The food-effect of a standardized Dutch breakfast on the pharmacokinetics of oral alectinib (Alecensa®) using a stable isotopically labelled microtracer approach

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To determine the food-effect of a standardised Dutch breakfast on the pharmacokinetics of oral alectinib (Alecensa®), especially Cmax, AUC and relative bioavailability, at steady state using a stable isotopically labelled microtracer approach.

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56401

Source
ToetsingOnline

Brief title
Het food-effect on the pharmacokinetics of alectinib.

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: NKI-AVL

Intervention

Keyword: alectinib, food-effect, microtracer, pharmacokinetics

Outcome measures

Primary outcome

To determine the food-effect of the standardised breakfast on alectinib-d6

pharmacokinetics, the pharmacokinetic metrics will be analyzed with a Wilcoxin

signed-rank test.

Secondary outcome

Not applicable

Study description

Background summary

Alectinib (Alecensa®) is a highly selective inhibitor of anaplastic lymphoma kinase (ALK) [1]. Its efficacy against oncogenic ALK fusion gene-rearrangements (ALK-positive) and good penetration through the blood-brain-barrier makes alectinib an effective agent against ALK-positive non-small cell lung cancer (NSCLC) [1]. Alectinib is recommended as first-line treatment of ALK-positive NSCLC [2]. The registered dose is 600 mg bidaily (BID) in Western countries [1] and patients are recommended to administer their daily alectinib doses with food [3].

The advice to administer alectinib with food is based on the results from a cross-over, food-effect study in 18 healthy volunteers [4]. Subjects received a single oral dose of 600 mg alectinib in a fasted state and a fed state [4]. In the fed state, patients received a standardized high-calorie, high-fat meal containing 900 calories (56% of fat) [4]. The maximum concentration (Cmax) and Area-under-the-concentration-time-Curve (AUC) increased with 2.7- and 2.92-fold in the fed state compared to the fasted state [4].

The standardized breakfast used in the above described study is conform guidelines for food-effect studies by the European Medicines Agency (EMA) and US Food and Drug administration (FDA) [5,6]. However, a high-calorie, high-fat breakfast is not an accurate representation for the average Dutch breakfast [7]. Furthermore, other studies have reported a moderate food-effect on alectinib pharmacokinetics: reporting an elongated time to maximum concentration (Tmax) [8] and an increase in Cmax and AUC0-t of approximately 20% [9]. Continuing, a recent retrospective study reported an inter-individual variability of 57.2% and intra-individual variability of 27.0% in alectinib pharmacokinetics [10]. Therefore, an increase in Cmax and AUC0-t of approximately 20% is not clinically relevant.

Physiochemical properties of alectinib show low solubility and moderate permeability, resulting in a moderate absolute bioavailability of 36.9% [11]. High fat constituents of food could increase alectinib solubility in the intestines and thereby increase uptake. This could explain the difference in food-effect seen after a high-calorie, high-fat meal in comparison to other food-effect studies [8,9,4]. Furthermore, alectinib is majorly metabolized by cytochrome P450 3A (CYP3A) to its major metabolite M4 [12]. M4 exhibits similar active potency to alectinib and is therefore expected to contribute to the efficacy of alectinib [1]. The previously described high-calorie, high-fat breakfast increased the Cmax and AUCinf with 3.77 and 3.28 fold, respectively [4]

The aim of this study is to determine the food-effect of a standardized Dutch breakfast on the pharmacokinetics of alectinib. Despite the fact that three studies have reported a food-effect on alectinib pharmacokinetics [4,8,9], it is still unclear what the food-effect is on alectinib exposure in the daily lives of patients. It is important to understand this effect due the high inter- and intra-individual variability observed in alectinib exposure as well as the observed exposure-response relationship [10]. Food might be a strategy to increase exposure without dose increase or reduce intra-individual variability.

A conventional, cross-over, food-effect study requires the participating patients to administer the investigational drug with and without food over several days until steady-state is reached (approximately 5 times the half-life of the respective drug). When steady-state is reached, blood samples will be collected for the determination of exposure of the investigational drug. However, this study design is inappropriate for the determination of the food-effect of alectinib due to possibly underexposure. A previously reported exposure-response analysis reported significantly decreased survival for NSCLC patients with an alectinib trough plasma concentrations (Ctrough) <435 ng/mL [10]. Clinical trial simulations demonstrated that 55.5% of patients will have Ctrough below the target when alectinib is administered under fasting conditions assuming a food-effect of 40%.

A microtracer approach was chosen to determine the food-effect on alectinib pharmacokinetics without influencing the therapeutic treatment. A microtracer is a 100 µg dose of a stable isotopically labelled (SIL) drug [13]. These microtracers have been used for the determination of absolute food-effect [13]. Due to the mass difference between the therapeutic administered drug and the microtracer, the concentrations of both compounds can be simultaneously quantified in the same sample.

Study objective

To determine the food-effect of a standardised Dutch breakfast on the pharmacokinetics of oral alectinib (Alecensa®), especially Cmax, AUC and relative bioavailability, at steady state using a stable isotopically labelled microtracer approach.

Study design

A prospective, single-center, open-label, food-effect stable isotopically labelled microtracer study with oncology patients, who will receive an oral dose of alectinib-d6. After obtaining informed consent, blood will be drawn for pharmacokinetics after administration of alectinib-d6 in a fed state and a fasted state (see Pharmacokinetics). The fed state consists of a standardised Dutch breakfast (320-392 kCal, 7.5-7.8 gram fat). The fasted state consists of an overnight fast of minimal 10 hours.

Intervention

Patients will receive twice a 100 microgram dose of alectinib-d6 (microtracer). The first dose will be administered with the standardized breakfast en de second dose will be administered after a washout periode and an ovenright fast of minimal 10 hours.

Study burden and risks

Patients participating will be hospitalized for 8 hours on two separate occasions. Blood sampling for pharmacokinetic research will be done at 8 time points. As alectinib-d6 is administered as a single low dose oral treatment, no additional risk is expected to be associated with study participation.

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

1. Currently treated with alectinib for an oncological indication;
2. On alectinib treatment at a stable dose of 600 mg twice daily according to standard of care;

Exclusion criteria

1. Any treatment with investigational drugs within 30 days or 5 half-lives prior to receiving the investigational treatment;
2. Any treatment with inhibitors of CYP3A4 (e.g. boceprevir, claritromycine, erytromycine, indinavir, itraconazol, ketoconazole, ritonavir and voriconazol), or inductors of CYP3A4 within two weeks or 5 half-lives prior to the start of the study. Alectinib is not a substrate for P-gp, BCRP, OATP1B1 or OATP1B3 [15].
3. Patients suffering from any known disease or dysfunction that might influence the dissolution and/or absorption of alectinib (e.g. inflammatory bowel disease, gastric bypass).

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-02-2024
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	07-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	19-05-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-12-2023
Application type:	Amendment
Review commission:	METC NedMec

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
EudraCT	EUCTR2021-006957-69-NL
CCMO	NL80254.041.23
Other	Not yet applicable