Sponsor

Novartis

Generic Drug Name

Pradigastat

Therapeutic Area of Trial

Chylomicronemia

Approved Indication

Investigational

Protocol Number

CLCQ908B2101

Title

An open-label, single-dose, parallel group study to evaluate the pharmacokinetics of pradigastat in subjects with mild, moderate and severe hepatic impairment compared to healthy control subjects

Study Phase

Phase I

Study Start/End Dates

24-Apr-2012 to 02-Apr-2013

Study Design/Methodology

An open-label, single-dose, parallel group study to evaluate the pharmacokinetics of pradigastat (LCQ908) in subjects with mild, moderate and severe hepatic impairment compared to healthy control subjects.
This is a two-part study, single-dose, open label, parallel-group design in subjects with mild, moderate and severe hepatic impairment along with matched healthy control subjects with normal hepatic function. Healthy subjects were matched pair-wise by sex, race, age (±10 years) and weight (±20%) to subjects with hepatic impairment.
Part I primary objective was to characterize the single-dose pharmacokinetics (PK) of 20 mg of pradigastat in subjects with mild and moderate hepatic impairment in comparison to matched healthy control subjects.
Part II primary objective was to characterize the single-dose PK of pradigastat (5, 10 or 20 mg, dose determined by Part I data) in subjects with severe hepatic impairment in comparison to matched healthy control subjects.

For both parts of the study there was up to 21-day screening period, one treatment period followed by a Study Completion evaluation approximately 28 days after the drug administration.

Centers

2 centers in USA

Publication

None

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

One single oral tablet of pradigastat 20 mg

Statistical Methods

Pharmacokinetics: The PK parameters were summarized for each hepatic impairment category and for matched healthy volunteers per hepatic impairment category as well as a combined group by dose level.
The PK parameters of pradigastat (AUClast, AUCinf, Cmax, CL/F) were compared for each hepatic 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 hepatic impairment group and control with corresponding 90% CI on the log-scale was calculated. Back-transformed ratios and 90% CI were provided.
Plasma protein binding (PPB) results were >99% for all the subjects and comparable between hepatic impaired and control subjects, therefore the unbound PK parameters were calculated but not summarized.

Safety: All vital signs, ECG, laboratory data was listed by hepatic impairment group, subject, and visit/time and if ranges were available abnormalities were flagged. Summary statistics were provided by hepatic impairment group and visit/time.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria:

All individuals:

- Male and female subjects aged 18 to 65 years (inclusive). Subjects were required to weigh at least 50 kg to participate in the study and were required to have a body mass index (BMI) within the range of 18 to 38 kg/m2.

Individuals with hepatic impairment only

- Hepatic impairment evidenced by a Child-Pugh score
  Mild hepatic impairment defined Child-Pugh Class A
  (5-6 points)
  Moderate hepatic impairment defined Child-Pugh Class B (7-9 points)
  Severe hepatic impairment defined Child-Pugh Class C (10-15 points).

Healthy subjects only

- Good health determined.

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 hepatic impairment

- History of drug or alcohol abuse within 3 months prior to dosing.
- History or presence of significant uncontrolled disease of any major organ class.
- Any surgical or medical condition other than hepatic impairment which might alter the drug metabolism.

Healthy subjects

- History or presence of significant uncontrolled disease of any major organ class.
- Any surgical or medical condition other than hepatic impairment which might alter the drug metabolism.
- 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

Subject disposition – n (percent) of subjects by group (Safety analysis set)

	Mild hepatic impaired subjects N=10	Control subjects (mild) N=10	Moderate hepatic impaired subjects N=11	Control subjects (moderate) N=10	Severe hepatic impaired subjects N=6	Control subjects (severe) N=6	Total N=53
Subjects							
Completed	10 (100%)	10 (100%)	10 (90.9%)	10 (100%)	6 (100%)	6 (100%)	52(98.1%)
Discontinued	0	0	1 (9.1%)	0	0	0	1 (1.9%)
Adverse Event(s)	0	0	1 (9.1%)	0	0	0	1 (1.9%)

Baseline Characteristics

Demographic summary and background characteristics by group (Safety analysis set)

