



## Clinical trial results:

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

#### Summary

EudraCT number	2009-013667-19
Trial protocol	DK GB DE IT ES
Global end of trial date	14 August 2013

#### Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	06 August 2015

#### Trial information

##### Trial identification

Sponsor protocol code	CAFQ056A2212
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01253629
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)	No
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?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 August 2013
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	14 August 2013
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To assess the efficacy of three doses of AFQ056 versus placebo in reducing the ABC-C Total score (using the FXS specific algorithm - ABC-CFX) 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	12 November 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
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	Germany: 12
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	United States: 73
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Switzerland: 18
Worldwide total number of subjects	184
EEA total number of subjects	60

Notes:

<b>Subjects enrolled per age group</b>	
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)	0
Adults (18-64 years)	184
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

There were 343 patients who entered into the screening period; 184 (53.6%) patients completed the screening phase.

### Period 1

Period 1 title	Single-blind Placebo Run-in
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Single blind <sup>[1]</sup>
Roles blinded	Subject, Carer

### Arms

<b>Arm title</b>	Placebo -Single blind period
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Arm description:

Placebo bid (2 capsules of placebo per intake)

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

Dosage and administration details:

matching placebo of AFQ056

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: As per protocol, patients and their caregivers were blinded..

<b>Number of subjects in period 1</b>	Placebo -Single blind period
Started	184
Completed	175
Not completed	9
Adverse Event, any	2
Lost to follow-up	3
Protocol deviation	4

**Period 2**

Period 2 title	Double blind randomized period
Is this the baseline period?	Yes <sup>[2]</sup>
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

**Arms**

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	Placebo -Double blind period
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Arm description:

2 matching placebo capsules , twice daily

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

Dosage and administration details:

matching placebo of AFQ056

<b>Arm title</b>	AFQ056 25 mg bid
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Arm description:

1 capsule of 25 mg and 1 capsule of placebo per intake twice daily

Arm type	Experimental
Investigational medicinal product name	AFQ056
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.

<b>Arm title</b>	AFQ056 50 mg bid
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Arm description:

2 capsules of 25 mg per intake, twice daily

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

Dosage and administration details:

50 mg bid, oral, swallow it whole.

<b>Arm title</b>	AFQ056 100 mg bid
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Arm description:

1 capsule of 100 mg and 1 capsule of placebo per intake, twice daily

Arm type	Experimental
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Investigational medicinal product name	AFQ056
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.	

Notes:

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

Justification: Period 1 is the Placebo run in period; that is why it is not the baseline period.

<b>Number of subjects in period 2<sup>[3]</sup></b>	Placebo -Double blind period	AFQ056 25 mg bid	AFQ056 50 mg bid
Started	44	44	42
Completed	43	40	40
Not completed	1	4	2
Consent withdrawn by subject	-	1	-
Adverse Event, any	1	2	2
Administrative problems	-	1	-

<b>Number of subjects in period 2<sup>[3]</sup></b>	AFQ056 100 mg bid
Started	45
Completed	39
Not completed	6
Consent withdrawn by subject	-
Adverse Event, any	6
Administrative problems	-

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: Worldwide enrolled number included all patients who were enrolled to Placebo run in period where as baseline period (double blind period) included randomized patients only.

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo -Double blind period
Reporting group description: 2 matching placebo capsules , twice daily	
Reporting group title	AFQ056 25 mg bid
Reporting group description: 1 capsule of 25 mg and 1 capsule of placebo per intake twice daily	
Reporting group title	AFQ056 50 mg bid
Reporting group description: 2 capsules of 25 mg per intake, twice daily	
Reporting group title	AFQ056 100 mg bid
Reporting group description: 1 capsule of 100 mg and 1 capsule of placebo per intake, twice daily	

