NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ceritinib (LDK378)

Trial Indication(s)

ALK rearranged (ALK-positive) metastatic non-small cell lung cancer (NSCLC)

Protocol Number

CLDK378A2112

Protocol Title

A multi-center, randomized open label study to assess the systemic exposure, effiacy, and safety of 450 mg ceritinib taken with a low-fat meal and 600 mg ceritinib taken with a low-fat meal as compared with that of 750 mg ceritinib taken in the fasted state in adult patients with ALK rearranged (ALK-positive) metastatic non-small cell lung cancer (NSCLC)

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase I

Study Start/End Dates

Study Start Date: April 2015 (Actual)

Primary Completion Date: June 2016 (Actual)
Study Completion Date: March 2020 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was an open-label, randomized, multi-center, parallel design, Phase I study in which the systemic exposure, efficacy and safety of ceritinib administered at 450 mg or 600 mg with a low-fat meal vs 750 mg in the fasted state was assessed in subjects with ALK+ NSCLC following multiple oral daily dosing of ceritinib. Subjects were randomized in a 1:1:1 ratio to once daily doses of oral ceritinib (450 mg following a low-fat meal, 600 mg following a low-fat meal or ceritinib 750 mg administered on an empty stomach). Randomization was stratified by brain metastases at Screening (presence or absence) and by prior treatment (prior crizotinib use with ALK+ determined by Fluorescent in situ hybridization (FISH); crizotinib-naïve but could be previously treated with other systemic anti-cancer therapy with ALK+ determined by FISH, or treatment-naïve subjects with ALK+ by IHC).

Centers

74 centers in 24 countries: United States(7), Belgium(1), Canada(4), Australia(2), Italy(11), Korea, Republic of(4), Czech Republic(1), Austria(2), Netherlands(1), Bulgaria(2), Germany(4), Spain(5), Lebanon(1), United Kingdom(2), Greece(2), Poland(3), Russia(1), Taiwan(3), Colombia(1), Thailand(3), India(5), Malaysia(2), Brazil(6), Turkey(1)

Objectives:

Primary objective: To assess the steady-state pharmacokinetics (PK) of 450 mg or 600 mg ceritinib taken daily with a low-fat meal as compared with that of 750 mg ceritinib taken daily in the fasted state in subjects with metastatic ALK+ NSCLC.

Key secondary objective:

To assess the antitumor activity of ceritinib, as measured by overall response rate (ORR) and duration of response (DOR) based on blinded independent review committee (BIRC) assessment per Response Evaluation Criteria In Solid Tumors (RECIST 1.1), of 450 mg or 600 mg ceritinib taken daily with a lowfat meal as compared with that of 750 mg ceritinib taken daily in the fasted state in treatment-naïve subjects with metastatic ALK+ NSCLC who have had ALK+ status determined prospectively at a Novartis central laboratory using the Ventana anti-ALK (D5F3) immunohistochemistry (IHC) test (Ventana IHC).

Other secondary objectives:

- To assess the safety profile (including frequency of subjects with gastrointestinal (GI) adverse events (AEs) by severity and overall) of 450 mg or 600 mg ceritinib taken daily with a low-fat meal as compared with that of 750 mg ceritinib taken daily in the fasted state in subjects with metastatic ALK+ NSCLC
- To assess the single-dose PK of 450 mg or 600 mg ceritinib taken with a low-fat meal as compared with that of 750 mg ceritinib taken in the fasted state in subjects with metastatic ALK+ NSCLC.
- To assess the antitumor activity of ceritinib as measured by:
    - ORR and DOR by Investigator assessment per RECIST 1.1
    - Time to response (TTR), disease control rate (DCR) and progression free survival (PFS) by BIRC and by Investigator assessment per RECIST 1.1 in treatment-naïve subjects with metastatic ALK-positive NSCLC who have had ALK+ status determined centrally by Ventana IHC following oral dosing of 450 mg or 600 mg ceritinib taken daily with a low-fat meal and 750 mg ceritinib taken daily in the fasted state
- To assess overall survival (OS) in treatment-naïve subjects with metastatic ALK-positive NSCLC who have had ALK-positive status determined centrally by Ventana IHC following oral dosing of 450 mg or 600 mg ceritinib taken daily with a low-fat meal and 750 mg ceritinib taken daily in the fasted state

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

Ceritinib was supplied as 150 mg hard gelatin capsules and was administered orally, once-daily, at 450 mg and 600

mg following a low-fat meal and 750 mg under fasted state.

Statistical Methods

Analysis Sets:

The Full Analysis Set (FAS): FAS comprised all subjects to whom study treatment was assigned by randomization. According to the intent to treat principle, subjects were analyzed according to the treatment they had been assigned to during the randomization procedure.

Safety Set: The Safety Set included all subjects who received at least one dose of ceritinib. Subjects were classified according to treatment received, where treatment received was defined as (i) the intended ceritinib dose, if it was received at least once, or (ii) the first ceritinib dose received when starting therapy with study medication, if intended dose was never received. Each subject was classified into and analyzed consistently within one (and only one) treatment arm.

Pharmacokinetic Analysis Set (PAS): The PAS consisted of all subjects who had received at least one dose of ceritinib and had at least one evaluable PK sample.

Primary endpoints and analyses:

The primary endpoints were plasma concentration of ceritinib and PK parameters, including but not limited to AUClast, AUC0-24h, Cmax, Tmax, Tlast, Racc, and CLss/F.

Secondary endpoints and analyses:

Efficacy: In this primary efficacy analysis, the key secondary endpoints and other secondary endpoints for efficacy were analyzed based on the treatment-naïve NSCLC subjects with ALK+ by IHC.

The key secondary endpoints were overall response rate (ORR) and duration of response (DOR) as assessed by BIRC per RECIST 1.1.

ORR was defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) as assessed by BIRC per RECIST 1.1. ORR was estimated and the exact binomial 95% CI was reported by treatment arm per BIRC assessment.

Among subjects with a confirmed response (PR or CR) per RECIST 1.1 per BIRC assessment, DOR (defined as the duration of time between the date of first documented response (CR or PR) and the date of first documented progression or death due to any cause) was analyzed by treatment arm by using the Kaplan-Meier method .

Other secondary endpoints for efficacy were ORR and DOR as assessed by investigator; Disease control rate (DCR), time to response (TTR), progression-free survival (PFS) as assessed by BIRC and Investigator; and overall survival (OS). ORR as assessed by Investigator, and DCR by BIRC and Investigator were estimated and the exact binomial 95% CI were reported by treatment arm, per RECIST 1.1. DOR by investigator, TTR and PFS by BIRC and investigator, and OS were analyzed by using the Kaplan-Meier method. TTR was also summarized by using descriptive statistics for subjects with confirmed CR or PR per RECIST 1.1.

