A multi-center, randomized open label study to assess the systemic exposure, efficacy, 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) (CLDK378A2112)

Published: 30-06-2015
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Primary: To assess the steady-state 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 patients with metastatic ALK-positive NSCLC.Secondary: Overall response...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON43595

Source
ToetsingOnline

Brief title
CLDK378A2112

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
non small cell lung cancer; lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: Ceritinib, food, lung cancer, NSCLC

Outcome measures

Primary outcome

Steady state PK parameters.

Secondary outcome

Adverse events. ORR, DOR, DCR, TTR, PFS, OS. Single dose PK.

Study description

Background summary

Cisplatin or carboplatin in combination with other chemotherapy agents, with or without bevacizumab is standard first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), unless a patient has a known targetable gene mutation or aberration, and is therefore a candidate for a targeted therapy.
Although chemotherapy has led to clinical improvements in patients with locally advanced or metastatic NSCLC, the outcome of treatment in the first-line setting remains poor, with median progression-free survival (PFS) and overall survival (OS) of 5-7 months and 10-16 months, respectively.
A clinically relevant molecular subset of NSCLC is driven by the anaplastic

lymphoma kinase (ALK) translocation. It ALK is translocated, mutated, or amplified, it plays a key role in the pathogenesis in several tumor types, including NSCLC.
Metastatic ALK-positive NSCLC remains an incurable disease. Recent studies have demonstrated the efficacy of ALK inhibitors in ALK-positive NSCLC and of immunotherapy with PD-1 antibodies/blocking agents, such as nivolumab, in NSCLC patients.
Ceritinib is an orally available potent ALK inhibitor. Ceritinib shows potent antitumor activity in animal models. Efficacy was seen in the ongoing phase I clinical trial in patients, which led to the approval of ceritinib by the EMA and FDA for the treatment of patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.
However, safety data from this study showed a high frequency of overall GI adverse effects when ceritinib was administered on an empty stomach at a dose of 750 mg daily, the recommended phase II/III dose. The majority of GI events were mild to moderate. However, GI symptoms can affect patients* general well-being as well as drug absorption.
A food effect study conducted in healthy subjects showed that the bioavailability of ceritinib is increased when given with a meal. Compared to the fasted condition, a low-fat meal increased Cmax and AUCinf by 43% and 58%, respectively, whereas a high-fat meal increased Cmax and AUCinf by 41% and 73%, respectively.
The primary aim of this study is to assess the steady-state 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-positive NSCLC.

Study objective

Primary: To assess the steady-state 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 patients with metastatic ALK-positive NSCLC.
Secondary: Overall response rate (ORR), duration of response (DOR), disease control rate (DCR), time to response (TTR), PFS, OS. Safety and tolerability. Single dose PK.

Study design

Multicenter open-label parallel group phase I study. Food effect part and efficacy part. Randomization (1:1:1) to
4. Ceritinib once daily 450 mg in the morning within 30 minutes following a low-fat meal. Patients should refrain from eating one hour after dosing.
5. Ceritinib once daily 600 mg in the morning within 30 minutes following a low-fat meal. Patients should refrain from eating one hour after dosing.
6. Ceritinib once daily 750 mg in the morning on an empty stomach.
At least 90 patients (up to 150) who satisfy the PK evaluability criteria for

the primary objective, will be randomized (see protocol page 43-44).
After these 90 evaluable patients have been confirmed, enrollment into the study will be restricted to treatment-naive ALK-positive NSCLC patients (approximately n=210) for the key secondary efficacy endpoint.
Treatment until disease progression or unacceptable side effects. Patients who discontinue study treatment for any reason other than disease progression will be followed up for progression of disease and all patients will be followed for survival.
Approx. 300 subjects.

Intervention

Treatment with ceritinib.

Study burden and risks

Risk: Adverse effects of study drug.
Burden: Cycles of 3 weeks. Cycle 1: 4 visits, cycle 2: 2 visits, from cycle 3 onwards: 1 visit. Duration mostly 2 hours. 2 visits 8 hours.
Low-fat diet for treatment groups 1-2 (incl. meal record on PK days).
Physical examination: cycle 1: 3 times, from cycle 2 onwards once/cycle.
Blood tests (10-15 ml/occasion): nearly every visit. PK (9 times); 2-12 ml extra. Biomarkers: 10 ml (screening 16 ml) extra (screening plus every 4th cycle).
Pregnancy test: once/cycle.
Urine testing once.
Tumor measurements: every 2 cycles for the 1st 9 cycles, every 4 cycles thereafter.
ECG: cycle 1: 3 times, cycle 2: twice, from cycle 3 onwards once/cycle.
Tumor biopsy: 0-2 times (1st mandatory if no archival sample is available, 2nd optional).

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Female and male patients * 18 years of age.
* Stage IIIB or IV ALK-positive NSCLC. Pre-treated and treatment-naive. See protocol page 14 for details.
* Clinically and neurologically stable CNS metastases who have not required increasing doses of steroids within 2 weeks prior to study entry to manage CNS symptoms are eligible.
* Prior treatment with ceritinib is allowed (washout at least 7 days). Prior treatment with all other ALK-inhibitors is excluded.
* Pre-treatment with chemotherapy, biologicals, investigational drugs is allowed (washout at least 2 weeks).
* WHO performance status 0 or 1 or 2.
* Measurable disease for treatment-naive subjects. See protocol page 15 for details.
* For treatment-naive subjects (neo)adjuvant treatment (excl. a regimen with an ALK-inhibitor) is allowed only if a relapse occurred more than 12 months after the end of this treatment.

Exclusion criteria

* Prior treatment with ALK-inhibitor other than crizotinib.
* History of carcinomatous meningitis.
* Clinically significant, uncontrolled heart disease and/or recent cardiac event (within 6 months). See protocol page 16 for details.
* (History of) interstitial lung disease or interstitial pneumonitis (incl. radiation pneumonitis), affecting activities of daily living or requiring therapeutic intervention.
* Impairment of GI function or GI disease that may significantly alter the absorption of

ceritinib
* Comedications/cotreatments etc. listed on page 16-17 of the protocol (items 10-16).
* Pregnancy, lactation, inadequate contraception (males and females). See protocol page 17-18 for details.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-11-2015
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zykadia
Generic name:	ceritinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	30-06-2015

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-09-2015
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-02-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-05-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-06-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	25-10-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-04-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-09-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2017
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-08-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
Other	clinicaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2014-004001-32-NL
CCMO	NL53629.100.15