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Generic Drug Name
AFQ056A

Trial Indication(s)
Fragile X Syndrome

Protocol Number
CAFQ056A2204

Protocol Title
A multi-centre, randomized, double-blind, placebo-controlled, two-period, crossover, proof-of-concept study in male patients with Fragile X Syndrome to assess the efficacy, safety and tolerability of multiple oral doses of AFQ056

Clinical Trial Phase
Phase II

Study Start/End Dates
05-Jun-2008 to 16-Jan-2009

Reason for Termination
Not applicable

Study Design/Methodology
This study was performed in two parts. The first part was a multi-centre, randomized, double-blind, placebo-controlled, two treatment, two-period, crossover, proof-of-concept (PoC) study performed in patients with Fragile X Syndrome. Patients were randomized to one of two sequences: AFQ056 (Treatment A) in period 1 followed by placebo (Treatment B)

in period 2, or placebo in period 1 followed by AFQ056 in period 2. The treatment consisted of a flexible titration phase lasting 8 days (Day 1 to 8) followed by a phase at the highest titrated dose which lasted 12 days (Day 9 to 20) and by a down-titration phase which lasted 8 days (Day 21 to 28). AFQ056 dosing started at 50mg b.i.d, could be titrated to a dose as high as 150mg b.i.d. and then down-titrated to 50mg b.i.d.

In part 2 of the study, patients from part 1 were age-matched with healthy volunteers who received no treatment.

Centers

This study was conducted in one center in each of Switzerland, France and Italy

Objectives:

Primary objective(s)

- To assess the efficacy of multiple oral doses of AFQ056 in reducing the global score of the Aberrant Behavior Checklist – Community Edition (ABC-C) in FXS patients
- To assess the safety and tolerability of multiple titrated oral doses of AFQ056 in FXS patients

Secondary objective(s)

- To assess the efficacy of multiple oral doses of AFQ056 in reducing social withdrawal in Fragile X patients by using the Repetitive Behavior Scale (RBS), the Vineland Adaptive Behavior Scale (VABS) and the Social Responsiveness Scale (SRS)
- To assess the efficacy of multiple oral doses of AFQ056 on the global improvement of symptoms in Fragile X patients by using the Clinical Global Impression Scale (CGI) and the Visual Analogue Scale (VAS), which rates the changes in one target behavior chosen by the caregiver
- To assess the efficacy of multiple doses of AFQ056 in reducing cognitive deficits in Fragile X patients by using the KITAP test battery (attentional performance) and the Peabody Vocabulary Test Revised (receptive language)

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

AFQ056A capsules, 25 mg and 100 mg, taken orally

Statistical Methods

All data collected in this study were listed by sequence and subject. In addition, demographic data, plasma concentrations, pharmacokinetic parameters and safety data were summarized by treatment or by treatment and period using n, mean, SD, median and range or frequency tables as appropriate to the data.

A longitudinal mixed effects model was fitted to ABC-C total score which included fixed effect terms for period, day within period, treatment and day by treatment interaction, random effects for subject and subject by period interaction and the period baseline score as a continuous covariate. All random effects and the residual error were assumed to be independent. A sequence effect and/or a period*time interaction effect was included if necessary; needless effects were omitted if deemed appropriate. Within this model, the main contrasts of interest were AFQ056 vs placebo treatment effect (overall), and the day*treatment interaction effect on each post-baseline time point. Point estimates and confidence intervals were displayed for these contrasts. F tests were carried out testing the null hypothesis that the respective contrast was 0, and corresponding p-values were displayed. The primary analysis consisted of the test of no treatment difference in the primary variable at day 19/20, to the two-sided level 10%.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Male, non-smoking patients between 18 and 35 years of age (both inclusive).
- Patients with fmr1 full mutation (> 200 CGG repeats)
- Patients with a Clinical Global Impression Severity Score (CGI-S) of > 4 (moderately ill)
- Patients with a score of >20 in the ABC-C scale (at screening)
- Patients with a mental age of ≥ 48 months as measured by the Stanford-Binet test

Exclusion Criteria:

- Patients with DSM-IV diagnosis of schizophrenia, history and/or presence of psychosis, confusional states and/or repeated hallucinations
- Patients with a history of seizures in the past 5 years without any therapeutic treatment controlling the disorders

- Patients under stable anti-convulsant therapies that experienced seizures in the 2 years prior to randomization
- Patients with ECG abnormalities, autonomic dysfunctions, bronchospastic diseases, drug or atopic allergy
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs
- Patients using (or have used within four weeks before randomization) concomitant medications that are potent inhibitors of CYP3A4 (e.g., ketoconazole, ritonavir, etc.)

