Sponsor

Novartis

Generic Drug Name

AFQ056

Therapeutic Area of Trial

Neuroscience

Approved Indication

Investigational

Study Number

CAFQ056A2203

Title

A multi-centre, randomized, double-blind, placebo-controlled, parallel-group, multiple oral dose titration study in patients with Parkinson's disease to assess the efficacy of AFQ056 in reducing L-dopa induced dyskinesias, and the safety and tolerability of AFQ056 in combination with L-dopa

Phase of Development

Phase II

Study Start/End Dates

12-Oct-2007 to 14-May-2008

Study Design/Methodology

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, multiple oral dose titration proof-of-concept (PoC) study in Parkinson's patients with moderate to severe LIDs.

Thirty (30) patients ware randomized to obtain 29 completed patients. Fourteen (14) of the 30 patients was randomized to receive the active drug AFQ056 and the other 16 patients received placebo.

Each patient received multiple doses of AFQ056 or placebo over 16 days (Day 1 to Day 16) using the following dose titration scheme:

- Day 1 to 4: 25 mg bid (50 mg/day) or placebo
- Day 5 to 8: 50 mg bid (100 mg/day) or placebo
- Day 9 to 12: 100 mg bid (200 mg/day) or placebo
- Day 13 to 16: 150 mg bid (300 mg/day) or placebo

Centres

Five centers in Germany

Publication

None

Objectives

Primary objectives

- To assess the anti-dyskinetic efficacy of multiple titrated doses of AFQ056 on moderate to severe L-dopa induced dyskinesias (LIDs) in patients with Parkinson's disease using the Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS).
- To assess the potential anti-parkinsonian effect of multiple titrated doses of AFQ056 in combination with L-dopa in Parkinson's patients with moderate to severe LIDs using the Unified Parkinson's Disease Rating Scale (UPDRS) – part III.
- To assess the safety and tolerability of multiple titrated doses of AFQ056 in combination with L-dopa in Parkinson's patients with moderate to severe LIDs.

Secondary objective

- To assess the anti-dyskinetic efficacy of multiple titrated doses of AFQ056 in combination with L-dopa in Parkinson's patients with moderate to severe LIDs using the Abnormal Involuntary Movement Scale (AIMS) and $UPDRS_{(32-33)}$.

Exploratory objectives

- To explore the potential relationship between the exposure of AFQ056 and the efficacy assessments after multiple dose treatment with AFQ056 in Parkinson's patients with moderate to severe LIDs.
- To explore the potential effect of multiple doses of AFQ056 on the mGlu5 receptor pathway in Parkinson's patients with moderate to severe LIDs.

Test Product (s), Dose(s), and Mode(s) of Administration

Each patient will receive twice-daily multiple oral doses of AQ056 or placebo over 16 days according to the dose titration scheme.

Reference Product(s), Dose(s), and Mode(s) of Administration

NA

Criteria for Evaluation

Primary variables

Safety and tolerability assessments

- Vital signs and body measurements (height, weight, body temperature, blood pressure)
- ECG evaluation
- Hematology; Blood chemistry; Urinalysis
- Adverse events
- Serious adverse events

Efficacy assessments

- Abnormal Involuntary Movement Scale (AIMS)
- Unified Parkinson Disease Rating Scale (UPDRS – part III)
- Unified Parkinson Disease Rating Scale (UPDRS – part IV)
- Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS, sum score)
- Parkinson Disease Sleep Scale (PDSS)
- Beck depression scale
- Computerized CANTAB test battery including following cognitive functions tests:
    - Motor/visual control task, visual memory, attention and reaction time, decision making and response control, executive function
    - Intra-extra dimensional set shift (as part of executive function)
- Patient diary

Statistical Methods

Statistical methods for efficacy analyses

Primary target variable to measure the anti-dyskinetic effect of AFQ056 was the LFADLDS sum score; key secondary target variable was the AIMS sum score. For the latter, the four baseline measurements were averaged, and the two measurements per day on treatment were also averaged. The absolute changes from baseline were used as outcome measures. An analysis of covariance model was fitted to the data, including the respective baseline value as continuous covariate. The contrast, AFQ056 minus placebo, was estimated within this model, and confidence intervals were displayed. The null hypothesis of no treatment difference was tested to the two-sided level 10%. This was done separately and in the same way for the primary and key secondary target variable, and separately and in the same way for each of the treatment-days with LFADLDS/AIMS assessment. In addition, one analysis was performed on the maximal negative change from baseline (among the treatment-days with

LFADLDS/AIMS assessment). The analysis for day 16, corresponding to a dose of 150 mg bid, was considered the primary analysis.

