Concomitant Intake of Coca-Cola to Manage the Drug–Drug Interaction Between Velpatasvir and Omeprazole Studied in Healthy Volunteers

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We aimed to evaluate the effect of the acid beverage Coca-Cola on the pharmacokinetics of velpatasvir (VEL) when given with omeprazole. This was an open-label, randomized, crossover trial in 11 healthy adults. A single dose of sofosbuvir/velpatasvir (SOF/VEL) 400/100 mg was administered alone (reference) or with omeprazole 40 mg once daily with water (intervention I); in the intervention II arm, omeprazole 40 mg was combined with 250 mL of Coca-Cola. Geometric mean ratios (GMRs) were calculated for VEL area under the concentration-time curve from zero to infinity (AUC_{0-inf}) and maximum plasma concentration (C_{max}). VEL exposure was reduced by 26.7% when SOF/VEL was coadministered with omeprazole vs. reference: GMRs (90% confidence interval (CI)) were 73.3% (55.6–96.8) and 69.1% (52.3–91.2) for AUC_{0-inf} and C_{max}, respectively. Intake of SOF/VEL with Coca-Cola compensated for the interaction with omeprazole and resulted in a higher VEL exposure. GMRs (90% CI) were 161.6% (122.4–213.3) for AUC_{0-inf} and 143.9% (109.0–190.0) for C_{max}. Therefore, Coca-Cola can be used to overcome the drug–drug interaction between VEL and omeprazole.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Velpatasvir (VEL) is a lipophilic weak base with pH-dependent solubility. Proton pump inhibitors (PPIs) increase gastric pH resulting in a decrease in VEL absorption. Coadministration of PPIs is restricted to a maximum dose comparable to omeprazole 20 mg taken 4 hours after sofosbuvir/velpatasvir (SOF/VEL) with food.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ In this trial, the effect of the acid beverage Coca-Cola on the pharmacokinetics of velpatasvir when given with omeprazole 40 mg is investigated.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ Intake of SOF/VEL with Coca-Cola following treatment with omeprazole 40 mg once daily restores the extent of drug absorption of VEL in healthy volunteers.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ Concomitant intake of a glass of Coca-Cola can be used to overcome the clinical relevant drug–drug interaction between SOF/VEL and omeprazole.

The fixed-dose combination of the NS5B polymerase inhibitor sofosbuvir (SOF) and the NS5A inhibitor velpatasvir (VEL) is a pan-genotypic, once-daily tablet for the treatment of chronic hepatitis C virus (HCV) infection.

VEL is a lipophilic weak base (log D 6.31 (pH 8); acid dissociation constants (pKa) 3.2 and 4.6[1]) with pH-dependent solubility ranging from soluble at pH 1.2 (>36 mg/mL) to practically insoluble above pH 4.5 (<0.1 mg/mL).[2,3] As a result, pH-dependent dissolution of the drug is a rate-limiting step for absorption. In general, proton pump inhibitors (PPIs) elevate the stomach pH and achieve a gastric pH > 4 by reducing gastric secretion.[4] This increase in gastric pH impairs VEL absorption. It has been shown that, in subjects treated with omeprazole, the absorption of VEL is reduced by 26–56%, depending on the dose of omeprazole, concomitant food intake, and timing/sequence of VEL vs. omeprazole intake.[5,6] This is the reason why concomitant use of SOF/VEL with PPIs (such as omeprazole) is not recommended. The package insert recommends the administration of SOF/VEL with food and taken 4 hours before PPI at maximum doses comparable to omeprazole 20 mg, if PPI use is necessary.[6]

For a number of reasons, the restrictions on the concomitant use of PPIs with VEL are a clinically relevant problem. First, PPI use is highly frequent in the HCV-infected subject population with a variable prevalence reported in a range of 7.1–23%.[7,8] Second, a

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Received February 22, 2019; accepted April 17, 2019. doi:10.1002/cpt.1569

high dose PPI (>20 mg omeprazole or equivalent) is needed in at least 40% of the patients,[8] which is contraindicated according to the package insert.[6] Third, PPIs are available as over-the-counter medications and, thus, can be used by subjects without informing their physician.

The proposed strategy in this study was to temporarily lower gastric pH by adding a glass of the acidic beverage Coca-Cola at the time of SOF/VEL administration in subjects concurrently treated with omeprazole. Coca-Cola may temporarily lower gastric pH and has the potential to improve absorption of a number of drugs from other therapeutic classes that share with VEL a reduced solubility (and, thus, reduced absorption) at higher intragastric pH, for example erlotinib, itraconazole, and ketoconazole.[9–11] We hypothesized that coadministration of Coca-Cola could overcome the drug–drug interaction (DDI) between SOF/VEL and omeprazole by temporarily lowering gastric pH.

RESULTS

Baseline characteristics

Eleven healthy adult subjects (82% women; 91% white and 9% Asian) were enrolled in the study and all completed the study. Their median (range) age was 38 years (22–55 years) and median (range) body mass index was 23.6 kg/m^2 (19.2–26.9 kg/m^2). Subjects were in normal health based on medical history, physical examination, vital signs, and biochemical and hematology data. The CYP2C19 metabolizer status, as defined by the Clinical Pharmacogenetics Implementation Consortium (CPIC), was intermediate metabolizer (n = 4), extensive metabolizer (n = 4), or rapid metabolizer (n = 3). No poor metabolizers and ultrarapid metabolizers were identified.

One subject missed the intake of one omeprazole tablet in the intervention I arm. This deviation did not lead to exclusion of the study participant, because intake of omeprazole at the pharmacokinetic (PK) sampling day was observed by the trial nurse and investigator. In addition, the PK curve in this intervention arm was representative for the group.

PKs of VEL

The geometric mean concentration-time curves of VEL for all treatments are shown in **Figure 1**. PK parameters and geometric mean ratios (GMRs) are summarized in **Table 1**. Fixed factors (period and sequence) were not statistically significant (P > 0.05).

Intake of SOF/VEL with concomitant omeprazole use (intervention I) decreased the extent of VEL absorption and resulted in a reduction in area under the concentration-time curve from zero to infinity ($AUC_{0\text{-inf}}$) and maximum plasma concentration (C_{max}) of 27% and 31%, respectively. VEL exposure for intervention II (SOF/VEL with concomitant omeprazole use administered with Coca-Cola) was 62% higher compared with reference treatment. An increase of 44% was observed for C_{max}. The 90% confidence interval (CI) for both parameters exceeded the predefined boundaries of PK equivalence of 70–143%.

Figure 2 demonstrates VEL exposure of the individual subjects for all regimens. There was a high intersubject variability (47%) of VEL exposure during reference treatment, and we observed a wide variation in the effect of omeprazole on VEL. Most subjects (n = 6) had a lower VEL exposure, but exposure remained unchanged in two subjects and increased in three subjects. After intake of SOF/VEL with Coca-Cola, intersubject variability decreased and all subjects reached drug exposures above the mean exposure of reference treatment.

PKs of SOF and GS-331007

SOF and its predominant metabolite GS-331007 exposures were unaffected after intake of SOF/VEL with omeprazole and Coca-Cola (intervention II). Compared with reference treatment we found GMRs (90% CI) for SOF and GS-331007 $AUC_{0\text{-inf}}$ of 112.6 (95.2–133.3) and 101.2 (93.0–110.1), respectively. Descriptive

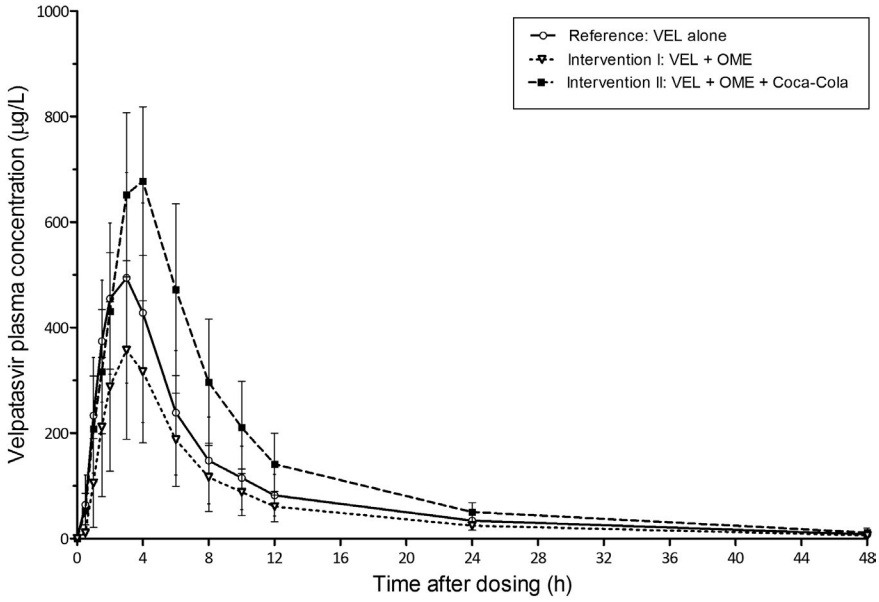

Figure 1 Mean plasma concentration-time curves for velpatasvir (VEL) after administration of a single dose sofosbuvir/VEL in fasted state for each treatment arm. OME, omeprazole.

Table 1 PK parameters for VEL, including GMRs for intervention I and II vs. the reference treatment

PK parameter	Reference VEL alone GM (CV%)	Intervention I VEL + OME GM (CV%)	Intervention II VEL + OME + Coca-Cola GM (CV%)	Intervention I vs. reference GMR (90% CI)	Intervention II vs. reference GMR (90% CI)
$AUC_{0\text{-}inf}$ (μg/L · hour)	3,742.5 (46.8)	2,705.3 (47.5)	5,981.0 (27.5)	73.3 (55.6–96.8)	161.6 (122.4–213.3)
C_{max} (μg/L)	471.5 (40.3)	325.3 (56.7)	683.0 (21.1)	69.1 (52.3–91.2)	143.9 (109.0–190.0)
T_{max} (hour)[a]	3 (3–4)	3 (3–3)	3 (3–4)	—	—
t½ (hour)[a,b]	10.1 (7.1–15.4)	12.2 (7.6–17.5)	10.3 (7.1–13.2)	—	—

Reference treatment consisted of sofosbuvir (SOF)/VEL with 250 mL water; intervention I, SOF/VEL with 250 mL water with omeprazole 40 mg once daily; intervention II, SOF/VEL with 250 mL Coca-Cola with omeprazole 40 mg once daily.
$AUC_{0\text{-}inf}$, area under the time curve from 0 to infinity; CI, confidence interval; C_{max}, maximal plasma concentration; CV, coefficient of variation; GM, geometric mean; GMR, geometric mean ratio; OME, omeprazole; PK, pharmacokinetic; $t_{1/2}$ apparent elimination half-life; T_{max}, time to reach maximal plasma concentration; VEL, velpatasvir.
[a]Values presented are medians (range). [b]The apparent elimination half-life ($t_{1/2}$) is calculated.

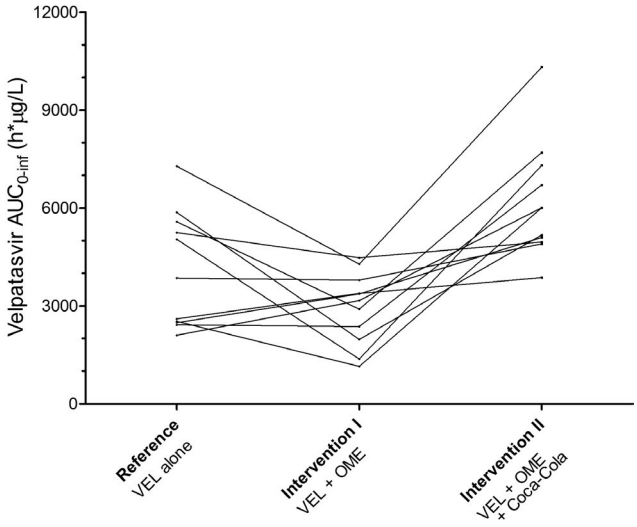

Figure 2 Velpatasvir area under the concentration-time curve from zero to infinity (AUC_{0-inf}) after administration of a single dose of sofosbuvir/velpatasvir in the fasted state for each treatment arm. Each line represents an individual subject. OME, omeprazole; VEL, velpatasvir.

statistics for SOF and GS-331007 of the reference and intervention arms are presented in **Table S1**.

Safety and tolerability

No serious adverse events (AEs) were reported during the trial. Overall, 8 of the 11 subjects (72%) reported a total of 16 AEs (**Table S2**). Seven AEs (44%) were judged to be probably or possibly related to SOF/VEL, and one AE (indigestion) was probably related to the intake of Coca-Cola. The most frequently reported AEs were headache (grade 1, $n = 1$; and grade 2, $n = 4$), gastrointestinal events (grade 1, $n = 4$), and common cold (grade 1, $n = 2$). There were no clinically significant laboratory and physical abnormalities during the study.

DISCUSSION

This study demonstrates that intake of SOF/VEL with Coca-Cola under omeprazole use (40 mg once daily) restored, or even improved, drug absorption of VEL. VEL $AUC_{0\text{-}inf}$ and C_{max} exceeded predefined PK equivalence boundaries, without impacting drug safety of this generally well-tolerated drug. Safety and tolerability of VEL following the administration of multiple doses up to 450 mg once daily (4.5-fold higher than the licensed dose of 100 mg) for 14 days were demonstrated in a phase I study. Mean $AUC_{0\text{-}inf}$ and C_{max} for a single dose of 450 mg were 1.6-fold higher than the exposures we found for SOF/VEL with Coca-Cola.[2] Although VEL exposure falls within the safety margins, individual considerations are recommended for patients with a risk for high VEL exposure, such as patients with comorbidities (i.e., severe renal function impairment) or interaction medication.[6]

Mean exposure in the reference arm was comparable with the geometric least-squares mean of 3,828 (hour · μg/L) for VEL $AUC_{0\text{-}inf}$ found in a phase I registration study after administration of SOF/VEL under fasted conditions in 30 healthy subjects (GS-US-342-0104).[12] Compared with these reference values, administration of VEL with omeprazole reduced the systemic exposure of VEL. These findings correspond with a previous DDI study, which resulted in the restrictions for the use of PPIs. Although the effect was more pronounced in the study with SOF/VEL 400/100 mg and omeprazole 20 mg simultaneously (−37%), we observed an effect of −27% (90% CI 55.6–96.8) that fell out of the PK equivalence boundaries.[5] This difference might be explained by study design (e.g., fasting conditions and omeprazole intake) and patient characteristics (e.g., CYP2C19 genotype and stomach acidity). For example, we found no decrease in VEL exposure for all rapid CYP2C19 metabolizers after intake of omeprazole. This might indicate that the effect of omeprazole on VEL exposure is less pronounced in subjects with increased omeprazole metabolism.

Because the pH of gastrointestinal fluids was not measured in our study, it is unknown whether a difference in acidity could explain the differences in exposure between subjects in our trial. Earlier research of Walravens *et al.*[13] showed a high variability in the effect of Coca-Cola on gastric pH when coadministered with PPIs. Despite the lack of a significant effect on gastric pH, intake of an acid beverage significantly improved the solubility and absorption of the weak base posaconazole. The invasive nature of obtaining gastrointestinal fluid, which was not the primary objective of our study, withheld us to include this procedure in our study.

We studied simultaneous administration of the PPI and SOF/VEL knowing that the maximum effect of PPIs is achieved 2 hours

after PPI intake.[14] Therefore, the impact of omeprazole on VEL exposure could be higher when the PPI is dosed before SOF/VEL. However, we chose simultaneous administration because this method of administration is considered to be the most patient friendly and most probably mimics the real life situation. We cannot recommend taking Coca-Cola when omeprazole is not taken simultaneously with SOF/VEL.

Although the findings of this study are interesting, a limitation is the lack of data on exposure-efficacy. The minimal VEL exposure in patients has not yet been established. A phase II study (GS-US-342-0109) in treatment-experienced subjects with HCV genotype 3 infection suggested that 25 mg VEL (sustained virological response (SVR) rate of 81% instead of 96%) was suboptimal in this population. In addition, in the ASTRAL 3 study with HCV genotype 3 infected patients, VEL AUC exposures were 30% lower in relapsers compared with nonrelapsers.[12] Thus, it is likely that the minimal effective drug exposure depends on genotype,[15] patient characteristics, and disease status. A relatively small degree of decrease in VEL AUC may result in inefficacy in a selected group of patients. Therefore, the selected approach of a glass of the acid beverage Coca-Cola may be applied to all patients without making an individual risk assessment.

Efficacy of HCV treatment with concomitant PPI use was studied in a retrospective analysis of data from phase II and phase III clinical trials, in which 87 patients of all genotypes with and without compensated cirrhosis received SOF/VEL. The SVR12 rate was 97%. Authors concluded that these data support the use of SOF/VEL according to labeled recommendations with respect to coadministration of PPIs.[16] However, these patients were treated according to the package insert with restrictions on PPI dose, food intake, and the sampling schedule. Whether all patients are able to follow these recommendations is unknown, and this may affect results. For example, individual studies on ledipasvir did not show a significant effect on SVR in real-world cohorts.[17] However, the use of a PPI twice daily was associated with lower odds ratio for SVR.[8] In addition, in a comprehensive literature review by Wijarnpreecha *et al.*[18] on efficacy and safety of direct-acting antivirals in patients with concomitant use of PPIs, a significantly increased risk of failure to achieve SVR was shown. Therefore, any negative effect on VEL exposure should be prevented to circumvent the risk of viral relapse.

Despite the disadvantages of Coca-Cola, including high-sugar intake and risk for dental erosion, we recommend the use of the acid beverage Coca-Cola (regular) and to be cautious with the use of other acid beverages. Solubility of VEL decreases strongly as the pH increases (3.6 mg/mL at pH 2 and <0.1 mg/mL at pH 4.5). As shown in **Table S3**, the pH of acid beverages can differ between brands (e.g., type of orange juice) or change when the beverage contains different (sweetening) ingredients (e.g., regular vs. diet cola).[19] Therefore, it is hard to predict influence of other acid beverages on the absorption of VEL when combined with omeprazole. Coca-Cola (regular) has the advantage of global availability, and its disadvantages are minimized as intake is only required for the short treatment period of 12 weeks.

Other solutions for a DDI with PPIs are mentioned in treatment guidelines (for example, stop PPI treatment temporarily or change the direct-acting antiviral combination or acid-reducing agent), but are frequently insufficient. If patients must continue PPI treatment, the use of an acid beverage offers a simple solution to overcome a DDI in case standard solutions are not sufficient.

CONCLUSION

In summary, intake of SOF/VEL with Coca-Cola under PPI treatment with omeprazole 40 mg once daily increases drug absorption of VEL without affecting SOF PKs. Concomitant intake of a glass of Coca-Cola can be used to overcome the DDI between SOF/VEL and omeprazole. However, individual considerations are recommended for patients with a risk for increased VEL exposure (i.e., severe renal impairment and DDIs) above safety margins because safety is uncertain in this population.

METHODS

Study design

This open-label, three-period, randomized, single-dose, crossover trial in healthy adult subjects was conducted in August 2018 at the Radboud University Medical Center, Nijmegen, The Netherlands.

A single dose of SOF/VEL was administered on day 5 alone (treatment A, reference) or with omeprazole 40 mg once daily with water (treatment B, intervention I); in treatment C (intervention II), SOF/VEL was also combined with omeprazole 40 mg once daily but now water was replaced by 250 mL of Coca-Cola (regular) ingested immediately as a bolus. In order to reach steady-state omeprazole plasma concentrations, omeprazole 40 mg once daily was administered on days 1–6 in both intervention arms. Subjects randomly received the reference and intervention treatments, with a washout period of 7 days.

Study participants

Healthy volunteers that were eligible for inclusion had to be between 18 and 55 years of age, weighed at least 40 kg with a body mass index of 18–30 kg/m^2, were able and willing to sign the Informed Consent Form prior to screening evaluations, and were in good age-appropriate health condition (physical examination, electrocardiography and biochemical, and hematological and urinalysis testing). Main exclusion criteria were positive hepatitis B or C tests, sensitivity/idiosyncrasy to the medicinal products used in the study, and pregnancy. No concomitant therapy with any drug was allowed, except for acetaminophen ≤2,000 mg/day and an intrauterine device for contraception.

Study objectives

The primary objective of this study was to evaluate the effect of concomitant Coca-Cola ingestion on VEL PKs when given with omeprazole 40 mg in healthy volunteers. The secondary objectives were to evaluate safety and tolerability of SOF/VEL in the three treatment arms and to evaluate the effect of concomitant Coca-Cola ingestion on the PKs of SOF and its predominant metabolite GS-331007.

Dosing and adherence

During the PK sampling day on study days 5, 12, and 19, omeprazole and SOF/VEL were administered with water or Coca-Cola supervised by the study personnel. In between study days, subjects took omeprazole at home, and adherence was assessed as follows: (i) tablets were counted by the trial nurses, and (ii) subjects were instructed to record the time of medication intake (and any AE) in a diary.

Statistics

Power calculation was performed by using a mixed linear model with fixed factors period and treatment. A total sample size of 10 evaluable

subjects was considered sufficient for a power of 80% in case of PK equivalence.

PK sampling, bioanalysis, and pharmacogenetics

PK curves were collected after a single dose SOF/VEL on days 5, 12, and 19. SOF/VEL and omeprazole were taken concomitantly after an overnight fast. Blood was drawn at the following timepoints: $t = 0$ (predose), 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, and 48 hours after ingestion. Blood samples were stored in a refrigerator and centrifuged (5 minutes at 1,900*g*) within 2 hours. Plasma was transferred into polypropylene tubes and stored at −80°C until bioanalysis. VEL, SOF, and GS-331007 plasma concentrations were analyzed by the use of a validated ultra-high-performance liquid chromatography mass spectrometry method.[20] Validation was established over the range of 7.5–1,500 µg/L for VEL, 5.0–2,500 µg/L for SOF, and 25–5,000 µg/L for GS-331007. The precision for low, medium, and high quality control samples was <10%.

Due to the influence of CYP2C19 polymorphism on the PKs of omeprazole,[21] a pharmacogenetic test (alleles *2, *3, and *17) was conducted to identify CYP2C19 genotype. Genotyping was conducted by the laboratory of the department of Human Genetics of the Radboud University Medical Center. Data were collected using Castor EDC (Castor Electronic Data Capture; Ciwit BV, Amsterdam, The Netherlands).

PK analysis

A noncompartmental analysis in WinNonlin version 8.1 (Certara, Princeton, NJ) was used to assess PK parameters for VEL. The primary PK parameters of interest were the C_{max} and the $AUC_{0\text{-}inf}$. Secondary PK parameters were time to C_{max} (T_{max}) and terminal half-life ($t_{1/2}$).

GMRs with 90% CIs of $AUC_{0\text{-}inf}$ and C_{max} were calculated for intervention I and II vs. the reference treatment after log transformation of within-subject ratios using a fixed-effects bioequivalence module in WinNonlin/Phoenix. Two treatments were considered PK equivalent if the 90% CI of the GMR of $AUC_{0\text{-}inf}$ and C_{max} fell within 70% and 143%.

Safety and tolerability

Safety and tolerability were assessed during the study based on AE monitoring, physical examinations, 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 2.0, January 2014).

Ethics

The trial was approved by the local ethics committee of Arnhem-Nijmegen (reference number 2017-3990). The study was conducted in accordance with Good Clinical Practice, International Committee on Harmonization guidelines, and the Declaration of Helsinki and has been registered at ClinicalTrials.gov (NCT03513393). All participants signed informed consent forms before screening evaluations.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

Table S1. Pharmacokinetic parameters for sofosbuvir and GS-331007, including geometric mean ratios for intervention I and II vs. the reference treatment.
Table S2. Adverse events during study period and relation to study medication or procedure.
Table S3. pH of different commercial available beverages adapted from Reddy *et al*.[19]

ACKNOWLEDGMENTS

The authors thank the volunteers for their participation in this study. The authors also thank the study personnel at the Radboudumc Technology Center Clinical studies, Radboud University Medical Center, Nijmegen, The Netherlands, for conducting this trial and the laboratory personnel of the Department of Pharmacy, Radboud University Medical Center, The Netherlands, for sample analysis.

FUNDING

Medication for this trial was donated by Gilead; the trial was sponsored by Radboud University Medical Center.

CONFLICT OF INTEREST

D.B. and J.D. have received research grants from Gilead, the manufacturer of velpatasvir; J.D. has been part of an advisory board for Gilead. All other authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

M.vS., A.C., and D.B. wrote the manuscript. M.vS., A.C., J.D., and D.B. designed the research. M.vS., A.C., and E.A. performed the research. M.vS., A.C., and D.B. analyzed the data.

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