Clinical trial results:
An open-label study to evaluate the long-term safety, tolerability and efficacy of AFQ056 in adult patients with Fragile X Syndrome

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-001952-12
Trial protocol	DE FR GB DK ES IT
Global end of trial date	10 September 2014

Results information

Result version number	v1 (current)
This version publication date	10 June 2016
First version publication date	10 June 2016

Trial information

Trial identification

Sponsor protocol code	CAFQ056B2279

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01348087
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	10 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 September 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the safety and tolerability of AFQ056 in adult patients with FXS as assessed by:
Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).
Changes in vital signs, laboratory assessments, and electrocardiograms (ECGs).

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	19 August 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 19
Country: Number of subjects enrolled	Germany: 12
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Switzerland: 14
Country: Number of subjects enrolled	United States: 65
Worldwide total number of subjects	148
EEA total number of subjects	45

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)	0
Adults (18-64 years)	148
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 28 centers in
10 countries

Pre-assignment

Screening details:

A total of 148 patients were enrolled and treated, including 1 patient who discontinued and was later re-enrolled under a new patient number. Category 1 patients received AFQ056 in the core study and enrolled in the extension within 7 days of completing the core study; Category 2 included all other patients enrolled into the extension study

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AFQ056 Total

Arm description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

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

Dosage and administration details:

Oral capsules

Number of subjects in period 1	AFQ056 Total
Started	148
Completed	0
Not completed	148
Subject withdrew consent	7
Adverse event, non-fatal	25
Unsatisfactory therapeutic effect	35
Administrative problems	79
protocol deviation	1
Lost to follow-up	1

Baseline characteristics

Reporting groups

Reporting group title	AFQ056 Total

Reporting group description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Reporting group values	AFQ056 Total	Total	
Number of subjects	148	148	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	148	148	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous | Units: years			
arithmetic mean	26.6		
standard deviation	± 6.85	-	
Gender, Male/Female Units: Participants			
Female	10	10	
Male	138	138	

Subject analysis sets

Subject analysis set title	AFQ056
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Subject analysis set title	Prior to Ext first dose
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Subject analysis set title	AFQ056 25mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were

administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Subject analysis set title	AFQ056 50mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Subject analysis set title	AFQ056 75mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Subject analysis set title	AFQ056 100mg bid
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Subject analysis set title	AFQ056 Total
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals

Reporting group values	AFQ056	Prior to Ext first dose	AFQ056 25mg bid
Number of subjects	148	40	147
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	148	40	147
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: years			
arithmetic mean	26.6		
standard deviation	± 6.85	±	±
Gender, Male/Female Units: Participants			
Female	10		
Male	138		

Reporting group values	AFQ056 50mg bid	AFQ056 75mg bid	AFQ056 100mg bid
Number of subjects	148	141	135

Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	148	141	135
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous | Units: years arithmetic mean standard deviation	±	±	±
Gender, Male/Female Units: Participants			
Female			
Male			

Reporting group values	AFQ056 Total		
Number of subjects	148		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	148		
From 65-84 years	0		
85 years and over	0		
Age Continuous | Units: years arithmetic mean standard deviation	±		
Gender, Male/Female Units: Participants			
Female			
Male			

End points

End points reporting groups

Reporting group title	AFQ056 Total
Reporting group description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	AFQ056
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	Prior to Ext first dose
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	AFQ056 25mg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	AFQ056 50mg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	AFQ056 75mg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	AFQ056 100mg bid
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	
Subject analysis set title	AFQ056 Total
Subject analysis set type	Safety analysis
Subject analysis set description:	
Participants from a previous AFQ056 study who entered the open-label extension study were administered AFQ056 capsules at a starting dose of 25 milligram (mg) twice daily (bid) and then titrated to 50 mg bid, 75 mg bid and 100 mg bid at weekly intervals	

Primary: Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).

End point title	Incidence and severity of adverse events (AEs) and serious adverse events (SAEs).[1]

End point description:

Adverse events were summarized for the open-label treatment period, where the open-label treatment period is defined based on how AEs were collected and reported according to the manner in which patients entered the current study and which treatment (AFQ056 or placebo) they were receiving in the previous study. AEs which were continuing from the core study or that started after the end of core study but prior to first dose of open-label study medication in the extension study for Category 1 patients are shown under ('Prior to Ext. first dose'). AEs which started during the open-label treatment period are presented based on the last AFQ056 dose taken on or before the onset date of the AE (25 mg bid; 50 mg bid; 75 mg bid; or 100 mg bid). No efficacy data presented as study was terminated. No statistical analysis was planned for this primary outcome.
No statistical analysis was planned for this primary outcome.

End point type	Primary

End point timeframe:

Prior to first dose in extension study, Baseline (start of study treatment in extension study) to End of trial

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

End point values	Prior to Ext first dose	AFQ056 25mg bid	AFQ056 50mg bid	AFQ056 75mg bid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	40	147	148	141
Units: Participants				
At least one AE	9	49	47	50
At least one severe AE	1	1	2	5
Any serious or significant AE	0	1	0	1
SAE	0	1	0	1
Discontinued due to SAE	0	1	0	1
Discontinued due to non serious AE	0	4	5	4

End point values	AFQ056 100mg bid	AFQ056 Total		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	135	148		
Units: Participants				
At least one AE	112	138		
At least one severe AE	18	24		
Any serious or significant AE	6	7		
SAE	6	7		
Discontinued due to SAE	1	3		
Discontinued due to non serious AE	11	22		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Prior to Ext first dose
Reporting group description:	
Prior to Ext first dose	
Reporting group title	AFQ 25
Reporting group description:	
AFQ 25	
Reporting group title	AFQ 50
Reporting group description:	
AFQ 50	
Reporting group title	AFQ 75
Reporting group description:	
AFQ 75	
Reporting group title	AFQ 100
Reporting group description:	
AFQ 100	
Reporting group title	Total
Reporting group description:	
Total	

Serious adverse events	Prior to Ext first dose	AFQ 25	AFQ 50
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	0 / 148 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Epilepsy			

subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	0 / 148 (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
Panic attack			
subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	0 / 148 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AFQ 75	AFQ 100	Total
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 141 (0.71%)	6 / 135 (4.44%)	7 / 148 (4.73%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nervous system disorders			
Epilepsy			
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 141 (0.71%)	2 / 135 (1.48%)	3 / 148 (2.03%)
occurrences causally related to treatment / all	1 / 1	1 / 2	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Agitation			
subjects affected / exposed	0 / 141 (0.00%)	2 / 135 (1.48%)	2 / 148 (1.35%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, auditory			
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Panic attack			
subjects affected / exposed	0 / 141 (0.00%)	1 / 135 (0.74%)	1 / 148 (0.68%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Prior to Ext first dose	AFQ 25	AFQ 50
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 40 (15.00%)	26 / 147 (17.69%)	28 / 148 (18.92%)
Nervous system disorders			

Dizziness			
subjects affected / exposed	1 / 40 (2.50%)	5 / 147 (3.40%)	4 / 148 (2.70%)
occurrences (all)	1	5	5
Headache			
subjects affected / exposed	0 / 40 (0.00%)	4 / 147 (2.72%)	3 / 148 (2.03%)
occurrences (all)	0	4	7
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	0 / 148 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	2 / 148 (1.35%)
occurrences (all)	0	1	2
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	1 / 148 (0.68%)
occurrences (all)	0	1	1
Vomiting			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	2 / 148 (1.35%)
occurrences (all)	0	1	2
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 40 (2.50%)	4 / 147 (2.72%)	0 / 148 (0.00%)
occurrences (all)	1	4	0
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 40 (0.00%)	6 / 147 (4.08%)	8 / 148 (5.41%)
occurrences (all)	0	12	12
Anxiety			
subjects affected / exposed	0 / 40 (0.00%)	1 / 147 (0.68%)	3 / 148 (2.03%)
occurrences (all)	0	1	3
Agitation			
subjects affected / exposed	0 / 40 (0.00%)	0 / 147 (0.00%)	1 / 148 (0.68%)
occurrences (all)	0	0	1
Irritability			

subjects affected / exposed	1 / 40 (2.50%)	0 / 147 (0.00%)	7 / 148 (4.73%)
occurrences (all)	1	0	7
Insomnia			
subjects affected / exposed	1 / 40 (2.50%)	4 / 147 (2.72%)	3 / 148 (2.03%)
occurrences (all)	1	5	6
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 40 (0.00%)	4 / 147 (2.72%)	1 / 148 (0.68%)
occurrences (all)	0	5	1
Nasopharyngitis			
subjects affected / exposed	3 / 40 (7.50%)	2 / 147 (1.36%)	4 / 148 (2.70%)
occurrences (all)	3	2	6

Non-serious adverse events	AFQ 75	AFQ 100	Total
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 141 (25.53%)	88 / 135 (65.19%)	117 / 148 (79.05%)
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 141 (0.71%)	5 / 135 (3.70%)	13 / 148 (8.78%)
occurrences (all)	1	6	18
Headache			
subjects affected / exposed	7 / 141 (4.96%)	14 / 135 (10.37%)	21 / 148 (14.19%)
occurrences (all)	8	23	42
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 141 (3.55%)	8 / 135 (5.93%)	9 / 148 (6.08%)
occurrences (all)	5	8	10
Fatigue			
subjects affected / exposed	3 / 141 (2.13%)	3 / 135 (2.22%)	9 / 148 (6.08%)
occurrences (all)	3	3	9
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 141 (0.71%)	7 / 135 (5.19%)	10 / 148 (6.76%)
occurrences (all)	1	9	12
Vomiting			
subjects affected / exposed	2 / 141 (1.42%)	14 / 135 (10.37%)	18 / 148 (12.16%)
occurrences (all)	2	21	26

Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 141 (1.42%)	9 / 135 (6.67%)	16 / 148 (10.81%)
occurrences (all)	2	9	16
Psychiatric disorders			
Aggression			
subjects affected / exposed	5 / 141 (3.55%)	11 / 135 (8.15%)	22 / 148 (14.86%)
occurrences (all)	5	20	48
Anxiety			
subjects affected / exposed	3 / 141 (2.13%)	10 / 135 (7.41%)	16 / 148 (10.81%)
occurrences (all)	3	10	16
Agitation			
subjects affected / exposed	3 / 141 (2.13%)	10 / 135 (7.41%)	13 / 148 (8.78%)
occurrences (all)	3	11	15
Irritability			
subjects affected / exposed	4 / 141 (2.84%)	6 / 135 (4.44%)	15 / 148 (10.14%)
occurrences (all)	4	8	17
Insomnia			
subjects affected / exposed	7 / 141 (4.96%)	12 / 135 (8.89%)	23 / 148 (15.54%)
occurrences (all)	7	12	28
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	3 / 141 (2.13%)	16 / 135 (11.85%)	24 / 148 (16.22%)
occurrences (all)	5	31	42
Nasopharyngitis			
subjects affected / exposed	3 / 141 (2.13%)	21 / 135 (15.56%)	27 / 148 (18.24%)
occurrences (all)	3	33	47

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2011	For women of child bearing potential, the requirements for contraceptives were changed from effective to highly effective and additional pregnancy testing was introduced as a further precautionary measure for all female participants and not only for women of childbearing potential.
11 December 2011	The protocol was modified to include 24 months of open-label treatment or until commercial availability of AFQ056, whichever occurred later. In addition, 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. The criterion excluding patients currently treated with 2 or more psychoactive medications, excluding anti-epileptics, and the requirement prohibiting administration of more than 2 psychoactive medications during the study were removed. The criterion that excluded patients on the basis of a past medical history of clinically significant ECG abnormalities or QTcF >450 msec (males) and >470 msec (females) was modified to clarify that for Group 1 patients, ECGs were assessed at the completion visit of the CAFQ056A2212 study and this served as the ECG baseline for the CAFQ056B2279 study. The protocol was also amended to remove post-baseline assessments of the Clinical Global Impression – Severity (CGI-S). Additionally, instructions were added to the protocol to guide investigators concerning the need to assess patients for the presence of suicidality as part of monitoring of AEs.
13 August 2013	The protocol was amended to include new requirements for liver safety monitoring, including an additional blood draw at Month 6 to monitor liver function. The criteria requiring discontinuation of study medication were also revised to include liver function test abnormalities or liver-related adverse events and QTc prolongation. The description and use of the ABC-CFX scoring algorithm were added throughout the protocol. Changes were also made throughout the protocol related to the optional testing to determine the extent of methylation of the FMR1 gene. In addition, the protocol was modified to allow the possibility for eligible subjects from other studies of AFQ056 to be enrolled and the inclusion criteria were modified to reflect that eligible patients had to have been at least 18 years of age at the time of entry into the previous study. An instruction for subjects to avoid drinking grapefruit juice was added to exclusion criterion, and the protocol was modified to state that local anesthetics were specifically allowed for phlebotomy. Criteria excluding patients whose current medications had not been stable for at least 6 weeks prior to baseline and excluding patients planning to initiate or change pharmacologic or non-pharmacologic interventions during the study were removed, and instructions concerning the use of concomitant therapies were clarified.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The sponsor decided to terminate this study prematurely, as the study treatment failed to demonstrate efficacy in target population in two other clinical studies: CAFQ056B2214 (NCT01357239) and CAFQ056A2212 (NCT01253629).

Notes: