Sponsor

Novartis

Generic Drug Name

NA (not existing yet)

Therapeutic Area of Trial

Parkinson's Disease – L-dopa induced dyskinesia

Approved Indication

Investigational.

Study Number

CAFQ056A2206

Title

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

Phase of Development

Phase II

Study Start/End Dates

First patient screened: 24-Mar-2009

Last patient completed: 18-Aug-2009

Study Design/Methodology

This was a multi-center, randomized, double-blind, placebo-controlled, parallel-group, multiple oral dose titration study in Parkinson's patients with severe L-dopa-induced dyskinesias. Efficacy assessments were done using Abnormal Involuntary Movement Scale, Unified Parkinson Disease Rating Scale (part III and IV), Lang-Fahn Activities of Daily Living Dyskinesia Scale, Parkinson Disease Sleep Scale, Beck depression scale, and Computerized CANTAB battery of tests. A total of 28 patients were randomized using a central randomization process, and fourteen of the 28 patients were randomized to receive the active drug AFQ056 and the other fourteen patients received placebo. Each patient was administered multiple doses of AFQ056 or placebo over 20 days (Day 1 to Day 20) 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

Day 17 to 20: 50 mg bid (100 mg/day) or placebo

Centres

5 centers in Germany

Publication

None

Objectives

The primary objectives of the study were to assess the anti-dyskinetic efficacy and potential anti-parkinsonian effect of AFQ056 administration to Parkinson's patients with L-dopa induced dyskinesia. Additionally, the safety and tolerability of multiple titrated doses of AFQ056 in combination with L-dopa was assessed in this patient population.

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

Oral capsules of AFQ056 25 mg, 100 mg and matching placebo were administered by mouth twice a day

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

None

Criteria for Evaluation

Primary variables

- Change in the Abnormal Involuntary Movement Scale (AIMS) from baseline to day 16
- Change in the Unified Parkinson's Disease Rating Scale (UPDRS) – part III from baseline to day 16

Secondary variables

- Change in the Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS) and $UPDRS_{(32-33)}$ from baseline to day 16

Safety and tolerability

Frequency of adverse events, incidence of clinically notable laboratory abnormalities, particularly involving vital signs, pulmonary function tests, and ECG data.

Pharmacology

None

Other

After obtaining a separate consent covering the pharmacogenetic aspects of this study, on days -4, 8 and 16 a blood sample was collected from each subject who agreed to participate in pharmacogenetic evaluations for information on the intermediate product of gene expression.

Statistical Methods

Primary target variable to measure the anti-dyskinetic effect of AFQ056 was the AIMS sum score; key secondary target variable was the LFADLDS sum score. The anti-parkinsonian effect of AFQ056 in combination with L-dopa was assessed by the UPDRS part III sum score. 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%. In addition, the maximal change from baseline (among the treatment-days with LFADLDS/AIMS assessment) was also assessed. The analysis for day 16, corresponding to a dose of 150 mg bid, was considered the primary analysis. Descriptive statistics by treatment group and time point were used for sum scores of LFADLDS, AIMS, UPDRS part III, UPDRS part IV items 32-33, PDSS and BDI scales. All single items of all tests of the CANTAB battery were summarized descriptively by treatment group and time point.

Study Population: Inclusion/Exclusion Criteria and Demographics

Males and females, aged between 30 and 85 years of age (both inclusive), non-smokers, with idiopathic Parkinson's disease were enrolled into the study. Eligibility for the study was assessed from background, demographic and laboratory data at screening and/or baseline, and included relevant medical history, current medical conditions, date of birth, sex, race, height. Routine clinical chemistry, hematology and urinalysis screens were evaluated in addition to screens of substance abuse, hepatitis B and C, HIV (and a pregnancy test in female subjects).

Parkinson's specific inclusion criteria was related to the diagnosis of Parkinson's disease (diagnosed by UK Parkinson's disease Society Brain Bank criteria), an AIMS score of greater than or equal to 18, the L-dopa induced dyskinesia being greater than 20% (UPDRS item of 32, rating ≥1), of moderate to severe (complete disabling) intensity (UPDRS item 33 rating ≥ 2), and with dyskinesias for at least 3 months before randomization. Key exclusion criteria included smokers, with a prior surgery for Parkinson's Disease, with a Hoehn and Yahr score of 5 when 'off', with cognitive impairment (MMSE less than 24), with atypical Parkinson's disease (Progressive Supranuclear Palsy (PSP), Multi Systemic Atrophy (MSA)), with history or presence of psychosis and/or confusional states, with a history or presence of nephrolithiasis, renal impairment, and/or liver disease, who participated in an anti-dyskinetic clinical study within the 6 months before randomization, who are under deep brain stimulation, who received anti-dyskinetic medication (i.e. antipsychotics, amantadine) within 15 days before randomization and/or neuroleptics during 2 months before randomization.

