NOVARTIS

Clinical Trial Results Database

Sponsor

Novartis

Generic Drug Name

Ceritinib (LDK378)

Trial Indication

Impaired hepatic function

Protocol Number

CLDK378A2110

Protocol Title

A Phase I, open label, multi-center, single dose study to evaluate the pharmacokinetics of LDK378 in subjects with hepatic impairment compared to subjects with normal hepatic function.

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase III

Study Start/End Dates

07-Jan-2014 (first subject first visit) to 22-Sep-2016 (last subject last visit).

Reason for Termination (If applicable)

Not applicable.

Study Design/Methodology

A Phase I, multi-center, open-label, parallel group study to assess the PK and safety of a single oral dose (750 mg) of ceritinib in subjects with impaired hepatic function and healthy subjects with demographically-matched normal hepatic function. Subjects were assigned to a hepatic group based on hepatic function (according to the Child-Pugh classification) as determined at the Screening visit: Group 1, normal hepatic function; Group 2, mild hepatic impairment; Group 3, moderate hepatic impairment; and Group 4, severe hepatic impairment.

Centers

USA (5 centers)

Publication

None.

Objectives:

Primary objective

- To evaluate the pharmacokinetics (PK) of a single oral dose of ceritinib in subjects with impaired hepatic function as compared to healthy subjects with normal hepatic function.

Secondary objectives

- To evaluate the safety and tolerability of a single oral dose of ceritinib in healthy subjects and subjects with varying degrees of hepatic function impairment (mild to severe).
- To evaluate the plasma protein binding of ceritinib and PK expressed as unbound drug in subjects with impaired hepatic function as compared to healthy subjects with normal hepatic function.

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

Ceritinib 750 mg single oral dose administered under fasting conditions.

Statistical Methods

A formal comparison was conducted for the following primary PK parameters: Cmax, AUClast, and AUCinf. A linear model including group as a covariate was fitted to the log-transformed PK parameters. The hepatic impairment groups (mild, moderate, severe) were the test treatments and the normal group was the reference treatment. Point estimates and the corresponding 90% confidence intervals (CIs) for the mean difference between each test and the reference group were calculated. These were anti-logged to obtain the point estimate and 90% CI for the ratio of the geometric means (GMR) on the original scale. For Tmax, the difference of medians was provided to compare between hepatic impairment groups and the normal group.

Summary statistics for PK parameters for ceritinib (Tmax, Cmax, AUClast, AUCinf, T1/2, CL/F, Vz/F) was provided by hepatic group using the pharmacokinetic analysis set (PAS). Summary statistics included n, geometric mean and geometric CV%, arithmetic mean and CV%, median, SD, minimum and maximum. Only n, median, minimum, and maximum was provided for Tmax.

To fulfill a secondary objective, summary statistics for plasma protein binding of ceritinib, expressed as unbound fraction in plasma, was provided by hepatic group using the full analysis set (FAS).

The linear model described above was rerun on the unbound primary PK parameters (Cmax,u, AUClast,u, and AUCinf,u) for ceritinib using PAS.

Adverse events (AE) were summarized by system organ class (SOC), as well as most frequent AEs (i.e. $\geq 5\%$ in any of the hepatic impairment groups) by preferred term (PT). Death and SAEs were also summarized.

Study Population: Key Inclusion/Exclusion Criteria

Key criteria for inclusion of subjects in all groups: Male and sterile or postmenopausal female age ≥ 18 to ≤ 70 years old. Body mass index (BMI) of 18-36 kg/m2, with body weight ≥ 50 kg.

Key criteria for inclusion of subjects in normal group (control group): Healthy subjects with no clinically significant abnormalities as determined by past medical history, physical examination, vital signs, ECG and clinical laboratory tests; adequate end organ function and laboratory values.

Key criteria for inclusion of subjects in mild, moderate and severe groups:

- Subjects with confirmed cirrhosis by at least one of the following criteria:
  - Histologically by prior liver biopsy showing cirrhosis.
  - Clinically by physical examination (e.g., liver firmness to palpation, splenic enlargement, spider angioma, palmar erythema, parotid hypertrophy, testicular atrophy, ascites, presence of asterixis or gynecomastia), and/or laboratory data, and/or liver imaging (CT, and/or US and/or Magnetic Resonance Imaging (MRI) scans), and/or endoscopic findings.
  - Child-Pugh Clinical Assessment Score consistent with degree of hepatic impairment.

Exclusion criteria:

Key criteria for exclusion of subjects in normal group (control group):

- Used any prescription drug or over-the-counter (OTC) medication within 5 half-lives prior to dosing, except for acetaminophen within 7 days before dosing. Use of proton pump inhibitors within 10 days prior to or 2 days after ceritinib dosing.
- History or evidence of liver disease or liver injury, hepatocellular carcinoma or liver metastasis.
- Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism or excretion of drugs or which may jeopardize the subject in case of participation in the study. The Investigator was guided by evidence of any of the following:
  - History of inflammatory bowel syndrome, gastritis, or gastric or duodenal ulcers
  - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, cholecystectomy or bowel resection

- History of, or clinical evidence of, pancreatic injury or pancreatitis
- History or presence of impaired renal function as indicated by:
- Administered strong and moderate CYP3A4/5 inhibitors (including herbal products) within 5 half-lives prior to dosing

Key criteria for exclusion of subjects in mild, moderate and severe groups:

- Used proton pump inhibitors within 10 days prior to or 2 days after ceritinib dosing.
- Symptoms or history of encephalopathy (grade 3 or worse) within 3 months prior to dosing.
- Clinical evidence of severe ascites.
- International normalized ratio (INR) >2.5.
- Any evidence of progressive liver disease (within the last 4 weeks) as indicated by liver transaminases (>3.0 × ULN), alkaline phosphatase (>2.5 × ULN), and GGT (>5.0 × ULN), or a ≥ 50% worsening of serum bilirubin or prothrombin time.
- Administered strong and moderate CYP3A4/5 inhibitors (including herbal products) within 5 half-lives prior to dosing

Participant Flow Table

Subject disposition, by hepatic group (Full analysis set)

Disposition reason	Normal N=8 n (%)	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)	All subjects N=37 n (%)
Completed study	8 (100)	9 (100)	10 (100)	9 (90.0)	36 (97.3)
Discontinued	0	0	0	1 (10.0)	1 (2.7)
Adverse event(s)	0	0	0	1 (10.0)	1 (2.7)

Baseline Characteristics

Demographics, by hepatic group (Full analysis set)

Demographic variable	Normal N=8	Mild N=9	Moderate N=10	Severe N=10	All subjects N=37
Age (years)					
n	8	9	10	10	37
Mean	55.5	57.0	59.4	55.2	56.8
SD	6.39	4.95	3.53	8.15	6.01
Median	55.5	59.0	61.0	56.0	58.0
Minimum	42	47	53	37	37
Maximum	63	63	65	63	65
Age category (years) -n (%)					
<65	8 (100)	9 (100)	9 (90.0)	10 (100)	36 (97.3)
≥65	0	0	1 (10.0)	0	1 (2.7)
Sex -n (%)					
Male	7 (87.5)	9 (100)	9 (90.0)	6 (60.0)	31 (83.8)
Female	1 (12.5)	0	1 (10.0)	4 (40.0)	6 (16.2)
Race -n (%)					
Caucasian	6 (75.0)	9 (100)	8 (80.0)	9 (90.0)	32 (86.5)
Black	2 (25.0)	0	2 (20.0)	0	4 (10.8)
Asian	0	0	0	1 (10.0)	1 (2.7)
Ethnicity -n (%)					
Hispanic/Latino	3 (37.5)	2 (22.2)	0	5 (50.0)	10 (27.0)
Indian (Indian subcontinent)	0	0	0	1 (10.0)	1 (2.7)
Mixed Ethnicity	0	1 (11.1)	0	0	1 (2.7)

