Clinical trial results:
A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of AFQ056 in adolescent patients with Fragile X Syndrome

Summary

EudraCT number	2010-022638-96
Trial protocol	GB SE FR DK DE ES Outside EU/EEA IT BE NL
Global end of trial date	06 January 2014

Results information

Result version number	v1 (current)
This version publication date	17 July 2016
First version publication date	17 July 2016

Trial information

Trial identification

Sponsor protocol code	CAFQ056B2214

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01357239
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111 ,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001003-PIP01-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 January 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 January 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of AFQ056 100 mg bid versus placebo in reducing the ABC-CFX (Aberrant Behavior Checklist-Community edition analyzed using the FXS specific algorithm) Total score after 12 weeks of treatment in FXS patients with fully methylated FMR1 gene.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	02 May 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 10
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	United States: 48
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Switzerland: 12
Country: Number of subjects enrolled	Sweden: 4

Worldwide total number of subjects	142
EEA total number of subjects	68

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	142
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 38 centers in 16 countries.

Pre-assignment

Screening details:

A total of 309 subjects were screened, and 142 subjects continued into the single-blind placebo run-in period. Remaining 167 subjects were screening failures, the majority of whom failed due to methylation stratum capping.

Period 1

Period 1 title	Single-blind Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Subject, Carer

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling and schedule. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

Arms

Arm title	Placebo- Single blind period

Arm description:

Placebo capsule was administered orally twice daily (bid) for 4 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule was administered orally bid for 4 weeks.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: Caregiver or carer was blinded due to direct contact with subjects, and was capable of supervising treatment, providing input into efficacy and safety assessments.

Number of subjects in period 1	Placebo- Single blind period
Started	142
Completed	139
Not completed	3
Consent withdrawn by subject	1
Adverse event, non-fatal	2

Period 2

Period 2 title	Double blind Treatment Period
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

The identity of the treatments was concealed by the use of study drugs that were all identical in packaging, labeling and schedule. Unblinding was allowed only in case of subjects emergencies and at the conclusion of the study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo -Double blind Treatment Period

Arm description:

2 placebo capsules were administered bid for 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Placebo capsule was administered b.i.d for 12 weeks.

Arm title	AFQ056 25 mg bid

Arm description:

One AFQ056 25 mg capsule and one placebo capsule were administered bid for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Mavoglurant
Investigational medicinal product code	AFQ056
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

25 mg bid, oral, swallow it whole.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule matched to AFQ056 25 mg capsule was administered orally bid for 12 weeks.

Arm title	AFQ056 50 mg bid

Arm description:

Two AFQ056 25 mg capsules were administered bid for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Mavoglurant
Investigational medicinal product code	AFQ056
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

50 mg bid (2 of 25 mg capsules) , oral, swallow it whole.

Arm title	AFQ056 100 mg bid

Arm description:

One AFQ056 100 mg capsule and one placebo capsule were administered bid for 12 weeks.

Arm type	Experimental
Investigational medicinal product name	Mavoglurant
Investigational medicinal product code	AFQ056
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

100 mg bid, oral, swallow it whole.

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

One placebo capsule matched to AFQ056 100 mg capsule was administered orally b.i.d for 12 weeks.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The study design comprised of a single-blind placebo run-in period prior randomization of subjects into the double blind treatment period. The double-blind treatment period was considered as baseline period.

Number of subjects in period 2[3]	Placebo -Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid
Started	42	31	27
Completed	40	31	27
Not completed	2	0	0
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	1	-	-

Number of subjects in period 2[3]	AFQ056 100 mg bid
Started	39
Completed	37
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The baseline period i.e. double blind period has randomized patients, where as worldwide number is enrolled patients who were in single blind placebo run-in period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo -Double blind Treatment Period
Reporting group description:	
2 placebo capsules were administered bid for 12 weeks.	
Reporting group title	AFQ056 25 mg bid
Reporting group description:	
One AFQ056 25 mg capsule and one placebo capsule were administered bid for 12 weeks.	
Reporting group title	AFQ056 50 mg bid
Reporting group description:	
Two AFQ056 25 mg capsules were administered bid for 12 weeks.	
Reporting group title	AFQ056 100 mg bid
Reporting group description:	
One AFQ056 100 mg capsule and one placebo capsule were administered bid for 12 weeks.	

