Bioequivalence study of CRUshed Sofosbuvir/velpAtasvir compareD to the wholE tablet (CRUSADE-1)/Hep-NED004

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Primary objective:To assess the bioequivalence of SOF/VEL as a crushed (test) tablet compared to a whole (reference) tablet in patients treated with SOF/VELSecondary objective:To evaluate the safety and tolerability of crushed SOF/VEL tablets in...

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

Summary

ID

NL-OMON45504

Source
ToetsingOnline

Brief title
CRUSADE-1

Condition

- Viral infectious disorders

Synonym
Hepatitis C; liver disease caused by the hepatitis C virus

Research involving
Human

Sponsors and support

Primary sponsor: Afdeling Apotheek
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: crushed, epclusa, hepatits C

Outcome measures

Primary outcome

The primary aim of this study is to assess the bioequivalence of SOF/VEL administered as a crushed (test) tablet compared to a whole (reference) tablet in patients treated with SOF/VEL.

Geometric Mean Ratios and the 90% CI interval of the pharmacokinetic parameters (AUC0-tau, Cmax,ss and Ctrough) and median of t* and tmax,ss of sofosbuvir, GS-331007 and velpatasvir of a crushed tablet (intervention) compared to a whole tablet (reference).

AUC0-24 and Cmax,ss GMR with a 90% CI falling entirely within the range of 0.8 to 1.25 are considered bioequivalent.

Secondary outcome

To evaluate the safety and tolerability of crushed SOF/VEL tablets in patients.

Adverse events after administration of (crushed) SOF/VEL will be described and compared (including clinically relevant laboratory abnormalities).

Study description

Background summary

Epclusa® is a pan-genotypic, once-daily tablet for the treatment of chronic hepatitis C virus (HCV) infection containing the NS5B- polymerase inhibitor

sofosbuvir (SOF, nucleotide analogue) 400 mg and the NS5A inhibitor velpatasvir (VEL) 100 mg.

For patients with swallowing difficulties, administration of whole tablets can be problematic. In addition, HCV patients that are hospitalized (at intensive care units) due to severe illness (co-infections/ liver failure) might not be able to swallow medication. Therefore it is useful to know whether it is possible to administer SOF/VEL through a different route, like a feeding tube.

In daily practice, information about the safety and efficacy of crushed tablets is lacking which might result in interruption or discontinuation of expensive HCV therapy. However, it is not recommended to interrupt treatment because there is no evidence about the efficacy of the therapy after discontinuation. Currently, patients and healthcare professionals are crushing SOF/VEL tablets without information about efficacy and safety. Depending on the biopharmaceutical characteristics of a drug formulation, crushing tablets can lead to altered pharmacokinetics of drugs.
It is important to know whether pharmacokinetic parameters are influenced by crushing of tablets; both a decrease and an increase in exposure may occur. A decrease of the plasma concentrations of SOF and/or VEL potentially reduces the therapeutic effect of the drugs. Higher doses or switching to other HCV-drugs might be needed. In contrast, in case a higher Cmax,ss and/or exposure occurs there might be an increased risk of toxicity.

As a result, crushing the drug is a contra-indication based on the available data.
Therefore this study will be conducted to investigate whether a crushed SOF/VEL tablet is bioequivalent to SOF/VEL as a whole tablet.

Study objective

Primary objective:
To assess the bioequivalence of SOF/VEL as a crushed (test) tablet compared to a whole (reference) tablet in patients treated with SOF/VEL

Secondary objective:
To evaluate the safety and tolerability of crushed SOF/VEL tablets in patients.

Study design

Open-label, 2-period, randomised, cross-over, multiple-centre, phase-IV, multi dose trial in 14 HCV infected patients.

Intervention

Administration of a crushed tablet

Study burden and risks

For a number of reasons, administration of the large Epclusa® tablet can lead to administration difficulties. Pharmacokinetic properties and information about safety and efficacy of SOF/VEL after crushing are unknown. This also accounts for other DAAs. Because no data are available on bioavailability of SOF/VEL after crushing, crushing the drug is a contra-indication. The efficacy after interruption or discontinuation of the expensive HCV therapy is unknown.

There are currently no treatment options with DAAs for patients with administration difficulties like swallowing disorders. Therefore, potential value of this research is to provide information about whether it is possible to crush the tablets and/or administer SOF/VEL through a different route, like a feeding tube.
Because SOF/VEL is the first DAA regimen with potent pan-genotypic activity it is useful to determine whether a crushed SOF/VEL tablet is bioequivalent to SOF/VEL as a whole tablet for this specific DAA.

Due to ethical considerations, this study will be performed in adult patients who are currently treated with SOF/VEL instead of healthy patients. Patients who are included have tolerated SOF/VEL for at least eleven weeks. Therefore the risk for adverse events with the administration of one additional dose in this population is very low. Using this study design, healthy patients are not unnecessarily exposed to SOF/VEL.
Based on the list of excipients no large differences in bioavailability will be expected. Although no large differences will be expected the crushed tablet will be administrated during the last week of treatment in order to ensure the efficacy.

The study participants are patients >= 18 years.

Patients will visit the clinical research centre for 1 short visit (15 minutes) and 2 full days (9 hours).
Study duration will be between 3 and 8 days, depending study treatment days (window day 78 - day 84).
Note: There will be an additional short visit (15 minutes) for patients who prefer not to have the PK days on two consecutive days.

For pharmacokinetic purposes 15 blood samples will be taken for the standard protocol. For safety assessment (haematology and clinical chemistry), a total of six blood samples will be collected. The total blood volume taken will be approximately 123 ml maximum. During the days that blood samples will be collected for a PK-curve, an intravenous cannula will be inserted to facilitate blood sampling and limit the amount of venous punctures.
Note: During the first short visit three additional blood samples (one PK sample and two samples for safety assessment) will be taken for patients who

prefer not to have the PK days on two consecutive days. The total blood volume taken will be approximately 136 ml maximum instead of 123 ml.

The patients will not benefit from the participation in this clinical trial.

Epclusa® is a registered product and is well tolerated in healthy and HCV-infected subjects. As decribed previously the risk for included patients is very low. See chapter 10.1.4 for information on the risks assessment.
A potential issue of concern might be the administration of the crushed tablet. Crushing tablets can lead to altered pharmacokinetics of drugs, both a decrease or an increase of exposure may occur.
In this study, only a single crushed dose will be administered during the last week of the treatment. A decrease in exposure is assessed as not clinically relevant.

A higher maximum concentration and/or exposure may result in an increased risk of toxicity.
No dose- or exposure-response relationship for safety was explored for VEL and SOF. The phase 3 studies only tested one single dose of SOF/VEL (400 mg/100 mg), and the FDA Office of Clinical Pharmacology (OCP) team did not identify any prominent adverse events or adverse events of special interest for further investigation. Thorough QT studies have been conducted for SOF and VEL. VEL (500 mg) and SOF (1200 mg) do not prolong QTc interval to any clinically relevant extent. (8)

Although no exposure-response relationship for safety was explored changes in pharmacokinetic parameters for SOF and VEL have been investigated in drug-drug interaction studies.
Recommendations concerning co-administration of a single drug with SOF or VEL as a victim suggest no dose adjustment of Epclusa when the drug-drug interaction leads to a higher Cmax or AUC.(8)
For example, a 60% increase in Cmax and 100% increase in AUC were observed when VEL (100 mg) was coadministered with cyclosporine (600 mg). When SOF (400mg) was coadministered with cyclosporine (600 mg) a 150% increase in Cmax and 350% increase in AUC were observed. The magnitude of increase in VEL and SOF Cmax and AUC when coadministered with cyclosporine was not considered clinically significant since no dose adjustment is required. (8)

In addition, previously bioequivalence studies on crushing medication show differences in maximum concentration and exposure. However, in comparable study designs in HIV medication (without a gastro-resistant coating or slow-release profile), no large increases in maximum concentration and exposure were found relative to the range of bioequivalence (0.8-1.25)(6, 7).

The risk for adverse events with the administration of one additional dose in this population is very low.

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.Patients with sofosbuvir/velpatasvir treatment for the treatment of chronic hepatitis C genotype 1 through 6.
2. Patient is at least 18 at the day of screening.
3. Patient is able and willing to sign the Informed Consent Form.
4. Patient is able and willing to follow protocol requirements.

Exclusion criteria

1. Pregnant female (as confirmed by an hCG test performed 4 weeks before Day 84) or breast-feeding female.
2. Relevant history or current condition that might interfere with drug absorption,

distribution, metabolism or excretion except for conditions related to HCV.
3. Inability to understand the nature and extent of the study and the procedures required.
4. Clinically relevant low hemoglobin concentration at screening judged by the patient*s own physician.

Study design

Design

Study phase:	4
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):	01-12-2017
Enrollment:	11
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Epclusa
Generic name:	Sofosbuvir/ Velpatasvir
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	11-10-2017

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-12-2017
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	EUCTR2016-003941-27-NL
CCMO	NL59363.091.17