A phase I, multi-center, open-label, drug-drug interaction study to assess the effect of the CYP1A2 inhibitor, fluvoxamine, on TKI258 (dovitinib) pharmacokinetics in patients with advanced solid tumors.

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Primary objectivesTo evaluate the effect of the CYP1A2 inhibitor, fluvoxamine, on steady state pharmacokinetics of TKI258 in patients with advanced solid tumors, excluding breast cancerSecondary objectives• To characterize the safety and...

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

Summary

ID

NL-OMON39285

Source
ToetsingOnline

Brief title
A phase I drug-drug interaction study of fluvoxamin on TKI258 (dovitinib)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutiche industrie

Intervention

Keyword: dovitinib, drug-drug interaction, fluvoxamin, TKI258

Outcome measures

Primary outcome

TKI258 (dovitinib) Pharmacokinetic parameters:

Primary - AUC 0-72h, Cmax; and secondary - T1/2, Cmin,ss, Tmax, AUC 0-24h

Secondary outcome

Incidence and severity of adverse events according to the CTCAE criteria

Version 4.03, unless otherwise specified; changes from baseline in clinical

laboratory tests, physical examinations, vital signs, ECGs, and cardiac imaging

Overall response based on investigator assessment and best overall response

using RECIST version 1.1

Study description

Background summary

Dovitinib (TKI258) inhibits three RTKs (VEGF, FGF, and PDGF) involved in tumor cell growth.
Based on its potency as an inhibitor of these RTKs both in vitro and in vivo, and the compound*s
oral availability, dovitinib has been investigated as a single agent in many solid tumor studies.

Following a continuous daily dose, the time-dependent and nonlinear PK resulted

in dose-dependent time to reach steady state, as well as dose-dependent accumulation at steady state.
Following a 5 days on/2 days off dosing schedule no accumulation was observed at the tested dose levels of 500 mg/day and 600 mg/day. The MTD of the 5 days on/2 days off dosing schedule was 500 mg/day because of 2 dose-limiting toxicities observed at 600 mg/day. At MTD, steady state was achieved after the second week, and the half-life at steady state was around 13 hours.
The maximum tolerated dose (MTD) of dovitinib is 400 mg/day for the continuous once daily
dosing regimen and 500 mg/day for the 5 days on / 2 days off dosing regimen. Based on safety data and preliminary evidence of clinical efficacy obtained in Phase I and Phase II trials, 500 mg/day (MTD) on a 5 days on/2 days off dosing schedule is being used in the ongoing pivotal phase III trial in advanced RCC as well as ongoing phase II clinical trials.

Study CTKI258A2101, a phase 1 dose escalating study in patients with advanced solid
tumors, provided evidence implicating CYP1A2 as a relevant metabolic pathway for dovitinib.

No formal drug-drug interaction studies with dovitinib have been conducted. Available data
from human, as well as in vitro studies, demonstrate that dovitinib has low or no inhibition
potential for CYP450s. Dovitinib, however, does induce CYP1A2, CYP2C9 and CYP2C19 functional activities, as well as CYP3A4 mRNA; hence co-administration with substrates of CYP1A2/2C9/2C19/3A4 could
reduce the exposure of these substrates.

In the current study dose selection for dovitinib is based principally on consideration of safety while still allowing for a robust evaluation of inhibition of the dovitinib clearance pathway. Fluvoxamine is a strong CYP1A2 inhibitor. Given the fact that ~1/3 of administered dose of dovitinib is eliminated via the CYP1A1/A2 pathway, complete inhibition of CYP1A2 by fluvoxamine could result in about 33% increase of dovitinib exposure on the day that fluvoxamine is administered. Due to the potential safety risk posed by the increase in dovitinib exposure, a dose of 400 mg rather than the maximum tolerated dose (MTD) of 500 mg has been selected for this study during the PK phase.

During the DDI test, dovitinib will be administered at a dose of 400 mg on a 5 days on/2 days off dosing schedule. At the 400 mg dose level, pharmacodynamic activity as well as preliminary evidence of efficacy have been observed. After completion of the DDI test patients will be given the option to continue treatment with dovitinib at 500 mg/day (MTD) on a 5 days on/2 days off dosing schedule, provided these patients do not have any toxicities which would

preclude treatment with the 500 mg dose.

