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PF-04494700, an Oral Inhibitor of Receptor For Advanced Glycation End Products (RAGE), in Alzheimer's disease

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Abstract

Objective—To evaluate the safety and tolerability of PF-04494700, an oral Inhibitor of receptor for advanced glycation end products (RAGE), in subjects with mild-to-moderate dementia of the Alzheimer's type.

Methods—Subjects 50 years and older who met NINCDS-ADRDA criteria for AD with an MMSE score between 12–26 (inclusive) were randomized to 10-weeks of double-blind treatment with either a 10 mg “low dose” of PF-04494700 (after a 6-day loading dose of 30 mg/d to); or a 20 mg “high dose” of PF-04494700 (after a loading dose of 60 mg/d); or placebo. Safety measures included adverse events, laboratory tests, vital signs, and 12-lead ECG.

Results—27 subjects received PF-04494700 30/10 mg (female, 63%; mean age, 74.6 years; mean MMSE, 21.1), 28 subjects received PF-04494700 60/20 mg (female, 57%; mean age, 76.6 years; mean MMSE, 21.6), and 12 subjects received placebo (female, 67%; mean age, 74.1 years; mean MMSE, 19.2). A higher proportion of subjects completed 10 weeks of double-blind treatment on both the “low dose” regimen of PF-04494700 (88.9%) and the “high dose” regimen (85.7%) than completed on placebo (66.7%). Discontinuation due to adverse events, and incidence of severe adverse events, respectively, were lower on the “low dose” regimen (7.4%,11.1%) and the “high dose” regimen (3.6%,10.7%) compared to placebo (25.0%,16.7%). There were no clinically meaningful differences in vital signs, laboratory test results, or mean ECG parameters in subjects treated with PF-04494700. PF-04494700 had no consistent effect on plasma levels of A β , inflammatory biomarkers, or secondary cognitive outcomes.

Conclusions—Ten weeks of treatment with PF-04494700 was safe and well-tolerated in subjects with mild-to-moderate AD, indicating the feasibility of a larger long-term efficacy trial.

Keywords

Alzheimer's disease; randomized clinical trial; RAGE

INTRODUCTION

Alzheimer's Disease (AD) is a neurodegenerative disease that is the leading cause of dementia in the elderly.^{1,2} It is characterized by the extracellular accumulation of β -amyloid (A β) plaques consisting of A β ₁₋₄₂ and A β ₁₋₄₀ peptides, and neurofibrillary tangles consisting of hyperphosphorylated tau protein filaments, accompanied by progressive cell loss, especially in cholinergic neurons in the basal forebrain region.^{3,4}

There is increasing evidence that the accumulation of A β peptides in brain may play a pivotal role in the pathophysiologic process of AD,⁵ disrupting the synthesis and release of acetylcholine (ACh).⁴ Available therapies for AD attempt to provide symptomatic relief via cholinergic mechanisms,⁶ or by altering NMDA receptor mechanisms.⁷ Currently, no disease-modifying or anti-amyloid therapies are available.

One promising disease-modifying treatment strategy targets the receptor for advanced glycation end-products (RAGE). RAGE is a multiligand receptor of the immunoglobulin superfamily which is composed of three immunoglobulin-like domains: a "V"-type domain involved in ligand binding, and two "C"-type domains (a short transmembrane domain, and cytoplasmic tail involved in intracellular signaling).⁸ RAGE is expressed in multiple cell types, and the receptor has been shown to bind a broad array of ligands. Notably, RAGE recognizes not only specific amino acid sequences, but also three-dimensional structures such as β -sheets and fibrils.^{8,9,10} Thus, RAGE appears to be a pattern recognition receptor that binds ligands which typically accumulate in tissues during aging (including A β peptide), inflammation, or in response to other tissue stresses.^{8,11,12,13}

Ligands binding to RAGE have been shown to activate multiple cellular signaling cascades. In adults, RAGE is expressed at low levels in normal CNS tissues. However, RAGE is rapidly upregulated in the presence of its ligands, most notably A β .^{8,14}