Participant Flow Table

Subject disposition – n (%) of subjects (Safety population)

Part		AFQ056 / Placebo N=16 n (%)	Placebo / AFQ056 N=14 n (%)	Total Patients N=30 n (%)	Healthy Volunteers N=21 n (%)
1	Completed	15 (94)	14 (100)	29 (97)	
	Discontinued	1 (6)	0	1 (3)	
	Main cause of discontinuation				
	Adverse event	1 (6)	0	0	
2	Completed	9 (100)	11 (100)	20 (100)	20 (95)
	Discontinued				1 (5)
	Main cause of discontinuation				
	Protocol deviation	0	0	0	1 (5)

Baseline Characteristics

Summary of demographic and baseline characteristics by treatment group for Parts 1 and 2 (safety population)

Part 1		AFQ056 / Placebo (N=16)	Placebo / AFQ056 (N=14)	Total patients (N=30)
Age (years)	Mean (SD)	25 (5.7)	26 (5.5)	26 (5.5)
	Range	18 - 34	19 - 36	18 - 36
Gender – n (%)	Male	16 (100%)	14 (100%)	30 (100%)
Race – n (%)	Caucasian	16 (100%)	14 (100%)	30 (100%)
Weight (kg)	Mean (SD)	76.0 (18.69)	85.1 (16.03)	80.2 (17.80)
	Range	50.0 - 117.8	63.5 - 111.0	50.0 - 117.8
Height (cm)	Mean (SD)	176 (6.9)	177 (8.1)	176 (7.3)
	Range	165 - 186	162 - 189	162 - 189
S-B Mental Age (months)	Mean (SD)	67 (9.9)	68 (12.5)	67 (11.0)
	Range	51 - 81	54 - 96	51 - 96
CGG repeats	Mean (SD)	641 (308.5)	766 (287.0)	699 (300.4)
	Range	260 - 1000	330 - 1000	260 - 1000

Part 2		Total patients (N=20)	Healthy volunteers (N=20)
Age (years)	Mean (SD)	26 (5.6)	25 (5.1)
	Range	18 - 36	19 - 34
Gender – n (%)	Male	20 (100%)	20 (100%)
Race – n (%)	Caucasian	20 (100%)	20 (100%)
Weight (kg)	Mean (SD)	76.6 (18.33)	79.9 (14.67)
	Range	50.0 - 117.8	61.4 - 120.0
Height (cm)	Mean (SD)	176 (7.8)	180 (7.0)
	Range	162 - 189	169 - 195

Part 1		AFQ056 / Placebo (N=16)	Placebo / AFQ056 (N=14)	Total patients (N=30)
S-B Mental Age	Mean (SD)	68 (11.1)		
(months)	Range	53 - 96		
CGG repeats	Mean (SD)	689 (325.2)		
	Range	260 - 1000		

Summary of Efficacy

Primary Outcome Result(s)

Summary of the statistical analysis of ABC-C total score and subscores on day 19 (Efficacy population – Part 1)

Day	Efficacy Variable	Treatment Difference* AFQ056 versus placebo	Lower 90% CI	Upper 90% CI	P-value
19	Total of subscales	-2.10	-8.26	4.06	0.573
	Total of subscale I (Irritability)	-0.88	-2.63	0.87	0.404
	Total of subscale II (Lethargy)	1.17	-1.19	3.54	0.411
	Total of subscale III (Stereotypy)	-0.30	-1.48	0.88	0.671
	Total of subscale IV (Hyperactivity)	-1.52	-3.42	0.38	0.188
	Total of subscale V (Inappropriate speech)	-0.53	-1.66	0.59	0.431

* Adjusted for baseline covariate. A decrease in ABC-C scores indicates an improvement

Secondary Outcome Result(s)

Summary of the statistical analysis of ABC-C total score and subscores on day 28 (Efficacy population – Part 1)

Day	Efficacy Variable	Treatment Difference* AFQ056 versus placebo	Lower 90% CI	Upper 90% CI	P-value
28	Total of subscales	-5.25	-11.41	0.91	0.160
	Total of subscale I (Irritability)	-2.53	-4.28	-0.78	0.019
	Total of subscale II (Lethargy)	0.23	-2.13	2.59	0.872
	Total of subscale III (Stereotypy)	-1.10	-2.28	0.09	0.127
	Total of subscale IV (Hyperactivity)	-1.37	-3.27	0.54	0.236
	Total of subscale V (Inappropriate speech)	-0.45	-1.57	0.67	0.508

* Adjusted for baseline covariate. A decrease in ABC-C scores indicates an improvement

ABC-C results by FMR1 methylation status (reclassified)

Study population	Day	Efficacy variable	Treatment difference*	Lower 90% CI	Upper 90% CI	*P* value**
Patients with full methylation (determined by MSP and sequencing) (n=7)	19	Total of subscales	-27.82	-39.05	-16.59	<0.001
		Subscale I (Irritability)	-2.66	-5.37	0.05	0.106
		Subscale II (Lethargy)	-5.53	-10.87	-0.18	0.090
		Subscale III (Stereotype)	-5.06	-8.66	-1.46	0.027
		Subscale IV (Hyperactivity)	-8.55	-12.27	-4.84	<0.001
		Subscale V (Inappropriate Speech)	-4.31	-6.26	-2.36	0.001

Patients with partial methylation (determined by MSP and sequencing) (n=18)	19	Total of subscales	3.10	-5.61	11.82	0.554
		Subscale I (Irritability)	-1.15	-3.45	1.16	0.410
		Subscale II (Lethargy)	2.66	-0.81	6.13	0.206
		Subscale III (Stereotype)	0.78	-0.70	2.25	0.383
		Subscale IV (Hyperactivity)	-0.21	-2.85	2.43	0.894
		Subscale V (Inappropriate Speech)	0.81	-0.80	2.41	0.403

*AFQ056 versus placebo. Adjusted for baseline values.
**Mixed model.
A decrease in ABC-C scores indicates an improvement.

CGI results by FMR1 methylation status (reclassified)

Study population	Day	Efficacy variable	Treatment difference*	Lower 90% CI	Upper 90% CI	*P* value**
Patients with full methylation (by MSP and sequencing) (n=7)	19	CGI-global improvement	-1.78	-2.34	-1.22	<0.001
		CGI-efficacy index	1.76	1.13	2.39	<0.001
Patients with partial methylation (by MSP and sequencing) (n=18)	19	CGI-global improvement	0.58	0.04	1.11	0.079
		CGI-efficacy index	-0.43	-0.96	0.11	0.193

*AFQ056 versus placebo. Adjusted for baseline values.
**Mixed model.
A decrease in CGI-global improvement indicates an improvement.
An increase in CGI-efficacy index indicates an improvement.

Additional secondary endpoints by FMR1 methylation status (reclassified)

Endpoint	Study population	Day	Efficacy variable	Treatment difference*	Lower 90% CI	Upper 90% CI	*P* value**
RBS	Patients with full methylation (determined by MSP and sequencing) (n=7)	19	Sum	-9.81	-16.57	-3.05	0.038
			Stereotyped	-4.13	-6.47	-1.79	0.017
			Self-Injurious	-0.60	-1.62	0.43	0.323
			Compulsive	-1.27	-2.88	0.35	0.165
			Ritualistic	-1.92	-4.12	0.28	0.135
			Sameness	-1.30	-3.05	0.46	0.208
			Restricted	-1.32	-2.17	-0.48	0.016
	Patients with partial methylation (determined by MSP and sequencing) (n=18)	19	Sum	-0.81	-5.06	3.43	0.747
			Stereotyped	-0.31	-1.24	0.62	0.573
			Self-Injurious	-0.30	-0.94	0.34	0.429
			Compulsive	-0.35	-1.31	0.60	0.540
			Ritualistic	0.162	-0.84	1.16	0.786
			Sameness	0.09	-1.86	2.05	0.937
			Restricted	-0.36	-0.96	0.24	0.316
SRS	Patients with full methylation (determined by MSP and sequencing) (n=7)	19	Total	-17.91	-30.04	-5.77	0.031
	Patients with partial methylation (determined by MSP and sequencing) (n=18)	19	Total	3.22	-6.54	12.99	0.582

