Biocomparison study of crushed elbasvir/grazoprevir compared to the whole tablet (CRUSADE-2)/Hep-NED005

Published: 09-10-2018
Last updated: 04-01-2025

Primary objective:To assess pharmacokinetic similarity of EBR/GZR as a crushed (test) Zepatier tablet compared to a whole (reference) tablet.Secondary objective:To assess Cmax similarity of EBR/GZR as a crushed (test) Zepatier tablet compared to a…

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

Summary

ID

NL-OMON47715

Source
ToetsingOnline

Brief title
CRUSADE-2

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, Hepatitis C, Zepatier

Outcome measures

Primary outcome

Geometric Mean Ratios and the 90% confidence interval of the AUC0-72h and

AUC0-inf of a crushed tablet (test) compared to a whole tablet (reference).

AUC0-72h/ AUC0-inf GMR with a 90% CI falling entirely within the range of 0.7

to 1.43 are considered pharmacokinetic similar.

Secondary outcome

Geometric Mean Ratios and the 90% confidence interval of the AUC0-72h and

AUC0-inf of a crushed tablet (test) compared to a whole tablet (reference).

AUC0-72h/ AUC0-inf GMR with a 90% CI falling entirely within the range of 0.7

to 1.43 are considered pharmacokinetic similar

Study description

Background summary

For patients with swallowing difficulties, administration of whole tablets can be problematic and might lead to noncompliance. Studies indicate that between 10% and 40% of adults have difficulties swallowing solid oral medication, while general practitioners underestimated these problems.
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 Zepatier through alternative methods, like crushed with water or through a feeding tube. MSD showed that at least 92% recovery of both components (EBR and GZR) was achieved through three types of tube. However, 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 (and restarting).

Currently, patients and healthcare professionals are crushing 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. Therefore, 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 EBR and/or GZR 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 and/or AUC occur there might be an increased risk of toxicity.
As a result, crushing of EBR/GZR is contraindicated.

This study will be conducted to investigate whether a crushed EBR/GZR tablet is pharmacokinetic similar to EBR/GZR as a whole tablet.

Study objective

Primary objective:
To assess pharmacokinetic similarity of EBR/GZR as a crushed (test) Zepatier tablet compared to a whole (reference) tablet.

Secondary objective:
To assess Cmax similarity of EBR/GZR as a crushed (test) Zepatier tablet compared to a whole (reference) tablet.
To evaluate the safety and tolerability of crushed Zepatier tablets in healthy volunteers.

Study design

12 healthy volunteers will be divided into one of the following treatment sequences: RT:TR.

Treatment period
* R: Single-dose EBR/GZR as a whole tablet administered with 250 milliliters of water in a fasted state.
* T: Single-dose crushed EBR/GZR tablet administered with 250 milliliters of water in a fasted state.

Between the different treatment periods a wash-out period of 14 days is scheduled. Blood samples for a pharmacokinetic curve will be collected up to 72 hours after observed intake of the study medication on days 1, 2 and 3, and 15, 16 and 17.
The by MSD recommended procedure will be followed including the use of a specified tablet crusher.

Intervention

Administration of a crushed tablet

Study burden and risks

Geometric Mean Ratios and the 90% confidence interval of the Cmax a crushed tablet (test) compared to a whole tablet (reference). Cmax GMR with a 90% CI falling entirely within the range of 0.7 to 1.43 are considered pharmacokinetic similar.

Median of t* and tmax of elbasvir and grazoprevir of a crushed tablet (test) compared to a whole tablet (reference).

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

Contacts

Public
Selecteer

Geert Grooteplein 10
Nijmegen 6525 GA
NL
Scientific
Selecteer

Geert Grooteplein 10
Nijmegen 6525 GA
NL

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 does not smoke more than 10 cigarettes, 2 cigars, or 2 pipes per day for at least 3 months prior to Day 1.
3. Subject weighs at least 40 kg.
4. Subject has a Quetelet Index (Body Mass Index) of 18 to 35 kg/m2, extremes included.
5. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
6. Subject is in good age-appropriate health condition as established by medical history, physical examination, and electrocardiography, 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.
7. Subject has a normal blood pressure and pulse rate, according to the Investigator's judgment.

Exclusion criteria

1. Creatinine clearance below 60 mL/min.
2. Documented history of sensitivity/idiosyncrasy to medicinal products or excipients.
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, 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 study.
5. Therapy with any drug (for two weeks preceding Day 1), except for acetaminophen (max 2 gram/day), intrauterine device.
6. Relevant history or presence of pulmonary disorders (especially COPD), cardiovascular disorders, neurological disorders (especially seizures), psychiatric disorders, gastro-intestinal disorders, renal and hepatic disorders (clinically relevant increased ALAT/ASAT or hyperbilirubinemia), hormonal disorders (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 (positive drugs of abuse test).
9. Inability to understand the nature and extent of the study and the procedures required.
10. Participation in a drug study within 60 days prior to Day 1.
11. Donation of blood within 60 days prior to Day 1.
12. Febrile illness within 3 days before Day 1.
13. Co-worker of Radboud university medical center.

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:	Completed
Start date (anticipated):	23-04-2019
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Zepatier
Generic name:	elbasvir/grazoprevir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	09-10-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-01-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	25-02-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-04-2019
Application type:	Amendment
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	EUCTR2017-000415-17-NL
CCMO	NL61215.091.17

Study results

Date completed:	24-05-2019

Results posted:	03-11-2020
Actual enrolment:	11

First publication
02-12-2019