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

CAFQ056A2299

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/III

Study Start/End Dates

09-Mar-2012 to 04-Nov-2013

The study was terminated based on the results of studies CAFQ056A2222 and CAFQ056A2223 (due to lack of efficacy) and the sponsor's 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 (CAFQ056A2222, CAFQ056A2223) or were otherwise eligible for the extension study as defined in the core study protocol. All patients who entered this study were titrated from a starting dose of 25 mg b.i.d. Patients were titrated from 25 mg b.i.d to 50 mg b.i.d., and 100 mg b.i.d. or the highest tolerated dose at weekly intervals. In the event that dyskinesias were not sufficiently controlled at the starting dose of 25 mg b.i.d., a faster up-titration was performed during the first week of treatment.

Dose adjustments (up- and down-titrations) were allowed as needed to manage tolerability during the course of this study and to ensure that patients reached their highest tolerated dose.

Patients who did not tolerate the 25 mg b.i.d. dose level during the up-titration or fixed-dose treatment period were discontinued from the study.

Centers

32 centers in 10 countries: Austria (3), Canada (1), France (3), Germany (8), Hungary (2), Italy (4), Slovakia (2), Spain (5), Switzerland (1), United states (3)

Publication

None

Objectives

Primary objective:

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

- Incidence and severity of AEs and SAEs
- Changes in vital signs, laboratory assessments, and ECGs
- Changes in underlying symptoms of PD as measured by
    - The UPDRS (Unified Parkinson's Disease Rating Scale) part III (Motor Examination)
    - AEs potentially related to an exacerbation of the movement disorder of PD

Secondary objective

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

- mAIMS total score
- the Revised Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS) patient and caregiver versions
- items 32, 33 and 34 of Part IV of the UPDRS

To evaluate the changes in

- Cognitive function as measured by the Mini-Mental State Examination (MMSE)
- Psychiatric symptoms as measured by the Scales for Outcome in Parkinson's (SCOPA-PC)
- Suicidal ideation and behavior, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)

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

Oral tablets of AFQ056, 25 mg, 50 mg, 75 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 prescribed dose).

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria:

1. Written informed consent was obtained before any assessment was performed and before any open-label study drug was taken
2. Have completed the core study or are eligible as defined in the core study protocol
3. Male and females
4. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must have used highly effective methods of contraception during dosing and for 96 hours (= 5 times the terminal half-life) after study medication discontinuation.
5. Outpatients
6. Have a primary caregiver willing and able to accept responsibility for assessing the condition of the patient throughout the study and for providing input to assessments in accordance with all protocol requirements

Exclusion criteria:

1. Clinical evidence suggestive of an atypical or secondary form of PD (e.g. Progressive Supranuclear Palsy, Multi Systemic Atrophy)
2. A history of surgical treatment for PD, including deep brain stimulation
3. A score of 5 in the "ON"-state on the Modified Hoehn and Yahr Staging (UPDRS Part V) assessment
4. Any advanced, severe or unstable disease (other than PD) that may have interfered with the primary and secondary study outcome evaluations
5. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or non-invasive, non-metastatic prostate cancer that has been effectively treated), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases
6. Evidence of dementia (or MMSE $\leq$ 26)
7. Untreated or ineffectively treated major depressive disorder; currently experiencing hallucinations/psychosis requiring antipsychotic treatment, and/or confusional states (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised)
8. Use of other investigational drugs within 5 half-lives or within 30 days of the baseline visit, whichever was longer
9. Lab values that include aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin or creatinine $\geq$ 1.5 X ULN (upper limit of normal) for the central laboratory
10. Long QT syndrome or QTc > 450 msec for males and > 470 msec for females (Fridericia's corrections used).
11. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes

Participant Flow

Patient disposition, by mode dose

Disposition/Reason	AFQ056 25 mg b.i.d. (N=20) n (%)	AFQ056 50 mg b.i.d. (N=20) n (%)	AFQ056 75 mg b.i.d. (N=20) n (%)	AFQ056 100 mg b.i.d. (N=69) n (%)	Total (N=129) n (%)
Discontinued from study	20 (100.0)	20 (100.0)	20 (100.0)	69 (100.0)	129 (100.0)
Study Terminated By Sponsor	10 (50.0)	10 (50.0)	17 (85.0)	47 (68.1)	84 (65.1)
AE	5 (25.0)	7 (35.0)	2 (10.0)	13 (18.8)	27 (20.9)
Lack Of Efficacy	0	0	0	7 (10.1)	7 (5.4)
Subject/Guardian Decision	2 (10.0)	1 (5.0)	0	1 (1.4)	4 (3.1)
Physician Decision	1 (5.0)	1 (5.0)	0	1 (1.4)	3 (2.3)
Lost To Follow-Up	1 (5.0)	0	1 (5.0)	0	2 (1.6)
Protocol Deviation	0	1 (5.0)	0	0	1 (0.8)
New Therapy For Study Indication	1 (5.0)	0	0	0	1 (0.8)

