Sponsor

Novartis

Generic Drug Name

AFQ056

Therapeutic Area of Trial

L-dopa induced dyskinesia in Parkinson's disease (PD-LID)

Approved Indication

None

Protocol Number

CAFQ056A2217

Title

An open-label treatment study to evaluate the safety, tolerability and efficacy of AFQ056 in Parkinson's patients with L-dopa induced dyskinesias

Study Phase

II

Study Start/End Dates

13 Oct 2010 to 15 Oct 2013

The study was terminated based on the results of studies CAFQ056A2222 and CAFQ056A2223 (due to lack of efficacy) and Novartis decision to terminate the program.

Study Design/Methodology

This was an open-label, flexible dose, long-term safety study in PD-LID patients who had completed an AFQ056 core study (CAFQ056A2203, CAFQ056A2206, CAFQ056A2208, CAFQ056A2216).

All patients who entered this study were titrated from a starting dose of 25 mg b.i.d. to maintain blinding of treatment in ongoing core studies. Patients were titrated from 25 mg b.i.d to 50 mg b.i.d., 75 mg b.i.d. and 100 mg b.i.d. at weekly intervals. Patients who did not tolerate the 25 mg b.i.d. dose level were allowed to down-titrate to 10 mg b.i.d. However, this dose level was only available until a protocol amendment, which dropped the 10 mg b.i.d. dose level. Dose adjustments (up- and down-titrations) were allowed as needed to handle any tolerability issues during the study and to ensure that patients reached their highest tolerated dose.

Centers

22 centers in six countries: Australia (3), Canada (3), France (3), Germany (7), Italy (3), United states (3)

Publication

None

Objectives

Primary objective(s)

To evaluate the safety and tolerability of AFQ056 in patients with PD-LID as assessed by

- Incidence and severity of adverse events and serious adverse events
- Changes in vital signs, laboratory assessments, and ECGs
- Changes in cognitive function as measured by the MMSE
- Changes in psychiatric symptoms as measured by the SCOPA-PC
- Changes in underlying symptoms of PD as measured by the UPDRS part III, by the PD symptom items in the Clinical Global Impression of Change (CGIC) and Patient Global Impression of Change (PGIC), and by AEs potentially related to an exacerbation of the movement disorder of PD
- Occurrence of rebound symptoms upon discontinuation of study drug

Secondary objectives

To evaluate the anti-dyskinetic efficacy of AFQ056 treatment in patients with PD-LID on dyskinesia as assessed by

- Change from baseline in mAIMS total score
- Investigator and patient assessment of clinical changes in dyskinetic symptoms and disability due to dyskinesia compared to baseline, as measured by the corresponding CGIC and PGIC items respectively

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

Oral tablets of AFQ056 5 mg, 25 mg and 100 mg

Statistical Methods

The safety set comprised of all patients who were enrolled in this study and received at least one dose of AFQ056 in this study and who had at least one post-baseline safety assessment. All safety and efficacy analyses were performed on the safety analysis set. All efficacy and safety data were summarized. Summary tables for efficacy data and safety data were presented by mode dose (most frequently administered dose) and for Total AFQ056 group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

1. Was eligible for the core study i.e. met inclusion and not met any exclusion criteria at the time of entry into the core study
2. Had completed the core study
3. Female patients were of non-childbearing potential
4. Outpatients, residing in the community (nursing home patients were not allowed)

5. Provided written informed consent before any assessment were performed and before any open-label study drug was taken
6. Had a caregiver/family informant unless the investigator considered support not necessary

Exclusion criteria:

1. A score of 5 in the "ON"-state on the Modified Hoehn and Yahr Staging (UPDRS Part V) assessment at baseline
2. Any advanced, severe or unstable disease (other than PD) that may have interfered with the primary and secondary study outcome evaluations
3. Malignancy of any organ system (other than localized basal cell carcinoma of the skin or non-invasive, non-metastatic prostate cancer that was effectively treated), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
4. Evidence of dementia (or MMSE ≤ 26 at the baseline visit); untreated or ineffectively treated major depressive disorder; currently experiencing hallucinations/psychosis requiring antipsychotic treatment, and/or confusional states (DSM-IVR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised)
5. Lab values (at the last visit prior to the taper-off period of the respective core study or at any subsequent unscheduled visit prior to the baseline visit) that included AST, ALT, total bilirubin or creatinine ≥ 1.5 X ULN (upper limit of normal) for the central laboratory
6. Long QT syndrome or QTc > 450 msec for males and > 470 msec for females at the last visit prior to taper-off of the core study (Fridericia's corrections used)
7. Any patient who were unable or unwilling to participate in all study-related activities
8. A history of surgical treatment for PD, including deep brain stimulation
9. Treatment with any of the following prior to the baseline visit
    - current treatment with concomitant medications that were strong or moderate inhibitors or inducers of CYP3A4 within 1 week
    - amantadine within 3 days
    - metoclopramide within 3 days
    - typical or atypical neuroleptic agents within 1 week
    - other investigational drugs within 30 days or 5 half-lives of the BL visit, whichever is longer

Participant Flow

Patient disposition (study completion), by mode dose

Disposition Reason	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)

Disposition Reason	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Discontinued from study	3 (100.0)	16 (100.0)	13 (100.0)	15 (100.0)	19 (100.0)	66 (100.0)
Adverse Event(s)	1 (33.3)	8 (50.0)	3 (23.1)	8 (53.3)	5 (26.3)	25 (37.9)
Administrative problems	0	5 (31.3)	3 (23.1)	3 (20.0)	5 (26.3)	16 (24.2)
Unsatisfactory therapeutic effect	1 (33.3)	1 (6.3)	4 (30.8)	2 (13.3)	5 (26.3)	13 (19.7)
Subject withdrew consent	1 (33.3)	0	3 (23.1)	1 (6.7)	4 (21.1)	9 (13.6)
Death	0	1 (6.3)	0	1 (6.7)	0	2 (3.0)
Lost to follow-up	0	1 (6.3)	0	0	0	1 (1.5)
Abnormal laboratory value(s)	0	0	0	0	0	0
Abnormal test procedure result(s)	0	0	0	0	0	0
Protocol deviation	0	0	0	0	0	0
Subject's condition no longer requires study drug	0	0	0	0	0	0

Baseline Characteristics

Demographics, by mode dose (FAS)

Demographic variable	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Age (years) n	3	16	13	15	19	66
Mean (SD)	64.7 (14.50)	63.3 (6.82)	65.5 (6.42)	62.6 (9.09)	64.2 (6.88)	63.9 (7.53)
Minimum- Maximum	50-79	49-75	54-80	43-79	46-76	43-80
Median	65.0	63.0	66.0	66.0	64.0	65.0
Sex, n (%)						
Female	1 (33.3)	13 (81.3)	6 (46.2)	5(33.3)	9 (47.4)	34 (51.5)
Male	2 (66.7)	3 (18.8)	7 (53.8)	10 (66.7)	10 (52.6)	32 (48.5)
Race, n (%)						
Caucasian	3 (100.0)	15 (93.8)	13 (100.0)	15 (100.0)	18 (94.7)	64 (97.0)
Black	0	0	0	0	0	0
Asian	0	1 (6.3)	0	0	1 (5.3)	2 (3.0)
Native American	0	0	0	0	0	0
Pacific Islander	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Other	0	0	0	0	0	0
Ethnicity, n (%)						
Hispanic/latino	0	3 (18.8)	1 (7.7)	0	1 (5.3)	5 (7.6)
Chinese	0	0	0	0	0	0
Indian subcontinent	0	0	0	0	0	0
Japanese	0	1 (6.3)	0	0	0	1 (1.5)
Mixed ethnicity	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
Other	3 (100.0)	12 (75.0)	12 (92.3)	15 (100.0)	18 (94.7)	60 (90.9)
Baseline weight (kg), n	3	16	13	15	19	66
Mean	75.17 (17.294)	60.15 (11.097)	76.90 (14.652)	71.17 (16.334)	66.92 (16.211)	68.58 (15.595)
Minimum- Maximum	60.0-94.0	42.1-83.5	55.0-108.0	52.4-106.0	42.0-87.0	42.0-108.0
Median	71.50	60.40	76.00	68.00	74.80	69.20
Baseline height (cm), n	3	16	13	15	18	65
Mean (SD)	172.3 (11.59)	164.2 (9.79)	168.2 (7.32)	172.4 (10.68)	170.2 (12.81)	168.9 (10.71)
Minimum- Maximum	160-183	150-180	157-182	154-190	150-189	150-190
Median	174.0	165.5	170.0	168.0	172.0	168.0
Baseline BMI (kg/m²), n	3	16	13	15	18	65
Mean (SD)	25.28 (5.104)	22.22 (2.983)	26.97 (3.505)	23.71 (3.269)	22.60 (3.454)	23.76 (3.726)
Minimum- Maximum	21.4-31.0	17.3-27.3	22.0-35.3	19.1-30.0	17.5-28.7	17.3-35.3
Median	23.44	22.73	26.42	22.90	23.91	23.71
Current smoker, n (%)						
Yes	0	1 (6.3)	2(15.4)	1 (6.7)	0	4 (6.1)
No	3 (100.0)	15(93.8)	11(84.6)	14(93.3)	19 (100.0)	62(93.9)

Summary of Safety

Safety Results

Adverse Events (AEs) by primary System Organ Class (SOC) and mode dose- open-label and taper-off treatment phase (Safety set)

Primary SOC	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Patients with any AE	3 (100.0)	16 (100.0)	13 (100.0)	15 (100.0)	17 (89.5)	64 (97.0)
Nervous system disorders	2 (66.7)	12 (75.0)	9 (69.2)	14 (93.3)	14 (73.7)	51 (77.3)
Psychiatric disorders	1 (33.3)	10 (62.5)	4 (30.8)	8 (53.3)	8 (42.1)	31 (47.0)
Musculoskeletal and connective tissue disorders	1 (33.3)	2 (12.5)	5 (38.5)	10 (66.7)	7 (36.8)	25 (37.9)
Infections and infestations	0	3 (18.8)	3 (23.1)	7 (46.7)	8 (42.1)	21 (31.8)
Gastrointestinal disorders	2 (66.7)	3 (18.8)	1 (7.7)	6 (40.0)	5 (26.3)	17 (25.8)
Injury, poisoning and procedural complications	0	3 (18.8)	4 (30.8)	4 (26.7)	6 (31.6)	17 (25.8)
General disorders and administration site conditions	0	1 (6.3)	5 (38.5)	3 (20.0)	7 (36.8)	16 (24.2)
Investigations	0	0	3 (23.1)	5 (33.3)	7 (36.8)	15 (22.7)
Eye disorders	0	5 (31.3)	3 (23.1)	0	3 (15.8)	11 (16.7)
Respiratory, thoracic and mediastinal disorders	0	2 (12.5)	1 (7.7)	3 (20.0)	5 (26.3)	11 (16.7)
Metabolism and nutrition disorders	1 (33.3)	1 (6.3)	3 (23.1)	2 (13.3)	2 (10.5)	9 (13.6)
Renal and urinary disorders	0	0	2 (15.4)	2 (13.3)	5 (26.3)	9 (13.6)
Vascular disorders	0	1 (6.3)	0	5 (33.3)	2 (10.5)	8 (12.1)
Skin and subcutaneous tissue disorders	0	0	2 (15.4)	3 (20.0)	2 (10.5)	7 (10.6)
Cardiac disorders	0	2 (12.5)	0	2 (13.3)	2 (10.5)	6 (9.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (6.3)	2 (15.4)	0	2 (10.5)	5 (7.6)
Blood and lymphatic system disorders	0	2 (12.5)	1 (7.7)	1 (6.7)	0	4 (6.1)
Ear and labyrinth disorders	0	1 (6.3)	0	2 (13.3)	0	3 (4.5)
Endocrine disorders	0	0	0	1 (6.7)	0	1 (1.5)
Immune system disorders	0	0	0	1 (6.7)	0	1 (1.5)
Reproductive system and breast disorders	0	0	1 (7.7)	0	0	1 (1.5)

AEs by preferred term (PT) and mode dose (at least 5% in total column) - open-label and taper-off treatment phase (Safety set)

Preferred term	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Patients with any AE	3 (100.0)	16 (100.0)	13 (100.0)	15 (100.0)	17 (89.5)	64 (97.0)

Preferred term	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Dizziness	0	2 (12.5)	5 (38.5)	6 (40.0)	4 (21.1)	17 (25.8)
On and off phenomenon	2 (66.7)	2 (12.5)	1 (7.7)	3 (20.0)	6 (31.6)	14 (21.2)
Parkinson's disease	0	0	3 (23.1)	6 (40.0)	3 (15.8)	12 (18.2)
Dyskinesia	0	3 (18.8)	2 (15.4)	3 (20.0)	3 (15.8)	11 (16.7)
Hallucination, visual	0	3 (18.8)	1 (7.7)	3 (20.0)	3 (15.8)	10 (15.2)
Headache	0	3 (18.8)	1 (7.7)	3 (20.0)	3 (15.8)	10 (15.2)
Somnolence	0	4 (25.0)	2 (15.4)	1 (6.7)	2 (10.5)	9 (13.6)
Akinesia	0	4 (25.0)	1 (7.7)	3 (20.0)	0	8 (12.1)
Back pain	0	0	1 (7.7)	5 (33.3)	2 (10.5)	8 (12.1)
Fall	0	2 (12.5)	3 (23.1)	1 (6.7)	2 (10.5)	8 (12.1)
Abnormal dreams	0	3 (18.8)	0	2 (13.3)	2 (10.5)	7 (10.6)
Insomnia	1 (33.3)	0	1 (7.7)	0	5 (26.3)	7 (10.6)
Pain in extremity	0	2 (12.5)	2 (15.4)	2 (13.3)	1 (5.3)	7 (10.6)
Depression	0	2 (12.5)	1 (7.7)	3 (20.0)	0	6 (9.1)
Freezing phenomenon	0	2 (12.5)	2 (15.4)	0	2 (10.5)	6 (9.1)
Illusion	0	2 (12.5)	1 (7.7)	2 (13.3)	1 (5.3)	6 (9.1)
Urinary tract infection	0	1 (6.3)	0	2 (13.3)	3 (15.8)	6 (9.1)
Weight decreased	0	0	2 (15.4)	1 (6.7)	3 (15.8)	6 (9.1)
Disturbance in attention	1 (33.3)	1 (6.3)	0	2 (13.3)	1 (5.3)	5 (7.6)
Nasopharyngitis	0	2 (12.5)	0	3 (20.0)	0	5 (7.6)
Visual impairment	0	2 (12.5)	1 (7.7)	0	2 (10.5)	5 (7.6)
Constipation	0	0	0	1 (6.7)	3 (15.8)	4 (6.1)
Dyspnoea	0	2 (12.5)	0	0	2 (10.5)	4 (6.1)
Fatigue	0	0	0	1 (6.7)	3 (15.8)	4 (6.1)
Hypoaesthesia	0	2 (12.5)	0	1 (6.7)	1 (5.3)	4 (6.1)
Nausea	1 (33.3)	2 (12.5)	0	0	1 (5.3)	4 (6.1)
Oedema peripheral	0	0	2 (15.4)	0	2 (10.5)	4 (6.1)

Principal cause of death, by primary SOC, PT and mode dose (Safety set)

Primary SOC PT	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg * b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Deaths	0	1 (6.3)	0	1 (6.7)	0	2 (3.0)
Cardiac disorders	0	0	0	1 (6.7)	0	1 (1.5)
Cardiac arrest	0	0	0	1 (6.7)	0	1 (1.5)
Infections and infestations	0	1 (6.3)	0	0	0	1 (1.5)
Meningitis	0	1 (6.3)	0	0	0	1 (1.5)

SAEs, by PT and mode dose (at least 3% in total column) — open-label and taper-off treatment phase (Safety set)

Preferred term	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Patients with any SAE	1 (33.3)	4 (25.0)	4 (30.8)	8 (53.3)	8 (42.1)	25 (37.9)
Parkinson's disease	0	0	1 (7.7)	2 (13.3)	2 (10.5)	5 (7.6)
Fall	0	1 (6.3)	2 (15.4)	0	0	3 (4.5)
Road traffic accident	0	0	0	1 (6.7)	1 (5.3)	2 (3.0)
Cardiac arrest	0	0	0	2 (13.3)	0	2 (3.0)
Hallucination, visual	0	1 (6.3)	0	1 (6.7)	0	2 (3.0)
On and off phenomenon	1 (33.3)	0	0	1 (6.7)	0	2 (3.0)
Prostate cancer	0	0	1 (7.7)	0	1 (5.3)	2 (3.0)
Pneumonia	0	0	1 (7.7)	1 (6.7)	0	2 (3.0)

AEs leading to study drug discontinuation, by primary SOC, PT and mode dose — open-label and taper-off treatment phase (Safety set)

Primary SOC PT	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Patients with any AE leading to discontinuation	1 (33.3)	8 (50.0)	3 (23.1)	8 (53.3)	5 (26.3)	25 (37.9)
Blood and lymphatic system disorders	0	1 (6.3)	0	1 (6.7)	0	2 (3.0)
Anaemia	0	1 (6.3)	0	0	0	1 (1.5)
Bicytopenia	0	0	0	1 (6.7)	0	1 (1.5)
Leukopenia	0	1 (6.3)	0	0	0	1 (1.5)
Ear and labyrinth disorders	0	0	0	1 (6.7)	0	1 (1.5)
Tinnitus	0	0	0	1 (6.7)	0	1 (1.5)
Eye disorders	0	1 (6.3)	0	0	0	1 (1.5)
Vision blurred	0	1 (6.3)	0	0	0	1 (1.5)
Injury, poisoning and procedural complications	0	0	1 (7.7)	0	1 (5.3)	2 (3.0)
Fracture	0	0	1 (7.7)	0	0	1 (1.5)
Ulna fracture	0	0	0	0	1 (5.3)	1 (1.5)
Metabolism and nutrition disorders	0	0	1 (7.7)	0	0	1 (1.5)
Diabetes mellitus inadequate control	0	0	1 (7.7)	0	0	1 (1.5)
Nervous system disorders	1 (33.3)	5 (31.3)	2 (15.4)	6 (40.0)	3 (15.8)	17 (25.8)
On and off phenomenon	1 (33.3)	1 (6.3)	1 (7.7)	1 (6.7)	2 (10.5)	6 (9.1)
Parkinson's disease	0	0	0	2 (13.3)	1 (5.3)	3 (4.5)
Akinesia	0	1 (6.3)	0	1 (6.7)	0	2 (3.0)
Dyskinesia	0	1 (6.3)	1 (7.7)	0	0	2 (3.0)
Hyperkinesia	0	0	0	0	1 (5.3)	1 (1.5)

Primary SOC PT	AFQ056 10 mg b.i.d. N=3 n (%)	AFQ056 25 mg b.i.d. N=16 n (%)	AFQ056 50 mg b.i.d. N=13 n (%)	AFQ056 75 mg b.i.d. N=15 n (%)	AFQ056 100 mg b.i.d. N=19 n (%)	Total N=66 n (%)
Hypoaesthesia	0	1 (6.3)	0	0	0	1 (1.5)
Paraesthesia	0	0	0	1 (6.7)	0	1 (1.5)
Sensory disturbance	0	0	0	1 (6.7)	0	1 (1.5)
Somnolence	0	1 (6.3)	0	0	0	1 (1.5)
Status epilepticus	0	0	0	1 (6.7)	0	1 (1.5)
Psychiatric disorders	0	4 (25.0)	1 (7.7)	0	1 (5.3)	6 (9.1)
Hallucination, visual	0	2 (12.5)	0	0	1 (5.3)	3 (4.5)
Anxiety	0	0	1 (7.7)	0	0	1 (1.5)
Depersonalisation	0	1 (6.3)	0	0	0	1 (1.5)
Panic attack	0	1 (6.3)	0	0	0	1 (1.5)

Other Relevant Findings

None

Conclusion

Long-term treatment with flexible doses of AFQ056 was not associated with major safety concerns. The safety profile was compatible with the known data on AFQ056.

Date of Clinical Trial Report

08-Aug-2014

Date Inclusion on Novartis Clinical Trial Results Database

03 Oct 2014

Date of Latest Update