Reporting group values	Placebo -Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid
Number of subjects	42	31	27
Age categorical Units: Subjects			
Adolescents (12-17 years)	42	31	27
Age continuous Units: years			
arithmetic mean	14.4	14.4	14.6
standard deviation	± 1.85	± 1.7	± 1.58
Gender categorical Units: Subjects			
Female	3	5	3
Male	39	26	24

Reporting group values	AFQ056 100 mg bid	Total	
Number of subjects	39	139	
Age categorical Units: Subjects			
Adolescents (12-17 years)	39	139	
Age continuous Units: years			
arithmetic mean	14.6		
standard deviation	± 1.77	-	
Gender categorical Units: Subjects			
Female	4	15	
Male	35	124	

End points

End points reporting groups

Reporting group title	Placebo- Single blind period
Reporting group description:	
Placebo capsule was administered orally twice daily (bid) for 4 weeks.	
Reporting group title	Placebo -Double blind Treatment Period
Reporting group description:	
2 placebo capsules were administered bid for 12 weeks.	
Reporting group title	AFQ056 25 mg bid
Reporting group description:	
One AFQ056 25 mg capsule and one placebo capsule were administered bid for 12 weeks.	
Reporting group title	AFQ056 50 mg bid
Reporting group description:	
Two AFQ056 25 mg capsules were administered bid for 12 weeks.	
Reporting group title	AFQ056 100 mg bid
Reporting group description:	
One AFQ056 100 mg capsule and one placebo capsule were administered bid for 12 weeks.	

Primary: Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)]

End point title	Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)][1]

End point description:

The Aberrant Behavior Checklist – Community edition (ABC-C) is a caregiver-rated symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, and work training centers. The raw data collected from the full, 58-item ABC-C were analyzed according to the modified FXS ABC-C algorithm (ABC-CFX), for which 55 items and six subscales plus the total score were considered. The assessment is done by attributing to each item of the questionnaire a score from 0 (“not at all a problem”) to 3 (“problem is severe in degree”) and the total score ranks from 0 to 165.A negative change from baseline indicated improvement. Analysis was performed in full analysis set (FAS) population, defined as all randomized subjects 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.

End point type	Primary

End point timeframe:

Baseline to Week 12

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The primary end point was to compare only 2 arms (AFQ056 100 mg vs Placebo), hence this end point is not reporting data of other two arms mentioned in the baseline period.

End point values	Placebo - Double blind Treatment Period	AFQ056 100 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[2]	16[3]		
Units: Units on a scale				
least squares mean (standard error)	-9.4 (± 3.88)	8.6 (± 4.48)		

Notes:

[2] - Only participants with a value at given time and assessment was within the window for analysis

[3] - Only participants with a value at given time and assessment was within the window for analysis

Statistical analyses

Statistical analysis title	Change in ABC-CFX total score

Statistical analysis description:

A mixed-effect model with repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect.

Comparison groups	Placebo -Double blind Treatment Period v AFQ056 100 mg bid
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.004
Method	Mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference
Point estimate	18
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.2
upper limit	29.9

Notes:

[4] - Null hypothesis considered no difference in the treatments being compared while alternative hypothesis suggested there was difference in treatments.

Secondary: Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point title	Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point description:

The Aberrant Behavior Checklist – Community edition (ABC-C) is a caregiver-rated symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, and work training centers. The raw data collected from the full, 58-item ABC-C were analyzed according to the modified FXS ABC-C algorithm (ABC-CFX), for which 55 items and six subscales plus the total score were considered. The assessment is done by attributing to each item of the questionnaire a score from 0 (“not at all a problem”) to 3 (“problem is severe in degree”) and the total score ranks from 0 to 165. A negative change from baseline indicated improvement. Analysis was performed in full analysis set (FAS) population, defined as all randomized subjects 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.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	18[5]	23[6]	21[7]	20[8]
Units: Units on a scale				
least squares mean (standard error)	-3.5 (± 4.3)	-6.8 (± 3.88)	-2.8 (± 4.07)	-5.7 (± 4.06)

Notes:

[5] - Only participants with a value at given time and assessment was within the window for analysis

[6] - Only participants with a value at given time and assessment was within the window for analysis

[7] - Only participants with a value at given time and assessment was within the window for analysis

[8] - Only participants with a value at given time and assessment was within the window for analysis

Statistical analyses

Statistical analysis title	Change in ABC-CFX total score

Statistical analysis description:

A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect.

