Sponsor

Novartis

Generic Drug Name

AFQ056

Therapeutic Area of Trial

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

Approved Indication

Investigational

Protocol Number

CAFQ056A2223

Title

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

Study Phase

II

Study Start/End Dates

16-Apr-2012 (first patient first visit) to 24-Apr-2013 (last patient last visit)

Study Design/Methodology

This study used a randomized, double-blind, placebo-controlled, fixed-dose, parallel-group design to evaluate the safety and efficacy of modified release AFQ056 200 mg b.i.d. or 150 mg b.i.d. compared to placebo in patients with moderate to severe PD-LID.

The studied aimed to randomize a total of 140 patients (92 patients in Group 1 and 48 patients in Group 2). The anticipated screen failure rate was approximately 25%. Therefore, about 187 patients were expected to be screened for the study in order to randomize 140 patients.

Patients were designated to be in Group 1 or Group 2 as follows.

- **Group 1**: Patients were not permitted to take amantadine within 2 weeks prior to the BL1 (Baseline 1) visit or after entry into the placebo run-in epoch (BL1 visit).
- **Group 2**: Patients were on a stable and well tolerated dose of amantadine for at least 4 weeks prior to BL1 and maintained the stable dose of amantadine during the remainder of the study.

Placebo run-in epoch: At the BL1 visit, eligible patients entered a 2-week, single-blind, placebo run-in epoch, during which the patients and their caregivers were not aware that the patient received placebo, but the clinician was unblinded to the medication status.

Double-blind treatment epoch: Patients who successfully completed the placebo run-in epoch at BL2 entered the 12-week double-blind treatment epoch where they were randomly assigned to modified release AFQ056 200 mg b.i.d., modified release AFQ056 150 mg b.i.d. or placebo treatment groups in a ratio of 2:1:1. Patients were assigned to one of two groups by their amantadine status. Patients were titrated to the target dose and then remained on this dose until they reached the end of the 12-week double-blind treatment epoch.

Taper-off epoch: At the end of the 12-week double-blind treatment epoch there was a one-week, randomized, blinded taper-off epoch.

Centers

There were 39 sites in 10 countries as follows: Austria (3), Canada (1), France (4), Germany (9), Hungary (3), Italy (5), Slovakia (2), Spain (5), Switzerland (2), and United States (5)

Publication

Primary objectives

To assess how titration of modified release AFQ056 at 2-week intervals to a target dose of 200 mg b.i.d. or 150 mg b.i.d. *versus* placebo affects the tolerability profile in patients with moderate to severe PD-LID.

To demonstrate the anti-dyskinetic efficacy, as measured by change from baseline to Week 12 in the mAIMS (modified Abnormal Involuntary Movement Scale) total score, of titration of modified release AFQ056 at 2-week intervals to a target dose of 200 mg b.i.d. or 150 mg b.i.d. *versus* placebo in patients with moderate to severe PD-LID.

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Secondary objectives

1. To assess the anti-dyskinetic efficacy as measured by the UDysRS (Unified Dyskinesia Rating Scale), parts I-IV
2. To assess the anti-dyskinetic efficacy as measured by the Revised Lang-Fahn Activities of Daily Living Dyskinesia Scale (LFADLDS) patient and caregiver versions
3. To evaluate change from baseline on patient's disability caused by the dyskinesia as assessed by a clinician-rated global impression of change (CGIC)
4. To evaluate the Total ON- and OFF-times and ON-time with dyskinesia and with troublesome dyskinesias (patient diary)
5. To evaluate anti-dyskinetic efficacy as measured by items 32, 33 and 34 of Part IV of the UPDRS (Unified Parkinson's Disease Rating Scale)
6. To evaluate the safety of AFQ056 as measured by changes in vital signs, laboratory values and ECGs (electrocardiogram) and percentages of treatment-emergent adverse events and serious adverse events
7. To evaluate the effect of AFQ056 on the underlying symptoms of Parkinson's disease as measured by:
   a. UPDRS Part III (Motor Examination)
   b. Adverse events (AEs) potentially related to exacerbation of movement disorder of PD
8. To evaluate cognitive function as measured by the MMSE and a computerized test battery (CogState)
9. To evaluate any effect of AFQ056 on psychiatric and compulsive behaviors, as measured by the Scales for Outcomes in Parkinson's disease – Psychiatric Complications (SCOPA-PC)
10. To evaluate any effect of AFQ056 on suicidal ideation and behavior, as measured by the Columbia-Suicide Severity Rating Scale (C-SSRS)
11. To evaluate the pharmacokinetics of AFQ056 in patients with Parkinson's disease with moderate to severe dyskinesias
12. To assess the safety of concomitant administration of AFQ056 with amantadine

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

- AFQ056
- Dosage form: tablets of 25 mg, 50 mg, 100 mg, 150 mg, 200 mg.
- Presentation: modified release tablets

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

- Placebo
- Dosage form: tablets
- Presentation: modified release tablets

The AFQ056 25 mg, 50 mg, and 100 mg tablets were of one size and the AFQ056 150 mg and 200 mg tablets were of a different size. Therefore, two different matching placebo medications identical in appearance to active medication were provided.

