Sponsor

Novartis Pharma

Generic Drug Name

AFQ056

Therapeutic Area of Trial

L-dopa induced dyskinesia

Approved Indication

Investigational

Protocol Number

CAFQ056A2123

Title

A single-dose, open-label, parallel study to assess the pharmacokinetics of AFQ056 in subjects with mild, moderate and severe hepatic impairment compared with healthy control subjects

Study Phase

Phase I

Study Start/End Dates

Study Start: 16-May-2011

End Date: 31-Jul-2012

Study Design/Methodology

This study employed a single-dose (15mg of AFQ056), multi- center, open label, parallel-group design in subjects with mild, moderate and severe hepatic impairment along with demographically matched healthy control subjects with normal hepatic function. The subjects were matched by, sex, age (±8 years) and weight (±15%). The exposure of subjects with hepatic impairment was done sequentially. In part 1 of the study, subjects with mild and moderate hepatic impairment (groups 1 and 2) received the study medication. Healthy subjects (group 4) were matched pair-wise and hence enrolled as soon as the corresponding hepatic impaired subject (from group 1 and 2) has received the study medication. Severe hepatic impaired subjects (group 3) were not enrolled before part 1 of the study had ended and a safety and tolerability review had been performed.

Centers

3 centers in 3 countries: Hungary (1), USA (1), Germany (1)

Publication

Not Applicable

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

The investigational drug, AFQ056 15 mg (in three 5 mg capsules) was administered as a single dose

Statistical Methods

All subjects that received at least one dose of study drug were included in the safety data analysis “safety population”.

All subjects with evaluable pharmacokinetic (PK) parameter data and no major protocol deviations with impact on PK data were included in PK analysis set.

The primary objective of this study was to assess (and compare) the pharmacokinetics of AFQ056 in subjects with mild, moderate and severe hepatic impairment with that in matched healthy control subjects. AUCinf, AUC0-24h and Cmax were considered as the primary PK parameters for analysis.

Secondary PK parameters: Tmax, T1/2, CL/F and Vz/F.

Summary statistics of plasma protein binding results were provided for all subjects.

Descriptive statistics of pharmacokinetic parameters included mean, SD, CV, minimum and maximum.

The following pharmacokinetic parameters were determined using non-compartmental method(s): Cmax, Tmax, AUClast, AUCinf, CL/F, T1/2 and Vz/F.

PK parameters AUClast, AUCinf, and Cmax of AFQ056A were compared between each hepatically impaired group (mild, moderate and severe) vs. the matched control group. Log-transformed PK parameters were analyzed separately using a Linear mixed model with group as fixed effect and matched pair as random effect. Least square means for each group as well as contrasts between control and each hepatically impaired group with corresponding 90% confidence intervals on the log-scale were calculated. Back-transformed ratios and 90% confidence interval was also provided.

The evaluation of the terminal plasma elimination phase for determination of the terminal slope (lambda z) was performed by the best fit method. Regression analysis of the terminal plasma elimination phase for the determination of T1/2 included at least 3 data points after Cmax. If the adjusted R^2 value of the regression analysis of the terminal phase was less than 0.75, no values were reported for T1/2, AUCinf, Vz/F and CL/F. The PK parameter AUCinf was not estimated when the AUCinf% extrapolated was >20% for subjects.

Descriptive statistics was provided for PK parameters.

Vital signs:

All vital signs data were listed by subject group, subject, and visit/time and if ranges were available abnormalities (and relevant orthostatic changes) were flagged. Summary statistics were provided by subject group and visit/time.

ECG evaluations:

All ECG data was listed by subject group, subject and visit/time, abnormalities were flagged. Summary statistics was provided by subject and visit/time.

Standard clinical laboratory evaluations:

All laboratory data were listed by subject group, subject, and visit/time and abnormalities were flagged. Summary statistics were provided by subject and visit/time.

Special clinical laboratory evaluations:

All laboratory data were listed by subject group, subject, and visit/time and if ranges were available abnormalities were flagged. Summary statistics were provided by subject and visit/time.

Adverse events:

All information obtained on adverse events was displayed by subject group and subject.

