PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

COMPOUND NUMBER: PF-04447943

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00930059

PROTOCOL NO.: B0401005

PROTOCOL TITLE: A Phase 2 Multicenter, Double-Blind, Placebo Controlled, Parallel Group Study of PF-04447943 in Subjects with Mild to Moderate Alzheimer's Disease

Study Centers: The study was conducted at 36 centers: 5 in Canada, 8 in Chile, 6 in the Czech Republic, and 17 in the United States of America (USA). An additional 4 centers were shipped study drug but did not randomize any subjects.

Study Initiation Date and Primary Completion or Completion Dates:
10 September 2009 to 22 September 2010

Phase of Development: Phase 2

Study Objectives: The primary objective of this study was to assess the efficacy of PF-04447943, relative to placebo, on a performance-based measure of cognition in subjects with mild to moderate Alzheimer's Disease (AD).

The secondary objectives of this study were:

1. To evaluate the effects of PF-04447943 on other clinically relevant measures including behavior, and clinician-rated global change.

2. To evaluate the safety and tolerability of PF-04447943, relative to placebo, in subjects with mild to moderate AD.

3. To evaluate the pharmacokinetics (PK) of PF-04447943 in subjects with mild to moderate AD.

METHODS

Study Design: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of 12 weeks of treatment with PF-04447943 relative to placebo in healthy subjects with mild to moderate AD. A screening period of up to 28 days before the baseline visit was followed by 12 weeks treatment with either PF-04447943 or placebo, randomized 1:1. Efficacy and/or safety assessments were

performed at baseline (Day 1), Week 1, Week 3, Week 6, Week 9, and Week 12/early termination.

Number of Subjects (Planned and Analyzed): The study was planned to be conducted in approximately 150 healthy subjects with mild to moderate AD; however, it was intended to also allow all subjects in screening at the time the target was achieved to continue to randomization if eligible. A large increase in screening activity occurred in the last few weeks of enrollment and the target of 150 was achieved while many subjects were still in the screening phase. Allowing such subjects to continue to the double-blind phase resulted in a total of 191 subjects being randomized. Of the 293 subjects screened for this study, 91 subjects were randomized to the PF-04447943 group and 100 subjects were randomized to the placebo group. The sample size was adjusted to approximately 190 subjects and the statistical power was adjusted for the increased sample size.

Diagnosis and Main Criteria for Inclusion: Subjects were to be male and/or female subjects (not of child-bearing potential), with ages ranging from 55 to 85 years, with diagnostic evidence of probable AD consistent with *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition and National Institute of Neurological and Communicative Disorders and Stroke – Alzheimer's Disease and Related Disorders Association criteria.

Subjects also had to have mild to moderate probable AD with a Mini-Mental State Examination (MMSE) score between 14-26 inclusive at screening, a Modified Hachinski Ischemia score ≤4, live in the community and have a reliable caregiver or family member who agreed to accompany the subject to all clinic visits, provide information about the subject as required by the protocol, and ensure compliance with the study medication. Cholinesterase inhibitors and memantine were not permitted.

Study Treatment: PF-0447943 was supplied as 5-mg and 15-mg tablets, with matching 5-mg and 15-mg placebo tablets.

Eligible subjects were randomized 1:1 to receive 12 weeks of treatment with PF-04447943 25 mg or placebo. Study medication was to be taken orally twice daily every 12 hours (Q12H), once in the morning and once in the evening beginning the evening of the baseline visit, under the supervision of the caregiver. Study medication was to be taken with 240 mL (8 fluid ounces) of water. Study medication could have been taken with or without food.

Efficacy Evaluations: The Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-cog) is an 11-item scale designed to assess the severity of cognitive impairments in AD subjects. Total scores range from 0 to 70. The ADAS-cog was performed at screening (at least 14 days before the baseline visit), baseline, Week 3, Week 6, Week 9, and Week 12/early termination.

The Neuropsychiatric Inventory (NPI) is a caregiver interview-based rating scale assessing 12 behavioral disturbances occurring in dementia subjects. Items were scored for both frequency and severity. Total scores range from 0 to 144 with higher scores indicating greater behavioral disturbances. For each item, the associated caregiver distress was also

assessed. The NPI was performed at screening, baseline, Week 3, Week 6, Week 9, and Week 12/early termination.

The Clinical Global Impression of Improvement scale (CGI-I) was used to assess global change in the subject's condition compared to baseline before treatment. This is a 7-point scale ranging from (1) very much improved to (7) very much worse. The CGI-I was performed at Week 3, Week 6, Week 9, and Week 12/early termination.

The primary efficacy endpoint was the change from baseline to Week 12 on the ADAS-cog.

The secondary efficacy endpoints were:

- The change from baseline to Weeks 3, 6, and 9 on the ADAS-cog;
- Ratings on the CGI-I at Weeks 3, 6, 9, and 12/early termination; and
- The change from baseline to Weeks 3, 6, 9, and 12/early termination on the NPI.

Pharmacokinetic Evaluations: PK blood samples were collected prior to dosing at Week 1 and 0 to 3 hours following cognitive testing at Weeks 3, 6, 9, and 12/early termination. PF-0447943 concentrations in plasma were measured using a validated high-performance liquid chromatography tandem mass spectrometric method. The PK endpoint was plasma concentrations of PF-04447943 over time.

Pharmacogenomic Evaluations: Pharmacogenomic blood samples were collected at baseline for apolipoprotein E (ApoE) genotyping.

Safety Evaluations: Safety evaluations included adverse event (AE) monitoring (screening, baseline, Weeks 1, 3, 6, 9, 12/early termination), vital signs and body weight (screening, baseline, Weeks 1, 3, 6, 9, 12/early termination), electrocardiogram (ECG) measurements (screening, Weeks 1, 6, 12/early termination), physical examinations (baseline, Weeks 3, 6, and 9), laboratory tests (hematology, blood chemistry, and urinalysis at screening, baseline, Weeks 6, 12/early termination). The Columbia Suicide Severity Rating Scale (C-SSRS) was conducted at screening, b*aseline, Weeks 1, 3, 6, 9, 12/early termination and the Suicidal Behaviors Questionnaire* Revised was conducted only at screening.

Statistical Methods

Safety: No formal analyses were planned for safety data. The safety endpoints were listed and summarized in accordance with sponsor reporting standards, where the resulting data presentations consisted of subjects from the safety analysis set. The safety analysis set was defined as all subjects who consumed at least 1 dose of the investigational or control drug.

Pharmacokinetics: PF-04447943 PK parameters were not determined for this study. Plasma drug concentration data for PF-04447943 were listed and summarized.

Pharmacogenomics: ApoE status was listed and summarized.

Efficacy:

Primary Endpoint

The full analysis set (FAS) was defined as all subjects who consumed at least 1 dose of randomized study medication, and was used for the primary endpoint analysis of ADAS-cog. Analyses were also presented for the per-protocol analysis set (PPAS). The PPAS was defined as subjects who contributed a 12-week ADAS-cog measurement and who correctly consumed at least 80% of their randomly assigned study medication as measured by tablet counts for each bottle returned at each visit.

With the primary endpoint, the effect of PF-04447943 on the mean change in ADAS-cog over 12 weeks of treatment was estimated. A single linear model with fixed effects for baseline covariates, scheduled measurement occasion (nominal scale), and scheduled measurement occasion by treatment interaction, plus a random effect for subject was employed for both estimation and significance testing. Inference was based on the estimates of expected values by treatment by measurement occasion as derived from this model. Baseline covariates included baseline ADAS-cog.

The primary significance test tested the null hypothesis that the mean difference in ADAS-cog between the active and control groups at 12 weeks was ≥ 0. The primary test of significance was 1-sided, and a nominal Type I error rate $\alpha = 0.05$ was employed.

The same analysis was carried out using the PPAS for the purpose of assessing the sensitivity of the primary inference to early discontinuation and nonadherence. Sensitivity to the assumed covariance structure was assessed by fitting the data in the FAS to the same set of fixed effects as for the primary analysis, but without the random subject term, and specifying an "unstructured" (in the language of SAS) covariance within subjects.

Secondary Endpoints

The NPI and CGI-I secondary endpoints were analyzed via the strategy and model used in the analysis of the primary endpoint (ADAS-cog), but with the obvious modifications specific to these 2 scales. Analyses of secondary endpoints and analyses of the primary endpoint at secondary time points were conducted to further elucidate the relative effects of the treatments on cognitive function.

Mean differences in all 3 measures of efficacy (ADAS-cog, NPI, and CGI-I) at the Weeks 3, 6, 9, and 12 time points were estimated as well. The linear model described in connection with the primary endpoint, with the obvious modifications for the different time points and endpoints, was used for inferences at intermediate scheduled measurement occasions. Confidence coefficients for interval estimates and levels of significance for secondary hypothesis tests were not adjusted a priori for multiplicity.

Also, the totality of the ADAS-cog data was used to estimate the time course of the treatment effect, and specifically the time at which 50% of the maximum symptomatic effect was achieved.

For NPI, individual item responses were summarized overall and by symptoms present at baseline. The NPI caregiver distress scale was summarized separately. The CGI-I evaluations were also cross-tabulated according to a 3-value scale of improved, no change, or worsened.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 1. Of the 293 subjects screened for this study, 91 subjects were randomized to the PF-04447943 group and 100 subjects were randomized to the placebo group. The most common reason for screen-failure was that the subject did not meet entrance criteria.

This study was conducted in male and female subjects, aged 54-85 years old at screening (1 placebo subject who was 54 years old at screening turned 55 years old by the baseline visit). PF-04447943 and placebo treatment groups were generally similar in demographic and screening characteristics; there were more females than males and the majority of subjects were white. The mean age was 73.6 years for the PF-04447943 group and 73.5 years for the placebo group. The mean duration since AD diagnosis was 1.2 years for the PF-04447943 group and 1.3 years for the placebo group.

Table 1. Subject Disposition

Number (%) of Subjects	PF-04447943	Placebo
Screened: 293		
Randomized/assigned to study treatment	91	100
Treated	91	100
Completed	79 (86.8)	92 (92.0)
Discontinued	12 (13.2)	8 (8.0)
Number of subjects at:		
Baseline	91 (100)	100 (100)
Week 1	88 (96.7)	99 (99.0)
Week 3	89 (97.8)	100 (100)
Week 6	84 (92.3)	97 (97.0)
Week 9	82 (90.1)	97 (97.0)
Week 12	80 (87.9)	93 (93.0)
Discontinuations		
Subject died	0	1 (1.0)
Related to study drug, not defined	6 (6.6)	6 (6.0)
Does not meet entrance criteria	1 (1.1)	1 (1.0)
No longer willing to participate in study	4 (4.4)	3 (3.0)
Other	0	1 (1.0)
Study terminated by sponsor	1 (1.1)	1 (1.0)
Related to study drug	3 (3.3)	0
Adverse event	3 (3.3)	0
Not related to study drug	3 (3.3)	1 (1.0)
Adverse event	3 (3.3)	1 (1.0)

[a] One placebo subject discontinued treatment due to an AE on Day 44 and died on Day 98. This subject was included in this table as died. An additional placebo subject is captured in the ARGUS data (serious adverse event) as having died on 13 July 2010, 7 days after discontinuation from treatment, but this death is not captured in the final dataset used for creation of this table.

Efficacy Results:

Primary: As summarized in Table 2, there was no statistically significant difference between PF-04447943 and placebo at Week 12 in mean ADAS-cog scores (p = 0.3353). The results of the PPAS were consistent with the FAS (p = 0.3157). The least squares (LS) mean changes from baseline to Week 12 were -1.91 and -1.60 for the PF-04447943 and placebo groups (FAS), respectively, suggesting improvement in cognition after 12 weeks of study treatment in both treatment groups.

Table 2. Inferential Analysis of ADAS-cog: Change from Baseline to Week 12 (FAS)

	PF-04447943	Placebo
Baseline		
N	91	100
Mean (SD)	22.66 (10.39)	21.87 (10.42)
95% CI	20.50, 24.82	19.80, 23.93
Week 12 change from baseline		
N	80	93
Least squares mean (SE)	-1.91 (0.54)	-1.60 (0.50)
90% CI	-2.80, -1.03	-2.43, -0.77
Difference PF-04447943 minus placebo at Week 12[a]		
LS mean (SE)	-0.31 (0.73)	
90% CI	-1.52, 0.90	
One-sided p-value	0.3353	

ADAS-cog scores range from 0 (best) to 70 (worst).
A change from baseline <0 is an improvement.
ADAS-cog = Alzheimer's Disease Assessment Scale - Cognitive Subscale; FAS = full analysis set; SD = standard deviation; CI = confidence interval; LS = least squares; SE = standard error; N = number of subjects.
[a] The LS means and p-values are based on analysis of covariance on change from baseline with treatment, baseline value, scheduled visit and visit by treatment interaction as covariates. Subject effect was treated as random.

Secondary: There were no statistically significant differences between PF-04447943 and placebo at Weeks 3, 6, or 9 in mean ADAS-cog scores. The LS mean changes from baseline showed a decrease in ADAS-cog scores for both PF-04447943 and placebo treatment groups suggesting a trend for improvement in cognition over time. The results of the PPAS were consistent with the FAS. Mean changes in ADAS-cog scores over time were similar between PF-04447943 and placebo treatment groups for both mild and moderate MMSE severity categories.

There were no statistically significant differences between PF-04447943 and placebo treatment groups at Weeks 3, 6, or 9 in mean changes in NPI total scores. The LS mean changes from baseline showed a decrease in NPI scores for both PF-04447943 and placebo treatment groups, suggesting a trend for improvement in behavioral disturbance over time. Mean changes in NPI scores from baseline to Week 12 were similar between PF-04447943 and placebo treatment groups for both mild and moderate MMSE severity categories.

Descriptive statistics for each symptom of the NPI at baseline and postbaseline assessments for subjects with the given symptom present at baseline were summarized for the FAS. For all symptoms, there were no apparent differences between PF-04447943 and placebo

treatment groups in mean changes from baseline. There were also no apparent differences between PF-04447943 and placebo treatment groups in mean changes from baseline to Week 12 in NPI Caregiver Distress Scale scores.

Inferential analysis of CGI-I scores did not result in any statistically significant treatment differences. Of the 7 ratings (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse), a higher percentage of subjects had scores of minimally improved or no change at each time point for both treatment groups. Findings were similar for both mild and moderate MMSE severity categories.

For all efficacy measures, differences between PF-04447943 and placebo were generally similar for each of the 4 participating countries.

Pharmacokinetic and Pharmacogenomic Results: Plasma drug concentration data for PF-04447943 were listed and summarized. ApoE status was listed and summarized.

Safety Results: The incidence of treatment-emergent AEs was slightly higher in the PF-04447943 group (63.7%) than the placebo group (58.0%) (Table 3). In the PF-04447943 group, 4 subjects had serious adverse events (SAEs) (no subjects died), 5 subjects had severe AEs, and 6 subjects discontinued treatment due to 1 or more AEs. One additional SAE was reported in a PF-04447943-treated subject 87 days after the last dose of study drug and the event was not considered to be treatment emergent or treatment related. In the placebo group, 4 subjects had SAEs (including 2 subjects who died), 3 subjects had severe AEs, and 2 subjects discontinued treatment due to 1 or more AEs.

Table 3. Treatment-Emergent Adverse Events, All Causalities and Treatment-Related

	All Causality		Treatment-Related	
Number (%) of Subjects	**PF-04447943**	**Placebo**	**PF-04447943**	**Placebo**
Subjects evaluable for AEs	91	100	91	100
Number of AEs	109	109	59	47
Subjects with AEs	58 (63.7)	58 (58.0)	31 (34.1)	27 (27.0)
Subjects with SAEs[a]	3 (3.3)	4 (4.0)	0	1 (1.0)
Subjects with severe AEs	5 (5.5)	3 (3.0)	1 (1.1)	0
Subjects discontinued due to AEs[b]	6 (6.6)	2 (2.0)	3 (3.3)	0
Subjects with dose reduced or temporary discontinuation due to AEs	1 (1.1)	3 (3.0)	0	0

Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs were according to the investigator's assessment.
AE = adverse event; SAE = serious adverse event.
[a] After completion of the study and database lock, the sponsor was notified of an additional SAE. One PF-04447943-treated subject had an SAE 87 days after the last dose of study drug; the event was not considered to be treatment related and was not included in this table.
[b] One placebo-treated subject discontinued treatment due to an AE on Day 44 and died on Day 98. This subject was included in this table as discontinued treatment due to an AE (also refer to Table 6).

When evaluated by system organ class, all-causality AEs in the gastrointestinal disorders class occurred in a higher percentage of subjects in the PF-04447943 group (19.8%) than in the placebo group (5.0%). These gastrointestinal AEs included abdominal pain, diarrhea, dry

mouth, dyspepsia, gastroesophageal reflux disease, intestinal obstruction, nausea, and upper gastrointestinal hemorrhage. No other major treatment differences were noted in incidence of AEs by system organ class.

The incidence (in 2% or more subjects in either treatment group) of treatment-emergent AEs, all causalities and treatment related, by Medical Dictionary for Regulatory Activities (version 13.0) system system organ class and preferred term, is presented by treatment in Table 4. The majority of treatment-emergent AEs were considered to be mild in severity by the investigator.

Table 4. Incidence of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term in 2% or More Subjects in Either Treatment Group, All Causalities and Treatment Related

	All Causality		Treatment Related	
System Organ Class Preferred Term, n (%)	**PF-04447943 N = 91**	**Placebo N = 100**	**PF-04447943 N = 91**	**Placebo N = 100**
Ear and labyrinth disorders	**3 (3.3)**	**4 (4.0)**	**2 (2.2)**	**3 (3.0)**
Vertigo	2 (2.2)	4 (4.0)	2 (2.2)	3 (3.0)
Gastrointestinal disorders	**18 (19.8)**	**5 (5.0)**	**13 (14.3)**	**3 (3.0)**
Abdominal pain	4 (4.4)	2 (2.0)	4 (4.4)	2 (2.0)
Diarrhoea	5 (5.5)	3 (3.0)	2 (2.2)	2 (2.0)
Nausea	5 (5.5)	1 (1.0)	5 (5.5)	1 (1.0)
General disorders and administration site conditions	**4 (4.4)**	**6 (6.0)**	**1 (1.1)**	**4 (4.0)**
Asthenia	0	2 (2.0)	0	2 (2.0)
Chest pain	2 (2.2)	0	1 (1.1)	0
Irritability	0	2 (2.0)	0	1 (1.0)
Oedema peripheral	1 (1.1)	2 (2.0)	0	0
Infections and infestations	**15 (16.5)**	**12 (12.0)**	**2 (2.2)**	**1 (1.0)**
Bronchitis	3 (3.3)	2 (2.0)	1 (1.1)	1 (1.0)
Influenza	3 (3.3)	2 (2.0)	0	1 (1.0)
Nasopharyngitis	4 (4.4)	5 (5.0)	0	0
Injury, poisoning and procedural complications	**5 (5.5)**	**6 (6.0)**	**1 (1.1)**	**1 (1.0)**
Joint sprain	2 (2.2)	1 (1.0)	1 (1.1)	0
Investigations	**9 (9.9)**	**4 (4.0)**	**6 (6.6)**	**4 (4.0)**
Blood glucose increased	3 (3.3)	2 (2.0)	3 (3.3)	2 (2.0)
Metabolism and nutrition disorders	**4 (4.4)**	**4 (4.0)**	**0**	**1 (1.0)**
Hyperglycaemia	2 (2.2)	2 (2.0)	0	0
Nervous system disorders	**14 (15.4)**	**14 (14.0)**	**11 (12.1)**	**11 (11.0)**
Dizziness	4 (4.4)	2 (2.0)	4 (4.4)	2 (2.0)
Headache	7 (7.7)	7 (7.0)	7 (7.7)	6 (6.0)
Somnolence	3 (3.3)	2 (2.0)	2 (2.2)	2 (2.0)
Tension headache	0	2 (2.0)	0	0
Psychiatric disorders	**11 (12.1)**	**12 (12.0)**	**7 (7.7)**	**8 (8.0)**
Anxiety	1 (1.1)	2 (2.0)	1 (1.1)	0
Insomnia	4 (4.4)	3 (3.0)	4 (4.4)	3 (3.0)
Respiratory, thoracic and mediastinal disorders	**3 (3.3)**	**4 (4.0)**	**2 (2.2)**	**0**
Dyspnoea	0	2 (2.0)	0	0
Skin and subcutaneous tissue disorders	7 (7.7)	5 (5.0)	3 (3.3)	2 (2.0)
Hyperhidrosis	2 (2.2)	2 (2.0)	2 (2.2)	1 (1.0)
Skin lesion	2 (2.2)	0	0	0

Subjects were only counted once per treatment for each row.
Medical Dictionary for Regulatory Activities (MedDRA, v13.0) coding applied.
N = number of subjects evaluable for adverse events; n = number of subjects with adverse events.

Permanent discontinuations from treatment and the study due to AEs are listed by treatment in Table 5. Seven subjects permanently discontinued treatment and the study due to AEs: 6 in the PF-04447943 treatment group and 1 in the placebo group. Three of the 6 PF-04447943-treated subjects permanently discontinued due to gastrointestinal disorders AEs (dyspepsia, abdominal pain, and diarrhea) that were considered to be treatment related by the investigator. One additional placebo subject discontinued treatment due to an AE on Day 44 and died on Day 98.

Table 5. Permanent Discontinuations Due to Adverse Events

Subject Sex/Age[a] (years)	AE Start Day[b]	AE Preferred Term[c]	Severity	Causality	SAE[d]
PF-04447943					
M/84	35	Agitation	Severe	Disease under study	No
F/85	78	Intestinal obstruction	Severe	Other illness-intestinal obstruction	Yes
F/81	2	Dyspepsia	Mild	Study drug	No
M/70	2	Abdominal pain	Severe	Study drug	No
F/67	11	Diarrhoea	Moderate	Study drug	No
M/84	35	Hip fracture	Severe	Other-fall	Yes
Placebo					
F/79	69	Pneumonia	Moderate	Other illness-head injury	Yes
	60	Traumatic brain injury	Severe	Other illness-severe rheumatoid arthritis	Yes

This table includes subjects who discontinued treatment and the study due to AEs.
One placebo subject, who is not listed in this table, discontinued treatment due to an AE on Day 44 and died on Day 98 (refer to Table 6).
AE = adverse event; SAE = serious adverse event.
[a] Age at screening.
[b] Day relative to start of study treatment. First day of study treatment = Day 1.
[c] Medical Dictionary for Regulatory Activities (MedDRA, v13.0) coding applied.
[d] SAE according to investigator's assessment.

Two placebo-treated subjects died due to causes unrelated to the study drug. A summary of the 2 subjects who died during the study is provided in Table 6.

Table 6. Deaths

Subject Sex/Age[a] (years)	Day of Death[b]	Date of Death	Adverse Event with Fatal Outcome (Preferred Term)[c]	Cause of Death (Preferred Term)[c]
Placebo				
M/60	63	13 July 2010	Cardiac arrest	Hypertension Respiratory arrest Cardiac arrest Type 2 diabetes mellitus
			Respiratory arrest	Hypertension Respiratory arrest Cardiac arrest Type 2 diabetes mellitus
F/84	98	13 September 2010	Chronic hepatic failure	Chronic hepatic failure

[a] Age at onset.
[b] Day of death was calculated as death date minus first active therapy date plus 1.
[c] Medical Dictionary for Regulatory Activities (MedDRA, v13.0) coding applied.

All treatment-emergent SAEs are listed by treatment group in Table 7. The information for SAEs reported here is based on data compiled in the central AE monitoring database of the sponsor and available at the time of this report. One subject had a pre-randomization SAE of cholecystitis. The subject was hospitalized and the event resolved. Seven subjects had treatment-emergent SAEs (including the 2 deaths): 3 subjects in the PF-04447943 group and 4 subjects in the placebo group. Only 1 SAE of syncope in a placebo-treated subject was considered to be treatment related by the investigator.

After completion of the study and database lock, the sponsor was notified of an additional SAE. One PF-04447943-treated subject had a SAE of gastric cancer 87 days after the last dose of study drug and the event was not considered to be treatment-related. Therefore, the event was not included in the safety database as it did not meet the reporting criteria.

Table 7. Serious Adverse Events

Subject Sex/ Age[a] (years)	SAE MedDRA Preferred Term[b]	SAE Start Day[c]	Drug Stop Day[d]	Investigator Causality[e]	Clinical Outcome
PF-04447943					
F/86	Intestinal obstruction	77	76	Unrelated	Recovered/resolved
F/78	Cerebral hematoma	101	83	Unrelated	Recovered/resolved with sequel
M/85	Hip fracture	35	47	Unrelated	Recovering/resolving
	Fall	35	47	Unrelated	Recovered/resolved with sequel
M/69[f]	Gastric cancer	09-Dec-2010	14-Sep-2010	Unrelated	Not recovered/not resolved
Placebo					
M/77	Syncope	46	89	Related	Recovered/resolved
M/60	Cardiac arrest	63	56	Unrelated	Fatal
	Respiratory arrest	63	56	Unrelated	Fatal
F/80	Traumatic brain injury	60	66	Unrelated	Recovered/resolved with sequel
	Pneumonia	69	66	Unrelated	Recovered/resolved
F/84	Hepatic cirrhosis	58	44	Unrelated	Recovered/resolved
	Chronic hepatic failure	54	44	Unrelated	Fatal
	Ankle fracture	65	44	Unrelated	Recovered/resolved with sequel
	Postoperative wound infection	67	44	Unrelated	Recovered/resolved with sequel
	Fall	65	44	Unrelated	Recovered/resolved

SAE = serious adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
[a] Age at onset.
[b] MedDRA v13.0 coding applied.
[c] Start day was calculated as onset date minus first active therapy date plus 1.
[d] Stop day was calculated as therapy stop date minus first active therapy date plus 1.
[e] Causality according to investigator's assessment.
[f] After completion of the study and database lock, the sponsor was notified of an additional SAE. This PF-04447943-treated subject had an SAE 87 days after the last dose of study drug; the event was not considered to be treatment related and was not included in the safety database.

The results of the C-SSRS assessment were summarized for screening, baseline, and postbaseline. No major differences were observed in C-SSRS results between PF-04447943 and placebo treatment groups or within each treatment group over time. No subjects in either treatment group had suicidal behavior; a small percentage of subjects in both treatment groups had suicidal ideation at screening, baseline, and postbaseline; and 1 subject in the PF-04447943 group had non-suicidal self injurious behavior at postbaseline. One subject in the placebo group had an AE of suicidal ideation that was considered to be moderate in severity and treatment related by the investigator.

The incidence of laboratory abnormalities, vital signs abnormalities, and ECG abnormalities was comparable between PF-04447943 and placebo groups.

CONCLUSIONS:

- Overall, the results of this study did not show PF-04447943 to be more effective compared to placebo on measurements of cognition as measured by the ADAS-cog, behavior as measured by the NPI, and clinician-rated global change as measured by the CGI-I in subjects with mild to moderate AD.

- Plasma PF-04447943 concentrations were measured for each subject; a population PK analysis will be reported external to this report.

- PF-04447943 administered at a dose of 25 mg Q12H appeared to be safe and well-tolerated relative to placebo, in subjects with mild to moderate AD.