Sponsor

Novartis

Generic Drug Name

AFQ056

Therapeutic Area of Trial

L-dopa induced dyskinesias in Parkinson's disease (PD-LID)

Approved Indication

Not approved yet for any indication.

Study Number

CAFQ506A2208

Title

13-week, double-blind, placebo-controlled, fixed-dose, multicenter study to evaluate the efficacy and safety of AFQ056 in reducing moderate to severe L-dopa induced dyskinesias in patients with Parkinson's disease

Phase of Development

IIb

Study Start/End Dates

15-Sep-2009 to 03-Dec-2010

Study Design/Methodology

This was a multicenter study using a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group design to evaluate the efficacy and safety of five doses of AFQ056 compared to placebo in patients with moderate to severe PD-LID. Of the 197 patients randomized, 133 received treatment with one of five doses of AFQ056 and 64 patients received placebo.

Patients were titrated at one-week intervals until they reached their target dose. Patients remained on the target dose until they reached the end of the 12-week fixed-dose phase. For patients who were unable to tolerate the protocol-specified dosing scheme, a limited number of dose adjustments (dose maintenance or up to two down-titrations) were permitted. Patients who completed

the 12-week fixed-dose phase entered a 1-week randomized, placebo-controlled, taper-off phase.

A total of 234 patients were planned to be randomized to one of the six groups including five AFQ056 dose groups: 10 mg, 25 mg, 50 mg, 75 mg and 100 mg b.i.d. and placebo with an allocation ratio of 1:1:1:1:2:3. Assumptions for the dropout rate and standard deviation were reassessed based on a blinded review of interim data, and based on these, the sample size was reduced to 198 patients.

Centres

42 centers in 8 countries: Australia (5), Canada (5), Finland (3), France (5), Germany (8), Italy (4), Japan (7), Spain (5).

Publication

None.

Objectives

Primary objectives

- To investigate the anti-dyskinetic efficacy, as measured by change from baseline to endpoint at Week 12 in the modified Abnormal Involuntary Movement Scale (mAIMS) total score, of five fixed doses of AFQ056 versus placebo in patients with moderate to severe PD-LID.
- To estimate the dose-response relationship among five fixed doses of AFQ056 and placebo after 12 weeks of treatment, as measured by the changes from baseline in mAIMS total score.

Secondary objectives

- To evaluate the efficacy of five fixed doses of AFQ056 versus placebo on disability due to dyskinesias as measured by change from baseline to endpoint at Week 12 in the 26-Item Parkinson Disease Dyskinesia Scale (PDYS-26) total score (key secondary assessment)
- To evaluate change from baseline on patient's dyskinesia, disability caused by the dyskinesia and the underlying symptoms of PD as assessed by a clinician-rated (CGIC) and a patient-rated (PGIC) global impression of change
- To evaluate the anti-dyskinetic efficacy as measured by items 32 and 33 of Part IV of the Unified Parkinson's Disease Rating Scale (UPDRS)
- To evaluate the safety of AFQ056 as measured by changes in vital signs, laboratory values and ECGs and percentages of treatment-emergent adverse events and serious adverse events
- To evaluate the effect of AFQ056 on the underlying symptoms of Parkinson's disease as measured by e.g. UPDRS Part III (Motor Examination)

Test Product (s), Dose(s), and Mode(s) of Administration

AFQ056 was provided as hard gelatin capsules for oral use. Dosage strengths were 5 mg, 25 mg and 100 mg. Matching placebo was provided.

Reference Product(s), Dose(s), and Mode(s) of Administration

Placebo medication identical in appearance to active medication.

Criteria for Evaluation

Primary efficacy variable

The primary efficacy variable was the change from baseline to endpoint at Week 12 in the modified AIMS total score.

Secondary efficacy variables

The key secondary efficacy variable was the change from baseline to endpoint at Week 12 in the total score of the PDYS-26.

Further secondary efficacy variables included the change from baseline to endpoint at Week 12 in the total score of the Unified Parkinson Disease Rating Scale (UPDRS- Parts III and IV), of Clinical Global Impression of Change Scale (CGIC) – investigator rating, and of Patient Global Impression of Change Scale (PGIC) – patient rating.

Safety and tolerability

Recording of adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug. Regular monitoring of hematology, blood chemistry and urine performed at a central laboratory. Regular assessments of vital signs, ECGs, physical condition, and body weight.

Cognitive function was assessed using the Mini-Mental State Examination (MMSE), the Cognitive Test Battery (CogState) and the Controlled Oral Word Association Test (COWAT). Psychiatric symptoms were assessed using the Scales for Outcomes in Parkinson's disease – Psychiatric Complications (SCOPA-PC).