The number and percentage of subjects with adverse events were tabulated by body system and preferred term with a breakdown by subject group. An adverse event starting in one period and continuing into the next period was counted only in the onset period. A subject with multiple adverse events within a body system was only counted once towards the total of this body system.

24h- Holters:

Cardiac monitoring was done by means of 24h-holter ECGs. These ECG data was summarized by subject group and time point by means of descriptive statistics. The mean change from time-match baseline was similarly summarized.

Concomitant medications / Significant non-drug therapies :

All concomitant therapies were listed by subject group and subject.

Other safety evaluations

All information obtained C-SSRS were displayed by subject group and subject.

Study Population: Inclusion/Exclusion Criteria and Demographics

Subjects eligible for inclusion in this study had to fulfill all of the following criteria:

Groups 1, 2, 3 and 4 (all subjects)

Written informed consent had to be obtained before any assessment could be performed. Male and female Caucasian subjects 18 to 65 years of age (inclusive), subjects had to weigh at least 50 kg to participate in the study, and a body mass index (BMI) within the range of 18 - 35 kg/m2, female subjects had to be of non-child bearing potential, all female subjects had a negative pregnancy test at screening and at each baseline visit (regardless of reported reproductive status) and had the ability to communicate well with the investigator, to understand and comply with the requirements of the study.

Group 1, 2 and 3 (subjects with hepatic impairment)

Subjects had to satisfy (1) the criteria for hepatic impairment as evidenced by a Child-Pugh score of A, B or C at screening, (2) at screening and baseline, vital signs (systolic and diastolic blood pressure and pulse rate) were assessed in the sitting position after the subject had rested for at least three minutes and again when required after three minutes in the standing position. Sitting vital signs had to be within the following normal ranges: oral body temperature between 35.0-37.5°C; systolic blood pressure, 90-160 mm Hg; diastolic blood pressure, 50-100 mm Hg; pulse rate, 40 - 100 bpm. When blood pressure and pulse were

taken after at least 3 minutes standing, there should be no more than a 20 mmHg drop in systolic or 10 mmHg drop in diastolic blood pressure and increase in heart rate (>20 bpm) (compared to the sitting results) associated with clinical manifestation of postural hypotension. Any subject who exhibited clinical manifestations of postural hypotension had to be excluded.

Group 4 (healthy subjects)

(1) Each healthy subject had to match in age (±8 years), gender, weight (±15%) to an individual subject with hepatic impairment in group 1, 2 or 3, (2) subject had to be in good health as determined by past medical history, physical examination, vital signs, electrocardiogram, and laboratory tests at screening, (3) at screening, and baseline, vital signs (systolic and diastolic blood pressure and pulse rate) were assessed in the sitting position after the subject had rested for at least three (3) minutes and again when required after three (3) minutes in the standing position. Sitting vital signs had to be within the following normal ranges: oral body temperature between 35.0-37.5 °C; systolic blood pressure, 90-140 mm Hg; diastolic blood pressure, 50-90 mm Hg; pulse rate, 40 - 90 bpm. When blood pressure and pulse were taken after at least 3 minutes standing, there should be no more than a 20 mm Hg drop in systolic or 10 mm Hg drop in diastolic blood pressure and increase in heart rate (>20 bpm) (compared to the sitting results) associated with clinical manifestation of postural hypotension. Any subject who exhibited clinical manifestations of postural hypotension had to be excluded.

Participant Flow

	Mild		Moderate		Severe		
	Hepatic impaired patients N=10	Matched healthy subjects N=10	Hepatic impaired patients N=10	Matched healthy subjects N=10	Hepatic impaired patients N=10	Matched healthy subjects N=10	All healthy subjects N=30
Subjects							
Completed	10 (100%)	10 (100%)	9 (90%)	10 (100%)	10 (100%)	10 (100%)	30 (100%)
Discontinued	0	0	1 (10%)	0	0	0	0
Main cause of discontinuation							
Adverse Event(s)			1 (10%)				0

Baseline Characteristics

		Mild		Moderate		Severe		
		Hepatic impaired patients N=10	Matched healthy subjects N=10	Hepatic impaired patients N=10	Matched healthy subjects N=10	Hepatic impaired patients N=10	Matched healthy subjects N=10	All healthy subjects N=30
Age (years)	Mean (SD)	54.2 (6.80)	54.6 (5.06)	55.1 (3.81)	53.6 (3.72)	52.9 (8.54)	53.0 (5.14)	53.7 (4.57)
	Median	55.5	55.5	53.5	55.0	55.5	54.5	55.0
	Range	41 - 62	47 - 63	51 - 61	49 - 60	33 - 63	40 - 58	40 - 63
Height (cm)	Mean (SD)	169.6 (6.45)	173.2 (9.38)	168.7 (9.23)	172.4 (6.72)	171.3 (6.12)	174.7 (7.18)	173.4 (7.63)
	Median	170.5	172.5	169.5	172.0	171.0	174.5	173.5
	Range	156 - 177	163 - 184	151 - 180	160 - 184	163 - 184	163 - 186	160 - 186

		Mild		Moderate		Severe		
		Hepatic impaired patients N=10	**Matched healthy subjects N=10**	**Hepatic impaired patients N=10**	**Matched healthy subjects N=10**	**Hepatic impaired patients N=10**	**Matched healthy subjects N=10**	**All healthy subjects N=30**
Weight (kg)	Mean (SD)	77.54 (16.108)	77.30 (12.340)	77.93 (16.823)	82.30 (14.423)	82.20 (15.339)	81.83 (13.448)	80.48 (13.160)
	Median	73.45	78.05	74.00	77.50	83.50	78.00	78.00
	Range	54.3 - 101.0	59.1 - 95.0	58.0 - 113.0	61.0 - 109.0	52.0 - 103.8	60.0 - 103.5	59.1 - 109.0
BMI (kg/m^2)	Mean (SD)	26.72 (3.835)	25.71 (3.023)	27.32 (4.894)	27.55 (3.307)	27.89 (4.167)	26.67 (2.839)	26.64 (3.052)
	Median	25.29	25.92	26.23	27.42	28.54	26.33	26.62
	Range	22.3 - 33.4	21.1 - 30.7	21.6 - 34.9	21.6 - 32.2	19.6 - 34.2	22.6 - 31.9	21.1 - 32.2
Sex - n(%)	Male	6 (60 %)	6 (60 %)	7 (70 %)	7 (70 %)	8 (80 %)	8 (80 %)	21 (70 %)
	Female	4 (40 %)	4 (40 %)	3 (30 %)	3 (30 %)	2 (20 %)	2 (20 %)	9 (30 %)
Race - n(%)	Caucasian	10 (100 %)	10 (100 %)	10 (100 %)	10 (100 %)	10 (100 %)	10 (100 %)	30 (100 %)
Ethnicity - n(%)	Hispanic/Latino					1 (10 %)		
	Other	10 (100 %)	10 (100 %)	10 (100 %)	10 (100 %)	9 (90 %)	10 (100 %)	30 (100 %)

Outcome Measures

Primary Outcome Result(s)

Summary statistics for total AFQ056 plasma PK parameters of primary interest

Subject group $	Statistic	Cmax (ng/mL)	AUC0-24h (hr*ng/mL)	AUCinf (hr*ng/mL)
Mild HI	N	10	10	10
	Mean ± SD (CV%)	59.2 ± 21.4 (36.2)	345 ± 161 (46.6)	445 ± 207 (46.5)
Matched healthy to mild HI	N	10	10	9
	Mean ± SD (CV%)	49.0 ± 24.5 (50.1)	257 ± 132 (51.2)	288 ± 160 (55.6)
Moderate HI	N	10	10	10
	Mean ± SD (CV%)	69.1 ± 21.7 (31.3)	493 ± 206 (41.9)	661 ± 296 (44.8)
Matched healthy to moderate HI	N	10	10	10
	Mean ± SD (CV%)	71.6 ± 44.9 (62.7)	418 ± 274 (65.5)	539 ± 412 (76.5)
Severe HI	N	10	10	10
	Mean ± SD (CV%)	50.2 ± 18.8 (37.5)	482 ± 183 (37.9)	775 ± 242 (31.2)
Matched healthy to severe HI	N	10	10	10
	Mean ± SD (CV%)	33.4 ± 13.2 (39.5)	206 ± 78.6 (38.2)	243 ± 98.5 (40.5)

$ HI- Hepatic Impaired patients.

Statistical assessment (Geometric mean ratio and 90% confidence intervals) of total AFQ056 PK parameters for subjects with hepatic impairment vs. matched healthy subjects

Parameter (unit)	Subject group $	N	Geometric mean*	Ratio of geometric means*	90% CI for ratio*
Cmax (ng/mL)	Mild HI	10	55.8	1.28	(0.85,1.92)
	Matched healthy to mild HI	10	43.7		
	Moderate HI	10	65.5	1.22	(0.81,1.83)
	Matched healthy to moderate HI	10	53.7		
	Severe HI	10	47.2	1.56	(1.04,2.34)
	Matched healthy to severe HI	10	30.3		
AUC0-24h (hr*ng/mL)	Mild HI	10	310	1.35	(0.87,2.09)
	Matched healthy to mild HI	10	229		
	Moderate HI	10	451	1.51	(0.97,2.33)
	Matched healthy to moderate HI	10	300		
	Severe HI	10	458	2.40	(1.55,3.71)
	Matched healthy to severe HI	10	191		
AUCinf (hr*ng/mL)	Mild HI	10	397	1.58	(0.96,2.59)
	Matched healthy to mild HI	9	252		
	Moderate HI	10	588	1.65	(1.02,2.67)
	Matched healthy to moderate HI	10	357		
	Severe HI	10	747	3.32	(2.05,5.38)
	Matched healthy to severe HI	10	225		

$ HI- Hepatic Impaired patients.

***** back transformed from log scale.

Model: The log transformed PK parameter data analyzed using a linear mixed effect model with subject group as fixed effect and subject matched pair as random effect.

Secondary Outcome Result(s)

Summary statistics for total AFQ056 plasma PK parameters of secondary interest

Subject group $	Statistic	Tmax** (hr)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Mild HI	N	10	10	10	10
	Mean (SD)	1.25 (1.00 - 3.00)	14.2 ± 2.52 (17.7)	43.4 ± 25.9 (59.6)	863 ± 447 (51.8)
Matched healthy to mild HI	N	10	9	9	9
	Mean (SD)	1.50 (1.00 - 2.00)	11.0 ± 4.20 (38.0)	68.5 ± 40.0 (58.4)	964 ± 432 (44.8)
Moderate HI	N	10	10	10	10
	Mean (SD)	1.50 (1.00 - 4.00)	14.3 ± 6.33 (44.1)	29.5 ± 18.2 (61.6)	552 ± 278 (50.4)
Matched healthy to moderate HI	N	10	10	10	10
	Mean (SD)	1.25 (1.00 - 3.00)	10.9 ± 5.45 (49.9)	80.4 ± 108 (134.8)	778 ± 674 (86.7)
Severe HI	N	10	10	10	10
	Mean (SD)	2.00 (1.00 - 6.00)	21.0 ± 7.50 (35.7)	20.8 ± 5.29 (25.5)	622 ± 252 (40.5)
Matched healthy to severe HI	N	10	10	10	10
	Mean (SD)	1.75 (1.00 - 4.00)	10.9 ± 2.08 (19.0)	72.7 ± 32.3 (44.5)	1130 ± 512 (45.3)

$ HI- Hepatic Impaired patients.

** Values for Tmax are median (min – max)

Table Error! No text of specified style in document.**-1** **Summary statistics for plasma unbound PK parameters of AFQ056**

Subject group $	Statistic	Cmax_u (ng/mL)	AUC0-24h_u (hr*ng/mL)	AUCinf_u (hr*ng/mL)	CL/F_u (L/hr)	Vz/F_u (L)
Mild HI	n	10	10	10	10	10
	Mean ± SD (CV%)	1.45 ± 0.389 (26.9)	8.47 ± 3.49 (41.2)	11.0 ± 4.68 (42.7)	1690 ± 907 (67.2)	33600 ± 15600 (46.4)
Matched healthy to mild HI	n	10	10	9	9	9
	Mean ± SD (CV%)	0.947 ± 0.510 (53.9)	5.02 ± 2.97 (59.2)	5.71 ± 3.63 (63.6)	3630 ± 2170 (59.9)	50500 ± 22200 (43.9)
Moderate HI	n	10	10	10	10	10
	Mean ± SD (CV%)	2.75 ± 0.977 (35.6)	19.5 ± 8.26 (42.3)	26.5 ± 13.2 (49.7)	779 ± 545 (69.9)	14400 ± 8740 (60.7)
Matched healthy to moderate HI	n	10	10	10	10	10
	Mean ± SD (CV%)	1.60 ± 0.971 (60.6)	8.96 ± 4.72 (52.7)	11.3 ± 7.07 (62.4)	3050 ± 3870 (127)	29900 ± 21100 (70.4)
Severe HI	n	10	10	10	10	10
	Mean ± SD (CV%)	2.54 ± 0.794 (31.2)	24.6 ± 8.05 (32.7)	39.9 ± 11.0 (27.5)	402 ± 107 (26.6)	11900 ± 4440 (37.3)
Matched healthy to severe HI	n	10	10	10	10	10
	Mean ± SD (CV%)	0.928 ± 0.364 (39.2)	5.72 ± 2.18 (38.0)	6.76 ± 2.77 (40.9)	2580 ± 1070 (41.4)	40000 ± 16600 (41.6)

$ HI- Hepatic Impaired patients.

Safety Results

Adverse events overall and frequently affected system organ classes - n (%) of subjects- Safety analysis set

	Mild				Moderate				Severe				All				
	Hepatic impaired patients		Matched healthy subjects		Hepatic impaired patients		Matched healthy subjects		Hepatic impaired patients		Matched healthy subjects		Hepatic impaired subjects		All healthy subjects		Total subjects
	N=10		N=10		N=10		N=10		N=10		N=10		N=30		N=30		N=60
	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with AE(s)	4	(40.0)	1	(10.0)	1	(10.0)	1	(10.0)	3	(30.0)	1	(10.0)	8	(26.7)	3	(10.0)	11	(18.3)
System organ class																		
Gastrointestinal disorders	1	(10.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(10.0)	1	(10.0)	3	(10.0)	1	(3.3)	4	(6.7)
Investigations	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	1	(10.0)	0	(0.0)	1	(3.3)	1	(3.3)	2	(3.3)
Nervous system disorders	3	(30.0)	1	(10.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	4	(13.3)	1	(3.3)	5	(8.3)
Cardiac disorders	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Eye disorders	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
General disorders and administration site conditions	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Infections and infestations	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)

Note: Arranged in descending order of frequency (in total column)

Adverse events overall and most frequent events - n (%) of subjects - Safety analysis set

	Mild				Moderate				Severe				All					
	Hepatic impaired patients		Matched healthy subjects		Hepatic impaired patients		Matched healthy subjects		Hepatic impaired patients		Matched healthy subjects		Hepatic impaired subjects		All healthy subjects		Total subjects	
	N=10		N=10		N=10		N=10		N=10		N=10		N=30		N=30		N=60	
	n	(%)	N	(%)	n	(%)	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with AE(s)	4	(40.0)	1	(10.0)	1	(10.0)	1	(10.0)	3	(30.0)	1	(10.0)	8	(26.7)	3	(10.0)	11	(18.3)
Constipation	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(3.3)	1	(1.7)
Dizziness	2	(20.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	2	(6.7)	1	(3.3)	3	(5.0)
Headache	1	(10.0)	1	(10.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	2	(6.7)	1	(3.3)	3	(5.0)
Hepatic enzyme increased	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	1	(1.7)
Amylase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Ascites	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Atrioventricular block second degree	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Haematemesis	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Lipase increased	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(10.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Nausea	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Oedema peripheral	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Oral herpes	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)
Vision blurred	1	(10.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(3.3)	0	(0.0)	1	(1.7)

Note: Arranged in descending order of frequency (in total column).

Other Relevant Findings

Statistical assessment (Geometric mean ratio and 90% confidence intervals) of free AFQ056 PK parameters for subjects with hepatic impairment vs. matched healthy subjects

Parameter (unit)	Subject group $	N	Geometric mean*	Ratio of geometric means*	90% CI for ratio*
Cmax,u (ng/mL)	Mild HI	10	1.4	1.68	(1.15,2.47)
	Matched healthy to mild HI	10	0.831		
	Moderate HI	10	2.56	2.03	(1.38,2.98)
	Matched healthy to moderate HI	10	1.26		
	Severe HI	10	2.44	2.88	(1.96,4.24)
	Matched healthy to severe HI	10	0.846		
AUClast,u (hr*ng/mL)	Mild HI	10	7.75	1.83	(1.20,2.79)
	Matched healthy to mild HI	9	4.36		
	Moderate HI	10	17.7	2.51	(1.66,3.79)
	Matched healthy to moderate HI	10	7.03		
	Severe HI	10	23.6	4.43	(2.93,6.69)
	Matched healthy to severe HI	10	5.34		
AUCinf,u (hr*ng/mL)	Mild HI	10	9.94	2.05	(1.29,3.26)
	Matched healthy to mild HI	9	4.84		
	Moderate HI	10	23	2.75	(1.75,4.31)
	Matched healthy to moderate HI	10	8.38		
	Severe HI	10	38.6	6.15	(3.92,9.65)
	Matched healthy to severe HI	10	6.28		

***** back transformed from log scale.

Model: The log transformed unbound PK parameter data analyzed using a linear mixed effect model with subject group as fixed factor and subject matched pair as random factor.

Summary of AFQ056 unbound fraction in plasma by hepatic impaired and matched healthy group

Subject group $	Unbound fraction (fu,p) (Unitless)
Mild HI (n=10)	0.0255 ± 0.00463
Matched healthy to mild HI (n=10)	0.0192 ± 0.00268
Moderate HI (n=10)	0.0394 ± 0.00496
Matched healthy to moderate HI (n=10)	0.0242 ± 0.00622
Severe HI (n=10)	0.0519 ± 0.00536
Matched healthy to severe HI (n=10)	0.0281 ± 0.00289

$ HI- Hepatic Impaired patients.

Summary statistics for plasma unbound PK parameters of AFQ056

Subject group $	Statistic	Cmax_u (ng/mL)	AUC0-24h_u (hr*ng/mL)	AUCinf_u (hr*ng/mL)	CL/F_u (L/hr)	Vz/F_u (L)
Mild HI	n	10	10	10	10	10
	Mean ± SD (CV%)	1.45 ± 0.389 (26.9)	8.47 ± 3.49 (41.2)	11.0 ± 4.68 (42.7)	1690 ± 907 (67.2)	33600 ± 15600 (46.4)
Matched healthy to mild HI	n	10	10	9	9	9
	Mean ± SD (CV%)	0.947 ± 0.510 (53.9)	5.02 ± 2.97 (59.2)	5.71 ± 3.63 (63.6)	3630 ± 2170 (59.9)	50500 ± 22200 (43.9)
Moderate HI	n	10	10	10	10	10
	Mean ± SD (CV%)	2.75 ± 0.977 (35.6)	19.5 ± 8.26 (42.3)	26.5 ± 13.2 (49.7)	779 ± 545 (69.9)	14400 ± 8740 (60.7)
Matched healthy to moderate HI	n	10	10	10	10	10
	Mean ± SD (CV%)	1.60 ± 0.971 (60.6)	8.96 ± 4.72 (52.7)	11.3 ± 7.07 (62.4)	3050 ± 3870 (127)	29900 ± 21100 (70.4)
Severe HI	n	10	10	10	10	10
	Mean ± SD (CV%)	2.54 ± 0.794 (31.2)	24.6 ± 8.05 (32.7)	39.9 ± 11.0 (27.5)	402 ± 107 (26.6)	11900 ± 4440 (37.3)
Matched healthy to severe HI	n	10	10	10	10	10
	Mean ± SD (CV%)	0.928 ± 0.364 (39.2)	5.72 ± 2.18 (38.0)	6.76 ± 2.77 (40.9)	2580 ± 1070 (41.4)	40000 ± 16600 (41.6)

$ HI- Hepatic Impaired patients

Date of Clinical Trial Report

30 Jan 2013

Date Inclusion on Novartis Clinical Trial Results Database

25-July 2013

Date of Latest Update