Baseline Characteristics

Demographics, by mode dose (Full analysis set)

Demographic variable	AFQ056 25 mg b.i.d. N=20	AFQ056 50 mg b.i.d. N=20	AFQ056 75 mg b.i.d. N=20	AFQ056 100 mg b.i.d. N=69	Total N=129
Age (years)					
n	20	20	20	69	129
Mean (SD)	65.9 (8.69)	67.5 (7.93)	62.9 (8.64)	65.9 (8.79)	65.7 (8.63)
Median	68.0	71.0	63.0	67.0	67.0
Range	49 to 78	53 to 79	43 to 78	41 to 81	41 to 81
Sex, n (%)					
Male	13 (65.0)	7 (35.0)	14 (70.0)	40 (58.0)	74 (57.4)
Female	7 (35.0)	13 (65.0)	6 (30.0)	29 (42.0)	55 (42.6)
Race, n (%)					
Caucasian	20 (100.0)	20 (100.0)	20 (100.0)	69 (100.0)	129 (100.0)
Ethnicity, n (%)					
Hispanic or Latino	2 (10.0)	2 (10.0)	4 (20.0)	14 (20.3)	22 (17.1)
Mixed ethnicity	0	0	1 (5.0)	0	1 (0.8)
Not reported	2 (10.0)	0	0	4 (5.8)	6 (4.7)
Unknown	0	1 (5.0)	3 (15.0)	5 (7.2)	9 (7.0)
Other	16 (80.0)	17 (85.0)	12 (60.0)	46 (66.7)	91 (70.5)
Baseline weight (kg)					
n	20	20	20	68	128

Demographic variable	AFQ056 25 mg b.i.d. N=20	AFQ056 50 mg b.i.d. N=20	AFQ056 75 mg b.i.d. N=20	AFQ056 100 mg b.i.d. N=69	Total N=129
Mean (SD)	72.7 (12.59)	70.0 (13.50)	70.7 (14.00)	67.3 (12.23)	69.1 (12.79)
Median	73.5	71.4	70.4	67.7	69.5
Range	51.0 to 94.6	49.0 to 105.0	50.0 to 99.0	40.5 to 91.9	40.5 to 105.0
Baseline height (cm)					
n	20	20	20	66	126
Mean (SD)	167.4 (6.68)	167.0 (10.94)	169.9 (9.87)	167.0 (9.92)	167.5 (9.59)
Median	167.5	166.5	171.5	168.0	168.0
Range	155 to 180	150 to 194	147 to 191	146 to 187	146 to 194
Baseline BMI (kg/m^2)					
n	20	20	20	66	126
Mean (SD)	25.9 (3.87)	25.0 (3.66)	24.5 (4.41)	24.0 (3.25)	24.5 (3.64)
Median	26.0	24.6	23.7	24.0	24.3
Range	19.0 to 31.6	18.4 to 33.3	19.1 to 35.1	17.1 to 32.0	17.1 to 35.1
Current smoker, n (%)					
Never	11 (55.0)	16 (80.0)	11 (55.0)	52 (75.4)	90 (69.8)
Current	4 (20.0)	2 (10.0)	5 (25.0)	5 (7.2)	16 (12.4)
Former	4 (20.0)	2 (10.0)	3 (15.0)	12 (17.4)	21 (16.3)

Summary of Safety

Safety Results

Number (%) of patients with treatment emergent AEs by primary system organ class and mode dose (Safety set)

