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