Accumulating evidence suggests that RAGE may play a significant role in the pathophysiology of AD. Data implicating RAGE include the identification of known RAGE ligands including AGEs, S100b (a member of the superfamily of EF-hand Ca²⁺-binding proteins), and A β proteins in tissue surrounding the senile plaque in man.^{15,16} RAGE has also been reported to be upregulated in astrocytes and microglial cells in the hippocampus of individuals with AD compared to individuals that did not have AD.¹⁷ Furthermore, inhibition of RAGE/ligand interactions, using either an sRAGE or an anti-RAGE antibody, reduces amyloid plaque formation in a mouse model of systemic amyloidosis.¹⁸

PF-04494700 (previously known as TTP488) is an orally bioavailable small molecule inhibitor of RAGE which is being developed as a potential treatment for AD (as well as diabetic nephropathy). *In vitro* studies have shown that PF-04494700 inhibits sRAGE from binding to RAGE ligands, S100b, amphotericin and carboxymethyl-lysine (CML; TransTech Internal Report). Additionally, PF-04494700 has been shown, in a fluorescent polarization assay, to inhibit the binding of sRAGE to A β ₁₋₄₂ (TransTech Internal Report).

In a mouse model of systemic amyloidosis, PF-04494700 reduced accumulation in the spleen of A β peptides and the expression of IL-6 and macrophage colony stimulating factor. In a transgenic mouse model with Swedish and London mutations that over-express human APP, 90 days of treatment with orally administered PF-04494700 was associated with a significant reduction in both inflammatory markers (TNF- α , TGF- β and IL-1) and CNS amyloid deposition (TransTech Internal Report).

The results of initial Phase I studies suggest that daily doses of PF-04494700 in the range of 10–60 mg per day administered orally for up to 4 weeks are safe and well-tolerated in

healthy volunteers. In one study (TTP488-102; data-on-file) 7 of 40 subjects treated with PF-04494700 had a maximum increase 30 msec in QTcNi. The QTcNi values for 4 of these subjects were 450 msec. These findings were consistent with preclinical studies which found increases in QTc in dogs administered doses 10 mg/kg.

The primary objective of the current study was to evaluate the safety and tolerability of short-term treatment with PF-04494700 in subjects with mild to moderate AD. Secondary objectives were to assess the pharmacokinetic (PK) profile, and to evaluate the effect of short-term treatment with PF-04494700 on measures of cognitive function, and on plasma biomarkers related to the RAGE mechanism of action.

METHODS

Subjects

Male or female outpatients were enrolled who were at least 50 years of age and who met National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer Disease and Related Disorders Association (NINCDS-ADRDA)¹⁹ criteria for probable AD of at least one year duration, with mild-to-moderate dementia (Mini-Mental State Examination [MMSE]²⁰ score of 12–26 at both the screening and baseline visit). Additional inclusion criteria required that there be an adult informant who had significant direct contact with the patient on at least 3 days per week, and that a CT or MRI scan was consistent with the diagnosis of AD, and showed no evidence of significant focal lesions or other pathology which might account for the dementia.

Exclusion criteria included: living alone or in a long-term care facility; a history within the previous 2 years of a neurological or psychiatric illness that could contribute to dementia; a history within the previous 3 years of Parkinson's disease, seizure disorder, head injury with loss of consciousness, or meeting DSM IV criteria for any major psychiatric disorder; current (within the past year) history of poorly controlled hypertension, myocardial infarction or unstable coronary artery disease; a QTc greater than 450 msec (females) or greater than 430 msec (males), or a family history of prolonged QT syndrome; a history in the last 2 years of symptomatic congestive heart failure, syncope, or recurrent hypokalemia; severe pulmonary disease; poorly controlled diabetes mellitus (HbA1C >9%); significant thyroid disease, unless euthyroid on treatment for at least 6 months; active neoplastic disease; clinically significant hematologic or coagulation disorder including any unexplained anemia or a platelet count less than 100,000 μ L at screening; clinically significant hepatic or renal disease, including presence of Hepatitis B or C antigen/antibody or an elevated transaminase levels of greater than 2 times the upper limit of normal (ULN) or creatinine greater than $1.5 \times$ ULN. Excluded medications included: drugs known to significantly increase QTc and/or have increased risk of torsades de pointe; immunosuppressive agents; cancer chemotherapeutic agents; oral corticosteroids other than maintenance doses equivalent to 7.5 mg prednisone per day; and radiotherapy.