Reporting group values	Placebo -Double blind period	AFQ056 25 mg bid	AFQ056 50 mg bid
Number of subjects	44	44	42
Age categorical			
Randomized set			
Units: Subjects			
Adult (18 years to 44 years)	44	44	42
Age continuous			
Randomized set			
Units: years			
arithmetic mean	26.2	26.9	26.7
standard deviation	± 7.21	± 6.76	± 6.9
Gender categorical			
All randomized patients			
Units: Subjects			
Female	3	3	2
Male	41	41	40

Reporting group values	AFQ056 100 mg bid	Total	
Number of subjects	45	175	
Age categorical			
Randomized set			
Units: Subjects			
Adult (18 years to 44 years)	45	175	
Age continuous			
Randomized set			
Units: years			
arithmetic mean	24.2		
standard deviation	± 6.07	-	
Gender categorical			
All randomized patients			
Units: Subjects			
Female	3	11	

Male	42	164	
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## End points

### End points reporting groups

Reporting group title	Placebo -Single blind period
Reporting group description: Placebo bid (2 capsules of placebo per intake)	
Reporting group title	Placebo -Double blind period
Reporting group description: 2 matching placebo capsules , twice daily	
Reporting group title	AFQ056 25 mg bid
Reporting group description: 1 capsule of 25 mg and 1 capsule of placebo per intake twice daily	
Reporting group title	AFQ056 50 mg bid
Reporting group description: 2 capsules of 25 mg per intake, twice daily	
Reporting group title	AFQ056 100 mg bid
Reporting group description: 1 capsule of 100 mg and 1 capsule of placebo per intake, twice daily	

### Primary: Change from baseline to Week 12 for the Aberrant Behavior Checklist – Community edition (ABC-CFX ) total score [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]

End point title	Change from baseline to Week 12 for the Aberrant Behavior Checklist – Community edition (ABC-CFX ) total score [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]
End point description: The Aberrant Behavior Checklist – Community edition (ABC-C) is a 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. 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.	
End point type	Primary
End point timeframe: Baseline, Week 12	

End point values	Placebo - Double blind 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	20 <sup>[1]</sup>	15 <sup>[2]</sup>	17 <sup>[3]</sup>	15 <sup>[4]</sup>
Units: unit on a scale				
least squares mean (standard error)	-11.4 (± 3.73)	-14.3 (± 4)	1.8 (± 3.95)	-1.8 (± 4.04)

Notes:

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

## Statistical analyses

<b>Statistical analysis title</b>	Placebo versus AFQ056 25 mg bid
Statistical analysis description:	
Null Hypothesis: There is no difference in the change from baseline to Week 12 in ABC-CFX total score between any AFQ056 dose and placebo among FM patients	
Alternative Hypothesis: There is a difference in the change from baseline to Week 12 in ABC-CFX total score between at least one doses of AFQ056 and placebo among FM patients	
Comparison groups	Placebo -Double blind period v AFQ056 25 mg bid
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.589
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.9
upper limit	8

<b>Statistical analysis title</b>	Placebo versus AFQ056 50 mg bid
Statistical analysis description:	
Null hypothesis : There is no difference in the change from baseline to Week 12 in ABC-CFX total score between any AFQ056 dose and placebo among ully-methylated (FM) patients. Alternative hypothesis : There is a difference in the change from baseline to Week 12 in ABC-CFX total score between at least one doses of AFQ056 and placebo among FM patients.	
Comparison groups	Placebo -Double blind period v AFQ056 50 mg bid
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.018
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	13.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.3
upper limit	24

<b>Statistical analysis title</b>	Placebo versus AFQ056 100 mg bid
Comparison groups	Placebo -Double blind period v AFQ056 100 mg bid
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.087
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	9.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	20.5

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

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

The Aberrant Behavior Checklist – Community edition (ABC-C) is a 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. 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.