Study objective

Primary objectives
To evaluate the effect of the CYP1A2 inhibitor, fluvoxamine, on steady state pharmacokinetics of TKI258 in patients with advanced solid tumors, excluding breast cancer

Secondary objectives
• To characterize the safety and tolerability of TKI258 following a 5 days on/2 days off dosing schedule in patients with advanced solid tumors, excluding breast cancer
• To evaluate preliminary evidence of anti-tumor activity of TKI258 in patients with advanced solid tumors, excluding breast cancer

Study design

A multi-center, open-label, single-sequence, crossover, drug-drug interaction (DDI) study to assess the effect of the CYP1A2 inhibitor, fluvoxamine, on the PK of dovitinib in patients with advanced solid tumors, excluding breast cancer. The study will consist of 2 phases: a Pharmacokinetic (PK) phase. The DDI test will be conducted in the PK phase. The DDI test will assess the steady state PK profile of dovitinib when administered alone and in the presence of the CYP1A2 inhibitor, fluvoxamineThe PK phase will last 28 days. On days 19 and 26 full pk will be assessed. On days 26-27 and 28 fluvoxamin will be taken.
After the PK phase the patient may continue in a clinical treatment phase.

Intervention

Dovitinib (TKI258) capsules in a 5 days on/ 2 days off schedule
PK phase: 300mg
Clinical treatment phase: 500mg
Fluvoxamin 100mg on day 22, 23, 24, 25, 26, 27 and 28 in the Pk phase

Study burden and risks

Side effects of dovitinib and fluvoxamin.
Most common possible side effects of dovitinib are: Diarrhea, nausea, vomiting, asthenia, fatigue, decreased, headache, dyspnea, anemia, constipation, rash, abdominal pain, fever, cough, increased liverfunction tests, distortion of the sense of taste, hypertriglyceridemia, hypertension, weight decreased, periferal edema, urinary track infection, backpain, dizziness, dyspepsia, dry mouth and thrombocytopenia.
Most common side effects of fluvoxamin are: somnolence, insomnia, nervousness, tremor, nausea, dyspepsia, anorexia, vomiting, abnormal ejaculation, asthenia,

and sweating.
Unexpected serious adverse evetn: aphasia (transient), pneumonitis, cardiac tamponade, colon fistula, asymptomatic aortic dissection, osteonecrosis of the jaw and reversible leucoencephalopathy syndrome.

Fluvoxamine may increase the side effects or lessen the effectiveness of some medications.

other risk / inconveniences: taking blood mayu cause pain, bleeding and/or bruising. Patients will be exposed to radiation (CT-scan, MUGA-scan and X-rays). The rdiation will not exceed tha maximum ranges that are set within the Netherlands. Allergic reaction on contrast used for CT-scans may occur.

Contacts

Public
Novartis

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NL
Scientific
Novartis

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Patients diagnosed with either an advanced solid tumor, excluding breast cancer, or advanced hepatocellular carcinoma, which has progressed despite standard therapy, or for which no standard therapy exists
2. ECOG performance status <= 2
3. Absolute neutrophil count >= 1.5 x 109/L
4. Platelets >= 100 x 109/L
5. Hemoglobin >= 8.0 g/dL = 4.96 mmol/L
6. Serum creatinine <= 1.5 x ULN or 24-hour urine collection creatinine clearance >= 30 mL/min/1.73m2 (>= 50 mL/min/1.73m2 in the presence of proteinuria as defined in inclusion criterion #9) or,
Serum creatinine > 1.5 - 3 x ULN with calculated creatinine clearance >= 30 mL/min using the Cockcroft-Gault equation
7. Serum total bilirubin <= 1.5 x ULN
8. AST and ALT <= 3.0 x ULN
9. Urine dipstick negative for proteinuria or, if documentation of +1 results (+ 2 for patients with RCC) for protein on dipstick reading, then total urinary protein <= 500 mg and measured creatinine clearance >= 50 L/min/1.73m3 from a 24 hour urine collection
10. Patients with a life expectance of > 3 month

