Sponsor

Novartis

Generic Drug Name

Ceritinib

Trial Indication(s)

ALK-positive advanced tumors including non-small cell lung cancer (NSCLC)

Protocol Number

CLDK378A2103

Protocol Title

A phase I, multi-center, open label, drug-drug interaction study to assess the effect of ceritinib on the pharmacokinetics of warfarin and midazolam administered as a two-drug cocktail in patients with ALK-positive advanced tumors including non-small cell lung cancer (NSCLC)

Clinical Trial Phase

Phase 1

Phase of Drug Development

Phase III

Study Start/End Dates

Study start date: 23 Oct 2015
Study end date: 12 Dec 2017

Reason for Termination (If applicable)

N/A

Study Design/Methodology

Study A2103 used a multicenter, open-label, single-sequence, crossover design to evaluate the effects of multiple doses of ceritinib (750 mg once daily dosing under fasted conditions) on the PK of the probe drugs midazolam and warfarin, which are metabolized by CYP3A4 and CYP2C9, respectively, in patients with ALK-positive advanced tumors including NSCLS. This study was divided into two phases, drug-drug interaction (DDI) phase and post-DDI clinical treatment phase (subsequent treatment). In the DDI phase, patients were administered a single dose of the probe drug cocktail, containing warfarin (10 mg) and midazolam (2.5 mg) on Study Day 1 and a full PK profile for each probe drug was collected over 144 hours post-dose (probe alone). Administration of oral ceritinib 750 mg once daily, on an empty stomach, was started on Day 7 following the collection of last blood sample for the probe drugs and continued in order for ceritinib to reach PK steady-state. On Day 28, patients received a dose of 750 mg ceritinib and a concomitant single dose of the cocktail, followed by collection of a full PK profile of each probe drug over 144 hours. Daily administration of ceritinib continued during the days of PK profile sample collection. The PK profiles of probe drugs administered on Day 28 were compared to baseline PK data on Day 1 to assess the extent of inhibitory effects of ceritinib daily dosing on CYP3A4 and CYP2C9 activities. Tumor evaluation was determined locally by the Investigator using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. Assessments of tumor response were performed every two cycles (i.e., every six weeks) through Cycle 9. Subsequently the frequency of tumor assessments was reduced to as clinically indicated, at the discretion of the Investigator, but no less than once every four cycles until disease progression or lack of clinical benefit following disease progression, start of new anti-neoplastic therapy, death, lost to follow-up or patient decision involving withdrawal of consent. The clinical study report (CSR) was to be based on data from all patients, up to the time at which all enrolled patients completed at least 1 cycle of ceritinib treatment in the post-DDI phase, or discontinued study treatment, whichever was earlier. Ongoing patients were to continue receiving study treatment and be followed as per the schedule of assessments, as long as patients derived benefit from ceritinib.

Centers

Four countries enrolled patients: Italy (3 centers), Denmark (1 center), Spain (3 centers) and USA (3 centers)

Objectives:

Primary objective was to evaluate the inhibitory effect of ceritinib on the pharmacokinetics (PK) of a drug cocktail containing midazolam and warfarin in patients with anaplastic lymphoma kinase (ALK)-positive advanced tumors including NSCLC.

Secondary objectives were to assess the PK, safety and tolerability of ceritinib in patients with ALKpositive advanced tumors including NSCLC, and to evaluate preliminary evidence of antitumor activity of ceritinib in patients with ALK-positive advanced tumors including NSCLC.

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

The investigational or study treatment refers to ceritinib, midazolam or warfarin, or the combination. Study drug refers to ceritinib only. Probe drugs warfarin (10 mg) and midazolam (2.5 mg) and/or ceritinib orally 750mg (5x150mg) on an empty stomach at least 1 hour before or 2 hours after a light breakfast.

Statistical Methods

Statistical methods: Data were analyzed by Novartis Oncology Biostatistics and Statistical Programming personnel according to the data analysis described in the protocol. SAS ® version 9.4 was used in all analyses.

Full Analysis Set and Efficacy Analysis Set- The FAS included all patients in the study who received at least one dose of any study medication (probe drugs or ceritinib).

Safety Set- The Safety Set included all patients in the study who received at least one dose of any study medication (probe drugs or ceritinib). The FAS, Efficacy Analysis Set (EAS), and Safety Set in this study were identical.

Pharmacokinetic Analysis Set- Three separate Pharmacokinetic Analysis Sets (PAS) were considered for the evaluation of PK, one for each of the probe substrates (midazolam and warfarin) and one for ceritinib. PAS for probe X consisted of all patients who had evaluable PK profiles for probe X from both periods (first PK profile was after the probe drug cocktail administration and second PK profile was after administration of probe drug cocktail + ceritinib).

PAS for ceritinib included all patients who received at least one dose of ceritinib and provided at least one evaluable PK blood sample.

Primary endpoints and analyses:
A formal statistical analysis was conducted to compare the single-dose PK of each of the individual probe drugs (midazolam and warfarin) co-administered with and without multiple doses of ceritinib 750 mg. The single-dose PK parameters (AUClast, AUCinf and Cmax) for each probe were log transformed and analyzed with a linear mixed effect model. The model included a fixed effect for treatment (probe + ceritinib 750 mg, probe alone) and a random effect for patient. The model-based, between-treatment mean differences (probe + ceritinib – probe alone) and corresponding two-sided 90% confidence intervals (CIs) were calculated on the log-scale. The between-treatment differences and 90% CIs were then back transformed to the original scale to obtain the geometric mean ratios (probe + ceritinib 750 mg / probe alone) and corresponding 90% CIs. No adjustments for multiplicity were considered in the statistical comparisons. Both parent drugs (midazolam, S-warfarin, R-warfarin) and their metabolites (1'-hydroxymidazolam and 7-hydroxy-S-warfarin) were analyzed.
Probe drug concentrations: Descriptive statistics (n, mean, SD, median, geometric mean, CV%, geometric CV (%), minimum, and maximum) were presented for probe (warfarin and midazolam) concentrations and their metabolites by treatment (cocktail alone, cocktail + ceritinib) and scheduled time point. A graphical presentation of the probe concentration profiles was also provided by treatment using the arithmetic mean (+/- SD) and geometric mean values at each scheduled time point.
Probe drug PK parameters: The single-dose pharmacokinetic parameters of probe drugs and their metabolites were summarized by treatment (cocktail alone, cocktail + ceritinib) using descriptive statistics including n, mean, standard deviation, median, geometric mean, CV%, geometric CV (%), minimum, and maximum. For Tmax, median values and ranges were provided.

All PK data was listed by treatment using the FAS.

Secondary endpoints and analyses:

Efficacy analyses: All efficacy analyses of secondary variables were performed using FAS for the DDI and post-DDI phase together for all patients, unless otherwise specified. The results were displayed for patients with NSCLC and patients with other type of cancer separately.

Overall Response Rate (ORR) was defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR) as assessed per RECIST 1.1. ORR was estimated and the exact binomial 95% CI was reported based on Investigator assessment.

