The effects of the proton pump inhibitor esomeprazole on the bioavailability of regorafenib in patients with a metastatic colorectal cancer (mCRC) or gastrointestinal stromal tumour (GIST).

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To determine the influence of esomeprazole on the AUC of regorafenib in patients with mCRC or GIST.

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

Summary

ID

NL-OMON43377

Source
ToetsingOnline

Brief title
REGORA

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Gastrointestinal stromal tumours and metastatic colorectal carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Bayer,Bayer Pharma AG

Intervention

Keyword: GIST, mCRC, PPI, Regorafenib

Outcome measures

Primary outcome

To determine the influence of esomeprazole on the AUC of regorafenib in

patients with mCRC or GIST.

Secondary outcome

1. Other pharmacokinetic outcomes (i.e. clearance (CL), maximum concentration

(Cmax) and time to Cmax (tmax)).

2. To evaluate the incidence and severity of side-effects of treatment with

regorafenib in absence and presence of esomeprazole

Study description

Background summary

Regorafenib is a novel oral multi-kinase inhibitor which targets angiogenic, stromal and oncogenic receptor tyrosine kinases. Regorafenib shows anti-angiogenic activity based on to its dual targeted VEGFR2-TIE2 tyrosine kinase inhibition. It is currently registered for GIST and mCRC. When regorafenib is co-administered with an acid suppressive agent, the intragastric pH increases, and as a result the equilibrium of ionized/non-ionized regorafenib may shift to the less soluble non-ionized form which reduces regorafenib bioavailability and exposure. Since proton pump inhibitors (PPI*s) are often used during regorafenib therapy, this drug-drug interaction (DDI) confronts pharmacists and oncologists with challenges in clinical practice. In this study we will therefore evaluate the impact of PPI induced intragastric pH elevation on regorafenib pharmacokinetics in patients with GIST and mCRC.

Study objective

To determine the influence of esomeprazole on the AUC of regorafenib in patients with mCRC or GIST.

Study design

This is a single centre, open label two-period, randomized, cross-over pharmacokinetic study.

Intervention

Patients will start with regorafenib in a loading phase of 21 days and will be admitted for 24 hours to the hospital for pharmacokinetic blood sampling on day 21, 49 and 77. Patients will be randomized into 2 sequence groups (respectively sequences A-B-C or C-B-A). The patient will use regorafenib alone (phase A) or with (Phase B and C) esomeprazole. During phase B of the study regorafenib is given concomitantly for 5 days, while during phase C regorafenib is given 3 hours after esomeprazole for 5 days.

Study burden and risks

Patients will be admitted to the hospital for a total of three days, during which pharmacokinetic blood withdrawals will be performed. Patients will be randomised into 2 sequence group consisting of 3 phases. In 2 phases, prior to one of the hospital admissions, patients are pre-treated with esomeprazole 40 mg for 5 consecutive days (concomitantly or 3 hours before regorafenib depending on study phase). Patients do not benefit individually from this study. Major risks to be expected are side effects of one of the investigational medicinal products regorafenib or esomeprazole, for which patients will be carefully observed.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Groene Hilledijk 301
Rotterdam 3075 EA
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Groene Hilledijk 301

Rotterdam 3075 EA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age >= 18 years
2. Histological or cytological confirmed diagnosis of mCRC or GIST
3. ECOG Performance Status <= 1
4. Signed Informed Consent Form prior to screening evaluations
5. No concurrent (over the counter) use of other acid reducing drugs, other than esomeprazole 40mg (PPIs, H2As and/or antacids) once daily during the study
6. No concurrent medication or supplements which can interact with esomeprazole or regorafenib during the study period
7. Abstain from grapefruit, grapefruit juice, herbal dietary supplements, and herbal tea during the study period.
8. Adequate baseline patient characteristics

Exclusion criteria

1. Pregnant or lactating patients
2. Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria)
3. Known serious illness or medical unstable conditions that could interfere with this study
4. Patients with evidence or history of any bleeding diathesis, irrespective of severity
5. Cardiac history (recent myocardial infarction, unstable or new-onset angina, uncontrolled cardiac arrhythmias)
6. Uwillingness to abstain from grapefruit (juice), (herbal) dietary supplements, herbals, over-the-counter medication (except for paracetamol and ibuprofen) and other drugs known to seriously interact with esomeprazole and regorafenib during the study period.
7. Unwillingness to abstain from acid beverages such as jus d*orange and other acidic

beverages in the morning during regorafenib treatment in this study.
8. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation.
9. Symptomatic CNS metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	26-05-2016
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nexium
Generic name:	Esomeprazole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Stivarga
Generic name:	Regorafenib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-03-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-05-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-005784-17-NL
CCMO	NL56302.078.16