A Phase I, Open-Label, Non-Randomised, Multicentre Study to Assess the Effect of Rifampicin (a CYP3A4 Inducer) on the Pharmacokinetics of AZD9291 in Patients with EGFRm Positive NSCLC whose disease has Progressed on an EGFR TKI

Published: 21-08-2014
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To investigate the effect of a CYP3A4 inducer (rifampicin) on the PK of AZD9291.

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

Summary

ID

NL-OMON44697

Source
ToetsingOnline

Brief title
AZD9291 - study D5160C00013

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, Progressive EGFRmutation positive Non Small Cell Lung Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: pharmaceutical company

Intervention

Keyword: AZD9291, Non Small Cel Lung Cancer, Phase I, Rifampicin

Outcome measures

Primary outcome

To investigate the effect of multiple oral dosing of rifampicin on the

steady-state exposure of AZD9291 (Css,max and AUCtau), following oral

dosing in patients with EGFRm+ NSCLC following progression on a EGFR TKI.

Secondary outcome

Secondary Objective:

To characterise the PK of AZD9291 and metabolites (AZ5104 and AZ7550) following

oral dosing of the tablet formulation in the presence

and absence of rifampicin.

Safety Objectives:

Part A: To examine the safety and tolerability of AZD9291 in patients with

EGFRm+ NSCLC in the presence and absence of co-administered

rifampicin.

Part B: To examine the safety and tolerability of AZD9291 following extended

administration in patients with EGFRm+ NSCLC.

Exploratory Objectives:

Part A: To assess the induction potential of AZD9291 on cytochrome P450 3A4 (CYP3A4).

Part A: To perform genetic research in the AZD9291 clinical pharmacology development programme to explore how genetic variations may affect the clinical pharmacokinetics of AZD9291.

Part A: To provide data to allow analysis using population PK approaches.

Study description

Background summary

AZD9291 is a potent irreversible inhibitor of both the single EGFRm+ (TKI sensitivity conferring mutation) and dual EGFRm+/T790M+ (TKI resistance conferring mutation) receptor forms of EGFR with a significant selectivity margin over wild-type EGFR. Therefore AZD9291 has the potential to provide clinical benefit to patients with advanced NSCLC harbouring both the single sensitivity mutations and the resistance mutation following prior therapy with an EGFR TKI. The clinical development programme with AZD9291 will initially assess the safety and efficacy of AZD9291 in patients with advanced NSCLC whose cancers have progressed following an EGFR TKI regimen (with or without additional chemotherapy regimens), as they currently represent a major unmet medical need population. The principal P450 isoenzymes responsible for human metabolism of AZD9291, AZ5104 and AZ7550 in recombinant microsomes were CYP3A4 and/or CYP3A5. Hence the current study has been designed to investigate the effect of a CYP3A4 inducer (rifampicin) on the PK of AZD9291.

Study objective

To investigate the effect of a CYP3A4 inducer (rifampicin) on the PK of AZD9291.

Study design

Part A will assess the effect of rifampicin on the PK parameters of AZD9291 and metabolites AZ5104 and AZ7550 following multiple oral dosing of both rifampicin and AZD9291 in a fasted state.
Part B will allow patients further access to AZD9291 after the PK phase (Part

A) and will provide for additional safety data collection.

Intervention

In Part A, each patient will receive AZD9291 80 mg once daily for 77 days (Days 1 to 77). Patients will also receive oral daily doses of rifampicin for 21 days (Day 29 to 49) concurrently with AZD9291.
In part B, each patient will receive continuous dosing of AZD9291 80 mg once daily (od) for the duration of their participation.

Study burden and risks

From the subject information form:
Risks Associated with AZD9291: The side effects listed below are those that have occurred most commonly with AZD9291 or may be due to AZD9291 mechanism of action and knowledge of similar drugs:
• Diarrhoea - occurring as very common (more than 1 in 10 patients).
• Rash and acne - occurring as common (more than 1 in 100 patients and less than 1 in 10 patients) to very common (more than 1 in 10 patients).
• Dry skin - occurring as common (more than 1 in 100 patients and less than 1 in 10 patients) to very common (more than 1 in 10 patients). These types of skin effects can be treated with creams and lotions, or antibiotic therapy.
• Nail changes; nail infections or changes to eyelashes. These types of effects can be treated with creams and lotions, and may require antibiotic therapy.
• Heart problems. Tell your doctor right away if you have symptoms of a heart problem which may include: new or worsening shortness of breath while at rest or with activity; cough; tiredness; swelling of your ankles, feet, or legs; feeling that your heart is pounding, racing (palpitations), or irregular; sudden weight gain. You will be monitored throughout the study and your study doctor may tell you to stop taking AZD9291 or may give you specific treatment.
• Dryness of the eyes, or thinning of the front layer of the eye. You should tell your study doctor right away if you have eye symptoms (such as burning, irritation or smarting; itching; blurred vision; redness with or without discharge; light sensitivity) during the study.
• Changes to the lining of the gut, which may lead to problems with diarrhoea, swallowing, feeling or being sick (nausea or vomiting), heartburn or indigestion.
• Inflammation of the lungs (symptoms may include being breathless, a new or worsening cough or shortness of breath, possibly with fever). This can be a lifethreatening condition and may need to be treated urgently.Tell your study doctor right away if you have any of these symptoms.
• Potential risk of harm to unborn babies.
Risks Associated with Rifampicin
Some possible serious side effects including: allergy, jaundice, bruising, anaemia, blood in urine, headache, hallucinations, diarrhoea, flu-like symptoms, water retention, muscle weakness and dizziness have been reported in

patients receiving rifampicin.

Contacts

Public
Astra Zeneca

Not applicable Not applicable
Sodertalje SE-151-85
SE
Scientific
Astra Zeneca

Not applicable Not applicable
Sodertalje SE-151-85
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For inclusion in the study patient should fulfil the following criteria:;1. Male or female, aged at least 18 years.;2. Histological or cytological confirmation diagnosis of NSCLC.;3. Radiological documentation of disease progression while on a previous continuous treatment with an EGFR TKI, eg gefitinib, erlotinib or afatinib. In addition, other lines of therapy may have been given. All patients must have documented radiological progression on the last treatment administered prior to enrolling in the study. ;4. Confirmation that the tumour harbours an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, L861Q). ;5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1 with no deterioration over the previous 2 weeks.;6. Patients must have a life expectancy

of >=12 weeks as estimated at the time of screening. ;7. Females should be using adequate contraceptive measures and must have a negative pregnancy test prior to start of dosing if of child-bearing potential, or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening: Post-menopausal defined as aged more than 50 years and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments. Women under 50 years old would be considered post-menopausal if they have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels in the post-menopausal range for the institution. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy, but not tubal ligation.;8. Male patients should be willing to use barrier contraception, ie, condoms, until 6 months after last study drug is taken.;9. Contact lens wearers must be prepared to not wear contact lenses and wear glasses for the duration of the rifampicin dosing.

Exclusion criteria

1. Participation in another clinical study with an IP during the last 14 days (or a longer period depending on the defined characteristics of the agents used).;2. Treatment with any of the following: Treatment with an EGFR TKI (eg, erlotinib or gefitinib) w/in 8 days or approx. 5 x half-life, whichever is the longer, of the first dose of study treatment; any cytotoxic chemo, investigational agents or other anticancer drugs from a previous treatment regimen w/in 14 days of the first dose of study treatment; major surgery (excluding placement of vascular access) w/in 4 weeks of the first dose of study treatment; radiotherapy with a limited field of radiation for palliation w/in 1 week of the first dose of study treatment, with the exception of patients receiving radiation to more than 30% of bone marrow or with a wide field of radiation which must be completed w/in 4 weeks of the first; patients currently receiving (or unable to stop use prior to receiving the first dose) medications or herbal supplements known to be potent inhibitors of CYP3A4 (at least 1 week prior) and potent inducers of CYP3A4 (at least 3 week prior). All patients in part B and continued access must avoid concomitant use of any medications, herbal supplements and/or ingestion of foods with known potent inducer effects on CYP3A4.;3. Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting study treatment with the exception of alopecia and Grade 2, prior platinum-therapy related neuropathy.;4. Any intake of grapefruit, grapefruit juice, Seville oranges, Seville orange marmalade, or other products containing grapefruit or Seville oranges within 7 days of the first administration of the IP until the final PK sample collection on Day 78 of Part A.;5. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment.;6. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which in the Investigator*s opinion makes it undesirable for the patient to participate in the study or which would jeopardise compliance with the protocol, or active infection including hepatitis B, hepatitis C and HIV. Screening for chronic conditions is not required.;7. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values: ANC <1.5 x 10^9/L; Platelet count <100 x 10^9/L; Haemoglobin <90 g/L; ALT >2.5 times the ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases; AST >2.5 times ULN if no

demonstrable liver metastases or >5 times ULN in the presence of liver metastases; Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert*s Syndrome (unconjugated hyperbilirubinaemia) or liver metastases; creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times ULN.;8. Any of the following cardiac criteria: Mean resting corrected QT interval corrected for heart rate using Fridericia*s correction factor (QTcF) >470 msec obtained from 3 electrocardiograms (ECGs); any clinically important abnormalities in rhythm, conduction or morphology of resting ECG eg, complete left bundle branch block, third degree heart block, second degree heart block, PR interval >250 msec; any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family history of long QT syndrome or unexplained sudden death under 40 years of age or any concomitant medication known to prolong the QT interval.;9. Patients unable to swallow oral medication or patients with GI disorders or significant GI resection likely to interfere with the absorption of AZD9291.;10. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.;11. Women who are breastfeeding.;12. Patients with a known hypersensitivity to AZD9291 or rifampicin or any of the excipients of the products.;13. Concomitant medication contraindicated for use with rifampicin (including, but not limited to): cisapride, oral midazolam, nisoldipine, pimozide, quinidine, dofetilide, triazolam, levacetylmethadol (levomethadyl), 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA)-reductase inhibitors metabolised by CYP3A4, such as lovastatin and simvastatin, ergot alkaloids metabolised by CYP3A4, such as dihydroergotamine, ergometrine (ergonovine), ergotamine and methylergometrine (methylergonovine).;14. For optional genetic research: .Previous allogenic bone marrow transplant or Non-leukocyte depleted whole blood transfusion within 120 days of the date of the genetic sample collection.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-01-2015

Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TAGRISSO
Generic name:	Osimertinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-08-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-01-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	15-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	01-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	23-03-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	15-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

	Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-03-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Not approved Date:	25-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-05-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-08-2019

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2014-001525-32-NL
ClinicalTrials.gov	NCT02197247
CCMO	NL49921.031.14