Sponsor

Novartis

Generic Drug Name

AFQ056 / mavoglurant

Trial Indication(s)

Fragile X syndrome (FXS)

Protocol Number

CAFQ056A2212

Protocol Title

A randomized, double-blind, placebo-controlled, parallel group study to evaluate AFQ056 in adult patients with Fragile X Syndrome

Clinical Trial Phase

Phase IIb

Phase of Drug Development

Phase II

Study Start/End Dates

12-Nov-2010 to 14-Aug-2013

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a multi-center, randomized, double-blind, placebo-controlled, parallel group study designed to assess the safety and efficacy of three doses of AFQ056 compared to placebo in adult patients with FXS. The study included a 4-week, single-blind placebo run-in period, during which patients and their caregivers were unaware that the patient was receiving treatment with placebo; the investigator and site personnel were unblinded to treatment status during this period. After successfully completing the Placebo Run-in period, eligible patients entered the 12-week double-blind treatment period, where they were randomly assigned to 25 mg bid AFQ056, 50 mg bid AFQ056, 100 mg bid AFQ056, or placebo treatment groups in a ratio of 1:1:1:1. The patients were divided into two strata depending on methylation status of their Fragile X Mental Retardation 1 (FMR1) gene; fully methylated (FM) and partially methylated (PM).

During the double-blind treatment period, all patients were titrated up to the target dose for their assigned treatment group. For patients assigned to the active treatment groups, the starting dose was 25 mg bid and, based on their assigned treatment group, patients either remained on 25 mg bid of AFQ056 or were titrated to 50 mg bid or 100 mg bid AFQ056 at weekly intervals. After reaching the target dose, dose changes were not permitted and patients were discontinued from the study if the assigned dose was not tolerated.

Centers

31 centers in the following 10 countries: Australia (3 centers), Canada (2 centers), Denmark (1 center), France (2 centers), Germany (4 centers), Italy (2 centers), Spain (2 centers), Switzerland (2 centers), United Kingdom (1 center), United States (12 centers)

Publication

None

Objectives:

Primary objective

The primary objective was to assess the efficacy of three doses of AFQ056 versus placebo in reducing the Aberrant Behavior Checklist – Community edition (ABC-C) Total score (using the FXS specific algorithm - ABC-C_{FX}) after 12 weeks of treatment in FXS patients with fully-methylated FMR1 gene (FM stratum).

Secondary objective(s)

The key secondary objective was to assess the efficacy of three doses of AFQ056 versus placebo in reducing the ABC-C_{FX} Total score after 12 weeks of treatment in FXS patients with partially-methylated FMR1 gene (PM stratum).

The other secondary objectives (applied to both FM and PM strata) were:

- To assess the safety and tolerability of AFQ056 after 12 weeks of treatment.
- To assess the efficacy of three doses of AFQ056 versus placebo on the global improvement of symptoms in Fragile X patients using the Clinical Global Impression - Improvement (CGI-I) scale after 12 weeks of treatment.
- To assess the efficacy of AFQ056 versus placebo in reducing irritability, lethargy/withdrawal, stereotypic behavior, hyperactivity, inappropriate speech and social avoidance assessed by the corresponding individual subscales of the ABC-C_{FX} after 12 weeks of treatment.
- To assess the efficacy of AFQ056 versus placebo with respect to the proportion of patients with clinical response, where response is defined as reduction of at least 25% from baseline in the ABC-C_{FX} total score and a score of 1 (very much improved) or 2 (much improved) on the CGI-I scale at Week 12.
- To assess the efficacy of AFQ056 versus placebo on the improvement of repetitive behavior as measured by changes in the Repetitive Behavior Scale – Revised (RBS-R) total and subscale scores after 12 weeks of treatment.
- To collect pharmacokinetic data of AFQ056 in the target patient population.

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

The investigational drug, AFQ056, was provided as hard gelatin capsules. The following oral dosage strengths, identical in appearance, were used: 25 mg and 100 mg.

After completing the Placebo Run-in period, eligible patients were randomized to one of the following four treatment arms in a ratio of 1:1:1:1.

- 25 mg bid AFQ056 (1 capsule of 25 mg and 1 capsule of placebo per intake)
- 50 mg bid AFQ056 (2 capsules of 25 mg per intake)

- 100 mg bid AFQ056 (1 capsule of 100 mg and 1 capsule of placebo per intake)
- placebo bid (2 capsules of placebo per intake)

Patients received 2 bottles of medication for each intended dosing period. Patients took one capsule from each bottle in the morning and one capsule from each bottle in the evening, i.e. two capsules in the morning and two capsules in the evening.

Reference therapy: Placebo medication was identical in appearance to active medication.

Statistical Methods

The Full Analysis Set (FAS) consisted of all randomized patients who received at least one dose of study drug and had a baseline and at least one post-baseline assessment for the primary efficacy parameter. Following the intent-to-treat (ITT) principle, patients were analyzed according to the treatment they were assigned to at randomization, irrespective of compliance or any deviations from the study protocol. No data was excluded from the FAS analyses because of protocol deviations.

The Safety Set consisted of all patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to treatment received.

The Randomized Analysis Set**,** which consisted of all randomized patients, was used for summaries of patient disposition, demographics and other baseline characteristics.

The primary and key secondary analyses on change from baseline in ABC-C_{FX} total score were based on a mixed-effect model for repeated measures (MMRM) including region, treatment (3 AFQ056 dose groups vs. placebo), week, treatment by week interaction as fixed effects and baseline ABC-C_{FX} total score as covariate, with an unstructured covariance structure. From the model, the contrast between each AFQ056 dose vs. placebo after 12 weeks of treatment was estimated and presented together with a two-sided 95% confidence interval and p-value.

To control the overall type I error rate, a multiplicity adjustment was applied to the primary and the key secondary analysis. As a consequence of this adjustment, comparisons between each of the AFQ056 doses and placebo have to be significant on a level smaller than the ordinal significant level of 0.05. Such an adjustment is required by regulation and was agreed with Health Authorities.

All secondary efficacy analyses were performed separately based on FAS in both FM and PM strata and overall. Comparisons were made between each AFQ056 dose group and placebo at the two-sided 5% type I error rate with no adjustment for multiplicity.

The assessment of safety was based primarily on the frequency of adverse events, serious adverse events, and laboratory abnormalities. Other safety data were summarized as appropriate.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- 18 and 45 years of age, inclusive
- males and females; females had to be following an acceptable method of birth control according to the protocol
- Previous diagnosis of FXS. The diagnosis needed to be confirmed by genetic testing prior to the patient entering the Placebo Run-in Period
- a Clinical Global Impression Severity Score (CGI-S) of ≥ 4 (moderately ill)
- a score of > 20 in the ABC-C total scale
- a documented Intelligence Quotient (IQ) score lower than two standard deviations below the IQ test median
- a caregiver or caregivers who spent, on average, at least six hours per day with the patient, who were willing and capable of supervising treatment, providing input into efficacy and safety assessments, and accompanying the patient to all study visits

Exclusion criteria

- Advanced, severe or unstable disease that may interfere with the study outcome evaluations
- Cancer within the past 5 years, other than localized skin cancer
- Current treatment with more than two psychoactive medications, excluding anti-epileptics
- History of severe self-injurious behavior

Participant Flow Tables

Patient disposition — Screening and single-blind (SB) placebo run-in period (Screened patients)

	Total n (%)
Total screened patients [a]	343 (100.0)
Screened patients not entering SB placebo run-in	159 (46.4)
Patients rescreened under new patient ID and failed rescreening	3 (0.9)
Patients rescreened under new patient ID and entered SB placebo run-in	7 (2.0)
Primary reason(s) for not continuing [b]	
Unacceptable past medical history / concomitant diagnosis	1 (0.3)
Intercurrent medical event	1 (0.3)
Unacceptable laboratory value(s)	17 (5.0)
Unacceptable test procedure result(s)	3 (0.9)
Did not meet diagnostic / severity criteria	18 (5.2)
Unacceptable use of excluded medications / therapies	7 (2.0)
Subject withdrew consent	4 (1.2)
Other	121 (35.3)
Entered SB placebo run-in	184 (53.6)
Completed SB placebo run-in	175 (51.0)
Discontinued SB placebo run-in	9 (2.6)
Patients rescreened under new patient ID and failed rescreening	0
Patients rescreened under new patient ID and completed SB placebo run-in	3 (0.9)

	Total n (%)
Primary reason for premature discontinuation [c]	
Adverse Event(s)	2 (1.1)
Protocol deviation	4 (2.2)
Subject withdrew consent	3 (1.6)

One patient was entered into the SB placebo run-in period in error and did not receive any SB study medication therefore this patient is not included in the enrolled patient analysis set.

[a] Unless noted otherwise, percentage (%) is calculated based on the total number of screened patients.

[b] Other includes patients who were screening failures due to methylation stratum capping.

[c] Percentage (%) is calculated based on the number of patients entered in SB placebo run-in period.

Patient disposition – Double-blind treatment period, by methylation status and treatment (Randomized set)

Stratum: All patients

	Placebo N=44 n (%)	AFQ056 25 mg bid N=44 n (%)	AFQ056 50 mg bid N=42 n (%)	AFQ056 100 mg bid N=45 n (%)
Completed	43 (97.7)	40 (90.9)	40 (95.2)	39 (86.7)
Discontinued	1 (2.3)	4 (9.1)	2 (4.8)	6 (13.3)
Primary reason for premature discontinuation				
Administrative problems	0	1 (2.3)	0	0
Adverse event(s)	1 (2.3)	2 (4.5)	2 (4.8)	6 (13.3)
Subject withdrew consent	0	1 (2.3)	0	0

Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Completed	20 (100.0)	19 (86.4)	19 (95.0)	18 (90.0)
Discontinued	0	3 (13.6)	1 (5.0)	2 (10.0)
Primary reason for premature discontinuation				
Adverse event(s)	0	2 (9.1)	1 (5.0)	2 (10.0)
Subject withdrew consent	0	1 (4.5)	0	0

Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

	Placebo N=24 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=22 n (%)	AFQ056 100 mg bid N=25 n (%)
Completed	23 (95.8)	21 (95.5)	21 (95.5)	21 (84.0)
Discontinued	1 (4.2)	1 (4.5)	1 (4.5)	4 (16.0)
Primary reason for premature discontinuation				
Administrative problems	0	1 (4.5)	0	0
Adverse event(s)	1 (4.2)	0	1 (4.5)	4 (16.0)

Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum

Baseline Characteristics

Demographics, by methylation status and treatment (Randomized set)

Stratum: All patients

Demographic variable	Placebo N=44	AFQ056 25 mg bid N=44	AFQ056 50 mg bid N=42	AFQ056 100 mg bid N=45
Age (years)				
n	44	44	42	45
Mean (SD)	26.2 (7.21)	26.9 (6.76)	26.7 (6.90)	24.2 (6.07)
Median	25.0	26.5	25.0	23.0
Range	18 to 43	18 to 40	18 to 44	18 to 36
Sex, n(%)				
Female	3 (6.8)	3 (6.8)	2 (4.8)	3 (6.7)
Male	41 (93.2)	41 (93.2)	40 (95.2)	42 (93.3)
Race, n(%)				
Caucasian	43 (97.7)	41 (93.2)	40 (95.2)	44 (97.8)
Black	0	0	2 (4.8)	1 (2.2)
Other	1 (2.3)	3 (6.8)	0	0
Ethnicity, n(%)				
Hispanic/Latino	2 (4.5)	2 (4.5)	2 (4.8)	1 (2.2)
Indian (Indian subcontinent)	0	1 (2.3)	0	0
Mixed Ethnicity	2 (4.5)	3 (6.8)	0	0
Other	40 (90.9)	38 (86.4)	40 (95.2)	44 (97.8)
Region, n(%)				
Non-European region	25 (56.8)	30 (68.2)	21 (50.0)	25 (55.6)
European region	19 (43.2)	14 (31.8)	21 (50.0)	20 (44.4)
Baseline weight (kg)				
n	44	44	42	45
Mean (SD)	78.37 (18.629)	83.39 (15.990)	83.47 (14.149)	77.35 (19.443)
Median	73.60	82.05	83.15	72.30
Range	45.0 to 141.0	59.7 to 125.0	60.0 to 121.4	42.7 to 128.7

Demographic variable	Placebo N=44	AFQ056 25 mg bid N=44	AFQ056 50 mg bid N=42	AFQ056 100 mg bid N=45
Baseline height (cm)				
n	44	44	41	45
Mean (SD)	174.3 (8.69)	173.2 (8.88)	176.4 (5.89)	175.2 (7.58)
Median	174.0	175.0	176.8	175.0
Range	152 to 195	142 to 190	165 to 190	151 to 192

N: Number of patients in the Randomized set within the specified stratum.
n: Number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Non-European region includes United States, Canada, and Australia. European region includes Italy, Switzerland, Denmark, France, Germany, Spain and United Kingdom.
Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Demographic variable	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Age (years)				
n	20	22	20	20
Mean (SD)	25.4 (6.68)	24.7 (5.01)	25.3 (6.27)	24.6 (6.18)
Median	24.5	24.5	24.0	23.0
Range	18 to 42	18 to 38	18 to 37	18 to 36
Sex, n(%)				
Male	20 (100.0)	22 (100.0)	20 (100.0)	20 (100.0)
Race, n(%)				
Caucasian	20 (100.0)	21 (95.5)	20 (100.0)	20 (100.0)
Other	0	1 (4.5)	0	0
Ethnicity, n(%)				
Hispanic/Latino	0	1 (4.5)	0	0
Indian (Indian subcontinent)	0	1 (4.5)	0	0
Mixed Ethnicity	2 (10.0)	0	0	0
Other	18 (90.0)	20 (90.9)	20 (100.0)	20 (100.0)

Demographic variable	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Region, n(%)				
Non-European region	9 (45.0)	14 (63.6)	12 (60.0)	11 (55.0)
European region	11 (55.0)	8 (36.4)	8 (40.0)	9 (45.0)
Baseline weight (kg)				
n	20	22	20	20
Mean (SD)	82.53 (14.838)	78.94 (15.257)	81.89 (14.568)	80.57 (22.383)
Median	84.25	73.90	79.45	71.80
Range	59.5 to 120.4	59.7 to 110.9	60.0 to 116.2	49.7 to 128.7
Baseline height (cm)				
n	20	22	19	20
Mean (SD)	176.7 (8.10)	175.2 (6.83)	175.9 (5.60)	175.5 (6.50)
Median	174.3	176.5	174.0	175.0
Range	166 to 195	162 to 188	167 to 190	163 to 186

N: Number of patients in the Randomized set within the specified stratum.
n: Number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Non-European region includes United States, Canada, and Australia. European region includes Italy, Switzerland, Denmark, France, Germany, Spain and United Kingdom.
Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Demographic variable	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Age (years)				
n	24	22	22	25
Mean (SD)	26.9 (7.71)	29.1 (7.63)	28.0 (7.33)	23.8 (6.08)
Median	25.5	30.0	29.0	22.0
Range	18 to 43	18 to 40	18 to 44	18 to 36

Demographic variable	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Sex, n(%)				
Female	3 (12.5)	3 (13.6)	2 (9.1)	3 (12.0)
Male	21 (87.5)	19 (86.4)	20 (90.9)	22 (88.0)
Race, n(%)				
Caucasian	23 (95.8)	20 (90.9)	20 (90.9)	24 (96.0)
Black	0	0	2 (9.1)	1 (4.0)
Other	1 (4.2)	2 (9.1)	0	0
Ethnicity, n(%)				
Hispanic/Latino	2 (8.3)	1 (4.5)	2 (9.1)	1 (4.0)
Mixed Ethnicity	0	3 (13.6)	0	0
Other	22 (91.7)	18 (81.8)	20 (90.9)	24 (96.0)
Region, n(%)				
Non-European region	16 (66.7)	16 (72.7)	9 (40.9)	14 (56.0)
European region	8 (33.3)	6 (27.3)	13 (59.1)	11 (44.0)
Baseline weight (kg)				
n	24	22	22	25
Mean (SD)	74.91 (20.963)	87.85 (15.787)	84.90 (13.939)	74.77 (16.759)
Median	68.25	89.30	86.65	74.00
Range	45.0 to 141.0	62.5 to 125.0	62.2 to 121.4	42.7 to 107.8
Baseline height (cm)				
n	24	22	22	25
Mean (SD)	172.2 (8.81)	171.2 (10.31)	176.9 (6.23)	174.9 (8.47)
Median	172.0	173.0	177.0	175.0
Range	152 to 190	142 to 190	165 to 186	151 to 192

N: Number of patients in the Randomized set within the specified stratum.
n: Number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Non-European region includes United States, Canada, and Australia. European region includes Italy, Switzerland, Denmark, France, Germany, Spain and United Kingdom.
Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.

Baseline characteristics, by methylation status and treatment (Randomized set)

Stratum: All patients

Baseline characteristic	Placebo N=44	AFQ056 25 mg bid N=44	AFQ056 50 mg bid N=42	AFQ056 100 mg bid N=45
Baseline ABC-C_{FX} total score [a]				
n	44	44	42	45
Mean (SD)	44.6 (25.85)	40.9 (23.44)	48.4 (29.11)	38.3 (23.04)
Median	40.0	32.5	41.5	35.0
Range	11 to 139	7 to 115	5 to 121	4 to 118
Baseline ABC-C total score [b]				
n	44	44	42	45
Mean (SD)	46.5 (27.14)	42.6 (24.32)	50.6 (30.05)	40.0 (23.98)
Median	40.5	34.0	44.5	36.0
Range	12 to 145	8 to 119	5 to 128	5 to 120
Baseline CGI-S score, n (%)				
3 (Mildly ill)	0	1 (2.3)	0	1 (2.2)
4 (Moderately ill)	14 (31.8)	17 (38.6)	18 (42.9)	18 (40.0)
5 (Markedly ill)	18 (40.9)	20 (45.5)	15 (35.7)	19 (42.2)
6 (Severely ill)	11 (25.0)	6 (13.6)	8 (19.0)	6 (13.3)
7 (Among the most extremely ill patients)	1 (2.3)	0	1 (2.4)	1 (2.2)
Patient IQ score in percentiles [c]				
n	44	44	42	45
Mean (SD)	0.06 (0.156)	0.03 (0.075)	0.09 (0.193)	0.11 (0.307)
Median	0.01	0.01	0.01	0.01
Range	0.0 to 0.8	0.0 to 0.5	0.0 to 0.8	0.0 to 1.6

N: Number of patients in the Randomized set within the specified stratum.
n: Number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.
[a] Based on the 55 item scale.
[b] Based on the full 58 item scale.
[c] Percentile was calculated using a standard normal distribution.

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Baseline characteristic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Baseline ABC-C_{FX} total score [a]				
n	20	22	20	20
Mean (SD)	43.8 (22.76)	42.6 (24.30)	53.2 (32.53)	41.0 (24.74)
Median	40.5	33.5	49.5	34.5
Range	11 to 95	14 to 115	5 to 119	8 to 91
Baseline ABC-C total score [b]				
n	20	22	20	20
Mean (SD)	45.7 (23.81)	44.5 (25.01)	55.4 (33.31)	42.8 (26.16)
Median	41.0	35.0	53.5	36.0
Range	12 to 98	15 to 119	5 to 121	9 to 100
Baseline CGI-S score, n (%)				
3 (Mildly ill)	0	0	0	1 (5.0)
4 (Moderately ill)	6 (30.0)	7 (31.8)	7 (35.0)	6 (30.0)
5 (Markedly ill)	9 (45.0)	12 (54.5)	8 (40.0)	9 (45.0)
6 (Severely ill)	4 (20.0)	3 (13.6)	4 (20.0)	4 (20.0)
7 (Among the most extremely ill patients)	1 (5.0)	0	1 (5.0)	0
Patient IQ score in percentiles [c]				
n	20	22	20	20
Mean (SD)	0.08 (0.143)	0.05 (0.102)	0.08 (0.157)	0.06 (0.122)
Median	0.01	0.01	0.01	0.01
Range	0.0 to 0.5	0.0 to 0.5	0.0 to 0.5	0.0 to 0.5

N: Number of patients in the Randomized set within the specified stratum.
n: Number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.
[a] Based on the 55 item scale.
[b] Based on the full 58 item scale.
[c] Percentile was calculated using a standard normal distribution.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Baseline characteristic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Baseline ABC-C_{FX} total score [a]				
n	24	22	22	25
Mean (SD)	45.2 (28.64)	39.2 (22.98)	44.0 (25.60)	36.1 (21.87)
Median	38.0	30.5	36.0	36.0
Range	19 to 139	7 to 76	8 to 121	4 to 118
Baseline ABC-C total score [b]				
n	24	22	22	25
Mean (SD)	47.2 (30.13)	40.8 (24.05)	46.2 (26.79)	37.8 (22.40)
Median	39.0	32.0	39.0	38.0
Range	21 to 145	8 to 78	8 to 128	5 to 120
Baseline CGI-S score, n (%)				
3 (Mildly ill)	0	1 (4.5)	0	0
4 (Moderately ill)	8 (33.3)	10 (45.5)	11 (50.0)	12 (48.0)
5 (Markedly ill)	9 (37.5)	8 (36.4)	7 (31.8)	10 (40.0)
6 (Severely ill)	7 (29.2)	3 (13.6)	4 (18.2)	2 (8.0)
7 (Among the most extremely ill patients)	0	0	0	1 (4.0)
Patient IQ score in percentiles [c]				
n	24	22	22	25
Mean (SD)	0.05 (0.168)	0.02 (0.028)	0.11 (0.225)	0.15 (0.395)
Median	0.01	0.01	0.02	0.01
Range	0.0 to 0.8	0.0 to 0.1	0.0 to 0.8	0.0 to 1.6

N: Number of patients in the Randomized set within the specified stratum.
n: Number of patients meeting the criterion (for categorical variables); number of patients with non-missing assessment (for continuous variables).
Percentage (%) is calculated based on the patients in the Randomized set within the specified stratum.
[a] Based on the 55 item scale.
[b] Based on the full 58 item scale.
[c] Percentile was calculated using a standard normal distribution.

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline to Week 12 for ABC-C_{FX} total score — Mixed-effect model for repeated measures treatment comparisons during the double-blind treatment period, FXS patients with fully-methylated FMR1 gene (FM, Full analysis set)

Statistic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Baseline				
n	20	22	20	20
Mean (SD)	43.8 (22.76)	42.6 (24.30)	53.2 (32.53)	41.0 (24.74)
Week 12				
n	20	15	17	15
Mean (SD)	32.6 (18.39)	25.5 (15.35)	56.1 (33.67)	40.7 (27.42)
Change from baseline to Week 12				
LS Mean (SE)	-11.4 (3.73)	-14.3 (4.00)	1.8 (3.95)	-1.8 (4.04)
Diff (95% CI) [a]		-3.0 (-13.9, 8.0)	13.2 (2.3, 24.0)	9.6 (-1.4, 20.5)
p-value		0.589	0.018 *	0.087

Based on the 55 item scale. A negative change from baseline indicates improvement.
A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and baseline ABC-C_{FX} total score as fixed effects and individual patient as a random effect.
[a] Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.
+ Indicates statistical significance after adjustment for multiple testing using Bretz gatekeeping procedure.

Secondary Outcome Results

Key Secondary Outcome Results: Change from baseline to Week 12 for ABC-C_{FX} total score — Mixed-effect model for repeated measures treatment comparisons during the double-blind treatment period, FXS patients with partially-methylated FMR1 gene (PM, Full analysis set)

Statistic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Baseline				
n	24	22	22	25
Mean (SD)	45.2 (28.64)	39.2 (22.98)	44.0 (25.60)	36.1 (21.87)
Week 12				
n	22	19	21	20
Mean (SD)	36.5 (18.45)	36.3 (20.91)	39.3 (33.98)	31.9 (15.44)
Change from baseline to Week 12				
LS Mean (SE)	-8.9 (4.39)	-1.9 (4.64)	-5.1 (4.48)	-4.6 (4.53)
Diff (95% CI) [a]		7.1 (-5.6, 19.7)	3.9 (-8.6, 16.4)	4.3 (-8.2, 16.9)
p-value		0.269	0.540	0.495

Based on the 55 item scale. A negative change from baseline indicates improvement.
A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and baseline ABC-C_{FX} total score as fixed effects and individual patient as a random effect.
[a] Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.
+ Indicates statistical significance after adjustment for multiple testing using Bretz gatekeeping procedure.

CGI-I score at Week 12 during the double-blind treatment period, by methylation status and treatment (Full analysis set)

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Response	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Number of patients [a]	20	15	17	15
1 (Very much improved)	0	1 (6.7)	0	0
2 (Much improved)	2 (10.0)	3 (20.0)	3 (17.6)	3 (20.0)
3 (Minimally improved)	6 (30.0)	3 (20.0)	4 (23.5)	5 (33.3)
4 (No change)	11 (55.0)	8 (53.3)	10 (58.8)	4 (26.7)
5 (Minimally worse)	1 (5.0)	0	0	3 (20.0)
6 (Much worse)	0	0	0	0
7 (Very much worse)	0	0	0	0

[a] Number of patients with non-missing values.
Percentage (%) is calculated based on the number of patients with non-missing values within the specified stratum.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Response	**Placebo N=24 n (%)**	**AFQ056 25 mg bid N=22 n (%)**	**AFQ056 50 mg bid N=22 n (%)**	**AFQ056 100 mg bid N=25 n (%)**
Number of patients [a]	22	19	21	20
1 (Very much improved)	0	1 (5.3)	1 (4.8)	0
2 (Much improved)	3 (13.6)	2 (10.5)	6 (28.6)	4 (20.0)
3 (Minimally improved)	7 (31.8)	8 (42.1)	7 (33.3)	5 (25.0)
4 (No change)	10 (45.5)	8 (42.1)	6 (28.6)	9 (45.0)
5 (Minimally worse)	2 (9.1)	0	0	1 (5.0)

Response	Placebo N=24 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=22 n (%)	AFQ056 100 mg bid N=25 n (%)
6 (Much worse)	0	0	1 (4.8)	1 (5.0)
7 (Very much worse)	0	0	0	0

[a] Number of patients with non-missing values.
Percentage (%) is calculated based on the number of patients with non-missing values within the specified stratum.

CGI-I score at Week 12 - Mixed-effect model for repeated measures treatment comparisons during the double-blind treatment period, by methylation status and treatment (Full analysis set)

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Week Statistic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Week 12				
n	20	15	17	15
LS Mean (SE)	3.5 (0.20)	3.2 (0.22)	3.5 (0.21)	3.5 (0.22)
Diff (95% CI) [a]		-0.3 (-0.9, 0.3)	-0.1 (-0.6, 0.5)	0.0 (-0.6, 0.6)
p-value		0.272	0.814	0.951

A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and baseline CGI-S score as fixed effects and individual patient as a random effect. CGI-I scores range from 1 (very much improved) to 7 (very much worse). A lower score indicates improvement.
[a] Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Week Statistic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Week 12				
n	22	19	21	20
LS Mean (SE)	3.6 (0.21)	3.4 (0.22)	3.0 (0.21)	3.6 (0.21)
Diff (95% CI) [a]		-0.2 (-0.8, 0.4)	-0.5 (-1.1, 0.1)	0.0 (-0.5, 0.6)
p-value		0.498	0.080	0.884

A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and baseline CGI-S score as fixed effects and individual patient as a random effect. CGI-I scores range from 1 (very much improved) to 7 (very much worse). A lower score indicates improvement.

[a] Comparisons of each dose group with placebo.

* Indicates statistical significance at 5% level.

Change from baseline to Week 12 for ABC-C_{FX} subscale scores - Mixed-effect model for repeated measures treatment comparisons during the double-blind treatment period, by methylation status (Full analysis set)

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Irritability				
Change from baseline to Week 12				
LS Mean (SE)	-2.4 (1.40)	-4.5 (1.56)	2.0 (1.51)	-0.5 (1.56)
Diff (95% CI)		-2.1 (-6.3, 2.1)	4.5 (0.3, 8.6)	1.9 (-2.3, 6.1)
p-value		0.326	0.035 *	0.368
Lethargy/withdrawal				
Change from baseline to Week 12				
LS Mean (SE)	-2.1 (0.91)	-2.5 (0.96)	0.2 (0.95)	-0.1 (0.97)
Diff (95% CI)		-0.4 (-3.0, 2.2)	2.3 (-0.3, 5.0)	2.0 (-0.6, 4.7)
p-value		0.764	0.079	0.129

	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Stereotypic behavior				
Change from baseline to Week 12				
LS Mean (SE)	-2.1 (0.58)	-2.0 (0.63)	-1.0 (0.62)	-0.5 (0.63)
Diff (95% CI)		0.1 (-1.6, 1.8)	1.1 (-0.6, 2.8)	1.5 (-0.2, 3.3)
p-value		0.908	0.194	0.079
Hyperactivity				
Change from baseline to Week 12				
LS Mean (SE)	-2.0 (0.78)	-3.0 (0.84)	0.1 (0.83)	-1.4 (0.85)
Diff (95% CI)		-0.9 (-3.2, 1.4)	2.1 (-0.1, 4.4)	0.6 (-1.7, 2.9)
p-value		0.429	0.065	0.610
Inappropriate speech				
Change from baseline to Week 12				
LS Mean (SE)	-1.1 (0.52)	-0.6 (0.55)	0.4 (0.54)	0.3 (0.55)
Diff (95% CI)		0.5 (-1.0, 2.0)	1.5 (0.0, 3.0)	1.4 (-0.2, 2.9)
p-value		0.499	0.049 *	0.077
Social avoidance				
Change from baseline to Week 12				
LS Mean (SE)	-1.2 (0.50)	-0.9 (0.55)	-0.3 (0.53)	0.3 (0.55)
Diff (95% CI)		0.3 (-1.2, 1.7)	0.9 (-0.6, 2.3)	1.5 (0.0, 3.0)
p-value		0.728	0.246	0.054

Based on the 55 item scale. A negative change from baseline indicates improvement.
A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and the baseline ABC-C_{FX} subscale score as fixed effects and individual patient as a random effect.
Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Irritability				
Change from baseline to Week 12				
LS Mean (SE)	-3.8 (1.71)	-1.3 (1.82)	0.0 (1.75)	-0.7 (1.76)
Diff (95% CI)		2.5 (-2.4, 7.5)	3.8 (-1.1, 8.7)	3.1 (-1.7, 8.0)
p-value		0.309	0.129	0.204
Lethargy/withdrawal				
Change from baseline to Week 12				
LS Mean (SE)	-2.1 (1.09)	-0.9 (1.15)	-1.8 (1.11)	-1.9 (1.13)
Diff (95% CI)		1.2 (-2.0, 4.3)	0.3 (-2.8, 3.4)	0.2 (-2.9, 3.4)
p-value		0.460	0.835	0.887
Stereotypic behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.1 (0.63)	-0.3 (0.68)	-0.7 (0.65)	-0.1 (0.65)
Diff (95% CI)		-0.2 (-2.0, 1.6)	-0.5 (-2.3, 1.3)	0.0 (-1.8, 1.8)
p-value		0.819	0.572	0.989
Hyperactivity				
Change from baseline to Week 12				
LS Mean (SE)	-1.4 (0.98)	-0.2 (1.03)	-1.2 (1.00)	-1.5 (1.01)
Diff (95% CI)		1.1 (-1.7, 4.0)	0.2 (-2.6, 3.0)	-0.2 (-3.0, 2.6)
p-value		0.427	0.899	0.899
Inappropriate speech				
Change from baseline to Week 12				
LS Mean (SE)	-0.7 (0.58)	0.3 (0.61)	-0.1 (0.58)	0.2 (0.59)
Diff (95% CI)		1.0 (-0.7, 2.6)	0.6 (-1.1, 2.2)	0.9 (-0.7, 2.5)
p-value		0.245	0.500	0.269

	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Social avoidance				
Change from baseline to Week 12				
LS Mean (SE)	-1.1 (0.50)	0.5 (0.53)	-1.4 (0.51)	-0.8 (0.52)
Diff (95% CI)		1.6 (0.1, 3.0)	-0.3 (-1.8, 1.1)	0.3 (-1.2, 1.7)
p-value		0.034 *	0.649	0.711

Based on the 55 item scale. A negative change from baseline indicates improvement.
A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and the baseline ABC-C_{FX} subscale score as fixed effects and individual patient as a random effect.
Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.

Clinical response - Logistic regression model treatment comparisons at Week 12 (LOCF) during the double-blind treatment period, by methylation status (Full analysis set)

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Statistic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Total	20	22	20	20
Responder, n (%)	2 (10.0)	4 (18.2)	2 (10.0)	0
Odds ratio [a]		1.91	0.97	NE
95% interval for odds ratio		(0.30, 12.13)	(0.12, 7.74)	(NE, NE)
p-value [b]		0.491	0.975	NE

Total is the number of patients with non-missing baseline ABC-C_{FX} total score and at least one non-missing post-baseline ABC-C_{FX} total score and CGI-I assessment.
Clinical response is defined as patients with a reduction of at least 25% from baseline in ABC-C_{FX} total score and a CGI-I of 1 (very much improved) or 2 (much improved).
[a] The odds of an AFQ056 treated patient being a responder relative to the odds of a placebo treated patient based on a logistic regression model with treatment and region as factors and baseline CGI-S score as a covariate.
[b] Comparisons of each dose group with placebo. * Indicates statistical significance at 5% level.
NE=Not estimable.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Statistic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Total	24	22	22	25
Responder, n (%)	1 (4.2)	2 (9.1)	5 (22.7)	4 (16.0)
Odds ratio [a]		1.73	6.81	3.93
95% interval for odds ratio		(0.14, 21.51)	(0.67, 69.20)	(0.39, 39.67)
p-value [b]		0.670	0.105	0.246

Total is the number of patients with non-missing baseline ABC-C_{FX} total score and at least one non-missing post-baseline ABC-C_{FX} total score and CGI-I assessment.

Clinical response is defined as patients with a reduction of at least 25% from baseline in ABC-C_{FX} total score and a CGI-I of 1 (very much improved) or 2 (much improved).

[a] The odds of an AFQ056 treated patient being a responder relative to the odds of a placebo treated patient based on a logistic regression model with treatment and region as factors and baseline CGI-S score as a covariate.

[b] Comparisons of each dose group with placebo. * Indicates statistical significance at 5% level.

NE=Not estimable.

Change from baseline to Week 12 for Repetitive behavior scale - Revised (RBS-R) total and subscale scores - Mixed-effect model for repeated measures treatment comparisons during the double-blind treatment period, by methylation status (Full analysis set)

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Week Statistic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Total score				
Baseline				
n	20	22	20	20
Mean (SD)	28.0 (18.14)	27.8 (18.16)	32.6 (22.20)	29.2 (16.51)
Week 12				
n	20	15	17	15
Mean (SD)	22.7 (16.18)	17.4 (16.12)	32.1 (22.26)	28.1 (21.32)

Week Statistic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Change from baseline to Week 12				
LS Mean (SE)	-5.3 (2.50)	-7.2 (2.84)	-1.2 (2.69)	-1.3 (2.82)
Diff (95% CI)		-1.9 (-9.5, 5.6)	4.1 (-3.2, 11.5)	4.0 (-3.6, 11.5)
p-value		0.613	0.268	0.297
Stereotyped behavior				
Change from baseline to Week 12				
LS Mean (SE)	-1.2 (0.51)	-1.3 (0.58)	0.0 (0.55)	-0.1 (0.58)
Diff (95% CI)		0.0 (-1.6, 1.5)	1.3 (-0.2, 2.8)	1.1 (-0.5, 2.6)
p-value		0.969	0.097	0.166
Self-injurious behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.1 (0.45)	-0.3 (0.50)	1.1 (0.48)	-0.1 (0.49)
Diff (95% CI)		-0.3 (-1.6, 1.1)	1.1 (-0.2, 2.5)	-0.1 (-1.4, 1.3)
p-value		0.700	0.086	0.932
Compulsive behavior				
Change from baseline to Week 12				
LS Mean (SE)	-1.2 (0.64)	-1.1 (0.72)	-0.3 (0.69)	0.1 (0.72)
Diff (95% CI)		0.1 (-1.8, 2.0)	0.8 (-1.1, 2.7)	1.2 (-0.7, 3.2)
p-value		0.931	0.386	0.202
Ritualistic behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.8 (0.37)	-0.7 (0.42)	-0.6 (0.40)	-1.0 (0.42)
Diff (95% CI)		0.1 (-1.0, 1.2)	0.2 (-0.9, 1.3)	-0.2 (-1.3, 0.9)
p-value		0.881	0.691	0.730
Sameness behavior				
Change from baseline to Week 12				
LS Mean (SE)	-1.5 (1.04)	-2.1 (1.20)	-1.0 (1.13)	-0.5 (1.18)
Diff (95% CI)		-0.7 (-3.8, 2.5)	0.4 (-2.6, 3.5)	0.9 (-2.2, 4.1)
p-value		0.675	0.773	0.553

Week Statistic	Placebo N=20	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=20	AFQ056 100 mg bid N=20
Restricted behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.5 (0.35)	-1.3 (0.40)	-0.2 (0.38)	0.4 (0.40)
Diff (95% CI)		-0.8 (-1.9, 0.3)	0.3 (-0.7, 1.4)	0.9 (-0.1, 2.0)
p-value		0.142	0.532	0.085

A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and the baseline RBS-R total or subscale score (as appropriate) as fixed effects and individual patient as a random effect.
A negative change from baseline indicates improvement.
Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Week Statistic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Total score				
Baseline				
n	24	22	22	25
Mean (SD)	24.8 (19.68)	21.0 (19.19)	23.4 (16.91)	20.3 (15.00)
Week 12				
n	22	19	21	20
Mean (SD)	20.4 (13.59)	19.8 (18.54)	19.0 (13.04)	14.6 (10.37)
Change from baseline to Week 12				
LS Mean (SE)	-4.5 (1.82)	-2.4 (1.96)	-4.9 (1.85)	-5.6 (1.89)
Diff (95% CI)		2.2 (-3.1, 7.4)	-0.3 (-5.5, 4.8)	-1.0 (-6.2, 4.2)
p-value		0.418	0.898	0.697

Week Statistic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Stereotyped behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.3 (0.37)	-0.3 (0.40)	-0.6 (0.38)	-0.5 (0.39)
Diff (95% CI)		0.0 (-1.1, 1.1)	-0.3 (-1.4, 0.8)	-0.3 (-1.3, 0.8)
p-value		0.984	0.567	0.641
Self-injurious behavior				
Change from baseline to Week 12				
LS Mean (SE)	-1.0 (0.31)	-0.5 (0.33)	0.0 (0.31)	-0.6 (0.32)
Diff (95% CI)		0.5 (-0.4, 1.4)	1.0 (0.1, 1.9)	0.5 (-0.4, 1.4)
p-value		0.231	0.030 *	0.299
Compulsive behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.8 (0.44)	-0.5 (0.48)	-0.9 (0.45)	-0.9 (0.46)
Diff (95% CI)		0.4 (-0.9, 1.6)	-0.1 (-1.4, 1.2)	-0.1 (-1.4, 1.2)
p-value		0.585	0.865	0.848
Ritualistic behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.7 (0.48)	0.1 (0.51)	-1.6 (0.48)	-1.1 (0.50)
Diff (95% CI)		0.8 (-0.6, 2.2)	-0.9 (-2.3, 0.4)	-0.5 (-1.8, 0.9)
p-value		0.240	0.178	0.500
Sameness behavior				
Change from baseline to Week 12				
LS Mean (SE)	-1.5 (0.80)	-0.7 (0.87)	-1.3 (0.82)	-2.1 (0.84)
Diff (95% CI)		0.8 (-1.5, 3.2)	0.2 (-2.1, 2.5)	-0.6 (-2.9, 1.7)
p-value		0.475	0.866	0.607

Week Statistic	Placebo N=24	AFQ056 25 mg bid N=22	AFQ056 50 mg bid N=22	AFQ056 100 mg bid N=25
Restricted behavior				
Change from baseline to Week 12				
LS Mean (SE)	-0.2 (0.40)	-0.6 (0.42)	-0.4 (0.40)	-0.3 (0.41)
Diff (95% CI)		-0.3 (-1.5, 0.8)	-0.2 (-1.4, 0.9)	-0.1 (-1.2, 1.1)
p-value		0.549	0.710	0.909

A mixed effects model with repeated measures and unstructured covariance matrix is used with region, treatment, week, treatment by week interaction and the baseline RBS-R total or subscale score (as appropriate) as fixed effects and individual patient as a random effect.
A negative change from baseline indicates improvement.
Comparisons of each dose group with placebo.
* Indicates statistical significance at 5% level.

Summary of Safety

Safety Results

Adverse events during the double-blind treatment period, by primary system organ class, methylation status and treatment (Safety set)

Stratum: All patients

Primary system organ class	Placebo N=44 n (%)	AFQ056 25 mg bid N=44 n (%)	AFQ056 50 mg bid N=42 n (%)	AFQ056 100 mg bid N=45 n (%)
Patients with any adverse event	27 (61.4)	25 (56.8)	29 (69.0)	37 (82.2)
Blood and lymphatic system disorders	0	0	0	1 (2.2)
Cardiac disorders	0	2 (4.5)	0	1 (2.2)
Ear and labyrinth disorders	0	0	1 (2.4)	0
Endocrine disorders	0	0	1 (2.4)	1 (2.2)
Eye disorders	0	0	1 (2.4)	4 (8.9)
Gastrointestinal disorders	7 (15.9)	8 (18.2)	9 (21.4)	14 (31.1)

Primary system organ class	Placebo N=44 n (%)	AFQ056 25 mg bid N=44 n (%)	AFQ056 50 mg bid N=42 n (%)	AFQ056 100 mg bid N=45 n (%)
General disorders and administration site conditions	2 (4.5)	2 (4.5)	5 (11.9)	6 (13.3)
Immune system disorders	0	0	0	1 (2.2)
Infections and infestations	12 (27.3)	9 (20.5)	9 (21.4)	13 (28.9)
Injury, poisoning and procedural complications	2 (4.5)	2 (4.5)	0	6 (13.3)
Investigations	3 (6.8)	1 (2.3)	3 (7.1)	1 (2.2)
Metabolism and nutrition disorders	1 (2.3)	2 (4.5)	2 (4.8)	5 (11.1)
Musculoskeletal and connective tissue disorders	1 (2.3)	2 (4.5)	2 (4.8)	1 (2.2)
Nervous system disorders	4 (9.1)	4 (9.1)	6 (14.3)	11 (24.4)
Psychiatric disorders	3 (6.8)	4 (9.1)	11 (26.2)	17 (37.8)
Renal and urinary disorders	0	0	0	1 (2.2)
Reproductive system and breast disorders	0	0	1 (2.4)	1 (2.2)
Respiratory, thoracic and mediastinal disorders	1 (2.3)	3 (6.8)	4 (9.5)	5 (11.1)
Skin and subcutaneous tissue disorders	2 (4.5)	2 (4.5)	2 (4.8)	2 (4.4)
Vascular disorders	0	0	1 (2.4)	0

Primary system organ classes are sorted alphabetically. A patient with multiple occurrences of an AE for a primary system organ class is counted only once in each specific category. Adverse events with onset on or after the first dose date of double-blind study drug through the later of (date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs and AEs leading to discontinuation with onset on or after the first dose date of double-blind study drug are included.

Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Primary system organ class	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Patients with any adverse event	13 (65.0)	16 (72.7)	15 (75.0)	15 (75.0)
Cardiac disorders	0	1 (4.5)	0	0
Endocrine disorders	0	0	1 (5.0)	1 (5.0)
Eye disorders	0	0	0	2 (10.0)
Gastrointestinal disorders	2 (10.0)	5 (22.7)	6 (30.0)	6 (30.0)
General disorders and administration site conditions	1 (5.0)	2 (9.1)	2 (10.0)	2 (10.0)
Infections and infestations	8 (40.0)	6 (27.3)	4 (20.0)	5 (25.0)
Injury, poisoning and procedural complications	0	1 (4.5)	0	2 (10.0)
Investigations	2 (10.0)	1 (4.5)	1 (5.0)	1 (5.0)
Metabolism and nutrition disorders	1 (5.0)	1 (4.5)	1 (5.0)	3 (15.0)
Musculoskeletal and connective tissue disorders	1 (5.0)	1 (4.5)	1 (5.0)	1 (5.0)
Nervous system disorders	1 (5.0)	3 (13.6)	4 (20.0)	4 (20.0)
Psychiatric disorders	1 (5.0)	2 (9.1)	6 (30.0)	7 (35.0)
Respiratory, thoracic and mediastinal disorders	0	2 (9.1)	0	5 (25.0)
Skin and subcutaneous tissue disorders	2 (10.0)	2 (9.1)	2 (10.0)	2 (10.0)

Primary system organ classes are sorted alphabetically. A patient with multiple occurrences of an AE for a primary system organ class is counted only once in each specific category. Adverse events with onset on or after the first dose date of double-blind study drug through the later of (date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs and AEs leading to discontinuation with onset on or after the first dose date of double-blind study drug are included.

Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Primary system organ class	Placebo N=24 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=22 n (%)	AFQ056 100 mg bid N=25 n (%)
Patients with any adverse event	14 (58.3)	9 (40.9)	14 (63.6)	22 (88.0)
Blood and lymphatic system disorders	0	0	0	1 (4.0)
Cardiac disorders	0	1 (4.5)	0	1 (4.0)
Ear and labyrinth disorders	0	0	1 (4.5)	0
Eye disorders	0	0	1 (4.5)	2 (8.0)
Gastrointestinal disorders	5 (20.8)	3 (13.6)	3 (13.6)	8 (32.0)
General disorders and administration site conditions	1 (4.2)	0	3 (13.6)	4 (16.0)
Immune system disorders	0	0	0	1 (4.0)
Infections and infestations	4 (16.7)	3 (13.6)	5 (22.7)	8 (32.0)
Injury, poisoning and procedural complications	2 (8.3)	1 (4.5)	0	4 (16.0)
Investigations	1 (4.2)	0	2 (9.1)	0
Metabolism and nutrition disorders	0	1 (4.5)	1 (4.5)	2 (8.0)
Musculoskeletal and connective tissue disorders	0	1 (4.5)	1 (4.5)	0
Nervous system disorders	3 (12.5)	1 (4.5)	2 (9.1)	7 (28.0)
Psychiatric disorders	2 (8.3)	2 (9.1)	5 (22.7)	10 (40.0)
Renal and urinary disorders	0	0	0	1 (4.0)
Reproductive system and breast disorders	0	0	1 (4.5)	1 (4.0)
Respiratory, thoracic and mediastinal disorders	1 (4.2)	1 (4.5)	4 (18.2)	0
Vascular disorders	0	0	1 (4.5)	0

Primary system organ classes are sorted alphabetically. A patient with multiple occurrences of an AE for a primary system organ class is counted only once in each specific category. Adverse events with onset on or after the first dose date of double-blind study drug through the later of (date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs and AEs leading to discontinuation with onset on or after the first dose date of double-blind study drug are included.

Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Adverse events (at least 5% in any group) during the double-blind treatment period, by preferred term, methylation status and treatment (Safety set)

Stratum: All patients

Preferred term	Placebo N=44 n (%)	AFQ056 25 mg bid N=44 n (%)	AFQ056 50 mg bid N=42 n (%)	AFQ056 100 mg bid N=45 n (%)
Patients with any adverse event	27 (61.4)	25 (56.8)	29 (69.0)	37 (82.2)
Dizziness	1 (2.3)	1 (2.3)	0	8 (17.8)
Insomnia	0	1 (2.3)	4 (9.5)	8 (17.8)
Nasopharyngitis	2 (4.5)	3 (6.8)	3 (7.1)	6 (13.3)
Decreased appetite	0	0	1 (2.4)	4 (8.9)
Headache	2 (4.5)	1 (2.3)	4 (9.5)	4 (8.9)
Nausea	0	0	1 (2.4)	4 (8.9)
Upper respiratory tract infection	2 (4.5)	3 (6.8)	2 (4.8)	4 (8.9)
Vomiting	2 (4.5)	3 (6.8)	5 (11.9)	4 (8.9)
Agitation	0	1 (2.3)	2 (4.8)	3 (6.7)
Diarrhoea	3 (6.8)	2 (4.5)	1 (2.4)	3 (6.7)
Irritability	0	2 (4.5)	2 (4.8)	3 (6.7)
Aggression	1 (2.3)	1 (2.3)	3 (7.1)	2 (4.4)

Preferred terms are sorted in descending order of frequency based on the AFQ056 100 mg bid column. A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category. Adverse events with onset on or after the first dose date of double-blind study drug through the later of (the date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs and AEs leading to discontinuation with onset on or after the first dose date of double-blind study drug are included.
Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

Preferred term	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Patients with any adverse event	13 (65.0)	16 (72.7)	15 (75.0)	15 (75.0)
Agitation	0	0	1 (5.0)	3 (15.0)
Dizziness	0	1 (4.5)	0	3 (15.0)
Insomnia	0	0	2 (10.0)	3 (15.0)
Nasopharyngitis	1 (5.0)	3 (13.6)	2 (10.0)	3 (15.0)
Vomiting	1 (5.0)	1 (4.5)	2 (10.0)	3 (15.0)
Cough	0	1 (4.5)	0	2 (10.0)
Decreased appetite	0	0	0	2 (10.0)
Headache	1 (5.0)	0	2 (10.0)	2 (10.0)
Nausea	0	0	0	2 (10.0)
Upper respiratory tract infection	1 (5.0)	2 (9.1)	0	2 (10.0)
Vision blurred	0	0	0	2 (10.0)
Abdominal pain	1 (5.0)	2 (9.1)	0	1 (5.0)
Acne	0	0	0	1 (5.0)
Aggression	0	1 (4.5)	1 (5.0)	1 (5.0)
Anger	0	0	0	1 (5.0)
Diarrhoea	1 (5.0)	2 (9.1)	1 (5.0)	1 (5.0)
Ear infection	0	0	0	1 (5.0)
Fatigue	1 (5.0)	0	1 (5.0)	1 (5.0)
Hallucination, auditory	0	0	0	1 (5.0)
Hallucination, visual	0	0	0	1 (5.0)
Hyperprolactinaemia	0	0	1 (5.0)	1 (5.0)
Increased appetite	0	0	0	1 (5.0)
Ingrowing nail	0	0	0	1 (5.0)
Muscle strain	0	0	0	1 (5.0)
Musculoskeletal chest pain	0	0	0	1 (5.0)

Preferred term	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Nasal congestion	0	0	0	1 (5.0)
Non-cardiac chest pain	0	0	0	1 (5.0)
Obsessive-compulsive disorder	0	0	0	1 (5.0)
Oropharyngeal pain	0	1 (4.5)	0	1 (5.0)
Oxytocin increased	0	0	0	1 (5.0)
Personality change	0	0	0	1 (5.0)
Procedural pain	0	0	0	1 (5.0)
Rhinorrhoea	0	0	0	1 (5.0)
Social avoidant behaviour	0	0	0	1 (5.0)
Tearfulness	1 (5.0)	0	0	1 (5.0)
Abdominal discomfort	0	0	1 (5.0)	0
Alanine aminotransferase increased	0	0	1 (5.0)	0
Amylase increased	1 (5.0)	0	0	0
Anxiety	0	0	1 (5.0)	0
Apathy	0	0	1 (5.0)	0
Aphthous stomatitis	0	0	1 (5.0)	0
Aspartate aminotransferase increased	0	0	1 (5.0)	0
Blood triglycerides increased	1 (5.0)	0	0	0
Emotional distress	1 (5.0)	0	0	0
Food poisoning	0	0	1 (5.0)	0
Fungal infection	0	0	1 (5.0)	0
Gamma-glutamyltransferase increased	0	0	1 (5.0)	0
Gastroenteritis	1 (5.0)	0	0	0
Hyperhidrosis	0	0	1 (5.0)	0
Hypertriglyceridaemia	1 (5.0)	1 (4.5)	1 (5.0)	0
Intertrigo	1 (5.0)	0	0	0
Irritability	0	2 (9.1)	0	0

