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| **Sponsor**<br>Novartis Pharma AG |
| **Generic Drug Name**<br>AFQ056 |
| **Therapeutic Area of Trial**<br>Parkinson's Disease with L-dopa induced dyskinesia |
| **Approved Indication**<br>Investigational |
| **Protocol Number**<br>CAFQ056A2216 |
| **Title**<br>A 6-week, double-blind, placebo-controlled, randomized, multicenter study to explore the efficacy and safety of AFQ056 when combined with increased doses of L-dopa in Parkinson's Disease (PD) patients with OFF time and moderate – severe L-dopa induced dyskinesia |
| **Phase of Development**<br>Phase II |
| **Study Start/End Dates**<br>31-Mar-2010 (first patient first visit) to 18-Jul-2011 (last patient last visit).<br>This study was terminated early due to recruitment challenges. |
| **Study Design/Methodology**<br>This was a 6-week, double-blind, placebo-controlled, randomized, multicenter study to explore the efficacy and safety of AFQ056 when combined with increased doses of L-dopa in Parkinson's Disease (PD) patients with OFF time and moderate – severe L-dopa induced dyskinesia. This study was broken into five distinct periods: screening period, AFQ056/placebo up-titration period, L-dopa up-titration period, blinded taper-off period, and follow-up period. During a 4-week screening period, L-dopa was titrated to achieve the best balance between parkinsonism and L-dopa induced dyskinesia (LID). Patients were then randomized to AFQ056 or placebo (PBO). AFQ056 was up-titrated during a 2-week period from 25 mg bid to 100 mg bid (L-dopa kept stable) followed by a 3-week period during which the L-dopa-dose was increased |

following a pre-defined scheme (AFQ056/PBO kept stable). The taper-off period gradually down titrated the dose of AFQ056 to the lowest AFQ056 dose (25mg) or placebo. During the same interval the L-dopa dose was down-titrated to the initial L-Dopa dose used during the run-in phase.

**Centres**

7 centers in the United States.

**Publication**

Kumar, R., Hauser, R., Mostillo, J., Dronamraju, N., Graf, A., Kenney, C., Merschhemke, M. (2012, June). A 6-week, double-blind, multicenter RCT in Parkinson's Disease patients to explore the efficacy and safety of AFQ056 when combined with increased doses of L-dopa. Poster presented at the 16th annual congress of Parkinson's disease and Movement Disorders, Dublin, Ireland.

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

The investigational medication, AFQ056, was provided as an oral hard gelatin capsule in 25mg and 100mg strengths with the maximum dose administered as 100 mg b.i.d. Patients had to swallow the medication whole, without chewing. Drinking grapefruit juice during the study was to be avoided.

Additionally, patients received treatment with Sinemet® 25-100 (carbidopa/levodopa). They were instructed to split the Sinemet® tablets in two halves and take one half of a tablet with their regular L-dopa dose at the times indicated by the physician.

**Statistical Methods**

In general, variables were summarized by treatment, using frequency distributions (for categorical variables) and summary statistics (for continuous variables).

The following analysis sets were used for the analyses: Full analysis set, modified full analysis set, and safety set.

The primary efficacy variable was the change from baseline to week 5 endpoint in total OFF time collected from patient diary. The primary efficacy variable, change from baseline to week 5 in total OFF time collected from patient diary, was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, pooled center, dopamine agonist strata and baseline total OFF time as a covariate. The treatment difference was estimated with a two-sided 90% confidence interval.

The key secondary efficacy variable was the change from baseline to the endpoint at week 5 in ON time with dyskinesia.

All efficacy analyses were performed on the modified full analysis set.

Safety assessments included: adverse events, laboratory tests, vital signs, ECG data, and SCOPA-PC (Scales for Outcomes in Parkinson's Disease – Psychiatric Complications) scores. All safety analyses were performed on the safety set.

**Study Population: Inclusion/Exclusion Criteria and Demographics**

Inclusion criteria

- clinical diagnosis of Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis criteria

- on L-dopa for at least 3 years prior to randomization or, if duration of treatment is less than 3 years, then must have shown clear responsiveness (Unified Parkinson Disease Rating Scale (UPDRS), part III) to L-dopa treatment
- score of ≥ 2 on UPDRS item 32 (i.e. dyskinesia present for greater than 25% of the waking day) and score of ≥ 2 on UPDRS item 33 (i.e. moderate to severely disabling)
- onset of dyskinesias at least 3 months before randomization
- recognizable ON and OFF states (motor fluctuations), with the presence of at least 3 cumulative hours of ON time with dyskinesia during the waking day, as evidenced by the average of two patient diaries completed before randomization.
- receiving an optimized L-dopa regimen (plus dopamine decarboxylase inhibitor [DDI]) therapy) that allows the best balance between the control of PD symptoms and the emergence of LID, in the investigator's opinion. The patient must receive L-dopa treatment at least 4 and up to 8 times daily (including bedtime/night time doses). Patients who are also treated with DA, MAOB inhibitors or other anti-PD drugs must be on stable doses for at least 4 weeks prior to the Screening Visit and must remain on stable treatment throughout the study. Only the L-dopa (and the associated DDI therapy) dosage can be adjusted during the double-blind treatment phase.
- outpatients, residing in the community (nursing home patients are not allowed)
- demonstrate capacity to complete an office-based training session and, during the baseline period prior to randomization, there must be diary evidence of at least one transition of OFF to ON or from ON to OFF, with at least 66% concordance between patient and investigator/coordinator on a day in which the patient experienced ON without dyskinesia, ON with dyskinesia, and OFF time

Exclusion criteria

- clinical evidence suggestive of an atypical or secondary form of Parkinson's disease (e.g. Progressive Supranuclear Palsy, Multi Systemic Atrophy)
- history of surgical treatment for PD, including deep brain stimulation
- score of 5 in the ON state on the Modified Hoehn and Yahr Staging (UPDRS Part V) assessment at screening
- daily, abrupt and unpredictable loss of efficacy greater than 30 minutes, unrelated to the timing of L-dopa administration
- evidence of dementia (or Mini Mental State Examination/MMSE ≤ 26 at Screening); untreated or ineffectively treated major depressive disorder; experiencing hallucinations/psychosis requiring antipsychotic treatment and/or confusional states within 4 weeks of randomization (DSM-IVR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition, revised)

## Participant Flow

### Patient disposition (study completion) by treatment (Full analysis set)

| Disposition Reason | Placebo N = 7 n (%) | AFQ056 N = 7 n (%) | Total N = 14 n (%) |
|---|---|---|---|
| **Completed study** | 6 (85.7) | 6 (85.7) | 12 (85.7) |
| **Discontinued study** | 1 (14.3) | 1 (14.3) | 2 (14.3) |
| Abnormal laboratory value(s) | 0 | 0 | 0 |
| Abnormal test procedure result(s) | 0 | 0 | 0 |
| Administrative problems | 0 | 0 | 0 |
| Adverse event(s) | 1 (14.3) | 1 (14.3) | 2 (14.3) |
| Death | 0 | 0 | 0 |
| Lost to follow-up | 0 | 0 | 0 |
| Protocol deviation | 0 | 0 | 0 |
| Subject withdrew consent | 0 | 0 | 0 |
| Subject's condition no longer requires study drug | 0 | 0 | 0 |
| Unsatisfactory therapeutic effect | 0 | 0 | 0 |

## Baseline Characteristics

### Demographics by treatment (Full analysis set)

| Demographic variable | Placebo N=7 | AFQ056 N=7 | Total N=14 |
|---|---|---|---|
| **Age (years)** | | | |
| n | 7 | 7 | 14 |
| Mean | 61.3 | 61.4 | 61.4 |
| SD | 8.98 | 6.00 | 7.33 |
| Minimum | 46 | 54 | 46 |
| Median | 61.0 | 62.0 | 61.5 |
| Maximum | 74 | 69 | 74 |
| **Sex, n(%)** | | | |
| Female | 3 (42.9) | 5 (71.4) | 8 (57.1) |
| Male | 4 (57.1) | 2 (28.6) | 6 (42.9) |
| **Race, n(%)** | | | |
| Caucasian | 7 (100.0) | 7 (100.0) | 14 (100.0) |
| Black | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |
| Native American | 0 | 0 | 0 |
| Pacific Islander | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Other | 0 | 0 | 0 |
| **Ethnicity, n(%)** | | | |
| Hispanic/latino | 0 | 1 (14.3) | 1 (7.1) |
| Chinese | 0 | 0 | 0 |
| Indian (Indian subcontinent) | 0 | 0 | 0 |
| Japanese | 0 | 0 | 0 |
| Mixed ethnicity | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Other | 7 (100.0) | 6 (85.7) | 13 (92.9) |
| **Baseline weight (kg)** | | | |
| n | 7 | 7 | 14 |

| | | | |
|---|---|---|---|
| Mean | 81.01 | 73.67 | 77.34 |
| SD | 17.855 | 18.248 | 17.758 |
| Minimum | 58.1 | 44.4 | 44.4 |
| Median | 82.00 | 73.60 | 73.95 |
| Maximum | 104.0 | 99.1 | 104.0 |
| **Baseline height (cm)** | | | |
| n | 7 | 7 | 14 |
| Mean | 176.6 | 164.6 | 170.6 |
| SD | 10.16 | 10.89 | 11.88 |
| Minimum | 160 | 154 | 154 |
| Median | 177.0 | 162.0 | 171.0 |
| Maximum | 190 | 182 | 190 |
| **Baseline BMI (kg/m²)** | | | |
| n | 7 | 7 | 14 |
| Mean | 25.82 | 26.90 | 26.36 |
| SD | 4.460 | 4.583 | 4.381 |
| Minimum | 21.4 | 18.7 | 18.7 |
| Median | 23.96 | 27.77 | 26.85 |
| Maximum | 34.1 | 31.6 | 34.1 |
| **Current smoker, n(%)** | | | |
| Yes | 0 | 0 | 0 |
| No | 7 (100.0) | 7 (100.0) | 14 (100.0) |

## Safety Results

### Adverse Events by System Organ Class

**Adverse events, by primary system organ class, by treatment - Up-titration and fixed-dose treatment phase (Safety set)**

| Primary system organ class<br>Preferred term | Placebo<br>N = 7<br>n (%) | AFQ056<br>N = 7<br>n (%) | Total<br>N = 14<br>n (%) |
|---|---|---|---|
| **Patients with any adverse event** | 7 (100.0) | 7 (100.0) | 14 (100.0) |
| Nervous system disorders | 7 (100.0) | 6 (85.7) | 13 (92.9) |
| Gastrointestinal disorders | 4 (57.1) | 3 (42.9) | 7 (50.0) |
| Psychiatric disorders | 1 (14.3) | 5 (71.4) | 6 (42.9) |
| Skin and subcutaneous tissue disorders | 2 (28.6) | 3 (42.9) | 5 (35.7) |
| General disorders and administration site conditions | 2 (28.6) | 1 (14.3) | 3 (21.4) |
| Injury, poisoning and procedural complications | 2 (28.6) | 1 (14.3) | 3 (21.4) |
| Musculoskeletal and connective tissue disorders | 3 (42.9) | 0 | 3 (21.4) |
| Infections and infestations | 0 | 2 (28.6) | 2 (14.3) |
| Investigations | 1 (14.3) | 1 (14.3) | 2 (14.3) |
| Cardiac disorders | 0 | 1 (14.3) | 1 (7.1) |
| Eye disorders | 0 | 1 (14.3) | 1 (7.1) |
| Metabolism and nutrition disorders | 0 | 1 (14.3) | 1 (7.1) |
| Renal and urinary disorders | 1 (14.3) | 0 | 1 (7.1) |
| Respiratory, thoracic and mediastinal disorders | 0 | 1 (14.3) | 1 (7.1) |

**10 Most Frequently Reported AEs Overall by Preferred Term n (%)**

**Adverse events, by preferred term, by treatment - Up-titration and fixed-dose treatment phase (Safety set)**

| Primary system organ class<br>Preferred term | Placebo<br>N = 7<br>n (%) | AFQ056<br>N = 7<br>n (%) | Total<br>N = 14<br>n (%) |
|---|---|---|---|
| Dyskinesia | 6 (85.7) | 4 (57.1) | 10 (71.4) |
| On and off phenomenon | 4 (57.1) | 0 | 4 (28.6) |
| Dizziness | 1 (14.3) | 2 (28.6) | 3 (21.4) |
| Nausea | 1 (14.3) | 2 (28.6) | 3 (21.4) |
| Edema peripheral | 2 (28.6) | 0 | 2 (14.3) |
| Euphoric mood | 0 | 2 (28.6) | 2 (14.3) |
| Headache | 1 (14.3) | 1 (14.3) | 2 (14.3) |
| Insomnia | 1 (14.3) | 1 (14.3) | 2 (14.3) |
| Somnolence | 2 (28.6) | 0 | 2 (14.3) |
| Vomiting | 0 | 2 (28.6) | 2 (14.3) |

**Serious Adverse Events and Deaths**

There were no deaths in this study. One patient in the placebo group experienced an SAE of deep brain stimulation (due to worsening of dyskinesias), which was not suspected by the investigator to be related to study drug.

**Other Relevant Findings**

None

**Date of Clinical Trial Report**

25-Jan-2012 (content final)

**Date Inclusion on Novartis Clinical Trial Results Database**

18 June 2012

**Date of Latest Update**

No updates