Pharmacology

Blood samples (6 mL) for pharmacokinetic evaluation were collected at Visit 4 (Week 1) and at Visits 7 and 9 (Weeks 6 and 12, respectively).

Other

Not applicable.

Statistical Methods

The primary efficacy variable was the change from baseline to endpoint at Week 12 in the modi-

fied AIMS total score.

The primary efficacy variable was analyzed using the analysis of covariance (ANCOVA) model with terms for treatment group, country, and baseline score. The null hypothesis was that there would be no difference between placebo and any of the dose groups with respect to the primary efficacy variable; the alternative hypothesis was that at least one of the doses would be superior to placebo. Comparisons of different dose groups with placebo were made at the one-sided family-wise error rate of 2.5%. Dunnett's procedure was applied to adjust for the multiple comparisons.

To characterize the dose-response profile, five candidate models were selected to cover possible shapes anticipated for the dose-response relationship. Each model was fit to the primary efficacy variable with terms for country and baseline score. The model with the smallest AIC (Akaike Information Criterion) was selected and the dose-response curve was estimated with a two-sided 95% confidence interval.

The key secondary efficacy variable was the change from baseline to endpoint at Week 12 in the total score of the PDYS-26. It was analyzed using the same method as the primary efficacy variable.

These analyses were performed for the ITT (intent-to-treat) population.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria

- Males and females (females not of child-bearing potential) between 30 and 80 years of age
- Outpatients, residing in the community (nursing home patients were not allowed)
- Clinical diagnosis of Parkinson's disease according to the UK Parkinson's Disease Society Brain Bank Clinical Diagnosis criteria
- Score of ≥ 2 on UPDRS item 32 (i.e. dyskinesia present for greater than 25% of the time) and score of ≥ 2 on UPDRS item 33 (i.e. moderate to severely disabling)
- Onset of dyskinesias at least 3 months before randomization
- On L-dopa for at least 3 years prior to randomization or, if duration of treatment was ≤ 3 years, then must have shown clear responsiveness (UPDRS, Part III) to L-dopa treatment
- On stable treatment regimen with L-dopa and other anti-parkinsonian treatment for at least 4 weeks prior to the first baseline visit (BL1) with optimized dosing as determined by the enrolling clinician. In addition to this stable treatment, up to three doses per week of soluble L-dopa or subcutaneous apomorphine were allowed to optimize the treatment regimen to alleviate fluctuations (OFF-periods).

Key exclusion criteria

- Clinical evidence suggestive of an atypical or secondary form of Parkinson's disease (e.g. Progressive Supranuclear Palsy, Multi Systemic Atrophy)
- A history of surgical treatment for PD, including deep brain stimulation
- A score of 5 in the "ON"-state on the Modified Hoehn and Yahr Staging (UPDRS Part V) assessment at screening

- Any advanced, severe or unstable disease (other than PD) that might interfere with the primary and secondary study outcome evaluations
- History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or non-invasive, non-metastatic prostate cancer that had been effectively treated), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases
- Evidence of dementia; untreated or ineffectively treated major depressive disorder; currently experiencing hallucinations/psychosis requiring antipsychotic treatment, and/or confusional states

Number of Subjects

Out of 260 patients screened, 197 patients were randomized.

Patient disposition (Study Completion) by treatment (Randomized population)

	Placebo	AFQ056					Total
Disposition Reason	N=64 n (%)	10mg N=22 n (%)	25mg N=22 n (%)	50mg N=23 n (%)	75mg N=22 n (%)	100mg N=44 n (%)	N=197 n (%)
Completed study	47 (73.4)	20 (90.9)	18 (81.8)	14 (60.9)	11 (50.0)	35 (79.5)	145 (73.6)
Discontinued from study	17 (26.6)	2 (9.1)	4 (18.2)	9 (39.1)	11 (50.0)	9 (20.5)	52 (26.4)
Adverse Event(s)	7 (10.9)	1 (4.5)	2 (9.1)	6 (26.1)	4 (18.2)	5 (11.4)	25 (12.7)
Death	0	0	0	1 (4.3)	0	0	1 (0.5)
Protocol deviation	3 (4.7)	0	0	1 (4.3)	2 (9.1)*	0	6 (3.0)
Subject withdrew consent	2 (3.1)	0	0	0	1 (4.5)	1 (2.3)	4 (2.0)
Unsatisfactory therapeutic effect	5 (7.8)	1 (4.5)	2 (9.1)	1 (4.3)	4 (18.2)	3 (6.8)	16 (8.1)

* For one of these patients the reason for discontinuation from study was recorded inconsistently, i.e. once as “subject withdrew consent” (study phase completion eCRF) and once as “protocol deviation” (study phase completion eCRF).
Subjects had to complete pre-randomization, fixed-dose, taper, and follow-up phases of the study in order to be considered completers.

