Sponsor

Novartis Pharma AG

Generic Drug Name

AFQ056

Therapeutic Area of Trial

Parkinson's Disease with L-dopa induced dyskinesia

Approved Indication

Investigational

Protocol Number

CAFQ056A2207

Title

A multi-centre, randomized, double-blind, placebo-controlled, parallel-group, multiple oral dose titration Proof of Concept study in patients with Huntington's disease to assess the efficacy, safety and tolerability of AFQ056 in reducing chorea

Phase of Development

Phase II

Study Start/End Dates

11-Nov-2009 to 23 Aug 2011

Terminated early at interim analysis, primary endpoints not met. No safety issue.

Study Design/Methodology

This was an exploratory multi-center, randomized, double-blind, placebo-controlled, parallel-group, multiple oral dose titration Proof-of-Concept study in Huntington's disease (HD) patients in clinical stages I-III to assess the efficacy, safety and tolerability of AFQ056 in reducing chorea.

Following a screening period, each patient received multiple doses of AFQ056 or placebo over 32 days following the dose titration scheme of 12 days of up-titration, followed by maintenance on days 13 to 28 and 4 days of down titration. A follow-up period occurred after the down

titration.

The timing of the pharmacodynamic assessments had been selected to coincide with the titration and Pharmacokinetic (PK) of AFQ056 to allow assessment of the primary endpoints at that dose level.

The Unified Huntington's Disease Rating Scale (UHDRS) is considered the gold standard in assessing important aspects of the HD phenotype and in tracking the progression of HD. The Maximal Chorea score, a subsection of seven items of the UHDRS total motor score assessing severity of chorea in different body regions was used to rate the severity of involuntary choreatic movements, and was selected as one of the primary endpoints of the study. The other co-primary endpoint was the orientation index of the non-dominant hand, measured during the quantitative grip force task.

Centres

Total of 8 centers: Germany (5), United Kingdom (3)

Publication

None

Outcome measures

Primary outcome measures(s)

Efficacy of AFQ056 on the severity of chorea in Huntington's disease measured by Unified Huntington's Disease Rating Scale (UHDRS) Maximal Chorea score between Baseline and day 28

Efficacy of AFQ056 on the severity of chorea in Huntington's disease measured by the Orientation index during the quantitative grip force task (Quantitative motor assessment) from non-dominant hand between Baseline and day 28.

Secondary outcome measures(s)

Safety and tolerability of AFQ056 in Huntington's disease patients between first dose administration till study completion

Potential effect of AFQ056 on the motor, cognitive, behavioral and functional assessments using UHDRS between first dose administration till study completion

Potential effect of AFQ056 on functional and quality of life scales, neuropsychiatric assessments and cognitive assessments in Huntington's Disease patients from first dose administration till study completion

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

Oral administration
AFQ056 25 mg Capsules
AFQ056 100 mg Capsules
Placebo 25 mg, 100 mg Capsules

Statistical Methods

The primary analyses were based on the Maximal Chorea rating of the UHDRS motor component and the orientation index (non-dominant hand) at the end of the maintenance treatment phase on day 28 after the morning dose. The absolute changes from baseline were used as the outcome measures.

An analysis of covariance model was fitted to the change from baseline in maximal chorea rating including the respective baseline value as a continuous covariate and treatment as a categorical covariates. Within this model, the null hypothesis of no treatment difference was tested to the one-sided level 10%. Additionally for PoC criterion 2 the shifted null hypothesis investigating if 50% level of proof that the additional reduction due to AFQ056 was greater than 1.5 on maximal chorea scale was assessed.

An analysis of covariance model was fitted to the natural log transformed orientation index from the non-dominant hand, including the respective log transformed baseline value as a continuous covariate and treatment as a categorical covariate. Within this model, the null hypothesis of no treatment difference was tested to the one-sided level 10%.

Study Population: Inclusion/Exclusion Criteria and Demographics

All 42 patients enrolled were included in safety and PD analysis set. Only 21 patients exposed to AFQ056 treatment were included in PK analysis set.

Diagnosis and main criteria for inclusion

- Male and female patients between 30 and 85 years of age (both inclusive).
- Patients diagnosed with Huntington's Disease based on DNA testing (polyQ ≥36).

- Patients with a UHDRS maximal chorea score of >10.
- Patients treated with neuroleptics, antidepressants, and/or benzodiazepines are allowed to enter the study provided that they were on a stable regimen for at least 4 weeks prior to randomization.
- Female patients had to be without childbearing potential (post-menopausal or surgically sterilized).

Main criteria for exclusion

- Patients with marked cognitive impairment (MMSE score of less than 18).
- Patients with a presence of psychosis, confusional states and/or repeated hallucinations.
- Patients who participated in an anti-dyskinetic clinical study within 6 months prior to randomization, and/or in any clinical investigation within 4 weeks prior to randomization or longer if required by local regulations and any other limit on participation based on local regulations.

Participant Flow

	AFQ056 N=21 n (%)	Placebo N=21 n (%)	Total N=42 n (%)
Patients			
Completed	18 (85.7)	20 (95.2)	38 (90.5)
Discontinued	3 (14.3)	1 (4.8)	4 (9.5)
Main cause of discontinuation			
Adverse event(s)	2 (9.5)	1 (4.8)	3 (7.1)
Administrative reasons	1 (4.8)		

Baseline Characteristics

		AFQ056 N=21	Placebo N=21	Total N=42
Age (years)	Mean (SD)	56.6 (8.72)	53.8 (7.62)	55.2 (8.21)
	Median	57.0	54.0	55.0
	Range	40, 72	40, 66	40, 72
Gender- n (%)	Male	13 (61.9%)	15 (71.4%)	28 (66.7%)
	Female	8 (38.1%)	6 (28.6%)	14 (33.3%)
Race- n (%)	Caucasian	21 (100.0%)	21 (100.0%)	42 (100.0%)
Ethnicity- n (%)	Hispanic/Latino	2 (9.5%)	3 (14.3%)	5 (11.9%)
	Other	19 (90.5%)	18 (85.7%)	37 (88.1%)
Height (cm)	Mean (SD)	172.3 (8.54)	175.8 (8.06)	174.1 (8.39)
	Median	170.5	178.0	174.0
	Range	160, 189	156, 187	156, 189
Weight (kg)	Mean (SD)	67.10 (12.838)	73.35 (8.781)	70.22 (11.314)
	Median	67.50	73.90	71.15
	Range	47.1, 92.0	55.9, 86.4	47.1, 92.0
BMI (kg/m2)	Mean (SD)	22.470 (3.1888)	23.729 (2.4458)	23.099 (2.8782)
	Median	22.340	23.699	23.021
	Range	18.06, 30.39	19.34, 27.56	18.06, 30.39

BMI = body mass index

Outcome measures

Primary Outcome Result(s)

Change from baseline in maximal chorea scores, Day 28

LS-mean (one sided 90% CI)		Difference (one-sided 90% CI)	One sided p-value	
AFQ056 (N=18)	Placebo (N=19)	AFQ056-Placebo	diff of 0	diff of -1.5
-2.17 (-1.27)	-1.18 (-0.31)	-0.99 (0.27)	0.155	0.701

LSmean: Least squares mean.

N is the number of subjects used in the analysis for each treatment.

Change in Orientation index (non-dominant hand), Day 28

Geometric LSmean (90% CI)		Ratio (one-sided 90% CI)	
AFQ056 (N=17)	Placebo (N=20)	AFQ056 - Placebo	P-value
21.16 (24.27)	20.20 (22.92)	1.05 (1.26)	0.626

Secondary Outcome Result(s)

Change from baseline in total UHDRS motor score on Day 28

LSmean (90% CI)		Difference (90% CI)	
AFQ056 (N=18)	Placebo (N=20)	AFQ056 - Placebo	P-value
-3.56 (-6.47,-0.65)	-2.45 (-5.20,0.31)	-1.12 (-5.16,2.93)	0.644

LSmean: Least squares mean

N is the number of subjects used in the analysis for each treatment.

Data were analyzed using an ANCOVA model including treatment as a fixed effect and baseline as a covariate.

All other key secondary efficacy endpoints showed no difference between AFQ056 and placebo.

Safety Results

All patients were exposed to the treatments according to the randomization schedule.

Of the 42 patients enrolled in the study, a total of 38 patients completed the study. Three patients developed AEs which led individual study discontinuation and one patient discontinued the study due to administrative reason.

