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| **Sponsor**<br>Novartis |
| **Generic Drug Name**<br>AFQ056 |
| **Therapeutic Area of Trial**<br>Renal impairment study |
| **Approved Indication**<br>Investigational |
| **Protocol Number**<br>CAFQ056A2124 |
| **Title**<br>An open-label, parallel-group study to determine the pharmacokinetics of a single 50 mg dose of AFQ056 in subjects with mild, moderate or severe renal impairment compared to age, sex, and body weight-matched healthy subjects |
| **Phase of Development**<br>I |
| **Study Start/End Dates**<br>21-Jan-2011 to 05-Aug-2011 |
| **Study Design/Methodology**<br>This was single-dose, open-label, parallel-group study in subjects with mild, moderate, severe renal impairment and healthy volunteers. The study consisted of a 21-day screening period, a baseline period, one treatment period followed by an end of study evaluation.<br>On Day 1 all subjects received a single oral dose of 50 mg AFQ056. |
| **Centres**<br>Germany (one center) |

**Publication**

None

**Outcome measures**

Primary outcome measures(s)

Primary PK variables:

- Area under the plasma concentration-time curve from time zero to infinity (AUCinf)
- Area under the curve from time zero to the last measurable concentration sampling time (Tlast) [mass x time x volume-1] (AUClast) of AFQ056
- Maximum observed plasma concentration (Cmax) of AFQ056
- Secondary PK variables:Time to Reach Maximum Observed Plasma Concentration (Tmax) of AFQ056
- Terminal elimination half-life (T1/2) of AFQ056
- The apparent systemic (or total body) clearance from plasma following extravascular administration [volume / time] (CL/F) of AFQ056
- The apparent volume of distribution during the terminal elimination phase following oral administration [volume] (Vz/F) of AFQ056
- Amount of drug excreted into the urine from time zero to time't' where t is a defined time point after administration [mass units or % of dose] (Ae0-t) of AFQ056
- The renal clearance from plasma [volume / time] (CLr) of AFQ056

Secondary outcome measures(s)

- Safety and tolerability of 50 mg AFQ056 in subjects with mild, moderate and severe renal impairment; based on results of:
- Physical examination, vital signs, body measurements, ECG, pulse oximetry, hematology, blood chemistry, urinalysis, adverse events, serious adverse events

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

The investigational drug was AFQ056, 50 mg (as two 25 mg capsules), immediate release size ‘0’ capsule for oral administration.

**Statistical Methods**

Primary PK parameters include AUClast, AUCinf, Cmax and secondary PK parameters include Tmax; T1/2 and CL/F and Vz/F and Ae0-t were determined. Pharmacokinetic parameters (AUClast, AUCinf and Cmax) were compared between each renally impaired group (mild, moderate and severe respectively) vs. matched control group, using an analysis of variance model for the (natural) logtransformed PK values, with subject match as random effect. Descriptive statistics of PK parameters included mean, standard deviation (SD), coefficient of variation (CV), minimum and maximum. When a geometric mean was presented it was stated as such. Since Tmax was generally evaluated by a nonparametric method, median values and ranges were

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

**Study Population: Inclusion/Exclusion Criteria and Demographics**

**Key inclusion criteria:**

This study was conducted in male and female subjects aged from 18 to 75 years with different stages of renal impairment as well as age, sex, and body weight matching healthy subjects. Significant inclusion criteria for all subjects included: Body weight: ≥50kg; body mass index (BMI): 18-34 kg/$m^2$ (inclusive) at Screening.

**For subjects with renal impairment**

- No current clinically significant disease (other than renal impairment), except for stable underlying disease that caused renal impairment, as determined by clinical history and physical examination.
- Modified Diet in Renal Disease (MDRD)-calculated eGFR of <90 mL/min/1.73 $m^2$ based on serum creatinine.
- Vital signs (after 3 minutes resting measured in the supine position) were required to be within normal ranges as deemed by the Investigator. The Investigator confirmed the vital signs were within the following ranges: Oral body temperature between 35.0-37.5 °C; Systolic blood pressure (SBP), 90-180 mm Hg; Diastolic blood pressure (DBP), 50-110 mm Hg; Pulse rate, 40-100 bpm.
  Blood pressure was measured again in a standing position. After 3 minutes standing, there should not be more than a 20 mm Hg drop in SBP or 10 mm Hg drop in DBP associated with symptomatic postural hypotension.

**For healthy subjects only**

- No current clinically significant disease as determined by clinical history and physical examination.
- MDRD-calculated eGFR of ≥90 mL/min/1.73 $m^2$ based on serum creatinine.
- Vital signs (after 3 minutes resting measured in the supine position) were required to be within normal ranges as deemed by the Investigator. The Investigator confirmed the vital signs were within the following ranges: Oral body temperature between 35.0-37.5 °C; SBP, 90-140 mm Hg; DBP, 50-90 mm Hg; Pulse rate, 40-90 bpm Blood pressure was measured again in a standing position. After 3 minutes standing, there should not be more than a 20 mm Hg drop in SBP or 10 mm Hg drop in DBP associated with symptomatic postural hypotension.