Statistical Methods

The primary efficacy variable was the change from baseline 2 to Week 12 on the mAIMS total score.

Change from baseline 2 to Week 12 on the mAIMS total score was analyzed using a mixed-model for repeated measures (MMRM) including treatment, country, week, treatment by week interaction, as fixed effects and baseline mAIMS total score as a covariate, with an unstructured covariance structure.

Individual patient random effects were included in the model. The contrast between each AFQ056 dose group and placebo at Week 12 was estimated and presented together with a two-sided 95% confidence interval and p-value. The 95% confidence intervals and p-values for treatment effects at each visit were also computed using this model. The mean and LS mean change from baseline in mAIMS total score over time were plotted.

The primary efficacy analysis was performed on Group 1 patients of the Full Analysis Set (FAS-1).

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria:

- Males and females, 30-80 years of age (inclusive)
- Outpatients, residing in the community (nursing home patients are 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 (United Parkinson's Disease Rating Scale) 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 BL1
- On L-dopa for at least 3 years prior to BL1 or, if duration of treatment was ≤ 3 years, then had shown clear responsiveness (UPDRS, part III) to L-dopa treatment
- On a stable treatment regimen with L-dopa and other anti-parkinsonian treatment for at least 4 weeks prior to the first baseline visit (BL1)
- Demonstrated capacity to complete accurate diary ratings
- Group 2 only: on a stable and well-tolerated dose of amantadine for at least 4 weeks prior to BL1 and must maintain the stable dose during the remainder of the study

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 could interfere with the primary and secondary study outcome evaluations
- Evidence of dementia (or MMSE $\leq$ 26 at Screening), untreated or ineffectively treated major depressive disorder or currently experiencing hallucinations/psychosis requiring antipsychotic treatment, and/or confusional states Treatment prior to first baseline visit (BL1) with any of the following
    - Previous treatment with AFQ056
    - Treatment with strong or moderate inhibitors of CYP3A4 (cytochrome P450, family 3, subfamily A, polypeptide 4)
    - Treatment with strong or moderate inducers of CYP3A4
    - Warfarin or digoxin (within 1 week)
    - Centrally acting anti-cholinergic medication (within 1 week)
    - Amantadine (within 2 weeks) (applies to Group 1 only)
    - Metoclopramide (within 4 weeks)
    - Unstable treatment with domperidone, antidepressants, or anxiolytics (within 6 weeks)
    - Typical or atypical neuroleptic agents (within 3 months)
    - Duodopa or apomorphine pumps.

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Participant Flow

Patient disposition – double-blind treatment period by treatment (Randomized Set)

Disposition/Reason	AFQ056 150 mg (N=39) n (%)	AFQ056 200 mg (N=78) n (%)	Total AFQ056 (N=117) n (%)	Placebo (N=37) n (%)	Total (N=154) n (%)
Completed double-blind treatment period	30 (76.9)	46 (59.0)	76 (65.0)	33 (89.2)	109 (70.8)
Discontinued prior to completion of double-blind treatment period	9 (23.1)	32 (41.0)	41 (35.0)	4 (10.8)	45 (29.2)
Adverse Event	6 (15.4)	24 (30.8)	30 (25.6)	1 (2.7)	31 (20.1)
Lack of Efficacy	0	2 (2.6)	2 (1.7)	1 (2.7)	3 (1.9)
Non-Compliance With Study Treatment	0	0	0	1 (2.7)	1 (0.6)
Physician Decision	1 (2.6)	0	1 (0.9)	0	1 (0.6)
Protocol Deviation	0	1 (1.3)	1 (0.9)	1 (2.7)	2 (1.3)
Subject/Guardian Decision	2 (5.1)	5 (6.4)	7 (6.0)	0	7 (4.5)

N is the number of patients who entered the double-blind treatment period.

Baseline Characteristics

Demographic summary by treatment (Randomized Set)

Demographic variable	AFQ056 150 mg N=39	AFQ056 200 mg N=78	Total AFQ056 N=117	Placebo N=37	Total N=154
Age (years)					
n	39	78	117	37	154
Mean (SD)	64.4 (8.68)	64.4 (8.84)	64.4 (8.75)	64.2 (9.02)	64.4 (8.78)
Median	65.0	65.5	65.0	65.0	65.0
Range	45 to 78	40 to 80	40 to 80	43 to 79	40 to 80
Age group (years), n (%)					
< 65	19 (48.7)	35 (44.9)	54 (46.2)	18 (48.6)	72 (46.8)
≥ 65	20 (51.3)	43 (55.1)	63 (53.8)	19 (51.4)	82 (53.2)
Sex, n (%)					
Male	22 (56.4)	41 (52.6)	63 (53.8)	21 (56.8)	84 (54.5)
Female	17 (43.6)	37 (47.4)	54 (46.2)	16 (43.2)	70 (45.5)
Race, n (%)					
Caucasian	39 (100.0)	78 (100.0)	117 (100.0)	37 (100.0)	154 (100.0)
Ethnicity, n (%)					
Hispanic or Latino	9 (23.1)	10 (12.8)	19 (16.2)	6 (16.2)	25 (16.2)
Mixed ethnicity	1 (2.6)	0	1 (0.9)	0	1 (0.6)
Not reported	4 (10.3)	7 (9.0)	11 (9.4)	4 (10.8)	15 (9.7)

