A Phase I, open-label, randomized, 2-panel, sequential treatment study in healthy subjects to investigate the potential pharmacokinetic interactions between multiple doses of phenytoin or carbamazepine and telaprevir at steady-state

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OBJECTIVES AND HYPOTHESISPrimary ObjectivesThe primary objectives are to determine- the effect of steady-state telaprevir 750 mg every 8 hours (q8h) on the multiple dose pharmacokinetics ofphenytoin 200 mg every 12 hours (q12h) in healthy subjects,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON37071

Source
ToetsingOnline

Brief title
VX-950HPC1002

Condition

- Viral infectious disorders
- Seizures (incl subtypes)

Synonym

Epilepsy, Hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen Research & Development

Intervention

Keyword: Healthy men and women, Multiple dose

Outcome measures

Primary outcome

Safety and tolerability

Secondary outcome

Pharmacokinetics

Study description

Background summary

Telaprevir is a hepatitis C virus (HCV) non structural (NS) 3 protease inhibitor, indicated, in combination with pegylated interferon (Peg-IFN) alfa and ribavirin (RBV), for the treatment of genotype 1 chronic hepatitis C in adult patients with compensated liver disease (including cirrhosis) who are treatment naïve, or who have previously been treated with interferon-based treatment, including prior null responders, partial responders, and relapsers.
Telaprevir is a substrate and strong inhibitor of cytochrome P450 (CYP) 3A enzyme. Telaprevir is also a substrate of P-glycoprotein (Pgp), and it can inhibit and/or saturate this drug transporter in the gut when present in high local concentrations.
Phenytoin and carbamazepine are antiepileptic drugs (AEDs). Both drugs are known to induce the expression of drug metabolizing enzymes and transporters, including CYP3A and Pgp. Due to their similar metabolic and

transport pathways, as well as their effects on these pathways, a clinically relevant interaction between telaprevir
and phenytoin or carbamazepine may be anticipated. Telaprevir may be added to standardized antiepileptic
regimens during the treatment of HCV infections within epileptic populations, therefore understanding the
interaction between telaprevir and common AEDs is important to maintain seizure control and inhibition of viral
replication. Hence, in this study the drug-drug interaction between telaprevir and a stable phenytoin regimen and
between telaprevir and a stable carbamazepine regimen will be assessed. The results of this study will provide
guidance on the need for dosage adjustment for coadministration of telaprevir with phenytoin or carbamazepine.
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Study objective

OBJECTIVES AND HYPOTHESIS
Primary Objectives
The primary objectives are to determine
- the effect of steady-state telaprevir 750 mg every 8 hours (q8h) on the multiple dose pharmacokinetics of
phenytoin 200 mg every 12 hours (q12h) in healthy subjects, and vice versa.
- the effect of steady-state telaprevir 750 mg q8h on the multiple dose pharmacokinetics of carbamazepine
200 mg q12h in healthy subjects, and vice versa.
Secondary Objectives
The secondary objectives are to determine:
- the effect of multiple dose pharmacokinetics of phenytoin 200 mg q12h or carbamazepine 200 mg q12h on the
single dose pharmacokinetics of telaprevir 750 mg in healthy subjects.
- to evaluate the short-term safety and tolerability of telaprevir in combination with phenytoin or carbamazepine.
Exploratory Objective
The exploratory objective is to assess serial plasma 4β-hydroxycholesterol levels as a potential endogenous marker
of relative CYP3A4 activity.
Hypothesis
This study is designed to obtain a sufficiently reliable estimate of the drug-drug interaction between telaprevir and
phenytoin (Panel 1) and between telaprevir and carbamazepine (Panel 2), expressed as a ratio of pharmacokinetic
(PK) parameters and its 90% confidence interval (CI). No formal hypothesis will be tested.