**Key exclusion criteria:**

- Usage of any prescribed drugs within three weeks or five half lives (whichever is longer) prior to dosing with AFQ056 until study completion. This did not include drugs that were used as (symptomatic) treatment of renal impairment (e.g. antihypertensive and antidiabetic drugs) provided such drugs were: used at

the same dose within three weeks or five half lives (whichever is longer) prior to dosing with AFQ056 until study completion and not known as inhibitors or inducers of CYP1A1, 1A2, 2C8, 2C9, 2C19, 3A4, 3A5.

- History or presence of prolonged QTc interval or abnormal ECG
- Undergoing any method of dialysis
- Smoking (use of tobacco products in previous 3 months)

Other protocol-defined inclusion/exclusion criteria may apply.

## Participant Flow

**Patient disposition (safety analysis set)**

| | Mild | | Moderate | | Severe | | |
|---|---|---|---|---|---|---|---|
| | Renal impaired patients N=8 | Matched healthy subjects N=8 | Renal impaired patients N=8 | Matched healthy subjects N=8 | Renal impaired patients N=8 | Matched healthy subjects N=8 | All healthy subjects N=24 |
| Subjects Completed | 8 (100%) | 8 (100%) | 8 (100%) | 8 (100%) | 8 (100%) | 8 (100%) | 24 (100%) |

## Baseline Characteristics

| | | Subjects with mild renal impairment N=8 | Matched healthy subjects N=8 | Subjects with moderate renal impairment N=8 | Matched healthy subjects N=8 | Subjects with severe renal impairment N=8 | Matched healthy subjects N=8 | All healthy subjects N=24 |
|---|---|---|---|---|---|---|---|---|
| Age (years) | Mean (SD) | 65.4 (9.93) | 61.9 (8.18) | 65.3 (8.65) | 63.9 (4.76) | 59.3 (15.91) | 56.9 (14.92) | 60.9 (10.20) |
| | Median | 68.5 | 65.0 | 65.0 | 66.0 | 67.0 | 63.5 | 64.5 |
| | Range | 47 - 75 | 48 - 72 | 49 - 75 | 57 - 69 | 35 - 75 | 33 - 75 | 33 - 75 |
| Height (cm) | Mean (SD) | 172.5 (9.15) | 172.0 (9.40) | 172.6 (5.60) | 170.8 (8.10) | 172.4 (9.69) | 175.6 (13.72) | 172.8 (10.42 |
| | Median | 170.0 | 172.5 | 172.5 | 171.0 | 169.5 | 170.0 | 172.0 |
| | Range | 163 - 191 | 158 - 188 | 163 - 179 | 160 - 183 | 158 - 188 | 162 - 195 | 158 - 195 |
| Weight (kg) | Mean (SD) | 74.26 (11.776) | 72.88 (8.801) | 87.48 (10.826) | 81.66 (7.347) | 82.85 (16.414) | 82.85 (16.614) | 79.13 (12.02 |
| | Median | 72.75 | 71.70 | 86.40 | 79.90 | 78.25 | 79.20 | 75.80 |
| | Range | 63.0 - 101.0 | 63.6 - 88.1 | 69.0 - 105.2 | 74.6 - 94.8 | 64.0 - 119.2 | 65.2 - 117.0 | 63.6 - 117.0 |
| BMI (kg/m$^2$) | Mean (SD) | 24.85 (2.088) | 24.57 (0.988) | 29.38 (3.498) | 28.12 (3.038) | 27.80 (4.037) | 26.95 (4.749) | 26.55 (3.500 |
| | Median | 24.72 | 24.84 | 28.72 | 28.35 | 27.70 | 26.41 | 25.52 |
| | Range | 21.8 - 27.7 | 22.6 - 25.7 | 23.1 - 33.8 | 23.4 - 33.7 | 22.4 - 33.7 | 19.5 - 33.1 | 19.5 - 33.7 |
| Sex - n(%) | Male | 4 (50 %) | 4 (50 %) | 6 (75 %) | 6 (75 %) | 5 (62.5 %) | 5 (62.5 %) | 15 (62.5 %) |
| | Female | 4 (50 %) | 4 (50 %) | 2 (25 %) | 2 (25 %) | 3 (37.5 %) | 3 (37.5 %) | 9 (37.5 %) |
| Race - n(%) | Caucasian | 8 (100 %) | 8 (100 %) | 8 (100 %) | 8 (100 %) | 8 (100 %) | 8 (100 %) | 24 (100 %) |
| Ethnicity - n(%) | Other | 8 (100 %) | 8 (100 %) | 8 (100 %) | 8 (100 %) | 8 (100 %) | 8 (100 %) | 24 (100 %) |