End point type	Secondary
End point timeframe:	
Baseline, week 12	

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<b>End point values</b>	Placebo - Double blind 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 <sup>[5]</sup>	19 <sup>[6]</sup>	21 <sup>[7]</sup>	20 <sup>[8]</sup>
Units: Unit on a scale				
least squares mean (standard error)	-8.9 (± 4.39)	-1.9 (± 4.64)	-5.1 (± 4.48)	-4.6 (± 4.53)

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

No statistical analyses for this end point

### Secondary: Number of patients with Clinical Global Impression-Improvement (CGI-I) score responses at Week 12 [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]

End point title	Number of patients with Clinical Global Impression-Improvement (CGI-I) score responses at Week 12 [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]
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End point description:

The Clinical Global Impression (CGI) scale is used to assess treatment response in psychiatric patients. The scale is divided in two parts, one assessing the severity of illness (CGI-S) and one assessing the global improvement (CGI-I). The CGI-I reports the global changes of the symptoms rated on a seven-point scale i.e. from 1 to 7 (with 1 being "very much improved", 4 being "no change" to 7 being "very much worse"). Lower scores indicate improvement. Full analysis set (FAS) was used for the analysis. 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
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End point timeframe:

Week 12

End point values	Placebo - Double blind 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	20	15	17	15
Units: Patients				
1 (Very much improved)	0	1	0	0
2 (Much improved)	2	3	3	3
3 (Minimally improved)	6	3	4	5
4 (No change)	11	8	10	4
5 (Minimally worse)	1	0	0	3
6 (Much worse)	0	0	0	0
7 (Very much worse)	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of patients with Clinical Global Impression-Improvement (CGI-I) score responses at Week 12 [Stratum II: FXS patients with partially-methylated FMR1 gene (PM)]

End point title	Number of patients with Clinical Global Impression-Improvement (CGI-I) score responses at Week 12 [Stratum II: FXS patients with partially-methylated FMR1 gene (PM)]
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End point description:

The CGI scale is used to assess treatment response in psychiatric patients. The scale is divided in two parts, one assessing the severity of illness (CGI-S) and one assessing the global improvement (CGI-I). The CGI-I reports the global changes of the symptoms rated on a seven-point scale i.e. from 1 to 7 (with 1 being "very much improved", 4 being "no change" to 7 being "very much worse"). Lower scores indicate improvement. Full analysis set (FAS) was used for the analysis. 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:	
Week 12	

End point values	Placebo - Double blind 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	19	21	20
Units: Subjects				
1 (Very much improved)	0	1	1	0
2 (Much improved)	3	2	6	4
3 (Minimally improved)	7	8	7	5
4 (No change)	10	8	6	9
5 (Minimally worse)	2	0	0	1
6 (Much worse)	0	0	1	1
7 (Very much worse)	0	0	0	0

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline to Week 12 for the Aberrant Behavior Checklist – Community edition (ABC-CFX) subscale scores [Stratum I: FXS patients with fully-methylated FMR1 gene (FM)]

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

The Aberrant Behavior Checklist – Community edition (ABC-C) is a 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. 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, week 12	

End point values	Placebo - Double blind 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	20	15	17	15
Units: units on scale				
least squares mean (standard error)				
Irritability	-2.4 (± 1.4)	-4.5 (± 1.56)	2 (± 1.51)	-0.5 (± 1.56)
Lethargy/withdrawal	-2.1 (± 0.91)	-2.5 (± 0.96)	0.2 (± 0.95)	-0.1 (± 0.97)
Stereotypic behavior	-2.1 (± 0.58)	-2 (± 0.63)	-1 (± 0.62)	-0.5 (± 0.63)
Hyperactivity	-2 (± 0.78)	-3 (± 0.84)	0.1 (± 0.83)	-1.4 (± 0.85)
Inappropriate speech	-1.1 (± 0.52)	-0.6 (± 0.55)	0.4 (± 0.54)	0.3 (± 0.55)
Social avoidance	-1.2 (± 0.5)	-0.9 (± 0.55)	-0.3 (± 0.53)	0.3 (± 0.55)