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Demographic variable	AFQ056 150 mg N=39	AFQ056 200 mg N=78	Total AFQ056 N=117	Placebo N=37	Total N=154
Unknown	3 (7.7)	4 (5.1)	7 (6.0)	4 (10.8)	11 (7.1)
Other	22 (56.4)	57 (73.1)	79 (67.5)	23 (62.2)	102 (66.2)
Baseline weight (kg)					
n	39	77	116	37	153
Mean (SD)	70.5 (13.13)	69.2 (14.78)	69.7 (14.20)	76.4 (18.01)	71.3 (15.42)
Median	68.0	65.3	66.8	73.0	68.5
Range	49.0 to 103.5	44.0 to 117.0	44.0 to 117.0	49.5 to 134.3	44.0 to 134.3
Baseline height (cm)					
n	38	77	115	36	151
Mean (SD)	168.0 (9.60)	168.6 (9.83)	168.4 (9.71)	169.4 (9.32)	168.7 (9.60)
Median	168.0	168.0	168.0	168.0	168.0
Range	146 to 191	147 to 190	146 to 191	146 to 194	146 to 194
Baseline BMI (kg/m^2)					
n	38	77	115	36	151
Mean (SD)	24.8 (4.01)	24.2 (3.88)	24.4 (3.92)	26.7 (4.73)	24.9 (4.22)
Median	23.6	23.3	23.5	26.1	23.9
Range	19.4 to 36.7	17.6 to 35.4	17.6 to 36.7	18.6 to 39.2	17.6 to 39.2
Current smoker, n (%)					
Never	30 (76.9)	60 (76.9)	90 (76.9)	28 (75.7)	118 (76.6)
Current	2 (5.1)	7 (9.0)	9 (7.7)	4 (10.8)	13 (8.4)
Former	7 (17.9)	11 (14.1)	18 (15.4)	5 (13.5)	23 (14.9)
Amantadine status, n (%)					
Group 1 (not on amantadine)	27 (69.2)	52 (66.7)	79 (67.5)	27 (73.0)	106 (68.8)
Group 2 (on amantadine)	12 (30.8)	26 (33.3)	38 (32.5)	10 (27.0)	48 (31.2)
Region, n (%)					
North America	6 (15.4)	8 (10.3)	14 (12.0)	5 (13.5)	19 (12.3)
Europe	33 (84.6)	70 (89.7)	103 (88.0)	32 (86.5)	135 (87.7)

Group 1: not permitted to take amantadine within 2 weeks prior to baseline 1 visit.
Group 2: patients were on a stable and well tolerated dose of amantadine for at least 4 weeks prior to baseline 1 and maintained the stable dose of amantadine during the remainder of the study.

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Parkinson's disease characteristics by treatment (Randomized Set)

	AFQ056 150 mg N=39	AFQ056 200 mg N=78	Total AFQ056 N=117	Placebo N=37	Total N=154
Age at onset of PD (years) [1]					
n	39	78	117	37	154
Mean (SD)	52.0 (8.59)	51.9 (9.05)	52.0 (8.86)	51.7 (8.90)	51.9 (8.84)
Median	53.0	51.5	53.0	51.0	53.0
Range	37 to 69	26 to 74	26 to 74	38 to 73	26 to 74
Years since onset of PD symptoms [2]					
n	39	78	117	37	154
Mean (SD)	13.41 (5.320)	13.27 (4.853)	13.32 (4.991)	13.49 (5.571)	13.36 (5.118)
Median	12.00	13.00	13.00	13.00	13.00
Range	6.0 to 30.0	4.0 to 25.0	4.0 to 30.0	4.0 to 23.0	4.0 to 30.0
Years since PD diagnosis [2]					
n	39	78	117	37	154
Mean (SD)	12.21 (4.996)	12.47 (4.796)	12.38 (4.844)	12.51 (5.621)	12.42 (5.022)
Median	12.00	12.00	12.00	12.00	12.00
Range	5.0 to 29.0	3.0 to 25.0	3.0 to 29.0	2.0 to 22.0	2.0 to 29.0
Years since onset of on-time dyskinesia [2]					
n	39	78	117	37	154
Mean (SD)	5.36 (5.645)	4.42 (3.325)	4.74 (4.239)	4.78 (3.351)	4.75 (4.033)
Median	3.00	4.00	4.00	4.00	4.00
Range	1.0 to 23.0	0.0 to 13.0	0.0 to 23.0	0.0 to 14.0	0.0 to 23.0
History of amantadine induced hallucinations, n (%)					
Yes	0	1 (1.3)	1 (0.9)	0	1 (0.6)
No	37 (94.9)	74 (94.9)	111 (94.9)	37 (100.0)	148 (96.1)
Unknown	2 (5.1)	3 (3.8)	5 (4.3)	0	5 (3.2)
Years since onset of amantadine induced hallucinations [2]					
n	0	1	1	0	1
Mean (SD)		3.00 (-)	3.00 (-)		3.00 (-)
Median		3.00	3.00		3.00
Amantadine induced hallucinations ongoing, n (%)					
Yes	0	1 (1.3)	1 (0.9)	0	1 (0.6)
N/A	39 (100.0)	77 (98.7)	116 (99.1)	37 (100.0)	153 (99.4)
Range		3.0 to 3.0	3.0 to 3.0		3.0 to 3.0
Years since first initiation of L-dopa [2]					
n	39	78	117	37	154
Mean (SD)	9.82 (5.808)	10.45 (5.231)	10.24 (5.413)	11.03 (6.002)	10.43 (5.551)
Median	9.00	10.00	9.00	11.00	10.00
Range	2.0 to 29.0	1.0 to 24.0	1.0 to 29.0	2.0 to 22.0	1.0 to 29.0

[1] Age at onset of PD = (Date of PD diagnosis - birth date +1)/365.25 rounded down to the nearest integer.
[2] Time since event in years is defined as (the screening assessment date - event date + 1)/365.25.

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Outcome Measures

Primary Outcome Results

Change from baseline 2 to Week 12 in Modified AIMS total score by group and treatment (MMRM) (Full Analysis Set)

					AFQ056 vs. Placebo Difference in LS Mean Change		
Treatment	**n**	**Baseline Mean (SE)**	**Week 12 Mean (SE)**	**Change LS Mean (SE)**	**Mean (SE)**	**95% CI**	**p-value**
Group 1 (not on amantadine)							
AFQ056 150 mg (N=27)	24	12.7 (0.89)	9.1 (0.81)	-2.9 (0.96)	-1.1 (1.31)	(-3.71, 1.49)	0.3990
AFQ056 200 mg (N=52)	42	12.4 (0.81)	9.7 (0.92)	-2.0 (0.74)	-0.2 (1.15)	(-2.50, 2.08)	0.8537
Placebo (N=27)	26	10.8 (1.09)	8.8 (1.02)	-1.7 (0.94)			
Group 2 (on amantadine)							
AFQ056 150 mg (N=12)	11	8.6 (1.66)	7.2 (1.74)	-3.8 (1.50)	-1.8 (1.95)	(-5.74, 2.17)	0.3655
AFQ056 200 mg (N=25)	19	11.1 (1.29)	9.1 (1.14)	-2.1 (1.08)	-0.1 (1.71)	(-3.59, 3.36)	0.9467
Placebo (N=10)	10	12.0 (1.80)	9.8 (1.94)	-2.0 (1.58)			
Total (Group 1 + Group 2)							
AFQ056 150 mg (N=39)	35	11.4 (0.85)	8.5 (0.78)	-2.8 (0.85)	-1.3 (1.16)	(-3.58, 1.01)	0.2707
AFQ056 200 mg (N=77)	61	12.0 (0.69)	9.5 (0.72)	-1.7 (0.65)	-0.2 (1.03)	(-2.21, 1.85)	0.8640
Placebo (N=37)	36	11.1 (0.92)	9.1 (0.90)	-1.5 (0.88)			

N is the number of patients in the subgroup;
- n is the number of patients with a value at baseline and week 12 or discontinued after week 6 and had ED visit.
- Baseline is the last pre-randomization value.
- Least square means, confidence intervals and p-values are derived from MMRM model with treatment, country, baseline mAIMS total score, week, and treatment*week interaction for the subgroup analysis, additional terms of group (amantadine status) and treatment*group interaction added as explanatory variables for the overall analysis.

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Secondary Outcome Results

UDysRS and LFADLDS change from baseline 2 to Week 12 in total score by group and treatment (MMRM) (Full Analysis Set)

	AFQ056 150 mg vs. Placebo Difference in LS Mean Change			AFQ056 200 mg vs. Placebo Difference in LS Mean Change		
Total Score	**Mean (SE)**	**95% CI**	**p-value**	**Mean (SE)**	**95% CI**	**p-value**
Group 1 (not on amantadine)						
UDysRS	-0.2 (4.13)	(-8.46, 8.03)	0.9589	1.9 (3.63)	(-5.34, 9.17)	0.5997
LFADLDS Patient	-0.6 (1.17)	(-2.97, 1.70)	0.5908	-0.7 (1.03)	(-2.80, 1.31)	0.4729
LFADLDS Caregiver	0.3 (1.27)	(-2.18, 2.87)	0.7877	-0.1 (1.12)	(-2.29, 2.18)	0.9596
Group 2 (on amantadine)						
UDysRS	-3.3 (5.27)	(-14.03, 7.49)	0.5397	2.1 (4.78)	(-7.66, 11.87)	0.6626
LFADLDS Patient	-0.9 (1.66)	(-4.32, 2.46)	0.5808	0.2 (1.48)	(-2.77, 3.26)	0.8693
LFADLDS Caregiver	0.0 (1.43)	(-2.89, 2.93)	0.9869	1.8 (1.30)	(-0.89, 4.43)	0.1834
Total (Group 1 + Group 2)						
UDysRS	-0.9 (3.33)	(-7.51, 5.70)	0.7870	2.0 (3.01)	(-3.94, 7.99)	0.5021
LFADLDS Patient	-0.7 (1.02)	(-2.73, 1.30)	0.4839	-0.2 (0.90)	(-2.00, 1.56)	0.8068
LFADLDS Caregiver	0.1 (1.03)	(-1.98, 2.11)	0.9531	0.8 (0.93)	(-1.04, 2.63)	0.3937

Only includes patients with a value at baseline and week 12 or discontinued after week 8 and had ED visit. UDysRS was administered only where local language translations were available.
- Baseline is the last pre-randomization value.
- Least square means, confidence intervals and p-values are derived from MMRM model with treatment, country, corresponding baseline total score, week, and treatment*week interaction for the subgroup analysis, additional terms of group (amantadine status) and treatment*group interaction added as explanatory variables for the overall analysis.

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CGIC-disability at Week 12 by group and treatment (GLMM) (Full Analysis Set)

Score	AFQ056 150 mg N=27 Total n (%)	AFQ056 200 mg N=52 Total n (%)	Placebo N=27 Total n (%)
Group 1 (not on amantadine)			
1 Markedly improved	20 5 (25.0)	36 3 (8.3)	25 4 (16.0)
2 Moderately improved	20 4 (20.0)	36 7 (19.4)	25 8 (32.0)
3 Minimally improved	20 3 (15.0)	36 13 (36.1)	25 5 (20.0)
4 Unchanged	20 5 (25.0)	36 10 (27.8)	25 5 (20.0)
5 Minimally worse	20 2 (10.0)	36 2 (5.6)	25 3 (12.0)
6 Moderately worse	20 1 (5.0)	36 1 (2.8)	25 0
7 Markedly worse	20 0	36 0	25 0
Odds Ratio	0.51	0.41	
95% CI	(0.10, 2.51)	(0.11, 1.57)	
p-value	0.4064	0.1895	
Group 2 (on amantadine)			
1 Markedly improved	11 3 (27.3)	16 2 (12.5)	9 1 (11.1)
2 Moderately improved	11 3 (27.3)	16 7 (43.8)	9 2 (22.2)
3 Minimally improved	11 2 (18.2)	16 2 (12.5)	9 2 (22.2)
4 Unchanged	11 3 (27.3)	16 4 (25.0)	9 3 (33.3)
5 Minimally worse	11 0	16 1 (6.3)	9 0
6 Moderately worse	11 0	16 0	9 1 (11.1)
7 Markedly worse	11 0	16 0	9 0
Odds Ratio	6.07	2.43	
95% CI	(0.45, 80.97)	(0.23, 25.36)	
p-value	0.1695	0.4514	
Total (Group 1+ Group 2)			
1 Markedly improved	31 8 (25.8)	52 5 (9.6)	34 5 (14.7)
2 Moderately improved	31 7 (22.6)	52 14 (26.9)	34 10 (29.4)
3 Minimally improved	31 5 (16.1)	52 15 (28.8)	34 7 (20.6)
4 Unchanged	31 8 (25.8)	52 14 (26.9)	34 8 (23.5)
5 Minimally worse	31 2 (6.5)	52 3 (5.8)	34 3 (8.8)
6 Moderately worse	31 1 (3.2)	52 1 (1.9)	34 1 (2.9)
7 Markedly worse	31 0	52 0	34 0
Odds Ratio	1.27	0.71	
95% CI	(0.33, 4.90)	(0.22, 2.30)	
p-value	0.7261	0.5626	

GLMM – Generalized Linear Mixed Model
N is the number of FAS patients; Total is the number of patients with a value at Week 12 or discontinued after week 8 and had ED visit.
-- P-value is from the generalized linear mixed model with treatment, country, week, and treatment*week interaction as explanatory variables with cumlogit as link function.

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Change from baseline 2 to Week 12 in patient diary hours by treatment for groups 1 and 2 combined (Full Analysis Set)

					AFQ056 vs. Placebo Difference in LS Mean Change		
Treatment	**n**	**Baseline Mean (SE)**	**Week 12 Mean (SE)**	**Change LS Mean (SE)**	**Mean (SE)**	**90% CI**	**p-value**
Total ON time (hours)							
AFQ056 150 mg (N=39)	30	12.8 (0.45)	12.9 (0.64)	0.0 (0.46)	0.7 (0.63)	(-0.51, 1.99)	0.2442
AFQ056 200 mg (N=77)	45	13.6 (0.29)	13.3 (0.36)	-0.3 (0.40)	0.4 (0.58)	(-0.71, 1.58)	0.4560
Placebo (N=37)	32	13.0 (0.30)	12.0 (0.54)	-0.7 (0.48)			
Total OFF time (hours)							
AFQ056 150 mg (N=39)	30	3.3 (0.34)	3.4 (0.56)	0.1 (0.43)	-0.5 (0.59)	(-1.67, 0.67)	0.3951
AFQ056 200 mg (N=77)	45	2.5 (0.28)	2.8 (0.40)	0.3 (0.37)	-0.3 (0.54)	(-1.34, 0.81)	0.6284
Placebo (N=37)	32	3.4 (0.33)	4.2 (0.56)	0.6 (0.44)			
ON time with dyskinesia (hours)							
AFQ056 150 mg (N=39)	30	8.1 (0.61)	6.2 (0.83)	-1.2 (0.66)	0.5 (0.90)	(-1.25, 2.34)	0.5469
AFQ056 200 mg (N=77)	45	8.4 (0.52)	6.4 (0.57)	-1.5 (0.57)	0.3 (0.83)	(-1.36, 1.91)	0.7397
Placebo (N=37)	32	8.2 (0.68)	6.1 (0.69)	-1.8 (0.69)			
ON time with troublesome dyskinesia (hours)							
AFQ056 150 mg (N=39)	30	3.1 (0.51)	1.8 (0.47)	-1.1 (0.43)	0.2 (0.58)	(-0.98, 1.32	0.7695
AFQ056 200 mg (N=77)	45	3.2 (0.48)	2.1 (0.47)	-1.0 (0.37)	0.3 (0.53)	(-0.73, 1.38)	0.5449
Placebo (N=37)	32	3.1 (0.48)	1.7 (0.39)	-1.3 (0.45)			

SE = Standard error, CI = confidence interval, LS = least square.
- N is the total number of FAS patients; n is the number of patients with a value at both baseline and at each visit or discontinued prior to that visit and had ED visit. Baseline is the last pre-randomization value.
- Least square means, confidence intervals and p-values are derived from MMRM model with treatment, country, corresponding baseline score, week, and treatment*week interaction, group (amantadine status) and treatment*group (amantadine status) interaction as explanatory variables.

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Change from baseline 2 to Week 12 in UPDRS part III total score by treatment for groups 1 and 2 combined (MMRM) (Full Analysis Set)

					AFQ056 vs. Placebo Difference in LS Mean Change		
Treatment	**n**	**Baseline Mean (SE)**	**Week 12 Mean (SE)**	**Change LS Mean (SE)**	**Mean (SE)**	**95% CI**	**p-value**
AFQ056 150 mg (N=39)	31	18.0 (1.84)	17.5 (1.67)	0.6 (1.31)	0.1 (1.79)	(-3.46, 3.62)	0.9649
AFQ056 200 mg (N=77)	52	19.2 (1.33)	17.5 (1.29)	-1.3 (1.03)	-1.9 (1.59)	(-5.05, 1.23)	0.2310
Placebo (N=37)	34	18.6 (1.70)	19.6 (1.72)	0.6 (1.36)			

N is the number of FAS patients;
- n is the number of patients with a value at baseline and week 12 or discontinued after week 8 and had ED visit.
- Baseline is the last pre-randomization value.
- Least square means, confidence intervals and p-values are derived from MMRM model with treatment, country, amantadine group, baseline UPDRS part III total score, week, treatment*week and treatment*amantadine group interaction as explanatory variables.

Change from baseline 2 to Week 12 in items 32, 33 and 34 of the UPDRS part IV by treatment for groups 1 and 2 combined (Full Analysis Set)