Comparison groups	Placebo -Double blind Treatment Period v AFQ056 25 mg bid
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.579
Method	Mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference
Point estimate	-3.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.7
upper limit	8.3

Notes:

[9] - Null hypothesis considered no difference in the treatments being compared while alternative hypothesis suggested there was difference in treatments

Statistical analysis title	Change in ABC-CFX total score

Statistical analysis description:

A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect.

Comparison groups	Placebo -Double blind Treatment Period v AFQ056 50 mg bid
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.899
Method	Mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference
Point estimate	0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11
upper limit	12.5

Notes:

[10] - Null hypothesis considered no difference in the treatments being compared while alternative hypothesis suggested there was difference in treatments

Statistical analysis title	Change in ABC-CFX total score

Statistical analysis description:

A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect.

Comparison groups	Placebo -Double blind Treatment Period v AFQ056 100 mg bid
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority[11]
P-value	= 0.716
Method	Mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.9
upper limit	9.6

Notes:

[11] - Null hypothesis considered no difference in the treatments being compared while alternative hypothesis suggested there was difference in treatments.

Secondary: Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score for two lower doses of drug [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)]

End point title	Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score for two lower doses of drug [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)][12]

End point description:

The Aberrant Behavior Checklist – Community edition (ABC-C) is a caregiver-rated symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, and work training centers. The raw data collected from the full, 58-item ABC-C were analyzed according to the modified FXS ABC-C algorithm (ABC-CFX), for which 55 items and six subscales plus the total score were considered. The assessment is done by attributing to each item of the questionnaire a score from 0 (“not at all a problem”) to 3 (“problem is severe in degree”) and the total score ranks from 0 to 165. A negative change from baseline indicated improvement. Analysis was performed in full analysis set (FAS) population, defined as all randomized subjects 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.

End point type	Secondary

End point timeframe:

Baseline to Week 12

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point was planned to get the results from two lower doses of AFQ056 (i.e AFQ056 25 mg v Placebo and AFQ056 50 mg v Placebo), hence this end point is not reporting statistics for other

AFQ056 100 mg in the baseline period.

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[13]	8[14]	6[15]	
Units: Units on a scale				
least squares mean (standard error)	-9.4 (± 3.88)	-11.8 (± 6.43)	-3.4 (± 7.4)	

Notes:

[13] - Only participants with a value at given time and assessment was within the window for analysis

[14] - Only participants with a value at given time and assessment was within the window for analysis

[15] - Only participants with a value at given time and assessment was within the window for analysis

Statistical analyses

Statistical analysis title	Change in ABC-CFX total score

Statistical analysis description:

A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect.

Comparison groups	Placebo -Double blind Treatment Period v AFQ056 25 mg bid
Number of subjects included in analysis	30
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 0.758
Method	Mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference
Point estimate	-2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.6
upper limit	12.9

Notes:

[16] - Null hypothesis considered no difference in the treatments being compared while alternative hypothesis suggested there was difference in treatments.

Statistical analysis title	Change in ABC-CFX total score

Statistical analysis description:

A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect.

Comparison groups	Placebo -Double blind Treatment Period v AFQ056 50 mg bid
Number of subjects included in analysis	28
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.475
Method	Mixed-effect model for repeated measures
Parameter estimate	Least Square Mean Difference
Point estimate	6.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.9
upper limit	23

Notes:

[17] - Null hypothesis considered no difference in the treatments being compared while alternative hypothesis suggested there was difference in treatments.