Study design

OVERVIEW OF STUDY DESIGN
This is a Phase I, open-label, randomized, 2-panel, sequential treatment study in healthy subjects to investigate the
potential PK interactions between multiple doses of phenytoin or carbamazepine and telaprevir at steady-state. The
study population will consist of 24 healthy subjects, randomized equally into 2 panels. All subjects in individual
panels will receive the same sequence of treatments.
Panel 1:
• Part 1: telaprevir 750 mg q8h from Day 1 to Day 9 followed by a single 750-mg dose in the morning on Day 10.
• Part 2: phenytoin 200 mg q12h from Day 1 to Day 16 followed by a single 200-mg dose in the morning on
Day 17; and telaprevir 750 mg q8h from Day 8 to Day 16 followed by a single 750-mg dose in the morning on
Day 17.
Panel 2:
• Part 1: telaprevir 750 mg q8h from Day 1 to Day 9 followed by a single 750-mg dose in the morning on Day 10.
• Part 2: carbamazepine 200 mg q12h from Day 1 to Day 16 followed by a single 200-mg dose in the morning on
Day 17; and telaprevir 750 mg q8h from Day 8 to Day 16 followed by a single 750-mg dose in the morning on
Day 17.
In both panels, Part 1 and Part 2 are separated by a washout period of at least 2 weeks, but not longer than 4 weeks,
between the last intake of study drug in Part 1, and the first intake of study drug in Part 2. Day 10 of Part 1 is the
first day of the washout period.
On Days 1 and 10 (Part 1) and Days 8 and 17 (Part 2) and for both panels, samples for the determination of plasma
concentrations for telaprevir will be collected at several time points.
On Days 7 and 17 of Part 2 (days of intensive PK sampling), samples for the determination of plasma
concentrations for phenytoin (Part 2 - Panel 1) or carbamazepine (Part 2 - Panel 2) will be collected at several time
points.
Additional samples will be taken for the determination of plasma concentrations prior to intensive PK sampling to
document steady-state.
Safety and tolerability evaluations will be recorded throughout the study

Intervention

See section E4.

Study burden and risks

Telaprevir is a registered drug (trade name: Incivek and Incivo) has been previously tested in humans and was generally well tolerated. A number of side-effects, possibly linked to use of the test medication, were reported. Very common side effects included: anaemia, skin itching (pruritus) and red eruption of the skin (rash), nausea, diarrhea, hemorrhoids, vomiting, pain in the rectum (proctalgia).

Phenytoin and carbamazepin are both registered drugs for the treatment of epilepsy.
For phenytoin the following side-effects have been reported: central nervous system disorders, including involuntary eye movement (nystagmus), problems with coordination (ataxia), slurred speech, decreased co-ordination, mental confusion, a sensation of tingling, burning, pricking, or numbness of a person's skin (paraesthesia), somnolence, drowsiness and vertigo; suicidal thoughts or behavior and hypersensitivity reactions, including skin rash.

(Very) common side effects observed with carbamazepine intake are: blood and lymphatic system disorders (e.g. a decrease/increase in the number of certain types of blood cells in the blood), endocrine disorders such as, but not limited to, oedema, fluid retention and weight increase, nervous system disorders (e.g. dizziness, problems with coordination (ataxia), drowsiness, fatigue, headache, double vision (diplopia), inability of the eye to automatically change focus (accommodation disorders)), gastro-intestinal disorders (e.g. nausea, vomiting, dry mouth), diseases that affect the liver and/or biliary tract (hepatobiliary disorders) and skin and subcutaneous tissue disorders (inflammation of the skin due to allergy or a kind of skin rash notable for pale red, raised, itchy bumps (urticarial, which may be severe)).

The dose levels are selected on the basis of research results in animals and humans. The risk to health at these dose levels is limited but they may experience one of the above mentioned side-effects or other symptoms not previously reported. The health will be closely monitored during the trial to minimize these risks.

The blood collection procedure is not dangerous, but may cause discomfort or bruising. Occasionally, fainting or an infection at the blood sampling site can occur.

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

Each potential subject must satisfy all of the following criteria to be enrolled in the study.;- Be a man or woman 18 to 55 years of age, inclusive.;- If a woman, before entry she must be:;• postmenopausal for at least 2 years (amenorrheal for at least 3 years), OR;• surgically sterile (have had a total hysterectomy or bilateral oophorectomy, tubal ligation/bilateral tubal clips without reversal operation, or otherwise be incapable of becoming pregnant).;- Non-smoking for at least 3 months prior to selection, to be confirmed by a nicotine screening test according to the local standard of care.

Exclusion criteria

- Subjects of Asian ancestry, or previous identification as a positive carrier of the human leukocyte antigen (HLA) -B*1502.;- Hepatitis A, B or C or human immunodeficiency virus-type 1 or 2 (HIV-1 or HIV-2) infection at screening.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-05-2012
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epanutin
Generic name:	Phenytoin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Incivo
Generic name:	Telaprevir
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tegretal
Generic name:	Carbamazepine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	01-05-2012

Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-05-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2012-001411-23-NL
CCMO	NL40550.056.12