					AFQ056 vs. Placebo Difference in LS Mean Change		
Treatment	**n**	**Baseline Mean (SE)**	**Week 12 Mean (SE)**	**Change LS Mean (SE)**	**Mean (SE)**	**90% CI**	**p-value**
UPDRS, item 32 (Duration of dyskinesia)							
AFQ056 150 mg (N=39)	32	2.5 (0.15)	1.9 (0.18)	-0.5 (0.17)	0.0 (0.24)	(-0.50, 0.43)	0.8898
AFQ056 200 mg (N=77)	52	2.4 (0.10)	1.9 (0.13)	-0.5 (0.14)	0.0 (0.21)	(-0.42, 0.41)	0.9845
Placebo (N=37)	34	2.5 (0.12)	1.9 (0.16)	-0.5 (0.18)			
UPDRS, item 33 (Disability due to dyskinesia)							
AFQ056 150 mg (N=39)	32	2.0 (0.13)	1.4 (0.19)	-0.7 (0.15)	0.1 (0.21)	(-0.34, 0.47)	0.7523
AFQ056 200 mg (N=77)	52	2.2 (0.09)	1.5 (0.13)	-0.6 (0.12)	0.1 (0.18)	(-0.22, 0.51)	0.4402
Placebo (N=37)	34	2.2 (0.10)	1.5 (0.16)	-0.7 (0.16)			
UPDRS, item 34 (Painful dyskinesia)							
AFQ056 150 mg (N=39)	32	0.6 (0.16)	0.4 (0.13)	0.0 (0.12)	0.2 (0.16)	(-0.10, 0.53)	0.1817
AFQ056 200 mg (N=77)	52	0.5 (0.12)	0.5 (0.12)	0.0 (0.09)	(0.3 (0.14)	(-0.01, 0.55)	0.0567
Placebo (N=37)	34	0.6 (0.12)	0.3 (0.11)	-0.3 (0.12)			

SE = Standard error, CI = confidence interval, LS = least square.
- N is the total number of FAS patients; n is the number of patients with a value at both baseline and at each visit or discontinued prior to that visit and had ED visit. Baseline is the last pre-randomization value.
- Least square means, confidence intervals and p-values are derived from MMRM model with treatment, country, corresponding baseline score, week, and treatment*week interaction, group (amantadine status) and treatment*group (amantadine status) interaction as explanatory variables.

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Pharmacokinetics: Plasma AFQ056 concentrations (ng/mL) by week and time window for groups 1 and 2 combined (PK Set)

Week	AFQ056 dose	Time window	n	Geometric mean	Coefficient of variation (%)
2	25 mg	1-3 h	93	43.3	69.4
		3-5 h	1		
		5-7 h	1		
	50 mg	1-3 hr	1	57.0	
4	50 mg	1-3 h	98	97.3	57.6
6	50 mg	1-3 h	1	100.0	
	100 mg	1-3 h	93	195.9	61.3
		3-5 h	2	63.3	82.2
		5-7 h	2	43.8	42.2
8	75 mg	1-3 h	1	411.0	
	150 mg	1-3 h	30	313.6	48.2
	200 mg	1-3 h	48	355.3	64.5
12	100 mg	1-3 h	3	354.6	57.3
		3-5 h	3	328.7	39.8
		5-7 h	3	295.3	22.1
	150 mg	1-3 h	34	301.0	72.6
		3-5 h	35	328.0	54.8
		5-7 h	31	300.7	61.6
	200 mg	1-3 h	37	352.6	59.9
		3-5 h	36	427.3	57.8
		5-7 h	37	330.4	65.0

- All concentrations below the lower limit of quantification (LLOQ) were treated as zero.
- Time window is after the morning study medication (i.e. AFQ056/placebo) dose.

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Safety Results

The tables in this Safety Results section support secondary objectives 6, 7-10 and 12.

Number (%) of patients with treatment-emergent AEs during double-blind treatment period by primary system organ class (Safety Set)

Primary system organ class	AFQ056 150mg N = 39 n (%)	AFQ056 200mg N = 78 n (%)	Total AFQ056 N = 117 n (%)	Placebo N = 37 n (%)
Number of patients with at least one AE	24 (61.5)	56 (71.8)	80 (68.4)	20 (54.1)
Psychiatric disorders	9 (23.1)	31 (39.7)	40 (34.2)	6 (16.2)
Nervous system disorders	12 (30.8)	24 (30.8)	36 (30.8)	9 (24.3)
Infections and infestations	3 (7.7)	10 (12.8)	13 (11.1)	7 (18.9)
Injury, poisoning and procedural complications	3 (7.7)	8 (10.3)	11 (9.4)	2 (5.4)
Musculoskeletal and connective tissue disorders	4 (10.3)	7 (9.0)	11 (9.4)	5 (13.5)
Gastrointestinal disorders	1 (2.6)	9 (11.5)	10 (8.5)	2 (5.4)
General disorders and administration site conditions	2 (5.1)	7 (9.0)	9 (7.7)	4 (10.8)
Eye disorders	3 (7.7)	4 (5.1)	7 (6.0)	1 (2.7)
Respiratory, thoracic and mediastinal disorders	2 (5.1)	4 (5.1)	6 (5.1)	0
Skin and subcutaneous tissue disorders	2 (5.1)	4 (5.1)	6 (5.1)	1 (2.7)
Vascular disorders	3 (7.7)	3 (3.8)	6 (5.1)	0
Cardiac disorders	1 (2.6)	4 (5.1)	5 (4.3)	1 (2.7)
Investigations	3 (7.7)	2 (2.6)	5 (4.3)	2 (5.4)
Ear and labyrinth disorders	0	3 (3.8)	3 (2.6)	0
Renal and urinary disorders	0	2 (2.6)	2 (1.7)	1 (2.7)
Reproductive system and breast disorders	0	1 (1.3)	1 (0.9)	0
Social circumstances	0	1 (1.3)	1 (0.9)	0
Metabolism and nutrition disorders	1 (2.6)	0	1 (0.9)	0

Primary system organ classes are presented in a descending order for the total AFQ treatment group.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- A patient with multiple adverse events within a primary system organ class is counted only once.
- MedDRA Version 16.0 has been used for the reporting of adverse events.

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Most frequently reported (preferred term > 5% in any treatment group) treatment-emergent AEs during double-blind treatment period by preferred term (Safety Set)

Preferred term	AFQ056 150 mg N=39 n (%)	AFQ056 200 mg N=78 n (%)	Total AFQ056 N=117 n (%)	Placebo N=37 n (%)
Number of patients with at least one AE	24 (61.5)	56 (71.8)	80 (68.4)	20 (54.1)
Hallucination, visual	3 (7.7)	11 (14.1)	14 (12.0)	0
Dyskinesia	4(10.3)	5 (6.4)	9 (7.7)	2 (5.4)
Akinesia	2 (5.1)	6 (7.7)	8 (6.8)	5 (13.5)
Abnormal dreams	2 (5.1)	4 (5.1)	6 (5.1)	1 (2.7)
Confusional state	2 (5.1)	4 (5.1)	6 (5.1)	1 (2.7)
Insomnia	4 (10.3)	2 (2.6)	6 (5.1)	2 (5.4)
Fall	0	5 (6.4)	5 (4.3)	1 (2.7)
Fatigue	1 (2.6)	4 (5.1)	5 (4.3)	0
Nasopharyngitis	1 (2.6)	4 (5.1)	5 (4.3)	3 (8.1)
Depression	0	4 (5.1)	4 (3.4)	1 (2.7)
Dizziness	0	4 (5.1)	4 (3.4)	1 (2.7)
Dyspnoea	2 (5.1)	2 (2.6)	4 (3.4)	0
Illusion	0	4 (5.1)	4 (3.4)	1 (2.7)
Parkinson's disease	2 (5.1)	2 (2.6)	4 (3.4)	1 (2.7)
Vision blurred	2 (5.1)	2 (2.6)	4 (3.4)	0
Influenza	0	3 (3.8)	3 (2.6)	2 (5.4)
Back pain	1 (2.6)	1 (1.3)	2 (1.7)	2 (5.4)
Blood creatinine increased	2 (5.1)	0	2 (1.7)	0
Disturbance in attention	2 (5.1)	0	2 (1.7)	1 (2.7)
Headache	2 (5.1)	0	2 (1.7)	1 (2.7)
Muscle spasms	0	2 (2.6)	2 (1.7)	2 (5.4)

- Preferred terms are sorted in descending frequency by total AFQ056 column.
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- MedDRA Version 16.0 has been used for the reporting of adverse events.

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Overall summary of treatment-emergent AEs during double-blind treatment period - n (%) of patients (Safety Set)

	AFQ056 150 mg N = 39 n (%)	AFQ056 200 mg N = 78 n (%)	Total AFQ056 N = 117 n (%)	Placebo N = 37 n (%)
Patients with at least one TEAE	24 (61.5)	56 (71.8)	80 (68.4)	20 (54.1)
Patients with at least one SAE	4 (10.3)	8 (10.3)	12 (10.3)	1 (2.7)
Patients who died	0	0	0	0
Patients who discontinued from study due to AEs	6 (15.4)	24 (30.8)	30 (25.6)	1 (2.7)
Discontinued from study due to SAEs	0	1 (1.3)	1 (0.9)	0
Discontinued from study due to non-serious AEs	6 (15.4)	23 (29.5)	29 (24.8)	1 (2.7)

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.
- MedDRA Version 16.0 has been used for the reporting of adverse events.

Tolerability profile by treatment for Group 1 vs Group 2 (Safety Set)

Variable	AFQ056150 mg n (%)		AFQ056 200 mg n (%)		Placebo n (%)	
	Group 1 (N=27)	Group 2 (N=27)	Group 1 (N=52)	Group 2 (N=26)	Group 1 (N=27)	Group 2 (N=10)
Number of patients with AEs in psychosis and psychotic disorder SMQ	3 (11.1)	1 (8.3)	7 (13.5)	7 (26.9)	0	1 (10)
Number of patients with dizziness AE	0	0	3 (5.8)	1 (3.8)	1 (3.7)	0
Number of patients discontinued due to AE	5 (18.5)	1 (8.3)	15 (28.8)	9 (34.6)	0	1(10)
Number of patients who maintained the target dose during the fixed dose period	18 (66.7)	10 (83.3)	25 (48.1)	13 (50)	23 (85.2)	9 (90)

Date of Clinical Trial Report

CSR published: 28-Mar-2014

Date Inclusion on Novartis Clinical Trial Results Database

3 April, 2014

Date of Latest Update


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