Safety: All safety analyses were conducted based on the subjects in the Safety Set. All AEs were coded using Medical dictionary for regulatory activities (MedDRA) version 22.1 and were graded using CTCAE version 4.03. All AEs were summarized (frequency counts and percentages) by system organ class (SOC) and preferred term (PT): AEs regardless of study drug relationship, AEs suspected to be study drug related, all deaths, on-treatment deaths, SAEs regardless of study drug relationship, SAEs suspected to be study drug related, AEs leading to discontinuation of study drug, AEs requiring dose adjustment or study drug interruption, AEs requiring significant additional therapy. Laboratory abnormalities were graded per CTCAE version 4.03. AEs of special interest, and ECG data were also summarized.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

- Histologically or cytologically confirmed diagnosis of stage IIIB (and is not a candidate for definitive multimodality therapy) or IV ALK-positive NSCLC.
- Patients may have received one prior treatment regimen with crizotinib (all other ALK inhibitors are excluded).
- Patients may have received prior chemotherapy, biologic therapy, or other investigational agents. ALK inhibitors other than

crizotinib are excluded.
- Patient has a World Health Organization (WHO) performance status 0-2.

Exclusion Criteria:
- Prior treatment with an ALK inhibitor other than crizotinib.
- History of carcinomatous meningitis.
- Presence or history of a malignant disease other than an ALK-positive advanced tumor that has been diagnosed and/or required therapy within the past 3 years.
- Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months)
- Patient has history of interstitial lung disease or interstitial pneumonitis, including clinically significant radiation pneumonitis (i.e., affecting activities of daily living or requiring therapeutic intervention).
- Patient has other severe, acute, or chronic medical conditions
- Patient is currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants.

Participant Flow Table

Overall Study

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach	Total
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)	
Started	108	87[1]	111[2]	306

Completed	0	0	0	0
Not Completed	108	87	111	306
Physician Decision	3	7	8	18
Lost to Follow-up	0	0	1	1
Death	6	10	3	19
Adverse Event	7	3	10	20
Protocol Violation	0	2	0	2
Progressive disease	49	33	40	122
Entered into next trial or other patient programs	38	28	45	111
Subject/guardian decision	5	4	4	13

[1] 2 participants disc. prior to treatment
[2] 1 pt. in this arm received 600 mg dosing, fed.

Baseline Characteristics

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**	**Total**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule)	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule)	

	the morning immediately (within 30 minutes)following a low-fat meal.	administered in the morning immediately (within 30 minutes) following a low-fat meal.	administered in the morning on an empty stomach (i.e., fasted from food and drink except water)	
Number of Participants [units: participants]	108	87	111	306
Age, Customized (units: Participants) Count of Participants (Not Applicable)				
In utero	0	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0	0
Newborns (0-27 days)	0	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0	0
Children (2-11 years)	0	0	0	0
Adolescents (12-17 years)	0	0	0	0
Adults (18-64 years)	88	64	92	244
From 65-84 years	18	23	18	59
85 years and over	2	0	1	3
Age Continuous[1] (units: years) Median (Full Range)				
	54.0 (26 to 87)	56.0 (21 to 82)	52.0 (22 to 87)	54.0 (21 to 87)

Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	65	39	51	155
Male	43	48	60	151

[1] FAS

Primary Outcome Result(s)

Plasma concentration of ceritinib at steady state - AUC0-24h

(Time Frame: Day 22)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	36	30	31

Plasma concentration of ceritinib at steady state - AUC0-24h (units: ng/hr/mL) Mean ± Standard Deviation			
Day 22	20400 ± 8040	24400 ± 9750	19900 ± 6880

Statistical Analysis

Groups	ceritinib 450 mg with a low-fat meal, ceritinib 750 mg on an empty stomach
Other geo mean ratio	1.04
90 % Confidence Interval 2-Sided	0.869 to 1.24

Statistical Analysis

Groups	ceritinib 600 mg with a low-fat meal, ceritinib 750 mg on an empty stomach
Other geo mean ratio	1.24
90 % Confidence Interval 2-Sided	1.03 to 1.49

Plasma concentration of ceritinib at steady state steady state – Cmax

(Time Frame: Day 22)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an**

			empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	36	30	31
Plasma concentration of ceritinib at steady state steady state – Cmax (units: ng/mL) Mean ± Standard Deviation			
Day 22	987 ± 384	1200 ± 461	971 ± 340

Statistical Analysis

Groups	ceritinib 450 mg with a low-fat meal, ceritinib 750 mg on an empty stomach	day 22
Other geo mean ratio	1.03	
90 % Confidence Interval 2-Sided	0.865 to 1.22	

Statistical Analysis

Groups	ceritinib 600 mg with a low-fat meal, ceritinib 750 mg on an empty stomach
Other geo mean ratio	1.25
90 % Confidence Interval 2-Sided	1.04 to 1.49

Plasma concentration of ceritinib at steady state - Tlast

(Time Frame: Day 22)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	36	30	31
Plasma concentration of ceritinib at steady state - Tlast (units: hour)			

Mean ± Standard Deviation			
Day 22	24.0 ± 0.399	23.8 ± 0.373	24.0 ± 0.440

Plasma concentration of ceritinib at steady state - Tmax

(Time Frame: Day 22)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	36	30	31
Plasma concentration of ceritinib at steady state - Tmax (units: hour) Median (Full Range)			
Day 22	6.03 (2.00 to 24.1)	6.00 (0 to 24.0)	5.90 (0 to 24.0)

Secondary Outcome Result(s)

Overall response rate (ORR) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full Analysis Set)

(Time Frame: Tumor assessments every 6 weeks until cycle 9. At least every 12 weeks thereafter until progressive disease)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Overall response rate (ORR) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
	78.1 (66.9 to 86.9)	72.5 (58.3 to 84.1)	75.7 (64.3 to 84.9)

Overall response rate (ORR) per investigator assessment, by treatment arm (Full Analysis Set)

(Time Frame: Tumor assessments every 6 weeks until cycle 9. At least every 12 weeks thereafter until progressive disease.)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Overall response rate (ORR) per investigator assessment, by treatment arm (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
	75.3 (63.9 to 84.7)	78.4 (64.7 to 88.7)	78.4 (67.3 to 87.1)

Duration of response (DOR) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full Analysis Set)