Demographic and Background Characteristics

	Placebo	AFQ056					Total
Demographic variable	N=64	10mg N=22	25mg N=22	50mg N=23	75mg N=22	100mg N=44	N=197
Age (years)							
n	64	22	22	23	22	44	197
Mean	64.8	66.2	66.4	65.6	66.0	63.4	65.1
SD	8.17	8.16	7.96	9.47	10.54	8.98	8.73
Minimum	43	47	43	38	33	35	33
Median	65.0	67.5	66.5	65.0	67.5	66.0	66.0
Maximum	80	79	78	78	80	78	80
Sex, n (%)							
Female	34 (53.1)	12 (54.5)	9 (40.9)	9 (39.1)	8 (36.4)	20 (45.5)	92 (46.7)
Male	30 (46.9)	10 (45.5)	13 (59.1)	14 (60.9)	14 (63.6)	24 (54.5)	105 (53.3)
Race, n (%)							
Caucasian	50 (78.1)	18 (81.8)	18 (81.8)	18 (78.3)	18 (81.8)	36 (81.8)	158 (80.2)
Black	0	0	0	0	0	0	0
Asian	10 (15.6)	4 (18.2)	4 (18.2)	4 (17.4)	4 (18.2)	6 (13.6)	32 (16.2)
Other	4 (6.3)	0	0	1 (4.3)	0	2 (4.5)	7 (3.6)
Ethnicity, n (%)							
Hispanic/Latino	10 (15.6)	4 (18.2)	3 (13.6)	1 (4.3)	2 (9.1)	4 (9.1)	24 (12.2)
Chinese	1 (1.6)	0	0	0	0	0	1 (0.5)
Japanese	9 (14.1)	4 (18.2)	4 (18.2)	4 (17.4)	3 (13.6)	6 (13.6)	30 (15.2)
Other	44 (68.8)	14 (63.6)	15 (68.2)	18 (78.3)	17 (77.3)	34 (77.3)	142 (72.1)
Baseline height (cm)							
n	63	22	21	23	22	44	195

Mean	164.3	163.4	164.5	166.0	168.6	164.9	165.0
SD	10.49	10.32	10.24	10.84	9.63	9.60	10.17
Minimum	146	141	146	138	145	150	138
Median	165.0	165.0	168.0	165.0	170.0	165.0	166.0
Maximum	189	181	180	186	181	187	189
Baseline BMI (kg/m²)							
n	63	21	20	23	22	44	193
Mean	24.32	23.41	24.02	24.15	23.94	25.31	24.35
SD	3.981	4.261	2.651	3.976	5.141	4.184	4.083
Minimum	17.3	17.3	20.1	16.0	17.2	17.4	16.0
Median	24.14	22.94	23.67	23.84	22.97	25.22	24.02
Maximum	36.1	34.3	28.0	31.6	40.9	35.4	40.9
Current smoker n (%)							
Yes	4 (6.3)	1 (4.5)	3 (13.6)	1 (4.3)	1 (4.5)	2 (4.5)	12 (6.1)
No	60 (93.8)	21 (95.5)	19 (86.4)	22 (95.7)	21 (95.5)	42 (95.5)	185 (93.9)

Primary Objective Result(s)

Modified AIMS total score - ANCOVA treatment comparisons for change from baseline to Week 12 (LOCF) by treatment - Fixed-dose treatment phase (ITT population)

	n	Baseline Mean (SD)	Week 12 (LOCF) Mean (SD)	Adjusted change from baseline Mean (SE)	Difference 95% CI	Pair-wise comparisons p-value [2]
Overall F-test p-value [1]						0.015
Placebo (N=63)	61	13.4 (4.71)	10.4 (5.35)	-2.9 (0.61)		
AFQ056						
10mg (N=22)	22	14.5 (4.64)	11.3 (5.73)	-2.7 (0.99)	0.2 (-2.7, 3.2)	0.743
25mg (N=22)	22	12.9 (5.03)	7.6 (6.57)	-5.5 (0.99)	-2.6 (-5.5, 0.4)	0.046
50mg (N=23)	22	13.5 (5.29)	9.8 (5.90)	-3.6 (0.99)	-0.6 (-3.6, 2.3)	0.571
75mg (N=22)	22	13.9 (5.08)	10.8 (4.50)	-2.8 (0.99)	0.1 (-2.8, 3.1)	0.743
100mg (N=42)	40	13.2 (4.99)	7.5 (5.00)	-5.7 (0.75)	-2.8 (-5.2, -0.4)	0.007

Change from baseline = post-baseline assessment - baseline assessment.
A negative change from baseline indicates improvement. An analysis of covariance (ANCOVA) model is used with baseline value as a covariate and treatment and country as factors.
[1] The overall F-test tests if at least one dose group differs from placebo.
[2] Comparisons of each dose group with placebo are made at the one-sided family-wise error rate of 2.5%. Dunnett's step-down procedure is applied to adjust for multiple comparisons.

Modified AIMS total score - ANCOVA treatment comparisons for change from baseline to Week 12 (LOCF) by actual dose at the end of fixed-dose phase- Fixed-dose treatment phase (ITT population)

	n	Baseline Mean (SD)	Week 12 (LOCF) Mean (SD)	Adjusted change from baseline Mean (SE)	Difference 95% CI	Pair-wise comparisons p-value [2]
Overall F-test p-value [1]						0.073
Placebo (N=63)	61	13.4 (4.71)	10.4 (5.35)	-2.9 (0.62)		

AFQ056						
10mg (N=32)	31	14.2 (4.51)	10.4 (5.72)	-3.3 (0.84)	-0.4 (-3.0, 2.3)	0.394
25mg (N=40)	38	12.9 (5.08)	9.2 (5.78)	-3.6 (0.80)	-0.7 (-3.2, 1.8)	0.394
50mg (N=22)	22	13.5 (5.23)	8.7 (5.41)	-4.7 (1.02)	-1.8 (-4.8, 1.2)	0.161
75mg (N=20)	20	13.9 (5.68)	9.1 (6.15)	-5.0 (1.07)	-2.0 (-5.2, 1.1)	0.158
100mg (N=17)	17	13.4 (4.60)	7.2 (4.96)	-6.5 (1.14)	-3.6 (-7.0, -0.3)	0.012

Change from baseline = post-baseline assessment - baseline assessment. A negative change from baseline indicates improvement. An analysis of covariance (ANCOVA) model is used with baseline value as a covariate and treatment and country as factors.
[1] The overall F-test tests if at least one dose group differs from placebo.
[2] Comparisons of each dose group with placebo are made at the one-sided family-wise error rate of 2.5%. Dunnett's step-down procedure is applied to adjust for multiple comparisons.

Secondary Objective Result(s)

PDYS-26 total score - ANCOVA treatment comparisons for change from baseline to Week 12 (LOCF) by treatment - Fixed-dose treatment phase (ITT population)

	n	Baseline Mean (SD)	Week 12 (LOCF) Mean (SD)	Adjusted change from baseline Mean (SE)	Difference 95% CI	Pair-wise comparisons p-value [2]
Overall F-test p-value [1]						0.840
Placebo (N=63)	58	45.0 (21.05)	35.2 (20.45)	-8.8 (2.45)		
AFQ056						
10mg (N=22)	22	51.6 (19.87)	44.9 (21.60)	-3.6 (3.88)	5.2 (-6.5, 16.9)	0.874
25mg (N=22)	20	44.4 (20.12)	36.8 (19.36)	-8.8 (4.03)	-0.0 (-12.1, 12.1)	0.869
50mg (N=23)	19	44.0 (21.09)	35.5 (23.91)	-8.3 (4.16)	0.4 (-11.8, 12.7)	0.869
75mg (N=22)	20	47.1 (23.63)	39.0 (23.71)	-6.6 (4.05)	2.2 (-9.8, 14.2)	0.869
100mg (N=42)	40	45.1 (22.16)	34.6 (23.39)	-10.0 (2.93)	-1.2 (-10.7, 8.4)	0.802

Note: Change from baseline = post-baseline assessment - baseline assessment. A negative change from baseline indicates improvement. An analysis of covariance (ANCOVA) model is used with baseline value as a covariate and treatment and country as factors.
[1] The overall F-test tests if at least one dose group differs from placebo.
[2] Comparisons of each dose group with placebo are made at the one-sided family-wise error rate of 2.5%. Dunnett's step-down procedure is applied to adjust for multiple comparisons.

CGIC scores - ANOVA treatment comparisons for Week 12 (LOCF) scores by treatment - Fixed-dose treatment phase (ITT population)

	n	Week 12 (LOCF) Mean (SD)	Least squares Mean (SE)	Difference 95% CI	Pair-wise comparisons p-value [2]
Dyskinesia					
Overall F-test p-value [1]					0.215
Placebo (N=63)	58	3.0 (1.36)	3.0 (0.18)		
AFQ056					
10mg (N=22)	21	3.5 (1.33)	3.4 (0.30)	0.5 (-0.2, 1.2)	0.152
25mg (N=22)	18	2.7 (1.33)	2.5 (0.32)	-0.4 (-1.1, 0.3)	0.265
50mg (N=23)	19	3.1 (1.33)	3.1 (0.31)	0.1 (-0.6, 0.8)	0.754
75mg (N=22)	20	3.2 (1.61)	3.1 (0.30)	0.2 (-0.5, 0.9)	0.578

100mg (N=42)	40	2.7 (1.24)	2.6 (0.22)	-0.3 (-0.9, 0.2)	0.252
Disability consequences of dyskinetic symptoms					
Overall F-test p-value [1]					0.237
Placebo (N=63)	58	3.1 (1.38)	3.1 (0.18)		
AFQ056					
10mg (N=22)	21	3.4 (1.12)	3.4 (0.28)	0.3 (-0.3, 1.0)	0.327
25mg (N=22)	18	2.8 (1.04)	2.7 (0.30)	-0.3 (-1.0, 0.4)	0.364
50mg (N=23)	19	3.4 (1.17)	3.4 (0.30)	0.3 (-0.3, 1.0)	0.323
75mg (N=22)	20	3.4 (1.60)	3.4 (0.29)	0.3 (-0.4, 1.0)	0.371
100mg (N=42)	40	2.8 (1.20)	2.8 (0.21)	-0.3 (-0.8, 0.2)	0.266
Overall Parkinson's disease symptoms					
Overall F-test p-value [1]					0.839
Placebo (N=63)	58	4.2 (0.88)	4.1 (0.12)		
AFQ056					
10mg (N=22)	21	4.3 (0.56)	4.2 (0.19)	0.1 (-0.3, 0.6)	0.578
25mg (N=22)	18	4.0 (0.77)	4.0 (0.20)	-0.1 (-0.6, 0.3)	0.608
50mg (N=23)	19	3.9 (1.08)	3.9 (0.20)	-0.2 (-0.7, 0.2)	0.305
75mg (N=22)	20	4.1 (0.85)	4.1 (0.19)	-0.1 (-0.5, 0.4)	0.748
100mg (N=42)	40	4.1 (0.87)	4.0 (0.14)	-0.1 (-0.4, 0.3)	0.665

A score of 4 indicates no change from baseline. A score of <4 indicates improvement. An analysis of variance (ANOVA) model is used with treatment and country as factors.
[1] The overall F-test tests if at least one dose group differs from placebo.
[2] Comparisons of each dose group with placebo are made at the two-sided significance level of 5%.

UPDRS part IV (sum of items 32-33), dyskinesia duration and disability - ANCOVA treatment comparisons for change from baseline to Week 12 (LOCF) by treatment - Fixed-dose treatment phase (ITT population)

	n	Baseline Mean (SD)	Week 12 (LOCF) Mean (SD)	Adjusted change from baseline Mean (SE)	Difference 95% CI	Pair-wise comparisons p-value [2]
Total score (item 32 + 33)						
Overall F-test p-value [1]						0.118
Placebo (N=63)	58	5.0 (0.82)	3.9 (1.53)	-1.1 (0.20)		
AFQ056						
10mg (N=22)	21	5.2 (0.87)	3.8 (1.63)	-1.3 (0.33)	-0.2 (-1.0, 0.5)	0.539
25mg (N=22)	18	4.9 (0.94)	2.8 (1.65)	-2.2 (0.35)	-1.1 (-1.9, -0.3)	0.008
50mg (N=23)	19	4.7 (0.73)	3.4 (1.54)	-1.5 (0.34)	-0.4 (-1.1, 0.4)	0.339
75mg (N=22)	21	4.8 (0.75)	3.7 (1.49)	-1.2 (0.32)	-0.1 (-0.8, 0.6)	0.769
100mg (N=42)	40	5.0 (0.92)	3.4 (1.46)	-1.6 (0.24)	-0.6 (-1.2, 0.0)	0.068
Dyskinesia duration						
Overall F-test p-value [1]						0.014
Placebo (N=63)	58	2.6 (0.65)	2.2 (0.86)	-0.4 (0.12)		
AFQ056						
10mg (N=22)	21	2.8 (0.68)	2.1 (0.96)	-0.6 (0.19)	-0.1 (-0.6, 0.3)	0.489
25mg (N=22)	18	2.7 (0.69)	1.6 (0.78)	-1.1 (0.20)	-0.7 (-1.1, -0.2)	0.003
50mg (N=23)	19	2.4 (0.51)	1.8 (0.79)	-0.8 (0.20)	-0.3 (-0.8, 0.1)	0.126