		Mild hepatic impaired subjects N=10	Control subjects (mild) N=10	Moderate hepatic impaired subjects N=11	Control subjects (moderate) N=10	Severe hepatic impaired subjects N=6	Control subjects (severe) N=6	Total N=53
Age (years)	Mean (SD)	54.6 (6.9)	54.3 (4.6)	54.5 (5.0)	53.1 (5.6)	54.5 (6.8)	54.7 (7.4)	54.2 (5.7)
	Median	53.0	54.5	54.0	53.5	56.0	56.0	54.0
	Range	42 - 62	46 - 61	47 - 61	45 - 62	43 - 61	42 - 64	42 - 64
Height (cm)	Mean (SD)	172.6 (8.7)	170.1 (7.9)	167.6 (7.1)	173.0 (6.2)	176.0 (14.1)	177.4 (7.4)	172.1 (8.6)
	Median	172.5	167.8	168.0	174.0	171.4	175.5	172.0
	Range	158 - 189	157 - 182	160 - 179	163 - 180	160 - 201	168 - 189	157 - 201
Weight (kg)	Mean (SD)	90.8 (18.1)	84.8 (15.2)	89.0 (21.1)	89.7 (15.5)	102.0 (29.9)	94.7 (17.4)	90.8 (19.1)
	Median	89.9	85.4	91.0	85.0	96.1	93.0	91.0
	Range	67 - 125	66 - 112	54 - 119	64 - 112	64 - 154	73 - 126	54 - 154
BMI (kg/m^2)	Mean (SD)	30.2 (3.9)	29.2 (4.0)	31.4 (5.7)	29.8 (3.9)	32.2 (4.4)	29.9 (3.2)	30.4 (4.3)
	Median	30.2	27.5	32.3	29.9	32.8	29.0	30.1
	Range	25 - 37	25 - 36	20 - 38	22 - 35	25 - 38	26 - 35	20 - 38
Gender - n(%)	Male	7 (70%)	7 (70%)	9 (82%)	9 (90%)	5 (83%)	5 (83%)	42 (79%)
	Female	3 (30%)	3 (30%)	2 (18%)	1 (10%)	1 (17%)	1 (17%)	11 (21%)
Predominant race - n(%)	Caucasian	9 (90%)	9 (90%)	10 (91%)	9 (90%)	6 (100%)	6 (100%)	49 (92%)
	Black	1 (10%)	1 (10%)	1 (9%)	1 (10%)			4 (8%)
Ethnicity - n(%)	Missing	1 (10%)						1 (2%)
	Hispanic/Latino	4 (40%)	8 (80%)	5 (45%)	7 (70%)	4 (67%)	2 (33%)	30 (57%)
	Other	5 (50%)	2 (20%)	6 (55%)	3 (30%)	2 (33%)	4 (67%)	22 (42%)
Pack years	Mean (SD)	5.5 (7.9)	0.4 (1.3)	3.3 (7.0)	0.5 (1.7)	2.5 (3.5)	3.5 (5.4)	2.6 (5.3)
	Median	1.9	0.0	0.0	0.0	1.2	0.0	0.0
	Range	0 - 23	0 - 4	0 - 23	0 - 5	0 - 9	0 – 11	0 - 23

BMI = body mass index
SD = standard deviation
All mild, moderate, and severe matched groups received a single 20 mg dose of pradigastat.
Pack years was calculated by multiplying the number of packs of cigarettes smoked per day by the number of years the person has smoked.

Outcome Measures

Primary Outcome Results

- Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUClast) of LCQ908 for part I of the study.
- Area under the plasma concentration-time profile from time zero extrapolated to infinite time [AUC(0-inf)] of LCQ908 for part I of the study.

- Maximum plasma concentration of LCQ908 (Cmax) for Part I of the study.
- The apparent systemic clearance (CL/F) of LCQ908 following extra vascular administration for Part I of the study.
- Area under the plasma concentration-time profile from time zero to the time of the last quantifiable concentration (AUClast) of LCQ908 for Part II of the study.
- Area under the plasma concentration-time profile from time zero extrapolated to infinite time [AUC(0-inf)] of LCQ908 for Part II of the study.
- Maximum plasma concentration of LCQ908 (Cmax) for Part II of the study.
- The apparent systemic clearance (CL/F) of LCQ908 following extra vascular administration for Part II of the study.

Secondary Outcome Result(s)

- Number of participants with adverse events, serious adverse events and death (for both Part I and Part II).
- Time to maximum plasma concentration of LCQ908 (Tmax) (for both Part I and Part II).
- The time required for the concentration of the drug to reach half of its original value (T1/2) (for both Part I and Part II).
- The apparent volume of distribution of LCQ908 during the terminal elimination phase following extra vascular administration (Vz/F) (for both Part I and Part II).
- LCQ908 protein binding: unbound area under curve (AUCu) of LCQ908 (for both Part I and Part II).
- LCQ908 protein binding: unbound observed maximum plasma (Cmax) of LCQ908 (for both Part I and Part II).
- LCQ908 protein binding: unbound apparent systemic clearance from plasma (CL/Fu) following extra vascular administration (for both Part I and Part II).

Summary statistics for PK parameters for pradigastat for hepatic impaired and matching healthy subjects by compound, matrix, analyte, and actual group (Pharmacokinetic analysis set)

Compound: LCQ908, Matrix: plasma, Analyte: LCQ908

Actual group	Statistic	Cmax (ng/mL)	AUCinf (h*ng/mL)	AUClast (h*ng/mL)	CL/F (L/h)	Tmax (h)	T1/2 (h)	Vz/F (L)	Protein binding (%)
Mild hepatic impaired subjects (N=10)	Mean (SD)	95.1 (82.0)	21800* (16100)	18900 (15200)	1.23* (0.576)	36.0	154* (57.9)	272* (154)	99.3 (0.103)
	CV%	86.3	74.0	80.5	46.7	4.00 - 96.0	37.5	56.8	0.1
Control subjects (mild) (N=10)	Mean (SD)	87.1 (43.8)	13200 (6390)	12700 (6060)	1.79 (0.697)	17.0	127 (16.3)	326 (133)	99.2 (0.110)
	CV%	50.3	48.3	47.8	38.9	4.00 - 72.0	12.9	40.8	0.1
Moderate hepatic impaired subjects (N=10)	Mean (SD)	145 (72.5)	22900 (14700)	21600 (13400)	1.37 (1.16)	7.00	131 (28.2)	247 (213)	99.3 (0.316)
	CV%	50.0	64.4	61.9	84.3	2.00 - 72.0	21.5	86.1	0.3
Control subjects (moderate) (N=10)	Mean (SD)	141 (139)	20300 (10900)	19100 (10400)	1.34 (0.882)	48.0	153 (47.7)	280 (169)	99.2 (0.218)
	CV%	98.5	53.9	54.7	66.0	4.00 - 144	31.2	60.1	0.2
Severe hepatic impaired subjects (N=6)	Mean (SD)	180 (99.2)	24400 (12200)	23700 (11800)	1.13 (0.854)	24.0	109 (24.1)	161 (80.0)	99.1 (0.216)
	CV%	55.3	49.9	49.8	75.2	1.00 - 96.0	22.0	49.6	0.2
Control subjects (severe) (N=6)	Mean (SD)	59.6 (22.6)	11600 (5140)	11200 (5210)	2.02 (0.836)	48.0	111 (64.1)	313 (179)	99.1 (0.160)
	CV%	37.9	44.4	46.4	41.4	24.0 - 72.0	57.5	57.3	0.2
All healthy subjects (N=26)	Mean (SD)	102 (94.4)	15600 (8810)	14800 (8370)	1.67 (0.821)	48.0	133 (45.0)	305 (153)	99.2 (0.164)
	CV%	92.9	56.6	56.5	49.2	4.00 - 144	33.7	50.1	0.2

All mild, moderate, and severe matched groups received a single 20 mg dose of pradigastat.

Note: arithmetic mean and standard deviation (SD) presented, except for Tmax where median and range are presented

CV% = coefficient of variation (%)=sd/mean*100

*N=9

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

Safety Results

Incidence of AEs by primary system organ class - n (percent) of subjects by group (Safety analysis set)

	Mild hepatic impaired subjects N=10 n (%)	Control subjects (mild) N=10 n (%)	Moderate hepatic impaired subjects N=11 n (%)	Control subjects (moderate) N=10 n (%)	Severe hepatic impaired subjects N=6 n (%)	Control subjects (severe) N=6 n (%)	All healthy subjects N=26 n (%)	Total N=53 n (%)
Patients with AE(s)	2 (20.0%)	2 (20.0%)	4 (36.4%)	0	4 (66.7%)	1 (16.7%)	3 (11.5%)	13 (24.5%)
Gastrointestinal disorders	0	1 (10.0%)	2 (18.2%)	0	3 (50.0%)	0	1 (3.8%)	6 (11.3%)
Injury, poisoning and procedural complications	0	0	2 (18.2%)	0	0	0	0	2 (3.8%)
Infections and infestations	0	1 (10.0%)	0	0	1 (16.7%)	0	1 (3.8%)	2 (3.8%)
Skin and subcutaneous tissue disorders	0	0	0	0	0	1 (16.7%)	1 (3.8%)	1 (1.9%)
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (16.7%)	0	0	1 (1.9%)
Renal and urinary disorders	1 (10.0%)	0	0	0	0	0	0	1 (1.9%)
Nervous system disorders	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
Musculoskeletal and connective tissue disorders	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
General disorders and administration site conditions	1 (10.0%)	0	0	0	0	0	0	1 (1.9%)

All mild, moderate, and severe matched groups received a single 20 mg dose of pradigastat.

Arranged in descending order of frequency (in total group) and by system organ class.

Incidence of AEs by preferred term - n (percent) of subjects by group (Safety analysis set)

	Mild hepatic impaired subjects N=10 n (%)	Control subjects (mild) N=10 n (%)	Moderate hepatic impaired subjects N=11 n (%)	Control subjects (moderate) N=10 n (%)	Severe hepatic impaired subjects N=6 n (%)	Control subjects (severe) N=6 n (%)	All healthy subjects N=26 n (%)	Total N=53 n (%)
Patients with AE(s)	2 (20.0%)	2 (20.0%)	4 (36.4%)	0	4 (66.7%)	1 (16.7%)	3 (11.5%)	13 (24.5%)
Vomiting	0	0	1 (9.1%)	0	1 (16.7%)	0	0	2 (3.8%)
Diarrhoea	0	1 (10.0%)	1 (9.1%)	0	0	0	1 (3.8%)	2 (3.8%)
Toothache	0	0	0	0	1 (16.7%)	0	0	1 (1.9%)
Subcutaneous haematoma	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
Rash	0	0	0	0	0	1 (16.7%)	1 (3.8%)	1 (1.9%)
Oropharyngeal pain	0	0	0	0	1 (16.7%)	0	0	1 (1.9%)
Nasopharyngitis	0	1 (10.0%)	0	0	0	0	1 (3.8%)	1 (1.9%)
Muscle spasms	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
Laceration	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
Hunger	1 (10.0%)	0	0	0	0	0	0	1 (1.9%)
Headache	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
Furuncle	0	0	0	0	1 (16.7%)	0	0	1 (1.9%)
Constipation	0	0	0	0	1 (16.7%)	0	0	1 (1.9%)
Ascites	0	0	0	0	1 (16.7%)	0	0	1 (1.9%)
Ankle fracture	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)
Acute prerenal failure	1 (10.0%)	0	0	0	0	0	0	1 (1.9%)
Abdominal pain	0	0	1 (9.1%)	0	0	0	0	1 (1.9%)

All mild, moderate, and severe matched groups received a single 20 mg dose of pradigastat.

Arranged by frequency in the total column

Brief summary of adverse events and serious adverse events by group (Safety analysis set)

	Mild hepatic impaired subjects N=10 n (%)	Control subjects (mild) N=10 n (%)	Moderate hepatic impaired subjects N=11 n (%)	Control subjects (moderate) N=10 n (%)	Severe hepatic impaired subjects N=6 n (%)	Control subjects (severe) N=6 n (%)	All healthy subjects N=26 n (%)	Total N=53 n (%)
Total number of AE(s)	2	2	8	0	6	1	3	19
Subjects with AE(s)	2 (20.0)	2 (20.0)	4 (36.4)	0	4 (66.7)	1 (16.7)	3 (11.5)	13 (24.5)
AEs of Grade 1	1 (10.0)	2 (20.0)	1 (9.1)	0	3 (50.0)	1 (16.7)	3 (11.5)	8 (15.1)
AEs of Grade 2	1 (10.0)	0	1 (9.1)	0	0	0	0	2 (3.8)
AEs of Grade 3	0	0	2 (18.2)	0	0	0	0	2 (3.8)
AEs of Grade 4	0	0	0	0	1 (16.7)	0	0	1 (1.9)
Study drug-related AEs	2 (20.0)	1 (10.0)	2 (18.2)	0	1 (16.7)	0	1 (3.8)	6 (11.3)
Serious AEs	0	0	1 (9.1)	0	1 (16.7)	0	0	2 (3.8)

All mild, moderate, and severe matched groups received a single 20 mg dose of pradigastat.
A subject experiencing multiple AEs of different grades is counted with the highest grade only.
N = number of subjects studied; n = number of subjects with at least one AE on the category
Only adverse events occurring at or after first drug intake are included

No deaths were reported during the study or 30-day follow-up period.

Other Relevant Findings

None

Date of Clinical Trial Report

03-March-2014

Date Inclusion on Novartis Clinical Trial Results Database

02-April-2014

Date of Latest Update

27-March-2014