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change from baseline to Week 12 for the Aberrant Behavior Checklist – Community edition (ABC-CFX) subscale scores [Stratum II: FXS patients with partially-methylated FMR1 gene (PM)]

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

The Aberrant Behavior Checklist – Community edition (ABC-C) is a 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. 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, week 12	

End point values	Placebo - Double blind 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	19	21	20
Units: units on scale				
least squares mean (standard error)				
Irritability	-3.8 (± 1.71)	-1.3 (± 1.82)	0 (± 1.75)	-0.7 (± 1.76)
Lethargy/withdrawal	-2.1 (± 1.09)	-0.9 (± 1.15)	-1.8 (± 1.11)	-1.9 (± 1.13)
Stereotypic behavior	-0.1 (± 0.63)	-0.3 (± 0.68)	-0.7 (± 0.65)	-0.1 (± 0.65)
Hyperactivity	-1.4 (± 0.98)	-0.2 (± 1.03)	-1.2 (± 1)	-1.5 (± 1.01)

Inappropriate speech	-0.7 (± 0.58)	0.3 (± 0.61)	-0.1 (± 0.58)	0.2 (± 0.59)
Social avoidance	-1.1 (± 0.5)	0.5 (± 0.53)	-1.41 (± 0.51)	-0.8 (± 0.52)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of patients with clinical response by methylation status at week 12

End point title	Percentage of patients with clinical response by methylation status at week 12
End point description:	
Clinical response was defined as reduction of at least 25% from baseline in the modified Aberrant Behavior Checklist – Community edition (ABC-CFX) total score and a score of 1 (very much improved) or 2 (much improved) on the CGI-I scale at Week 12 (or with last observation carried forward (LCOF)). Percentgae of patients with clinical response were reported by methylation status i.e FM stratum (i.e. Stratum I) for FXS patients with fully-methylated FMR1 gene and PM stratum (i.e. Stratum II) for FXS patients with partially-methylated FMR1 gene. FAS was used for analysis population. The 'n' signifies the number of patients with non-missing baseline ABC-CFX total score and at least one non-missing post-baseline ABC-CFX total score and CGI-I assessment for respective stratum and arms.	
End point type	Secondary
End point timeframe:	
Week 12	

End point values	Placebo - Double blind 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	44	44	42	45
Units: Percentage of subjects				
number (not applicable)				
FM Stratum (n=20, 22, 20, 20)	10	18.2	10	0
PM Stratum (n= 24, 22, 22, 25)	4.2	9.1	22.7	16

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline to Week 12 for Repetitive behavior scale - Revised (RBS-R) total and subscale scores

End point title	Change from baseline to Week 12 for Repetitive behavior scale - Revised (RBS-R) total and subscale scores
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, Week 12	

End point values	Placebo - Double blind 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	42	34	38	35
Units: Units on scale				
least squares mean (standard error)				
Total score	-5.1 (± 1.53)	-4.4 (± 1.69)	-2.8 (± 1.6)	-3.4 (± 1.65)
Stereotypic behavior	-0.7 (± 0.31)	-0.8 (± 0.34)	-0.3 (± 0.32)	-0.4 (± 0.34)
Self-injurious behavior	-0.6 (± 0.27)	-0.4 (± 0.29)	0.5 (± 0.28)	-0.3 (± 0.29)
Compulsive behavior	-1 (± 0.38)	-0.8 (± 0.42)	-0.5 (± 0.39)	-0.5 (± 0.41)
Ritualistic behavior	-0.8 (± 0.32)	-0.3 (± 0.35)	-1.1 (± 0.33)	-1 (± 0.35)
Sameness behavior	-1.5 (± 0.64)	-1.3 (± 0.72)	-1 (± 0.68)	-1.4 (± 0.7)
Restricted behavior	-0.4 (± 0.27)	-1 (± 0.29)	-0.2 (± 0.28)	0 (± 0.29)

## Statistical analyses

No statistical analyses for this end point

## Secondary: Pharmacokinetics of AFQ056: concentration levels

End point title	Pharmacokinetics of AFQ056: concentration levels <sup>[9]</sup>
End point description:	
Parent drug AFQ056 concentrations in plasma were determined by a validated liquid chromatography-mass spectrometry (LC-MS-MS) method with a lower limit of quantification (LLOQ) of 2 ng/mL. Full analysis set is used for this endpoint. The 'n' signifies those subjects evaluable for this measure at specified time points for each arm, respectively.	
End point type	Secondary
End point timeframe:	
Week 4, Week 12	

Notes:

[9] - 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: Pharmacokinetics is only on study drug i.e. AFQ056, not on Placebo.

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	44	42	45	
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4 (n = 43, 39, 43)	51.567 (± 48.6258)	113.882 (± 101.6432)	194.314 (± 149.7874)	

Week 12 (n=35, 38, 35)	50.487 ( $\pm$ 47.7737)	120.389 ( $\pm$ 123.5039)	183.16 ( $\pm$ 140.074)	
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## Statistical analyses

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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
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

### Reporting groups

Reporting group title	Placebo -Double blind period
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Reporting group description:

2 matching placebo capsules , twice daily

Reporting group title	AFQ056 100 mg bid
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Reporting group description:

1 capsule of 100 mg and 1 capsule of placebo per intake, twice daily

Reporting group title	AFQ056 50 mg bid
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Reporting group description:

2 capsules of 25 mg per intake, twice daily

Reporting group title	AFQ056 25 mg bid
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Reporting group description:

1 capsule of 25 mg and 1 capsule of placebo per intake twice daily

Serious adverse events	Placebo -Double blind period	AFQ056 100 mg bid	AFQ056 50 mg bid
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 44 (2.27%)	2 / 45 (4.44%)	1 / 42 (2.38%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 44 (0.00%)	0 / 45 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 44 (0.00%)	2 / 45 (4.44%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			

subjects affected / exposed	0 / 44 (0.00%)	1 / 45 (2.22%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			
subjects affected / exposed	0 / 44 (0.00%)	1 / 45 (2.22%)	0 / 42 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lobar pneumonia			
subjects affected / exposed	1 / 44 (2.27%)	0 / 45 (0.00%)	0 / 42 (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
Upper respiratory tract infection			
subjects affected / exposed	0 / 44 (0.00%)	0 / 45 (0.00%)	1 / 42 (2.38%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

<b>Serious adverse events</b>	AFQ056 25 mg bid		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 44 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hallucination, visual			

subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Insomnia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Lobar pneumonia			
subjects affected / exposed	0 / 44 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 44 (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 %

<b>Non-serious adverse events</b>	Placebo -Double blind period	AFQ056 100 mg bid	AFQ056 50 mg bid
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 44 (25.00%)	24 / 45 (53.33%)	18 / 42 (42.86%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 44 (2.27%)	8 / 45 (17.78%)	0 / 42 (0.00%)
occurrences (all)	1	14	0
Headache			
subjects affected / exposed	2 / 44 (4.55%)	4 / 45 (8.89%)	3 / 42 (7.14%)
occurrences (all)	3	11	3
General disorders and administration site conditions			
Irritability			
subjects affected / exposed	0 / 44 (0.00%)	3 / 45 (6.67%)	2 / 42 (4.76%)
occurrences (all)	0	4	2
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0	4 / 45 (8.89%) 5	1 / 42 (2.38%) 1
Diarrhoea subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 4	3 / 45 (6.67%) 3	1 / 42 (2.38%) 3
Vomiting subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	4 / 45 (8.89%) 4	5 / 42 (11.90%) 6
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1	2 / 45 (4.44%) 2	3 / 42 (7.14%) 3
Insomnia subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0	7 / 45 (15.56%) 8	4 / 42 (9.52%) 4
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	6 / 45 (13.33%) 6	3 / 42 (7.14%) 3
Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2	4 / 45 (8.89%) 4	1 / 42 (2.38%) 1
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0	4 / 45 (8.89%) 4	1 / 42 (2.38%) 1

<b>Non-serious adverse events</b>	AFQ056 25 mg bid		
Total subjects affected by non-serious adverse events subjects affected / exposed	13 / 44 (29.55%)		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
Headache			

subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 1		
General disorders and administration site conditions Irritability subjects affected / exposed occurrences (all)	2 / 44 (4.55%) 2		
Gastrointestinal disorders Nausea subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0  2 / 44 (4.55%) 2  3 / 44 (6.82%) 3		
Psychiatric disorders Aggression subjects affected / exposed occurrences (all)  Insomnia subjects affected / exposed occurrences (all)	1 / 44 (2.27%) 2  1 / 44 (2.27%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 44 (6.82%) 3  3 / 44 (6.82%) 3		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	0 / 44 (0.00%) 0		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2010	<p>This amendment introduced the following changes:</p> <ul style="list-style-type: none"><li>• the criterion which excluded patients from the study based upon previous methylation status testing was removed</li><li>• The SRS-A was changed to an exploratory measure to be performed only in selected countries</li><li>• a clarification was added to indicate that an interim analysis of safety data for the external Data Monitoring Committee (DMC) would be performed.</li><li>• the description of the analysis of pharmacokinetics (PK) samples was revised</li></ul>
05 April 2011	<p>This amendment introduced the following changes:</p> <ul style="list-style-type: none"><li>• to allow participating centers to adapt the consent process according to local regulations, the protocol was modified to reflect that consent had to be obtained from the patient's legal guardian or a legally acceptable representative</li><li>• the required duration of contraceptive use following the last dose of study medication in females of child-bearing potential was extended to 96 hours</li><li>• the exclusion criteria was modified to increase the allowable upper limit of bilirubin (total and unconjugated (indirect)) levels in patients with a diagnosis of Gilbert's syndrome</li><li>• as there tended to be an increased prevalence of concomitant symptomatic medication use in the US, Canada, and Australia, the protocol was revised such that each region could not contribute more than 60% of the total number of target patients to be enrolled in each stratum</li><li>• sections of the protocol which referred to the unblinded interim analysis of safety were revised to take into account the timing of the DMC reviews and the possibility for an unblinded interim analysis of safety data.</li><li>• requirements for the Follow-up visit were modified in consideration of patients who would enter the separate open-label extension study</li></ul>
19 October 2011	<p>This was an urgent safety amendment which introduced the following changes:</p> <ul style="list-style-type: none"><li>• for women of child bearing potential, the requirements for contraceptives was changed from effective to highly effective and the frequency of pregnancy testing was increased</li></ul>
15 December 2011	<p>This amendment introduced the following changes:</p> <ul style="list-style-type: none"><li>• 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 performed at Visit 1</li><li>• the inclusion criterion describing the requirements for a caregiver was clarified so as to avoid implying only one caregiver was required to oversee study participation for a patient.</li><li>• regional capping of recruitment into each stratum, previously introduced under Protocol Amendment 2, was removed</li><li>• the assessment schedule was revised to indicate that the optional biomarker samples were not required to be collected at Visit 3 for patients who discontinued during the Placebo Run-in Period</li><li>• instructions regarding the assessment for the presence of suicidality as part of monitoring of adverse events were added</li><li>• isoflurane was added to the list of prohibited medications</li></ul>

26 July 2012	<p>This amendment introduced the following changes:</p> <ul style="list-style-type: none"> <li>• 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</li> <li>• the protocol was amended such that the raw data from the ABC-C would be analyzed according to a modified scoring algorithm (ABC-CFX)</li> <li>• following recommendations from the PDCO, wording about isoflurane and grapefruit juice was added in the exclusion criteria section and local anesthetics added to the protocol as being specifically allowed for phlebotomy.</li> </ul>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported