A Three Part Study Evaluating the Pharmacokinetics of Intravenous (IV) Danoprevir (DNV)/Oral Low Dose Ritonavir (RTV), a Drug-Drug Interaction Study Between IV DNV/Oral Low Dose RTV and Oral Cyclosporine, and the Absolute Bioavailability of IV DNV as Compared to DNV Tablets Together With Oral Low Dose RTV in Healthy Adult Volunteers

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

Summary

ID

NL-OMON37643

Source
ToetsingOnline

Brief title
DNV DDI with Ritonavir and Cyclosporine and Absolute Bioavailability

Condition

- Viral infectious disorders

Synonym
Chronic Hepatitis C, Jaundice

Research involving
Human

Sponsors and support

Primary sponsor: Hoffmann-La Roche
Source(s) of monetary or material Support: farmaceutische industrie

Intervention

Keyword: Absolute bioavailability, Drug-Drug interaction, Hepatitis C

Outcome measures

Primary outcome

Pharmacokinetics :

Part 1: Plasma drug concentrations for DNV (following IV administration) and

RTV.

Part 2: Plasma drug concentrations for DNV (following oral and IV

administration) and RTV.

Part 3: Plasma drug concentrations for DNV (following IV administration), RTV,

and cyclosporine.

Urine drug concentrations for DNV and RTV (Parts 2 and 3), and

cyclosporine (Part 3 only).

Secondary outcome

AEs, vital signs, 12-lead ECGs, clinical laboratory testing

Study description

Background summary

Danoprevir (RO5190591) is a new compound that may be used in the treatment of Hepatitis C.

Study objective

The purpose of the study is to investigate how quickly Danoprevir is absorbed and the extent of absorption and elimination from the body (this is called pharmacokinetics and bioavailability) when it is administered intravenously (IV) or orally alone and in combination with Ritonavir (RTV) and with or without an cyclosporine. In addition, it will be investigated to what extent Danoprevir is tolerated by the volunteer if administered orally or intravenously with and without Ritonavir and cyclosporine. Ritonavir and Cyclosporine are known to interfere with the activity of the enzyme CYP3A and the transporter OATP, which are involved in the movement and metabolism of Danoprevir in the body and may therefore interfere with the presence of Danoprevir in the body.

Study design

This is a study in three parts:

In Part 1, 9 healthy volunteers will be dosed three times with IV doses of DNV or placebo after an oral dose of 100 mg Ritonavir. The IV doses of the 2nd and 3rd dosing will be determined based on the results of the previous dosings. Possibly 1, 2 or 3 additional periods are added,

In Part 2, 12 healthy volunteers will receive 3 IV doses DNV, 2 oral doses of DNV and 100 mg RTV b.i.d. during 13 days. 1 DRV IV dose and 1 DNV oral dose will be administered allone and 2 DNV IV doses and 1 DNV oral dose will be dosed during steady state of RTV.

In Part 3, 8 healthy volunteers will receive DNV IV twice in combination with 100 mg RTV. In one period this will be combined with 100 mg cyclosporine.

Intervention

Part 1:
Period 1: All volunteers will receive 100 mg Ritonavir (RTV). after 2 hours 2 mg Danoprevir (DNV) or placebo (2:1) will be administered as a 60 minutes IV.
Period 2: All volunteers will receive 100 mg Ritonavir (RTV). after 2 hours an amount of DNV based on the results from period 1 or placebo (2:1) will be

administered as a 60 minutes IV.
Period 3: All volunteers will receive 100 mg Ritonavir (RTV). after 2 hours an amount of DNV based on the results from periods 1 and 2 or placebo (2:1) will be administered as a 60 minutes IV.

Part 2:
The volunteers will receive 1 IV dose of DNV as determined based on the results of Part 1 and one 100 mg tablet DNV on two consecutive days. followed by 13 days of ritonavir 100 mg bid dosing combined with dosing of DNV IV (twice) or tablet on days 1, 10 and 13.

Part 3:
The volunteers will receive 100 mg RTV once and DNV IV once, 2 hours after the ritonavir dosing, as determined in Part 1 . They will also receive a single dose of 100 mg Ritonavir and a oral dose of 100 mg ciclosporine, and a IV dosering DNV zoals 2 hours after dosing, as determined in Part 1. The sequence is based on the dosing schedule.

Study burden and risks

During the study several assessments will be performed that may be conceived as more or less of a burden. This includes blood sampling using venopunction, a canulla and the IV administration of medication.

Danoprevir: In previous studies with Danoprevir in healthy volunteers oral doses up to 1600 mg were well tolerated. The most frequent side effects reported in healthy volunteers were headache, fatigue, chills and fever, nausea and vomiting, rash, muscle and joint pain, decreased appetite and GI disorders such as diarrhea, abdominal pain, and flatulence.
In Phase II studies with DNV in patients with Hepatitis C doses up to 1800 mg per day for up to 12 weeks were administered. The adverse events reported most commonly include fatigue, chills, pyrexia, irritability, nausea, diarrhea, vomiting, headache, rash, pruritus, insomnia, myalgia, arthralgia, and decreased appetite. The majority of adverse events were of mild or moderate intensity. In patients the following Serious Adverse Effects were observed: increase liver enzymes in the blood, accumulation of fluids in the abdominal cavity, pulmonary embolism, and changes in ECG parameters.

Ritonavir
Potential side effects of Ritonavir include:
feeling tired/weak, nausea and vomiting, diarrhea, loss of appetite, abdominal pain, changes in taste, tingling feeling or numbness in hands or feet, abnormal sensation, such as burning or prickling around the mouth, dizziness, insomnia (inability to fall asleep), increase in laboratory values such as cholesterol and liver enzymes, allergic reactions including skin eruptions, hives, and rash, inflammation of the pancreas and high blood sugar
The most common side effects of Ritonavir therapy are the following: malaise,

diarrhea, nausea and vomiting, abdominal pain, dizziness, insomnia, sweating and taste abnormality.

Cyclosporine:
The most common side effects of Cyclosporine are the following: Kidney problems, high blood pressure, headache including migraine, tremor, increased levels of lipids (for example cholesterol) in the blood, chest infections, urinary tract infections and infection with CMV (cytomegalovirus). Numbness or tingling, loss of appetite, feeling or being sick, stomach pain, diarrhea, swollen gums, liver disorders, high level of uric acid or potassium in the blood, low levels of magnesium in the blood, muscle pain or cramp, increased hair growth on the body, tiredness, herpes infection, candida infection, blood poisoning, skin disorders, cancers and overproduction of white blood cells.

Danoprevir in combination with Ritonavir:
Danoprevir and Ritonavir have been dosed as a combination in several studies in healthy volunteers and patients and were well tolerated at doses up to 400/100 mg administered twice daily for up to 10 days. The most prevalent adverse event reported in healthy volunteers is Diarrhea.

With the dose(s) used in this study no serious adverse effects are expected. The occurrence of known or other effects cannot be excluded. All potential drugs cause adverse events to some extent. Therefore you should take into account that some risks are still unknown at this moment

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

healthy male or female subjects
18-55 yrs, inclusive
BMI: 18.0-32.0 kg/m2, inclusive
Weight: * 50.0 kg

Exclusion criteria

Suffering from hepatitis B, hepatitis C, cancer or HIV/AIDS. In case of participation in another drug study within 60 days before the start of this study or being a blood donor within 60 days from the start of the study. In case of donating more than 1.5 liters of blood in the 10 months prior the start of this study.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-06-2012
Enrollment:	29
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Danoprevir
Generic name:	Danoprevir
Product type:	Medicine
Brand name:	Neoral
Generic name:	Cyclosporine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritanovir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	04-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2012
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-09-2012
Application type:	Amendment
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	EUCTR2012-000470-40-NL
CCMO	NL40164.056.12