Number of Subjects

	Novartis product	Comparator
Planned N	34	
Randomised n	28	
Intent-to-treat population (ITT) n (%)	28 (100%)	
Completed n (%)	28 (100%)	
Withdrawn n (%)	0	
Withdrawn due to adverse events n (%)	0	
Withdrawn due to lack of efficacy n (%)	0	
Withdrawn for other reasons n (%)	0	

Demographic and Background Characteristics

	Novartis product	Comparator
N (ITT)	28	
Females : males	11:17	
Mean age, years (SD)	65.8 (6.93)	
Mean weight, kg (SD)	70.95 (13.665)	
Race		

White n (%) Black n (%) Asian n (%) Other n (%)	28 (100%) 0 0 0	
Characteristics relevant to study population (eg, mean FEV1 % predicted [SD])	NA	

Primary Objective Result(s)

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

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
16	-9.75	-4.84	-4.91	(-8.61, -1.22)	0.032

Results from analysis of change from baseline in UPDRS part III sum score on day 16

Time of day	Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
Average	16	-6.09	-2.79	-3.30	(-8.39, 1.79)	0.279
Morning	16	-8.51	-5.18	-3.33	(-9.45, 2.79)	0.361
Afternoon	16	-3.79	-0.51	-3.26	(-8.22, 1.71)	0.273

Secondary Objective Result(s)

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

Day	Lsmean AFQ056	Lsmean Placebo	Mean difference (AFQ056-Placebo)	90% CI for mean difference	p-value
1	-0.26	0.76	-1.03	(-2.39, 0.33)	0.209
4	-1.95	-1.33	-0.62	(-1.79, 0.55)	0.373
8	-2.51	-1.49	-1.02	(-2.72, 0.69)	0.318
12	-3.49	-1.87	-1.62	(-3.56, 0.31)	0.165
16	-3.84	-2.30	-1.54	(-3.69, 0.61)	0.233

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	-0.32	-0.07	-0.24	(-0.76, 0.27)	0.425
4	-1.54	-0.92	-0.62	(-1.37, 0.13)	0.171
8	-1.81	-1.23	-0.58	(-1.29, 0.13)	0.173
12	-2.15	-1.17	-0.98	(-1.69, -0.27)	0.026
16	-2.56	-0.98	-1.58	(-2.32, -0.84)	0.001

Safety Results

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

	AFQ056 25 mg bid N=14 n(%)	AFQ056 50 mg bid N=13 n(%)	AFQ056 100 mg bid N=11 n(%)	AFQ056 125 mg bid N=1 n(%)	AFQ056 150 mg bid N=8 n(%)	Placebo N=14 n(%)
Patients with AE(s)	5 (35.7)	10 (76.9)	8 (72.7)	1 (100.0)	4 (50.0)	11 (78.6)
System organ class						
Psychiatric disorders	4 (28.6)	3 (23.1)	5 (45.5)	0 (0.0)	2 (25.0)	1 (7.1)
Nervous system disorders	2 (14.3)	5 (38.5)	2 (18.2)	0 (0.0)	1 (12.5)	4 (28.6)
Gastrointestinal disorders	3 (21.4)	2 (15.4)	2 (18.2)	0 (0.0)	1 (12.5)	4 (28.6)
General disorders and administration site conditions	2 (14.3)	2 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)
Eye disorders	1 (7.1)	2 (15.4)	1 (9.1)	0 (0.0)	1 (12.5)	1 (7.1)
Investigations	0 (0.0)	1 (7.7)	1 (9.1)	0 (0.0)	0 (0.0)	2 (14.3)
Musculoskeletal and connective tissue disorders	1 (7.1)	2 (15.4)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)
Ear and labyrinth disorders	1 (7.1)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	1 (7.1)
Infections and infestations	0 (0.0)	1 (7.7)	2 (18.2)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)	2 (25.0)	0 (0.0)
Skin and subcutaneous tissue disorders	2 (14.3)	0 (0.0)	1 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)
Vascular disorders	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)
Cardiac disorders	1 (7.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Adverse events overall and most frequent adverse events (at least 2 subjects in any single treatment group) – n (%) of subjects

	AFQ056												Placebo	
	25mg N=14		50mg N=13		100mg N=11		125mg N=1		150mg N=8		Total N=14		N=14	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients with AE(s)	5	(35.7)	10	(76.9)	8	(72.7)	1	(100)	4	(50.0)	13	(92.9)	11	(78.6)
Preferred term														
Dizziness	2	(14.3)	1	(7.7)	2	(18.2)	0	(0.0)	1	(12.5)	6	(42.9)	1	(7.1)
Fall	0	(0.0)	0	(0.0)	1	(9.1)	0	(0.0)	2	(25.0)	3	(21.4)	0	(0.0)
Nausea	1	(7.1)	0	(0.0)	2	(18.2)	0	(0.0)	0	(0.0)	3	(21.4)	0	(0.0)
Urinary tract infection	0	(0.0)	1	(7.7)	2	(18.2)	0	(0.0)	0	(0.0)	3	(21.4)	0	(0.0)
Visual impairment	1	(7.1)	1	(7.7)	0	(0.0)	0	(0.0)	1	(12.5)	3	(21.4)	0	(0.0)
Agitation	0	(0.0)	0	(0.0)	1	(9.1)	0	(0.0)	1	(12.5)	2	(14.3)	0	(0.0)
Confusional state	2	(14.3)	2	(15.4)	1	(9.1)	0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)
Diarrhoea	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	1	(12.5)	2	(14.3)	1	(7.1)
Disturbance in attention	0	(0.0)	1	(7.7)	1	(9.1)	0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)
Dyskinesia	0	(0.0)	2	(15.4)	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)	2	(14.3)
Fatigue	1	(7.1)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)	3	(21.4)
Headache	1	(7.1)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)
Muscle spasms	1	(7.1)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)
Psychotic disorder	1	(7.1)	1	(7.7)	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)
Sleep attacks	1	(7.1)	1	(7.7)	1	(9.1)	0	(0.0)	0	(0.0)	2	(14.3)	0	(0.0)
Toothache	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(14.3)

Serious Adverse Events and Deaths

2 increased/worsening dyskinesia, 1 worsening of PD, 1 psychotic disorder

Other Relevant Findings

None

Date of Clinical Trial Report Not yet final
Date Inclusion on Novartis Clinical Trial Results Database 14 Sept 2010
Date of Latest Update

January 16, 2008