The study was conducted at 14 sites in the United States from October, 2005 to June 2006, according to the Declaration of Helsinki and subsequent revisions, and approved by institutional review boards at each center. Prior to performing any study procedures, the patient (or their legally authorized representative if the patient was judged to be unable to provide informed consent), and the patient's informant read and signed an informed consent form.

Design

This was a 10-week, randomized, double-blind, placebo-controlled, parallel-group study of the safety and tolerability of 2 dose regimens of PF-04494700 in subjects who met criteria

for AD that was mild-to-moderate in severity. After completing a two-week screening phase, during which they were maintained on stable doses of their previously prescribed AD treatments, subjects were randomized to one of 3 treatment groups: (1) a “low dose” group (n=25), treated with PF-04494700 in a loading dose of 30 mg once daily for six days, followed by a 10 mg maintenance dose once daily for 63 days; (2) a “high dose” group (n=25), treated with PF-04494700 in a loading dose of 60 mg once daily for 6 days followed by a 20 mg maintenance dose once daily for 63 days; or (3) placebo (n=10). The reason for the loading dose was to quickly have subjects achieve steady state levels in this short term trial. At the end of the 10-week double-blind treatment period, study medication was discontinued and subjects returned for a final end of study follow-up visit 4 weeks after the last dose. Subjects who discontinued after randomization were not replaced.

Outcome measures

Safety—The primary objective of the present study was to evaluate the safety and tolerability of PF-04494700 administered for 10 weeks in AD subjects. All observed and volunteered adverse events were recorded, and rated as to severity, date of onset/offset, and possible relationship to study drug. Safety measures also included laboratory tests (hematologies, chemistries, urinalysis), physical exam, vital signs, weight, and 12-lead electrocardiogram (ECG). Safety measures were obtained at the screening and baseline visits, and at Weeks 1, 2, 4, 6, 8, and 10 (or study endpoint). A 24 hour 12-lead serial ECG (Holter Monitor) was also obtained at baseline and Week 10 (or study endpoint).

Efficacy—A secondary objective of the study was to evaluate the short-term effects of treatment with PF-04494700 on biomarkers in plasma related to the RAGE mechanism of action, consisting of the following: high sensitivity C-reactive Protein (hs-CRP; performed using a Roche CRP Latex particle-enhanced immunological agglutination assay); Beta-amyloid ($A\beta_{1-40}$, $A\beta_{1-42}$; performed by Pankaj D. Mehta, Ph.D., at the Institute for Basic Research in Developmental Disabilities, NY, NY using a double-antibody sandwich ELISA methodology); Interleukin 1- β (IL- β ; using the human IL-1 β immunoassay kit, Quantikine, R & D Systems); Interleukin-6 (IL-6; was performed on the DPC Immulite 2000 using a solid-phase, enzyme-labeled chemiluminescent sequential immunometric assay); Transforming Growth Factor- β -1 (TGF- β -1; performed using a Quantikine Human TGF- β 1 Immunoassay); and isoprostanes (performed by Domenico Praticò at the University of Pennsylvania via negative ion chemical ionization gas chromatography–mass spectrometry. Blood samples for biomarkers were collected at pre-treatment baseline, Week 4, and Week 10 (or endpoint).

Clinical and cognitive assessments were obtained at pre-treatment baseline and Week 10 (or endpoint), and consisted of the Mini Mental State Examination (MMSE),²¹ Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog),²² Alzheimer’s Disease Collaborative Study-Activities of Daily Living (ADCS-ADL),²³ and the Clinical Dementia Rating-Sum of Boxes (CDR- Sum-of-Boxes).²⁴ No pre-study investigator training or reliability assessment was performed in the use of the clinical assessment tools.

Pharmacokinetic—Blood samples to assess trough PF-04494700 concentrations were collected at pre-treatment baseline, and Weeks 1, 2, 4, 6, 8, and Week 10 (or endpoint).