Secondary: Percentage of subjects with Clinical Global Impression-Improvement (CGI-I) rating at Week 12 [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)]

End point title	Percentage of subjects with Clinical Global Impression-Improvement (CGI-I) rating at Week 12 [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)]

End point description:

The CGI scale, a clinician-rated scale was completed by the investigator or the investigator's designated deputy to assess treatment response in psychiatric subjects. The CGI-I reported the global changes of the symptoms ranging from 1 to 7 (1: very much improved, 2: much improved, 3:minimally improved, 4: no change, 5: minimally worse, 6: much worse and 7: very much worse). Lower scores indicate improvement. The analysis was performed in FAS population. The 'n' signifies only those participants who had a value at the given time and the assessment was within the window for analysis were included.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	8	6	17
Units: Percentage of subjects				
number (not applicable)				
Very much improved (n=22,8, 6,15)	0	12.5	0	0
Much improved (n=22, 8,6,15)	18.2	0	0	20
Minimally improved (n=22, 8, 6,15)	50	25	16.7	20
No change (n=22, 8, 6,15)	27.3	62.5	83.3	40
Minimally worse (n=22, 8,6,15)	4.5	0	0	20
Much worse (n=22, 8, 6,15)	0	0	0	0
Very much worse (n=22, 8, 6,15)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with Clinical Global Impression-Improvement (CGI-I) rating Week 12 [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point title	Percentage of subjects with Clinical Global Impression-

	Improvement (CGI-I) rating Week 12 [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point description:

The CGI scale, a clinician-rated scale was completed by the investigator or the investigator's designated deputy to assess treatment response in psychiatric subjects. The CGI-I reported the global changes of the symptoms ranging from 1 to 7 (1: very much improved, 2: much improved, 3:minimally improved, 4: no change, 5: minimally worse, 6: much worse and 7: very much worse). Analysis was performed in FAS population. The 'n' signifies those subjects who had a value at the given time and the assessment was within the window for analysis were included.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	23	21	22
Units: Percentage of subjects				
number (not applicable)				
Very much improved (n=18, 23, 21,20)	0	0	0	0
Much improved (n=18, 23, 21,20)	22.2	13	23.8	15
Minimally improved (n=18, 23, 21,20)	27.8	30.4	42.9	20
No change (n=18, 23, 21,20)	44.4	52.2	23.8	55
Minimally worse (n=18, 23, 21,20)	0	4.3	9.5	10
Much worse (n=18, 23, 21,20)	5.6	0	0	0
Very much worse (n=18, 23, 21,20)	0	0	0	0

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Global Impression-Improvement (CGI-I) score in fully methylated and partially methylated FMR1 gene strata at Week 12

End point title	Clinical Global Impression-Improvement (CGI-I) score in fully methylated and partially methylated FMR1 gene strata at Week 12

End point description:

The CGI scale is a clinician-rated scale completed by the investigator or the investigator's designated deputy to assess treatment response in psychiatric subjects. The CGI-I reported the global changes of the symptoms ranging from 1 to 7 (1: very much improved, 2: much improved, 3:minimally improved, 4: no change, 5: minimally worse, 6: much worse and 7: very much worse). Lower scores indicated improvement. Stratum-I included subjects with fully-methylated FMR1 gene and Stratum-II included subjects with partially-methylated FMR1 gene. Analysis was performed in FAS population. The 'n' signifies those subjects evaluable in fully and partially methylated FMR1 gene stratums who had a value at the given time and the assessment was within the window for analysis were included.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	40	31	27	35
Units: Units on a scale				
least squares mean (standard error)				
Stratum-I (n=22, 8, 6, 15)	3.1 (± 0.18)	3.3 (± 0.3)	3.8 (± 0.34)	3.5 (± 0.22)
Stratum-II (n=18, 23, 21, 20)	3.4 (± 0.21)	3.5 (± 0.19)	3.2 (± 0.2)	3.5 (± 0.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) subscale scores [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)]

End point title	Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) subscale scores [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)]

End point description:

The Aberrant Behavior Checklist – Community edition (ABC-C) is a caregiver-rated symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, and work training centers. The raw data collected from the full, 58-item ABC-C were analyzed according to the modified FXS ABC-C algorithm (ABC-CFX), for which 55 items and six subscales (irritability, lethargy/withdrawal, stereotypic behavior, hyperactivity, inappropriate speech and social avoidance) plus the total score were considered. The assessment is done by attributing to each item of the questionnaire a score from 0 (“not at all a problem”) to 3 (“problem is severe in degree”) and the total score ranks from 0 to 165. A negative change from baseline indicates improvement. Analysis was performed in FAS population. The 'n' signifies those subjects who had a value at given time and assessment was within the window for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	8	6	17
Units: Units on a scale				
least squares mean (standard error)				
Irritability (n=22, 8, 6, 16)	-2.5 (± 1.67)	-3.5 (± 2.74)	2.2 (± 3.21)	4.2 (± 1.94)
Lethargy/withdrawal (n=22, 8, 6, 16)	-1.9 (± 0.78)	-1.4 (± 1.29)	-3.5 (± 1.53)	1.3 (± 0.92)
Stereotypic behavior (n=22, 8, 6, 16)	-1.7 (± 0.58)	-2.2 (± 0.96)	-2.2 (± 1.1)	1.2 (± 0.67)