Demographic variable	Normal N=8	Mild N=9	Moderate N=10	Severe N=10	All subjects N=37
Other	5 (62.5)	6 (66.7)	9 (90.0)	4 (40.0)	24 (64.9)
Missing	0	0	1 (10.0)	0	1 (2.7)
Weight (kg)					
n	8	9	10	10	37
Mean	82.95	80.03	86.02	77.64	81.64
SD	14.774	10.860	23.041	20.437	17.793
Median	80.70	80.20	80.00	75.65	79.70
Minimum	65.0	58.7	63.2	50.9	50.9
Maximum	102.1	99.6	135.7	113.8	135.7
BMI (kg/m^2)					
n	8	9	10	10	37
Mean	27.88	25.77	26.99	26.62	26.79
SD	5.245	3.474	4.840	4.939	4.530
Median	28.07	26.04	26.76	25.36	26.48
Minimum	20.4	18.7	20.6	19.3	18.7
Maximum	34.5	30.4	34.5	35.9	35.9
Body surface area (m^2)					
n	8	9	10	10	37
Mean	2.004	1.987	2.061	1.917	1.992
SD	0.1884	0.1494	0.3215	0.2974	0.2504
Median	1.945	1.980	2.003	1.890	1.973
Minimum	1.80	1.70	1.74	1.48	1.48
Maximum	2.26	2.25	2.75	2.40	2.75

Demographic variable	Normal N=8	Mild N=9	Moderate N=10	Severe N=10	All subjects N=37

The baseline weight (kg) and baseline height (cm) were defined as the last non-missing assessment of weight and height before treatment.
BMI (kg/m^2) = weight (kg) / height (m)^2.
BSA (Gehan and George): BSA[m^2]=234.94*(height[cm]**0.422)*(weight[kg]**0.515)/10000.
BMI and BSA are calculated using the baseline weight and baseline height.

Child-Pugh classification and liver parameters at Screening visit, by hepatic group (Full analysis set)

Hepatic impairment classification	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)
Encephalopathy			
None	6 (66.7)	1 (10.0)	0
Grade 1-2	3 (33.3)	8 (80.0)	8 (80.0)
Grade 3-4	0	1 (10.0)	2 (20.0)
Ascites			
Absent	9 (100)	1 (10.0)	1 (10.0)
Slight	0	6 (60.0)	1 (10.0)
Moderate	0	3 (30.0)	8 (80.0)
Total Bilirubin (mg/dL)			
< 2.0	9 (100)	9 (90.0)	1 (10.0)
2-3	0	0	4 (40.0)
>3.0	0	1 (10.0)	5 (50.0)
Serum Albumin (g/dL)			
<2.8	0	0	1 (10.0)
2.8-3.5	0	4 (40.0)	9 (90.0)

Hepatic impairment classification	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)
>3.5	9 (100)	6 (60.0)	0
Prothrombin time (seconds over control)			
<4	9 (100)	10 (100)	6 (60.0)
4-6	0	0	3 (30.0)
>6	0	0	1 (10.0)
Score			
5	6 (66.7)	0	0
6	3 (33.3)	0	0
7	0	5 (50.0)	0
8	0	2 (20.0)	0
9	0	3 (30.0)	0
10	0	0	5 (50.0)
11	0	0	2 (20.0)
12	0	0	2 (20.0)
13	0	0	1 (10.0)

Mild: Score 5-6; Moderate: Score 7-9; Severe: Score 10-15.

Summary of Pharmacokinetics

Primary Outcome Results

Summary of statistical analysis of primary PK parameters (Cmax, AUClast, AUCinf, Tmax) for plasma ceritinib (Pharmacokinetic analysis set)

PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparisons	Group comparison Geo-mean ratio	Group comparison 90% CI Lower	Group comparison 90% CI Upper
Cmax (ng/mL)	Normal	8	130				
	Mild	8	183	Mild/Normal	1.40	0.829	2.37
	Moderate	7	118	Moderate/Normal	0.902	0.524	1.55
	Severe	7	100	Severe/Normal	0.767	0.445	1.32
AUClast (ng*hr/mL)	Normal	8	5940				
	Mild	8	7010	Mild/Normal	1.18	0.724	1.92
	Moderate	7	5990	Moderate/Normal	1.01	0.608	1.67
	Severe	7	9130	Severe/Normal	1.54	0.926	2.55
AUCinf (ng*hr/mL)	Normal	8	6090				
	Mild	8	7150	Mild/Normal	1.18	0.731	1.89
	Moderate	7	6240	Moderate/Normal	1.02	0.627	1.67
	Severe	7	10100	Severe/Normal	1.66	1.02	2.71
Tmax (hr)	Normal	8	8.00				
	Mild	8	7.00	Mild-Normal	-1.00		
	Moderate	7	4.00	Moderate-Normal	-4.00		
	Severe	7	4.00	Severe-Normal	-4.00		

Model is a linear model of the log-transformed PK parameters. Included in the model was hepatic group as a covariate. Results were back transformed to get adjusted geo-mean, GM ratio, and 90% CI.

n* = number of subjects with non-missing values.

For Tmax, median is presented under 'Adjusted geo-mean', difference of median under 'Geo-mean ratio'

Summary of primary PK parameters (AUCinf, AUClast, Cmax, Tmax) for ceritinib by hepatic group (Pharmacokinetic analysis set)

Hepatic group	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
Normal (N=8)	n	8	8	8	8
	Mean (SD)	7310 (4200)	7180 (4180)	164 (102)	N/A
	CV% mean	57.5	58.3	62.1	N/A
	Geo-mean	6090	5940	130	N/A
	CV% geo-mean	81.8	84.0	94.5	N/A
	Median	6180	6050	166	8.00
	[Min; Max]	[1380; 15200]	[1300; 15000]	[29.9; 304]	[6.00; 12.0]
Mild (N=8)	n	8	8	8	8
	Mean (SD)	7480 (2280)	7340 (2290)	196 (71.8)	N/A
	CV% mean	30.6	31.2	36.6	N/A
	Geo-mean	7150	7010	183	N/A
	CV% geo-mean	33.3	34.1	44.4	N/A
	Median	7260	7090	214	7.00
	[Min; Max]	[4060; 11000]	[3910; 10900]	[87.1; 306]	[3.00; 8.00]
Moderate (N=7)	n	7	7	7	7
	Mean (SD)	6530 (2070)	6280 (2010)	130 (62.7)	N/A
	CV% mean	31.8	32.1	48.3	N/A
	Geo-mean	6240	5990	118	N/A
	CV% geo-mean	34.3	34.9	51.6	N/A
	Median	6450	6240	114	4.00
	[Min; Max]	[3620; 9630]	[3500; 9100]	[52.1; 250]	[2.00; 8.00]
Severe (N=7)	n	7	7	7	7
	Mean (SD)	12400 (8570)	11300 (7900)	117 (62.4)	N/A
	CV% mean	69.3	69.8	53.2	N/A

Hepatic group	Statistics	AUCinf (ng*hr/mL)	AUClast (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
	Geo-mean	10100	9130	100	N/A
	CV% geo-mean	81.6	86.2	75.9	N/A
	Median	9350	8890	103	4.00
	[Min; Max]	[2900; 29600]	[2430; 27100]	[26.3; 228]	[3.00; 10.0]

n = number of subjects with evaluable PK data.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Secondary Outcome Results

Summary of secondary PK parameters (T1/2, CL/F, Vz/F) for plasma ceritinib by hepatic group (Pharmacokinetic analysis set)

Hepatic group	Statistics	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Normal (N=8)	n	8	8	8
	Mean (SD)	57.2 (14.1)	161 (159)	11700 (8210)
	CV% mean	24.6	98.3	70.4
	Geo-mean	55.7	123	9910
	CV% geo-mean	24.4	81.8	62.7
	Median	53.8	122	9340
	[Min; Max]	[38.9; 83.3]	[49.4; 544]	[5030; 30500]
Mild (N=8)	n	8	8	8
	Mean (SD)	61.6 (9.68)	110 (37.8)	9550 (2630)
	CV% mean	15.7	34.3	27.6
	Geo-mean	60.9	105	9210
	CV% geo-mean	15.6	33.3	29.9

Hepatic group	Statistics	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
	Median	59.1	104	9400
	[Min; Max]	[50.1; 75.2]	[68.4; 185]	[5810; 13400]
Moderate (N=7)	n	7	7	7
	Mean (SD)	89.4 (25.1)	126 (44.0)	16000 (6330)
	CV% mean	28.1	34.8	39.6
	Geo-mean	86.6	120	15000
	CV% geo-mean	26.9	34.3	38.4
	Median	73.7	116	14000
	[Min; Max]	[66.6; 125]	[77.8; 207]	[9460; 27200]
Severe (N=7)	n	7	7	7
	Mean (SD)	118 (29.2)	93.6 (77.0)	17000 (16300)
	CV% mean	24.7	82.3	96.1
	Geo-mean	115	74.3	12300
	CV% geo-mean	24.6	81.6	98.6
	Median	120	80.2	10800
	[Min; Max]	[83.9; 169]	[25.3; 259]	[4560; 50800]

n = number of subjects with evaluable PK data.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.

Summary of unbound fraction of ceritinib in plasma by hepatic group (Full analysis set)

Scheduled sampling	Statistics	Normal	Mild	Moderate	Severe

timepoint (hr)		N=8	N=9	N=10	N=10
6 hr	n	8	9	10	10
	m	8	9	10	10
	Mean (SD)	0.00401 (0.000472)	0.00454 (0.000755)	0.00485 (0.000820)	0.00526 (0.00115)
	CV% mean	11.8	16.6	16.9	21.8
	Geo-mean	0.004	0.0045	0.0048	0.0052
	CV% geo-mean	11.8	16.2	15.9	20
	Median	0.00392	0.00422	0.0047	0.00492
	[Min; Max]	[0.00336; 0.00472]	[0.00377; 0.00594]	[0.00406; 0.00668]	[0.00390; 0.00805]

n = number of subjects with non-missing values, m: number of non-zero concentrations.
CV% = coefficient of variation (%) = sd/mean*100, CV% geo-mean = sqrt (exp (variance for log transformed data)-1)*100.
Zero concentrations are considered as missing in geometric mean and CV% geo-mean calculations.

Summary of statistical analysis of plasma ceritinib PK parameters (Cmax, AUClast, AUCinf) expressed as unbound drug (Pharmacokinetic analysis set)

					Group comparison		
						90% CI	
PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparisons	Geo-mean ratio	Lower	Upper
Cmax,u (ng/mL)	Normal	8	0.52				
	Mild	8	0.839	Mild/Normal	1.61	0.969	2.69
	Moderate	7	0.559	Moderate/Normal	1.08	0.634	1.82
	Severe	7	0.499	Severe/Normal	0.96	0.566	1.63
AUClast,u (ng*hr/mL)	Normal	8	23.7				
	Mild	8	32.2	Mild/Normal	1.36	0.845	2.18

PK parameter (unit)	Hepatic group	n*	Adjusted geo-mean	Comparisons	Group comparison Geo-mean ratio	90% CI Lower	90% CI Upper
	Moderate	7	28.5	Moderate/Normal	1.2	0.736	1.96
	Severe	7	45.5	Severe/Normal	1.92	1.18	3.14
AUCinf,u (ng*hr/mL)	Normal	8	24.3				
	Mild	8	32.8	Mild/Normal	1.35	0.853	2.15
	Moderate	7	29.6	Moderate/Normal	1.22	0.758	1.97
	Severe	7	50.4	Severe/Normal	2.08	1.29	3.35

Model is a linear model of the log-transformed PK parameters. Included in the model was hepatic group as a covariate. Results were back transformed to get adjusted geo-mean, GM ratio, and 90% CI.

n* = number of subjects with non-missing values.

Summary of Safety

Safety Results

Adverse Events by System Organ Class

Adverse events, regardless of study drug relationship, by primary system organ class (Safety set)

Primary system organ class Preferred term	Normal N=8 n (%)	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)	All subjects N=37 n (%)
-Any primary system organ class					
Total	4 (50.0)	6 (66.7)	5 (50.0)	6 (60.0)	21 (56.8)
Gastrointestinal disorders	4 (50.0)	5 (55.6)	4 (40.0)	4 (40.0)	17 (45.9)

Primary system organ class Preferred term	Normal N=8 n (%)	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)	All subjects N=37 n (%)
General disorders and administration site conditions	0	0	1 (10.0)	0	1 (2.7)
Infections and infestations	0	0	0	1 (10.0)	1 (2.7)
Injury, poisoning and procedural complications	0	1 (11.1)	0	0	1 (2.7)
Investigations	0	0	1 (10.0)	0	1 (2.7)
Metabolism and nutrition disorders	0	0	0	1 (10.0)	1 (2.7)
Musculoskeletal and connective tissue disorders	1 (12.5)	0	0	0	1 (2.7)
Nervous system disorders	2 (25.0)	1 (11.1)	1 (10.0)	3 (30.0)	7 (18.9)
Respiratory, thoracic and mediastinal disorders	0	1 (11.1)	0	0	1 (2.7)
Skin and subcutaneous tissue disorders	1 (12.5)	0	0	0	1 (2.7)
Vascular disorders	0	1 (11.1)	0	0	1 (2.7)

Primary system organ classes are presented alphabetically.

A subject with multiple occurrences of an AE under one hepatic group is counted only once in the AE category for that group.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events, regardless of study drug relationship, with at least 5% incidence in any group, by preferred term and hepatic group (Safety set)

Primary system organ class Preferred term	Normal N=8 n (%)	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)	All subjects N=37 n (%)
Diarrhea	2 (25.0)	5 (55.6)	2 (20.0)	1 (10.0)	10 (27.0)

Primary system organ class Preferred term	Normal N=8 n (%)	Mild N=9 n (%)	Moderate N=10 n (%)	Severe N=10 n (%)	All subjects N=37 n (%)
Nausea	3 (37.5)	2 (22.2)	2 (20.0)	2 (20.0)	9 (24.3)
Abdominal pain	0	1 (11.1)	1 (10.0)	1 (10.0)	3 (8.1)
Vomiting	0	1 (11.1)	0	2 (20.0)	3 (8.1)
Constipation	0	0	1 (10.0)	0	1 (2.7)
Flatulence	0	0	1 (10.0)	0	1 (2.7)
Toothache	0	0	1 (10.0)	0	1 (2.7)
Pain	0	0	1 (10.0)	0	1 (2.7)
Urinary tract infection	0	0	0	1 (10.0)	1 (2.7)
Contusion	0	1 (11.1)	0	0	1 (2.7)
Laceration	0	1 (11.1)	0	0	1 (2.7)
Skin abrasion	0	1 (11.1)	0	0	1 (2.7)
Activated partial thromboplastin time prolonged	0	0	1 (10.0)	0	1 (2.7)
Decreased appetite	0	0	0	1 (10.0)	1 (2.7)
Pain in extremity	1 (12.5)	0	0	0	1 (2.7)
Headache	2 (25.0)	1 (11.1)	1 (10.0)	1 (10.0)	5 (13.5)
Hepatic encephalopathy	0	0	0	2 (20.0)	2 (5.4)
Epistaxis	0	1 (11.1)	0	0	1 (2.7)
Swelling face	1 (12.5)	0	0	0	1 (2.7)
Hypertension	0	1 (11.1)	0	0	1 (2.7)

Preferred terms are sorted within primary system organ class in descending frequency of AEs as reported in 'All subjects'.
A subject with multiple occurrences of an AE under one hepatic group is counted only once in the AE category for that group.

Serious Adverse Events and Deaths

There were no deaths reported in this study. Overall, two subjects (5.4%) had an SAE of grade 3 hepatic encephalopathy; both subjects were in the severe hepatic group and had pre-existing encephalopathy. One of these events was suspected to be related to study drug by the Investigator and led to study discontinuation. There were no other AEs leading to study drug discontinuation.

Other Relevant Findings

None

Conclusion:

The results of this PK study in subjects with normal hepatic function and subjects with varying degrees of hepatic impairment have shown that the systemic exposure of ceritinib after administration of a single oral 750 mg dose, as assessed by AUCinf, was increased in severe hepatic impairment group by approximately 66% relative to subjects with normal hepatic function, while the systemic exposures in moderate and mild hepatic groups were approximately similar to that of the normal hepatic group.

The treatment was generally well tolerated and consistent with the expected safety profile of ceritinib and the studied population; no new or unexpected safety concerns were identified in this study.

Date of Clinical Trial Report

15-May-2017