Statistical analysis

Since this was a pilot study of PF-04494700 designed to evaluate safety and tolerability in patients with AD, no power calculation was performed. A total sample size of 60 subjects was chosen based on clinical considerations and feasibility. All non-safety efficacy endpoints were secondary, and only descriptive statistics were performed. All analyses were

performed on the intent-to-treat sample, defined as all subjects who were randomized to study treatment and had data from at least one post-randomization assessment available. Because the primary objective of the study was to evaluate safety, if a patient terminated early, all Week 10 efficacy assessments were performed at that time point, and the results were carried forward to the subsequently missed time point analysis (LOCF).

Descriptive statistics were also calculated for the PF-04494700 plasma concentration at each dosage level. Week 10 PF-04494700 plasma levels were used as the C_{min} steady state value. If Week 10 plasma concentrations were not available, then Week 9 plasma concentrations were used. Trough plasma concentration were used to calculate mean plasma concentration versus time curves. The statistical software used in these analyses was SAS Version 8.2 (SAS Institute, Cary, NC).

RESULTS

Ninety-six subjects were screened of whom 67 were randomized to study drug (Figure 1). The most common reasons for screen failure were failure to meet AD severity criteria (N=11) and comorbid cardiovascular exclusions (N=8). A higher proportion of subjects completed 10 weeks of double-blind treatment on both the 30/10 mg regimen of PF-04494700 (88.9%) and the 60/20 regimen (85.7%) than completed on placebo (66.7%; Figure 1).

At baseline, the majority of subjects in each treatment group were female, with a mean age of approximately 75 years (Table 1). There were no clinically relevant between-group differences in baseline demographic or clinical characteristics. The mean MMSE score at baseline was consistent with AD of mild-to-moderate severity.

Concomitant anti-dementia medications were used during the course of the study by 26 subjects (92.6%) in the PF-04494700 60/20 mg dosage group, by 25 subjects (92.6%) in the 30/10 mg dosage group, and by 10 subjects (83.3%) in the placebo group. Other classes of concomitant medications, taken by >20% of subjects overall, included cholesterol and/or triglyceride reducing drugs, NSAID and non-NSAID analgesics, antithrombotic drugs, calcium supplements, beta blockers, and antidepressants.

Safety and tolerability

Sixty-eight percent of subjects treated with the 60/20 mg dose regimen of PF-04494700 experienced at least one adverse event compared with 67% of subjects treated with the 30/10 mg dose regimen, and 75% of subjects treated with placebo (Table 2). The incidence of individual adverse events was low, with no dose-response trend evident. Among subjects treated with the 60/20 mg dose regimen, 32% experienced an adverse event judged by the investigator to be possibly or probably related to study treatment, compared with 44% of subjects treated with the 30/10 mg regimen, and 50% of subjects treated with placebo.

A total of 6 (9.0%) of subjects withdrew from the study due to an adverse event. Five of these 6 adverse events were judged by the investigator to be probably related and one was judged to be possibly related to study treatment. One patient discontinued from the 60/20 mg dose regimen due to moderate agitation. Three subjects discontinued from the 30/10 mg dose regimen, one due to mild diarrhea and vomiting, one due to severe vomiting, and one due to mild diarrhea. Two subjects discontinued from the placebo group; one due to moderate pruritus, and one due to moderate hypomania.

There were four serious adverse events reported by three subjects participating in this study. None of the events were judged to be related to study treatment by the Investigators. Three

serious adverse events occurred in two subjects on the 60/20 mg dose regimen. An 80 year old white female suffered two separate fractures of the left and right femoral necks, both requiring separate hospitalizations. The third serious event occurred in a 75 year old white male hospitalized with a kidney stone. Finally, a 64 year old white female in the placebo group experienced a seizure resulting in hospitalization. No serious adverse events occurred on the 30/10 mg dose regimen. There were no deaths during the study.

The incidence of clinically significant laboratory abnormalities was similar across study treatments; none were considered by the investigators to be related to study treatment. One patient treated in the 60/20 mg dosage group had an abnormal urinalysis (abnormal urine protein, RBCs, and crystals), which occurred in the week after being diagnosed with a kidney stone. One patient in the 30/10 mg dosage group had abnormal AST, GGT, and LDH values on treatment day 7. The GGT and LDH values had both been elevated at the Screen visit, and continued to be elevated throughout double-blind treatment. The AST value was not elevated at the Screen or Baseline visits, and returned to normal on treatment day 14. Two subjects in the placebo group had clinically significant abnormal laboratory tests. One patient had an abnormal urinalysis which returned to normal on treatment day 42, except urine bacteria, which remained abnormal until the follow-up visit. The second patient had abnormal urinalysis results, which were also abnormal at the Screen visit, and remained abnormal throughout the study.

There were no consistent, dose-dependent, treatment-emergent changes in mean vital signs or ECG parameters during treatment with either dosing regimen of PF-04494700 or placebo. Four subjects on PF-04494700 had ECG findings that were considered to be adverse events. A maximum on-treatment change in QTcB of >30 msec was observed more frequently in subjects treated with the 60/20 mg dose regimen (5, 19%) and the 30/10 mg dose regimen (7, 26%) than on placebo (0, 0%). No subjects on the 60/20 mg dose regimen or placebo had a maximum on-treatment change in QTcB >60 msec; one patient (4%) on the 30/10 mg dose regimen had an on-treatment change in QTcB >60 msec.

Pharmacokinetic data

Blood samples were obtained for analysis of PF-04494700 plasma concentrations at each double-blind visit, in the morning prior to the patient taking his or her once-daily dose. The concentration-time curve for this presumptive C_{min} time point is shown in Figure 2. As expected, the observed mean (sd) trough was higher for the 60 mg dosage group (42.4 ± 17.7 ng/mL) than for the 30 mg dosage group (20.2 ± 8.1 ng/mL). For subjects on the 60 mg dose of PF-04494700, mean trough concentrations were higher in females versus males, respectively on day 7 (44.2 ± 17.9 vs. 40.0 ± 18.1), and Day 70 (66.3 ± 30.6 vs. 44.7 ± 25.2). Similarly, For subjects on the 30 mg dose, mean trough concentrations were higher in females versus males, respectively on day 7 (22.6 ± 8.0 vs. 15.3 ± 6.0), and Day 70 (28.5 ± 12.2 vs. 19.0 ± 6.2).

Efficacy

At baseline, subjects randomized to placebo had a somewhat greater impairment on both cognitive and functional measures when compared to subjects randomized to both PF-04494700 dosage regimens (Table 3). No consistent or meaningful treatment effect was observed at Week 10 on either PF-04494700 dosage regimen in the MMSE, ADCS-ADL, ADAS-Cog, or CDR-Sum of boxes.

At baseline, several inflammatory indices were either in the normal (IL-6) or low normal range (hs-CRP), though it should be noted that normative ranges have not been established for isoprostanes or TGG- β . Treatment with PF-04494700 was associated with a modestly

greater reduction in isoprostanes at Week 10 (Table 3). However, on other inflammatory markers there were no consistent treatment effects observed compared to placebo.

Subjects treated with PF-04494700 had a small dose dependent increase in $A\beta_{1-40}$ at Week 10, while $A\beta_{1-42}$ showed a small decrease (Table 3). Inspection of Week 10 values for individual subjects found no consistent change-from-baseline trends in either $A\beta_{1-40}$ or $A\beta_{1-42}$ levels.

DISCUSSION

Ten weeks of double-blind treatment with two dosing regimens of PF-04494700 was found to be safe and well-tolerated in subjects with mild to moderate AD. The majority of adverse events observed during treatment with PF-04494700 were mild-to-moderate in intensity. Furthermore, there was a lower incidence on both dosing regimens of PF-04494700 compared to placebo on 2 key tolerability measures, discontinuation due to adverse events and incidence of adverse events rated as severe. There was no dose-response effect, either in terms of the incidence of treatment-related adverse events, which were lower among subjects treated with the 60/20 mg dose regimen compared to the 30/10 mg dose regimen (32% vs. 44%), or in terms of the incidence of events rated as “severe”, which were 11% in each group.

There did not appear to be any clinically significant trend differences in vital signs or laboratory test results, nor were any dose-dependent differences in laboratory test results noted among subjects treated with PF-04494700. In addition, there were no consistent, dose-dependent differences in mean ECG parameters between subjects administered PF-04494700 and placebo, including heart rate, mean PR interval, QRS duration, or QTc. However, 5 subjects on the 60/20 mg regimen and 7 subjects on the 30/10 mg regimen had maximum on-treatment changes in the QTcB of >30 msec, and in one of these subjects, the increase was >60 msec. These results are consistent with transient increases in QTc reported in a previous Phase I study, and with QTc prolongation observed in dogs administered dose of PF-04494700 10 mg/kg.

Once daily dosing with PF-04494700 resulted in mean trough plasma concentrations of PF-04494700 that were dose-proportionately higher on the 20 mg maintenance dose compared to the 10 mg maintenance dose. On Day 70, the mean PF-04494700 trough concentration were approximately 67% lower for males compared to females on both the 20 mg and 10 mg dose regimens. This finding needs to be replicated with larger sample sizes, and in a study designed for comprehensive evaluation of PK parameters.

The results for the secondary efficacy parameters were inconclusive. Ten weeks of treatment with PF-04494700 had no consistent effects on plasma levels of $A\beta$ or inflammatory markers (hs-CRP, IL-1, IL-6, isoprostanes, TGF- β). For several measures, baseline values were in the normal or low-normal range; this, coupled with large measurement variability, limited the ability to detect a treatment effect.

No meaningful treatment effect was observed at Week 10 on PF-04494700 in secondary cognitive and functional measures, including MMSE, ADAS-Cog, ADCS-ADL, and CDR-Sum of boxes. This was anticipated, based on the proposed mechanisms: anti-amyloid and anti-inflammatory effects may slow disease progression, but are not expected to have short-term effects on disease symptoms.

A potential limitation of the current study was the absence of information on clinical variables that have been reported to influence the concentration of inflammatory markers,

such as alcohol and smoking status, hormone replacement therapy, level of physical activity, etc.

In conclusion, ten weeks of treatment of elderly AD Subjects with PF-04494700 was well-tolerated, with no treatment-emergent changes in laboratory, vital signs, or ECG parameters. PF-04494700 had no consistent or clinically meaningful effect on plasma levels of A β , inflammatory biomarkers, or secondary cognitive or functional outcomes in this brief pilot study. Further studies are planned to assess the impact of long-term treatment on cognitive and clinical measures in subjects with AD.

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Figure 1.
Flow Diagram

Figure 1.
Mean PF-04494700 Plasma Concentration-Time Curve: Results from Blood Samples
Obtained at Trough Time Points

Table 1

Summary of Patient Characteristics at Baseline, Safety Sample

PARAMETER	PF-04494700 30/10 MG N=27	PF-04494700 60/20 MG N=28	PLACEBO N=12
Gender , female, %	17 (63%)	16 (57%)	8 (67%)
Ethnicity , white, %	27 (100%)	28 (100%)	10 (83%)
Age , yrs, mean (sd)	74.6 (7.8)	76.6 (8.5)	74.1 (8.8)
Height , cm, mean (sd)	160.6 (10.6)	161.9 (9.7)	163.2 (16.8)
Weight , kg, mean (sd)	66.3 (13.1)	68.5 (14.4)	68.8 (21.0)
BMI , mean (sd)	25.5 (4.4)	25.8 (5.0)	24.8 (3.1)
ADAS-Cog , mean (sd)	27.8 (9.6)	27.6 (10.6)	29.8 (10.6)
CDR-Sum of Boxes , mean (sd)	1.0 (0.6)	0.9 (0.6)	1.3 (0.8)
ADCS-ADL , mean (sd)	63.3 (11.3)	62.9 (13.7)	57.9 (15.8)
MMSE , mean (sd)	21.1 (3.9)	21.6 (4.6)	19.2 (5.2)

BMI: body mass index, kg/m²; ADAS-Cog, Alzheimer's Disease Assessment Scale – Cognitive Subscale; CDR, Clinical Dementia Rating; ADCS-ADL, Alzheimer's Disease Collaborative Study-Activities of Daily Living

Table 2

Treatment-Related Adverse Events: All Causality, Reported by 2 Subjects

	PF-04494700 30/10 MG N=27	PF-04494700 60/20 MG N=28	PLACEBO N=12
Fall	3 (11%)	2 (7%)	0 (0%)
Upper Respiratory Tract Infection	2 (7%)	2 (7%)	2 (17%)
Headache	2 (7%)	1 (4%)	1 (8%)
Urinary Tract Infection	1 (4%)	2 (7%)	1 (8%)
Contusion (bruise)	1 (4%)	2 (7%)	0 (0%)
Nasopharyngitis	0 (0%)	3 (11%)	0 (0%)
Nausea	2 (7%)	1 (4%)	0 (0%)
Vomiting	2 (7%)	1 (4%)	0 (0%)
Agitation	1 (4%)	1 (4%)	1 (8%)
Dizziness	1 (4%)	1 (4%)	1 (8%)
Abdominal Pain	2 (7%)	0 (0%)	0 (0%)
Skin Laceration	2 (7%)	0 (0%)	0 (0%)
Any Severe Event	3 (11%)	3 (11%)	2 (17%)

Table 3

Summary of the effect of study treatment on secondary clinical/cognitive efficacy measures, and on AD biomarkers, mean (sem)

	PF-04494700 30/10 MG	PF-04494700 60/20 MG	PLACEBO
MMSE	N=25	N=28	N=12
Baseline	21.1 ± 0.8	21.6 ± 0.9	19.2 ± 1.5
Week 10 change	-0.6 ± 0.4	-1.2 ± 0.6	+1.1 ± 0.6
ADCS-ADL	N=26	N=28	N=12
Baseline	63.3 ± 2.2	62.9 ± 2.6	57.9 ± 4.6
Week 10 change	+0.2 ± 1.0	-1.8 ± 1.0	+1.1 ± 1.3
ADAS-Cog	N=24	N=27	N=11
Baseline	27.8 ± 2.0	27.6 ± 2.0	29.8 ± 3.2
Week 10 change	+3.1 ± 0.9	+2.2 ± 1.0	+1.6 ± 1.4
CDR-Sum of boxes	N=26	N=28	N=12
Baseline	1.0 ± 0.1	0.9 ± 0.1	1.3 ± 0.2
Week 10 change	-0.1 ± 0.1	+0.1 ± 0.1	-0.2 ± 0.1
Beta Amyloid (Aβ₁₋₄₀) (pg/mL)	N=25	N=25	N=10
Baseline	159.2 ± 9.1	157.3 ± 9.3	150.0 ± 12.4
Week 10 change	+2.4 ± 6.2	+3.8 ± 10.3	-16.7 ± 15.4
Beta Amyloid (Aβ₁₋₄₂) (pg/mL)	N=25	N=25	N=10
Baseline	27.3 ± 2.5	32.8 ± 3.2	25.6 ± 4.4
Week 10 change	-3.8 ± 2.7	-4.4 ± 2.2	+2.5 ± 3.1
hs-CRP (mg/dL)	N=9	N=14	N=4
Baseline	0.8 ± 0.4	0.4 ± 0.1	0.2 ± 0.0
Week 10 change	-0.6 ± 0.6	+0.9 ± 0.7	0.0 ± 0.1
IL-6 (pg/mL)	N=18	N=16	N=6
Baseline	3.2 ± 0.4	3.0 ± 0.3	3.0 ± 0.6
Week 10 change	+1.3 ± 0.7	+4.8 ± 3.8	+0.1 ± 0.6
Isoprostanes (pg/mL)	N=25	N=24	N=10
Baseline	1939.0 ± 204.8	2210.8 ± 196.5	1907.8 ± 186.8
Week 10 change	-486.2 ± 154.8	-598.0 ± 205.2	-421.4 ± 97.1
TGF-β (ng/mL)	N=24	N=25	N=10
Baseline	36.5 ± 1.8	36.3 ± 1.7	37.1 ± 4.1
Week 10 change	-5.3 ± 2.4	-7.3 ± 2.0	-9.0 ± 3.6

Week 10 sample size is shown; hs-CRP: high sensitivity C-reactive protein