Sponsor

Novartis

Generic Drug Name

Pradigastat (LCQ908)

Therapeutic Area of Trial

Renal impairment

Approved Indication

Investigational

Protocol Number

CLCQ908B2102

Title

An open-label, parallel-group, single dose study to assess the pharmacokinetics of pradigastat (LCQ908) in patients with mild, moderate and severe renal impairment compared to age, gender and weight-matched healthy volunteers

Study Phase

Phase I

Study Start/End Dates

14-May-2012 to 28-Mar-2013

Study Design/Methodology

This study was a single-dose, open label, parallel-group design in subjects with mild, moderate and severe renal impairment along with matched healthy control subjects with normal renal function. Healthy subjects were matched pair-wise by, gender, race, age (±15 years) and weight (±20%) to subjects with renal impairment. Each subject received a single 40 mg dose of pradigastat.

Centers

2 centers in USA

Publication

None

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

Pradigastat 20 mg tablets for oral administration. Single dose

Statistical Methods

The primary PK parameters of pradigastat (AUClast, AUCinf, Cmax, CL/F) were compared for each renal impairment group (mild, moderate and severe) vs. the matched control group. Log-transformed PK parameters were analyzed separately using a linear mixed effects model with group as fixed effect and matched pair as random effect. Least square means for each group as well as contrasts between each renal impaired group and control with corresponding 90% confidence intervals on the log-scale were calculated. Back-transformed ratios and 90% confidence interval were also provided. In addition, pradigastat protein binding was analyzed from measuring unbound drug concentrations.

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key Inclusion Criteria:

- Individuals with renal impairment only: Estimated Creatinine Clearance (CLcr) by the Cockroft-Gault equation ≤80mL/min;
    - Mild renal impairment defined as CLcr 50-80 mL/min
    - Moderate renal impairment defined as CLcr 30-50 mL/min
    - Severe renal impairment defined as CLcr <30 mL/min
- Healthy subjects only: Estimated CLcr by the Cockroft-Gault equation >80mL/min and had to be in good health as determined by past medical history, physical examination, vital signs, ECG and laboratory tests at screening.

Key Exclusion Criteria:

- All Individuals:
    - A past medical history of clinically significant ECG abnormalities or a family history of a prolonged QT-interval syndrome.
    - Female subjects must be of non child bearing potential or use an effective method of contraception.
- Individuals with renal impairment:
    - Renal transplant at any time.
    - Subjects undergoing any method of dialysis (hemodialysis, peritoneal dialysis) within the last 3 months.
    - History of clinically significant chronic or recurrent urinary tract infection active and requiring antibiotic treatment within the past 30 days.
    - Any medication that is contraindicated in moderate or severe renally impaired population
- Healthy subjects:
    - History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine or BUN and/or urea values, or abnormal urinary constituents (e.g., albuminuria)

- Evidence of urinary obstruction or difficulty in voiding at screening
- History or presence of hepatitis B or C and/or positive Hepatitis B surface antigen (HBsAg) or Hepatitis C test result at screening.

Participant Flow

Summary of subject disposition- Safety analysis set

	Mild renal impaired subjects	Control subjects (mild)	Moderate renal impaired subjects	Control subjects (moderate)	Severe renal impaired subjects	Control subjects (severe)	All subjects
	N=10 n (%)	N=10 n (%)	N=10 n (%)	N=10 n (%)	N=9 n (%)	N=9 n (%)	N=58 (%)
Completed	10 (100.0%)	10 (100.0%)	10 (100.0%)	10 (100.0%)	9 (100.0%)	8 (88.9%)	57 (98.3%)
Discontinued						1 (11.1%)	1 (1.7%)
Main cause of discontinuation							
Subject withdrew consent						1 (11.1%)	1 (1.7%)

Baseline Characteristics

Demographic summary and baseline characteristics by treatment group- Safety analysis set

		Renal impairment group						Total
		Mild		Moderate		Severe		
		Impaired N=10	Control N=10	Impaired N=10	Control N=10	Impaired N=9	Control N=9	N=58
Age (years)	Mean (SD)	63.8 (7.07)	56.4 (3.66)	64.7 (6.95)	59.2 (8.28)	66.0 (8.25)	57.7 (6.26)	61.3 (7.56)
Gender – n (%)	Male	7 (70)	7 (70)	6 (60)	6 (60)	6 (67)	6 (67)	38 (66)
	Female	3 (30)	3 (30)	4 (40)	4 (40)	3 (33)	3 (33)	20 (34)
Race – n (%)	Caucasian	8 (80)	8 (80)	6 (60)	6 (60)	6 (67)	6 (67)	40 (69)
	Black	2 (20)	2 (20)	4 (40)	4 (40)	3 (33)	3 (33)	18 (31)
Height (cm)	Mean (SD)	167 (10.9)	173 (10.3)	168 (9.8)	169 (8.0)	166 (10.9)	172 (8.7)	169 (9.7)
Weight (kg)	Mean (SD)	83.3 (21.74)	84.3 (18.78)	82.2 (17.91)	79.6 (13.68)	72.6 (18.59)	76.7 (10.80)	80.0 (17.08)
BMI (kg/m^2)	Mean (SD)	29.4 (5.44)	27.9 (4.17)	29.2 (5.30)	28.0 (4.18)	26.2 (4.78)	26.0 (2.82)	27.9 (4.55)
CLcr (mL/min)	Mean (SD)	67.4 (5.7)	107.4 (22.9)	42.0 (5.0)	101.8 (14.7)	26.2 (3.0)	100.2 (14.3)	74.1 (34.0)

Outcome Measures

Primary Outcome Results

Summary of plasma PK parameters of pradigastat in patients with impaired renal function (mild, moderate and severe) and matching healthy subjects (control) - PK Analysis set

Group		Cmax (ng/mL)	AUCinf (h.ng/mL)	AUClast (h.ng/mL)	CL/F (L/h)	Tmax (h)	T1/2 (h)	Vz/F (L)
Mild (N=9)	Mean (SD)	182 (202)	26600 (20300)	24900 (19200)	2.40 (1.66)	10.0 (4.00 – 48.0)	154 (53.2)	523 (386)
Control – mild (N=9)	Mean (SD)	184 (152)	37200 (35600)	34900 (32100)	1.90 (1.56)	24.0 (10.0 – 48.0)	145 (38.4)	382 (359)
Moderate (N=10)	Mean (SD)	237 (169)	54300 (63300)	50500 (56400)	1.40 (0.870)	36.0 (4.00 – 120)	134 (38.3)	250 (164)
Control - moderate (N=10)	Mean (SD)	218 (89.8)	34500 (8100)	33300 (7760)	1.22 (0.298)	18.0 (8.00 – 96.0)	129 (21.4)	228 (76.0)
Severe (N=9)	Mean (SD)	287 (99.0)	42200 (26700)	40700 (25500)	1.22 (0.547)	12.0 (2.00 – 48.0)	139 (34.4)	248 (145)
Control – severe (N=9)	Mean (SD)	232 (156)	40300* (37000)	36900 (31100)	1.54* (0.801)	48.0 (4.00 – 120)	142* (69.0)	271* (160)
All controls (N=28)	Mean (SD)	212 (131)	37100** (28100)	35000 (24800)	1.54** (1.02)	24 (4.00 - 120)	138** (44.1)	292** (230)

Note: arithmetic mean and standard deviation (SD) presented, except for Tmax where median and range are presented; *N=8, **N=27

Secondary Outcome Result(s)

Summary of protein binding (%) for pradigastat in patients with impaired renal function (mild, moderate and severe) and matching healthy subjects (control) -PK Analysis set

	N	Mean	Range
Mild	9	99.5	99.3, 99.7
Control – mild	4	99.4	99.4, 99.5
Moderate	10	99.6	99.3, 99.7
Control – moderate	10	99.8	99.5, 99.9
Severe	9	99.6	99.2, 99.8
Control - severe	9	99.8	99.7, 99.9

Safety and tolerability were secondary outcome of the study. **Please see Safety Results section**

Safety Results

Adverse Events by System Organ Class (SOC) and Preferred Term n (%) in patients with impaired renal function (mild, moderate and severe) and matching healthy subjects (control) - Safety analysis set

Primary SOC	Preferred term	Impaired N=29 n (%)	Control N=29 n (%)	Total N=58 n (%)
Subjects with at least one AE		9 (31)	4 (14)	13 (22)
Gastrointestinal disorders	Diarrhea	3 (10)*	0	3 (5%)
	Nausea	1 (3)[a]	0	1 (2)
	Toothache	0	1 (3)	1 (2)
	Vomiting	1 (3) [a]	0	1 (2)
Nervous system disorders	Dizziness	2 (7) [a]	0	2 (3)
	Headache	1 (3) [a]	0	1 (2)
	Migraine	1 (3) [a]	0	1 (2)
General disorders & administration site conditions	Non-cardiac chest pain	1 (3) [b]	0	1 (2)
Infections & infestations	Gastroenteritis viral	1 (3) [c]	0	1 (2)
Investigations	ALT increased	0	1 (3)	1 (2)
	AST increased	0	1 (3)	1 (2)
	Gamma GT increased	0	1 (3)	1 (2)
Musculoskeletal & connective tissue disorders	Back pain	0	1 (3)	1 (2)
	Bursitis	1 (3) [b]	0	1 (2)
Renal & urinary disorders	Pollakiuria	1 (3) [a]	0	1 (2)
Skin & subcutaneous tissue disorders	Dermatitis contact	0	1 (3)	1 (2)

[a] Mild impaired, [b] Moderate impaired, [c] Severe impaired, * all groups

Serious Adverse Events and Deaths:

No serious adverse events or deaths were reported in this study

Other Relevant Findings

None

Date of Clinical Trial Report

14 March 2014

Date Inclusion on Novartis Clinical Trial Results Database

18 March 2014

Date of Latest Update

06 March 2014