Preferred term	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Lipase increased	1 (5.0)	0	0	0
Myalgia	0	0	1 (5.0)	0
Orchitis	1 (5.0)	0	0	0
Otitis media	1 (5.0)	0	0	0
Paronychia	1 (5.0)	0	1 (5.0)	0
Pyrexia	0	0	1 (5.0)	0
Rash	1 (5.0)	1 (4.5)	0	0
Rash erythematous	0	0	1 (5.0)	0
Salivary hypersecretion	0	0	1 (5.0)	0
Sedation	0	0	1 (5.0)	0
Somnolence	0	1 (4.5)	1 (5.0)	0
Tendonitis	1 (5.0)	0	0	0
Tic	0	0	1 (5.0)	0
Tinea pedis	1 (5.0)	0	0	0
Tonsillitis	1 (5.0)	0	0	0
Weight increased	1 (5.0)	0	0	0

Preferred terms are sorted in descending order of frequency based on the AFQ056 100 mg bid column. A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category. Adverse events with onset on or after the first dose date of double-blind study drug through the later of (the date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs and AEs leading to discontinuation with onset on or after the first dose date of double-blind study drug are included.

Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

Preferred term	Placebo N=24 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=22 n (%)	AFQ056 100 mg bid N=25 n (%)
Patients with any adverse event	14 (58.3)	9 (40.9)	14 (63.6)	22 (88.0)
Dizziness	1 (4.2)	0	0	5 (20.0)
Insomnia	0	1 (4.5)	2 (9.1)	5 (20.0)
Irritability	0	0	2 (9.1)	3 (12.0)
Nasopharyngitis	1 (4.2)	0	1 (4.5)	3 (12.0)
Decreased appetite	0	0	1 (4.5)	2 (8.0)
Diarrhoea	2 (8.3)	0	0	2 (8.0)
Dyspepsia	0	0	0	2 (8.0)
Headache	1 (4.2)	1 (4.5)	2 (9.1)	2 (8.0)
Initial insomnia	0	0	0	2 (8.0)
Nausea	0	0	1 (4.5)	2 (8.0)
Tinea pedis	0	1 (4.5)	0	2 (8.0)
Upper respiratory tract infection	1 (4.2)	1 (4.5)	2 (9.1)	2 (8.0)
Aggression	1 (4.2)	0	2 (9.1)	1 (4.0)
Vomiting	1 (4.2)	2 (9.1)	3 (13.6)	1 (4.0)
Cough	0	0	2 (9.1)	0
Nasal congestion	0	0	2 (9.1)	0

Preferred terms are sorted in descending order of frequency based on the AFQ056 100 mg bid column. A patient with multiple occurrences of an AE for a preferred term is counted only once in each specific category. Adverse events with onset on or after the first dose date of double-blind study drug through the later of (the date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs and AEs leading to discontinuation with onset on or after the first dose date of double-blind study drug are included.
Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Overall summary of adverse events during the double-blind treatment period, by methylation status and treatment (Safety set)

Stratum: All patients

	Placebo N=44 n (%)	AFQ056 25 mg bid N=44 n (%)	AFQ056 50 mg bid N=42 n (%)	AFQ056 100 mg bid N=45 n (%)
Number of patients with:				
At least one adverse event	27 (61.4)	25 (56.8)	29 (69.0)	37 (82.2)
At least one severe adverse event	1 (2.3)	2 (4.5)	3 (7.1)	5 (11.1)
Any serious or significant AE:	1 (2.3)	0	1 (2.4)	2 (4.4)
- Death	0	0	0	0
- SAE	1 (2.3)	0	1 (2.4)	2 (4.4)
Discontinued due to AE:	1 (2.3)	2 (4.5)	2 (4.8)	6 (13.3)
- Discontinued due to SAE	0	0	0	1 (2.2)
- Discontinued due to non-serious AE	1 (2.3)	2 (4.5)	2 (4.8)	5 (11.1)

Adverse events with onset on or after the first dose date of double-blind study drug through the later of (the date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs, AEs leading to discontinuation, and deaths with onset on or after the first dose date of double-blind study drug are included.
Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Stratum: FXS patients with fully-methylated FMR1 gene (FM)

	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
Number of patients with:				
At least one adverse event	13 (65.0)	16 (72.7)	15 (75.0)	15 (75.0)
At least one severe adverse event	0	1 (4.5)	1 (5.0)	1 (5.0)
Any serious or significant AE:	0	0	0	2 (10.0)
- Death	0	0	0	0
- SAE	0	0	0	2 (10.0)
Discontinued due to AE:	0	2 (9.1)	1 (5.0)	2 (10.0)
- Discontinued due to SAE	0	0	0	1 (5.0)

	Placebo N=20 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=20 n (%)	AFQ056 100 mg bid N=20 n (%)
- Discontinued due to non-serious AE	0	2 (9.1)	1 (5.0)	1 (5.0)

Adverse events with onset on or after the first dose date of double-blind study drug through the later of (the date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs, AEs leading to discontinuation, and deaths with onset on or after the first dose date of double-blind study drug are included.
Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Stratum: FXS patients with partially-methylated FMR1 gene (PM)

	Placebo N=24 n (%)	AFQ056 25 mg bid N=22 n (%)	AFQ056 50 mg bid N=22 n (%)	AFQ056 100 mg bid N=25 n (%)
Number of patients with:				
At least one adverse event	14 (58.3)	9 (40.9)	14 (63.6)	22 (88.0)
At least one severe adverse event	1 (4.2)	1 (4.5)	2 (9.1)	4 (16.0)
Any serious or significant AE:	1 (4.2)	0	1 (4.5)	0
- Death	0	0	0	0
- SAE	1 (4.2)	0	1 (4.5)	0
Discontinued due to AE:	1 (4.2)	0	1 (4.5)	4 (16.0)
- Discontinued due to SAE	0	0	0	0
- Discontinued due to non-serious AE	1 (4.2)	0	1 (4.5)	4 (16.0)

Adverse events with onset on or after the first dose date of double-blind study drug through the later of (the date of last double-blind study drug dose + 4 days, Week 12/early discontinuation visit date) as well as all SAEs, AEs leading to discontinuation, and deaths with onset on or after the first dose date of double-blind study drug are included.
Percentage (%) is calculated based on the patients in the Safety set within the specified stratum.

Other Relevant Findings

None

Conclusion:

- In this study population of patients with Fragile X syndrome aged 18-45 years, treatment with AFQ056 over 12 weeks did not demonstrate benefit compared to placebo on behavioral symptoms as measured by the Aberrant Behavior Checklist – Community edition using the FXS specific algorithm - ABC-C_{FX}, Clinical Global Impression - Improvement, or Repetitive Behavior Scale – Revised.
- Methylation status did not predict efficacy of AFQ056 in this population based on the endpoints collected in this study.
- AFQ056 showed a dose-related increase in adverse events but with few discontinuations due to adverse events. Possible dose-dependent central nervous system adverse effects were expected (insomnia, agitation, hallucinations). Overall, the safety and tolerability profile of AFQ056 was similar to earlier studies.

Date of Clinical Trial Report

24 April 2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

8 August 2014

Date of Latest Update

Reason for Update

Not applicable