



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CAFQ056B2214 |
|-----------------------|--------------|

Additional study identifiers

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

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 06 January 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 06 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

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

Notes:

Subjects enrolled per age group

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

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 38 centers in 16 countries.

Pre-assignment

Screening details:

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

Period 1

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

Blinding implementation details:

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

Arms

| | |
|------------------|------------------------------|
| Arm title | Placebo- Single blind period |
|------------------|------------------------------|

Arm description:

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

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

Dosage and administration details:

Placebo capsule was administered orally bid for 4 weeks.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: Caregiver or carer was blinded due to direct contact with subjects, and was capable of supervising treatment, providing input into efficacy and safety assessments.

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

Period 2

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

Blinding implementation details:

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

Arms

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

Arm description:

2 placebo capsules were administered bid for 12 weeks.

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

Dosage and administration details:

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

| | |
|------------------|------------------|
| Arm title | AFQ056 25 mg bid |
|------------------|------------------|

Arm description:

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

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

Dosage and administration details:

25 mg bid, oral, swallow it whole.

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

Dosage and administration details:

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

| | |
|------------------|------------------|
| Arm title | AFQ056 50 mg bid |
|------------------|------------------|

Arm description:

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

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

Dosage and administration details:

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

| | |
|---|-------------------|
| Arm title | AFQ056 100 mg bid |
| Arm description: One AFQ056 100 mg capsule and one placebo capsule were administered bid for 12 weeks. | |
| Arm type | Experimental |
| Investigational medicinal product name | Mavoglurant |
| Investigational medicinal product code | AFQ056 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

100 mg bid, oral, swallow it whole.

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

Dosage and administration details:

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

Notes:

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

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

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

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

Notes:

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

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

Baseline characteristics

Reporting groups

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

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

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

End points

End points reporting groups

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

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

| | |
|--|--|
| End point title | Change from baseline to week 12 in the Aberrant Behavior Checklist - Community edition (ABC-CFX) total score [Stratum I: FXS subjects with fully-methylated FMR1 gene (FM)] ^[1] |
| End point description: The Aberrant Behavior Checklist – Community edition (ABC-C) is a caregiver-rated symptom checklist for assessing problem behaviors of children and adults with mental retardation at home, in residential facilities, and work training centers. The raw data collected from the full, 58-item ABC-C were analyzed according to the modified FXS ABC-C algorithm (ABC-CFX), for which 55 items and six subscales plus the total score were considered. The assessment is done by attributing to each item of the questionnaire a score from 0 (“not at all a problem”) to 3 (“problem is severe in degree”) and the total score ranks from 0 to 165. A negative change from baseline indicated improvement. Analysis was performed in full analysis set (FAS) population, defined as all randomized subjects who received at least one dose of study drug and had a baseline and at least one post-baseline assessment for the primary efficacy parameter. | |
| End point type | Primary |
| End point timeframe: Baseline to Week 12 | |

Notes:

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

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

Notes:

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

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

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Change in ABC-CFX total score |
| Statistical analysis description: A mixed-effect model with repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect. | |
| Comparison groups | Placebo -Double blind Treatment Period v AFQ056 100 mg bid |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[4] |
| P-value | = 0.004 |
| Method | Mixed-effect model for repeated measures |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 18 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.2 |
| upper limit | 29.9 |

Notes:

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

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

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

End point description:

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

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: Baseline to Week 12 | |

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

Notes:

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

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

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

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

Statistical analyses

| Statistical analysis title | Change in ABC-CFX total score |
|----------------------------|-------------------------------|
|----------------------------|-------------------------------|

Statistical analysis description:

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

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

Notes:

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

| Statistical analysis title | Change in ABC-CFX total score |
|----------------------------|-------------------------------|
|----------------------------|-------------------------------|

Statistical analysis description:

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

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

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

Notes:

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

| | |
|-----------------------------------|-------------------------------|
| Statistical analysis title | Change in ABC-CFX total score |
|-----------------------------------|-------------------------------|

Statistical analysis description:

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

| | |
|---|--|
| Comparison groups | Placebo -Double blind Treatment Period v AFQ056 100 mg bid |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[11] |
| P-value | = 0.716 |
| Method | Mixed-effect model for repeated measures |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | -2.2 |

Confidence interval

| | |
|-------------|---------|
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.9 |
| upper limit | 9.6 |

Notes:

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point was planned to get the results from two lower doses of AFQ056 (i.e AFQ056 25 mg v Placebo and AFQ056 50 mg v Placebo), hence this end point is not reporting statistics for other

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

Notes:

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

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

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

Statistical analyses

| Statistical analysis title | Change in ABC-CFX total score |
|--|---|
| Statistical analysis description: | |
| A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect. | |
| Comparison groups | Placebo -Double blind Treatment Period v AFQ056 25 mg bid |
| Number of subjects included in analysis | 30 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[16] |
| P-value | = 0.758 |
| Method | Mixed-effect model for repeated measures |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.6 |
| upper limit | 12.9 |

Notes:

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

| Statistical analysis title | Change in ABC-CFX total score |
|--|---|
| Statistical analysis description: | |
| A mixed-effect model for repeated measures (MMRM) and unstructured covariance matrix was used with region, treatment, week, treatment by week interaction and baseline ABC-CFX total score as fixed effects and individual subject as a random effect. | |
| Comparison groups | Placebo -Double blind Treatment Period v AFQ056 50 mg bid |
| Number of subjects included in analysis | 28 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | = 0.475 |
| Method | Mixed-effect model for repeated measures |
| Parameter estimate | Least Square Mean Difference |
| Point estimate | 6.1 |

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

Notes:

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

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

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

Statistical analyses

No statistical analyses for this end point

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

| | |
|-----------------|---|
| End point title | Percentage of subjects with Clinical Global Impression- |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Week 12

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Week 12 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Week 12 | |

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

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma concentrations of AFQ056

| | |
|-----------------|---|
| End point title | Plasma concentrations of AFQ056 ^[18] |
|-----------------|---|

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 4 and Week 12

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Plasma concentrations were evaluated only for treatment arms (AFQ056 25mg, 50mg and 100 mg) included in the baseline period.

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Placebo -Double blind Treatment Period |
|-----------------------|--|

Reporting group description:

2 placebo capsule was administered bid for 12 weeks.

| | |
|-----------------------|-------------------|
| Reporting group title | AFQ056 100 mg bid |
|-----------------------|-------------------|

Reporting group description:

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

| | |
|-----------------------|------------------|
| Reporting group title | AFQ056 50 mg bid |
|-----------------------|------------------|

Reporting group description:

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

| | |
|-----------------------|------------------|
| Reporting group title | AFQ056 25 mg bid |
|-----------------------|------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 19 October 2011 | For female subjects of child-bearing potential and the frequency of pregnancy testing was increased. |
| 12 January 2012 | <ol style="list-style-type: none">1.The inclusion criterion describing the requirements to establish the diagnosis of FXS was modified such that documented genetic testing results (prior to study entry) were no longer required, provided the diagnosis was confirmed by the genetic testing at Visit 12.The inclusion criterion describing the requirements for a caregiver was clarified to avoid implying only one caregiver was required to oversee study participation for a subject3.Regional capping of recruitment into each stratum was removed4.The protocol was amended to allow for the possibility of a futility analysis; however, a futility analysis was not performed, following consultation with health authorities5. Instructions regarding the assessment for the presence of suicidality as part of monitoring the adverse events were added and the neuropsychiatric inventory questionnaire (NPI-Q) was added as a safety assessment for potential neuropsychiatric events6.The assessment schedule was revised to indicate that the optional biomarker samples were not required to be collected at Visit 3 for subjects who discontinued during the Placebo Run-in Period7.Requirements for the Follow-up visit were modified in consideration of subjects entered the separate open-label extension study8.Isoflurane was added to the list of prohibited medications9.The upper limits of the clinically notable systolic and diastolic blood pressure criteria were revised. |
| 02 February 2012 | Under this amendment, subjects were randomized (1:1) to either 100 mg b.i.d AFQ056 or placebo, and no further subjects were randomized to the lower dose groups of 25 mg and 50 mg b.i.d AFQ056. The primary and key secondary objectives of the study were modified to reflect this focus on the 100 mg b.i.d vs. placebo comparison. |
| 26 July 2012 | <ol style="list-style-type: none">1. The protocol included the possibility for an interim analysis when 50% of subjects were randomized to the highest dose arm; the protocol was amended to allow for the possibility of a futility analysis without consideration of the percentage of subjects randomized to the highest dose arm; however, a futility analysis was not performed, following consultation with health authorities.2. The protocol was amended such that the raw data from the ABC-C would be analysed according to a modified scoring algorithm (ABC-CFX).3. The primary and key secondary objectives, and the minimal number of subjects to be randomized, were rephrased as requested by pediatric committee (PDCO) of European Medicines Agency.4. Following recommendations from the PDCO, wording about isoflurane and grapefruit juice was added in the exclusion criteria section and local anesthetics were added to the protocol as being specifically allowed for phlebotomy. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported