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# Pharmacokinetic similarity demonstrated after crushing of the elbasvir/grazoprevir fixed-dose combination tablet for HCV infection

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**Background:** Finding a suitable treatment for HCV patients with swallowing disorders is still a major challenge. In practice, direct-acting antivirals are crushed without knowledge of adequate absorption. Crushing can alter drug exposure, possibly leading to treatment failure, development of resistance or toxicity. Currently, there is no information about crushing of the fixed-dose combination tablet of elbasvir/grazoprevir; therefore, crushing of this tablet is not recommended.

**Objectives:** To investigate the influence of crushing on the pharmacokinetics of the elbasvir/grazoprevir fixed-dose combination tablet.

**Methods:** We conducted an open-label, two-period, randomized, cross-over, Phase I, single-dose trial in 11 healthy adult volunteers. Subjects randomly received whole-tablet elbasvir/grazoprevir or crushed and suspended elbasvir/grazoprevir in a fasted state. Pharmacokinetic similarity criteria (90% CIs lie within 70%–143% acceptance range) were used for $AUC_{0-\infty}$ and $AUC_{0-72}$.

**Results:** Mean plasma concentration–time curves of elbasvir and grazoprevir showed similar pharmacokinetic profiles. The primary pharmacokinetic parameters $AUC_{0-\infty}$ and $AUC_{0-72}$ of elbasvir and grazoprevir after intake of a crushed tablet were on average 12%–16% higher compared with the whole tablet, but 90% CIs were all within the predefined boundaries of pharmacokinetic similarity. Crushing leads to a higher $C_{max}$ of grazoprevir (42%); no significant difference was found between treatments with regard to the $C_{max}$ of elbasvir. No serious adverse events were reported during the trial.

**Conclusions:** Pharmacokinetic similarity could be demonstrated for a crushed and suspended tablet compared with a whole tablet, without impacting drug safety or efficacy. Crushed and suspended administration of elbasvir/grazoprevir can be used in patients with swallowing disorders.

## Introduction

Worldwide, approximately 71 million people are suffering from chronic HCV infection. Although asymptomatic in early stages, HCV is one of the main causes of chronic liver disease. If left untreated, chronic HCV may lead to liver-related morbidity, including decompensation, hepatocellular carcinoma and death. Chronic HCV has become a curable disease and direct-acting antivirals (DAAs) cure >90% of patients.[1]

Optimal target exposure to DAAs is needed to achieve therapeutic success. Oral drug delivery can be challenging in patients with swallowing disorders. These patients have prolonged oesophageal drug-transit time, which affects pharmacokinetics and compromises effectiveness. Swallowing disorders are prevalent and it is estimated that 10%–40% of adults have difficulties swallowing solid oral medications.[2–4] Most DAAs are formulated as fixed-dose combination tablets and are big in size. If not authorized in the drug label, manipulation of drugs, such as crushing, is

technically off-label. As a consequence, there is no therapy available for patients with swallowing disorders and efficacy after interruption or discontinuation of the expensive HCV therapy is unknown.

Although this is contraindicated, it is common practice to crush DAA tablets and dissolve or suspend the powder to ease administration, without information about efficacy and safety.[5–7] However, crushing tablets can lead to altered pharmacokinetics; either a decrease[8] or an increase[9] in exposure may occur. This may possibly lead to treatment failure, development of resistance or toxicity. A 2018 study by Oberoi *et al*.[7] demonstrated that grinding or crushing of glecaprevir/pibrentasvir, a fixed-dose DAA tablet, had a serious impact on exposures in healthy subjects, leading to a prohibition (in the label text) to chew, crush or break the tablets.[10]

Elbasvir/grazoprevir, a potent once-daily fixed-dose combination tablet, is approved for the treatment of HCV genotype 1a, 1b and 4 infection. It is a combination of the NS5A inhibitor elbasvir and the NS3/4A PI grazoprevir. The biopharmaceutical characteristics of the drug formulation make the 21×10 mm elbasvir/grazoprevir tablet without a specific release profile a suitable candidate for crushing.[1]

In 2018, Yap *et al*.[11] described successful treatment of a patient treated with elbasvir/grazoprevir for a 16 week course through a percutaneous endoscopic gastrostomy (PEG) tube. There are no further data available supporting the efficacy, safety and pharmacokinetics of crushed elbasvir/grazoprevir. The aim of this study was to investigate the influence of crushing on the pharmacokinetics of elbasvir/grazoprevir.

## Methods

This open-label, two-period, randomized, cross-over, Phase I, single-dose trial in healthy adult volunteers was conducted in April 2019 at the Radboud University Medical Center, Nijmegen, The Netherlands.

The protocol was approved by the local ethics committee of Arnhem-Nijmegen and registered at ClinicalTrials.gov under number NCT03817619. Data were collected using Castor EDC (Castor Electronic Data Capture CB, Amsterdam, The Netherlands).

Healthy volunteers who were eligible for inclusion had to be between 18 and 55 years of age, had to weigh at least 40 kg with a BMI of 18.5–35 kg/m$^2$, had to be able and willing to sign the Informed Consent Form, had to be in good age-appropriate health condition and had to not have smoked more than 10 cigarettes, 2 cigars or 2 pipes per day for at least 3 months prior to Day 1. Main exclusion criteria were: positive serology for hepatitis B or C; creatinine clearance below 60 mL/min/1.73 m$^2$; sensitivity/idiosyncrasy to the medicinal products or excipients used in this study; relevant history or current condition that might interfere with drug absorption, distribution, metabolism or excretion; pregnant or breastfeeding; therapy with any drug except for acetaminophen and/or a hormonal and non-hormonal intrauterine device; abuse of drugs or alcohol; and febrile illness within 3 days before Day 1.

The study was designed to show pharmacokinetic similarity between a whole elbasvir/grazoprevir tablet and a crushed tablet. Tablets were crushed in a plastic crushing bag with the Medline Silent Knight® pill crusher following the 'Procedures for Crushing Zepatier for NG or Stomach Tube Administration'.[12] Subjects randomly received the following oral treatment regimens: reference treatment (whole single-dose elbasvir/grazoprevir tablet) or test treatment (crushed single-dose elbasvir/grazoprevir tablet) in a fasted state with 250 mL of water. To prevent any residual crushed tablet in the crushing bag or the dosing cup, both were twice rinsed with 15 mL of water. The suspension was stirred thoroughly until the crushed tablet appeared to be evenly dispersed in the water and no substantial clumps remained just before administration. A washout period of 14 days was scheduled between each treatment period.

The sample size for this study was calculated using a mixed linear model with fixed factors subject, period and treatment assuming an intra-subject variability for AUC of ∼26% for grazoprevir and ∼27% for elbasvir.[13] A total sample size of nine evaluable subjects was considered sufficient for a power of 80% to evaluate absence of difference between whole and crushed tablet. A total of 11 subjects were included to account for possible dropouts.

Volunteers had to fast for at least 8 h prior to administration of elbasvir/grazoprevir on the pharmacokinetic sampling days. Water was allowed up to 1 h before and 1 h after administration of elbasvir/grazoprevir. For every healthy volunteer, a pharmacokinetic curve was collected up to 72 h after intake for determination of elbasvir and grazoprevir concentrations. Blood samples were collected in EDTA plasma tubes at the following timepoints: 0 h (pre-dose) and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 24, 48 and 72 h post-ingestion after observed intake of the study medication.

The main objective of this study was to investigate the influence of crushing on the pharmacokinetics of elbasvir/grazoprevir in healthy volunteers. The primary pharmacokinetic parameter of interest was the AUC extrapolated to infinite time ($AUC_{0-\infty}$) and to 72 h ($AUC_{0-72}$). Secondary pharmacokinetic parameters were the maximum plasma concentration ($C_{max}$), time to $C_{max}$ ($T_{max}$) and terminal half-life ($t_{1/2}$). The data obtained in this study were analysed according to the EMA 'Guideline on the Investigation of Bioequivalence' and FDA 'Guidance for Industry: Statistical Approaches to Establishing Bioequivalence'.[14,15]

Concentrations of elbasvir and grazoprevir in plasma were analysed by the use of a validated LC-MS/MS method. The calibration range was 3.0–1500 μg/L for elbasvir and grazoprevir in plasma.[16,17] Pharmacokinetic parameters were determined by non-compartmental analysis in WinNonlin (version 8.1, Certara, Princeton, NJ, USA). AUCs were calculated using the linear trapezoidal method for ascending concentrations and the log trapezoidal method for descending concentrations (linear-up/log-down). Geometric mean ratios (GMRs) with 90% CIs of $AUC_{0-\infty}$, $AUC_{0-72}$ and $C_{max}$ were calculated for the crushed tablet versus the whole tablet after log transformation of within-subject ratios using the bioequivalence module (mixed model) in WinNonlin/Phoenix, with fixed effects treatment, period, sequence and subject within sequence. The $AUC_{0-\infty}$ and $AUC_{0-72}$ were valid if it was possible to estimate a reliable $t_{1/2}$ and the $AUC_{0-t}$ covered more than 80% of the extrapolated part of the AUC. For a reliable estimate of $t_{1/2}$, at least three samples are required during the terminal log-linear phase in combination with a coefficient of determination ($R^2$) of >0.8. The two treatments were considered pharmacokinetically similar if the 90% CIs of the GMRs of AUCs were within 70% to 143%. These no-effect boundaries are based on recommendations concerning elbasvir/grazoprevir use when co-administered with interacting drugs; the boundaries represent the acceptable change in systemic exposure that is considered not significant enough to warrant clinical action.[10] Comparisons of $T_{max}$ were performed using the Wilcoxon signed-rank test with SPSS software (Version 25). Statistical significance was set at $P < 0.05$.

Furthermore, safety and tolerability of a single-dose crushed elbasvir/grazoprevir tablet was evaluated based on adverse event (AE) monitoring and laboratory tests. AEs were graded using the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (DAIDS AE Grading Table, version 2.1, July 2017).

## Results

Eleven healthy adult volunteers (five male and six female; 100% white race) were enrolled in this study, all of whom completed the study. Median (range) age was 26 (22–54) years and median

(range) BMI was 24.3 (18.1–27.1) kg/m$^2$. All subjects provided written informed consent for this study.

All 22 plasma concentration–time curves of elbasvir were valid. Seven of the 22 plasma concentration–time curves of grazoprevir (4 in the reference treatment and 3 in the test treatment) in four volunteers could not be included for $AUC_{0-\infty}$ analysis and 3 of the 22 plasma concentration–time curves (2 in the reference treatment and 1 in the test treatment) in two volunteers could not be included for $AUC_{0-72}$ analysis because the majority of the data points were below the lower limit of qualification (LLOQ) (<3.0 μg/L) (Figure S1 and Table S1, available as Supplementary data at *JAC* Online). A marked inter-individual variability in plasma concentration–time curves of grazoprevir was observed, as shown by their high percentage coefficient of variation values of 144% for whole tablet and 70% for crushed tablet for the $C_{max}$.

### Pharmacokinetics

#### AUC

Figure 1 shows the mean plasma concentration–time curves of elbasvir and grazoprevir for the reference and test treatments. Table 1 shows the pharmacokinetic parameters for all compounds for each treatment. It also shows the GMRs of the crushed tablet versus the whole tablet and the corresponding 90% CIs. The $AUC_{0-\infty}$ and $AUC_{0-72}$ of elbasvir of the crushed tablet were both 12% higher compared with the whole tablet. The $AUC_{0-\infty}$ and $AUC_{0-72}$ of grazoprevir of the crushed tablet were also higher compared with the whole tablet (13% and 16%, respectively). Figure S2 demonstrates grazoprevir $AUC_{0-72}$ of the individual participants. The 90% CIs of $AUC_{0-\infty}$ and $AUC_{0-72}$ for both compounds fell within the predefined boundaries of pharmacokinetic similarity of 70%–143%.

#### $C_{max}$

The $C_{max}$ of elbasvir increased by 10% and the $C_{max}$ of grazoprevir by 42% after intake of the crushed tablet compared with the whole tablet. Pharmacokinetic similarity between the crushed tablet and the whole tablet could not be demonstrated for grazoprevir as the 90% CIs for $C_{max}$ of grazoprevir exceeded the required limits of 70%–143%. The 90% CIs of the $C_{max}$ of elbasvir fell within the pharmacokinetic similarity limits of 70%–143%. Notably, no significant difference in the $T_{max}$ of elbasvir between the treatment groups was evident ($P = 0.67$; Wilcoxon signed-rank test), but the $T_{max}$ of grazoprevir was significantly shorter after intake of the crushed tablet compared with the whole tablet ($P = 0.02$; Wilcoxon signed-rank test).

### AEs

No serious AEs were reported during the trial. Four healthy adult volunteers reported a total of five AEs. Of these, three were judged to be probably or possibly related to elbasvir/grazoprevir. One volunteer experienced transient asymptomatic elevations of ALT and AST defined as grade 2 (2.5 to <5.0 × upper limit of normal) after both administrations. There was one case of headache (grade 1). Haematoma and sinus pain were reported as unrelated (grade 1).

## Discussion

In this study we showed that crushing of elbasvir/grazoprevir did not affect the main pharmacokinetic properties. Thus, pharmacokinetic similarity could be demonstrated.

Our data showed an increase in grazoprevir $C_{max}$ and a significantly shorter $T_{max}$ after crushing, without toxicity being observed. The mean grazoprevir $C_{max}$ for a single crushed dose of 100 mg was 1.5-fold higher than the mean grazoprevir $C_{max}$ for the whole tablet. In our opinion, the increased grazoprevir $C_{max}$ observed in this study is not clinically relevant in terms of safety because the safety and tolerability of grazoprevir have been demonstrated for multiple doses up to 800 mg once daily (8-fold higher than the licensed dose of 100 mg) for 12 weeks in a Phase II study.[18] In addition, exposure (AUC) rather than $C_{max}$ has been related to an increased risk of late ALT elevations[13] and AUC was not influenced by crushing in our study. However, individual considerations are

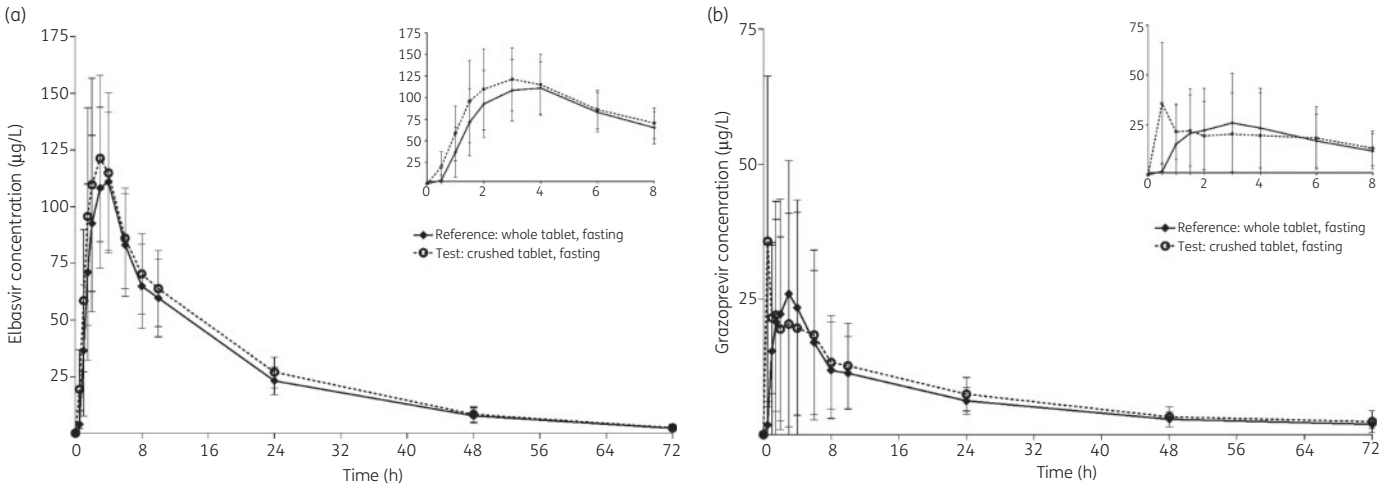


**Figure 1.** Mean (SD) plasma concentration versus time curves for elbasvir (a) and grazoprevir (b) following administration of a single dose of elbasvir/grazoprevir fixed-dose combination administered as a whole (reference) and a crushed (test) tablet. Inset: first 8 h. $n = 11$ for elbasvir reference and test, $n = 7$ for grazoprevir reference and $n = 8$ for grazoprevir test.

**Table 1.** Pharmacokinetic parameters for elbasvir and grazoprevir, including GMRs, for the interventions versus the reference treatment

| Pharmacokinetic parameter | *n* | Reference treatment (whole tablet) | *n* | Test treatment (crushed tablet) | Crushed versus whole tablet GMR (90% CI) |
|---|---|---|---|---|---|
| Elbasvir | | | | | |
| $AUC_{0-\infty}$ (μg/L·h) | 11 | 1718 (30) | 11 | 1913 (29) | 112 (98–128) |
| $AUC_{0-72}$ (μg/L·h) | 11 | 1673 (29) | 11 | 1863 (29) | 112 (98–128) |
| $C_{max}$ (μg/L) | 11 | 115 (28) | 11 | 126 (32) | 110 (92–132) |
| $T_{max}$ (h) | 11 | 3 (2–6) | 11 | 3 (2–6) | $P = 0.67$[b] |
| $t_{1/2}$ (h) | 11 | 14 (18) | 11 | 13 (18) | |
| Grazoprevir | | | | | |
| $AUC_{0-\infty}$ (μg/L·h) | 7[a] | 489 (44) | 8[a] | 523 (47) | 113 (99–129) |
| $AUC_{0-72}$ (μg/L·h) | 9[a] | 411 (47) | 10[a] | 456 (50) | 116 (98–138) |
| $C_{max}$ (μg/L) | 11 | 21 (144) | 11 | 30 (70) | 142 (99–202) |
| $T_{max}$ (h) | 11 | 3 (1.5–6) | 11 | 0.5 (0.5–6) | $P = 0.02$[b] |
| $t_{1/2}$ (h) | 8[a] | 19 (49) | 9[a] | 19 (25) | |

$AUC_{0-\infty}$, $AUC_{0-72}$, $C_{max}$ and $t_{1/2}$ are shown as geometric mean (percentage coefficient of variation). $T_{max}$ is shown as median (range).
[a]Volunteers were excluded because $t_{1/2}$ could not be reliably estimated and/or the extrapolated area of the $AUC_{0-\infty}$ and the $AUC_{0-72}$ was >20%.
[b]Wilcoxon signed-rank test.

recommended for patients with a risk for high grazoprevir exposure, such as patients with cirrhosis or using interactive medication.[10]

Remarkably, in 2018, Oberoi *et al*.[7] demonstrated that manipulation of glecaprevir/pibrentasvir tablets had a serious impact on exposure in healthy volunteers. Crushing the tablets resulted in a 36% lower $AUC_{0-\infty}$ for glecaprevir and a 33% higher $AUC_{0-\infty}$ for pibrentasvir. The exact reason for the different impact was not clear, but may be due to differences in disintegration and dissolution caused by the pH and the location of absorption.[7] The aqueous solubility of grazoprevir and elbasvir is low, with highest solubility being under basic and acid conditions, respectively. Grazoprevir has high permeability and is hence classified as Biopharmaceutics Classification System (BCS) class II. Elbasvir has permeability-dependent absorption and is classified as BSC class IV.[19] Theoretically, crushed application may influence drug solubility and therefore the rate and total amount of absorption. The trend towards increased $C_{max}$ and shortened $T_{max}$ of grazoprevir might be explained by the increased dissolution and the subsequently high permeability. In contrast, crushing did not affect total exposure of elbasvir/grazoprevir ($AUC_{0-\infty}$).

A possible explanation for the difference between glecaprevir/pibrentasvir and elbasvir/grazoprevir is the difference in formulation of the tablets. Glecaprevir/pibrentasvir tablets have a specific immediate-release bilayer formulation and this formulation does not seem suitable for crushing. The elbasvir/grazoprevir tablet has no specific release profile and therefore crushing is possible.

In the present study, the tablets were crushed with a standardized crushing protocol using the Medline Silent Knight® pill crusher in a controlled environment. The volunteers were healthy and in a fasted state. It is unknown whether a standard tablet crusher may have a different impact on the pharmacokinetic properties of elbasvir/grazoprevir, as well as food intake or the patient population. However, there is no indication that this affects the results. Caution is required when extrapolating this to patients with delayed oesophageal transit times or delayed gastric emptying, as this might have an impact on the pharmacokinetics.

Contrary to our expectations, we had to exclude three of the $AUC_{0-72}$ of grazoprevir and seven of the $AUC_{0-\infty}$ of grazoprevir because the majority of the data points were below the LLOQ. The exact reason is not clear. Notably, the excluded volunteers had the same concentration profile after administration of the crushed tablet as after administration of the whole tablet (Table S1). Therefore, it is unlikely that crushing is the cause of the low exposure. A plausible explanation is the high inter-individual variability as shown by their high percentage coefficient of variation values of 144% and 70% for the $C_{max}$ of grazoprevir. This is also described in Phase I studies.[10,13,20] The LLOQ was established for the detection of trough levels and pharmacokinetic evaluation for each compound in HCV patients (with higher exposure than healthy volunteers).[17] As a result, the analysis method was not sufficiently sensitive to be able to determine the grazoprevir plasma concentrations for all healthy volunteers following a single dose of 100 mg of grazoprevir administered under fasted conditions.[13,20] In our opinion, the results are reliable and valid because the power is sufficient to evaluate absence of difference in AUC with a total of nine evaluable subjects, so the missing data has no clinically relevant consequences for the conclusion.

In our practice, we are regularly asked by physicians how to treat HCV patients with swallowing difficulties or patients who require a feeding tube. In addition to our results, unpublished *in vitro* data of MSD showed at least 92% recovery of both components (elbasvir and grazoprevir) through three types of tube.

In conclusion, pharmacokinetic similarity could be demonstrated for a crushed and suspended tablet compared with a whole tablet, without impacting drug safety or efficiency of this generally well-tolerated drug. Crushed and suspended administration of elbasvir/grazoprevir can be used in patients with swallowing disorders or patients who require a feeding tube.

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## Supplementary data

Figures S1 and S2 and Table S1 are available as Supplementary data at *JAC* Online.

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