(Time Frame: Tumor assessments every 6 weeks until cycle 9. At least every 12 weeks thereafter until progressive disease.)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	57	37	56
Duration of response (DOR) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
% Event-free probability estimates - 3 months	100 (100 to 100)	89.2 (73.7 to 95.8)	91.1 (79.9 to 96.2)
% Event-free probability estimates - 6 months	89.1 (77.3 to 94.9)	83.8 (67.4 to 92.4)	80.4 (67.3 to 88.6)
% Event-free probability estimates - 9 months	78.0 (64.4 to 86.8)	78.3 (61.2 to 88.5)	71.3 (57.5 to 81.3)
% Event-free probability estimates - 12 months	70.5 (56.5 to 80.8)	75.5 (58.2 to 86.4)	65.6 (51.4 to 76.5)
% Event-free probability estimates - 15 months	62.5 (48.1 to 74.0)	72.7 (55.2 to 84.3)	59.5 (45.2 to 71.3)

% Event-free probability estimates - 18 months	54.2 (39.7 to 66.6)	66.9 (49.0 to 79.7)	45.2 (30.7 to 58.6)
% Event-free probability estimates - 21 months	54.2 (39.7 to 66.6)	57.1 (39.0 to 71.7)	42.4 (28.0 to 56.0)
% Event-free probability estimates - 24 months	54.2 (39.7 to 66.6)	57.1 (39.0 to 71.7)	42.4 (28.0 to 56.0)
% Event-free probability estimates - 27 months	54.2 (39.7 to 66.6)	57.1 (39.0 to 71.7)	42.4 (28.0 to 56.0)
% Event-free probability estimates - 30 months	54.2 (39.7 to 66.6)	49.0 (27.7 to 67.3)	42.4 (28.0 to 56.0)
% Event-free probability estimates - 33 months	54.2 (39.7 to 66.6)	49.0 (27.7 to 67.3)	42.4 (28.0 to 56.0)
% Event-free probability estimates - 36 months	54.2 (39.7 to 66.6)	NA (NA to NA)[123456]	42.4 (28.0 to 56.0)
% Event-free probability estimates - 39 months	54.2 (39.7 to 66.6)	NA (NA to NA)[123456]	NA (NA to NA)[123456]
Median	NA (14.5 to NA)[123456]	29.0 (18.0 to NA)[123456]	17.9 (12.5 to NA)[123456]

[1] Not Evaluable
[2] Not Evaluable
[3] Not Evaluable
[4] Not Evaluable
[5] Not Evaluable
[6] Not Evaluable

Duration of response (DOR) by Investigator Assessment, per treatment arm (Full Analysis Set)

(Time Frame: Tumor assessments every 6 weeks until cycle 9. At least every 12 weeks thereafter until progressive disease.)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach

Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	55	40	58
Duration of response (DOR) by Investigator Assessment, per treatment arm (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
% Event-free probability estimates - 3 months	98.2 (87.8 to 99.7)	95.0 (81.5 to 98.7)	96.6 (86.9 to 99.1)
% Event-free probability estimates - 6 months	89.1 (77.3 to 94.9)	85.0 (69.6 to 93.0)	93.1 (82.7 to 97.4)
% Event-free probability estimates - 9 months	83.6 (70.9 to 91.1)	77.5 (61.2 to 87.6)	75.8 (62.6 to 84.9)
% Event-free probability estimates - 12 months	74.5 (60.8 to 84.1)	75.0 (58.5 to 85.7)	67.0 (53.2 to 77.5)
% Event-free probability estimates - 15 months	70.8 (56.8 to 81.0)	70.0 (53.3 to 81.7)	65.1 (51.2 to 75.9)
% Event-free probability estimates - 18 months	62.2 (47.6 to 73.8)	57.5 (40.8 to 71.0)	56.2 (41.8 to 68.3)
% Event-free probability estimates - 21 months	57.6 (42.8 to 69.9)	54.6 (38.0 to 68.6)	56.2 (41.8 to 68.3)

% Event-free probability estimates - 24 months	57.6 (42.8 to 69.9)	51.0 (34.1 to 65.6)	52.7 (37.6 to 65.7)
% Event-free probability estimates - 27 months	57.6 (42.8 to 69.9)	51.0 (34.1 to 65.6)	43.9 (27.5 to 59.2)
% Event-free probability estimates - 30 months	57.6 (42.8 to 69.9)	44.6 (26.2 to 61.5)	38.4 (21.5 to 55.1)
% Event-free probability estimates - 33 months	51.8 (34.6 to 66.6)	44.6 (26.2 to 61.5)	38.4 (21.5 to 55.1)
% Event-free probability estimates - 36 months	51.8 (34.6 to 66.6)	44.6 (26.2 to 61.5)	38.4 (21.5 to 55.1)
% Event-free probability estimates - 39 months	51.8 (34.6 to 66.6)	NA (NA to NA)[12345]	NA (NA to NA)[12345]
Median	NA (17.8 to NA)[12345]	29.0 (15.2 to NA)[12345]	25.0 (15.2 to NA)[12345]

[1] Not Evaluable
[2] Not Evaluable
[3] Not Evaluable
[4] Not Evaluable
[5] Not Evaluable

Overall Survival (OS) (Full Analysis Set)

(Time Frame: Every 3 months until progressive disease)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning

	(within 30 minutes)following a low-fat meal.	immediately (within 30 minutes) following a low-fat meal.	on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Overall Survival (OS) (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
% Event-free probability estimates at 3 months	97.2 (89.4 to 99.3)	96.0 (84.8 to 99.0)	95.9 (88.0 to 98.7)
% Event-free probability estimates at 6 months	93.1 (84.2 to 97.1)	89.6 (76.7 to 95.5)	91.8 (82.7 to 96.2)
% Event-free probability estimates at 9 months	88.9 (79.0 to 94.3)	89.6 (76.7 to 95.5)	91.8 (82.7 to 96.2)
% Event-free probability estimates at 12 months	87.5 (77.4 to 93.3)	87.4 (74.1 to 94.1)	89.0 (79.2 to 94.3)
% Event-free probability estimates at 15 months	83.3 (72.5 to 90.2)	85.2 (71.5 to 92.7)	86.1 (75.6 to 92.3)
% Event-free probability estimates at 18 Months	82.0 (71.0 to 89.1)	85.2 (71.5 to 92.7)	84.5 (73.7 to 91.1)
% Event-free probability estimates at 21 months	80.3 (69.0 to 87.8)	80.7 (66.1 to 89.5)	79.2 (67.3 to 87.2)
% Event-free probability estimates at 24 months	76.5 (64.4 to 85.0)	75.7 (60.3 to 85.8)	79.2 (67.3 to 87.2)
% Event-free probability estimates at 27 months	76.5 (64.4 to 85.0)	72.9 (57.0 to 83.7)	79.2 (67.3 to 87.2)
% Event-free probability estimates at 30 months	76.5 (64.4 to 85.0)	72.9 (57.0 to 83.7)	75.8 (62.0 to 85.2)
% Event-free probability estimates at 33 months	76.5 (64.4 to 85.0)	72.9 (57.0 to 83.7)	60.3 (42.0 to 74.4)