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

	AFQ056 N=21		Placebo N=21		Total N=42	
	n	(%)	n	(%)	n	(%)
Patients with AE(s)	14	(66.7)	12	(57.1)	26	(61.9)
System organ class						
Psychiatric disorders	8	(38.1)	1	(4.8)	9	(21.4)
Nervous system disorders	5	(23.8)	3	(14.3)	8	(19.0)
General disorders and administration site conditions	2	(9.5)	5	(23.8)	7	(16.7)
Injury, poisoning and procedural complications	2	(9.5)	2	(9.5)	4	(9.5)
Skin and subcutaneous tissue disorders	1	(4.8)	3	(14.3)	4	(9.5)
Infections and infestations	2	(9.5)	1	(4.8)	3	(7.1)
Investigations	1	(4.8)	2	(9.5)	3	(7.1)
Eye disorders	1	(4.8)	1	(4.8)	2	(4.8)
Gastrointestinal disorders	0	(0.0)	1	(4.8)	1	(2.4)
Renal and urinary disorders	1	(4.8)	0	(0.0)	1	(2.4)
Reproductive system and breast disorders	0	(0.0)	1	(4.8)	1	(2.4)
Vascular disorders	0	(0.0)	1	(4.8)	1	(2.4)

Based on the frequency, the most commonly reported individual AEs with AFQ056 treatment were insomnia (23.8%) and depression (9.5%). Other notable AEs reported with AFQ056 were fall (4.8%), and headache (9.5%).

Adverse Events by System Organ Class

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

	AFQ056 N=21		Placebo N=21		Total N=42	
	n	(%)	n	(%)	n	(%)
Patients with AE(s)	14	(66.7)	12	(57.1)	26	(61.9)
System organ class						
Psychiatric disorders	8	(38.1)	1	(4.8)	9	(21.4)
Nervous system disorders	5	(23.8)	3	(14.3)	8	(19.0)
General disorders and administration site conditions	2	(9.5)	5	(23.8)	7	(16.7)
Injury, poisoning and procedural complications	2	(9.5)	2	(9.5)	4	(9.5)
Skin and subcutaneous tissue disorders	1	(4.8)	3	(14.3)	4	(9.5)
Infections and infestations	2	(9.5)	1	(4.8)	3	(7.1)
Investigations	1	(4.8)	2	(9.5)	3	(7.1)
Eye disorders	1	(4.8)	1	(4.8)	2	(4.8)

Gastrointestinal disorders	0	(0.0)	1	(4.8)	1	(2.4)
Renal and urinary disorders	1	(4.8)	0	(0.0)	1	(2.4)
Reproductive system and breast disorders	0	(0.0)	1	(4.8)	1	(2.4)
Vascular disorders	0	(0.0)	1	(4.8)	1	(2.4)

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

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

	AFQ056 N=21		**Placebo N=21**		**Total N=42**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**
Patients with AE(s)	14	(66.7)	12	(57.1)	26	(61.9)
Preferred term						
Insomnia	5	(23.8)	0	(0.0)	5	(11.9)
Depression	2	(9.5)	0	(0.0)	2	(4.8)
Fall	1	(4.8)	1	(4.8)	2	(4.8)
Fatigue	0	(0.0)	2	(9.5)	2	(4.8)
Headache	2	(9.5)	0	(0.0)	2	(4.8)
Hyperhidrosis	0	(0.0)	2	(9.5)	2	(4.8)
Irritability	1	(4.8)	1	(4.8)	2	(4.8)
Pyrexia	1	(4.8)	1	(4.8)	2	(4.8)
Restlessness	1	(4.8)	1	(4.8)	2	(4.8)
Speech disorder	1	(4.8)	1	(4.8)	2	(4.8)
Vision blurred	1	(4.8)	1	(4.8)	2	(4.8)

Serious Adverse Events and Deaths

There were no deaths reported during this study.

There were 3 SAEs reported during the study. In the AFQ056 treatment group, there was one patient who experienced SAE and in the placebo treatment group, there were two patients with SAEs.

AFQ056 treatment: one patient developed Pyrexia on Day 30 which led to hospitalization.

Placebo treatment: One patient developed Restlessness /Gait disturbance /Hyperkinesia /Speech disorder on Day 7 which led to hospitalization which eventually led to individual study discontinuation and one patient developed Pyrexia/Cystitis on Day 26 which led to hospitalization.

Other Relevant Findings

There were two patients from the AFQ056 treatment group with other significant AEs that led

to study discontinuation.

One patient discontinued from the study due to alopecia which was not suspected to be related to AFQ056 by the investigator.

One patient discontinued from the study due to disorientation which was suspected to be related to AFQ056 by the investigator.

There were also no clinically significant abnormalities of hematological, clinical chemistry, urinalysis, ECG or vital sign data compromising the subjects' safety.

Trajectories of trough levels and levels at 2-hrs post-dose (peak) were in line with the dosing regimen, with increasing levels during the up-titration phase, constant trough and peak levels at steady-state and decline in plasma levels after dose reduction at the end of the treatment phase.

Date of Clinical Trial Report

04 July 2012

Date Inclusion on Novartis Clinical Trial Results Database

14 Aug 2012

Date of Latest Update

N/A