Exclusion criteria

1. Patients with brain metastases as assessed by mandatory radiologic imaging at screening
2. Patients with a history of another primary malignancy that is currently clinically significant or currently requires active intervention
3. Prior anticancer therapies:
•targeted small molecule therapy <= 2 weeks prior to starting study drug,
•monoclonal antibody, immunotherapy, hormonal therapy, or chemotherapy <= 4 weeks prior to starting study drug,
•nitrosourea or mitomycin-C <= 6 weeks prior to starting study drug
•radiotherapy <= 4 weeks prior to starting the study drug (palliative radiotherapy for bone lesions <= 2 weeks prior to starting study drug is allowed)
and not recovered from anti-cancer therapy related toxicities
4. Major surgery <= 4 weeks prior to starting study treatment, or who have not recovered from side effects of such therapy
5. Pulmonary embolism or untreated deep venous thrombosis within 6 months prior to starting study drug
6. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
•History or presence of serious uncontrolled ventricular arrhythmias
•Clinically significant resting bradycardia
•LVEF < 50% (ECHO)or < 45% (MUGA)
•Myocardial infarction, severe/unstable angina, coronary artery bypass graft, congestive

heart failure, cerebrovascular accident, transient ischemic attack within 6 months prior to starting study drug
•Uncontrolled hypertension defined by a SBP >= 160 mm Hg and/or DBP >= 100 mm Hg, with or without anti-hypertensive medication(s). Initiation or adjustment of antihypertensive medication(s) is allowed prior to study entry
7. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of dovitinib.
8. Cirrhosis, chronic active hepatitis, or chronic persistent hepatitis.
9. Current use of prasugrel, clopidogrel, or full dose anticoagulation treatment with therapeutic doses of warfarin. Treatment with low doses of warfarin (e.g., <= 2 mg/day) or locally accepted low doses of acetylsalicylic acid (up to 100 mg daily) is allowed.
10. Other concurrent severe and/or uncontrolled concomitant medical conditions
11. Use of potent and moderate CYP1A2 inhibitors or potent and moderate CYP3A inhibitors within 5 days prior to starting study treatment, or during the PK phase (i.e., days 1-28, inclusive, of the PK phase).
12. CYP1A2 inducers (including tobacco) or CYP3A inducers within 30 days prior to starting study treatment, or during the PK phase (i.e., days 1-28, inclusive, of the PK phase))
13. Actively taking antidepressants, benzodiazepines, serotonergic drugs, and/or monoamine oxidase inhibitors (MAOIs).
14. Expected alcohol intake to exceed 1 drink/day within 3 days prior to the days of blood sample collection for PK assessment in the PK phase (i.e., <= 3 days prior to days 19 and 26 of the PK phase) and throughout the timeframe they are taking fluvoxamine (i.e., days 26, 27 and 28 of the PK phase).
15. Grapefruits, pomegranates, star fruits, Seville oranges or products containing the juice of each within 3 days prior to the days of blood sample collection for PK assessment in the PK phase (i.e., <= 3 days prior to days 19 and 26 of the PK phase).
16. Homeopathic or naturopathic medicines within 5 days prior to the days of blood sample collection for PK assessment in the PK phase (i.e., <= 5 days prior to days 19 and 26 of the PK phase). Note: vitamin supplements are allowed
17.Non-steroidal anti-inflammatory medications and/or aspirin on days of fluvoxamine dosing (i.e., d ays 26, 27 and 28 of the PK phase). Low doses of acetylsalicylic acid (up to 100 mg daily) to prevent cardiovascular events or stroke is allowed.
18. Pregnant or breast-feeding women
19. Women of child-bearing potential, not employing two forms of highly effective contraception.
20. Fertile males not willing to use contraception, as stated above. Fertile males must use condom with spermicide during the study and 3 months after the end of study treatment

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	31-03-2013
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Fevarin
Generic name:	fluvoxamine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Geen
Generic name:	dovitinib

Ethics review

Approved WMO

Date:	26-07-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	23-08-2012
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	17-09-2012
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-01-2014
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	EUCTR2012-001546-18-NL
ClinicalTrials.gov	NCT01596647
CCMO	NL40697.031.12