Safety analyses: All safety analyses were performed based on the Safety Set for the DDI and post-DDI phase together for all patients, unless otherwise specified. AEs were coded using MedDRA version 20.1 and were graded using Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. If CTCAE grading did not exist for an AE, grades 1, 2, 3, or 4 corresponding to the severity of mild, moderate, severe, and life-threatening, respectively, was used. The frequency counts and percentages of patients with AEs were summarized by system organ class (SOC) and/or preferred term (PT), maximum severity (based on the maximum CTCAE grades), and relation to study drug unless otherwise specified. A patient with multiple CTC grades for an AE was summarized under the maximum CTC grade recorded for the event.

Any AE, AEs related to study treatment, AEs leading to permanent discontinuation of study treatment, AE leading to dose reductions, AEs leading to dose interruptions, SAEs, SAEs related to study treatment, fatal SAEs, and fatal SAEs related to study treatment tables were produced.

Adverse events of special interest (AESIs) analyzed for the study were: gastrointestinal toxicity (nausea, vomiting and diarrhea), hepatotoxicity, interstitial lung disease/pneumonitis, QT interval prolongation, hyperglycemia, bradycardia, and pancreatitis (including lipase and amylase elevations).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

Patients eligible for inclusion in this study have to meet all of the following criteria:

- Histologically or cytologically confirmed diagnosis of stage IIIB (and is not a candidate for definitive multimodality therapy) or stage IV NSCLC demonstrated ALK-positive or an advanced tumor, other than NSCLC, that carries an ALK genetic alteration (mutation, translocation or amplification) and/or ALK overexpression that has progressed despite standard therapy, or for which no effective standard therapy exists.

Note: Patients with clinically and neurologically stable central nervous system (CNS) metastases who have not required increasing doses of steroids within the 2 weeks prior
to study entry to manage CNS symptoms are eligible.

- Age 18 years or older at the time of informed consent.
- Patients who have received prior chemotherapy, other ALK inhibitors, biologic therapy, or other investigational agents, must have recovered from all toxicities related to prior anticancer therapies to grade ≤ 1 (CTCAE v 4.03) prior to starting study drug. Patients with grade ≤ 2 peripheral neuropathy or any grade of alopecia, nail changes or skin changes are allowed to enter the study.
- Patients who have been treated with chemotherapy, with biological therapy or other investigational agent must have discontinued the treatment at least 2 weeks (14 days) prior to starting the study drug on Study Day 1. In case last chemotherapy contains nitroso urea or mitomycin C, the treatment must be discontinued at least 6 weeks prior to starting study drug.
- Patients, if previously treated with ALK inhibitor (such as crizotinib), must discontinue the ALK inhibitor at least 1 week (7 days) prior to the first dose of study drug on Study Day1.
- Patient must meet the following laboratory values at the screening visit:
  - WBC count ≥ 4.0 x 109/L
  - Absolute Neutrophil Count ≥ 1.5 x 109/L
  - Platelets ≥ 75 x 109/L
  - Hemoglobin (Hgb) ≥ 8 g/dL
  - Serum creatinine < 1.5 mg/dL and /or calculated creatinine clearance (using Cockcroft-Gault formula) ≥ 30 mL/min
  - Total bilirubin ≤ 1.5 x ULN except for patients with Gilbert's syndrome who may only be included if total bilirubin ≤ 3.0 x ULN or direct bilirubin ≤ 1.5 x ULN
  - Aspartate transaminase (AST) ≤ 3 x ULN, except for patients with liver metastasis, who are only included if AST ≤ 5 x ULN
  - Alanine transaminase (ALT) ≤3 x ULN, except for patients with liver metastasis, who are only included if ALT ≤ 5 x ULN
  - Alkaline phosphatase (ALP) ≤ 5.0 x ULN
  - Serum amylase < 2 x ULN
  - Serum lipase ≤ ULN
  - Fasting plasma glucose ≤ 175 mg/dL (≤ 9.8 mmol/L)

- Patient must have the following laboratory values within normal limits or corrected to within normal limits with supplements during screening:
  - Potassium
  - Magnesium
  - Phosphorus
  - Total calcium (corrected for serum albumin)
- Patient has a World Health Organization (WHO) performance status 0-2.
- Patient has the ability to understand and provide signed informed consent.
- Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests and other study requirements

Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

- Patients with known hypersensitivity to any of the excipients of ceritinib (microcrystalline cellulose, mannitol, crospovidone, colloidal silicon dioxide and magnesium stearate), midazolam and warfarin as described in the local product information.
- 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. Exceptions to this exclusion include the following: completely resected basal cell and squamous cell skin cancers, and completely resected carcinoma in situ of any type.
- Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months), such as:
  - Unstable angina within 6 months prior to screening.
  - Myocardial infarction within 6 months prior to screening.
  - History of documented congestive heart failure (New York Heart Association functional classification III-IV).
  - Uncontrolled hypertension defined by a Systolic Blood Pressure (SBP) ≥ 160 mmHg and/or Diastolic Blood Pressure (DBP) ≥ 100 mmHg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication (s) is allowed prior to screening.
  - Ventricular arrhythmias.
  - Supraventricular and nodal arrhythmias not controlled with medication.
  - Other cardiac arrhythmia not controlled with medication.

  - ● Corrected QT (QTcF) > 470 ms using Fridericia's correction on the screening ECG (as mean of triplicate ECGs).
- 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 including uncontrolled diabetes mellitus or psychiatric conditions or laboratory abnormalities that in the opinion of the investigator may increase the risk associated with study participation, or that may interfere with the interpretation of study results.
- Patient has impairment of GI function or GI disease that may significantly alter the absorption of ceritinib (e.g., ulcerative diseases, uncontrolled nausea, vomiting, diarrhea, or malabsorption syndrome).
- Patient receiving treatment with medications that meet one of the following criteria and that cannot be discontinued at least 4 week prior to the start of treatment with ceritinib and for the duration of the study (Appendix 1):
  - ● Strong inhibitors and inducers of CYP3A4/5
  - ● Medications with a low therapeutic index that are primarily metabolized by CYP3A4/5 and/or CYP2C9.
  - ● Medications with a known risk of prolonging the QT interval or inducing Torsades de Pointes.
  - ● Strong inhibitors and inducers of CYP2C9 (this criterion is applicable for DDI phase only)
- Patient is currently receiving treatment with warfarin sodium (Coumadin®) or any other coumarin-derivative anticoagulants, and treatment cannot be discontinued at least 2 weeks (14 days) prior to start of study treatment. Patient who is expected to receive the probe drug midazolam within 3 days prior to the days of blood sample collection for PK assessment in the DDI phase (i.e. ≤ 3 days prior to Study Day 1 and 28 of the DDI phase).
- Patient is receiving unstable or increasing doses of corticosteroids. If patients are on corticosteroids for endocrine deficiencies or tumor-associated symptoms (non-CNS), dose must have been stabilized (or decreasing) for at least 5 days before first dose of study treatment.
- Patient is receiving treatment with any enzyme-inducing anticonvulsant (Appendix 1) that cannot be discontinued at least 1 week before first dose of study treatment, and for the duration of the study. Patients on non-enzymeinducing anticonvulsants are eligible.
- Patient who has received thoracic radiotherapy to lung fields ≤ 4 weeks prior to starting the study treatment or patients who have not recovered from radiotherapy-related toxicities. For all other anatomic sites (including radiotherapy to thoracic vertebrae and ribs) radiotherapy ≤ 2 weeks prior to starting the study treatment or has not recovered from radiotherapy-related toxicities. Palliative radiotherapy for bone lesions ≤ 2 weeks prior to starting study treatment is allowed.