Hyperactivity (n=22, 8, 6, 16)	-1.3 (± 0.95)	-3.9 (± 1.57)	1.1 (± 1.78)	0.7 (± 1.09)
Inappropriate speech (n=22, 8, 6, 16)	-1 (± 0.42)	-0.8 (± 0.69)	0.3 (± 0.78)	0.9 (± 0.48)
Social avoidance (n=22, 8, 6, 16)	-1.2 (± 0.42)	-0.2 (± 0.71)	-1 (± 0.8)	-0.1 (± 0.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) subscale scores [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point title	Change from baseline to week 12 in the Aberrant Behavior Checklist -Community edition (ABC-CFX) subscale scores [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point description:

The Aberrant Behavior Checklist – Community edition (ABC-C) is a caregiver-rated symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, and work training centers. The raw data collected from the full, 58-item ABC-C were analyzed according to the modified FXS ABC-C algorithm (ABC-CFX), for which 55 items and six subscales (irritability, lethargy/withdrawal, stereotypic behavior, hyperactivity, inappropriate speech and social avoidance) plus the total score were considered. The assessment is done by attributing to each item of the questionnaire a score from 0 (“not at all a problem”) to 3 (“problem is severe in degree”) and the total score ranks from 0 to 165. A negative change from baseline indicates improvement. Analysis was performed in FAS population. The 'n' signifies those subjects who had a value at given time and assessment was within the window for analysis.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	23	21	22
Units: Units on a scale				
least squares mean (standard error)				
Irritability (n=18, 23, 21,20)	0 (± 1.75)	-1.5 (± 1.58)	-1.3 (± 1.65)	-0.8 (± 1.66)
Lethargy/withdrawal (n=18, 23, 21,20)	-0.8 (± 1.11)	-0.8 (± 1)	-0.4 (± 1.05)	-0.3 (± 1.05)
Stereotypic behavior (n= 18, 23, 21,20)	0.1 (± 0.64)	-1.4 (± 0.57)	0.1 (± 0.6)	-1 (± 0.6)
Hyperactivity (n= 18, 23, 21,20)	-0.8 (± 0.96)	-1.5 (± 0.87)	-0.3 (± 0.91)	-1.8 (± 0.91)
Inappropriate speech (n=18, 23, 21,20)	-0.8 (± 0.5)	-0.9 (± 0.44)	-0.1 (± 0.46)	-0.6 (± 0.47)
Social avoidance (n=18, 23, 21,20)	-1.1 (± 0.45)	-0.7 (± 0.4)	-0.9 (± 0.42)	-1.1 (± 0.42)

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects achieving a clinical response in fully methylated and partially methylated FMR1 gene strata at Week 12

End point title	Percentage of subjects achieving a clinical response in fully methylated and partially methylated FMR1 gene strata at Week 12

End point description:

Clinical response was defined as a reduction of at least 25% from baseline in ABC-CFX total score and a CGI-I of 1 (very much improved) or 2 (much improved). Analysis was performed in FAS population: all randomized patients who received at least 1 dose of study drug, had a baseline and at least 1 post-baseline assessment for the primary efficacy parameter. Total is number of patients with non-missing baseline ABC-CFX total score and at least 1 non-missing post-baseline ABC-CFX total score and CGI-I assessment. Stratum I included patients whose FMR1 gene was fully methylated; Stratum II included patients whose FMR1 gene was partially.

End point type	Secondary

End point timeframe:

Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	31	27	39
Units: Percentage of subjects				
number (not applicable)				
Stratum-I (n=22, 8, 6,17)	9.1	12.5	0	5.9
Stratum-II (n=19, 23, 21,22)	10.5	4.3	19	4.5

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in Repetitive Behavior Scale - Revised (RBS-R) total score in fully methylated and partially methylated FMR1 gene strata

End point title	Change from baseline to week 12 in Repetitive Behavior Scale - Revised (RBS-R) total score in fully methylated and partially methylated FMR1 gene strata

End point description:

The Repetitive Behavior Scale - Revised (RBS-R) is a caregiver rated tool that captures the breadth of repetitive behavior. It includes six domains: ritualistic behavior, sameness behavior, stereotypic behavior, self-injurious behavior, compulsive behavior, and restricted interests. Every behavior falling into one of the above categories is rated from 0 (behavior does not occur) to 3 (behavior occurs and it is a severe problem). The total score ranks from 0 to 129. It is a 43-item questionnaire. A negative change from baseline indicates improvement. Analysis was performed in FAS population. Only participants who had a value at the given time and the assessment was within the window for analysis were included. Stratum I was subjects with fully methylated FMR1 gene and Stratum II subjects were partially methylated for the FMR1 gene.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	41	31	27	39
Units: Units on a scale				
least squares mean (standard error)				
Stratum-I (n=22, 8, 6, 16)	-6.2 (± 2.03)	-2.3 (± 3.25)	-8.5 (± 3.95)	1.5 (± 2.31)
Stratum-II (n=18, 23, 21, 22)	-5 (± 2.67)	-4.3 (± 2.36)	-5.9 (± 2.51)	-2.4 (± 2.47)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in Repetitive Behavior Scale -Revised (RBS-R) subscale scores [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]

End point title	Change from baseline to week 12 in Repetitive Behavior Scale - Revised (RBS-R) subscale scores [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]

End point description:

The Repetitive Behavior Scale - Revised (RBS-R) is a caregiver rated tool that captures the breadth of repetitive behavior. It includes six domains: ritualistic behavior, sameness behavior, stereotypic behavior, self-injurious behavior, compulsive behavior, and restricted interests. Every behavior falling into one of the above categories is rated from 0 (behavior does not occur) to 3 (behavior occurs and it is a severe problem). The total score ranks from 0 to 129. It is a 43-item questionnaire. A negative change from baseline indicates improvement. Analysis was performed in FAS population. Only participants who had a value at the given time and the assessment was within the window for analysis were included.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	22	8	6	17
Units: Units on a scale				
least squares mean (standard error)				
Stereotyped behaviour (n=22, 8, 6,16)	-1 (± 0.56)	-1 (± 0.91)	-1.5 (± 1.03)	0.5 (± 0.64)
Self-injurious behaviour (n=22, 8, 6,16)	-1.1 (± 0.28)	0 (± 0.46)	0.8 (± 0.53)	-0.2 (± 0.33)
Compulsive behaviour (n=22, 8, 6,16)	-0.8 (± 0.51)	-0.1 (± 0.84)	-1.2 (± 1.06)	0.2 (± 0.6)
Ritualistic behavior (n=22, 8, 6,16)	-0.6 (± 0.57)	-0.2 (± 0.93)	-2.2 (± 1.12)	0.8 (± 0.66)
Sameness behavior (n=22, 8, 6,16)	-1.8 (± 0.73)	-0.8 (± 1.19)	-2.8 (± 1.42)	0.3 (± 0.85)
Restricted behavior (n=22, 8, 6,16)	-1.1 (± 0.39)	0 (± 0.65)	-1.2 (± 0.74)	-0.2 (± 0.46)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in Repetitive Behavior Scale -Revised (RBS-R) subscale scores [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point title	Change from baseline to week 12 in Repetitive Behavior Scale - Revised (RBS-R) subscale scores [Stratum II: FXS subjects with partially-methylated FMR1 gene (PM)]

End point description:

The Repetitive Behavior Scale - Revised (RBS-R) is a caregiver rated tool that captures the breadth of repetitive behavior. It includes six domains: ritualistic behavior, sameness behavior, stereotypic behavior, self-injurious behavior, compulsive behavior, and restricted interests. Every behavior falling into one of the above categories is rated from 0 (behavior does not occur) to 3 (behavior occurs and it is a severe problem). The total score ranks from 0 to 129. It is a 43-item questionnaire. A negative change from baseline indicates improvement. Analysis was performed in FAS population. Only participants who had a value at the given time and the assessment was within the window for analysis were included.

End point type	Secondary

End point timeframe:

Baseline to Week 12

End point values	Placebo - Double blind Treatment Period	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	19	23	21	22
Units: Units on a scale				
least squares mean (standard error)				
Stereotyped behaviour(n=18, 23, 21,20)	0.2 (± 0.59)	0.1 (± 0.53)	0.1 (± 0.56)	0.4 (± 0.56)
Self-injurious behaviour (n=18, 23, 21,20)	0.5 (± 0.59)	-0.6 (± 0.53)	-0.7 (± 0.55)	0 (± 0.56)
Compulsive behaviour (n=18, 23, 21,20)	-1 (± 0.65)	-0.9 (± 0.58)	-1.5 (± 0.62)	-0.2 (± 0.61)
Ritualistic behaviour (n=18, 23, 21,20)	-1.8 (± 0.62)	-0.1 (± 0.55)	-1.5 (± 0.58)	-1 (± 0.58)
Sameness behaviour (n=18, 23, 21,20)	-2.8 (± 0.88)	-2.2 (± 0.77)	-1.6 (± 0.83)	-1.3 (± 0.82)
Restricted behaviour (n=18, 23, 21,20)	-0.3 (± 0.45)	-0.6 (± 0.4)	-0.7 (± 0.43)	-0.4 (± 0.42)

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of AFQ056

End point title	Plasma concentrations of AFQ056[18]

End point description:

Blood samples were collected at regular intervals to evaluate the plasma concentrations of AFQ056. Analysis was performed in FAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

End point type	Secondary

End point timeframe:

Week 4 and Week 12

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Plasma concentrations were evaluated only for treatment arms (AFQ056 25mg, 50mg and 100 mg) included in the baseline period.

End point values	AFQ056 25 mg bid	AFQ056 50 mg bid	AFQ056 100 mg bid	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	27	39	
Units: nanogram/millilitre (ng/ml)				
arithmetic mean (standard deviation)				
Plasma concentration at Week 4 (n=31,25 and 38)	38.126 (± 31.9702)	107.376 (± 73.4818)	173.103 (± 140.2442)	
Plasma concentration at Week 12(n=31, 26 and 36)	37.03 (± 34.2249)	98.907 (± 65.6224)	169.704 (± 163.2669)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo -Double blind Treatment Period

Reporting group description:

2 placebo capsule was administered bid for 12 weeks.

Reporting group title	AFQ056 100 mg bid

Reporting group description:

One AFQ056 100 mg capsule and one placebo capsule were administered bid for 12 weeks.

Reporting group title	AFQ056 50 mg bid

Reporting group description:

Two AFQ056 25 mg capsules were administered bid for 12 weeks.

Reporting group title	AFQ056 25 mg bid

Reporting group description:

One AFQ056 25 mg capsule and one placebo capsule were administered bid for 12 weeks.

Serious adverse events	Placebo -Double blind Treatment Period	AFQ056 100 mg bid	AFQ056 50 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 42 (4.76%)	0 / 39 (0.00%)	0 / 27 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Convulsion			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 42 (2.38%)	0 / 39 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AFQ056 25 mg bid		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Convulsion			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo -Double blind Treatment Period	AFQ056 100 mg bid	AFQ056 50 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 42 (40.48%)	30 / 39 (76.92%)	9 / 27 (33.33%)
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 42 (9.52%)	10 / 39 (25.64%)	0 / 27 (0.00%)
occurrences (all)	6	13	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	1 / 27 (3.70%)
occurrences (all)	0	2	1
Pyrexia			
subjects affected / exposed	1 / 42 (2.38%)	3 / 39 (7.69%)	1 / 27 (3.70%)
occurrences (all)	1	3	1
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	0	2	0

Diarrhoea			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Vomiting			
subjects affected / exposed	0 / 42 (0.00%)	6 / 39 (15.38%)	1 / 27 (3.70%)
occurrences (all)	0	6	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 42 (2.38%)	1 / 39 (2.56%)	1 / 27 (3.70%)
occurrences (all)	1	1	3
Nasal congestion			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Oropharyngeal pain			
subjects affected / exposed	1 / 42 (2.38%)	1 / 39 (2.56%)	2 / 27 (7.41%)
occurrences (all)	1	1	2
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	0 / 42 (0.00%)	0 / 39 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 42 (2.38%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	1	2	0
Initial insomnia			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Insomnia			
subjects affected / exposed	0 / 42 (0.00%)	6 / 39 (15.38%)	0 / 27 (0.00%)
occurrences (all)	0	7	0
Self injurious behaviour			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Influenza			

subjects affected / exposed	2 / 42 (4.76%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Nasopharyngitis			
subjects affected / exposed	6 / 42 (14.29%)	5 / 39 (12.82%)	6 / 27 (22.22%)
occurrences (all)	7	8	7
Oral herpes			
subjects affected / exposed	0 / 42 (0.00%)	2 / 39 (5.13%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	0 / 42 (0.00%)	1 / 39 (2.56%)	1 / 27 (3.70%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 42 (9.52%)	5 / 39 (12.82%)	1 / 27 (3.70%)
occurrences (all)	4	5	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 42 (2.38%)	4 / 39 (10.26%)	1 / 27 (3.70%)
occurrences (all)	1	4	1

Non-serious adverse events	AFQ056 25 mg bid		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 31 (70.97%)		
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 31 (12.90%)		
occurrences (all)	5		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		

Diarrhoea subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Vomiting subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 3		
Nasal congestion subjects affected / exposed occurrences (all)	3 / 31 (9.68%) 6		
Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	2 / 31 (6.45%) 2		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Initial insomnia subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Insomnia subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Self injurious behaviour subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0		
Infections and infestations Influenza			

subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	7 / 31 (22.58%)		
occurrences (all)	9		
Oral herpes			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Rhinitis			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	3		
Upper respiratory tract infection			
subjects affected / exposed	2 / 31 (6.45%)		
occurrences (all)	2		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 31 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2011	For female subjects of child-bearing potential and the frequency of pregnancy testing was increased.
12 January 2012	1.The inclusion criterion describing the requirements to establish the diagnosis of FXS was modified such that documented genetic testing results (prior to study entry) were no longer required, provided the diagnosis was confirmed by the genetic testing at Visit 1 2.The inclusion criterion describing the requirements for a caregiver was clarified to avoid implying only one caregiver was required to oversee study participation for a subject 3.Regional capping of recruitment into each stratum was removed 4.The protocol was amended to allow for the possibility of a futility analysis; however, a futility analysis was not performed, following consultation with health authorities 5. Instructions regarding the assessment for the presence of suicidality as part of monitoring the adverse events were added and the neuropsychiatric inventory questionnaire (NPI-Q) was added as a safety assessment for potential neuropsychiatric events 6.The assessment schedule was revised to indicate that the optional biomarker samples were not required to be collected at Visit 3 for subjects who discontinued during the Placebo Run-in Period 7.Requirements for the Follow-up visit were modified in consideration of subjects entered the separate open-label extension study 8.Isoflurane was added to the list of prohibited medications 9.The upper limits of the clinically notable systolic and diastolic blood pressure criteria were revised.
02 February 2012	Under this amendment, subjects were randomized (1:1) to either 100 mg b.i.d AFQ056 or placebo, and no further subjects were randomized to the lower dose groups of 25 mg and 50 mg b.i.d AFQ056. The primary and key secondary objectives of the study were modified to reflect this focus on the 100 mg b.i.d vs. placebo comparison.
26 July 2012	1. The protocol included the possibility for an interim analysis when 50% of subjects were randomized to the highest dose arm; the protocol was amended to allow for the possibility of a futility analysis without consideration of the percentage of subjects randomized to the highest dose arm; however, a futility analysis was not performed, following consultation with health authorities. 2. The protocol was amended such that the raw data from the ABC-C would be analysed according to a modified scoring algorithm (ABC-CFX). 3. The primary and key secondary objectives, and the minimal number of subjects to be randomized, were rephrased as requested by pediatric committee (PDCO) of European Medicines Agency. 4. Following recommendations from the PDCO, wording about isoflurane and grapefruit juice was added in the exclusion criteria section and local anesthetics were added to the protocol as being specifically allowed for phlebotomy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported