Increasing pazopanib exposure by splitting intake moments

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45488

Source
ToetsingOnline

Brief title
N17PSI - pazopanib 800mg QD versus 400mg BID

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
renal cell carcinoma, soft tissue sarcoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Pazopanib, Pharmacokinetics

Outcome measures

Primary outcome

The primary outcome will be the increase in Cmin and AUC when comparing

pazopanib 800mg QD and 400mg BID.

Secondary outcome

To compare the incidence and severity of adverse events between the two dosing

schedules, according to CTC-AE v4.03.

Study description

Background summary

Pazopanib exposure has been linked to clinical efficacy in multiple studies. A large retrospective analysis by Suttle et al showed an increase in progression free survival and tumor shrinkage in patients with a Cmin * 20 mg/L.
A prospective clinical trial in cancer patients has shown that increasing pazopanib dose, based on measured Cmin levels, was feasible, safe and leads to an increase in pharmacokinetic exposure (Verheijen et al).
Pazopanib pharmacokinetics have been shown to be non-linear and recent efforts using a population pharmacokinetic two-compartmental model based on multiple clinical trials (n=96) support this (Yu et al) The model suggests that pazopanib bioavailability is non-linear and simulations comparing the exposure of 800mg QD versus 400mg BID were made. These results indicate a relevant increase in pazopanib Cmin and AUC0-24h of 75% and 59% respectively.
Splitting pazopanib intake in this way would offer a cost-neutral option to optimize pazopanib treatment for patients with low pharmacokinetic exposure. This is relevant for a significant subset of patients as based on our own clinical experience and published data. 20 - 56.7% of patients do not reach the threshold of Cmin * 20 mg/L using the current fixed dose of 800mg QD (Suttle et al, Verheijen et al).

Study objective

Based on the above, we propose to perform a prospective pharmacokinetic cross-over trial to test the hypothesis that splitting pazopanib intake moment will increase Cmin and AUC0-24h. In addition, we will show that this is a feasible, safe and cost-neutral strategy to optimize pazopanib therapy in patients with low pharmacokinetic exposure.

Study design

Prospective pharmacokinetic cross-over trial comparing pazopanib 800mg QD and 400mg BID.

Intervention

Patients will receive pazopanib 400mg BID for a period of one week (instead of 800mg QD).

Study burden and risks

Pazopanib will be used in patients for whom it is considered standard of care. Importantly, patients will receive the approved dose of 800 mg a day throughout this study, only the intake moments will be split during a one week period.

Theoretically, a possible risk of additional toxicity exists, as we expect an increase in exposure by splitting intake moments of pazopanib. However, this risk is minimized by:
- The short duration of the intervention (only seven days);
- The exclusion of patients with a high Cmin at screening.

Patients will undergo two days of intensive pharmacokinetic sampling (24 hours) requiring two overnight stays at the hospital (day 1 and day 8).
The total amount of blood required for pharmacokinetic sampling is estimated to remain below 100 mL for the entire study

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. Histological or cytological proof of cancer for which pazopanib is considered standard care;
2. Patients should have received pazopanib 800 mg QD as routine care for at least 3 weeks before day 1 of the trial;
3. Age * 18 years;
4. Able and willing to give written informed consent;
5. WHO performance status of 0, 1 or 2;
6. Adequate organ function per judgement of the treating physician;
7. Able and willing to undergo blood sampling for PK analysis.

Exclusion criteria

1. Concomitant use of medication(s) which could influence the pharmacokinetics of pazopanib within 14 days or five half-lives of the drug (whichever is shorter) before start of the study, consisting of (but not limited to) gastric acid suppressing agents, CYP3A4-inhibitors/inductors, PgP and/or BCRP modulators. In particular, proton pump inhibitors (such as omeprazole and pantoprazole) are to be avoided;
2. Woman who are pregnant or breast feeding;
3. Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study compliance;
4. Pazopanib related side effects that would require a dose reduction per judgement of the treating physician;
5. Legal incapacity;

6. (Calculated) pazopanib Cmin > 33 mg/L at screening visit.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-01-2018
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Votrient
Generic name:	pazopanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	07-03-2017
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	13-04-2017
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-07-2018
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	EUCTR2016-005252-21-NL
CCMO	NL60393.031.17

Study results