



Clinical trial results:

Sequential, two-period study to assess the pharmacokinetics, safety & tolerability of single and multiple oral doses of AFQ056 in patients with FXS (Fragile X syndrome) aged 5-11 years (Cohort 1) and 3-4 years (Cohort 2)

Summary

EudraCT number	2011-004867-65
Trial protocol	Outside EU/EEA ES
Global end of trial date	16 October 2013

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	23 July 2015

Trial information

Trial identification

Sponsor protocol code	CAFQ056B2154
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01482143
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)	EMA-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 October 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 October 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the pharmacokinetics of single and multiple oral AFQ056 doses in patients with Fragile X Syndrome (FXS) aged 5-11 years (cohort 1) and 3-4 years if included in the study (cohort 2)

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	23 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United States: 17
Worldwide total number of subjects	21
EEA total number of subjects	4

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)	21
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

A total of twelve patients with FXS aged 5-11 years inclusive were enrolled to cohort 1. As the results from cohort 1 allowed the study to progress to cohort 2, an additional nine patients aged 3-4 years inclusive were recruited.

Pre-assignment

Screening details:

Patient selection was established by checking through all inclusion/exclusion criteria at screening and first baseline visit.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1-Treatment Period 1

Arm description:

Cohort 1 included children in the age group of 5 to 11 years

Arm type	Experimental
Investigational medicinal product name	AFQ056
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Single dose of 15 mg (10 mg/ml oral suspension in water) administered to the patients via a syringe. Saccharin sodium as a sweetener and tutti-frutti aroma were added to improve the taste.

Arm title	Cohort 2-Treatment Period 1
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Arm description:

Cohort 2 included children in the age group of 3 to 4 years

Arm type	Experimental
Investigational medicinal product name	AFQ056
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Single dose of 15 mg (10 mg/ml oral suspension in water) administered to the patients via a syringe. Saccharin sodium as a sweetener and tutti-frutti aroma were added to improve the taste.

Number of subjects in period 1	Cohort 1-Treatment Period 1	Cohort 2-Treatment Period 1
Started	12	9
Completed	12	9

Period 2

Period 2 title	Treatment Period 2
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1-Treatment Period 2

Arm description:

Cohort 1 included children in the age group of 5 to 11 years

Arm type	Experimental
Investigational medicinal product name	AFQ056
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Day 1 to Day 7: multiple doses twice daily; 50 mg, 100 mg, or 1.25 mg/kg (10 mg/ml oral suspension in water) administered to the patients via a syringe. Doses were individualized based on the results obtained in period 1. Saccharin sodium as a sweetener and tutti-frutti aroma were added to improve the taste.

If the dose normalized C_{max} and the dose normalized AUC_{inf} from the 15 mg dose of period 1 for the individuals did not exceed the 90th percentile of the over all population (adults and adolescents), then the exposures from the 15 mg dose in period 1 guided the selection of doses for period 2 for each individual. If the dose normalized C_{max} and the dose normalized AUC_{inf} of the subjects from the 15 mg dose of period 1 fell above the 90th percentile, then mg/kg dosing was implemented instead of fixed dosing in period 2 for these subjects.

Arm title	Cohort 2-Treatment Period 2
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Arm description:

Cohort 2 included children in the age group of 3 to 4 years

Arm type	Experimental
Investigational medicinal product name	AFQ056
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Day 1 to Day 8: multiple doses twice daily (b.i.d.) 50 mg, 100 mg, or 1.25 mg/kg (10 mg/ml oral suspension in water) administered to the patients via a syringe. Doses were individualized and up-titrated based on the results obtained in period 1. Up-titration as follows: starting dose of 25 mg b.i.d. and daily increments of 25 mg up to the assigned target dose.

If the dose normalized C_{max} and the dose normalized AUC_{inf} from the 15 mg dose of period 1 for the

individuals did not exceed the 90th percentile of the over all population (adults and adolescents), then the exposures from the 15 mg dose in period 1 guided the selection of doses for period 2 for each individual. If the dose normalized C_{max} and the dose normalized AUC_{inf} of the subjects from the 15 mg dose of period 1 fell above the 90th percentile, then mg/kg dosing was implemented instead of fixed dosing in period 2 for these subjects.

Number of subjects in period 2	Cohort 1-Treatment Period 2	Cohort 2-Treatment Period 2
Started	12	9
Completed	12	9

Baseline characteristics

Reporting groups

Reporting group title	Cohort 1-Treatment Period 1
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Reporting group description:

Cohort 1 included children in the age group of 5 to 11 years

Reporting group title	Cohort 2-Treatment Period 1
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Reporting group description:

Cohort 2 included children in the age group of 3 to 4 years

Reporting group values	Cohort 1-Treatment Period 1	Cohort 2-Treatment Period 1	Total
Number of subjects	12	9	21
Age categorical Units: Subjects			
Children (2-11 years)	12	9	21
Age continuous Units: years			
arithmetic mean	7.7	3.9	
standard deviation	± 2.15	± 0.33	-
Gender categorical Units: Subjects			
Female	1	1	2
Male	11	8	19

End points

End points reporting groups

Reporting group title	Cohort 1-Treatment Period 1
Reporting group description: Cohort 1 included children in the age group of 5 to 11 years	
Reporting group title	Cohort 2-Treatment Period 1
Reporting group description: Cohort 2 included children in the age group of 3 to 4 years	
Reporting group title	Cohort 1-Treatment Period 2
Reporting group description: Cohort 1 included children in the age group of 5 to 11 years	
Reporting group title	Cohort 2-Treatment Period 2
Reporting group description: Cohort 2 included children in the age group of 3 to 4 years	

Primary: Dose-normalized Maximum Observed Plasma Concentration (C_{max}) After a Single Dose of AFQ056

End point title	Dose-normalized Maximum Observed Plasma Concentration (C _{max}) After a Single Dose of AFQ056 ^[1]
End point description: The observed maximum plasma concentration following AFQ056 administration [mass / volume] normalized for dose	
End point type	Primary
End point timeframe: Over 24 hours post dose on Day 1 of Treatment Period 1	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this primary outcome measure.	

End point values	Cohort 1-Treatment Period 1	Cohort 2-Treatment Period 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: ng/mL/mg				
geometric mean (confidence interval 90%)	2.88 (2.09 to 3.97)	4.67 (3.71 to 5.88)		

Statistical analyses

No statistical analyses for this end point

Primary: Dose-normalized Area Under The Plasma Concentration-Time Curve (AUC) From Time 0 to 12 Hours Post Dose (AUC_{0-12h}) After a Single Dose of AFQ056

End point title	Dose-normalized Area Under The Plasma Concentration-Time Curve (AUC) From Time 0 to 12 Hours Post Dose (AUC _{0-12h}) After a Single Dose of AFQ056 ^[2]
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End point description:

The AUC from time 0 to t= 12 hours, where t is a defined time point after AFQ056 administration [mass x time / volume] normalized for dose

End point type	Primary
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End point timeframe:

Over 12 hours post dose on Day 1 of Treatment Period 1

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome measure.

End point values	Cohort 1-Treatment Period 1	Cohort 2-Treatment Period 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: h*ng/mL/mg				
geometric mean (confidence interval 90%)	11.2 (8.32 to 15)	16.4 (13.3 to 20.3)		

Statistical analyses

No statistical analyses for this end point

Primary: Cmax After a Single Dose of AFQ056

End point title	Cmax After a Single Dose of AFQ056 ^[3]
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End point description:

The observed maximum plasma concentration following AFQ056 administration [mass / volume]

End point type	Primary
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End point timeframe:

Over 24 hours post dose on Day 1 of Treatment Period 1

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome measure.

End point values	Cohort 1-Treatment Period 1	Cohort 2-Treatment Period 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: ng/mL				
geometric mean (confidence interval 90%)	43.1 (31.3 to 59.5)	70 (55.7 to 88.1)		

Statistical analyses

No statistical analyses for this end point

Primary: AUC0-12h After a Single Dose of AFQ056

End point title	AUC0-12h After a Single Dose of AFQ056 ^[4]
End point description: The AUC from time 0 to t= 12 hours, where t is a defined time point after AFQ056 administration [mass x time / volume]	
End point type	Primary
End point timeframe: Over 24 hours post dose on Day 1 of Treatment Period 1	
Notes: [4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this primary outcome measure.	

End point values	Cohort 1- Treatment Period 1	Cohort 2- Treatment Period 1		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	9		
Units: h*ng/mL				
geometric mean (confidence interval 90%)	168 (125 to 225)	246 (199 to 304)		

Statistical analyses

No statistical analyses for this end point

Primary: Dose-normalized Cmax of AFQ056 at Steady State

End point title	Dose-normalized Cmax of AFQ056 at Steady State ^[5]
End point description: The observed maximum plasma concentration following AFQ056 administration [mass / volume] normalized for dose after multiple doses	
End point type	Primary
End point timeframe: Over 24 hours post dose on Day 7 or 8 of Treatment Period 2 for Cohort 1 and 2, respectively	
Notes: [5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical analysis was planned for this primary outcome measure.	

End point values	Cohort 1- Treatment Period 2	Cohort 2- Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: ng/mL/mg				
geometric mean (confidence interval 90%)	3.65 (2.84 to 4.69)	3.77 (2.36 to 6.01)		

Statistical analyses

No statistical analyses for this end point

Primary: Dose-normalized AUC0-12h of AFQ056 at Steady State

End point title	Dose-normalized AUC0-12h of AFQ056 at Steady State ^[6]
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End point description:

The AUC from time 0 to t= 12 hours, where t is a defined time point after AFQ056 administration [mass x time / volume] normalized for dose after multiple doses

End point type	Primary
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End point timeframe:

Over 24 hours post dose on Day 7 or 8 of Treatment Period 2 for Cohort 1 and 2, respectively

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this primary outcome measure.

End point values	Cohort 1-Treatment Period 2	Cohort 2-Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: h*ng/mL/mg				
geometric mean (confidence interval 90%)	13.1 (10.8 to 15.9)	19.5 (11.1 to 34.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Clinically Significant Abnormalities in Laboratory Values

End point title	Number of Patients With Clinically Significant Abnormalities in Laboratory Values
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End point description:

End point type	Secondary
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End point timeframe:

Screening: once anytime between Day -30 and Day -1; once anytime between 24-72 hours after Day 7 or 8 for Cohort 1 and 2, respectively

End point values	Cohort 1-Treatment Period 2	Cohort 2-Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: subjects				
Hematology	0	0		
Blood Chemistry	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Clinically Significant Abnormalities in Vital Signs And Body Measurements

End point title	Number of Patients With Clinically Significant Abnormalities in Vital Signs And Body Measurements
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End point description:

End point type	Secondary
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End point timeframe:

Screening: once anytime between Day -30 and Day -1; once anytime between 24-72 hours after Day 7 or 8 for Cohort 1 and 2, respectively

End point values	Cohort 1- Treatment Period 2	Cohort 2- Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: subjects				
Body Height	0	0		
Body Weight	0	0		
Body Temperature	0	0		
Blood Pressure/Pulse Rate	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Clinically Significant Abnormalities in Electrocardiogram Results

End point title	Number of Patients With Clinically Significant Abnormalities in Electrocardiogram Results
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End point description:

End point type	Secondary
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End point timeframe:

Screening: once anytime between Day -30 and Day -1; once anytime between 24-72 hours after Day 7 or 8 for Cohort 1 and 2, respectively

End point values	Cohort 1- Treatment Period 2	Cohort 2- Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Clinically Significant Abnormalities Upon Neurological Examination

End point title	Number of Patients With Clinically Significant Abnormalities Upon Neurological Examination
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End point description:

End point type	Secondary
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End point timeframe:

Screening: once anytime between Day -30 and Day -1; once on Day 7 or 8 for Cohort 1 and 2, respectively

End point values	Cohort 1- Treatment Period 2	Cohort 2- Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Adverse Events

End point title	Number of Patients With Adverse Events
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End point description:

End point type	Secondary
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End point timeframe:

During the study (total of approximately 32 days) and 3 days after study completion

End point values	Cohort 1- Treatment Period 2	Cohort 2- Treatment Period 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: subjects				
Serious adverse events	0	0		
Non-serious adverse events	9	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15.1

Reporting groups

Reporting group title	Cohort 1 Period 1 15mg AFQ056
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Reporting group description:

Cohort 1 Period 1 15mg AFQ056

Reporting group title	Cohort 1 Period 2 50mg AFQ056
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Reporting group description:

Cohort 1 Period 2 50mg AFQ056

Reporting group title	Cohort 1 Period 2 60mg AFQ056
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Reporting group description:

Cohort 1 Period 2 60mg AFQ056

Reporting group title	Cohort 1 Period 2 20mg AFQ056
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Reporting group description:

Cohort 1 Period 2 20mg AFQ056

Reporting group title	Cohort 1 Period 2 100mg AFQ056
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Reporting group description:

Cohort 1 Period 2 100mg AFQ056

Reporting group title	Cohort 1 Total
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Reporting group description:

Cohort 1 Total

Reporting group title	Cohort 2 Period 2 20mg AFQ056
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Reporting group description:

Cohort 2 Period 2 20mg AFQ056

Reporting group title	Cohort 2 Period 2 15mg AFQ056
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Reporting group description:

Cohort 2 Period 2 15mg AFQ056

Reporting group title	Cohort 2 Period 1 15mg AFQ056
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Reporting group description:

Cohort 2 Period 1 15mg AFQ056

Reporting group title	Cohort 2 Period 2 50mg AFQ056
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Reporting group description:

Cohort 2 Period 2 50mg AFQ056

Reporting group title	Cohort 2 Period 2 100mg AFQ056
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Reporting group description:

Cohort 2 Period 2 100mg AFQ056

Reporting group title	Cohort 2 Total
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Reporting group description:

Cohort 2 Total

Serious adverse events	Cohort 1 Period 1 15mg AFQ056	Cohort 1 Period 2 50mg AFQ056	Cohort 1 Period 2 60mg AFQ056
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 1 Period 2 20mg AFQ056	Cohort 1 Period 2 100mg AFQ056	Cohort 1 Total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 6 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 2 Period 2 20mg AFQ056	Cohort 2 Period 2 15mg AFQ056	Cohort 2 Period 1 15mg AFQ056
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 2 Period 2 50mg AFQ056	Cohort 2 Period 2 100mg AFQ056	Cohort 2 Total
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 4 (0.00%)	0 / 1 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Cohort 1 Period 1 15mg AFQ056	Cohort 1 Period 2 50mg AFQ056	Cohort 1 Period 2 60mg AFQ056
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 12 (33.33%)	3 / 3 (100.00%)	1 / 1 (100.00%)
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Nervous system disorders			
Coordination abnormal subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Dyskinesia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Hypersomnia subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 3 (33.33%) 3	0 / 1 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
General disorders and administration site conditions			
Feeling hot subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0

Mydriasis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	1 / 3 (33.33%) 1	0 / 1 (0.00%) 0
Food poisoning subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	2 / 3 (66.67%) 2	0 / 1 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	0 / 3 (0.00%) 0	0 / 1 (0.00%) 0
Psychiatric disorders			
Anticipatory anxiety			

subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Anxiety			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)
occurrences (all)	0	0	1
Initial insomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Renal and urinary disorders			
Pollakiuria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Gastrointestinal viral infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Hordeolum			
subjects affected / exposed	1 / 12 (8.33%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	1	0	0
Infected bites			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 3 (33.33%)	0 / 1 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 1 Period 2 20mg AFQ056	Cohort 1 Period 2 100mg AFQ056	Cohort 1 Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	4 / 6 (66.67%)	9 / 12 (75.00%)
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Nervous system disorders			
Coordination abnormal subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Dizziness subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	2 / 6 (33.33%) 3	2 / 12 (16.67%) 3
Dyskinesia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1
Headache subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 2	1 / 12 (8.33%) 2
Hypersomnia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 3	0 / 6 (0.00%) 0	2 / 12 (16.67%) 6
Somnolence subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
General disorders and administration site conditions			
Feeling hot subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1

Mydriasis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 2	1 / 12 (8.33%) 2
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	2 / 12 (16.67%) 2
Food poisoning subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1
Vomiting subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	3 / 6 (50.00%) 3	6 / 12 (50.00%) 6
Respiratory, thoracic and mediastinal disorders			
Nasal congestion subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Rash subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 1
Urticaria subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Psychiatric disorders			
Anticipatory anxiety			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 6 (16.67%) 1	1 / 12 (8.33%) 2
Anxiety subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1
Initial insomnia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	1 / 6 (16.67%) 1	2 / 12 (16.67%) 2
Insomnia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1
Infections and infestations Gastrointestinal viral infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Hordeolum subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1
Infected bites subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	1 / 12 (8.33%) 1
Pharyngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 6 (0.00%) 0	0 / 12 (0.00%) 0
Non-serious adverse events	Cohort 2 Period 2 20mg AFQ056	Cohort 2 Period 2 15mg AFQ056	Cohort 2 Period 1 15mg AFQ056
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	2 / 9 (22.22%)
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Nervous system disorders			
Coordination abnormal subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Dyskinesia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Hypersomnia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
General disorders and administration site conditions			
Feeling hot subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0

Mydriasis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Food poisoning subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Swelling face subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Psychiatric disorders			
Anticipatory anxiety			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Initial insomnia subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Insomnia subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Infections and infestations Gastrointestinal viral infection subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 1 (100.00%) 1	0 / 9 (0.00%) 0
Hordeolum subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Infected bites subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1

Non-serious adverse events	Cohort 2 Period 2 50mg AFQ056	Cohort 2 Period 2 100mg AFQ056	Cohort 2 Total
Total subjects affected by non-serious adverse events subjects affected / exposed	3 / 4 (75.00%)	1 / 1 (100.00%)	6 / 9 (66.67%)
Vascular disorders			

Hot flush subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Nervous system disorders			
Coordination abnormal subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Dizziness subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Dyskinesia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Headache subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Hypersomnia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Psychomotor hyperactivity subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Somnolence subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
General disorders and administration site conditions			
Feeling hot subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Non-cardiac chest pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Eye disorders			
Eye pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0

Mydriasis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Gastrointestinal disorders			
Diarrhoea subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Food poisoning subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Vomiting subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Respiratory, thoracic and mediastinal disorders			
Nasal congestion subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	1 / 1 (100.00%) 1	1 / 9 (11.11%) 1
Oropharyngeal pain subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Skin and subcutaneous tissue disorders			
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Rash subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
Swelling face subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Urticaria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
Psychiatric disorders			
Anticipatory anxiety			

subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Anxiety subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Initial insomnia subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
Insomnia subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 1 (0.00%) 0	2 / 9 (22.22%) 2
Renal and urinary disorders Pollakiuria subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Infections and infestations Gastrointestinal viral infection subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
Hordeolum subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Infected bites subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	0 / 9 (0.00%) 0
Pharyngitis subjects affected / exposed occurrences (all)	0 / 4 (0.00%) 0	0 / 1 (0.00%) 0	1 / 9 (11.11%) 1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 November 2011	This amendment introduced the following changes: The additional safety monitoring of study patients on days 2-6 (period 2) in case when the study medication is administered at patient's home by the patient's caregiver. For these days a daily telephone call was recommended to monitor for the potential AEs and safety issues. Initially planned two visits per day in the study center for the study drug administration were considered too stressful for the patients and considering the safety profile of AFQ056 it was judged that the daily telephone call was an appropriate measure to monitor for the safety of the study patients. In addition the meal restriction section was rewritten to provide more flexibility to the patients regarding the meal times on period 2. Further, the b.i.d. dose was introduced for day 1, period 2 (instead of single dose). Originally, it was planned to assess the single-dose pharmacokinetics from 0-24h post dosing. As this was no longer planned to be assessed, the b.i.d. dosing regimen was applied over the entire period 2 (i.e. from day 1-7). This was to ensure a consistent dosing regimen and it would allow for a more appropriate tolerability assessment after an overnight stay of the patients at the site. This assessment was done in the morning of day 2 before patients leave the study site.
24 February 2012	This amendment introduced the following changes: In order to further characterize any potential modification of attention after AFQ056 administration to children with FXS, it was decided to perform mental age-appropriate subtests of the Test of Everyday Attention in Childhood (TEA-Ch). In addition, TEA-Ch was included in order to comply with a request by the European Medicines Agency (EMA) received in the course of the PIP review. To minimize the burden for the patients, TEA-Ch subtests were only performed in the multiple-dosing period 2, as after administration of a considerably low, single dose of AFQ056 in period 1 (15 mg), no meaningful modification of behavior was expected. Further, these subtest would only be applied in cohort 1 (5-11 year-old patients), since it was not considered feasible to perform these tests in cohort 2 (3-4 year-old patients) given that these tests have been validated for children ≥ 6 years of age. The tests were done at baseline, 24 h after first dosing in period 2 and at final visit if possible based on the capabilities of study patients (as judged by Investigator).
11 May 2012	This amendment introduced the following changes: In the original study protocol, (a) sequential dosing within cohort 1 beginning with the older (8 to 11 years) followed by the younger patients (5 to 7 years) and (b) an equal number of 5 to 7 year-old and 8-11 year-old patients in cohort 1 was required. This had been implemented due to the absence of any PK data in the pediatric population of FXS patients younger than 12 years. As per this amendment sequential age-dependent dosing as well as an equal age distribution of patients aged 8-11 and 5-7yrs will no longer be required. This was to minimize the burden to the families/caregivers of the FXS patients, since there were often siblings interested in study participation. Therefore, it was expected to improve the recruitment in this study. This amendment would not affect the validity of the statistical analysis as this has originally been planned to be done on the entire cohort 1 without age discrimination. It was also not expected to affect the safety and tolerability of AFQ056 in this study population of pediatric FXS patients.
11 July 2012	This amendment introduced the following changes: After a review of Amendment 03, FDA stated via e-mail dated June 29, 2012, that the removal of an equal age distribution in cohort 1 is not acceptable. It was stated that an equal number of 5 to 7 year-old and 8 to 11 year-old patients was necessary for the PK trial to be informative given the expected difference in ontogeny among these age groups. Therefore, the requirement for an equal number of six patients aged 5 to 7 years and another six patients aged 8-11 years was re-introduced in this protocol amendment 04.

22 March 2013	This amendment introduced the following changes: This study evaluated the pharmacokinetics as well as safety and tolerability of AFQ056 in pediatric patients with FXS aged 5-11 years (cohort 1) and 3-4 years (cohort 2). As of 22- Mar-2013, cohort 1, consisting of 12 children with FXS, has completed the study. This was followed by a pre-planned interim analysis to decide upon continuation of this study with cohort 2. Based on the data obtained in cohort 1, it has been decided to continue with cohort 2 and to implement three key changes to the protocol * An up-titration scheme with a starting dose of 25mg b.i.d. and daily increments of 25mg up to the assigned target dose will be applied in period 2, cohort 2. This up-titration aims at reducing the incidence of AEs (e.g. vomiting) that are considered to be first-dose related, as these occurred primarily on the first day of the multiple-dosing period 2 in cohort 1. * As a consequence of the up-titration, the duration of the treatment in period 2, cohort 2 was extended from 7 to 8 days to assure that the steady state at the target dose is reached (the steady state is known to reach between 48h to 96 h for AFQ056) when the PK samples for AFQ056 measurements are collected. * The sample size required for cohort 2 has been re-evaluated based on the PK data obtained in cohort 1. This has been done in order to minimize the number of patients exposed which appears particularly important given the low age of patients in cohort 2 (3-4 years).
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported