Proof of principle and pharmacological phase 0 study with improved solubility Pazopanib (PazSol001)

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To determine the plasma pharmacokinetics of Pazopanib after intake of different doses of PazSol001.To determine the preliminary safety and tolerability profile of PazSol001.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON43192

Source
ToetsingOnline

Brief title
Improved solubility Pazopanib

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Advanced renal cell carcinoma; Advanced renal cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Het Nederlands Kanker Instituut / Modra Pharmaceuticals

Intervention

Keyword: Kinetics, Pazopanib, Safety, Solubility

Outcome measures

Primary outcome

The main study parameter will be the concentration of Pazopanib in patient

plasma.

Secondary outcome

The second study parameter will be the preliminary safety assessment of

PazSol001.

Study description

Background summary

Pazopanib is an oral drug registered as Votrient® (available as 200mg and 400mg film coated tablets) by GSK. Votrient® has a low solubility and therefore suffers from impaired and variable absorption.

The Department of Pharmacy and Pharmacology of the Antoni van Leeuwenhoek - Netherlands Cancer Institute developed an improved solubility solid oral dosage form for Pazopanib, PazSol 25 mg capsules. This formulation consists of Pazopanib Hydrochloride and Soluplus®, a graft polymer that has shown great potency in increasing the solubility of a range of poorly soluble compounds. In vitro, this formulation releases 100% of Pazopanib upon transition from the stomach to the duodenum. Votrient® shows ~1% dissolution upon this same transition. Therefore, the amount of Pazopanib available for absorption into the bloodstream is considerably higher for PazSol than for Votrient®.

This increased absorption of Pazopanib could give rise to higher plasma concentrations for the same amount of administered drug

With the low bioavailability of Votrient®, 10-30%, comes a large inter- and intrapatient variability. This may be reduced by administering a formulation that has a higher bioavailability, ideally 100%.

In this study, the pharmacokinetics of the new formulation will be tested and

compared to 800 mg Votrient®.

Different PazSol001 doses will be tested to examine if the formulation indeed increases the bioavailability of Pazopanib as predicted, and secondly to select the dose to reach the same drug exposure as with 800 mg Votrient®. Animal studies are not deemed feasible since limited animal (reference) PK data is available and animal PK may differ significantly from human PK. Translation and comparison may therefore not be fruitful.

It is expected that a dose of PazSol001 will be found that provides a similar exposure as 800 mg Votrient® with less Pazopanib load. Extending this expectation to variability in bioavailability, a higher and less variable solubility may result in a less variable bioavailability as well, which would be a major improvement.

If this is the case, the PazSol001 formulation will be taken into further development. A large scale production line will be designed, set up and validated. Furthermore, a larger patient study (phase 1) will be proposed with a direct in vivo comparison between 800 mg Votrient® and the predetermined PazSol001 dose to show bioequivalence.

Stretching into the future, the patent on Votrient® will expire in 2023 and its exclusivity in 2019. If and when Pazopanib is still standard care for cancer patients by then, the new formulation might provide a safer, more efficient and even a more cost-effective treatment option.

Study objective

To determine the plasma pharmacokinetics of Pazopanib after intake of different doses of PazSol001.
To determine the preliminary safety and tolerability profile of PazSol001.

Study design

This is a single center, open-label, pharmacological pilot proof of concept study in which the PK profile of a new oral formulation of Pazopanib, PazSol001, will be determined and compared to the PK profile of Votrient® 800 mg od. Patients will be hospitalized during 24 hours. On the first day they will receive one dose PazSol001 (a multiple of capsules of 25 mg) at approximately 9.00 a.m. After intake of PazSol001 blood samples will be sequentially collected for bioanalysis for the period of 24 hours.
The PK will be compared to the PK of Votrient 800 mg od. A dose evaluation committee will determine whether and how the dose will be adjusted for a possible next cohort. The study will continue until all 12 participants have finished the study or when 6 participants have taken part in the cohort of which the results yield an equivalent-to-Votrient exposure.

Study burden and risks

The potential issues of concern for the use of Pazopanib in this study are not different from those in the registered therapy of patients with Votrient®. We therefore refer to the Summary of Product Characteristics (SPC) of Votrient® The potential issues of concern for the improved absorption of Pazopanib are mainly linked to a possible higher Pazopanib plasma level and the possible toxicity this may bring with it. To adress this issue, the study is designed to start with a relatively low dose of Pazopanib (100 mg). Even if all the Pazopanib is absorbed from this dose, the plasma levels will still be below the plasma levels of a Votrient® 800 mg dose of which 20% is absorbed (160 mg).

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. Locally advanced or metastatic cancer;
2. Age >= 18 years;
3. Able and willing to give written informed consent;
4. WHO performance status of 0, 1 or 2;
5. Able and willing to undergo blood sampling for PK analysis;
6. Minimal acceptable safety laboratory values
a. ANC of >= 1.5 x 109 /L
b. Platelet count of >= 100 x 109 /L
c. Hepatic function as defined by serum bilirubin <= 1.5 x ULN, ALAT and ASAT <= 2.5 x ULN
d. Renal function as defined by serum creatinine <= 1.5 x ULN or creatinine clearance >= 50 ml/min (by Cockcroft-Gault formula).
7. Negative pregnancy test (urine/serum) for female patients with childbearing potential;
8. Able and willing to swallow oral medication;

Exclusion criteria

1. Any treatment with investigational drugs within 30 days prior to receiving the investigational treatment;
2. Any treatment with inhibitors of CYP3A4 (e.g. boceprevir, claritromycine, erytromycine, indinavir, itraconazol, ketoconazol, ritonavir and voriconazol), inhibitors of Pgp (e.g. ciclosporine, kinidine and verapamil), inhibitors of BCRP (e.g. lapatinib), inductors of CYP3A4, Pgp or BCRP or stomach pH increasing drugs;
3. Patients who have had previous treatment with Votrient®, less than 1 week ago;
4. Woman who are pregnant or breast feeding;
5. Patients suffering from any known disease or dysfunction that might influence the dissolution and/or absorption of Pazopanib (e.g. dyspepsia, inflammatory bowel disease).

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-11-2016
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pazopanib
Generic name:	Pazopanib

Ethics review

Approved WMO Date:	14-07-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-08-2016
Application type:	First submission
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	EUCTR2016-001105-16-NL
CCMO	NL57191.031.16