## Outcome measures

## Primary Outcome Result(s)

**Arithmetic mean of primary PK parameters for subjects with renal impairment and matching healthy subjects group (PK analysis set)**

| | Mild | | Moderate | | Severe | |
|---|---|---|---|---|---|---|
| PK parameter [unit] | Renally impaired subjects | Matched healthy subjects | Renally impaired subjects | Matched healthy subjects | Renally impaired subjects | Matched healthy subjects |
| Cmax [ng/mL] | 253 ± 100 (39.6%) | 112 ± 41.2 (36.9%) | 172 ± 114 (66.5%) | 155 ± 109 (70.3%) | 175 ± 62.4 (35.5%) | 101 ± 60.7 (60.3%) |
| AUClast [hr*ng/mL] | 1700 ± 543 (31.9%) | 740 ± 258 (34.8%) | 1390 ± 782 (56.3%) # | 803 ± 443 (55.2%) | 1910 ± 1240 (64.7%) | 779 ± 764 (98.1%) |
| AUCinf [hr*ng/mL] | 1770 ± 559 (31.6%) | 776 ± 266 (34.3%) | 1470 ± 818 (55.6%) # | 948 ± 399 (42.0%) # | 2020 ± 1340 (66.0%) | 821 ± 787 (95.8%) |

Note: Treatment administered was a single dose 50 mg AFQ056 and values are in Arithmetic mean ±SD (CV%)

N=8 for all groups

# N=7

**Arithmetic mean of secondary PK parameters for subjects with renal impairment and matching healthy subjects group (PK analysis set)**

| | Mild | | Moderate | | Severe | |
|---|---|---|---|---|---|---|
| PK parameter [unit] | Renally impaired subjects | Matched Healthy subjects | Renally impaired subjects | Matched healthy subjects | Renally impaired subjects | Matched healthy subjects |
| Tmax [hr]** | 1.00 (1.00-4.00) | 1.00 (0.50-1.00) | 1.02 (0.80-2.02) | 1.00 (0.50-2.00) | 2.00 (0.50-4.00) | 1.00 (0.50-2.00) |
| T1/2 [hr] | 10.32 ± 3.949 (38.26%) | 8.65 ± 3.076 (35.56%) | 15.26 ± 7.074 (46.36%)* | 11.35 ± 6.524 (57.47%) | 12.42 ± 6.159 (49.59%) | 9.59 ± 5.610 (58.46%) |
| CL/F [L/hr] | 30.89 ± 9.488 (30.71%) | 74.32 ± 33.880 (45.59%) | 56.09 ± 59.984 (106.95%)* | 75.55 ± 47.267 (62.57%) | 44.70 ± 44.920 (100.50%) | 252.1 ± 404.11 (160.31%) |
| Vz/F [L] | 454.5 ± 228.79 (50.34%) | 825.5 ± 176.34 (21.36%) | 934.7 ± 579.33 (61.98%)* | 1144 ± 727.45 (63.58%) | 544.8 ± 282.52 (51.85%) | 1509 ± 1274.7 (84.46%) |

Note: Treatment administered was a single dose 50 mg AFQ056 and values are in Arithmetic mean ± SD (CV%)

N=8 for all groups

* N=7

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

**Statistical assessment of AFQ056 PK parameters for subjects with renal impairment vs matched healthy subjects (PK analysis set)**

| Parameter (unit) | Subject group | Geometric mean* | Ratio of geometric means* | 90% CI for ratio* |
|---|---|---|---|---|
| Cmax [ng/mL] | Mild RI | 233 | 2.24 | (1.42-3.53) |
| | Matched healthy to mild RI | 104 | | |
| | Moderate RI | 128 | 1.00 | (0.63-1.57) |
| | Matched healthy to moderate RI | 129 | | |
| | Severe RI | 165 | 2.12 | (1.35-3.34) |
| | Matched healthy to severe RI | 78 | | |
| AUClast [hr*ng/mL] | Mild RI | 1626 | 2.35 | (1.39-3.97) |
| | Matched healthy to mild RI | 692 | | |
| | Moderate RI** | 1039 | 1.52 | (0.88-2.65) |
| | Matched healthy to moderate RI | 681 | | |
| | Severe RI | 1487 | 3.53 | (2.09-5.97) |
| | Matched healthy to severe RI | 421 | | |
| AUCinf [hr*ng/mL] | Mild RI | 1690 | 2.32 | (1.40-3.85) |
| | Matched healthy to mild RI | 727 | | |
| | Moderate RI | 1214 | 1.38 | (0.80-2.36) |
| | Matched healthy to moderate RI | 883 | | |
| | Severe RI | 1572 | 3.41 | (2.06-5.64) |
| | Matched healthy to severe RI | 461 | | |

Note: Treatment administered was single dose 50 mg of AFQ056.

* back transformed from log scale;

** N=7 and for other groups N=8; RI: Renal impairment;

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

**Summary statistics of urine PK parameters for subjects with renal impairment groups and respective matching healthy subjects group (PK analysis set)**

| | Mild | | Moderate | | Severe | | Pooled healthy subjects |
|---|---|---|---|---|---|---|---|
| PK parameter [unit] | Renally impaired subjects | Matched healthy subjects | Renally impaired subjects | Matched healthy subjects | Renally impaired subjects | Matched healthy subjects | |
| Ae0-72 h [ng] | 5678 ± 2933 (51.7%) | 0.00 ± 0.000 (0.0%) | 3505 ± 4452 (127.0%) | 609 ± 1390 (228.3%) | 1065 ± 1174 (110.3%) | 283 ± 801 (282.8) | 297 ± 921 (309.6%) |
| Percent AFQ056 dose excreted | 0.011 ± 0.0059 | 0.000 ± 0.0000 | 0.007 ± 0.0089 | 0.001 ± 0.0027 | 0.002 ± 0.0023 | 0.001 ± 0.0016 | 0.001 ± 0.0018 |

Note: values are in Arithmetic mean ± SD (CV %)

**Arithmetic mean of fraction unbound and bound to plasma proteins for AFQ056 in subjects with renal impairment and respective matching healthy subjects groups**

| Groups | Mean fraction unbound [%] | | | | Mean fraction bound [%] | |
|---|---|---|---|---|---|---|
| | 2 h | SD | 4 h | SD | 2 h | 4 h |
| Mild impairment | 1.95 | ± 0.625 | 2.01 | ± 0.495 | 98.1 | 98.0 |
| Moderate impairment | 2.05 | ± 0.518 | 2.04 | ± 0.537 | 98.0 | 98.0 |
| Severe impairment | 1.69 | ± 0.253 | 1.75 | ± 0.319 | 98.3 | 98.2 |
| Control matching mild | 1.86 | ± 0.218 | 1.96 | ± 0.269 | 98.1 | 98.0 |
| Control matching moderate | 1.59 | ± 0.398 | 1.83 | ± 0.387 | 98.4 | 98.2 |
| Control matching severe | 1.77 | ± 0.253 | 1.82 | ± 0.310 | 98.2 | 98.2 |

Note: Values are in mean ± SD

## Secondary Outcome Result(s)

## Safety results

| | Subjects with mild renal impairment N=8 | | Matched healthy subjects to mild renal impairment N=8 | | Subjects with moderate renal impairment N=8 | | Matched healthy subjects to moderate renal impairment N=8 | | Subjects with severe renal impairment N=8 | | Matched healthy subjects to severe renal impairment N=8 | | All subjects with renal impairment N=24 | | All healthy subjects N=24 | | Total subjects N=48 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) | n | (%) |
| Any AE | 5 | (62.5) | 5 | (62.5) | 3 | (37.5) | 2 | (25.0) | 2 | (25.0) | 3 | (37.5) | 10 | (41.7) | 10 | (41.7) | 20 | (41.7) |
| Dizziness | 3 | (37.5) | 3 | (37.5) | 1 | (12.5) | 0 | (0.0) | 2 | (25.0) | 1 | (12.5) | 6 | (25.0) | 4 | (16.7) | 10 | (20.8) |
| Feeling drunk | 1 | (12.5) | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 1 | (4.2) | 3 | (12.5) | 4 | (8.3) |
| Headache | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 3 | (12.5) | 3 | (6.3) |
| Illusion | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 3 | (12.5) | 0 | (0.0) | 3 | (6.3) |
| Fatigue | 1 | (12.5) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 2 | (8.3) | 0 | (0.0) | 2 | (4.2) |
| Acquired macroglossia | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (2.1) |
| Back pain | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 1 | (2.1) |
| Blood amylase increased | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 1 | (2.1) |
| Feeling abnormal | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (2.1) |
| Hypoaesthesia oral | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (2.1) |
| Lipase increased | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 1 | (2.1) |
| Paraesthesia oral | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 1 | (2.1) |
| Photopsia | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (2.1) |
| Sciatica | 1 | (12.5) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (2.1) |
| Visual impairment | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 1 | (12.5) | 0 | (0.0) | 1 | (4.2) | 0 | (0.0) | 1 | (2.1) |

AEs by preferred term are presented in descending order of overall frequency and none of these were SAEs

## Other Relevant Findings

None

## Date of Clinical Trial Report

15-Jun-2012

## Date Inclusion on Novartis Clinical Trial Results Database

10-Jul-2012

## Date of Latest Update