study discontinuation. Accepted drug compliance is compliance rate of 80% to 120%.

6.5 Prior and Concomitant Therapy

Concomitant treatment is any drug or substances administered between screening and end of study (Week 24).

Allowed Concomitant Therapy:

- Medications for chronic medical conditions are allowed at a stable dose during the study provided the subject has been on a stable dose for at least 3 months prior to randomization.
- Cholinesterase inhibitors and memantine are allowed provided the therapy has been stable for at least 3 months prior to screening and that the patient stays on a stable dose during the study.

- Anticholinergic medications allowed include the following: Ranitidine, Loratadine, fexofenadine, cetirizine, cyclobenzaprine

Disallowed Concomitant Therapy:

- Meperidine (Demerol), Propoxyphene and Tramadol
- Ciprofloxacin and other CYP1A2 Inhibitors
- MAO inhibitors such as but not limited to the following: Isocarboxazid, Phenelzine, Selegiline, and Tranylcypromine
- Dextromethorphan and Nuedexta
- St. John's wort
- Levodopa/Carbidopa
- Theophylline
- Sympathomimetic medications
- Hydroxyzine
- Diphenhydramine
- Scopolamine
- Cyproheptadine
- Oxybutynin
- Fesoterodine
- Solifenacin
- Darifenacin
- Dicyclomine
- Glycopyrrolate
- Antipsychotics such as but not limited to the following most commonly used antipsychotic medications: Haloperidol, Quetiapine, Ziprasidone, and Risperidone

Antidepressants are excluded with the following exceptions:

- Amitriptyline ≤ 25 mg/d
- Nortriptyline ≤ 50 mg/d
- Trazodone ≤ 50 mg/d
- Citalopram ≤ 20 mg/d
- Escitalopram ≤ 10mg/d
- Sertraline ≤ 100 mg/d
- Paroxetine ≤ 20 mg/d
- Mirtazapine ≤ 30 mg/d
- Buspirone ≤ 30mg/d
- Fluoxetine ≤ 40 mg/d
- Bupropion ≤ 150 mg/d
- Duloxetine ≤ 60 mg/d
- Venlafaxine ≤ 125 mg/d
- No hypnotics the night prior to or day of PET scan preceding the scan

High tyramine-containing foods will be **avoided**:

- Sausages, salami, pickled herring
- Fava beans
- Tap beers, non-pasteurized beers
- Sauerkraut, yeast extract, soybean products including soy sauce

- Aged cheeses

6.6 Blinding of Study Drug

An unblinded pharmacist or unblinded study personnel will administer and dispense the trial medication to the subjects to maintain the double-blinding of the study.

6.7 Receiving, Storage, Dispensing and Return

6.7.1 Receipt of Drug Supplies

All drugs for the study will be shipped to each of the three sites of the Cleveland Clinic Lou Ruvo Center for Brain Health. Upon receipt of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The unblinded pharmacist or unblinded study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study treatment product in a given shipment will be documented in the study files. Active drug and the matching placebo soft capsules will be provided by Teva Pharmaceuticals.

6.7.2 Storage

Rasagiline can be stored at room temperature. High temperatures will be avoided. The drug will be protected from light. No special temperature controls are necessary beyond those of room temperature.

6.7.3 Packaging of Study Drug

Study active medication and placebo will be packaged in 1-month supply bottles. There will be a total of 40 capsules in a bottle of either the rasagiline drug or the placebo. Each participant will return study medication bottles (including any unused study medication) at each visit for drug accountability purposes.

6.7.4 Dispensing of Study Drug

Participants will receive study drug or placebo in one-month supply bottles. At Baseline (Visit 2), the randomized subject will be given one (1) bottle containing either the active drug or the placebo. All subjects will be instructed to take one 0.5 mg tablet once a day for the first 4 weeks. A dosing instructions sheet will also be provided to all subjects as a dosing guide. At Visit 3 (Week 4), subjects will be seen at the clinic and, if there is no reason to discontinue therapy, will be advanced and instructed to take one 1 mg tablet once daily for 4 weeks. Patients will then be seen at Visit 4 (Week 8) at which time they will receive a 4-month supply of the study medication. Regular study drug reconciliation will be performed to document drug dispensed; drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated by the study coordinator.

6.7.5 Return or Destruction of Study Drug

There will be a final reconciliation of the study drug at the conclusion of the study. The reconciliation will be logged onto the drug reconciliation form, signed and dated. Any discrepancies noted will be investigated, resolved and documented prior to return of unused study drug.

7. DESCRIPTION OF STUDY VISITS

7.1 Visit 1 – Screening (Days -60 to -1)

Subjects will undergo all screening procedures within 60 days prior to baseline visit to confirm the study eligibility.

The following activities will be completed:

- Obtain IRB approved written inform consent from the subject and the subject's legal representative in accordance with regulation before initiating any procedures for both the main protocol and the **^{18}F-AV-1451 imaging companion** protocol
- Assess inclusion and exclusion criteria
- Obtain demographic data
- Obtain medical history and review medications
- Obtain history of prior procedures (radiation/PET)
- Record prior medication within the last 3 months
- Obtain Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) Questionnaire for the **^{18}F-AV-1451** TAU imaging **companion protocol.**
- Perform Mini Mental State Examination (MMSE)
- Perform physical and neurological examinations
- Record orthostatic vital signs, body weight and height
- Obtain standard single 12 lead EKG
- Collect non-fasting blood sample for routine laboratory test including:
    - Hematology
    - Blood chemistry
    - Liver function
    - TSH
    - B12
- Collect urine sample for screening urinalysis (UA)
- Obtain MRI: T1 sequence and two-dimensional T2*-GRE to detect micro-hemorrhages and T2 FLAIR sequences to identify ARIA-E
- Obtain fluorodeoxyglucose (FDG) PET imaging
- Obtain**^{18}F-AV-1451** Tau imaging pending positive FDG PET imaging results

The screening visit MRI, FDG PET imaging and **^{18}F-AV-1451** Tau PET imaging visits will be done on separate visits.

POST ^{18}F-AV-1451 TAU IMAGING FOLLOW-UP PHONE CALL

A follow-up phone call to the participant or the caregiver will be conducted between 2 and 3 business days after the imaging visit, but not before 48 hours post-injection, to confirm participant well-being and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.

7.2 Visit 2 – Baseline (Day 1)

Patients will be randomized within 60 days from the first day of screening.

The following activities will be completed PRIOR to dosing:

- Review Inclusion/Exclusion qualification
- Review laboratory studies performed at Screening Visit (laboratory results should be normal to continue randomization of subject)
- Review of MRI and PET Scan results
- Inquire about occurrence of adverse events since previous visit and changes to concomitant medications

If subject continues to be eligible for the study, he/she may be entered into the double-blind randomization phase and procedures listed below will occur:

- Record vital signs and body weight
- Perform Mini Mental State Examination (MMSE)
- Collect blood sample for ApoE genotyping test
- Collect blood sample for biomarker measures including:
    - Serum Aβ 40 and 42
    - sAPP-α, sAPP-β, Isoprostanes
    - Cytokines and other measures relevant to AD
- Perform the following assessments:
    - ADAS-Cog 11
    - CGIC
    - NPI
    - ADCS-ADL
    - Digit Span
    - COWAT
    - QoL–AD/Study Partner
- Dispense double blind study medication to patient and caregiver for outpatient dosing, with instructions to return bottle and unused study medication to clinic at next visit.
- Provide instructions to caregiver/subject on outpatient dosing, including storage, administration, and compliance assessment.

Patients will be given a one-month supply of medication at this visit. The dosing instruction at this visit is to take one 0.5mg capsule of study drug or matching placebo once a day for one month. Leftover medications will be brought to clinic visits for accountability.

7.3 Visit 3 – Week 4

This visit will occur at the end of Week 4 with a visit window of +/- 5 days.

The following activities will be completed:

- Record orthostatic vital signs and body weight
- Inquire about occurrence of adverse events since previous visit and any changes to concomitant medications since Baseline Visit
- Perform the following assessments:
    - ADAS-Cog 11
    - CGIC
    - NPI
    - ADCS-ADL
    - Digit Span
    - COWAT

- Assess drug adherence and accountability of study medication
- Dispense double blind study medication to patient and caregiver for outpatient dosing, with instructions to return bottle to clinic at next visit.
- Provide instructions to caregiver/subject on outpatient dosing, including storage, administration, and compliance assessment.

This is a check-up visit to determine if patients are able to tolerate the medication. If so, they will be instructed to take the medication to an increased dosage of 1 mg rasagiline or matching placebo tablet once daily.

7.4 Visit 4 – Week 8

This visit will occur at the end of Week 8 with a visit window of +/- 5 days.

The following activities will be completed:

- Record orthostatic vital signs and body weight
- Inquire about occurrence of adverse events since previous visit and any changes to concomitant medications since Baseline Visit
- Perform the following assessments:
    - ADAS-Cog 11
    - NPI
    - ADCS-ADL
    - Digit Span
    - COWAT
- Assess drug adherence and accountability for study medication
- Dispense double blind study medication to patient and caregiver for outpatient dosing, with instructions to return bottle to clinic at next visit.
- Provide instructions to caregiver/subject on outpatient dosing, including storage, administration, and compliance assessment.

This is a check-up visit to determine if patients are able to tolerate the medication. If so, they will be instructed to take the medication with the continued dosage of 1 mg rasagiline or matching placebo tablet once daily.

7.5 Visit 5 – Week 24

This visit will occur at the end of Week 24 with a visit window of +/- 5 days. This visit concludes the treatment phase of the study.

The following activities will be completed:

- Record orthostatic vital signs and body weight
- Obtain standard single 12 lead EKG
- Review medical history
- Inquire about occurrence of adverse events since previous visit and changes to concomitant medications
- Collect non-fasting blood sample for routine lab tests including:
    - Hematology
    - Blood chemistry
    - Liver function
    - TSH

- Collect blood sample for biomarker measures including:
  - Serum Aβ 40 and 42
  - sAPP-α, sAPP-β, Isoprostanes
  - Cytokines and other measure relevant to AD
- Perform the following assessments:
  - MMSE
  - ADAS-Cog 11
  - CGIC
  - NPI
  - ADCS-ADL
  - Digit Span
  - COWAT
  - QoL–AD/Study Partner
- Perform physical and neurological examinations
- Assess drug adherence and accountability of study medication
- Obtain fluorodeoxyglucose (FDG) PET imaging
- Obtain Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) Questionnaire for the 18F-AV-1451 TAU imaging companion protocol.
- Obtain **^{18}F-AV-1451** Tau PET imaging. This could be done **14 days before or 7 days after last study treatment dose.**

This visit will be the end of the treatment phase and participants will then be followed up for safety 4 weeks post-treatment.

POST ^{18}F-AV-1451 TAU IMAGING FOLLOW-UP PHONE CALL

A follow-up phone call to the participant or the caregiver will be conducted between 2 and 3 business days after the imaging visit, but not before 48 hours post-injection, to confirm participant well-being and to collect information about any new adverse events. If both of these days are not business

7.6 Visit 6 – Follow-up Visit/End of Study/Early Discontinuation (Week 28)

This visit will occur at the end of Week 28 with a visit window of +/- 5 days. This will be a follow-up visit after the treatment phase.

The following activities will be completed:

- Record orthostatic vital signs and body weight
- Perform the following assessments:
  - ADAS-Cog 11
  - CGIC
  - NPI
  - ADCS-ADL
  - Digit Span
  - COWAT

7.7 Unscheduled Visits

Patients will have unscheduled visits if they report unusual side effects. If the patient reports abrupt worsening of cognition, or experiencing one of the reported adverse effects, the patient will be evaluated by the study clinician.

7.8 Study Calendar of Procedures

The Schedule of Activities (Table 2) provides an overview of the protocol visits and procedures. Refer to Study Procedures (Section 8.0) for detailed information on each procedure and assessment required for compliance with the protocol.

Table 2 Schedule of Activities

	Screening	**Treatment Phase**				**Follow-Up**
Visit #	**Visit 1**	**Visit 2/ Baseline**	**Visit 3**	**Visit 4**	**Visit 5/ EOT**	**Visit 6/ EOS/ Early Discontinuation**
Visit Week	**Week -8**	**Week 0**	**Week 4**	**Week 8**	**Week 24**	**Week 28**
Visit Window	*Days -60 to -1*	***Day 1***	*(± 5 days)*	*(± 5 days)*	*(± 5 days)*	*(± 5 days)*
Informed consent	X					
Demographic data	X					
Medical history	X				X	
Review of medications	X				X	
Inclusion/Exclusion criteria	X					
Height	X					
Body weight	X	X	X	X	X	X
Hematology, Chemistry, TSH, B12 liver function, and UA	X				X	
ApoE genotyping		X				
AD biomarkers		X			X	
ECG	X				X	
Orthostatic vital signs	X	X	X	X	X	X
Physical & Neurological Examinations	X				X	
OSU-TBI-ID	X				X	
MMSE	X	X			X	
ADAS-Cog 11		X	X	X	X	X
CGIC		X	X		X	X
ADCS-ADL		X	X	X	X	X
NPI		X	X	X	X	X
Digit Span		X	X	X	X	X
COWAT		X	X	X	X	X
QoL–AD/Study Partner		X			X	
MRI	X					
FDG PET	X				X	
^{18}F-AV-1451 Tau PET	X				X [2]	
FU **^{18}F-AV-1451** PET Phone Call [1]	X				X	
Record adverse events		X	X	X	X	X
Dispense trial medication		X	X			
Drug adherence/ accountability assessment			X	X	X	X

[1] The Follow-up ^{18}F-AV-1451 Tau Pet Phone Call will be conducted between 2 and 3 business days after the imaging visit, but not before 48 post inject to confirm participant well-being.

[2] Week 24 visit **^{18}F-AV-1451** Tau PET can be done **14 days before or 7 days after the last study treatment dose.**

8. Study Specific Procedures

8.1 Cognitive Evaluations

8.1.1 Mini-Mental State Examination (MMSE)

The MMSE (Folstein et al., 1975) is a brief, frequently used screening instrument for AD drug studies. The MMSE evaluates orientation, memory, attention, concentration, naming, repetition, comprehension, and ability to create a sentence and to copy two overlapping pentagons. A lower score indicates more cognitive impairment. The highest score is 30. Participants with MMSE scores outside the range of 12-26 (inclusive) will not be included in this study. This test will be administered at Screening, Baseline, and Week 24.

8.1.2 Alzheimer's Disease Assessment Scale-Cognitive 11 (ADAS-Cog 11)

The ADAS-Cog (Rosen et al., 1984) is a psychometric instrument that evaluates memory, attention, reasoning, language, orientation, and praxis. A higher score indicates more impairment. Scores from the original portion of the test range from 0 (best) to 70 (worse). A positive change indicates cognitive worsening. This test will be administered at Baseline, Weeks 4, 8, 24 and 28.

8.2 Clinical and Functional Evaluations

8.2.1 Clinician Global Impression of Change (CGIC)

This is a rating scale of global impression of change. The CGIC is a clinician assessment of change in the patient's functioning administered to the patient and the caregiver. This test will be conducted at Baseline, Week 4, Week 24, and Week 28.

8.2.2 Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)

The ADCS-ADL is an activities-of-daily-living inventory developed by the ADCS to assess functional performance in participants with AD (Galasko et al., 1997). Using a structured interview format, study partners are queried as to whether participants attempted each item in the inventory during the past 4 weeks and their level of performance. The ADCS-ADL scale discriminates well between normal participants and those with mild AD and it has good test-retest reliability. The ADCS-ADL includes some items from traditional basic ADL tests (e.g., grooming, dressing, walking, bathing, feeding, toileting) as well as instrumental (complex) activities of daily living (e.g., shopping, preparing meals, using household appliances, keeping appointments, reading). This test will be administered at Baseline, Weeks 4, 8, 24, and 28.

8.2.3 Neuropsychiatric Inventory (NPI)

The behavioral outcome measure for this trial is the NPI (Cummings, 1997). The NPI is a well validated, reliable, multi-item instrument to assess psychopathology in AD based on interview with the study partner. The NPI evaluates both the frequency and severity of 10 neuropsychiatric disturbances. Frequency assessments range from 1 (occasionally, less than once per week) to 4 (very frequently, once or more per day or continuously) as well as severity (1=mild, 2=moderate, 3=severe). The overall score and the score for each subscale are the

product of severity and frequency. This test will be administered at Baseline, Weeks 4, 8, 24 and 28.

8.2.4 Controlled Oral Word Association Test (COWAT)

This is a 3-4 minute measure of phonological fluency that indexes a number of the processes described as 'executive function,' including, planning, strategy and working memory. Study participants are instructed, "*I want to see how many words you can say beginning with a certain letter in one minute. Don't say proper nouns or numbers or the same word with a different ending and try not to repeat yourself. The letter is '-, begin.*" The study participant's responses are recorded on the worksheet. Study participants are then given an additional one minute for each of two different letters using similar instructions.

Responses are then judged for their acceptability (example for the use of proper nouns, numbers, repetitions and stem word with a different ending). The score is the total number of acceptable words for the three trials combined. A higher score represents better performance. This test will be administered at Baseline, Week 4, Week 8, Week 24, and Week 28.

8.2.5 Digit Span

The Digit Span Test is adopted from the Wechsler Memory Scale and consists of repetition of increasing long strings of digits presented at 1 per second as read by the examiner and repeated by the subject. A normal Digit Span is 7 digits forward +/- 2 digits. The score is the maximum number of digits the patient can repeat until they fail twice in a row. The reverse digit span is identical to the forward digit span except that the patient repeats the presented digits in reverse order. A normal reverse digit span is 5 +/- 1 digit. The score is the maximum number of digits the patient can repeat in reverse order until they fail twice in a row. This test will be administered at Baseline, Weeks 4, 8, 24, and 28.

8.2.6 QoL-AD/Study Partner

The QoL-AD is a commonly used 13 item QoL scale that assesses items specific to QoL in patients with cognitive impairment. It is administered to the research partner with answers for the patient. This assessment will be performed at the Baseline and Week 24 visits.

8.2.7 Ohio State University Traumatic Brain Injury Identification Method (OSU TBI-ID) Questionnaire

Traumatic brain injury (TBI) can lead to tau protein deposition in the brain and these changes could be visualized on **^{18}F-AV-1451** Tau imaging. To account for any contribution of TBI to the imaging findings, th**e** Ohio State University (OSU) TBI Identification Method (OSU TBI-ID) is being utilized. The OSU TBI-ID is a standardized procedure for eliciting a person's lifetime history of TBI via a 3-5 minute structured interview. While recall by an individual, parent or significant other is not ideal for determining lifetime exposure to potentially damaging brain injury, self-report remains the gold standard for research and clinical use. Physicians, nurses and mental health professionals working with military personnel need this tool to elicit a complete history of TBI. The validity of the OSU TBI-ID is not based on elicitation of a veridical accounting of a person's lifetime history of TBI. Instead, the OSU TBI-ID provides data for calculating summary indices reflecting the likelihood that consequences have resulted from lifetime exposure to TBI. Initial validation research has supported the psychometric qualities of these summary indices. Reliability has been demonstrated by both inter-rater and test/re-test reliability (Corrigan & Bogner, 2007; Bogner & Corrigan, 2009). Predictive validity has been shown by the relationship between indices of lifetime history and

measures of cognitive performance, affective status, interpersonal functioning and aggression (Corrigan & Bogner, 2007; Bogner & Corrigan, 2009). Summary indices from the OSU TBI-ID can be used in both research and clinical care (35, 36). This assessment will be completed at the Screening and Week 24 visits.

9. Study Methods

9.1 Safety Assessments

At each study visit, adverse events (AEs) and serious adverse events (SAEs) will be reviewed; vital signs and weight will be done for safety assessments. Hematology, blood chemistry, and liver function tests will be collected at Screening visit and Week 24.

Potential adverse events will be reviewed by the Principal Investigator and documented. Adverse events include signs or symptoms that may or may not be related to study medication, abnormalities detected on physical examination, or clinically significant laboratory abnormalities. Adverse events will be graded (mild: causing no limitation of usual activities; moderate: causing some limitation of usual activities; severe: causing inability to carry out usual activities) and recorded on case report forms.

9.2 Concomitant Medications

Concomitant medications will be recorded at each visit based on the study partner interview and any other available information. After randomization, initiation of any excluded medication, or change in permitted agents will be discouraged. However, follow-up of all participants, regardless of compliance with medication restrictions, will be continued in order to maximize the data available for the intent to treat analysis.

Initiation during the study of medications which are excluded because of confounding effects on cognitive outcomes (such as sedating or anticholinergic medications) is discouraged, but will not require termination of study drug or exclusion from the ITT analysis. Cessation or change of anti-dementia therapies during the study is also discouraged, but will also not prevent continued participation in the protocol or inclusion in the intent to treat analysis.

9.3 Physical Examination

A brief physical examination will be performed by a medically qualified professional at the Screening visit and Week 24. A review of the major body systems will be performed for example: skin, head/ears/eyes/nose/throat (HEENT), cardiovascular, pulmonary, abdomen, musculoskeletal, neurological, and gastrointestinal. Assessments of height (Screening visit only), weight, and vital signs (systolic and diastolic blood pressure, pulse, temperature, and respiration) are included and will be done at every visit.

9.4 Neurological Examination

This examination will be performed by a medically qualified professional and includes an assessment of cranial nerves, strength, coordination, reflexes, sensation, tremor and gait at screening and week 24 visits.

9.5 Electrocardiogram (ECG)

A standard 12-lead resting ECG will be performed at the screening and week 24 visits. The ECG report will be reviewed, signed, and dated by the investigator. Those with clinically significant ECG findings will be referred for follow-up as deemed appropriate by the investigator.

Excluded participants are patients who have either: 1) Screening ECG with QTc > 450 msec if male or QTc > 470 msec if female; or 2) A history of additional risk factors for Torsades de Pointes (TdP) (e.g., hypokalemia, family history of Long QT Syndrome) or are taking drugs that are known to cause QT-prolongation; Patients with a prolonged QTc interval in the setting of intraventricular conduction block (examples right bundle branch block [RBBB] or left bundle branch block [LBBB], may be enrolled with sponsor approval; or 3) History of atrial fibrillation.

9.6 Orthostatic Vital Signs

Orthostatic vital signs are a series of vital signs of a patient taken while the patient is supine, then again while standing. Patient should be lying down for 3 minutes, and then take blood pressure and heart rate three times, 2 minutes apart each. Patient will be asked to stand for 3 minutes, and then blood pressure and heart rate will be taken again three times, 2 minutes apart each. Results will be recorded in the source document.

9.7 Clinical Laboratory Evaluation

Hematology, chemistry, liver function, B12, TSH levels and urinalysis will be collected at Screening and Week 24 visits. Laboratory samples to be tested consist of the following:

Hematology	Chemistry	Liver Function	Other Tests
Hemoglobin	*Na*	*Albumin*	*TSH*
Hematocrit	*K*	*Total bilirubin*	*B12*
RBC	*Cl*	*Direct bilirubin*	*Urinalysis*
Indices	*CO2*	*Alkaline phosphatase*	
WBC	*Glu*		
Platelet count	*BUN*	*Total Protein*	
Differential count	*Cr*	*AST - Aspartate Transaminase*	
	Ca	*ALT -- Alanine Transaminase*	

Laboratory reports will be reviewed, signed and dated by the principal investigator. If any laboratory abnormalities have emerged in the course of the 24-week clinical trial, laboratory measures of that test will be repeated. The investigator will determine if abnormal values are clinically significant or not. If abnormalities persist, patients will be referred to their primary care physicians for treatment of the abnormality.

Quest Diagnostics and the Cleveland Clinic Laboratory will function as the research reference laboratories and will conduct all laboratory assessments.

9.8 Biomarker Studies and ApoE Genotyping

Serum biomarker measures will be collected for this study. They will include the following: Serum Aβ 40 and 42; sAPP-α, sAPP-β, Isoprostanes; Cytokines and other measures relevant to AD at Baseline and Week 24 visits. These assays will be done by the Genomics laboratory of the University of Nevada Las Vegas and Cleveland Clinic.

All participants will be asked to consent to the ApoE genotyping. DNA will be extracted from blood samples taken from participants and will be analyzed for ApoE genotype at the Baseline visit. This will permit secondary analyses of data on the impact of ApoE genotype on biomarkers of Alzheimer's disease, clinical outcome measures and adverse events. ApoE genotyping will also be performed by the Genomics laboratory of the University of Nevada Las Vegas and Cleveland Clinic using established protocols.

9.9 MRI

A research grade (ADNI quality) MRI, acquired for each subject at the time of enrollment, will also be provided. T1, T2 and FLAIR or T2* sequence will be collected.
3D Sagittal T1 sequence: T1-weighted MPRAGE or MPRAGE-like sequence adhering to the Alzheimer's disease Neuroimaging Initiative (ADNI) specifications. Typical scanner sequence parameters that could be used include:

Scanner	Sequence	Type	TR (ms)	TE (ms)	TI (ms)	NEX/NSA	Flip Angle(°)	Bandwidth
Siemens 3T	3D MPRAGE	(tfl)	2300	2.98	TI = 900	1	9	240 Hz/px
GE 3T	3D	IR-FSPGR	--	Min full	TI = 400	1	11	31.25 kHz
Philips 3T	3D	T1-TFE	Shortest	Shortest	TFE delay=900	1	9	Water-fat shift=1.8

All scans in this study will be evaluated using a stringent quality control procedure to ensure suitability for analysis. Quality control will be performed within 3 business days of image receipt so that in the event of an issue, the visit may be rescheduled if issues cannot be addressed through re-reconstruction. Quality control steps will include header checks, visual inspection, and quantitative inter-frame motion measurement. Image headers will be checked to ensure that the protocol was followed with regard to injected dose, injected volume, and start time after injection, number of frames, scan duration, and reconstruction parameters. Visual inspection will include checks for anatomical truncation (e.g., omission of lower slices of cerebellum), adequate image counts, and image noise such as streaking, image blur indicative of subject motion, asymmetry indicative of misalignment between emission and transmission scan, and other apparent artifacts. Quantitative motion measurement will involve calculation of the inter-timeframe translation and rotation, with preset thresholds above which a frame (or scan, if multiple frames) will not be accepted as suitable for analysis.

ADMdx has developed and will utilize an automated image processing pipeline, PETMAX™, which has secure user access, version control with back-up, and complete audit trail for use in clinical trials. PETMAX facilitates user interaction for visual inspection and quality control at multiple stages in the pipeline, and streamlines the execution of the many steps (including SPM functions) employed in image preparation and analysis. Results are logged and saved under version control.

9.10 [18F]-FDG-PET Imaging

There are two FDG-PET scans to be conducted per participant in this study. The scans will be done at the Screening visit for study eligibility, and at Week 24 visit for end of treatment scan and comparison.

The scanning protocol and equipment qualification requirements for this study will be consistent with those implemented in ADNI 2 (30). FDG-PET imaging data will be obtained at two sites: the Cleveland Clinic facilities in Cleveland, Ohio and Las Vegas, Nevada. Each of these sites uses a Siemens Biograph PET/CT LSO 16 slice camera. As part of site qualification, site practices will be reviewed, along with recent equipment calibration logs. If the site has a 3D-Hoffman phantom

scan collected within the past 12 months available, the scan will be provided for examination. If a de-identified patient brain scan can be made available, it will be provided for examination. The requirements for subject management in preparation for the scan, during FDG uptake, and during image acquisition will be reviewed with staff to ensure that these can be met. Since the Cleveland Clinic participates in ADNI as well as numerous other clinical trials, it is anticipated that requirements will be met.

The scanner will have an up-to-date calibration and normalization on the date of each imaging session. A daily QC check will be done at the beginning of the day the scanning will be completed. The scan will be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the PET scan quality, the visit will be rescheduled.

Daily CT quality assurance will be performed as recommended by the specific vendor, and should typically include a "checkup/calibration" procedure and a water phantom scan. The checkup/calibration procedure guarantees optimum image quality by warming up the x-ray tube and should be performed at startup and within 1 hour prior to any scan. The water phantom provides quality measurements of 3 parameters. The parameters are the CRT value of water calculated in Hounsfield units (HU), the pixel noise of images calculated as a standard deviation, and the tube voltages measured directly on the x-ray tubes. These three measurements should be determined for all available kVp values.

Ideally, no hardware or software upgrades of the PET imaging system will occur during the study duration. If an upgrade needs to occur, ADMdx will be informed prior to the anticipated upgrade. Depending on the nature of the upgrade the site may be asked to repeat the phantom scans prior to scanning any additional subjects.

Quality control of blood glucose meter will be performed according to the manufacturer's or institution's procedure to ensure proper functioning. Quality control of dose calibrator will be performed throughout the course of the study. This typically will include daily constancy, quarterly linearity and annual accuracy.

9.11 ^{18}F-AV-1451 Tau PET Imaging

At Screening visit, subjects who qualify for the study will come to the imaging center at a later date and will have a catheter placed for IV administration of 18F-AV-1451. Vital signs will be taken in a supine position immediately prior to administration of 18F-AV-1451 (within 30 minutes prior to injection) and at the completion of imaging prior to subject discharge. Subjects will receive up to a target dose of 370 mBq as a single IV bolus of 18F-AV-1451. A 20 minute dynamic image starting approximately 80 minutes post injection will be obtained. With sponsor approval sites may elect an alternative imaging protocol (i.e. different duration or start time) with additional time points.

All datasets will be submitted to AVID Radiopharmaceuticals for analysis.

Adverse events will be continuously monitored during the imaging session. Subjects who experience any adverse event will not be discharged until the event has resolved or stabilized.

The **^{18}F-AV-1451** Tau PET imaging will also be performed within 30 days of Week 24/End of Treatment Visit.

Follow-Up Phone Call:
A follow-up phone call to the subject, or designated decision maker, will be conducted between 2 and 3 business days after **^{18}F-AV-1451** imaging day, but not before 48 hours post-injection, to confirm subject wellbeing and to collect information about any new adverse events. If both of these days are not business days, the follow-up phone call can occur the following business day.
A companion protocol for the non-optional ^{18}F-AV-1451 PET imaging study provides detailed information regarding the ^{18}F-AV-1451 component and study procedures.

10. Potential Risks

10.1 Rasagiline Treatment Risk

The principal side effects observed in clinical trials in patients with PD include dyskinesia, nausea, falls, weight loss, constipation, postural hypertension, arthralgia, vomiting, abdominal pain, anorexia, and abnormal dreams.

Drug-drug interactions are historically a concern with MAO inhibitors, particularly tyramine-rich foods and beverages. Although such interactions have not been problematic in patients with selective MAO-B inhibitors, foods with particularly high concentrations of tyramine (aged cheese, sauerkraut, sausage, pickled herring) will be avoided in the course of the study. Similarly, sympathomimetic agents will also be avoided in trial participants.

The most significant drawback to the use of nonselective MAOIs is the risk of hypertensive emergencies, which can occur when a patient is exposed to sympathomimetic drugs, foods containing tyramine, or dopamine. By blocking the effects of MAO in the gastrointestinal tract, catecholamine concentrations are increased; and, in extreme cases, a hypertensive crisis can potentially result in a cerebrovascular accident or death.

The potential for tyramine interaction with rasagiline (doses tested, 0.5-2 mg) was assessed in 5 placebo-controlled clinical trials in healthy volunteers and PD patients. The results of the formal tyramine studies indicate that rasagiline can be used safely without dietary tyramine restriction at a dose of 1 mg/day. These data allowed removal of the dietary tyramine restriction from the rasagiline. This information was taken from the package insert of Azilect.

10.2 MRI Risk

The risks of MRI primarily arise from the possible introduction of ferromagnetic objects into a high magnetic field, which can create a dangerous projectile or lead to dysfunction or heating of an implanted medical device. All participants will be rigorously screened by MRI personnel to be certain that they do not have any medical contraindications for MRI, which include metallic foreign bodies in the brain or eye or cardiac pacemaker. There is a slight risk of anxiety due to claustrophobia. Any participant who experiences anxiety when placed into the MR scanner will be removed from the scanner, offered reassurance by the MR tech doing the scan, and offered the option of continuing or terminating the scan. If the participant decides that the anxiety associated with MRI is uncomfortable for them and they wish to terminate the scan, then the examination will be ended at that time. There will be no attempt to coerce participants to complete exams that they are uncomfortable with. Use of anxiolytic agents for completion of MRI scans is at the discretion of the principal investigator.