% Event-free probability estimates at 36 months	76.5 (64.4 to 85.0)	67.7 (49.2 to 80.7)	54.8 (35.3 to 70.6)
% Event-free probability estimates at 39 months	76.5 (64.4 to 85.0)	54.2 (25.2 to 76.1)	54.8 (35.3 to 70.6)
Median	NA (40.1 to NA)[123]	NA (33.6 to NA)[123]	NA (32.0 to NA)[123]

[1] Not Evaluable
[2] Not Evaluable
[3] Not Evaluable

Time to Response (TTR) as assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full analysis set)

(Time Frame: up tp week 70)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	57	37	56

Time to Response (TTR) as assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full analysis set)

(units: weeks)

Time to response categories weeks - n - < 6	19	10	22
Time to response categories - n - 6 - < 12weeks	33	23	25
Time to response categories - n - 12 - < 18weeks	4	2	7
Time to response categories - n - 18 - < 24weeks	0	2	1
Time to response categories - n - 24 - < 30weeks	0	0	0
Time to response categories - n - 30 - < 36weeks	0	0	0
Time to response categories - n - 36 - < 42weeks	0	0	0
Time to response categories - n - 42 - < 48weeks	0	0	0
Time to response categories - n - >= 48weeks	1	0	1
Time to response (weeks) - N	57	37	56
Time to response (weeks) - Mean	7.92	7.47	7.86
Time to response (weeks) - SD	8.590	3.516	6.175

Time to response (weeks) - Median	6.14	6.29	6.14
Time to response (weeks) - Minimum	5.0	5.3	4.7
Time to response (weeks) - Maximum	69.3	18.3	48.0

Time to Response (TTR) per investigator assessment, by treatment arm (Full analysis set)

(Time Frame: up to week 72)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	55	40	58
Time to Response (TTR) per investigator assessment, by treatment arm (Full analysis set) (units: weeks)			
Time to response categories - n - < 6weeks	18	12	22

Time to response categories - n - 6 - < 12weeks	31	20	31
Time to response categories - n - 12 - < 18weeks	3	6	2
Time to response categories - n - 18 - < 24weeks	0	1	3
Time to response categories - n - 24 - < 30weeks	1	1	0
Time to response categories - n - 30 - < 36weeks	1	0	0
Time to response categories - n - 36 - < 42weeks	0	0	0
Time to response categories - n - 42 - < 48weeks	0	0	0
Time to response categories - n - >= 48weeks	1	0	0
Time to response weeks - N	55	40	58
Time to response weeks - Mean	8.59	8.15	6.98
Time to response weeks - SD	9.883	4.238	3.187
Time to response weeks - Median	6.14	6.29	6.14
Time to response weeks - Mimimum	5.0	5.1	4.7

Time to response weeks - Maximum	71.4	24.0	18.6

Progression-Free Survival (PFS) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full Analysis Set)

(Time Frame: every 3 months, up to month 39)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Progression-Free Survival (PFS) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
% Event-free probability estimates - 3 months	88.7 (78.7 to 94.2)	83.6 (69.8 to 91.4)	89.0 (79.3 to 94.4)
% Event-free probability estimates - 6 months	82.9 (71.9 to 89.9)	68.6 (53.3 to 79.7)	73.7 (62.0 to 82.4)

% Event-free probability estimates - 9 months	69.6 (57.3 to 79.0)	66.3 (51.0 to 77.9)	61.2 (49.0 to 71.4)
% Event-free probability estimates - 12 months	66.7 (54.2 to 76.5)	61.9 (46.5 to 74.1)	56.8 (44.5 to 67.3)
% Event-free probability estimates - 15 months	60.6 (48.0 to 71.1)	57.5 (42.1 to 70.2)	49.0 (36.8 to 60.1)
% Event-free probability estimates - 18 months	49.4 (36.9 to 60.8)	55.2 (39.9 to 68.1)	43.8 (31.8 to 55.2)
% Event-free probability estimates - 21 months	47.5 (34.9 to 59.0)	50.2 (34.9 to 63.6)	38.3 (26.5 to 50.0)
% Event-free probability estimates - 24 months	47.5 (34.9 to 59.0)	44.9 (29.8 to 58.8)	38.3 (26.5 to 50.0)
% Event-free probability estimates - 27 months	47.5 (34.9 to 59.0)	44.9 (29.8 to 58.8)	38.3 (26.5 to 50.0)
% Event-free probability estimates - 30 months	47.5 (34.9 to 59.0)	44.9 (29.8 to 58.8)	38.3 (26.5 to 50.0)
% Event-free probability estimates - 33 months	47.5 (34.9 to 59.0)	40.4 (24.8 to 55.4)	31.9 (17.7 to 47.0)
% Event-free probability estimates - 36 months	47.5 (34.9 to 59.0)	NA (NA to NA)[1234]	31.9 (17.7 to 47.0)
% Event-free probability estimates - 39 months	47.5 (34.9 to 59.0)	NA (NA to NA)[1234]	31.9 (17.7 to 47.0)
Median	17.6 (13.7 to NA)[1234]	21.9 (10.1 to NA)[1234]	15.0 (8.4 to 19.4)

[1] Not Evaluable
[2] Not Evaluable
[3] Not Evaluable
[4] Not Evaluable

Progression-Free Survival (PFS) by Investigator Assessment, by treatment arm (Full Analysis Set)

(Time Frame: every 3 months, up to 39 months)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Progression-Free Survival (PFS) by Investigator Assessment, by treatment arm (Full Analysis Set) (units: Percentage) Number (95% Confidence Interval)			
% Event-free probability estimates - 3 months	87.4 (77.1 to 93.2)	89.8 (77.2 to 95.6)	94.5 (86.0 to 97.9)
% Event-free probability estimates - 6 months	77.5 (65.9 to 85.6)	73.1 (58.2 to 83.4)	86.0 (75.6 to 92.2)
% Event-free probability estimates - 9 months	70.5 (58.4 to 79.6)	66.8 (51.6 to 78.2)	73.3 (61.4 to 82.1)
% Event-free probability estimates - 12 months	64.8 (52.5 to 74.7)	64.7 (49.5 to 76.4)	64.7 (52.4 to 74.6)
% Event-free probability estimates - 15 months	63.4 (51.1 to 73.4)	60.5 (45.4 to 72.7)	61.8 (49.5 to 72.0)

% Event-free probability estimates - 18 months	56.0 (43.6 to 66.7)	52.2 (37.3 to 65.1)	55.2 (42.6 to 66.1)
% Event-free probability estimates - 21 months	45.9 (33.6 to 57.3)	47.5 (32.7 to 60.8)	51.4 (38.7 to 62.7)
% Event-free probability estimates - 24 months	45.9 (33.6 to 57.3)	41.9 (27.3 to 55.8)	49.0 (36.1 to 60.7)
% Event-free probability estimates - 27 months	45.9 (33.6 to 57.3)	41.9 (27.3 to 55.8)	42.5 (28.7 to 55.6)
% Event-free probability estimates - 30 months	45.9 (33.6 to 57.3)	41.9 (27.3 to 55.8)	39.2 (25.3 to 52.8)
% Event-free probability estimates - 33 months	42.0 (28.8 to 54.7)	38.1 (23.4 to 52.6)	27.9 (12.7 to 45.3)
% Event-free probability estimates - 36 months	42.0 (28.8 to 54.7)	38.1 (23.4 to 52.6)	27.9 (12.7 to 45.3)
% Event-free probability estimates - 39 months	42.0 (28.8 to 54.7)	NA (NA to NA)[123]	27.9 (12.7 to 45.3)
Median	19.4 (15.3 to NA)[123]	19.4 (10.1 to NA)[123]	22.1 (12.7 to 30.4)

[1] Not Evaluable
[2] Not Evaluable
[3] Not Evaluable

Disease Control Rate (DCR) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full analysis set)

(Time Frame: Tumor assessments every 6 weeks until cycle 9. At least every 12 weeks thereafter until progressive disease)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150	Oral ceritinib QD (21 days/ cycle) at a dose of 600	Oral ceritinib QD (21 days/ cycle) at a dose of 750

	mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Disease Control Rate (DCR) as Assessed by the Blinded Independent Review Committee (BIRC), by treatment arm (Full analysis set) (units: Percentage) Number (95% Confidence Interval)			
	90.4 (81.2 to 96.1)	94.1 (83.8 to 98.8)	90.5 (81.5 to 96.1)

Disease Control Rate (DCR) as Assessed by Investigator, by treatment arm (Full analysis set)

(Time Frame: Tumor assessments every 6 weeks until cycle 9. At least every 12 weeks thereafter until progressive disease)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered

	immediately (within 30 minutes)following a low-fat meal.	in the morning immediately (within 30 minutes) following a low-fat meal.	in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	73	51	74
Disease Control Rate (DCR) as Assessed by Investigator, by treatment arm (Full analysis set) (units: Percentage) Number (95% Confidence Interval)			
	94.5 (86.6 to 98.5)	94.1 (83.8 to 98.8)	93.2 (84.9 to 97.8)

Plasma concentration of ceritinib - single-dose - AUC0-24h

(Time Frame: Day 1)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes)	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from

		following a low-fat meal.	food and drink except water)
Number of Participants Analyzed [units: participants]	43	38	37
Plasma concentration of ceritinib - single-dose - AUC0-24h (units: ng/hr/mL) Mean ± Standard Deviation			
	4010 ± 2850	4180 ± 2160	3700 ± 2580

Plasma concentration of ceritinib - single-dose - Cmax

(Time Frame: Day 1)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	43	38	37

Plasma concentration of ceritinib - single-dose - Cmax (units: ng/mL) Mean ± Standard Deviation			
	239 ± 141	253 ± 131	226 ± 162

Statistical Analysis

Groups	ceritinib 450 mg with a low-fat meal, ceritinib 750 mg on an empty stomach
Other geo mean ratio	1.19
90 % Confidence Interval 2-Sided	0.916 to 1.56

Statistical Analysis

Groups	ceritinib 600 mg with a low-fat meal, ceritinib 750 mg on an empty stomach
Other geo mean ratio	1.17
90 % Confidence Interval 2-Sided	0.894 to 1.54

Plasma concentration of ceritinib - single dose - Tlast

(Time Frame: Day 1)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an**

			empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	43	38	37
Plasma concentration of ceritinib - single dose - Tlast (units: hour) Mean ± Standard Deviation			
	23.9 ± 0.395	24.0 ± 0.301	23.9 ± 0.358

Plasma concentration of ceritinib - single-dose - Tmax

(Time Frame: Day 1)

	ceritinib 450 mg with a low-fat meal	ceritinib 600 mg with a low-fat meal	ceritinib 750 mg on an empty stomach
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150	Oral ceritinib QD (21 days/ cycle) at a dose of 600	Oral ceritinib QD (21 days/ cycle) at a dose of 750

	mg/capsule) administered in the morning immediately (within 30 minutes)following a low-fat meal.	mg (4×150 mg/capsule) administered in the morning immediately (within 30 minutes) following a low-fat meal.	mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e., fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	43	38	37
Plasma concentration of ceritinib - single-dose - Tmax (units: hour) Median (Full Range)			
	6.00 (4.00 to 24.3)	6.00 (3.92 to 24.0)	6.00 (2.00 to 23.8)

Safety profile

(Time Frame: The primary analysis will be based on data from all patients, up to the time at which all randomized patients have completed at least 12 weeks of ceritinib treatment or have discontinued study treatment, whichever is earlier.)

	ceritinib 450 mg with a low-fat meal	**ceritinib 600 mg with a low-fat meal**	**ceritinib 750 mg on an empty stomach**
Arm/Group Description	Oral ceritinib QD (21 days/ cycle) at a dose of 450 mg (3×150 mg/capsule) administered in the morning immediately (within 30	Oral ceritinib QD (21 days/ cycle) at a dose of 600 mg (4×150 mg/capsule) administered in the morning immediately (within 30	Oral ceritinib QD (21 days/ cycle) at a dose of 750 mg (5×150 mg/capsule) administered in the morning on an empty stomach (i.e.,

	minutes)following a low-fat meal.	minutes) following a low-fat meal.	fasted from food and drink except water)
Number of Participants Analyzed [units: participants]	108	86	110
Safety profile (units: number of participants)			
All deaths (on-treatment and off treatment)	38	35	38
On-treatment deaths	11	13	8
Adverse Events (AEs)	108	84	109
AEs Suspected to be study drug related	96	80	102
Serious adverse events (SAEs)	35	38	34
SAEs Suspected to be study drug related	8	13	12
AEs leading to study drug discontinuation	9	7	10
AEs requiring study drug interruption	60	60	77
AEs requiring dose adjustment	26	53	65
AEs requiring dose adjustment or interruption	61	67	85
AEs requiring significant additional therapy	104	75	104

Safety Results

All-Cause Mortality

	Ceritinib 450 mg fed N = 108	Ceritinib 600 mg fed N = 86	Ceritinib 750 mg fasted N = 110
Arm/Group Description	Ceritinib 450 mg fed	Ceritinib 600 mg fed	Ceritinib 750 mg fasted
Total participants affected	11 (10.19%)	13 (15.12%)	8 (7.27%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 232 weeks.
Source Vocabulary for Table Default	MedDRA 22.1
Assessment Type for Table Default	Systematic Assessment

	Ceritinib 450 mg fed N = 108	Ceritinib 600 mg fed N = 86	Ceritinib 750 mg fasted N = 110
Arm/Group Description	Ceritinib 450 mg fed	Ceritinib 600 mg fed	Ceritinib 750 mg fasted
Total participants affected	35 (32.41%)	38 (44.19%)	34 (30.91%)

Blood and lymphatic system disorders			
Febrile bone marrow aplasia	1 (0.93%)	0 (0.00%)	0 (0.00%)
Lymphadenopathy	0 (0.00%)	0 (0.00%)	1 (0.91%)
Cardiac disorders			
Atrial fibrillation	1 (0.93%)	0 (0.00%)	0 (0.00%)
Cardiac failure congestive	1 (0.93%)	0 (0.00%)	0 (0.00%)
Pericardial effusion	1 (0.93%)	2 (2.33%)	1 (0.91%)
Pericarditis	0 (0.00%)	0 (0.00%)	1 (0.91%)
Pleuropericarditis	1 (0.93%)	0 (0.00%)	0 (0.00%)
Supraventricular tachycardia	2 (1.85%)	0 (0.00%)	0 (0.00%)
Eye disorders			
Visual impairment	0 (0.00%)	1 (1.16%)	0 (0.00%)
Gastrointestinal disorders			
Abdominal pain	0 (0.00%)	1 (1.16%)	1 (0.91%)
Abdominal pain upper	0 (0.00%)	1 (1.16%)	0 (0.00%)
Diarrhoea	0 (0.00%)	0 (0.00%)	4 (3.64%)
Duodenal obstruction	0 (0.00%)	1 (1.16%)	0 (0.00%)
Incarcerated inguinal hernia	0 (0.00%)	1 (1.16%)	0 (0.00%)
Intestinal ischaemia	1 (0.93%)	0 (0.00%)	0 (0.00%)
Intestinal perforation	1 (0.93%)	0 (0.00%)	0 (0.00%)
Nausea	0 (0.00%)	1 (1.16%)	1 (0.91%)

Pancreatitis	1 (0.93%)	0 (0.00%)	1 (0.91%)
Stomatitis	1 (0.93%)	0 (0.00%)	0 (0.00%)
Vomiting	0 (0.00%)	1 (1.16%)	0 (0.00%)
General disorders and administration site conditions			
Asthenia	0 (0.00%)	4 (4.65%)	0 (0.00%)
Atrophy	0 (0.00%)	1 (1.16%)	0 (0.00%)
Fatigue	0 (0.00%)	1 (1.16%)	2 (1.82%)
General physical health deterioration	1 (0.93%)	0 (0.00%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	1 (1.16%)	0 (0.00%)
Pyrexia	2 (1.85%)	1 (1.16%)	0 (0.00%)
Hepatobiliary disorders			
Cholangitis	1 (0.93%)	0 (0.00%)	0 (0.00%)
Cholecystitis	0 (0.00%)	1 (1.16%)	0 (0.00%)
Cholecystitis chronic	1 (0.93%)	0 (0.00%)	0 (0.00%)
Drug-induced liver injury	0 (0.00%)	0 (0.00%)	1 (0.91%)
Hepatitis acute	0 (0.00%)	0 (0.00%)	1 (0.91%)
Hypertransaminasaemia	0 (0.00%)	1 (1.16%)	0 (0.00%)
Liver disorder	0 (0.00%)	1 (1.16%)	0 (0.00%)
Immune system disorders			
Contrast media reaction	0 (0.00%)	0 (0.00%)	1 (0.91%)
Infections and infestations			
Abdominal abscess	1 (0.93%)	0 (0.00%)	0 (0.00%)

Appendicitis	0 (0.00%)	0 (0.00%)	1 (0.91%)
Bronchitis	1 (0.93%)	0 (0.00%)	0 (0.00%)
Bursitis infective	1 (0.93%)	0 (0.00%)	0 (0.00%)
Cutaneous tuberculosis	1 (0.93%)	0 (0.00%)	0 (0.00%)
Dengue fever	1 (0.93%)	0 (0.00%)	0 (0.00%)
Device related infection	0 (0.00%)	1 (1.16%)	0 (0.00%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (0.91%)
Infected fistula	0 (0.00%)	0 (0.00%)	1 (0.91%)
Infection	0 (0.00%)	1 (1.16%)	0 (0.00%)
Pneumonia	4 (3.70%)	1 (1.16%)	3 (2.73%)
Pneumonia bacterial	0 (0.00%)	1 (1.16%)	0 (0.00%)
Pulmonary tuberculosis	0 (0.00%)	1 (1.16%)	0 (0.00%)
Sepsis	3 (2.78%)	0 (0.00%)	1 (0.91%)
Streptococcal sepsis	0 (0.00%)	1 (1.16%)	0 (0.00%)
Systemic infection	1 (0.93%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	1 (1.16%)	0 (0.00%)
Urosepsis	0 (0.00%)	1 (1.16%)	0 (0.00%)
Injury, poisoning and procedural complications			
Contusion	1 (0.93%)	0 (0.00%)	0 (0.00%)
Femur fracture	0 (0.00%)	0 (0.00%)	1 (0.91%)
Hand fracture	0 (0.00%)	0 (0.00%)	1 (0.91%)
Post procedural haemorrhage	0 (0.00%)	1 (1.16%)	0 (0.00%)
Radiation oesophagitis	0 (0.00%)	0 (0.00%)	1 (0.91%)
Wound secretion	0 (0.00%)	0 (0.00%)	1 (0.91%)

