Pharmacokinetic study of the HCV protease inhibitor bocePRevir and the proton pump inhibitor OMeprazOle (PROMO)

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Primary objectiveTo determine the effect of multiple dose OME on the pharmacokinetics (AUC0-8h, Cmax, C8h) of BOC.Secondary objectives:To determine the effect of steady state BOC on the pharmacokinetics (AUC0-8h, Cmax, C8h) of multiple dose OME.To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON36067

Source
ToetsingOnline

Brief title
PROMO

Condition

- Gastrointestinal conditions NEC
- Viral infectious disorders

Synonym
hepatitis C; inflammation of the liver

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: farmaceutische industrie,Merck

Intervention

Keyword: boceprevir, Hepatitis C, omeprazole, pharmacokinetics

Outcome measures

Primary outcome

To determine the effect of multiple dose OME on the pharmacokinetics (AUC0-8h,

Cmax, C8h) of BOC.

Secondary outcome

To determine the effect of steady state BOC on the pharmacokinetics (AUC0-8h,

Cmax, C8h) of multiple dose OME.

To study the safety of steady state BOC combined with multiple dose OME.

Study description

Background summary

It is known that some drugs can significantly influence the bioavailability of other drugs. For example the proton pump inhibitors decrease the absorption of some protease inhibitors used in HIV treatment or of some oral tyrosine kinase inhibitors used in oncology. Proton pump inhibitors increase the pH in the stomach and might there-fore decrease the solubility of other drugs with decreased absorption as a consequence.

Boceprevir (BOC) is an HCV NS3 serine protease inhibitor that has recently received FDA approval for the treatment of chronic HCV infection. The drug substance is slightly soluble in water and administration with food increases the oral bioavailability of BOC relative to the fasted state, by 40% to 60% based on AUC.

As proton pump inhibitors are widely used it is relevant to know if a drug-drug interaction between proton pump inhibitors and BOC exists which might influence the bioavailability of BOC.

Omeprazole (OME) is the most frequently used proton pump inhibitor. It is the second most prescribed drug in the Netherlands, with 5 million prescriptions a year.

OME is metabolized by CYP2C19 and CYP3A4 and is known to induce CYP1A2 and inhibit CYP2C19. BOC is a potent inhibitor of CYP3A4/5 and is not metabolised by CYP1A2 or CYP2C19. No interaction on me-tabolism of BOC is expected. However, an increase of OME levels may be expected due to the inhibition of CYP3A4 by BOC.

Study objective

Primary objective
To determine the effect of multiple dose OME on the pharmacokinetics (AUC0-8h, Cmax, C8h) of BOC.

Secondary objectives:
To determine the effect of steady state BOC on the pharmacokinetics (AUC0-8h, Cmax, C8h) of multiple dose OME.

To study the safety of steady state BOC combined with multiple dose OME.

Study design

Open-label, 3-period, randomized, cross-over, single-centre, phase-I trial

A total of 24 subjects will be enrolled. The 24 subjects will be divided into 6 treatment groups (1 to 6) of 4 subjects.

Each group will take the following medications, but in a different order:
A. OME 40 mg QD for 5 consecutive days (OME alone)
B. BOC 800 mg TID for 4 consecutive days + a single dose of 800 mg on Day 5 (BOC alone)
C. OME 40 mg QD for 5 consecutive days combined with BOC 800 mg TID for 4 consecutive days + a single dose of 800 mg on Day 5 (BOC+OME)

Washout periods of at least 9 days will be scheduled between treatments.
The treatment group will be assigned at random.

PK days will be on Day 5, 19 and 33.

Intervention

A. OME 40 mg QD for 5 consecutive days (OME alone)
B. BOC 800 mg TID for 4 consecutive days + a single dose of 800 mg on Day 5 (BOC alone)
C. OME 40 mg QD for 5 consecutive days combined with BOC 800 mg TID for 4 consecutive days + a single dose of 800 mg on Day 5 (BOC+OME)

All subjects get every treatment with a washout periods of at least 9 days between treatments.

Study burden and risks

The study participants are healthy volunteers and will not benefit from the participation in this clinical trial.
They will visit the centre for short visits (1 hour) 9 times and stay for appr. 10 hours on three occasions. The duration of the entire trial (excluding screening period) is 33 days.
For pharmacokinetic purposes, in total 39 times a blood sample will be taken; the total volume taken will be maximally appr. 350mL.
During the days that blood samples will be collected for a pharma-cokinetic curve an intravenous cannula will be inserted to facilitate blood sampling.
BOC is a compound which is currently in clinical development. It is expected to be marketed in 2011. A total of >350 healthy volunteers have been exposed to this drug already. The maximum single dose given to healthy volunteers was 800 mg; multiple doses up to 1200 mg TID were given to healthy subjects. The longest dosing period was 56 days.
Possible adverse events in healthy volunteers are: dysgeusia, head-ache, nausea, vomiting and elevated liver transaminases.

OME has been marketed since 1988. Common side effects (> 2%) are: Headache, diarrhoea, abdominal pain, constipation, flatulence, nausea and vomiting.

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. Subject is at least 18 and not older than 55 years at screening.
2. Subject des not smoke more than 10 cigarettes, 2 cigars, or 2 pipes per day for at least 3 months prior to the first dosing
3. Subject has a Quetelet Index (Body Mass Index) of 18 to 30 kg/m2, extremes included.
4. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
5. Subject is in good age-appropriate health condition as estab-lished by medical history, physical examination, electrocardi-ography, results of biochemistry, haematology and urinalysis testing within 4 weeks prior to Day 1. Results of biochemistry, haematology and urinalysis testing should be within the laboratory's reference ranges. If laboratory results are not within the reference ranges, the subject is included on condition that the Investigator judges that the deviations are not clinically relevant. This should be clearly recorded.
6. Subject has a normal blood pressure and pulse rate, according to the Investigator's judgement.

Exclusion criteria

1. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
2. Positive HIV test.
3. Positive hepatitis B or C test.
4. Pregnant female (as confirmed by an HCG test performed less than 4 weeks before Day 1) or breast-feeding female. Female subjects of childbearing potential without adequate contraception, e.g. hysterectomy, bilateral tubal ligation, (non-hormonal) intrauterine device, total abstinence, double barrier methods, or two years post-menopausal. They must agree to

take precautions in order to prevent a pregnancy throughout the entire conduct of the trial.
5. Therapy with any drug (for two weeks preceding dosing), except for paracetamol.
6. Relevant history or presence of pulmonary disorders (especially COPD), cardiovascular disorders, neurological disorders (especially seizures and migraine), psychiatric disorders, gastro-intestinal disorders, renal and hepatic disorders, hormonal dis-orders (especially diabetes mellitus), coagulation disorders.
7. Relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion.
8. History of or current abuse of drugs, alcohol or solvents.
9. Inability to understand the nature and extent of the trial and the procedures required.
10. Participation in a drug trial within 60 days prior to the first dose.
11. Donation of blood within 60 days prior to the first dose.
12. Febrile illness within 3 days before Day 1.

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:	Recruitment stopped
Start date (anticipated):	11-11-2011
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Losec
Generic name:	omeprazole
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Victrelis
Generic name:	boceprevir

Ethics review

Approved WMO Date:	24-06-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-10-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2010-024544-14-NL
CCMO	NL37305.091.11