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VAS	Patients with full methylation (determined by MSP and sequencing) (n=7)	19	Score	31.84	14.01	49.67	0.006
	Patients with partial methylation (determined by MSP and sequencing) (n=18)	19	Score	-4.15	-16.73	8.44	0.584
Vineland	Patients with full methylation (determined by MSP and sequencing) (n=7)	19	Total	2.02	-16.84	20.88	0.769
	Patients with partial methylation (determined by MSP and sequencing) (n=18)	19	Total	2.03	-1.52	5.58	0.333

*AFQ056 versus placebo. Adjusted for baseline values.
**Mixed model.
A decrease in RBS indicates an improvement
A decrease in SRS indicates an improvement
An increase in VAS indicates an improvement
An increase in Vineland indicates an improvement

Summary of peabody picture vocabulary test - revised (PPVT-R)
PD analysis set - Part I

Treatment		Period 1 Baseline	Period 1 Day 19/20	Period 2 Baseline	Period 2 Day 19/20	Period 2 EOS
AFQ056	n	16	16	14	14	14
	mean	101.9	99.8	97.9	90.6	93.1
	SD	18.30	19.73	25.49	30.48	22.63
	minimum	66	66	55	9	56
	median	97.5	95.5	94.5	94.0	90.5
	maximum	133	140	143	126	139
Placebo	n	14	14	16	15	16
	mean	96.2	98.4	99.1	103.5	103.8
	SD	33.42	22.45	21.15	19.82	19.14
	minimum	45	51	65	68	68
	median	108.5	104.0	96.0	106.0	101.0
	maximum	135	140	147	137	137

Summary of Safety

Safety Results

Adverse events overall and most frequent events - n (%) of patients (at least 2 subjects in any treatment group) (Safety population)

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Study drug	AFQ056 (N=30)			Placebo (N=30)		
Titration phase	Up	High dose	Down	Up	High dose	Down
Days	1-8	9-20	21-28	1-8	9-20	21-28
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients with AE(s)	9 (30.0)	14 (46.7)	9 (30.0)	9 (30.0)	6 (20.0)	7 (23.3)
Preferred term						
Fatigue	4 (13.3)	3 (10.0)	0	4 (13.3)	0	1 (3.3)
Temperature intolerance	1 (3.3)	1 (3.3)	1 (3.3)	0	0	1 (3.3)
Headache	2 (6.7)	1 (3.3)	1 (3.3)	0	0	0
Affect lability	1 (3.3)	1 (3.3)	0	0	1 (3.3)	1 (3.3)
Diarrhoea	1 (3.3)	0	1 (3.3)	0	1 (3.3)	0
Emotional distress	0	1 (3.3)	0	1 (3.3)	1 (3.3)	0
Oral herpes	0	1 (3.3)	1 (3.3)	0	0	0
Pancreatic enzymes increased	0	1 (3.3)	1 (3.3)	0	0	0
Food craving	0	1 (3.3)	1 (3.3)	0	0	0

Arranged by frequency in AFQ056 group

Serious Adverse Events and Deaths

Serious Adverse Events (Safety set)

	AFQ056/Placebo (N=16)	Placebo/AFQ056 (N=14)	Total Patients (N=30)
Respiratory, thoracic and mediastinal disorders			
Pneumothorax	1	0	1

No patients died during the study.

Date of Clinical Trial Report

02-Feb-2010