Investigations			
Alanine aminotransferase increased	1 (0.93%)	2 (2.33%)	1 (0.91%)
Aspartate aminotransferase increased	1 (0.93%)	2 (2.33%)	2 (1.82%)
Blood alkaline phosphatase increased	0 (0.00%)	1 (1.16%)	0 (0.00%)
Blood creatine phosphokinase increased	0 (0.00%)	0 (0.00%)	1 (0.91%)
Gamma-glutamyltransferase increased	0 (0.00%)	2 (2.33%)	0 (0.00%)
Lipase increased	0 (0.00%)	0 (0.00%)	1 (0.91%)
Platelet count decreased	1 (0.93%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Cachexia	1 (0.93%)	0 (0.00%)	0 (0.00%)
Decreased appetite	0 (0.00%)	2 (2.33%)	1 (0.91%)
Hyperglycaemia	2 (1.85%)	1 (1.16%)	4 (3.64%)
Hypocalcaemia	0 (0.00%)	0 (0.00%)	1 (0.91%)
Hypokalaemia	1 (0.93%)	1 (1.16%)	0 (0.00%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	1 (0.91%)
Musculoskeletal and connective tissue disorders			
Back pain	2 (1.85%)	0 (0.00%)	0 (0.00%)
Muscular weakness	1 (0.93%)	0 (0.00%)	0 (0.00%)

Musculoskeletal pain	0 (0.00%)	1 (1.16%)	0 (0.00%)
Myalgia	0 (0.00%)	1 (1.16%)	0 (0.00%)
Osteonecrosis of jaw	0 (0.00%)	1 (1.16%)	0 (0.00%)
Pain in extremity	0 (0.00%)	1 (1.16%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain	0 (0.00%)	1 (1.16%)	0 (0.00%)
Malignant melanoma	1 (0.93%)	0 (0.00%)	0 (0.00%)
Metastases to meninges	1 (0.93%)	0 (0.00%)	0 (0.00%)
Metastases to spine	0 (0.00%)	1 (1.16%)	0 (0.00%)
Tumour haemorrhage	0 (0.00%)	1 (1.16%)	0 (0.00%)
Uterine leiomyoma	1 (0.93%)	0 (0.00%)	0 (0.00%)
Nervous system disorders			
Balance disorder	0 (0.00%)	1 (1.16%)	0 (0.00%)
Brain oedema	1 (0.93%)	1 (1.16%)	0 (0.00%)
Cerebral haemorrhage	1 (0.93%)	0 (0.00%)	1 (0.91%)
Cerebrovascular accident	1 (0.93%)	0 (0.00%)	1 (0.91%)
Depressed level of consciousness	0 (0.00%)	0 (0.00%)	1 (0.91%)
Dizziness	0 (0.00%)	1 (1.16%)	1 (0.91%)
Dysaesthesia	1 (0.93%)	0 (0.00%)	0 (0.00%)
Dysarthria	0 (0.00%)	1 (1.16%)	1 (0.91%)
Epilepsy	1 (0.93%)	0 (0.00%)	1 (0.91%)
Headache	1 (0.93%)	2 (2.33%)	1 (0.91%)

Intracranial pressure increased	0 (0.00%)	0 (0.00%)	1 (0.91%)
Monoplegia	0 (0.00%)	1 (1.16%)	0 (0.00%)
Normal pressure hydrocephalus	0 (0.00%)	1 (1.16%)	0 (0.00%)
Seizure	1 (0.93%)	1 (1.16%)	3 (2.73%)
Somnolence	0 (0.00%)	0 (0.00%)	1 (0.91%)
Syncope	0 (0.00%)	1 (1.16%)	0 (0.00%)
Psychiatric disorders			
Confusional state	0 (0.00%)	2 (2.33%)	2 (1.82%)
Depression	0 (0.00%)	1 (1.16%)	0 (0.00%)
Suicide attempt	1 (0.93%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders			
Acute kidney injury	2 (1.85%)	0 (0.00%)	0 (0.00%)
Nephrolithiasis	1 (0.93%)	0 (0.00%)	0 (0.00%)
Renal cyst	0 (0.00%)	0 (0.00%)	1 (0.91%)
Renal impairment	0 (0.00%)	0 (0.00%)	1 (0.91%)
Urinary retention	0 (0.00%)	1 (1.16%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis	0 (0.00%)	0 (0.00%)	1 (0.91%)
Chronic obstructive pulmonary disease	0 (0.00%)	1 (1.16%)	0 (0.00%)
Dyspnoea	1 (0.93%)	3 (3.49%)	3 (2.73%)
Pleural effusion	1 (0.93%)	2 (2.33%)	0 (0.00%)

Pneumonia aspiration	1 (0.93%)	0 (0.00%)	0 (0.00%)
Pulmonary embolism	3 (2.78%)	1 (1.16%)	2 (1.82%)
Respiratory arrest	0 (0.00%)	0 (0.00%)	1 (0.91%)
Respiratory distress	0 (0.00%)	0 (0.00%)	2 (1.82%)
Respiratory failure	2 (1.85%)	1 (1.16%)	1 (0.91%)
Skin and subcutaneous tissue disorders			
Angioedema	0 (0.00%)	0 (0.00%)	1 (0.91%)
Rash	0 (0.00%)	1 (1.16%)	0 (0.00%)
Vascular disorders			
Deep vein thrombosis	0 (0.00%)	0 (0.00%)	1 (0.91%)
Embolism	1 (0.93%)	0 (0.00%)	0 (0.00%)
Venous thrombosis	0 (0.00%)	1 (1.16%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of 232 weeks.
Source Vocabulary for Table Default	MedDRA 22.1
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Ceritinib 450 mg fed N = 108	**Ceritinib 600 mg fed N = 86**	**Ceritinib 750 mg fasted N = 110**

Arm/Group Description	Ceritinib 450 mg fed	Ceritinib 600 mg fed	Ceritinib 750 mg fasted
Total participants affected	106 (98.15%)	84 (97.67%)	107 (97.27%)
Blood and lymphatic system disorders			
Anaemia	12 (11.11%)	9 (10.47%)	9 (8.18%)
Neutropenia	8 (7.41%)	3 (3.49%)	3 (2.73%)
Cardiac disorders			
Bradycardia	5 (4.63%)	5 (5.81%)	2 (1.82%)
Gastrointestinal disorders			
Abdominal pain	25 (23.15%)	23 (26.74%)	34 (30.91%)
Abdominal pain upper	22 (20.37%)	13 (15.12%)	27 (24.55%)
Constipation	14 (12.96%)	18 (20.93%)	20 (18.18%)
Diarrhoea	64 (59.26%)	57 (66.28%)	88 (80.00%)
Dyspepsia	11 (10.19%)	4 (4.65%)	12 (10.91%)
Dysphagia	1 (0.93%)	1 (1.16%)	6 (5.45%)
Flatulence	1 (0.93%)	0 (0.00%)	6 (5.45%)
Gastrooesophageal reflux disease	0 (0.00%)	5 (5.81%)	2 (1.82%)
Nausea	46 (42.59%)	49 (56.98%)	65 (59.09%)
Vomiting	41 (37.96%)	47 (54.65%)	72 (65.45%)
General disorders and administration site conditions			
Asthenia	11 (10.19%)	17 (19.77%)	8 (7.27%)
Fatigue	28 (25.93%)	27 (31.40%)	34 (30.91%)

Non-cardiac chest pain	13 (12.04%)	10 (11.63%)	20 (18.18%)
Oedema peripheral	10 (9.26%)	10 (11.63%)	9 (8.18%)
Pyrexia	10 (9.26%)	19 (22.09%)	27 (24.55%)
Infections and infestations			
Bronchitis	2 (1.85%)	2 (2.33%)	6 (5.45%)
Influenza	8 (7.41%)	6 (6.98%)	6 (5.45%)
Nasopharyngitis	9 (8.33%)	13 (15.12%)	14 (12.73%)
Upper respiratory tract infection	14 (12.96%)	15 (17.44%)	16 (14.55%)
Urinary tract infection	2 (1.85%)	5 (5.81%)	6 (5.45%)
Investigations			
Alanine aminotransferase increased	47 (43.52%)	41 (47.67%)	48 (43.64%)
Amylase increased	14 (12.96%)	10 (11.63%)	6 (5.45%)
Aspartate aminotransferase increased	41 (37.96%)	32 (37.21%)	42 (38.18%)
Blood alkaline phosphatase increased	23 (21.30%)	11 (12.79%)	16 (14.55%)
Blood bilirubin increased	7 (6.48%)	1 (1.16%)	4 (3.64%)
Blood creatinine increased	25 (23.15%)	17 (19.77%)	18 (16.36%)
Electrocardiogram QT prolonged	6 (5.56%)	7 (8.14%)	4 (3.64%)
Gamma-glutamyltransferase increased	37 (34.26%)	22 (25.58%)	27 (24.55%)

Lipase increased	17 (15.74%)	12 (13.95%)	13 (11.82%)
Weight decreased	17 (15.74%)	16 (18.60%)	19 (17.27%)
Metabolism and nutrition disorders			
Decreased appetite	24 (22.22%)	22 (25.58%)	34 (30.91%)
Dehydration	4 (3.70%)	4 (4.65%)	6 (5.45%)
Hyperglycaemia	14 (12.96%)	9 (10.47%)	15 (13.64%)
Hypokalaemia	4 (3.70%)	5 (5.81%)	8 (7.27%)
Hypophosphataemia	5 (4.63%)	6 (6.98%)	3 (2.73%)
Musculoskeletal and connective tissue disorders			
Arthralgia	13 (12.04%)	5 (5.81%)	13 (11.82%)
Back pain	18 (16.67%)	12 (13.95%)	19 (17.27%)
Muscle spasms	6 (5.56%)	4 (4.65%)	8 (7.27%)
Musculoskeletal chest pain	5 (4.63%)	2 (2.33%)	6 (5.45%)
Musculoskeletal pain	14 (12.96%)	7 (8.14%)	13 (11.82%)
Myalgia	7 (6.48%)	3 (3.49%)	4 (3.64%)
Neck pain	5 (4.63%)	6 (6.98%)	6 (5.45%)
Pain in extremity	12 (11.11%)	7 (8.14%)	9 (8.18%)
Nervous system disorders			
Dizziness	8 (7.41%)	9 (10.47%)	15 (13.64%)
Headache	21 (19.44%)	16 (18.60%)	29 (26.36%)
Paraesthesia	6 (5.56%)	1 (1.16%)	6 (5.45%)
Psychiatric disorders			

Insomnia	8 (7.41%)	4 (4.65%)	12 (10.91%)
Renal and urinary disorders			
Renal failure	2 (1.85%)	7 (8.14%)	8 (7.27%)
Respiratory, thoracic and mediastinal disorders			
Cough	27 (25.00%)	15 (17.44%)	28 (25.45%)
Dyspnoea	16 (14.81%)	13 (15.12%)	12 (10.91%)
Haemoptysis	2 (1.85%)	1 (1.16%)	7 (6.36%)
Oropharyngeal pain	9 (8.33%)	6 (6.98%)	9 (8.18%)
Productive cough	4 (3.70%)	1 (1.16%)	7 (6.36%)
Skin and subcutaneous tissue disorders			
Alopecia	2 (1.85%)	0 (0.00%)	6 (5.45%)
Dry skin	3 (2.78%)	3 (3.49%)	9 (8.18%)
Erythema	6 (5.56%)	2 (2.33%)	0 (0.00%)
Photosensitivity reaction	2 (1.85%)	0 (0.00%)	7 (6.36%)
Pruritus	8 (7.41%)	5 (5.81%)	13 (11.82%)
Rash	17 (15.74%)	13 (15.12%)	19 (17.27%)
Vascular disorders			
Hypertension	9 (8.33%)	4 (4.65%)	5 (4.55%)

Other Relevant Findings

None

Conclusion:

- No clinically meaningful difference in steady-state systemic exposure of ceritinib was observed between the 450 mg with food arm and the 750 mg fasted arm. This result translated into a comparable efficacy between the 450 mg fed arm and the 750 mg fasted arm.
- Similar trough levels for ceritinib were achieved between the 450 mg fed arm and the 750 mg fasted arm.
- Ceritinib 450 mg fed arm presented high and durable efficacy results (Overall response rate (ORR), Duration of response (DOR), Time to response (TTR) , Progression free survival (PFS) and Overall survival (OS)) which are comparable with the 750 mg fasted arm and with previous studies where subjects received ceritinib 750 mg fasted.
- The overall safety of ceritinib taken with food at a dose of 450 mg was consistent with 750 mg fasted with no clinically relevant differences except less frequent and less severe Gastrointestinal (GI) toxicity. Ceritinib 450 mg taken with food, presented a lower frequency and severity of GI toxicities than those observed with the ceritinib 750 mg fasted arms, a lower proportion of subjects with grade 3/4 GI toxicities, a lower proportion of subjects with study drug reduction and study drug interruption, and a lower proportion of subjects noted with Adverse Events (AEs) requiring dose adjustment or study drug interruption, in addition to a higher median relative dose intensity (RDI). Thus, the ceritinib 450 mg fed arm presents the most favorable GI safety profile among the three treatment arms investigated.
- No new safety signals were identified.
- The benefit/risk profile of the ceritinib 450 mg dose is favorable and supports the use of currently approved 450 mg with food as the recommended dose of ceritinib for the treatment of advanced anaplastic lymphoma kinase positive non-small cell lung cancer (ALK+NSCLC) to replace the originally approved recommended dose of 750 mg fasted.

Date of Clinical Trial Report

31-Jul-2020