10.3 [18F]-FDG-PET Scan Risk

The primary risk related to PET is that of radiation exposure associated with the CT scan or transmission scan and the injected radiotracers. There is also minor risk associated with the venipuncture and radioisotope injection (pain and bruising or painful infiltration of a failed injection). The radiation dose is not expected to produce any harmful effects, although there is no known minimum level of radiation exposure considered to be totally free of the risk of causing genetic defects or cancer. The risk associated with the amount of radiation exposure participants receive in this study is considered low and comparable to everyday risks. No PET studies will be performed on pregnant or potentially pregnant women, as the protocol requires female subjects to be postmenopausal as a condition of participation.

10.4 CT Scan Risk

Subjects will also receive radiation of approximately 1 mSv from a "low dose" computed tomography (CT) acquired along with each PET scan. The low-dose CT will be used to align the position of the subject's head for the PET image. The radiation dose from 1 combined PET/CT is about 8 mSv which is significantly less than the dose considered safe by the National Institute of Health (NIH) for research studies. However, this study will have 2 combined PET/CT scans during the study.

10.5 ^{18}F-AV-1451 Tau PET Scan Risk

^{18}F-AV-1451 will be administered IV up to a radioactive target dose of 370 MBq with a maximum human mass dose (MHD) limited to 20 μg of compound by weight. This dose is 150 fold lower than the NOAEL observed in the rat single dose toxicity study and is 50 fold lower than the NOAEL observed in the rat and dog repeat dose toxicity studies.

Human dosimetry has been obtained in nine subjects. The results estimated an Effective Dose of 8.92 mSv for an anticipated 370 MBq (10 mCi) injection and is comparable to the effective dose of approved 18F-labeled compounds such as FDG and florbetapir F 18 injection.

The proposed dose has been shown to be well tolerated and to have acceptable image quality in preliminary human studies.

10.6 Radiation Risk

One of the risks associated with radiation exposure is cancer. The natural incidence of getting cancer in the United States is about 40%. In this research study, including the companion protocol there will be four PET scans: FDG PET scan at Screening and at Week 24; and 18F-AV-1451 TAU PET scan at Screening and at Week 24. The annual radiation dose from the combined 2 FDG PET/CT scans is 16 mSv. The annual radiation dose from the combined 2 18F-AV-1451/CT scans is 19.84 mSv. The total radiation exposure for the four Pet Scans is 35.84 mSv. The maximum exposure allowed is 50 mSv per year.

10.7 Placebo Risk

Certain research participants in this study will receive a placebo. Taking a placebo may be similar to not taking any medication. Research participants who receive a placebo may have the disease stay the same or get worse, or the disease/condition may spontaneously get better just as it may have done without additional treatment.

10.8 Blood Draw Risk

The risks of blood draw include pain from the needle stick, bruising or infection at the site of venipuncture, or fainting as a response to blood draw.

11. STATISTICAL PLAN

11.1 Sample Size Determination

A study population of 25 subjects per arm (placebo, drug) has been estimated to be sufficient to detect a significant drug effect. Further, depending upon the effect size, a study population of 12 subjects per arm, assessed using an interim analysis, may also be sufficient to demonstrate effect. The number of subjects required to detect a significant change in regional cerebral glucose metabolism depends upon the drug action, patient variability within the regions affected, and the methods used to measure changes in glucose metabolism. For drugs causing a symptomatic effect, with or without additional disease-modifying properties, the N required is lower than that required to detect a modification to the rate of decline associated with disease. Specifically, we have modeled the number of subjects required to detect 5% and 10% increases in prefrontal cortex in mild to moderate AD patients using a region of interest approach, and have also confirmed estimates through review of published effect sizes from studies of donepezil, phenserine, and galantamine in AD patients.

11.2 Statistical Methods

Intent-to-Treat (ITT) - The primary FDG analysis will include all patients who received both a screening and end of study scan of acceptable quality. The primary clinical analysis will be a modified Intent-to-Treat (mITT) approach including all patients randomized and receiving at least one post-baseline assessment.

Per-Protocol (PP) population – All Intent-to-Treat subjects who complete the study (Week 24) and have ingested between 80% and 120% of the protocol prescribed study medication as measured by pill count.

Observed case – An observed case analysis of all patients completing the study will be conducted.

LOCF – Clinical data imputation will use the LOCF approach for missing patients

Responder analysis – Responders will be defined as those that have a significant improvement on brain metabolism on FDG for the whole brain or for any of the pre-specified regions.

A secondary analysis will compare the changes in FDG at 6 months compared to the projected expected metabolism based on the Baseline FDG findings.

11.3 Subject Populations for Analysis

With a subject population of 10 patients per arm (placebo and treatment), Kadir et al detected a significant increase ($p<0.05$) in frontal, parietal, and parietotemporal glucose metabolism within the treatment group, and a significant difference between placebo and treatment arms in parietotemporal glucose metabolism (26). The percent changes associated with these increases ranged from 5.5% to 8%. In two different studies of donepezil (27, 28), the change in glucose metabolism was measured in subjects who improved, rather than declined, in cognitive scores. Using region of interest analysis, Shimadai found significant differences ($p<0.05$) in frontal regions when comparing the ratio of pre-treatment to post-treatment in 7 responders with regard to ADAS-J cog score to that of 4 non-responders. Using voxel-based analyses, Mega et al found a significant difference in anterior cingulate, prefrontal cortex, and parietotemporal cortex between

6 cognitive responders as compared to similar untreated subjects, even after applying a Bonferroni correction for random effects.

Evaluation of the FDG PET scans of 70 mild AD subjects from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database indicates that, based upon mean and standard deviation of glucose metabolism in prefrontal cortex, a change in mean Standardized Uptake Value ratio (SUVr) of 5% could be statistically significant between two independent groups (drug, placebo) at 70% power ($p<0.05$, two-tailed) with 26 subjects per arm, or at 80% power with 32 subjects per arm. The number of subjects required reduces quickly with effect, as a change of 10% would require only 8 subjects per arm to achieve 80% power if variance within the study group is comparable to that within the mild AD ADNI population (greater variance would increase the number of subjects required or decrease the power). Region of interest evaluation is typically more conservative than voxel-based analysis because effects common across subjects often involve sub-regions and measurement of change may be diluted by the use of broader pre-determined measurement areas. Use of voxel-based approaches, and in addition, multivariate methods and a pattern-based classification approach, are expected to increase statistical power as they improve the signal to noise ratio and are not limited to predefined regions.

11.4 FDG PET Imaging Analysis

11.4.1. Screening Classification

The Screening FDG PET scan of each subject will be evaluated using ADMdx's dementia classifier, to assess whether the subject expresses a pattern consistent with AD or alternatively, that of other dementias. The classifier has developed machine learning methods and a comprehensive set of reference data from ADNI and other sources. The FDG PET scan of a subject will be independently compared to a set of canonical variant patterns that in combination characterize the patterns of relative hypometabolism caused by different types of dementia. A probability will be assigned to determine whether the subject is "AD-like" or better characterized as a different dementia.

In addition, hypometabolism will be assessed in frontal cortex and occipital cortex, and parietal asymmetry checked, to identify possible atypical or comorbid presentations that may impact clinical attributes. The AD-like or non-AD-like status of each subject will be reported back within 7 days of image receipt to allow enrollment decisions.

11.4.2 Screening Characterization

The Screening FDG PET scan of each subject will be evaluated using ADMdx's AD Progression classifier, to assess the subject's disease-related hypometabolism status relative to reference subjects and other study subjects. The FDG PET scan of a subject will be independently compared to a set of canonical variant patterns that in combination characterize the patterns of relative hypometabolism caused by different stages of progression toward AD dementia. This numeric score will be used to project likely cognitive trajectory for comparison to actual results. It can also be used to stratify groups for sub-analyses, creating more homogeneous analysis groups at baseline.

11.4.3 Longitudinal Voxel-based Evaluation

The spatially normalized longitudinal FDG PET scans of each subject will be analyzed using ADMdx's NPAIRS multivariate software. Classes will be defined according to treatment or placebo condition, and visit. Example analyses are shown in Table 1 below. The output of this

evaluation will be a series of patterns showing relative increases and decreases in cerebral glucose metabolism, quantification of the placement of each subject at each time point relative to these patterns of effect, and quantification of the contribution of each pattern to the overall effect. Metrics of reproducibility and predictive power are also provided. At preference of Sponsor, group assignments may be provided in a blinded manner – that is, Group A and Group B, without designation as treatment or placebo. In the table below, to better illustrate the comparisons, they are referred to as Placebo and Treatment, but these may instead be "Group A" and "Group B."

Table 3. NPAIRS analyses of treatment effect and stratification impact

Analysis	Group	Baseline	6 months
1	Treatment (within group only)	x	x
2	Placebo (within group only)	x	x
3	Treatment	x	x
	Placebo (both in a single analysis)	x	x
4	Treatment – mild subjects	x	x
	Treatment – later stage subjects	x	x
	Placebo – mild subjects	x	x
	Placebo – later stage subjects	x	x
5	Treatment – subjects age 50 - 65	x	x
	Treatment – subjects age >65	x	x
	Placebo – subjects age 50-65	x	x
	Placebo – subjects age >65	x	x

SPM-t contrasts will also be performed of selected groups, at thresholds of $p<0.005$, and a cluster extent threshold of 25 voxels. These are limited to paired contrasts (e.g., baseline vs. 6 months for treatment group), or to contrasts of the difference images between baseline and 6 months, treatment vs. placebo groups. Information is more limited with regard to individual subject distribution other than at specific voxel locations.

11.4.4 Longitudinal Region of Interest Evaluation

The SUVr calculated for each subject will be compared using t-tests, within groups and across groups, as shown in Table 4 below. While the pre-identified reference regions for testing will be whole brain, cerebellum, and pons, an alternate reference region may be identified through the use of NPAIRS multivariate analysis and applied.

Table 4 Regions of interest for FDG analysis

Analysis	Change in FDG PET measure:	Dorso-lateral PFC	Striatum	Hip - Med temp	Anterior cingulate	Post cing–precun	Lateral temp	Inferior parietal
1	Treatment: 6m vs. screening	x	x	x	x	x	x	x
2	Placebo: 6m vs. screening	x	x	x	x	x	x	x
3	Change in treatment vs. change in placebo groups	x	x	x	x	x	x	x
4	1, 2, and 3 in substrata for	x	x	x	x	x	x	x

Analysis	Change in FDG PET measure:	Dorso-lateral PFC	Striatum	Hip - Med temp	Anterior cingulate	Post cing–precun	Lateral temp	Inferior parietal
	disease severity and age							

11.4.5. Correlation to Cognitive Change

The relationship between glucose metabolism and cognitive endpoints will be evaluated as shown in Table 5 below.

Table 5 Relationships between FDG PET measures and cognitive endpoints

Analysis	Change in FDG PET measure:	ADAS-cog 11	Digit Span	COWAT	MMSE
1	AD progression score	x	x	x	x
2	Dorsolateral prefrontal cortex SUVr	x	x	x	x
3	Medial temporal cortex SUVr	x	x	x	x
4	NPAIRS derived pattern of change (CV score associated with pattern)	x	x	x	x

11.5 ^{18}F-AV-1451 Tau Imaging Analysis

^{18}F-AV-1451 SUVr will be determined by Avid Pharmaceuticals and analyzed. Change from baseline in rasagiline-treated patients will be compared to change from baseline in patients receiving placebo. Correlations will be sought between **^{18}F-AV-1451** drug-placebo differences and **^{18}F-AV-1451** changes in FDG PET as well as between drug-placebo difference in and changes in clinical outcomes.

12. SAFETY AND ADVERSE EVENTS

12.1 Definitions

International Conference on Harmonisation (ICH) guidelines define an adverse event (AE) as any medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example) symptom, or disease temporarily associated with the use of a medicinal product whether or not considered related to this medicinal product.

A serious adverse event (SAE) is any medical occurrence or effect that at any dose:

- Results in death
- Is life threatening
- Requires hospitalization or prolongation of existing inpatient hospitalization
- Results in persistent or a significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is cancer

- Life threatening in the definition of a SAE refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe.

12.2 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on AEs by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately in the source document, and also in the appropriate AE section of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results will also be recorded in the source document.

The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

12.3 Reporting of Serious Adverse Events

12.3.1 Study Sponsor-Investigator Notification by Investigator

A SAE will be reported to the study sponsor-investigator by telephone within 24 hours of the event. A SAE form will be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator will keep a copy of this SAE form on file at the study site. Report a SAE by phone and facsimile to Michelle Sholar, 702-483-6026, fax 702-483-6028.

At the time of the initial report the following information will be provided:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason event is classified as serious
- Investigator assessment of the association between the event and study treatment

Within the following 48 hours, the investigator will provide further information on the AE in the form of a written narrative. This will include a copy of the completed SAE form and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing SAEs will be provided promptly to the study sponsor-investigator.

12.3.2 IRB Notification by Investigator

Reports of all SAEs (including follow-up information) will be submitted to the Cleveland Clinic Foundation (CCF) IRB per the guidelines of the CCF IRB Standard Operating Procedures. Copies of each report and documentation of IRB notification and response will be filed in the regulatory binder.

The following four types of events will be reported to the IRB (these follow the Case Cancer IRB because this is an anti-cancer agent being used in patients with mild to moderate AD):

1. Adverse events which are serious, unexpected, and related or possibly related to participation in the research.
2. Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected.
3. Other unexpected adverse events, regardless of severity, that may alter IRB analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document.
4. Unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB.

12.3.3 FDA Notification by Sponsor-Investigator

The FDA will be notified by telephone or by facsimile transmission of any unexpected fatal or life threatening experience associated with the use of the drug as soon as possible, but no later than seven calendar days from original receipt of the information.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the study sponsor-investigator will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.

12.4 Unblinding Procedures

The research coordinator will inform the sponsor-investigator of all subjects whose treatment was unblinded within 24 hours of unblinding. Most unblinding will be part of managing a SAE and will be reported with the SAE. Unblinding that was not associated with a SAE will be reported in a timely manner. This will be done within 24 hours by telephone or facsimile, and will be followed by a written narrative of the reason for unblinding within 24 hours of the event.

12.5 Stopping Rules

If 4 or more patients worsen clinically in a manner greater than expected for untreated AD, the protocol will be stopped. Similarly, if 4 or more patients show ARIA-E or microhemorrhages on the 2nd MRI, the protocol will be stopped.

12.6 Medical Monitoring

The principal investigator will oversee the safety of patients in the rasagiline study. The safety monitoring will include careful assessment and appropriate reporting of adverse events as noted above as well as the construction and implementation of a site data and safety monitoring plan. Medical monitoring will include a regular assessment of the number and type of SAEs. Medical monitoring for the trial would be done by Charles Bernick , MD, of the Lou Ruvo Center for Brain Health.

12.6.1 Internal Data Safety Monitoring Board (DSMB)

A data safety monitoring committee is not deemed necessary for this fifty-patient initial study of rasagiline.

13. DATA HANDLING AND RECORD KEEPING

13.1 Confidentiality and Privacy

Information about study subjects will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Subjects or a legally acceptable surrogate will provide authorization that they have been informed of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke authorization for use of the PHI
- The HIPAA language is included as part of the informed consent form.

13.2 Source Documents

Source documentation for all entry criteria will be available in the patient's research record. These records will be retained as required by law.

13.3 Case Report Forms

The study CRFs have been constructed for this study. All data will be collected on the CRF and all missing data on the CRF will be explained.

13.4 Records Retention

All documents will be retained for a minimum period of two years following completion of the study.

13.5 Database

The database will be constructed by CCF Quantitative Health Sciences (QHS). The database will be populated by the study research coordinator.

14. STUDY MONITORING, AUDITING AND INSPECTING

14.1 Study Monitoring Plan

This study will be monitored according to the monitoring plan. The investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above-noted study-related documents and study related facilities and has adequate space to conduct the monitoring visit.

14.2 Audit and Inspection

The investigator will permit study-related monitoring, audits, and inspections by the IRB, the sponsor-investigator, government regulatory bodies, and institutional compliance and quality assurance groups of all related documents (for example, source documents, regulatory documents, data collection instruments, study data, etc.). The investigator will ensure the capability for inspections of applicable study-related facilities. Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Institutional compliance and quality assurance offices.

15. ETHICAL CONSIDERATIONS

This study will be conducted according to US and international standards of Good Clinical Practice (GCP) (FDA Title 21 part 312 and ICH guidelines), applicable government regulations and Institutional research policies and procedures.
This protocol and any amendments will be submitted to the IRB, in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor-investigator before commencement of this study. The investigator will have a list of IRB members and their affiliates.
All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects or legally acceptable surrogates to make an informed decision.

16. STUDY FINANCES

16.1 Funding Source

This study is being funded by the Alzheimer's Drug Discovery Foundation (ADDF). This foundation established in 1998 by co-chairmen Leonard A. and Ronald S. Lauder of the Estée Lauder cosmetics family, provides funding to leading scientists who are conducting the most promising, innovative Alzheimer's drug research worldwide. Funders did not participate in the design of the study and do not have any financial interest in the outcome of the study.

16.2 Conflict of Interest (COI)

Any investigator who has a conflict of interest with this study will have the conflict reviewed by the Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved prior to participation in this study. All Cleveland Clinic investigators will follow the Institutional Conflict of Interest Policy.

16.3 Subject Stipends or Payments

Subject stipend and study partner stipend is anticipated for this study.

17. PUBLICATION PLAN

Dr. Jeffrey L. Cummings, principal investigator, has primary responsibility for publication of the results of this study. It is the full intention of the investigator to publish the results of this study as soon as possible. Neither the complete study nor any part of the results of the study carried out under this protocol, nor any of the information provided by the sponsor-investigator for the purposes of performing the study, will be published or passed on to any third party without the consent of the study sponsor-investigator. Any investigator involved with this study is obligated to provide the sponsor-investigator with complete test results and all data derived from the study

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Appendix A

Technical Description of FDG PET Acquisition and Analysis

1). Imaging Site Qualification and Preparation

(Note that parameters and steps may be refined to align with the scanner model and practices at the Cleveland Clinic.)

The scanning protocol and equipment qualification requirements for this study will be consistent with those implemented in ADNI 2 (30). FDG-PET imaging data will be obtained at two sites: the Cleveland Clinic facilities in Cleveland, Ohio and Las Vegas, Nevada. Each of these sites uses a Siemens Biograph PET/CT LSO 16 slice camera. As part of site qualification, site practices will be reviewed, along with recent equipment calibration logs. If the site has a 3D-Hoffman phantom scan collected within the past 12 months available, the scan will be provided for examination. If a de-identified patient brain scan can be made available, it will be provided for examination. The requirements for subject management in preparation for the scan, during FDG uptake, and during image acquisition will be reviewed with staff to ensure that these can be met. Since the Cleveland Clinic participates in ADNI as well as numerous other clinical trials, it is anticipated that requirements will be met.

The scanner will have an up-to-date calibration and normalization on the date of each imaging session. A daily QC check will be done at the beginning of the day the scanning will be completed. The scan will be visually inspected for abnormalities. If there is a possibility that the abnormality could impact the PET scan quality, the visit will be rescheduled.

Daily CT quality assurance will be performed as recommended by the specific vendor, and should typically include a "checkup/calibration" procedure and a water phantom scan. The checkup/calibration procedure guarantees optimum image quality by warming up the x-ray tube and should be performed at startup and within 1 hour prior to any scan. The water phantom provides quality measurements of 3 parameters. The parameters are the CRT value of water calculated in Hounsfield units (HU), the pixel noise of images calculated as a standard deviation, and the tube voltages measured directly on the x-ray tubes. These three measurements should be determined for all available kVp values.

Ideally, no hardware or software upgrades of the PET imaging system will occur during the study duration. If an upgrade needs to occur, ADMdx will be informed prior to the anticipated upgrade. Depending on the nature of the upgrade the site may be asked to repeat the phantom scans prior to scanning any additional subjects.

Quality control of blood glucose meter will be performed according to the manufacturer's or institution's procedure to ensure proper functioning. Quality control of dose calibrator will be performed throughout the course of the study. This typically will include daily constancy, quarterly linearity and annual accuracy.

2) Image Data Collection

(i). Pre-Scan Subject Preparation

All participants will be screened by study personnel for contraindications to PET scanning (see Exclusion Criteria). Scans should be scheduled at the same time of day for a given subject – i.e., if in the morning for the baseline scan, then in the morning for any subsequent scans. In order to reduce the potential for first scan effects, prior to the first scan, for example at the Screening visit, each subject will be introduced to the PET scanner, sequence of data acquisition events, and FDG uptake room and activity.

Subjects to be imaged in the morning are asked to omit all food and fluids (except water) from midnight the night before the scan until after the imaging is completed. Subjects scanned later in the day are asked to omit food and fluids (except water) for at least 4 hours prior to the imaging session. When a participant arrives at the imaging center, compliance with the dietary requirement of not having food or drink in less than two hours will be confirmed. If a participant has ingested food or drink within two hours, participants will wait until two hours have elapsed. Once two hours have elapsed, blood glucose levels will be measured. If blood glucose levels are not less than 180 mg/dL, then waiting an additional amount of time to recheck blood glucose levels will be needed. Once blood glucose levels are below 180 mg/dL, the participant will be asked to use the restroom to empty his/her bladder. Then, the participant will be asked to sit or recline comfortably (but not in a position that will induce sleep) in a reclining chair in a room in which the ambient noise is minimal and the degree of lighting can be controlled and minimized. Blankets/pillows may be supplied as needed to maximize comfort. Intravenous access using a small butterfly needle or angiocath will be done. 185 MBq (5mCI +/- 10%) of [18F]-FDG will be drawn and assayed with a dose calibrator and assay time will be recorded to the nearest minute. The [18F]-FDG will be injected and the syringe and IV line will be flushed with 10mL of normal saline. The injection time will be recorded to the nearest minute and the IV line may be discontinued. The dose syringe will then be re-assayed and if the residual activity is 0.1 mCi or greater, the amount will be recorded and the amount of the injected dose will be corrected for the residual activity.

(ii) Subject Management During FDG Uptake

Control of the subject's activity and environment during the 30 minutes following tracer administration is essential. It is also necessary that the subjects' position during the uptake period, their activity and focus, their visual, audio, and temperature environment, and the room's ambient light conditions are consistent across all longitudinal scans.

The subject will be asked to rest comfortably in the room with lights dimmed to a level similar to twilight for 30 minutes for incorporation of [18F]-FDG in the brain. The subject's eyes will be open, away from any direct light, and the ears will remain un-occluded. The participant will be directed to maintain their gaze on a constant object throughout the uptake period. This point of focus (object) should be the same across subjects and across scans. The subject should also be instructed to avoid any motion, foot tapping, or other variable activity. Comfort should be assured in order to reduce the likelihood of movement. The participant must be monitored frequently to be certain of compliance and to ensure that the eyes do not close and they remain awake. It is important that no sudden noises or environmental changes occur within or just outside of the participant's room during [18F]-FDG uptake.

Just prior to injection, and at the end of the uptake period, the subject will be asked to answer a short set of questions regarding their affect. The clinician will also be asked to note the subject's affect, and particularly whether the subject exhibits signs of agitation, somnolence, or depression. These observations are important because differences between scanning sessions in the patient's affect can impact measured signal, creating confounds in the measurement of treatment effects. If a subject is notably agitated, the process should not

begin until that agitation can be alleviated. If this is not reasonably achievable, the scan should be rescheduled.

At the end of the 30-minute incorporation period, the participant will be encouraged to use the restroom to empty their bladder. Ample time will be given to ensure that the participant will be on the scanner and ready for data acquisition to begin at 30 minutes post-injection.

(iii) Image Acquisition

The participant will be positioned and secured in the scanner. Proper participant positioning and the prevention of subject motion during acquisition is critical for a reliable PET scan. Excessive motion between the emission scan and the CT scan used for attenuation correction is the single most common cause of failed studies. For this reason, the protocol includes several steps to reduce the likelihood of movement, as follows, and consistent with ADNI guidelines.

