



Clinical trial results:

A randomized, double-blind, placebo-controlled, parallel-group proof of concept study to evaluate the effect of AFQ056 in obsessive compulsive disorder (OCD) patients resistant to Selective Serotonin Reuptake Inhibitor (SSRI) therapy

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-005000-17 |
| Trial protocol | DE GB CZ BG |
| Global end of trial date | 11 November 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 June 2016 |
| First version publication date | 30 June 2016 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CAFQ056A2225 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01813019 |
| 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 | 11 November 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 11 November 2014 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the effects of AFQ056 (16 weeks treatment), using Yale - Brown Obsessive Compulsive Scale (Y-BOCS) change from baseline compared to placebo

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 November 2013 |
| 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 | Bulgaria: 19 |
| Country: Number of subjects enrolled | Czech Republic: 2 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Poland: 4 |
| Country: Number of subjects enrolled | Switzerland: 1 |
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects | 50 |
| EEA total number of subjects | 33 |

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) | 49 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study consisted of a screening period of up to 35 days, a Baseline evaluation, a treatment period of 19 weeks and an end of study evaluation approximately 14 days after the last study drug administration. The total duration for each patient in the study, was approximately 27 weeks.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Placebo |

Arm description:

Matching Placebo b.i.d. dosing

| | |
|--|---------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Following baseline, approximately 60 patients who are considered eligible will be randomized to Placebo arm and will receive the dosing regimen of 4 weeks Placebo b.i.d up-titration period of 50 mg,100 mg, 150 mg and 200 mg , followed by 12 weeks Placebo 200 mg fixed dose* and then a 3 week down-titration of 100 mg, 50 mg and 25 mg Placebo b.i.d) *patients that do not tolerate 200 matching placebo AFQ056 mg b.i.d may be down-titrated to 150 mg b.i.d.

| | |
|------------------|--------|
| Arm title | AFQ056 |
|------------------|--------|

Arm description:

AFQ056 b.i.d up-titration of 50mg,100mg, 150mg and 200 mg for 4 weeks then AFQ056 200mg b.i.d for 12 weeks and then a down-titration of AFQ056 100mg, 50mg and 25mg b.i.d for 3 weeks

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | AFQ056 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Following baseline, approximately 60 patients who are considered eligible will be randomized to AFQ056 arm and will receive the dosing regimen of 4 weeks AFQ056 b.i.d up-titration period of 50 mg,100 mg, 150 mg and 200 mg , followed by

| Number of subjects in period 1 | Placebo | AFQ056 |
|---------------------------------------|---------|--------|
| Started | 24 | 26 |
| Completed | 17 | 20 |
| Not completed | 7 | 6 |
| Consent withdrawn by subject | 3 | 2 |
| Protocol Deviation | 2 | 1 |
| Adverse event, non-fatal | - | 3 |
| administrative problems | 2 | - |

Baseline characteristics

Reporting groups

| | |
|---|---------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching Placebo b.i.d. dosing | |
| Reporting group title | AFQ056 |
| Reporting group description: | |
| AFQ056 b.i.d up-titration of 50mg,100mg, 150mg and 200 mg for 4 weeks then AFQ056 200mg b.i.d for 12 weeks and then a down-titration of AFQ056 100mg, 50mg and 25mg b.i.d for 3 weeks | |

| Reporting group values | Placebo | AFQ056 | Total |
|---|---------|---------|-------|
| Number of subjects | 24 | 26 | 50 |
| 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) | 24 | 25 | 49 |
| From 65-84 years | 0 | 1 | 1 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 39.9 | 41.3 | |
| standard deviation | ± 10.06 | ± 13.27 | - |
| Gender, Male/Female | | | |
| Units: participant | | | |
| Male | 11 | 13 | 24 |
| Female | 13 | 13 | 26 |

End points

End points reporting groups

| | |
|---|---------|
| Reporting group title | Placebo |
| Reporting group description: | |
| Matching Placebo b.i.d. dosing | |
| Reporting group title | AFQ056 |
| Reporting group description: | |
| AFQ056 b.i.d up-titration of 50mg,100mg, 150mg and 200 mg for 4 weeks then AFQ056 200mg b.i.d for 12 weeks and then a down-titration of AFQ056 100mg, 50mg and 25mg b.i.d for 3 weeks | |

Primary: Yale - Brown Obsessive Compulsive Scale (Y-BOCS) absolute change from baseline at Week 17 (end of 16-week dosing).

| | |
|--|--|
| End point title | Yale - Brown Obsessive Compulsive Scale (Y-BOCS) absolute change from baseline at Week 17 (end of 16-week dosing). |
| End point description: | |
| The Y-BOCS is a 10 item clinician-rated scale used to both determine the severity of OCD and to monitor symptom improvement throughout the course of the study. The Y-BOCS, specifically measures the severity of symptoms of OCD without being biased towards the type of obsessions or compulsions present. The scale includes questions about the amount of time spent on, how much impairment or distress experienced from, and how much resistance and control over these obsessive thoughts and compulsions. Each item is rated from 0 ("no symptoms") to 4 ("extreme symptoms") and yields a total possible score range from 0 to 40, with the following ranges indicating degree of severity: 0–7 = sub-clinical 8–15 = mild 16–23 = moderate 24–31 = severe 32–40 = extreme Baseline was compared to week 17 (end of week 16 dosing) to produce an absolute change. | |
| End point type | Primary |
| End point timeframe: | |
| baseline, week 17 | |

| End point values | Placebo | AFQ056 | | |
|-------------------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 17 | 21 | | |
| Units: Scores on a scale | | | | |
| least squares mean (standard error) | -8 (± 1.78) | -6.9 (± 1.75) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Yale-Brown Obsessive Compulsive Scale Change |
| Comparison groups | AFQ056 v Placebo |
| Number of subjects included in analysis | 38 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.671 |
| Method | Mixed models analysis |

Secondary: Y-BOCS reduction in total score from Baseline

| | |
|-----------------|---|
| End point title | Y-BOCS reduction in total score from Baseline |
|-----------------|---|

End point description:

If a subject demonstrates at least 25% reduction in total Y-BOCS from Baseline then they will be classed as a responder whereas if a subject has a reduction in Y-BOCS of less than 25% then they will be categorized as a nonresponder.

