A Phase 1 Drug-Drug Interaction Study Between Brigatinib and the CYP3A Substrate Midazolam in Patients With ALK-Positive or ROS1-Positive Solid Tumors

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Primary Objective: To characterize the effect of repeat-dose administration of brigatinib 180 mg QD on the single-dose PK of midazolam.Other Objectives:Safety: To assess the safety and tolerability of brigatinib in patients with ALK-positive or ROS1...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON48899

Source
ToetsingOnline

Brief title
Brigatinib-1001

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
solid tumor, tumor that develops in an organ

Research involving
Human

Sponsors and support

Primary sponsor: ARIAD wholly owned subsidiary of Takeda Pharmaceutical Company Limited
Source(s) of monetary or material Support: ARIAD;a wholly owned subsidiary of Takeda Pharmaceutical Company Ltd.

Intervention

Keyword: ALK-Positive or ROS1-Positive Solid Tumors, anaplastic lymphoma kinase, drug-drug interaction, non-small-cell lung cancer

Outcome measures

Primary outcome

Endpoints and Assessments:

* Primary: Midazolam PK parameters in the presence and absence of brigatinib,

including:

* Area under the concentration-time curve from time 0 to infinity (AUC*)

* Maximum observed concentration (Cmax)

* Time of first occurrence of Cmax (tmax).

Secondary outcome

Primary: Midazolam PK parameters in the presence and absence of brigatinib,

including:

* Area under the concentration-time curve from time 0 to infinity (AUC*)

* Maximum observed concentration (Cmax)

* Time of first occurrence of Cmax (tmax).

Other endpoints include safety and tolerability.

Statistical Considerations: Midazolam PK parameters in the presence and absence

of brigatinib will be summarized descriptively. For the estimation of the

effect of brigatinib on midazolam PK, the ratios of geometric mean midazolam AUC* and Cmax (with vs without brigatinib coadministration) and the associated 2-sided 90% CIs will be calculated on the basis of the within-patient variance using a mixed-effects analysis of variance. An interim analysis will be conducted after all patients complete Part A of the study.

Descriptive statistics will be presented for continuous safety variables (laboratory test values, vital signs, weight) by scheduled time point. Shift tables for laboratory parameters will be generated to show changes in National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, grade from Baseline to the worst post-Baseline value.

Sample Size Justification: It is anticipated that approximately 20 patients will be enrolled to obtain approximately 15 PK evaluable patients. The sample size calculation was based on the expected 2-sided 90% CI for the difference in the paired, log-transformed AUC* means of midazolam in the absence and presence of brigatinib. The within-patient coefficient of variation for midazolam AUC* was estimated to be 28% on the basis of a pooled analysis of data from 5 drug-drug interaction studies with midazolam conducted in patients with cancer [1-5]. Assuming that the AUC* ratio for midazolam in the presence versus absence of brigatinib is 1, with a sample size of 15, the 90% CI for the AUC* ratio is expected to be 0.84 to 1.19 on the basis of the variance assumptions.

If the AUC* ratio for midazolam in the presence versus absence of brigatinib is X, with a sample size of 15, the 90% CI for the AUC* ratio is expected to be 0.84X to 1.19X on the basis of the variance assumptions.

Study description

Background summary

In vitro studies using human hepatocytes have indicated that brigatinib, at clinically relevant concentrations of 1 to 2.5 *M, caused an increase in cytochrome P450 3A (CYP3A4) messenger RNA levels (see the Investigator*s Brochure for further details). Therefore, brigatinib may have the potential for pharmacokinetic (PK) drug interactions with substrates of CYP3A through induction of expression of this enzyme, potentially leading to decreased systemic exposures of its substrates.

The primary purpose of this study (Brigatinib-1001) is to evaluate the effect of repeated doses of brigatinib on the single-dose PK of midazolam, a sensitive CYP3A probe substrate, to determine if brigatinib, at therapeutic doses, produces clinically meaningful CYP3A induction in vivo, and if so, to inform strategies for the management of potential drug-drug interactions (DDIs) between brigatinib and substrates of CYP3A. Midazolam is an established sensitive substrate of CYP3A that is commonly used in clinical DDI studies to assess the effect of a coadministered drug on CYP3A activity. Oral doses of midazolam ranging from 2 to 7.5 mg have generally been used in clinical DDI studies. A 3 mg oral dose of midazolam was selected for use in this study to allow for adequate PK characterization of midazolam after administration in both the absence (ie, baseline CYP3A expression levels) and presence (ie, possibly induced CYP3A expression levels) of brigatinib.

The first part of this study (Part A) is designed to achieve the primary objective of the study, and the second part of the study (Part B) is exploratory and will allow patients to continue brigatinib until disease progression (PD). In addition to ALK-positive patients with NSCLC, patients with ROS1-positive NSCLC, and patients with ALK-positive or ROS1-positive nonlung solid tumors*all with locally advanced or metastatic disease*are eligible for enrollment, in an effort to gather exploratory efficacy data in these patient populations.

Study objective

Primary Objective: To characterize the effect of repeat-dose administration of brigatinib 180 mg QD on the single-dose PK of midazolam.
Other Objectives:
Safety: To assess the safety and tolerability of brigatinib in patients with ALK-positive or ROS1-positive solid tumors.

Study design

Study Design:
This study will consist of 2 parts: Part A (Cycle 1: pharmacokinetics [PK] cycle) and Part B (Cycle 2 and beyond: treatment cycles). Part A of the study will use a fixed-sequence design over a single 28-day treatment cycle. Patients will receive a 3 mg oral dose of midazolam on Day 1 of Part A, with serial PK sampling performed over 24 hours postdose to characterize the PK of midazolam in the absence of brigatinib. Brigatinib 90 mg will then be orally administered once daily (QD) on Days 2 through 8. If the 90 mg QD brigatinib dose is tolerated by the patient, the brigatinib dose will be increased to 180 mg QD, starting on Day 9 and continuing through Day 28 (in accordance with the United States [US] prescribing information). For patients who have escalated to brigatinib 180 mg QD, a 3 mg oral dose of midazolam will be administered on Day 21 of Part A, with serial PK sampling performed over 24 hours postdose to characterize the PK of midazolam in the presence of brigatinib.
Any patients in Part A who are not PK evaluable will be replaced. Patients will be considered PK evaluable if they receive the protocol-specified dosing regimen during Part A (including the 180 mg QD brigatinib dose) without dose reductions or interruptions through the completion of PK sampling (Day 22); do not receive any excluded concomitant medications through the completion of PK sampling; and have sufficient midazolam concentration-time data to permit the reliable estimation of PK parameters by noncompartmental analysis methods.
After completion of Part A, patients may continue to Part B to receive the potential therapeutic benefits of brigatinib. Any patients who are replaced because they are not PK evaluable in Part A will also be eligible to continue into Part B. The starting dose of brigatinib in Part B will be the dose that was tolerated by the patient at the end of Part A. Part B of the study will include 28-day treatment cycles in which brigatinib will continue to be dosed QD at the highest tolerated dose (up to 180 mg QD) until disease progression (PD), intolerable toxicity, or another discontinuation criterion is met.
Patients who cannot escalate to 180 mg QD in Part A will be maintained at 90 mg QD or lower. The available brigatinib daily oral doses for Part A and Part B will include 180, 120, 90, and 60 mg, allowing patients to have their dose reduced in cases of intolerability.
Disease assessments by the investigator, using Response Evaluation Criteria in Solid Tumors, version 1.1, and evaluated by computed tomography and/or magnetic resonance imaging, will be performed during Screening; at 8-week intervals during treatment (ie, on Day 28 [±3 days] of every even-numbered cycle) through Cycle 14; and every 12 weeks (ie, every 3 cycles) thereafter, and at end of treatment (EOT). Safety will be assessed throughout the study, including adverse event reporting through the 30 day follow-up period after EOT. Subsequent therapy will also be collected during the 30-day follow-up period.

Intervention

Part A:
Midazolam: 2 single 3 mg doses on Day 1 and Day 21.
Brigatinib: 90 mg QD×7 days, followed by 180 mg QD× 20 days.

Part B: Brigatinib at highest tolerated dose (180, 120, 90, or 60) QD×28 days per cycle. During Part B, patients may receive up to 23 months of treatment, or treatment until PD, intolerable toxicity, or another discontinuation criterion is met. If patients are still continuing to receive benefit at 23 months, they may have the option to continue brigatinib monotherapy at the same dose.

Study burden and risks

All drugs have the possibility of complications and undesirable side effects that are unknown at this time and could possibly occur.

The most common side effects from controlled clinical trials, (reported in 10% and more of patients), included:
* Pneumonia or lung infection; symtoms may include cough, shortness of breath, fevers, chills, chest pain, headache, sweating, and weakness
* Low levels of red blood cell count (which can cause you to feel tired)
* Low levels of white blood cell count (including white blood cell counts overall, or a certain typeof white blood cells, as lymphocytes or neutrophils), which could increase the risk of infection.
* High blood sugar levels
* High insulin levels which may cause low blood sugar, weakness, mental status changes, and/or weight gain
* Decreased appetite
* Low levels of sodium, potassium, magnesium and phosphate in the blood
* High levels of calcium in the blood
* Headache
* Peripheral neuropathy, a condition in which damage nerves outside the brain and spinal cord (peripheral nerves) which can result in symptoms such as numbness, tingling, prickly sensation, weakness or pain
* Dizziness
* Visual Disturbance
* High Blood Pressure
* Cough
* Shortness of breath
* Nausea
* Diarrhea
* Vomiting
* Constipation
* Abdominal pain
* Inflammation of the oral mucosa, including cheeks, gums, tongue, lips, throat and roof or floor of the mouth
* Increased liver enzymes (Aspartate aminotransferase (AST) increased or Alanine aminotransferase (ALT) increased) which can suggest damage to the liver
* Increased lipase and amylase level (an enzyme measured in the blood that reflects function of the pancreas; elevations in lipase and amylase may indicate inflammation of the pancreas)
* Increased alkaline phosphatase level, an enzyme in the blood produced by the

liver and other organs
* Skin rash
* Itchy skin
* Increased creatine phospokinase level (an enzyme measured in the blood), elevations may indicate injury or stress to muscle tissue, the heart, or brain
* Muscle pain (including muscle spasms)
* Joint Pain
* Increased creatinine level, which may indicate kidney damage
* Fatigue or Tiredness
* Edema (buildup of fluid in the body which causes the affected tissue to become swollen)
* Fever (>38°C)

Common side effects (reported in 1-9% of patients) included:
* Delayed blood clotting
* Problems with memory
* Distortion of the sense of taste
* Increased or slow heart rate
* Infection involving the upper respiratory tract; symptoms may include congestion, sneezing, coughing, fever, and sore throat
* Insomnia or inability to obtain an adequate amount or quality of sleep
* Electrocardiogram QT prolonged (a change in ECG), a study of the electrical system of the heart that may indicate an increased risk of serious abnormalities in the heart*s rhythm)
* Noticeably rapid, strong, or irregular heartbeats
* Pneumonitis (inflammation of the lung) or interstitial lung disease (ILD), diseases that affect the lungs
* Indigestion or upset stomach
* Dry mouth
* Flatulence or accumulation of gas, usually in excess, that is present in the instestinal tract and passed out of the body from the rectum
* Increased lactate dehydrogensade (LDH) level, an enzyme present in many body tissues, especially the heart, liver, kidney, muscles, brain, blood cells, and lungs. LDH is most often measured to check for tissue damage
* Dry skin
* Increased skin sensitivity to sunlight or lamps
* Pain in the extremity
* Musculoskeletal chest pain
* Non-cardiac chest pain
* Pain
* Chest discomfort or pain
* Loss of weight
* High levels of blood cholesterol

Uncommon side effects (reported in less than 1% of patients) included:
* Muscle and/or bone stiffness

Potential Risks of Midazolam
The potential risks associated with the use of brigatinib and midazolam in combination is not known. For detailed information about precautions, warnings, contraindications, and Adverse Events associated with midazolam therapy please ask your Study Doctor or review the midazolam prescribing information.

Discomfort from Blood Draws
There may be some discomfort such as swelling or bruising around the vein that was used to draw your blood. You may experience lightheadedness; however, fainting at the time of blood drawing is uncommon. Infection at the blood drawing site could occur, but this is also uncommon. Care will be provided to avoid these complications.
Risks associated with CT scan
CT scans are associated with exposure to a very small amount of radiation. In addition, you may have some discomfort from lying still in an enclosed space for a prolonged period of time.
Risks associated with MRI scan:
An MRI scan uses radio waves and a magnetic field, and will not expose you to radiation. Some patients may feel frightened by the cramped space inside the MRI machine or by the loud, repeated sounds the machine makes.
Risks Associated with Contrast Agents Used During Scans
There is a small risk with using a contrast agent that is injected into a vein during the CT scan or MRI. A contrast agent is a special dye that highlights organs, blood vessels or tissue to make them more visible. Depending on the type of contrast agent that is used, it may cause decreased kidney function or worsen kidney function in people who already have decreased kidney function. Therefore, we will monitor your kidney function closely while you participate in this study. If there is any change in your kidney function, we may have to remove you from the study.
Uncommonly, some people have allergic reactions (such as hives and itching) to the contrast agent. Serious reactions (for example, drop in blood pressure, difficulty breathing or severe allergic reaction and death) are rare.
Similar Drugs
Because brigatinib shares some features with other drugs already being investigated for non-small cell lung cancer and other cancers, it is possible that it will cause similar side effects to those drugs. These include visual disturbances, testosterone level decrease, inflammation of lung tissue which can be fatal, and liver dysfunction which can be fatal. Symptoms of liver dysfunction can include weakness, fatigue, anorexia, nausea, vomiting, abdominal pain, yellowing of the skin, dark urine, generalized itching, and can cause many complications including excessive bleeding.
You will be monitored closely for these side effects. If you develop symptoms, your doctors will give you the care that you need. You must tell the Study Doctor about any new health problems

Affects on ability to drive and use machines

There is no data on the effect of brigatinib on the ability to drive and use machines. Visual disturbance, dizziness, and fatigue have been observed in clinical trials. Patients should be advised not to drive or operate machines if they experience any of these symptoms while taking brigatinib.

There may be risks from the study drug to an unborn child or breast-feeding an infant that are not currently known. Due to unknown risks and potential harm to the unborn child, female participants should not become pregnant or breast-feed an infant, while participating in this study. Male participants should not try to conceive with their female partner(s) while in participating this study.

Contacts

Public
ARIAD wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Landsdowne Street 40
Cambridge MA 02139
US
Scientific
ARIAD wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Landsdowne Street 40
Cambridge MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Locally advanced or metastatic solid tumors who meet 1 of the following 4 criteria:;-With locally advanced or metastatic ALK-positive NSCLC who have progressed on or are intolerant to treatment with at least 1 other ALK inhibitor.;-With ALK-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available.;-With locally advanced or metastatic ROS1-positive NSCLC who have progressed on crizotinib therapy or are intolerant to crizotinib, or;-With ROS1-positive nonlung solid tumors that are locally advanced or metastatic and for whom no standard, nonexperimental therapy is available.;2. Eastern cooperative Oncology Group (ECOG) performance status of 0 or 1.;3. Have at least 1 target lesion per response evaluation criteria in solid tumors (RECIST) version 1.1.;4. Have recovered from toxicities related to prior anticancer therapy to National Cancer Institute common terminology criteria for adverse events (NCI CTCAE) version 4.03 Grade less than or equal to (<<=) 1.;5. Suitable venous access for study-required blood sampling (that is, including PK and laboratory safety tests).

Exclusion criteria

1. Systemic treatment with strong or moderate cytochrome P450 3A (CYP3A) inhibitors or inducers within 14 days before enrollment.;2. Prior therapy with brigatinib.;3. Received prior ALK-inhibitor therapy within 7 days before the first dose of study drug.;4. Treatment with any investigational systemic anticancer agents within 14 days or 5 half-lives, whichever is longer, before the first dose of study drug.;5. Received chemotherapy or radiation therapy within 14 days before the first dose of study drug, except for stereotactic radiosurgery (SRS) or stereotactic body radiation therapy.;6. Received antineoplastic monoclonal antibodies within 30 days before the first dose of study drug.;7. Had major surgery within 30 days before the first dose of study drug. Minor surgical procedures, such as catheter placement or minimally invasive biopsies, are allowed.;8. Have current spinal cord compression (symptomatic or asymptomatic and detected by radiographic imaging). Patients with leptomeningeal disease and without cord compression are allowed.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-07-2019
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	brigatinib
Generic name:	n.a.
Product type:	Medicine
Brand name:	midazolam
Generic name:	n.a.
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-08-2018
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-02-2019
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-03-2019

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-08-2019
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
Other	NCT03420742
EudraCT	EUCTR2018-001624-19-NL
CCMO	NL66230.031.18