Analogous secondary analyses were also done for the UPDRS(32-33). For the AIMS sum score, analogous secondary analyses were also performed separately for the morning and the afternoon measurement (not averaged). That is, the absolute change from baseline of the morning measurement on each of the treatment-days under consideration were analyzed (where the average of the morning doses of days -4 and -3 was used as "baseline"), and similarly for the afternoon measurement.

The LFADLDS sum score, the AIMS sum score and the UPDRS(32-33) sum score were additionally summarized by treatment group and time point by means of descriptive statistics. The single items of the LFADLDS, the AIMS and the UPDRS part IV were not summarized.

The anti-parkinsonian effect of AFQ056 in combination with L-dopa was assessed by the UPDRS part III sum score. Similarly as for the UPDRS(32-33) sum score, the four baseline measurements were averaged, and the two measurements per day on treatment were also averaged. The absolute changes from baseline were used as outcome measures. An analysis of covariance model was fitted to the data, including the baseline value as continuous covariate. The contrast, AFQ056 minus Placebo, was estimated within this model, and confidence intervals were displayed. This was done separately and in the same way for each of the treatment-days under consideration.

An analogous analysis of the UPDRS part III sum score was performed separately for the morning and the afternoon measurement (not averaged). That is, the absolute change from baseline of the morning measurement on each of the treatment-days under consideration was analyzed (where the average of the morning doses of days -4 and -3 was used as "baseline"), and similarly for the afternoon measurement.

The UPDRS part III sum score was additionally summarized by treatment group and time point by means of descriptive statistics. The single items of the UPDRS part III were not summarized.

The PDSS sum score was summarized by treatment group and time point by means of descriptive statistics. The single VAS scores of the PDSS were not summarized.

The BDI sum score was summarized by treatment group and time point by means of descriptive statistics. The single items of the BDI were not summarized.

Based on the patient diary, total times were calculated for each state (sleeping, "off", and severities during "on") and summarized by descriptive statistics.

All single items of all tests of the CANTAB battery were summarized descriptively by treatment group and time point by means of descriptive statistics.

Study Population: Inclusion/Exclusion Criteria and Demographics

The study population:

Male and female patients between 30 and 85 years of age (both inclusive); non-smokers.

Patients with idiopathic Parkinson's disease diagnosed by UK Parkinson's disease Society Brain Bank criteria.

Patients with L-dopa induced dyskinesia greater than 20% (UPDRS item of 32, rating ≥1) of moderate to severe (complete disabling) intensity (UPDRS item 33 rating ≥ 2)

Patients with dyskinesias for at least 3 months before randomization.

Patients have to be on L-dopa treatment for at least 3 years prior to randomization and the L-dopa treatment has to be stable for at least 1 month prior to randomization (i.e. the total daily dose and dosing regimen can vary among patients but has to be the stable for individual patients). Other concomitant anti-parkinsonian medication (e.g. pramipexole, cabergoline, ropinirole) is allowed but the total daily dose and dosing regimen has to be stable for at least one month prior to randomization.

Inclusion criteria

1. Male and female, non-smoking patients between 30 and 85 years of age (both inclusive).
2. Patients with idiopathic Parkinson's disease diagnosed by UK Parkinson's disease Society Brain Bank criteria
3. Patients with L-dopa induced dyskinesia greater than 20% (UPDRS item of 32, rating ≥1) of moderate to severe (complete disabling) intensity (UPDRS item 33 rating ≥ 2)
4. Patients with dyskinesias for at least 3 months before randomization.
5. Patients have to be on L-dopa treatment for at least 3 years prior to randomization and the L-dopa treatment has to be stable for at least 1 month prior to randomization (i.e. the total daily dose and dosing regimen can vary among patients but has to be the stable for individual patients). Other concomitant anti-parkinsonian medication (e.g. pramipexole, cabergoline, ropinirole) is allowed but the total daily dose and dosing regimen has to be stable for at least one month prior to randomization.
6. At Screening, and Baseline, vital signs (systolic and diastolic blood pressure and pulse rate) will be assessed after the patient has rested for at least three (3) minutes and again after three (3) minutes in the standing position. The investigator should be guided by the following ranges for vital signs:

   oral body temperature between 35.0-37.5 °C
   systolic blood pressure, 90-150 mm Hg
   diastolic blood pressure, 50-100 mm Hg
   pulse rate, 40 - 100 bpm

   When blood pressure and pulse will be taken again after 3 minutes standing, there shall be no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure and increase in heart rate (>20 bpm) associated with clinical manifestation of postural hypotension.

   If vital signs are out-of-range, the Investigator should obtain up to two additional readings, so that a total of three (3) consecutive assessments are made, each after at least 30 minutes (one hour is recommended). At least the last reading must be within the ranges provided above in order for the patient to qualify.

   All blood pressure measurements should be assessed utilizing the same arm for each determination.
7. Female patients must be without childbearing potential (post-menopausal or surgically sterilized).
   If sterilized, female patients must have been surgically sterilized at least 6 months prior to

screening. Surgical sterilization procedures must be supported with clinical documentation made available to sponsor and noted in the Relevant Medical History / Current Medical Conditions section of the eCRF.
OR:
Postmenopausal women must have no regular menstrual bleeding for at least 1 year prior to inclusion. Menopause will be confirmed by the plasma FSH level according to the reference range provided by the central laboratory.

For safety reasons, all female patients are asked to use a double-barrier local contraception for the entire duration of the study, i.e. from Screening up to the Study Completion visit.

8. Male patients must be using a double-barrier local contraception for the entire duration of the study (from Screening up to the Study Completion visit), and refrain from fathering a child in the 3 months following last study drug administration.
9. Able to communicate well with the investigator, to understand and comply with the requirements of the study. Understand and sign the written informed consent before starting any study procedures.

Exclusion criteria:

Patients meeting any of the following criteria were excluded from entry into the study:

1. Patients with a prior surgery for Parkinson's Disease (e.g. pallidotomy).
2. Patients with a Hoehn and Yahr score of 5 when 'off'.
3. Patients with cognitive impairment (MMSE score of less than 24).
4. Patients with atypical Parkinson's disease (Progressive Supranuclear Palsy (PSP), Multi Systemic Atrophy (MSA).
5. Patients with history and/or presence of psychosis, confusional states and/or repeated hallucinations.
6. Patients who are under deep brain stimulation.
7. Patients who participated in an anti-dyskinetic clinical study within 6 months before randomization, and/or in any clinical investigation within 4 weeks prior to randomization or longer if required by local regulations, and for any other limitation of participation based on local regulations.
8. Patients who received anti-dyskinetic medication (i.e. antipsychotics, amantadine) within 4 weeks before randomization and/or neuroleptics during 2 months before randomization.
9. Donation or loss of 400 ml or more of blood within 8 weeks prior to first dosing, or longer if required by local regulation.
10. Significant illness (other than related to Parkinson's disease) within two weeks prior to dosing.
11. A past medical history of clinically significant ECG abnormalities or a family history grandparents, parents and siblings) of a prolonged QT-interval syndrome.
12. History of autonomic dysfunction (e.g. history of fainting, orthostatic hypotension, sinus arrhythmia).
13. History of acute or chronic bronchospastic disease (including asthma and chronic obstructive pulmonary disease, treated or not treated)

14. History of clinically significant drug allergy or history of atopic allergy (asthma, urticaria, eczematous dermatitis). A known hypersensitivity to the study drug or drugs similar to the study drug.
15. Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the patient in case of participation in the study. The investigator should be guided by evidence of any of the following:
    - history of ulcers, gastrointestinal or rectal bleeding;
    - history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection;
    - history or clinical evidence of pancreatic injury or pancreatitis;
    - clinical evidence of liver disease or liver injury as indicated by clinically relevant abnormal liver function tests such as SGOT, SGPT, GGT, alkaline phosphatase, or serum bilirubin. If the total bilirubin concentration is increased above 1.5 times the upper normal limit total bilirubin should be differentiated into the direct and indirect reacting bilirubin and the Investigator will make his judgment on the clinical relevance of these data.
    - history or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN values or abnormal urinary constituents (e.g., albuminuria);
    - evidence of urinary obstruction or difficulty in voiding at screening;
16. History of immunodeficiency diseases, including a positive HIV (ELISA and Western blot) test result.
17. A positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result.
18. History of drug or alcohol abuse within the 12 months prior to randomization or evidence of such abuse as indicated by the laboratory assays conducted during the screening or baseline evaluations.
19. Smokers (use of tobacco products in the previous 3 months). Urine cotinine levels will be measured during screening for all patients. Smokers will be defined as any patient who reports tobacco use or has a urine cotinine greater than 500 ng/ml.
20. Patients using (or have used within four weeks before randomization) concomitant medications that are potent inhibitors of CYP3A4. E.g., ketoconazole, ritonavir, etc.
21. Patients unable to perform the cognitive assessments at screening as determined by the neurocognitive test guidelines provided with the CANTAB test battery.

Number of Subjects

Patient disposition - n (%) of patients

	AFQ056	Placebo	Total
Patients			
Completed	14 (93.3%)	16 (100.0%)	30 (96.8%)
Discontinued	1 (6.7%)	0	1 (3.2%)
Main cause of discontinuation			
Death	0	0	0
Adverse events(s)	1 (100.0%)	0	1 (100.0%)
Lack of efficacy	0	0	0
Protocol violation(s)	0	0	0
Administrative reasons	0	0	0
Other	0	0	0

Demographic and Background Characteristics

Demographic summary by treatment group

		AFQ056 (N=15)	Placebo (N=16)	Total (N=31)
Age (years)	Mean (SD)	60.7 (10.58)	61.4 (10.28)	61.1 (10.26)
	Median	63.0	62.5	63.0
	Range	36 - 75	33 - 77	33 - 77
Gender - n(%)	Male	9 (60.0 %)	7 (43.8 %)	16 (51.6 %)
	Female	6 (40.0 %)	9 (56.3 %)	15 (48.4 %)
Race - n(%)	Caucasian	15 (100.0 %)	16 (100.0 %)	31 (100.0 %)
Ethnicity - n(%)	Other	15 (100.0 %)	16 (100.0 %)	31 (100.0 %)
Weight (kg)	Mean (SD)	71.31 (12.119)	70.18 (10.302)	70.72 (11.042)
	Median	70.00	71.25	70.00
	Range	50.0 - 97.5	47.3 - 85.0	47.3 - 97.5
Height (cm)	Mean (SD)	174.4 (8.85)	168.4 (6.54)	171.3 (8.20)
	Median	170.0	167.5	170.0
	Range	164 - 187	159 - 180	159 - 187

Primary Objective Results

Primary efficacy results:

Results from analysis of change from baseline in LFADLDS sum score on day 16

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
16	-4.60	-1.57	-3.02	(-5.12, -0.93)	0.021

Results from analysis of change from baseline in UPDRS part III sum score by day

Time of day	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	16	-2.00	-4.25	2.24	(-1.65, 6.14)	0.335
Morning	16	-2.97	-6.06	3.09	(-2.01, 8.19)	0.311
Afternoon	16	-1.18	-2.57	1.39	(-3.25, 6.03)	0.614

Safety Results:

Adverse events overall and frequently affected system organ classes - n (%) of subjects (all patients)

	AFQ056 25 mg bid N=15 n(%)	AFQ056 50 mg bid N=15 n(%)	AFQ056 100 mg bid N=12 n(%)	AFQ056 150 mg bid N=9 n(%)	Placebo N=16 n(%)
Patients with AE(s)	11 (73.3%)	12 (80.0%)	6 (50.0%)	5 (55.6%)	11 (68.8%)
System organ class					
Nervous system disorders	7 (46.7%)	6 (40.0%)	3 (25.0%)	3 (33.3%)	7 (43.8%)
Psychiatric disorders	1 (6.7%)	7 (46.7%)	4 (33.3%)	2 (22.2%)	5 (31.3%)
Gastrointestinal disorders	3 (20.0%)	3 (20.0%)	1 (8.3%)	1 (11.1%)	8 (50.0%)
General disorders and administration site conditions	6 (40.0%)	4 (26.7%)	1 (8.3%)	1 (11.1%)	4 (25.0%)
Musculoskeletal and connective tissue disorders	3 (20.0%)	1 (6.7%)	1 (8.3%)	1 (11.1%)	1 (6.3%)
Eye disorders	1 (6.7%)	2 (13.3%)	1 (8.3%)	0	1 (6.3%)
Skin and subcutaneous tissue disorders	1 (6.7%)	2 (13.3%)	0	1 (11.1%)	0
Cardiac disorders	0	1 (6.7%)	1 (8.3%)	1 (11.1%)	0
Injury, poisoning and procedural complications	1 (6.7%)	0	0	1 (11.1%)	1 (6.3%)
Investigations	0	1 (6.7%)	2 (16.7%)	0	0
Infections and infestations	1 (6.7%)	1 (6.7%)	0	0	0
Reproductive system and breast disorders	0	1 (6.7%)	0	1 (11.1%)	0
Vascular disorders	1 (6.7%)	0	0	0	1 (6.3%)
Blood and lymphatic system disorders	0	1 (6.7%)	0	0	0
Ear and labyrinth disorders	0	0	1 (8.3%)	0	0
Metabolism and nutrition disorders	0	0	1 (8.3%)	0	0
Respiratory, thoracic and mediastinal disorders	1 (6.7%)	0	0	0	0

Adverse events overall and most frequent events - n (%) of subjects (all patients)

	AFQ056 25 mg bid N=15 n(%)	AFQ056 50 mg bid N=15 n(%)	AFQ056 100 mg bid N=12 n(%)	AFQ056 150 mg bid N=9 n(%)	Placebo N=16 n(%)
Patients with AE(s)	11 (73.3%)	12 (80.0%)	6 (50.0%)	5 (55.6%)	11 (68.8%)
Preferred term					
Abdominal pain	0	0	0	0	1 (6.3%)
Agitation	0	0	0	0	1 (6.3%)
Anxiety	0	1 (6.7%)	0	0	0
Arthralgia	2 (13.3%)	1 (6.7%)	0	0	0
Asthenia	0	0	0	0	2 (12.5%)
Attention deficit/hyperactivity disorder	0	1 (6.7%)	0	0	0
Blood pressure diastolic increased	0	0	1 (8.3%)	0	0
Blood pressure increased	0	0	2 (16.7%)	0	0
Blood pressure systolic increased	0	0	1 (8.3%)	0	0
Chills	0	0	0	0	1 (6.3%)
Confusional state	1 (6.7%)	1 (6.7%)	1 (8.3%)	0	0
Constipation	0	0	0	0	2 (12.5%)
Cystitis	1 (6.7%)	0	0	0	0
Diarrhoea	1 (6.7%)	1 (6.7%)	0	1 (11.1%)	1 (6.3%)
Disorientation	0	1 (6.7%)	0	0	0
Disturbance in attention	1 (6.7%)	0	0	0	1 (6.3%)
Dizziness	4 (26.7%)	4 (26.7%)	1 (8.3%)	0	3 (18.8%)
Dry mouth	0	0	0	0	3 (18.8%)
Dysgeusia	1 (6.7%)	0	0	0	0
Dyskinesia	0	0	0	2 (22.2%)	1 (6.3%)
Dyspnoea	1 (6.7%)	0	0	0	0
Erection increased	0	1 (6.7%)	0	0	0
Euphoric mood	0	0	1 (8.3%)	0	0
Excoriation	0	0	0	0	1 (6.3%)
Fall	1 (6.7%)	0	0	1 (11.1%)	1 (6.3%)
Fatigue	4 (26.7%)	1 (6.7%)	1 (8.3%)	1 (11.1%)	1 (6.3%)
Feeling drunk	1 (6.7%)	1 (6.7%)	0	0	0
Feeling hot	1 (6.7%)	0	0	0	0
Flatulence	0	0	0	0	1 (6.3%)
Gastrointestinal hypermotility	1 (6.7%)	0	0	0	0
Hallucination	0	1 (6.7%)	0	0	1 (6.3%)
Hallucination, visual	0	1 (6.7%)	1 (8.3%)	0	0
Headache	1 (6.7%)	1 (6.7%)	1 (8.3%)	0	2 (12.5%)
Heart rate increased	0	1 (6.7%)	0	0	0

Secondary Objective Results

Secondary efficacy results:

Results from analysis of change from baseline in LFADLDS sum score by day

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
1	0.27	-0.66	0.93	(-0.73, 2.60)	0.349
4	-1.46	-0.84	-0.61	(-2.38, 1.16)	0.562
8	-2.19	-1.47	-0.72	(-2.99, 1.55)	0.594
12	-4.82	-2.39	-2.44	(-4.81, -0.06)	0.092
16	-4.60	-1.57	-3.02	(-5.12, -0.93)	0.021

Results from analysis of change from baseline in AIMS sum score by day

Time of day	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	1	-0.96	-0.67	-0.29	(-2.36, 1.79)	0.815
	4	-4.44	-2.68	-1.76	(-4.22, 0.71)	0.236
	8	-4.79	-2.32	-2.48	(-4.65, -0.31)	0.062
	12	-6.52	-3.03	-3.50	(-5.58, -1.42)	0.008
	16	-6.93	-1.63	-5.31	(-7.15, -3.46)	<0.001
Morning	1	0.27	-0.11	0.38	(-2.68, 3.44)	0.833
	4	-3.93	-2.70	-1.23	(-3.77, 1.32)	0.419
	8	-4.56	-1.20	-3.36	(-6.13, -0.60)	0.048
	12	-5.83	-1.07	-4.76	(-7.27, -2.25)	0.003
	16	-5.53	-0.16	-5.38	(-7.85, -2.91)	<0.001
Afternoon	1	-2.75	-2.39	-0.36	(-3.54, 2.81)	0.846
	4	-5.60	-3.26	-2.35	(-5.93, 1.24)	0.274
	8	-5.63	-3.80	-1.83	(-4.71, 1.04)	0.286
	12	-7.44	-5.56	-1.88	(-5.28, 1.52)	0.354
	16	-8.89	-3.47	-5.42	(-8.17, -2.68)	0.002

Results from analysis of change from baseline in UPDRS(32-33) sum score by day

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
1	0.05	-0.43	0.48	(-0.19, 1.15)	0.236
4	-1.00	-0.88	-0.12	(-0.84, 0.61)	0.785
8	-1.42	-0.98	-0.45	(-1.18, 0.29)	0.308
12	-2.22	-0.98	-1.25	(-2.04, -0.46)	0.012
16	-1.99	-0.82	-1.16	(-1.92, -0.41)	0.014

Results from analysis of change from baseline in UPDRS part III sum score by day

Time of day	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	1	-0.01	-1.36	1.35	(-1.95, 4.65)	0.492
	4	2.08	-2.92	5.01	(-0.28, 10.30)	0.119
	8	1.45	-3.23	4.68	(-2.16, 11.52)	0.254
	12	-0.47	-3.03	2.55	(-2.48, 7.58)	0.395
	16	-2.00	-4.25	2.24	(-1.65, 6.14)	0.335
Morning	1	0.11	-2.51	2.62	(-2.81, 8.05)	0.418
	4	0.92	-2.55	3.46	(-1.94, 8.86)	0.284
	8	1.58	-4.58	6.16	(-1.52, 13.84)	0.183
	12	0.49	-4.59	5.07	(-2.77, 12.91)	0.280
	16	-2.97	-6.06	3.09	(-2.01, 8.19)	0.311
Afternoon	1	-0.06	0.74	-0.80	(-4.49, 2.89)	0.713
	4	3.48	-2.37	5.85	(-0.74, 12.44)	0.142
	8	0.94	-1.12	2.05	(-5.46, 9.56)	0.645
	12	-2.40	-0.95	-1.45	(-6.09, 3.18)	0.596
	16	-1.18	-2.57	1.39	(-3.25, 6.03)	0.614

Results from longitudinal analysis of change from baseline in LFADLDS sum score

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
1	0.48	-0.84	1.32	(-0.66, 3.31)	0.269
4	-1.12	-1.27	0.15	(-1.85, 2.16)	0.899
8	-2.25	-1.40	-0.85	(-2.83, 1.14)	0.478
12	-4.98	-2.21	-2.77	(-4.75, -0.79)	0.023
16	-4.78	-1.64	-3.14	(-5.14, -1.14)	0.011

Results from longitudinal analysis of change from baseline in AIMS sum score

Time of day	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	1	-0.94	-0.69	-0.25	(-2.29, 1.79)	0.841
	4	-4.67	-2.47	-2.20	(-4.24, -0.16)	0.076
	8	-4.67	-2.44	-2.23	(-4.27, -0.19)	0.072
	12	-6.57	-2.79	-3.78	(-5.84, -1.72)	0.003
	16	-6.77	-1.79	-4.99	(-7.03, -2.95)	<0.001
Morning	1	0.31	0.06	0.25	(-2.35, 2.85)	0.873
	4	-3.89	-2.54	-1.35	(-3.95, 1.25)	0.391
	8	-4.63	-1.24	-3.39	(-5.95, -0.82)	0.031
	12	-5.83	-0.88	-4.95	(-7.55, -2.35)	0.002
	16	-5.49	-0.30	-5.19	(-7.76, -2.62)	0.001
Afternoon	1	-2.67	-2.47	-0.19	(-3.12, 2.73)	0.912
	4	-6.10	-2.76	-3.34	(-6.26, -0.41)	0.061
	8	-5.02	-4.40	-0.62	(-3.55, 2.30)	0.724
	12	-7.81	-5.15	-2.66	(-5.64, 0.32)	0.141
	16	-8.74	-3.61	-5.12	(-8.05, -2.20)	0.005

Results from longitudinal analysis of change from baseline in UPDRS(32-33) sum score

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
1	0.16	-0.52	0.69	(-0.03, 1.40)	0.114
4	-0.97	-0.90	-0.07	(-0.79, 0.64)	0.865
8	-1.44	-0.96	-0.48	(-1.19, 0.24)	0.269
12	-2.31	-0.85	-1.45	(-2.17, -0.73)	0.001
16	-2.04	-0.77	-1.26	(-1.98, -0.55)	0.004

Results from longitudinal analysis of change from baseline in UPDRS part III sum score by day

Time of day	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	1	0.09	-1.48	1.57	(-3.25, 6.39)	0.590
	4	2.12	-2.98	5.10	(0.28, 9.92)	0.082
	8	1.09	-2.92	4.01	(-0.82, 8.83)	0.171
	12	-0.41	-3.03	2.62	(-2.26, 7.50)	0.375
	16	-1.85	-4.42	2.57	(-2.25, 7.40)	0.378
Morning	1	0.34	-2.59	2.93	(-3.23, 9.09)	0.432
	4	1.34	-2.96	4.30	(-1.86, 10.46)	0.249
	8	1.14	-4.25	5.39	(-0.70, 11.48)	0.144
	12	0.21	-4.29	4.50	(-1.66, 10.66)	0.228
	16	-2.93	-6.19	3.27	(-2.82, 9.36)	0.375
Afternoon	1	0.02	0.69	-0.67	(-6.04, 4.71)	0.837
	4	3.38	-2.24	5.62	(0.24, 11.00)	0.086
	8	0.81	-0.96	1.76	(-3.61, 7.14)	0.588
	12	-2.16	-1.11	-1.05	(-6.61, 4.50)	0.754
	16	-1.05	-2.67	1.62	(-3.76, 7.00)	0.618

Results from analysis of maximal negative change from baseline in LFADLDS sum score

LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
-5.60	-3.34	-2.26	(-4.56, 0.05)	0.107

Results from analysis of maximal negative change from baseline in AIMS sum score

Time of day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	-8.91	-4.96	-3.96	(-5.68, -2.23)	<0.001
Morning	-7.42	-4.07	-3.35	(-5.16, -1.55)	0.004
Afternoon	-11.06	-8.44	-2.62	(-5.21, -0.02)	0.097

Results from analysis of change from baseline in BDI by day

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
5	-1.11	-3.57	2.46	(-0.35, 5.27)	0.146
9	-1.75	-3.24	1.49	(-0.79, 3.77)	0.273
13	-2.22	-2.27	0.05	(-2.49, 2.59)	0.973
17	-3.03	-3.85	0.83	(-1.88, 3.54)	0.603

Results from analysis of change from baseline in PDSS by day

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
5	3.99	1.88	2.11	(-6.83, 11.05)	0.688
9	1.65	12.02	-10.38	(-20.14, -0.62)	0.081
13	4.78	15.49	-10.71	(-20.02, -1.40)	0.061
17	8.04	6.85	1.19	(-9.62, 12.01)	0.851

Results from analysis of change from baseline in CANTAB test battery by day - Motor screening (MOT)

Variable	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Mean latency (0-6000) (ms)	15	-122.92	-48.23	-74.69	(-165.80, 16.43)	0.174
	16	-66.48	-29.39	-37.09	(-154.40, 80.22)	0.595

Results from analysis of change from baseline in CANTAB test battery by day - Paired Associates Learning (PAL)

Variable	Day	LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
First trial memory score (0-21)	16	-1.32	0.47	-1.79	(-3.48, -0.10)	0.082
Total trials (adjusted) (4-24)	16	1.35	-0.43	1.78	(0.28, 3.28)	0.053
Total errors (adjusted) (0-103)	16	11.56	-0.31	11.87	(3.63, 20.10)	0.021
Number of patterns reached (2-8)	16	-0.63	0.12	-0.75	(-1.45, -0.05)	0.081

Results from analysis of change from baseline in CANTAB test battery by day - Reaction Time (RTI)

Variable	Day	LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Five choice reaction time (100-5000) (ms)	16	49.99	6.26	43.73	(3.91, 83.54)	0.072
Five choice movement time (100-5000) (ms)	16	-52.11	62.78	-114.90	(-241.66, 11.87)	0.134
Five choice accuracy score (0-35)	16	-0.04	0.79	-0.83	(-1.99, 0.34)	0.238

Results from analysis of change from baseline in CANTAB test battery by day - Cambridge Gambling Task (CGT)

Variable	Day	LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Quality of decision making (0-1)	15	0.00	-0.01	0.01	(-0.04, 0.07)	0.644
Deliberation time (ms)	15	262.83	-417.22	680.05	(11.77, 1348.33)	0.094
Delay aversion (-0.9-0.9)	15	-0.03	0.01	-0.04	(-0.18, 0.09)	0.579
Overall proportion bet (0-1)	15	0.03	0.03	-0.01	(-0.08, 0.07)	0.882

Results from analysis of change from baseline in CANTAB test battery by day - One Touch Stockings of Cambridge (OTS)

Variable	Day	LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Problems solved on first choice (0-20)	15	0.31	0.58	-0.27	(-2.02, 1.48)	0.796
Mean choices to correct (1-6)	15	0.02	-0.05	0.07	(-0.09, 0.23)	0.469
Mean latency to correct (ms)	15	12611.69	-3833.77	16445.47	(3956.27, 28934.67)	0.033

Results from analysis of change from baseline in CANTAB test battery by day - Spatial Working Memory (SWM)

Variable	Day	LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Between errors (0-360)	16	1.35	-2.92	4.27	(-1.59, 10.13)	0.225
Strategy (4-30)	16	0.56	-0.33	0.89	(-0.71, 2.49)	0.352
Within errors (0-360)	16	0.08	-0.01	0.09	(-2.24, 2.42)	0.947

Results from analysis of CANTAB test battery by day - Intra-Extra Dimensional Set Shift (IEDSS)

Variable	Day	LSmean AFQ056	LSmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
IED EDS errors (0-50)	16	9.53	10.44	-0.90	(-7.67, 5.86)	0.822
Stages completed (0-9)	16	7.40	7.69	-0.29	(-1.76, 1.19)	0.743

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