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

End point timeframe:

16 weeks

| End point values | Placebo | AFQ056 | | |
|-----------------------------|------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[1] | 0 ^[2] | | |
| Units: total score | | | | |
| number (not applicable) | | | | |

Notes:

[1] - Study terminated due to interim analysis. Secondary analysis not conducted.

[2] - Study terminated due to interim analysis. Secondary analysis not conducted.

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.

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 | AFQ056 |
|-----------------------|--------|

Reporting group description:

AFQ056 b.i.d up-titration of 50mg,100mg, 150mg and 200 mg for 4 weeks then AFQ056 200mg b.i.d for 12 weeks and then a down-titration of AFQ056 100mg, 50mg and 25mg b.i.d for 3 weeks

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Matching Placebo b.i.d. dosing

| Serious adverse events | AFQ056 | Placebo | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 2 / 24 (8.33%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Face injury | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Limb injury | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 24 (4.17%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| VIIIth nerve paralysis | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Otitis media | | | |
| subjects affected / exposed | 1 / 26 (3.85%) | 0 / 24 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | AFQ056 | Placebo | |
|---|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 18 / 26 (69.23%) | 15 / 24 (62.50%) | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 1 / 24 (4.17%) | |
| occurrences (all) | 2 | 1 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 2 / 24 (8.33%) | |
| occurrences (all) | 0 | 2 | |
| Nervous system disorders | | | |
| Disturbance in attention | | | |
| subjects affected / exposed | 2 / 26 (7.69%) | 0 / 24 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 5 / 26 (19.23%) | 2 / 24 (8.33%) | |
| occurrences (all) | 7 | 4 | |

| | | | |
|---|---|--|--|
| Headache subjects affected / exposed occurrences (all) | 10 / 26 (38.46%) 18 | 8 / 24 (33.33%) 13 | |
| Migraine subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 3 | 0 / 24 (0.00%) 0 | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | 1 / 24 (4.17%) 1 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 3 | 1 / 24 (4.17%) 1 | |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 2 / 26 (7.69%) 2 | 1 / 24 (4.17%) 2 0 / 24 (0.00%) 0 | |
| Psychiatric disorders Abnormal dreams subjects affected / exposed occurrences (all) Agitation subjects affected / exposed occurrences (all) Depression subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 2 / 26 (7.69%) 5 1 / 26 (3.85%) 1 6 / 26 (23.08%) 8 | 1 / 24 (4.17%) 1 0 / 24 (0.00%) 0 2 / 24 (8.33%) 3 2 / 24 (8.33%) 3 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|---------------------|----------------------|--|
| Back pain subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | 0 / 24 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | 4 / 24 (16.67%) 6 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 07 May 2013 | This amendment was issued prior to patient enrollment in the trial to respond to Investigators feedback to the protocol whereby the following point was addressed: Exclusion criterion 4 "History of failure to one augmentation therapy (e.g. an increase in dose of SSRI)" was removed from the protocol. In addition, as a result of Investigator feedback, inclusion criteria 9 related to the exclusion of patients with past medical history of bipolar disorder, schizophrenia or other psychotic disorders, schizoaffective disorder, autism, borderline personality disorder, or Gilles de laTourette syndrome was amended to allow patients with high functioning ASD, e.g. Asperger's Syndrome to be included in the study. Obsessive-compulsive disorder (OCD) and social anxiety disorder frequently co-occur in persons with ASD (Cath et al 2008). Therefore, it would be appropriate to include these patients in the study. |
| 07 February 2014 | This amendment was issued when there were two patients on the treatment and 13 were screened. Issued to respond to Investigators feedback from active study sites in light of the OCD population they were screening. •Inclusion criterion was modified to allow patients with a Y-BOCS score ≥ 16 to enter the study. The inclusion criterion was removed from entry criteria of the protocol. •Exclusion criterion 5 was removed from entry criteria of the protocol. •Exclusion criterion 8 was amended to allow Gilles de la Tourette syndrome patients to be included in the study, provided the primary diagnosis is OCD. Exclusion criterion 9 "History of substance dependence and/or substance abuse in the last 6 months prior to Screening, with the exception of nicotine has been amended to exclude nicotine "with the exception of nicotine" in order to be in line with Exclusion criteria 9 which was exclusion of the smokers. •Exclusion criterion 28 was amended in accordance with the AFQ056 Investigator Brochure (version 11 dated Jun-18-2013), confirming that contraception requirement for women of child-bearing potential changed from highly effective to effective. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|---|--------------|
| 09 June 2014 | In June 2014, the Company has decided to proceed with an interim analysis based on the data from all completed patients at week 16. The company has therefore placed recruitment on hold from June 9th onwards until the results from this interim analysis become available. | - |

Notes:

Limitations and caveats

None reported