75mg (N=22)	21	2.6 (0.60)	2.1 (1.01)	-0.5 (0.19)	-0.1 (-0.5, 0.4)	0.762
100mg (N=42)	40	2.7 (0.70)	1.8 (0.81)	-0.9 (0.14)	-0.5 (-0.8, -0.1)	0.005
Dyskinesia disability						
Overall F-test p-value [1]						0.761
Placebo (N=63)	58	2.4 (0.48)	1.7 (0.90)	-0.7 (0.12)		
AFQ056						
10mg (N=22)	21	2.4 (0.50)	1.7 (0.86)	-0.7 (0.18)	-0.0 (-0.5, 0.4)	0.832
25mg (N=22)	18	2.3 (0.46)	1.3 (1.02)	-1.0 (0.20)	-0.4 (-0.8, 0.1)	0.113
50mg (N=23)	19	2.3 (0.48)	1.6 (0.84)	-0.7 (0.19)	-0.1 (-0.5, 0.4)	0.775
75mg (N=22)	21	2.2 (0.44)	1.6 (0.81)	-0.7 (0.18)	-0.0 (-0.5, 0.4)	0.830
100mg (N=42)	40	2.4 (0.54)	1.6 (0.87)	-0.7 (0.14)	-0.1 (-0.4, 0.3)	0.714

Note: Change from baseline = post-baseline assessment - baseline assessment. A negative change from baseline indicates improvement. An analysis of covariance (ANCOVA) model is used with baseline value as a covariate and treatment and country as factors.
[1] The overall F-test tests if at least one dose group differs from placebo.
[2] Comparisons of each dose group with placebo are made at the two-sided significance level of 5%.

UPDRS part III total score - ANCOVA treatment comparisons for change from baseline to Week 12 (LOCF) by treatment - Fixed-dose treatment phase (ITT population)

	n	Baseline Mean (SD)	Week 12 (LOCF) Mean (SD)	Adjusted change from baseline Mean (SE)	Difference 95% CI	Pair-wise comparisons p-value [2]
Overall F-test p-value [1]						0.835
Placebo (N=63)	58	16.1 (8.76)	16.0 (9.62)	-0.5 (0.92)		
AFQ056						
10mg (N=22)	21	16.4 (8.27)	16.2 (9.62)	-0.7 (1.48)	-0.1 (-3.5, 3.3)	0.943
25mg (N=22)	18	19.8 (8.18)	20.1 (8.56)	1.1 (1.61)	1.6 (-2.0, 5.3)	0.377
50mg (N=23)	19	18.2 (9.40)	16.5 (8.24)	-1.6 (1.56)	-1.1 (-4.6, 2.5)	0.553
75mg (N=22)	21	18.1 (8.73)	16.9 (9.87)	-1.3 (1.48)	-0.8 (-4.1, 2.6)	0.655
100mg (N=42)	40	17.6 (9.53)	16.3 (9.68)	-1.3 (1.10)	-0.7 (-3.5, 2.0)	0.590

Change from baseline = post-baseline assessment - baseline assessment. A negative change from baseline indicates improvement. An analysis of covariance (ANCOVA) model is used with baseline value as a covariate and treatment and country as factors.
[1] The overall F-test tests if at least one dose group differs from placebo.
[2] Comparisons of each dose group with placebo are made at the two-sided significance level of 5%.

Safety Results

Adverse Events by System Organ Class

Incidence of AEs by primary system organ class, by treatment – Fixed dose treatment phase (Safety population)

	Placebo	AFQ056					Total
Primary system organ class Preferred term	N=63 n (%)	10mg N=22 n (%)	25mg N=22 n (%)	50mg N=23 n (%)	75mg N=22 n (%)	100mg N=44 n (%)	N=196 n (%)
Patients with any adverse event	41 (65.1)	13 (59.1)	13 (59.1)	19 (82.6)	15 (68.2)	33 (75.0)	134 (68.4)
Nervous system disorders	22 (34.9)	5 (22.7)	3 (13.6)	11 (47.8)	9 (40.9)	22 (50.0)	72 (36.7)
Psychiatric disorders	5 (7.9)	0	4 (18.2)	7 (30.4)	3 (13.6)	17 (38.6)	36 (18.4)
Gastrointestinal disorders	8 (12.7)	6 (27.3)	0	5 (21.7)	3 (13.6)	10 (22.7)	32 (16.3)
General disorders and administration site conditions	8 (12.7)	0	3 (13.6)	5 (21.7)	5 (22.7)	8 (18.2)	29 (14.8)
Musculoskeletal and connective tissue disorders	7 (11.1)	2 (9.1)	1 (4.5)	5 (21.7)	2 (9.1)	8 (18.2)	25 (12.8)
Injury, poisoning and procedural complications	11 (17.5)	1 (4.5)	4 (18.2)	1 (4.3)	3 (13.6)	5 (11.4)	25 (12.8)
Infections and infestations	4 (6.3)	3 (13.6)	2 (9.1)	4 (17.4)	2 (9.1)	5 (11.4)	20 (10.2)
Vascular disorders	5 (7.9)	2 (9.1)	0	1 (4.3)	3 (13.6)	4 (9.1)	15 (7.7)
Eye disorders	3 (4.8)	2 (9.1)	0	1 (4.3)	1 (4.5)	6 (13.6)	13 (6.6)
Investigations	3 (4.8)	0	1 (4.5)	2 (8.7)	2 (9.1)	4 (9.1)	12 (6.1)
Skin & subcutan. tissue disorders	3 (4.8)	2 (9.1)	1 (4.5)	1 (4.3)	2 (9.1)	1 (2.3)	10 (5.1)
Cardiac disorders	3 (4.8)	0	1 (4.5)	0	0	4 (9.1)	8 (4.1)
Renal and urinary disorders	1 (1.6)	0	0	0	1 (4.5)	3 (6.8)	5 (2.6)
Blood & lymphatic system disorders	1 (1.6)	1 (4.5)	1 (4.5)	1 (4.3)	0	0	4 (2.0)
Respiratory, thoracic and mediastinal disorders	1 (1.6)	0	0	0	1 (4.5)	1 (2.3)	3 (1.5)
Ear and labyrinth disorders	1 (1.6)	1 (4.5)	1 (4.5)	0	0	0	3 (1.5)
Neoplasms benign, malignant & unspecified (incl cysts & polyps)	1 (1.6)	0	0	0	0	1 (2.3)	2 (1.0)
Metabolism & nutrition disorders	0	0	1 (4.5)	0	0	0	1 (0.5)
Immune system disorders	0	1 (4.5)	0	0	0	0	1 (0.5)

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Incidence of AEs (at least 4% in total AFQ056 group) by preferred term, by treatment – Fixed dose treatment phase (Safety population)

	Placebo	AFQ056					
Preferred term	N=63 n (%)	10mg N=22 n (%)	25mg N=22 n (%)	50mg N=23 n (%)	75mg N=22 n (%)	100mg N=44 n (%)	Total AFQ056 N=133 n (%)
Patients with any AE	41 (65.1)	13 (59.1)	13 (59.1)	19 (82.6)	15 (68.2)	33 (75.0)	93 (69.9)
Dizziness	0 (0.0)	2 (9.1)	0 (0.0)	5 (21.7)	2 (9.1)	10 (22.7)	19 (14.3)
Dyskinesia	8 (12.7)	1 (4.5)	0 (0.0)	2 (8.7)	2 (9.1)	4 (9.1)	9 (6.8)
Hallucination	1 (1.6)	0 (0.0)	1 (4.5)	3 (13.0)	0 (0.0)	5 (11.4)	9 (6.8)
Fatigue	2 (3.2)	0 (0.0)	1 (4.5)	1 (4.3)	3 (13.6)	3 (6.8)	8 (6.0)
Nasopharyngitis	0 (0.0)	1 (4.5)	2 (9.1)	1 (4.3)	1 (4.5)	3 (6.8)	8 (6.0)
Diarrhoea	1 (1.6)	3 (13.6)	0 (0.0)	2 (8.7)	0 (0.0)	2 (4.5)	7 (5.3)
Insomnia	0 (0.0)	0 (0.0)	1 (4.5)	3 (13.0)	1 (4.5)	2 (4.5)	7 (5.3)
Nausea	6 (9.5)	1 (4.5)	0 (0.0)	1 (4.3)	1 (4.5)	4 (9.1)	7 (5.3)
Illusion	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.5)	5 (11.4)	6 (4.5)
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (4.5)	4 (9.1)	6 (4.5)

Serious Adverse Events and Deaths

Number of patients who died or experienced other serious or clinically significant adverse events by treatment – Fixed-dose treatment phase (Safety population)

	Placebo	AFQ056					Total
	N=63 n (%)	10mg N=22 n (%)	25mg N=22 n (%)	50mg N=23 n (%)	75mg N=22 n (%)	100mg N=44 n (%)	N=196 n (%)
Patients with any AE(s)	41 (65.1)	13 (59.1)	13 (59.1)	19 (82.6)	15 (68.2)	33 (75.0)	134 (68.4)
Death	0	0	0	1 (4.3)*	0	0	1 (0.5)
SAE (s)	6 (9.5)	0	1 (4.5)	2 (8.7)	1 (4.5)	5 (11.4)	15 (7.7)
Severe AE (s)	8 (12.7)	2 (9.1)	2 (9.1)	3 (13.0)	6 (27.3)	3 (6.8)	24 (12.2)
Study drug-related AE(s)	26 (41.3)	7 (31.8)	9 (40.9)	17 (73.9)	13 (59.1)	23 (52.3)	95 (48.5)
AE (s) leading to study discontinuation	7 (11.1)	1 (4.5)	2 (9.1)	7 (30.4)	4 (18.2)	5 (11.4)	26 (13.3)
AE (s) requiring dosing modification / interruption	3 (4.8)	2 (9.1)	2 (9.1)	5 (21.7)	5 (22.7)	10 (22.7)	27 (13.8)
Extrapyramidal syndrome (SMQ)-related AE (s)	14 (22.2)	3 (13.6)	2 (9.1)	5 (21.7)	7 (31.8)	9 (20.5)	40 (20.4)
Psychosis and Psychotic Disorders (SMQ)-related AE(s)	1 (1.6)	0	1 (4.5)	4 (17.4)	1 (4.5)	10 (22.7)	17 (8.7)

* One patient died on Day 19 of the study (sudden death). The patient had a family history of cardiovascular disease that included the death of patient's brother due to myocardial infarction. Although there was significant artifact in the patient's baseline ECG, the presence of an old inferior and or septal myocardial infarction could not be ruled out. In addition, bundle branch block left (bundle branch block left) was reported. There were no abnormal vital signs or laboratory values noted prior to the event (sudden death).The investigator suspected a relationship between the event (sudden death) and study drug.

Serious adverse events by treatment – Fixed-dose treatment phase (Safety population)

	Placebo	AFQ056					Total
Primary system organ class Preferred term	N=63 n (%)	10mg N=22 n (%)	25mg N=22 n (%)	50mg N=23 n (%)	75mg N=22 n (%)	100mg N=44 n (%)	N=196 n (%)
Patients with any SAE(s)	6 (9.5)	0	1 (4.5)	2 (8.7)	1 (4.5)	5 (11.4)	15 (7.7)
Cardiac disorders	1 (1.6)	0	0	0	0	0	1 (0.5)
Myocardial infarction	1 (1.6)	0	0	0	0	0	1 (0.5)
Gastrointestinal disorders	1 (1.6)	0	0	1 (4.3)	0	0	2 (1.0)
Inguinal hernia	1 (1.6)	0	0	1 (4.3)	0	0	2 (1.0)
General disorders and administration site conditions	0	0	0	1 (4.3)	0	0	1 (0.5)
Sudden death	0	0	0	1 (4.3)	0	0	1 (0.5)
Infections and infestations	0	0	0	0	0	1 (2.3)	1 (0.5)
Pneumonia	0	0	0	0	0	1 (2.3)	1 (0.5)
Injury, poisoning and procedural complications	2 (3.2)	0	1 (4.5)	0	1 (4.5)	1 (2.3)	5 (2.6)
Accidental overdose	0	0	0	0	0	1 (2.3)	1 (0.5)
Fall	0	0	1 (4.5)	0	0	0	1 (0.5)
Femur fracture	1 (1.6)	0	0	0	0	0	1 (0.5)
Rib fracture	0	0	0	0	1 (4.5)	0	1 (0.5)
Road traffic accident	1 (1.6)	0	0	0	0	0	1 (0.5)
Wrist fracture	0	0	1 (4.5)	0	0	0	1 (0.5)
Neoplasms benign, malignant & un-spec.(incl. cysts & polyps)	1 (1.6)	0	0	0	0	1 (2.3)	2 (1.0)
Renal cancer	1 (1.6)	0	0	0	0	0	1 (0.5)
Renal neoplasm	0	0	0	0	0	1 (2.3)	1 (0.5)
Nervous system disorders	1 (1.6)	0	0	0	0	1 (2.3)	2 (1.0)
Monoparesis	1 (1.6)	0	0	0	0	0	1 (0.5)
Paraesthesia	0	0	0	0	0	1 (2.3)	1 (0.5)
Transient ischaemic attack	0	0	0	0	0	1 (2.3)	1 (0.5)
Psychiatric disorders	0	0	0	0	0	1 (2.3)	1 (0.5)
Anxiety	0	0	0	0	0	1 (2.3)	1 (0.5)

Other Relevant Findings

In general, changes/shifts in biochemistry, hematology and endocrinology parameters were seen with similar frequency across treatment groups with no clinically meaningful or dose-dependent differences.

With respect to vital signs, overall there were no clinically meaningful trends or differences for blood pressure or pulse observed among the treatment groups.

The most frequently occurring new ECG abnormalities were all related to the QT-interval, namely QTc (Bazett) change from baseline > 30 msec, PR > 200 msec, QTc (Fridericia) change from baseline > 30 msec, and QTc (Bazett) > 450 msec. These changes were recorded in both the AFQ056 and placebo groups and no clinically meaningful differences were observed.

Overall, the extensive cognitive assessment tests did not show consistent or clinically relevant

changes and the overall F-tests for MMSE, CogState and COWAT were not significant.

A specific test utilized to assess psychiatric symptoms and compulsive behavior, the SCOPA-PC, did not show any significant worsening/emergence of these.

Date of Clinical Trial Report

07-Jul-2011

Date Inclusion on Novartis Clinical Trial Results Database

30 Nov 2011

Date of Latest Update