Primary system organ class	AFQ056 25 mg b.i.d N = 20 n (%)	AFQ056 50 mg b.i.d N = 20 n (%)	AFQ056 75 mg b.i.d N = 20 n (%)	AFQ056 100 mg b.i.d N = 69 n (%)	Total N = 129 n (%)
Number of patients with at least one AE	18 (90.0)	19 (95.0)	20 (100)	50 (72.5)	107 (82.9)
Nervous system disorders	10 (50.0)	11 (55.0)	14 (70.0)	32 (46.4)	67 (51.9)
Psychiatric disorders	7 (35.0)	13 (65.0)	12 (60.0)	16 (23.2)	48 (37.2)
Infections and infestations	3 (15.0)	3 (15.0)	5 (25.0)	18 (26.1)	29 (22.5)
Musculoskeletal and connective tissue disorders	6 (30.0)	4 (20.0)	3 (15.0)	13 (18.8)	26 (20.2)
Gastrointestinal disorders	3 (15.0)	3 (15.0)	4 (20.0)	12 (17.4)	22 (17.1)
Injury, poisoning and procedural complications	1 (5.0)	5 (25.0)	3 (15.0)	11 (15.9)	20 (15.5)
Vascular disorders	2 (10.0)	5 (25.0)	3 (15.0)	4 (5.8)	14 (10.9)

Primary system organ class	AFQ056 25 mg b.i.d N = 20 n (%)	AFQ056 50 mg b.i.d N = 20 n (%)	AFQ056 75 mg b.i.d N = 20 n (%)	AFQ056 100 mg b.i.d N = 69 n (%)	Total N = 129 n (%)
General disorders and administration site conditions	4 (20.0)	5 (25.0)	3 (15.0)	0	12 (9.3)
Investigations	1 (5.0)	2 (10.0)	3 (15.0)	6 (8.7)	12 (9.3)
Metabolism and nutrition disorders	2 (10.0)	2 (10.0)	3 (15.0)	3 (4.3)	10 (7.8)
Respiratory, thoracic and mediastinal disorders	0	3 (15.0)	1 (5.0)	5 (7.2)	9 (7.0)
Eye disorders	1 (5.0)	1 (5.0)	3 (15.0)	3 (4.3)	8 (6.2)
Renal and urinary disorders	0	2 (10.0)	0	5 (7.2)	7 (5.4)
Skin and subcutaneous tissue disorders	0	1 (5.0)	2 (10.0)	4 (5.8)	7 (5.4)
Cardiac disorders	1 (5.0)	1 (5.0)	2 (10.0)	2 (2.9)	6 (4.7)
Ear and labyrinth disorders	2 (10.0)	1 (5.0)	1 (5.0)	1 (1.4)	5 (3.9)
Blood and lymphatic system disorders	0	0	0	2 (2.9)	2 (1.6)
Immune system disorders	0	0	0	1 (1.4)	1 (0.8)

Most frequently reported (preferred term > 5% in total column) treatment emergent AEs by preferred term and mode dose (Safety set)

Primary system organ class	AFQ056 25 mg b.i.d N = 20 n (%)	AFQ056 50 mg b.i.d N = 20 n (%)	AFQ056 75 mg b.i.d N = 20 n (%)	AFQ056 100 mg b.i.d N = 69 n (%)	Total N = 129 n (%)
Number of patients with at least one AE	18 (90.0)	19 (95.0)	20 (100)	50 (72.5)	107 (82.9)
Dyskinesia	0	3 (15.0)	2 (10.0)	14 (20.3)	19 (14.7)
On and off phenomenon	1 (5.0)	3 (15.0)	4 (20.0)	7 (10.1)	15 (11.6)
Hallucination, visual	3 (15.0)	5 (25.0)	4 (20.0)	2 (2.9)	14 (10.9)
Nasopharyngitis	2 (10.0)	1 (5.0)	2 (10.0)	9 (13.0)	14 (10.9)
Fall	1 (5.0)	4 (20.0)	2 (10.0)	6 (8.7)	13 (10.1)
Confusional state	3 (15.0)	3 (15.0)	3 (15.0)	2 (2.9)	11 (8.5)
Dizziness	2 (10.0)	2 (10.0)	1 (5.0)	6 (8.7)	11 (8.5)
Akinesia	5 (25.0)	1 (5.0)	1 (5.0)	3 (4.3)	10 (7.8)
Illusion	1 (5.0)	4 (20.0)	3 (15.0)	1 (1.4)	9 (7.0)
Insomnia	1 (5.0)	1 (5.0)	2 (10.0)	4 (5.8)	8 (6.2)
Abnormal dreams	2 (10.0)	2 (10.0)	1 (5.0)	2 (2.9)	7 (5.4)
Constipation	0	1 (5.0)	1 (5.0)	5 (7.2)	7 (5.4)

Serious adverse events, by primary SOC, preferred term, and mode dose (Safety set)

Primary SOC Preferred term	AFQ056 25 mg b.i.d. N=20 n(%)	AFQ056 50 mg b.i.d. N=20 n(%)	AFQ056 75 mg b.i.d. N=20 n(%)	AFQ056 100 mg b.i.d. N=69 n(%)	Total N=129 n(%)
Patients with at least one SAEs	2 (10.0)	6 (30.0)	2 (10.0)	16 (23.2)	26 (20.2)

Primary SOC Preferred term	AFQ056 25 mg b.i.d. N=20 n(%)	AFQ056 50 mg b.i.d. N=20 n(%)	AFQ056 75 mg b.i.d. N=20 n(%)	AFQ056 100 mg b.i.d. N=69 n(%)	Total N=129 n(%)
Blood and lymphatic system disorders	0	0	0	1 (1.4)	1 (0.8)
Iron deficiency anaemia	0	0	0	1 (1.4)	1 (0.8)
Cardiac disorders	0	0	1 (5.0)	0	1 (0.8)
Myocardial infarction	0	0	1 (5.0)	0	1 (0.8)
Ear and labyrinth disorders	0	0	1 (5.0)	0	1 (0.8)
Sudden hearing loss	0	0	1 (5.0)	0	1 (0.8)
Gastrointestinal disorders	1 (5.0)	0	0	1 (1.4)	2 (1.6)
Abdominal pain upper	0	0	0	1 (1.4)	1 (0.8)
Inguinal hernia, obstructive	1 (5.0)	0	0	0	1 (0.8)
Injury, poisoning and procedural complications	0	2 (10.0)	0	5 (7.2)	7 (5.4)
Rib fracture	0	1 (5.0)	0	2 (2.9)	3 (2.3)
Cervical vertebral fracture	0	1 (5.0)	0	1 (1.4)	2 (1.6)
Femoral neck fracture	0	0	0	1 (1.4)	1 (0.8)
Femur fracture	0	0	0	1 (1.4)	1 (0.8)
Fractured sacrum	0	0	0	1 (1.4)	1 (0.8)
Hand fracture	0	1 (5.0)	0	0	1 (0.8)
Humerus fracture	0	0	0	1 (1.4)	1 (0.8)
Pelvic fracture	0	0	0	1 (1.4)	1 (0.8)
Skull fractured base	0	0	0	1 (1.4)	1 (0.8)
Tendon rupture	0	0	0	1 (1.4)	1 (0.8)
Ulna fracture	0	0	0	1 (1.4)	1 (0.8)
Investigations	0	1 (5.0)	0	0	1 (0.8)
Fibrin d dimer increased	0	1 (5.0)	0	0	1 (0.8)
Metabolism and nutrition disorders	0	0	0	1 (1.4)	1 (0.8)
Hypovolaemia	0	0	0	1 (1.4)	1 (0.8)
Musculoskeletal and connective tissue disorders	0	1 (5.0)	0	2 (2.9)	3 (2.3)
Cervical spinal stenosis	0	0	0	1 (1.4)	1 (0.8)
Intervertebral disc degeneration	0	0	0	1 (1.4)	1 (0.8)
Spinal column stenosis	0	0	0	1 (1.4)	1 (0.8)
Synovial cyst	0	1 (5.0)	0	0	1 (0.8)
Nervous system disorders	0	4 (20.0)	0	6 (8.7)	10 (7.8)
On and off phenomenon	0	1 (5.0)	0	2 (2.9)	3 (2.3)
Akinesia	0	0	0	1 (1.4)	1 (0.8)
Dyskinesia	0	0	0	1 (1.4)	1 (0.8)
Epilepsy	0	1 (5.0)	0	0	1 (0.8)
Freezing phenomenon	0	1 (5.0)	0	0	1 (0.8)
Ischaemic stroke	0	0	0	1 (1.4)	1 (0.8)
Metabolic encephalopathy	0	1 (5.0)	0	0	1 (0.8)
Nystagmus	0	0	0	1 (1.4)	1 (0.8)
Parkinson's disease	0	0	0	1 (1.4)	1 (0.8)
Psychiatric disorders	1 (5.0)	1 (5.0)	0	0	2 (1.6)
Apathy	1 (5.0)	0	0	0	1 (0.8)

Primary SOC Preferred term	AFQ056 25 mg b.i.d. N=20 n(%)	AFQ056 50 mg b.i.d. N=20 n(%)	AFQ056 75 mg b.i.d. N=20 n(%)	AFQ056 100 mg b.i.d. N=69 n(%)	Total N=129 n(%)
Hallucination	1 (5.0)	0	0	0	1 (0.8)
Mental status changes	0	1 (5.0)	0	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0	1 (5.0)	0	3 (4.3)	4 (3.1)
Dyspnoea	0	1 (5.0)	0	2 (2.9)	3 (2.3)
Diaphragmatic rupture	0	0	0	1 (1.4)	1 (0.8)
Vascular disorders	0	0	0	1 (1.4)	1 (0.8)
Hypotension	0	0	0	1 (1.4)	1 (0.8)

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

Primary SOC Preferred term	AFQ056 25 mg b.i.d. N=20 n(%)	AFQ056 50 mg b.i.d. N=20 n(%)	AFQ056 75 mg b.i.d. N=20 n(%)	AFQ056 100 mg b.i.d. N=69 n(%)	Total N=129 n(%)
Patients with at least one AE leading to study drug discontinuation	5 (25.0)	7 (35.0)	2 (10.0)	13 (18.8)	27 (20.9)
Cardiac disorders	0	0	1 (5.0)	0	1 (0.8)
Myocardial infarction	0	0	1 (5.0)	0	1 (0.8)
Ear and labyrinth disorders	0	1 (5.0)	0	0	1 (0.8)
Tinnitus	0	1 (5.0)	0	0	1 (0.8)
Gastrointestinal disorders	0	2 (10.0)	0	0	2 (1.6)
Nausea	0	2 (10.0)	0	0	2 (1.6)
General disorders and administration site conditions	1 (5.0)	0	0	0	1 (0.8)
Gait disturbance	1 (5.0)	0	0	0	1 (0.8)
Injury, poisoning and procedural complications	0	0	0	1 (1.4)	1 (0.8)
Cervical vertebral fracture	0	0	0	1 (1.4)	1 (0.8)
Femur fracture	0	0	0	1 (1.4)	1 (0.8)
Fractured sacrum	0	0	0	1 (1.4)	1 (0.8)
Pelvic fracture	0	0	0	1 (1.4)	1 (0.8)
Rib fracture	0	0	0	1 (1.4)	1 (0.8)
Road traffic accident	0	0	0	1 (1.4)	1 (0.8)
Skull fractured base	0	0	0	1 (1.4)	1 (0.8)
Ulna fracture	0	0	0	1 (1.4)	1 (0.8)
Musculoskeletal and connective tissue disorders	0	0	0	3 (4.3)	3 (2.3)
Pain in extremity	0	0	0	2 (2.9)	2 (1.6)
Mobility decreased	0	0	0	1 (1.4)	1 (0.8)
Nervous system disorders	2 (10.0)	4 (20.0)	1 (5.0)	7 (10.1)	14 (10.9)
Dizziness	2 (10.0)	1 (5.0)	0	2 (2.9)	5 (3.9)
Dyskinesia	0	0	1 (5.0)	2 (2.9)	3 (2.3)
Akinesia	0	0	0	1 (1.4)	1 (0.8)
Freezing phenomenon	0	1 (5.0)	0	0	1 (0.8)

Primary SOC Preferred term	AFQ056 25 mg b.i.d. N=20 n(%)	AFQ056 50 mg b.i.d. N=20 n(%)	AFQ056 75 mg b.i.d. N=20 n(%)	AFQ056 100 mg b.i.d. N=69 n(%)	Total N=129 n(%)
Hypoaesthesia	0	1 (5.0)	0	0	1 (0.8)
Metabolic encephalopathy	0	1 (5.0)	0	0	1 (0.8)
On and off phenomenon	0	0	0	1 (1.4)	1 (0.8)
Paraesthesia	0	1 (5.0)	0	0	1 (0.8)
Parkinson's disease	0	0	0	1 (1.4)	1 (0.8)
Somnolence	0	1 (5.0)	0	0	1 (0.8)
Psychiatric disorders	4 (20.0)	3 (15.0)	0	2 (2.9)	9 (7.0)
Hallucination, visual	3 (15.0)	1 (5.0)	0	1 (1.4)	5 (3.9)
Confusional state	1 (5.0)	1 (5.0)	0	1 (1.4)	3 (2.3)
Illusion	1 (5.0)	0	0	0	1 (0.8)
Mental status changes	0	1 (5.0)	0	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders	0	0	0	1 (1.4)	1 (0.8)
Diaphragmatic rupture	0	0	0	1 (1.4)	1 (0.8)
Vascular disorders	0	1 (5.0)	0	0	1 (0.8)
Circulatory collapse	0	1 (5.0)	0	0	1 (0.8)

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

01-Oct-2014

Date Inclusion on Novartis Clinical Trial Results Database

Oct 17 2014