- Patient has had major surgery (e.g., intra-thoracic, intra-abdominal or intrapelvic) within 4 weeks prior to starting study treatment or has not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can receive study treatment ≥1 week after these procedures.
- Patients who have had, or are expected to have, regular alcohol intake exceeding 1 drink/day on a daily basis within 3 days prior to the days of blood sample collection for PK assessment (i.e., ≤ 3 days prior to days 1 and 28) (note: 1 drink = 5 ounces of wine, 12 ounces of beer, or 1 ounce of hard liquor).
- Patients who have consumed, or are expected to consume, grapefruits, pomegranates, star fruits, seville orange or product containing the juice of each, or charbroiled meats within 3 days prior to the days of blood sample collection for PK assessment (i.e., ≤ 3 days prior to Study Days 1 and 28). Note: vitamin supplements are allowed.
- Herbal preparations/medications are not allowed throughout the study, as a potential drug-drug interaction is always possible. These herbal medications include, but are not limited to: St. John's wort, Kava, ephedra (ma huang), gingko biloba, dehydroepiandrosterone (DHEA), yohimbe, saw palmetto, and ginseng. Patients should stop using herbal medications at least 7 days prior to first dose of study treatment.
- Pregnant or nursing (lactating) women.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective contraception during the study and for 3 months after stopping ceritinib treatment.
- Sexually active males must use a condom during intercourse while taking ceritinib and for 3 months after stopping ceritinib treatment. Male patients should not father a child for 3 months after the last dose of ceritinib treatment. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
- Patient has history of pancreatitis or history of increased amylase or lipase that was due to pancreatic disease

Participant Flow Table

Patient disposition (FAS)

Disposition/reason	All Patients N=33 n (%)
Pharmacokinetic phase (DDI phase)	
Completed	
Discontinued from Pharmacokinetic phase	
Permanently discontinued from study	
Primary reason for discontinuation from pharmacokinetic phase	
Adverse event	8 (24.2)
Progressive disease	6 (18.2)
Death	1 (3.0)
Entered in post-DDI phase	21 (63.6)
Treatment phase (DDI phase + post-DDI phase)	
Discontinued from treatment phase	33 (100)
Primary reason for discontinuation from treatment phase	
Adverse event	6 (18.2)
Study terminated by sponsor[a]	12 (36.4)
Progressive disease	13 (39.4)
Subject/guardian decision	1 (3.0)
Death	1 (3.0)

[a] patients completed the study and were rolled over to the rollover study as per Protocol

Baseline Characteristics

	Demographic Variable	All patients N=33
Age (years)	N	33
	Mean	54.6
	SD	16.59
	Median	57.0
	Min - Max	22 - 78
Age category (years) – n (%)	<65	23 (69.7)
	≥ 65 years	10 (30.3)
Sex – n (%)	Female	21 (63.6)
	Male	12 (36.4)
Race – n (%)	Caucasian	32 (97.0)
	Unknown	1 (3.0)
Ethnicity-n (%)	Hispanic or Latino	5 (15.2)
	Not reported	3 (9.1)
	Other	24 (72.7)
	Unknown	1 (3.0)
Weight (kg)	N	33
	Mean	69.7
	SD	15.82
	Median	69.8
	Minimum	47
	Maximum	100
Height (cm)	N	33

	Mean	168.7
	SD	8.36
	Median	166.0
	Minimum	152
	Maximum	191
Body mass index (kg/m2)	N	33
	Mean	24.3
	SD	4.35
	Median	25.2
	Minimum	18
	Maximum	32
WHO performance status-n (%)	0	16 (48.5)
	1	15 (45.5)
	2	2 (6.1)
Smoking history-n (%)	Current smoker	2 (6.1)
	Former smoker	14 (42.4)
	Never smoked	17 (51.5)

Body Mass Index: BMI [kg/m2] = eight [kg] / (height[m]**2).

Summary of Efficacy

Primary Outcome Result(s)

Summary of statistical analysis of primary PK parameters for CYP3A probe substrate midazolam (Pharmacokinetic analysis set – midazolam)

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Treatment comparison 90% CI Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	midazolam	20	72.5				
	midazolam+ceritinib	20	393	midazolam+ceritinib / midazolam	5.42	4.64	6.34
AUClast (ng*hr/mL)	midazolam	20	70.2				
	midazolam+ceritinib	20	387	midazolam+ceritinib / midazolam	5.52	4.69	6.49
Cmax (ng/mL)	midazolam	20	23.0				
	midazolam+ceritinib	20	42.0	midazolam+ceritinib / midazolam	1.82	1.54	2.16
Tmax (hr)	midazolam	20	0.500				
	midazolam+ceritinib	20	0.750	midazolam+ceritinib / midazolam	0.100	-0.750	2.32

- Model was a linear mixed effects model of the log-transformed PK parameters. Included in the model was treatment as fixed factor and patient as a random factor.

- The analysis was conducted on the log-transformed PK parameters.
- The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
- n* = number of observations used for the analysis.
- For Tmax, median was presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio', and minimum and maximum differences under 90% CI.

Summary of primary PK parameters for midazolam by treatment (Pharmacokinetic analysis set – midazolam)

Treatment	Statistics	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
midazolam (N=20)	n	20	20	20	20
	Mean (SD)	77.3 (36.3)	79.4 (36.5)	26.0 (12.5)	N/A
	CV%	47.0	46.0	48.2	N/A
	Geo-mean	70.2	72.5	23.0	N/A
	Geo-CV%	46.7	45.8	56.2	N/A
	Median	70.5	72.9	23.9	0.500
	[Min; Max]	[32.5; 175]	[34.4; 178]	[7.06; 55.9]	[0.217; 1.00]
midazolam+ceritinib (N=20)	n	20	20	20	20
	Mean (SD)	410 (131)	415 (131)	44.9 (17.2)	N/A
	CV%	32.1	31.5	38.2	N/A
	Geo-mean	387	393	42.0	N/A

Geo-CV%	37.0	35.9	39.3	N/A
Median	437	439	40.7	0.750
[Min; Max]	[207; 616]	[209; 624]	[18.3; 84.6]	[0.250; 2.53]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = SD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- For Tmax only n, median, minimum and maximum were presented.

Summary of secondary PK parameters for midazolam by treatment (Pharmacokinetic analysis set – midazolam)

Treatment	Statistics	Lambda_z (1/hr)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
Midazolam (N=20)	n	20	20	20	20
	Mean (SD)	0.13 (0.0891)	6.55 (2.32)	37.6 (16.0)	342 (163)
	CV%	68.7	35.4	42.5	47.7
	Geo-mean	0.114	6.05	34.5	301
	Geo-CV%	47.8	47.8	45.8	58.5
	Median	0.109	6.33	34.3	307
	[Min; Max]	[0.0576; 0.46]	[1.51; 12.0]	[14.0; 72.8]	[94.6; 654]
midazolam+ ceritinib (N=20)	n	20	20	20	20
	Mean (SD)	0.0483 (0.0202)	16.3 (5.41)	6.76 (2.54)	148 (45.2)
	CV%	41.9	33.3	37.6	30.5
	Geo-mean	0.0451	15.4	6.36	141
	Geo-CV%	37.4	37.4	35.9	35.4
	Median	0.0419	16.6	5.69	144

[Min; Max]	[0.0241; 0.112]	[6.19; 28.7]	[4.01; 12.0]	[61.2; 231]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = SD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

Summary of statistical analysis of primary PK parameters for 1'- hydroxymidazolam (Pharmacokinetic analysis set – midazolam)

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	midazolam	19	16.2				
	midazolam+ceritinib	13	15.4	midazolam+ceritinib / midazolam	0.947	0.729	1.23
AUClast (ng*hr/mL)	midazolam	19	15.1				
	midazolam+ceritinib	19	11.9	midazolam+ceritinib / midazolam	0.788	0.644	0.964
Cmax (ng/mL)	midazolam	19	5.43				
	midazolam+ceritinib	19	1.90	midazolam+ceritinib / midazolam	0.351	0.260	0.472
Tmax (hr)	midazolam	19	0.500				
	midazolam+ceritinib	19	0.583	midazolam+ceritinib / midazolam	0.0583	-1.75	2.32

- Model was a linear mixed effects model of the log-transformed PK parameters. Included in the model was treatment as fixed factor and patient as a random factor.
- The analysis was conducted on the log-transformed PK parameters.
- The results were back transformed to get adjusted geometric mean, geometric mean ratio, and 90% CI.
- n* = number of observations used for the analysis.
- For Tmax, median is presented under 'Adjusted geo-mean', median difference under 'Geo-mean ratio'

Summary of primary PK parameters for 1'-hydroxymidazolam by treatment (Pharmacokinetic analysis set – midazolam)

Treatment	Statistics	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
midazolam (N=20)	n	19	19	19	19
	Mean (SD)	18.4 (15.0)	19.7 (15.2)	6.68 (4.81)	N/A
	CV%	81.6	77.1	72.0	N/A
	Geo-mean	14.7	15.9	5.41	N/A
	Geo-CV%	74.4	71.1	74.1	N/A
	Median	15.1	16.3	5.81	0.500
	[Min; Max]	[6.05; 70.2]	[6.84; 71.2]	[1.92; 20.8]	[0.217; 2.00]
midazolam+ceritinib (N=20)	n	19	13	19	19
	Mean (SD)	16.0 (13.4)	21.9 (14.3)	2.38 (1.84)	N/A
	CV%	83.6	65.2	77.5	N/A
	Geo-mean	12.1	18.3	1.90	N/A
	Geo-CV%	87.0	68.4	73.8	N/A
	Median	12.6	17.9	1.75	0.583
	[Min; Max]	[4.05; 54.2]	[6.41; 55.5]	[0.764; 8.32]	[0.250; 2.53]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = SD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.

For Tmax only n, median, minimum and maximum were presented.

Summary of secondary PK parameters for 1'-hydroxymidazolam by treatment (Pharmacokinetic analysis set – midazolam)

Treatment	Statistics	T1/2 (hr)	Lambda_z (1/hr)	Metabolic ratio (AUClast)
Midazolam (N=20)	n	19	19	19
	Mean (SD)	6.91 (4.18)	0.157 (0.118)	0.238 (0.214)
	CV%	60.4	74.8	89.9
	Geo-mean	5.61	0.124	0.193
	Geo-CV%	80.0	80.0	66.3
	Median	6.54	0.106	0.187
	[Min; Max]	[1.51; 14.5]	[0.0478; 0.458]	[0.058; 1.06]
midazolam+cer itinib (N=20)	n	19	19	19
	Mean (SD)	16.9 (8.6)	0.0537 (0.0369)	0.0349 (0.0249)
	CV%	51.0	68.8	71.4
	Geo-mean	15.0	0.0463	0.0289
	Geo-CV%	56.3	56.3	66.7
	Median	16.7	0.0415	0.0268
	[Min; Max]	[3.74; 45.0]	[0.0154; 0.185]	[0.0112; 0.116]

- n: number of patients with corresponding evaluable PK parameters.
- CV% = coefficient of variation (%) = SD/mean*100, Geo-CV% = sqrt (exp (variance for log transformed data)-1)*100.
- Metabolic ratio (AUClast) was defined as AUClast ratio of 1'-hydroxymidazolam / midazolam, multiplied by 325.77 (molecular weight of midazolam) / 341.77 (molecular weight of 1'- hydroxymidazolam)

Summary of statistical analysis of primary PK parameters for CYP2C9 probe substrate S-warfarin (Pharmacokinetic analysis set – warfarin)

					Treatment comparison 90% CI		
PK parameter (unit)	**Treatment**	**n***	**Adjusted geo-mean**	**Comparison(s)**	**Geo-mean ratio**	**Lower**	**Upper**
AUCinf (ng*hr/mL)	warfarin	18	21200				
	warfarin+ ceritinib	10	32800	warfarin+ ceritinib / warfarin	1.54	1.36	1.75
AUClast (ng*hr/mL)	warfarin	20	18200				
	warfarin+ ceritinib	19	28400	warfarin+ ceritinib / warfarin	1.57	1.30	1.89
Cmax (ng/mL)	warfarin	20	569				
	warfarin+ ceritinib	19	598	warfarin+ ceritinib / warfarin	1.05	0.912	1.21
Tmax (hr)	warfarin	20	1.47				
	warfarin+ ceritinib	19	2.75	warfarin+ ceritinib / warfarin	0.867	-3.42	4.43

Summary of primary PK parameters for S-warfarin by treatment (Pharmacokinetic analysis set – warfarin)

Treatment	Statistics	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
warfarin (N=20)	n	20	18	20	20
	Mean (SD)	19500 (6180)	22000 (6260)	597 (168)	N/A
	CV%	31.7	28.4	28.1	N/A
	Geo-mean	18200	21200	569	N/A
	Geo-CV%	46.6	28.1	34.9	N/A
	Median	18300	19500	588	1.47
	[Min; Max]	[3720; 29600]	[13000; 33900]	[199; 858]	[0.483; 3.92]
warfarin+ceritinib (N=20)	n	19	10	19	19
	Mean (SD)	29900 (9520)	29500 (6340)	621 (176)	N/A
	CV%	31.8	21.4	28.4	N/A
	Geo-mean	28400	28900	599	N/A
	Geo-CV%	36.0	22.8	27.5	N/A
	Median	28500	29000	617	2.75
	[Min; Max]	[11400; 48500]	[18400; 38900]	[361; 1070]	[0.25; 6.4]

Summary of secondary PK parameters for S-warfarin by treatment (Pharmacokinetic analysis set – warfarin)

Treatment	Statistics	Lambda_z (1/hr)	T1/2 (hr)	CL/F (L/hr)	Vz/F (L)
warfarin (N=20)	N	20	20	18	18
	Mean (SD)	0.0168 (0.0046)	44.9 (15.1)	0.488 (0.131)	27.6 (4.76)
	CV%	27.3	33.7	26.8	17.3
	Geo-mean	0.0162	42.9	0.471	27.2
	Geo-CV%	30.9	30.9	28.1	16.6
	Median	0.0163	42.4	0.512	26.0
	[Min; Max]	[0.00795; 0.0241]	[28.7; 87.1]	[0.295; 0.767]	[21.5; 39.3]
warfarin+ ceritinib (N=20)	N	19	19	10	10
	Mean (SD)	0.0137 (0.00663)	60.1 (24.1)	0.354 (0.0847)	23.6 (5.49)
	CV%	48.4	40.1	23.9	23.3
	Geo-mean	0.0125	55.4	0.346	22.9
	Geo-CV%	44.5	44.5	22.8	26.8
	Median	0.0129	53.7	0.345	24.2
	[Min; Max]	[0.00634; 0.0344]	[20.2; 109]	[0.257; 0.543]	[12.2; 33.3]

Summary of statistical analysis of primary PK parameters for 7- hydroxy-S-warfarin (Pharmacokinetic analysis set – warfarin)

PK parameter (unit)	Treatment	n*	Adjusted geo-mean	Comparison(s)	Treatment comparison 90% CI Geo-mean ratio	Lower	Upper
AUCinf (ng*hr/mL)	Warfarin	12	3090				
	warfarin+ ceritinib	5	3330	warfarin+ ceritinib / warfarin	1.08	0.814	1.43
AUClast (ng*hr/mL)	Warfarin	16	2920				
	warfarin+ ceritinib	13	3230	warfarin+ ceritinib / warfarin	1.11	0.972	1.26
Cmax (ng/mL)	Warfarin	16	39.1				
	warfarin+ ceritinib	13	34.8	warfarin+ ceritinib / warfarin	0.890	0.777	1.02
Tmax (hr)	Warfarin	16	24.2				
	warfarin+ ceritinib	13	47.2	warfarin+ ceritinib / warfarin	13.4	-14.7	40.5

Summary of primary PK parameters for 7-hydroxy-S-warfarin by treatment (Pharmacokinetic analysis set – warfarin)

Treatment	Statistics	AUClast (ng*hr/mL)	AUCinf (ng*hr/mL)	Cmax (ng/mL)	Tmax (hr)
warfarin (N=20)	N	16	12	16	16
	Mean (SD)	3470 (2540)	3660 (2740)	46.3 (27.9)	N/A
	CV%	73.1	74.9	60.3	N/A
	Geo-mean	2910	3090	39.7	N/A
	Geo-CV%	61.8	61.4	60.3	N/A
	Median	2640	3100	34.8	24.2
	[Min; Max]	[1240; 10100]	[1350; 11600]	[16.1; 115]	[2.97; 49.9]
warfarin+ceritinib (N=20)	N	13	5	13	13
	Mean (SD)	3910 (2490)	4710 (4220)	40.8 (26.4)	N/A
	CV%	63.8	89.7	64.6	N/A
	Geo-mean	3320	3450	34.9	N/A
	Geo-CV%	64.1	108.1	61.6	N/A
	Median	2960	4050	30.2	47.2
	[Min; Max]	[1280; 9840]	[1420; 11800]	[15.5; 110]	[8.5; 73.7]

Summary of secondary PK parameters for 7-hydroxy-S-warfarin by treatment (Pharmacokinetic analysis set – warfarin)

Treatment	Statistics	T1/2 (hr)	Lambda_z (1/hr)	Metabolic ratio (AUClast)
warfarin (N=20)	N	16	16	16
	Mean (SD)	45.0 (19.3)	0.0176 (0.00636)	0.173 (0.126)
	CV%	42.8	36.1	72.6
	Geo-mean	41.9	0.0165	0.143
	Geo-CV%	39.2	39.2	66.6
	Median	39.1	0.0177	0.135
	[Min; Max]	[20.4; 102]	[0.00681; 0.034]	[0.0565; 0.532]
warfarin+ ceritinib (N=20)	N	13	13	13
	Mean (SD)	67.5 (57.6)	0.014 (0.00622)	0.135 (0.0834)
	CV%	85.4	44.4	61.7
	Geo-mean	55.8	0.0124	0.117
	Geo-CV%	61.7	61.7	58.2
	Median	50.7	0.0137	0.113
	[Min; Max]	[25.3; 249]	[0.00278; 0.0274]	[0.0488; 0.363]

Summary of ceritinib concentrations (Pharmacokinetic analysis set – ceritinib)

Visit	Statistics	Concentration (ng/mL)
Day 28 (0 hr pre dose)	n	20
	m	20
	Mean (SD)	851 (377)
	CV%	44.4
	Geo-mean	767
	Geo-CV%	51.8
	Median	787
	[Min; Max]	[285; 1600]
Day 29 (0 hr pre dose)	n	16
	m	16
	Mean (SD)	870 (313)
	CV%	36
	Geo-mean	813
	Geo-CV%	42.0
	Median	842
	[Min; Max]	[290; 1480]
Day 30 (0 hr pre dose)	n	14
	m	14
	Mean (SD)	1030 (325)
	CV%	31.5
	Geo-mean	984

	Geo-CV%	34.0
	Median	1050
	[Min; Max]	[507; 1620]
Day 31 (0 hr pre dose)	n	13
	m	13
	Mean (SD)	1020 (335)
	CV%	33.0
	Geo-mean	960
	Geo-CV%	37.7
	Median	910
	[Min; Max]	[437; 1500]
Day 32 (0 hr pre dose)	n	10
	m	10
	Mean (SD)	1090 (353)
	CV%	32.5
	Geo-mean	1040
	Geo-CV%	31.7
	Median	984
	[Min; Max]	[689; 1740]
Day 33 (0 hr pre dose)	n	10
	m	10
	Mean (SD)	1080 (398)
	CV%	36.9
	Geo-mean	1010
	Geo-CV%	39.2

	Median	1020
	[Min; Max]	[533; 1740]
Day 34 (0 hr pre dose)	n	10
	m	10
	Mean (SD)	1070 (498)
	CV%	46.7
	Geo-mean	973
	Geo-CV%	47.0
	Median	903
	[Min; Max]	[512; 2090]

Secondary Outcome Result(s)

Best overall response per investigator assessment by cancer type (per RECIST 1.1) (FAS)

	NSCLC N=19			Other N=14			All patients N=33		
	n	(%)	95% CI [a]	n	(%)	95% CI [a]	n	(%)	95% CI [a]
Best overall response									
Complete Response (CR)	1	(5.3)		0			1	(3.0)	
Partial Response (PR)	7	(36.8)		1	(7.1)		8	(24.2)	
Stable Disease (SD)	2	(10.5)		2	(14.3)		4	(12.1)	
Progressive Disease (PD)	3	(15.8)		9	(64.3)		12	(36.4)	
Non-CR/Non-PD	2	(10.5)		0			2	(6.1)	
Unknown (UNK)	4	(21.1)		2	(14.3)		6	(18.2)	
Overall Response Rate (ORR: CR+PR)	8	(42.1)	(20.3, 66.5)	1	(7.1)	(0.2, 33.9)	9	(27.3)	(13.3, 45.5)
Disease Control Rate (DCR: CR+PR+SD+Non-CR/Non-PD)	12	(63.2)	(38.4, 83.7)	3	(21.4)	(4.7, 50.8)	15	(45.5)	(28.1, 63.6)

N was the denominator for percentage (%) calculation. [a] Exact binomial 95% CI.

Duration of response (CR+PR) per investigator assessment by cancer type (Full Analysis Set – patients with confirmed CR or PR)

	NSCLC N=19	Other N=14	All patients N=33
n/N (%)	2/8 (25.0)	0/1 (0.0)	2/9 (22.2)
Percentiles (95% CI) (months)			
25th			
Median			
75th			
% Event-free probability estimates (95% CI)			
3 months	100 (100, 100)	100 (100, 100)	100 (100, 100)
6 months	85.7 (33.4, 97.9)	NE	87.5 (38.7, 98.1)
9 months	85.7 (33.4, 97.9)	NE	87.5 (38.7, 98.1)
12 months	64.3 (15.1, 90.2)	NE	65.6 (15.7, 90.9)
15 months	64.3 (15.1, 90.2)	NE	65.6 (15.7, 90.9)
18 months	NE	NE	NE

Summary of Safety

Adverse Events by System Organ Class

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
-Any primary system organ class						
-Total	2 (6.1)	5 (15.2)	20 (60.6)	5 (15.2)	25 (75.8)	32 (97.0)
Blood and lymphatic system disorders						
-Total	2 (6.1)	4 (12.1)	3 (9.1)	0	3 (9.1)	9 (27.3)
Anaemia	1 (3.0)	5 (15.2)	2 (6.1)	0	2 (6.1)	8 (24.2)
Lymphopenia	1 (3.0)	0	1 (3.0)	0	1 (3.0)	2 (6.1)
Cardiac disorders						
-Total	1 (3.0)	1 (3.0)	0	1 (3.0)	1 (3.0)	3 (9.1)
Angina pectoris	1 (3.0)	0	0	0	0	1 (3.0)
Cardiac arrest	0	0	0	1 (3.0)	1 (3.0)	1 (3.0)
Pericarditis	0	1 (3.0)	0	0	0	1 (3.0)
Sinus tachycardia	1 (3.0)	0	0	0	0	1 (3.0)
Ear and labyrinth disorders						
-Total	3 (9.1)	0	0	0	0	3 (9.1)
Vertigo	2 (6.1)	0	0	0	0	2 (6.1)
Tinnitus	1 (3.0)	0	0	0	0	1 (3.0)
Eye disorders						
-Total	1 (3.0)	1 (3.0)	0	0	0	2 (6.1)
Conjunctival hyperaemia	1 (3.0)	0	0	0	0	1 (3.0)

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Visual acuity reduced	0	1 (3.0)	0	0	0	1 (3.0)
Gastrointestinal disorders						
-Total	8 (24.2)	16 (48.5)	5 (15.2)	0	5 (15.2)	29 (87.9)
Diarrhoea	16 (48.5)	8 (24.2)	1 (3.0)	0	1 (3.0)	25 (75.8)
Nausea	6 (18.2)	12 (36.4)	2 (6.1)	0	2 (6.1)	20 (60.6)
Vomiting	11 (33.3)	3 (9.1)	3 (9.1)	0	3 (9.1)	17 (51.5)
Abdominal pain	6 (18.2)	0	1 (3.0)	0	1 (3.0)	7 (21.2)
Constipation	6 (18.2)	1 (3.0)	0	0	0	7 (21.2)
Dyspepsia	6 (18.2)	1 (3.0)	0	0	0	7 (21.2)
Abdominal pain upper	5 (15.2)	1 (3.0)	0	0	0	6 (18.2)
Gastrooesophageal reflux disease	2 (6.1)	1 (3.0)	0	0	0	3 (9.1)
Stomatitis	2 (6.1)	1 (3.0)	0	0	0	3 (9.1)
Intestinal obstruction	0	0	2 (6.1)	0	2 (6.1)	2 (6.1)
Abdominal distension	1 (3.0)	0	0	0	0	1 (3.0)
Dry mouth	1 (3.0)	0	0	0	0	1 (3.0)
Dysphagia	1 (3.0)	0	0	0	0	1 (3.0)
Gastritis	0	1 (3.0)	0	0	0	1 (3.0)
Large intestinal haemorrhage	1 (3.0)	0	0	0	0	1 (3.0)
Tongue coated	1 (3.0)	0	0	0	0	1 (3.0)
General disorders and administration Site conditions						

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
-Total	4 (12.1)	9 (27.3)	4 (12.1)	0	4 (12.1)	17 (51.5)
Asthenia	5 (15.2)	3 (9.1)	2 (6.1)	0	2 (6.1)	10 (30.3)
Fatigue	2 (6.1)	3 (9.1)	2 (6.1)	0	2 (6.1)	7 (21.2)
Non-cardiac chest pain	4 (12.1)	2 (6.1)	0	0	0	6 (18.2)
Pyrexia	3 (9.1)	1 (3.0)	0	0	0	4 (12.1)
Oedema peripheral	2 (6.1)	0	1 (3.0)	0	1 (3.0)	3 (9.1)
Chills	1 (3.0)	0	0	0	0	1 (3.0)
Influenza like illness	1 (3.0)	0	0	0	0	1 (3.0)
Pain	1 (3.0)	0	0	0	0	1 (3.0)
Hepatobiliary disorders						
-Total	1 (3.0)	1 (3.0)	4 (12.1)	0	4 (12.1)	6 (18.2)
Cholangitis	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Cholelithiasis	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Cholestasis	0	1 (3.0)	0	0	0	1 (3.0)
Hepatotoxicity	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Jaundice	1 (3.0)	0	0	0	0	1 (3.0)
Liver injury	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Immune system disorders						
-Total	1 (3.0)	0	0	0	0	1 (3.0)
Seasonal allergy	1 (3.0)	0	0	0	0	1 (3.0)

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Infections and infestations						
-Total	4 (12.1)	6 (18.2)	5 (15.2)	0	5 (15.2)	15 (45.5)
Ear infection	0	2 (6.1)	0	0	0	2 (6.1)
Pneumonia	0	1 (3.0)	1 (3.0)	0	1 (3.0)	2 (6.1)
Urinary tract infection	1 (3.0)	1 (3.0)	0	0	0	2 (6.1)
Abscess limb	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Cystitis	0	1 (3.0)	0	0	0	1 (3.0)
Erysipelas	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Escherichia bacteraemia	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Gastroenteritis viral	1 (3.0)	0	0	0	0	1 (3.0)
Herpes virus infection	0	1 (3.0)	0	0	0	1 (3.0)
Herpes zoster	0	1 (3.0)	0	0	0	1 (3.0)
Klebsiella infection	1 (3.0)	0	0	0	0	1 (3.0)
Oral candidiasis	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Oral fungal infection	1 (3.0)	0	0	0	0	1 (3.0)
Pharyngitis	1 (3.0)	0	0	0	0	1 (3.0)
Respiratory tract infection	1 (3.0)	0	0	0	0	1 (3.0)
Rhinitis	1 (3.0)	0	0	0	0	1 (3.0)
Upper respiratory tract infection	1 (3.0)	0	0	0	0	1 (3.0)
Viral infection	1 (3.0)	0	0	0	0	1 (3.0)
Injury, poisoning and procedural complications						

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
-Total	1 (3.0)	0	0	0	0	1 (3.0)
Fall	1 (3.0)	0	0	0	0	1 (3.0)
Investigations						
-Total	4 (12.1)	8 (24.2)	12 (36.4)	2 (6.1)	14 (42.4)	26 (78.8)
Alanine aminotransferase increased	3 (9.1)	0	9 (27.3)	0	9 (27.3)	12 (36.4)
Gamma-glutamyltransferase increased	2 (6.1)	3 (9.1)	5 (15.2)	1 (3.0)	6 (18.2)	11 (33.3)
Aspartate aminotransferase increased	3 (9.1)	3 (9.1)	3 (9.1)	1 (3.0)	4 (12.1)	10 (30.3)
Blood alkaline phosphatase increased	4 (12.1)	4 (12.1)	2 (6.1)	0	2 (6.1)	10 (30.3)
Blood creatinine increased	3 (9.1)	3 (9.1)	1 (3.0)	0	1 (3.0)	7 (21.2)
Weight decreased	6 (18.2)	1 (3.0)	0	0	0	7 (21.2)
Electrocardiogram qt prolonged	4 (12.1)	1 (3.0)	0	0	0	5 (15.2)
Lipase increased	0	1 (3.0)	3 (9.1)	0	3 (9.1)	4 (12.1)
International normalised ratio increased	0	3 (9.1)	0	0	0	3 (9.1)
Amylase increased	1 (3.0)	0	1 (3.0)	0	1 (3.0)	2 (6.1)
Blood bilirubin increased	1 (3.0)	1 (3.0)	0	0	0	2 (6.1)
White blood cell count decreased	1 (3.0)	1 (3.0)	0	0	0	2 (6.1)
Activated partial thromboplastin time prolonged	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Blood albumin increased	1 (3.0)	0	0	0	0	1 (3.0)
Blood glucose increased	0	1 (3.0)	0	0	0	1 (3.0)
Blood urea increased	1 (3.0)	0	0	0	0	1 (3.0)

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
C-reactive protein increased	1 (3.0)	0	0	0	0	1 (3.0)
Heart rate decreased	1 (3.0)	0	0	0	0	1 (3.0)
Neutrophil count decreased	1 (3.0)	0	0	0	0	1 (3.0)
Prothrombin time prolonged	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Metabolism and nutrition disorders						
-Total	7 (21.2)	2 (6.1)	3 (9.1)	2 (6.1)	5 (15.2)	14 (42.4)
Decreased appetite	6 (18.2)	1 (3.0)	1 (3.0)	0	1 (3.0)	8 (24.2)
Hypokalaemia	3 (9.1)	1 (3.0)	2 (6.1)	1 (3.0)	3 (9.1)	7 (21.2)
Hyperglycaemia	2 (6.1)	0	0	1 (3.0)	1 (3.0)	3 (9.1)
Hypomagnesaemia	2 (6.1)	0	0	0	0	2 (6.1)
Electrolyte imbalance	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Hyperuricaemia	1 (3.0)	0	0	0	0	1 (3.0)
Hypoalbuminaemia	0	1 (3.0)	0	0	0	1 (3.0)
Hypophosphataemia	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Iron deficiency	1 (3.0)	0	0	0	0	1 (3.0)
Musculoskeletal and connective tissue disorders						
-Total	5 (15.2)	2 (6.1)	1 (3.0)	0	1 (3.0)	8 (24.2)
Musculoskeletal chest pain	2 (6.1)	1 (3.0)	0	0	0	3 (9.1)
Neck pain	3 (9.1)	0	0	0	0	3 (9.1)
Back pain	2 (6.1)	0	0	0	0	2 (6.1)

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Bone pain	0	1 (3.0)	0	0	0	1 (3.0)
Muscular weakness	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Spinal pain	0	1 (3.0)	0	0	0	1 (3.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
-Total	1 (3.0)	0	0	0	0	1 (3.0)
Tumour pain	1 (3.0)	0	0	0	0	1 (3.0)
Nervous system disorders						
-Total	11 (33.3)	3 (9.1)	2 (6.1)	0	2 (6.1)	16 (48.5)
Headache	5 (15.2)	1 (3.0)	0	0	0	6 (18.2)
Dizziness	4 (12.1)	0	0	0	0	4 (12.1)
Dysgeusia	2 (6.1)	1 (3.0)	0	0	0	3 (9.1)
Paraesthesia	2 (6.1)	0	0	0	0	2 (6.1)
Sciatica	0	2 (6.1)	0	0	0	2 (6.1)
Diabetic hyperglycaemic coma	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Epilepsy	1 (3.0)	0	0	0	0	1 (3.0)
Neuropathy peripheral	1 (3.0)	0	0	0	0	1 (3.0)
Partial seizures	1 (3.0)	0	0	0	0	1 (3.0)
Presyncope	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Psychomotor hyperactivity	1 (3.0)	0	0	0	0	1 (3.0)
Sonolence	1 (3.0)	0	0	0	0	1 (3.0)

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Syncope	1 (3.0)	0	0	0	0	1 (3.0)
Psychiatric disorders						
-Total	7 (21.2)	1 (3.0)	0	0	0	8 (24.2)
Depression	2 (6.1)	1 (3.0)	0	0	0	3 (9.1)
Insomnia	3 (9.1)	0	0	0	0	3 (9.1)
Anxiety	1 (3.0)	0	0	0	0	1 (3.0)
Confusional state	1 (3.0)	0	0	0	0	1 (3.0)
Disorientation	1 (3.0)	0	0	0	0	1 (3.0)
Restlessness	1 (3.0)	0	0	0	0	1 (3.0)
Renal and urinary disorders						
-Total	2 (6.1)	0	0	0	0	2 (6.1)
Renal impairment	1 (3.0)	0	0	0	0	1 (3.0)
Urinary retention	1 (3.0)	0	0	0	0	1 (3.0)
Reproductive system and breast disorders						
-Total	1 (3.0)	0	0	0	0	1 (3.0)
Pelvic pain	1 (3.0)	0	0	0	0	1 (3.0)
Respiratory, thoracic and mediastinal disorders						
-Total	10 (30.3)	2 (6.1)	4(12.1)	0	4 (12.1)	16 (48.5)

Primary system organ class Preferred term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 3/4 n (%)	All grades n (%)
Cough	7 (21.2)	0	0	0	0	7 (21.2)
Dyspnoea	2 (6.1)	2 (6.1)	2 (6.1)	0	2 (6.1)	6 (18.2)
Nasal congestion	2 (6.1)	0	0	0	0	2 (6.1)
Pulmonary embolism	0	0	2 (6.1)	0	2 (6.1)	2 (6.1)
Epistaxis	1 (3.0)	0	0	0	0	1 (3.0)
Haemoptysis	1 (3.0)	0	0	0	0	1 (3.0)
Hypoxia	0	1 (3.0)	0	0	0	1 (3.0)
Pharyngeal erythema	1 (3.0)	0	0	0	0	1 (3.0)
Productive cough	1 (3.0)	0	0	0	0	1 (3.0)
Rhinorrhoea	1 (3.0)	0	0	0	0	1 (3.0)
Tachypnoea	1 (3.0)	0	0	0	0	1 (3.0)
Skin and subcutaneous tissue disorders						
-Total	7 (21.2)	1 (3.0)	1 (3.0)	0	1 (3.0)	9 (27.3)
Rash	5 (15.2)	1 (3.0)	0	0	0	6 (18.2)
Rash pruritic	2 (6.1)	0	0	0	0	2 (6.1)
Alopecia	1 (3.0)	0	0	0	0	1 (3.0)
Dry skin	1 (3.0)	0	0	0	0	1 (3.0)
Hyperhidrosis	1 (3.0)	0	0	0	0	1 (3.0)
Photosensitivity reaction	0	1 (3.0)	0	0	0	1 (3.0)
Pruritus	1 (3.0)	0	0	0	0	1 (3.0)
Skin fissures	1 (3.0)	0	0	0	0	1 (3.0)
Urticaria	0	0	1 (3.0)	0	1 (3.0)	1 (3.0)
Vascular disorders						
-Total	2 (6.1)	3 (9.1)	0	0	0	5 (15.2)
Hypertension	1 (3.0)	3 (9.1)	0	0	0	4 (12.1)
Hot flush	1 (3.0)	0	0	0	0	1 (3.0)
Hypotension	1 (3.0)	0	0	0	0	1 (3.0)

Adverse events, regardless of study drug relationship by preferred term and maximum grade (greater than or equal to 10% in all grades) (Safety set)

Preferred term	All grades n (%)	Grade 3/4 n (%)
-Total	32 (97.0)	25 (75.8)
Diarrhoea	25 (75.8)	1 (3.0)
Nausea	20 (60.6)	2 (6.1)
Vomiting	17 (51.5)	3 (9.1)
Alanine aminotransferase increased	12 (36.4)	9 (27.3)
Gamma-glutamyltransferase increased	11 (33.3)	6 (18.2)
Aspartate aminotransferase increased	10 (30.3)	4 (12.1)
Asthenia	10 (30.3)	2 (6.1)
Blood alkaline phosphatase increased	10 (30.3)	2 (6.1)
Anaemia	8 (24.2)	2 (6.1)
Decreased appetite	8 (24.2)	1 (3.0)
Abdominal pain	7 (21.2)	1 (3.0)
Blood creatinine increased	7 (21.2)	1 (3.0)
Constipation	7 (21.2)	0
Cough	7 (21.2)	0
Dyspepsia	7 (21.2)	0
Fatigue	7 (21.2)	2 (6.1)
Hypokalaemia	7 (21.2)	3 (9.1)
Weight decreased	7 (21.2)	0
Abdominal pain upper	6 (18.2)	0
Dyspnoea	6 (18.2)	2 (6.1)
Headache	6 (18.2)	0
Non-cardiac chest pain	6 (18.2)	0
Rash	6 (18.2)	0
Electrocardiogram qt prolonged	5 (15.2)	0
Dizziness	4 (12.1)	0
Hypertension	4 (12.1)	0
Lipase increased	4 (12.1)	3 (9.1)

Pyrexia	4 (12.1)	0

Serious Adverse Events and Deaths

On treatment deaths, by principal cause, primary system organ class and preferred term (Safety set)

Principal cause of Death System organ class Preferred terms	All patients N=33 n(%)
Total on-treatment deaths	4 (12.1)
Study indication	4 (12.1)

- Principal cause of death was presented in descending order of frequency; preferred terms were sorted within principal cause also by descending frequency.
- On-treatment deaths were deaths which occurred up to 30 days after the last dose of study drug.
- If death was due to study indication, MedDRA coding was not applicable.
- MedDRA version 20.1 was used.

Serious adverse events, regardless of study drug relationship by preferred term and maximum grade (Safety set)

	All patients N=33	
Preferred term	**All grades n (%)**	**Grade 3/4 n (%)**
-Total	13 (39.4)	11 (33.3)
Abscess limb	1 (3.0)	1 (3.0)
Asthenia	1 (3.0)	1 (3.0)
Cardiac arrest	1 (3.0)	1 (3.0)
Cholangitis	1 (3.0)	1 (3.0)
Cholelithiasis	1 (3.0)	1 (3.0)
Diabetic hyperglycaemic coma	1 (3.0)	1 (3.0)
Dyspnoea	1 (3.0)	1 (3.0)
Electrolyte imbalance	1 (3.0)	1 (3.0)
Epilepsy	1 (3.0)	0
Erysipelas	1 (3.0)	1 (3.0)
Escherichia bacteraemia	1 (3.0)	1 (3.0)
Fatigue	1 (3.0)	1 (3.0)
Hypoxia	1 (3.0)	0
Intestinal obstruction	1 (3.0)	1 (3.0)
Liver injury	1 (3.0)	1 (3.0)
Oral candidiasis	1 (3.0)	1 (3.0)
Pericarditis	1 (3.0)	0
Pneumonia	1 (3.0)	1 (3.0)
Visual acuity reduced	1 (3.0)	0

- Preferred terms were sorted in descending frequency of "All Grades" column.
- A patient with multiple occurrences of an AE was counted only once in the AE category for that treatment.
- A patient with multiple adverse events was counted only once in the total row.
- Only AEs which occurred during treatment or within 30 days of the last dose of study drug were reported.
- AEs were graded according to the CTCAE V4.03; MedDRA version 20.1 was used.

Other Relevant Findings

Not applicable

Conclusion:

The primary objective of this phase I, multi-center, open-label, single sequence, crossover study was to evaluate the effects of daily ceritinib dosing on the single dose PK of the probe drugs midazolam and warfarin, which are metabolized by CYP3A and CYP2C9, respectively, in patients with ALK-positive advanced tumors including NSCLC.

- Coadministration of ceritinib (750 mg daily for 3 weeks) in patients increased the AUCinf of midazolam 5.4-fold (90% CI: 4.6 to 6.3) compared to midazolam alone, suggesting that ceritinib is a strong inhibitor of CYP3A.
- Coadministration of ceritinib (750 mg daily for 3 weeks) in patients increased the AUCinf of S-warfarin (the more potent enantiomer) by 54% (geometric mean ratio: 1.54; 90% CI: 1.36 to 1.75) compared to S-warfarin alone, suggesting that ceritinib is a weak inhibitor of CYP2C9. However, since warfarin is commonly prescribed as an anti-coagulant with narrow therapeutic index, a 54% increase in exposure is not considered negligible given the potential risk of changing the downstream pharmacodynamic effect of warfarin (i.e., anti-coagulation). Effect of ceritinib on chronic use of warfarin has not been investigated.
- Overall, the frequency, severity, and type of AEs were consistent with the known safety profile of ceritinib, and no new safety signals were reported.
- The efficacy results for patients with NSCLC in this heavily pretreated patient population were similar to those observed in previous studies in pretreated patients with ALK- positive NSCLC.

Date of Clinical Trial Report

22 Aug 2018