Time will be taken to ensure the participant is properly positioned and can comfortably maintain that position for 30 minutes during the scanning session. Participants will remove any bulky items from their pockets and remove eyeglasses, earrings, hair clips/combs, and hearing aids (if possible). The participant will be positioned so the head/neck is relaxed which may involve adding additional pads beneath the neck to provide sufficient support. It will be verified that the participant's ears are in a comfortable position, and not pinched, as this can cause movement to alleviate discomfort during the scan. Lasers will be used to ensure that there is little or no rotation in either plane. The head will be positioned parallel to the imaginary line between the external canthus of the eye and the external auditory meatus. Supportive devices under the back and/or legs will be used to help decrease the strain on these regions and prevention motion in the lower body. Once the participant is positioned, foam pads may be placed alongside the head for additional support. Velcro straps and preferably easily removed tape will be used to secure the head position. Vacuum bean bags may also be used in this process. One of the most common forms of motion in PET scans is a downward motion that causes the subject's head to move lower in the field of view, ultimately truncating the lower portion of cerebellum from view. To minimize the possibility of this, a (comfortable) "rod" or other device may ideally be positioned just below the chin, serving as a reminder to the subject not to move downward. The subject will be offered a "panic button" or be reassured that someone will be watching or able to hear them at all times.

Prior to initiation of the emission scan, a short "scout" scan is to be taken in order to verify that the subject's head is correctly positioned.

The subject's head position and ability to remain still must be monitored continuously throughout the acquisition period. If the subject moves, acquisition should cease, the head should be repositioned, the time at which the repositioning occurred noted, and acquisition resumed. It is imperative that if motion occurs between frames, the emission frames are correctly aligned with one another, and with the transmission scan, before attenuation correction is applied through the use of a transmission scan. The handling of motion will be a topic for discussion with PET technologist and depends upon the scanner model and options available.

A 30-minute dynamic, 3D scan consisting of six 5-minute frames (preferably ten 3-minute frames to allow for additional motion correction) will be acquired <to be verified as ADNI has indicated that Siemens Biograph scanners cannot collect dynamic images>. All images will need to be corrected using measured attenuation using standard CT acquisition parameters. A check will be performed to ensure that the emission and transmission scans are properly aligned before the participant leaves the imaging session. Upon completion, the participant is to be removed from the scanner and encouraged to void. The study participant will be instructed to drink fluids and to void throughout the day to help reduce radiation exposure.

(iv). Image Reconstruction

Images will be reconstructed using parameters specific to the scanning system and will be reviewed to check for artifacts and motion. Sinogram data (projection data) will be stored in a separate file. Iterative reconstruction will be performed, using the parameters recommended by ADNI for the scanner model [ref].

(v). Image De-identification and Transfer

The PET image sets produced by the reconstruction process will be converted to a standard Digital Imaging and Communications in Medicine (DICOM) file format. Image file naming will follow a standard format so that all scans can be easily identified. The file ID will be assigned by study personnel prior to the PET scan. Unless designated otherwise during study preparations, the naming convention will be XXX_S_#### where XXX is a three digit site ID determined by the Cleveland Clinic and #### is the unique four digit number assigned to the subject by the site, followed by a sequence uniquely identifying the scan.

All raw and processed study data including copies of the normalization and blank scans will be archived. Image data will be transferred to ADMdx (Chicago, IL), as soon as images have been acquired and reconstructed. A secure image transfer program such as AG Mednet that ensures de-identification of the data prior to transmission will be employed. Initial header checks may be performed using that software prior to image transmission.

2) MRI Scan

A research grade (ADNI quality) MRI, acquired for each subject at the time of enrollment, will also be provided. T1, T2 and FLAIR or T2* sequence will be collected.

3D Sagittal T1 sequence: T1-weighted MPRAGE or MPRAGE-like sequence adhering to the Alzheimer's disease Neuroimaging Initiative (ADNI) specifications. Typical scanner sequence parameters that could be used include:

Scanner	Sequence	Type	TR (ms)	TE (ms)	TI (ms)	NEX/NSA	Flip Angle(°)	Bandwidth
Siemens 3T	3D MPRAGE	(tfl)	2300	2.98	TI = 900	1	9	240 Hz/px
GE 3T	3D	IR-FSPGR	--	Min full	TI = 400	1	11	31.25 kHz
Philips 3T	3D	T1-TFE	Shortest	Shortest	TFE delay=900	1	9	Water-fat shift=1.8

(i) *Image Quality Control*

All scans in this study will be evaluated using a stringent quality control procedure to ensure suitability for analysis. Quality control will be performed within 3 business days of image receipt so that in the event of an issue, the visit may be rescheduled if issues cannot be addressed through re-reconstruction. Quality control steps will include header checks, visual inspection, and quantitative inter-frame motion measurement. Image headers will be checked to ensure that the protocol was followed with regard to injected dose, injected volume, and start time after injection, number of frames, scan duration, and reconstruction parameters. Visual inspection will include checks for anatomical truncation (e.g. omission of lower slices of cerebellum), adequate image counts, image noise such as streaking, image blur indicative of subject motion, asymmetry indicative of misalignment between emission and transmission scan, and other apparent artifacts. Quantitative motion measurement will involve calculation of the inter-timeframe translation and rotation, with preset thresholds above which a frame (or scan, if multiple frames) will not be accepted as suitable for analysis.

ADMdx has developed and will utilize an automated image processing pipeline, PETMAX™, which has secure user access, version control with back-up, and complete audit trail for use in clinical trials. PETMAX facilitates user interaction for visual inspection and quality control at multiple stages in the pipeline, and

streamlines the execution of the many steps (including SPM functions) employed in image preparation and analysis. Results are logged and saved under version control.

(ii) Image Processing

Discrete timeframes for each scan will be aligned and an aggregate image created by averaging the frames. Each subject's MRI will be co-registered to the baseline PET scan, and longitudinal PET scans will be co-registered to the baseline PET scan, as well. The MRI will be segmented into gray, white, and CSF tissue images. The MRI will be spatially transformed to a target template and the PET scan(s) will be likewise transformed using the same parameters. The spatially transformed images will be intensity normalized to a mean value of 1, and smoothing applied to achieve uniform resolution with other scanners for comparison to reference data and use in the dementia classifiers. A set of template ROIs will be transformed back to the subject's native (unwrapped) brain for signal measurement in unwrapped space, with individualized masking applied using the subject's gray matter segment. The mean, standard deviation, minimum, and maximum for each ROI will be measured, as well as those in different reference regions for comparison, including whole brain without ventricles, cerebellum, and pons. This is in order to examine consistency across reference regions, and to determine whether treatment effects may influence one or more reference regions as well as target ROIs. Standardized Uptake Value Ratios (SUVrs) will be generated by taking the ratio of regions of interest to the respective reference regions.

Appendix B.

Study Procedure Table

	Screening	Treatment Phase				Follow-Up
Visit #	**Visit 1**	**Visit 2/ Baseline**	**Visit 3**	**Visit 4**	**Visit 5/ EOT**	**Visit 6/ EOS/ Early Discontinuation**
Visit Week	**Week -8**	**Week 0**	**Week 4**	**Week 8**	**Week 24**	**Week 28**
Visit Window	*Days -60 to -1*	***Day 1***	*(± 5 days)*	*(± 5 days)*	*(± 5 days)*	*(± 5 days)*
Informed consent	X					
Demographic data	X					
Medical history	X				X	
Review of medications	X				X	
Inclusion/Exclusion criteria	X					
Height	X					
Body weight	X					
Hematology, Chemistry, TSH, B12 liver function, and UA	X				X	
ApoE genotyping		X				
AD biomarkers		X			X	
ECG	X				X	
Orthostatic vital signs	X	X	X	X	X	X
Physical & Neurological Examinations	X				X	
OSU-TBI-ID	X				X	
MMSE	X	X			X	
ADAS-Cog 11		X	X	X	X	X
CGIC		X	X		X	X
ADCS-ADL		X	X	X	X	X
NPI		X	X	X	X	X
Digit Span		X	X	X	X	X
COWAT		X	X	X	X	X
QoL–AD/Study Partner		X			X	
MRI	X					
FDG PET	X				X	
^{18}F-AV-1451 Tau PET	X				X [2]	
FU **^{18}F-AV-1451** PET Phone Call [1]	X				X	
Record adverse events		X	X	X	X	X
Dispense trial medication		X	X			
Drug adherence/ accountability assessment			X	X	X	X

[1] The Follow-up ^{18}F-AV-1451 Tau Pet Phone Call will be conducted between 2 and 3 business days after the imaging visit, but not before 48 post inject to confirm participant well-being.

[2] Week 24 visit **^{18}F-AV-1451** Tau PET can be done **14 days before or 7 days after the last study treatment dose.**