Population Pharmacokinetics of Remdesivir and GS-441524 in Hospitalized COVID-19 Patients

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ABSTRACT  The objective of this study was to describe the population pharmacokinetics of remdesivir and GS-441524 in hospitalized coronavirus disease 2019 (COVID-19) patients. A prospective observational pharmacokinetic study was performed in non-critically ill hospitalized COVID-19 patients with hypoxemia. For evaluation of the plasma concentrations of remdesivir and its metabolite GS-441524, samples were collected on the first day of therapy. A nonlinear mixed-effects model was developed to describe the pharmacokinetics and identify potential covariates that explain variability. Alternative dosing regimens were evaluated using Monte Carlo simulations. Seventeen patients were included. Remdesivir and GS-441524 pharmacokinetics were best described by a one-compartment model. The estimated glomerular filtration rate (eGFR) on GS-441524 clearance was identified as a clinically relevant covariate. The interindividual variability in clearance and volume of distribution for both remdesivir and GS-441524 was high (remdesivir, 38.9% and 47.9%, respectively; GS-441524, 47.4% and 42.9%, respectively). The estimated elimination half-life for remdesivir was 0.48 h, and that for GS-441524 was 26.6 h. The probability of target attainment (PTA) of the in vitro 50% effective concentration (EC50) for GS-441524 in plasma can be improved by shortening the dose interval of remdesivir and thereby increasing the total daily dose (PTA, 51.4% versus 94.7%). In patients with reduced renal function, the metabolite GS-441524 accumulates. A population pharmacokinetic model for remdesivir and GS-441524 in COVID-19 patients was developed. Remdesivir showed highly variable pharmacokinetics. The elimination half-life of remdesivir in COVID-19 patients is short, and the clearance of GS-441524 is dependent on the eGFR. Alternative dosing regimens aimed at optimizing the remdesivir and GS-441524 concentrations may improve the effectiveness of remdesivir treatment in COVID-19 patients.

KEYWORDS  COVID-19, pharmacokinetics, remdesivir

Remdesivir is the first direct antiviral therapy approved for the treatment of hospitalized coronavirus disease 2019 (COVID-19) patients. It was developed as a potential treatment for hepatitis C and previously investigated for Ebola virus disease. Currently, it is recommended by the NIH and the American College of Physicians as a supportive treatment option in hospitalized hypoxemic patients with COVID-19 (1, 2). The efficacy of remdesivir in COVID-19 treatment has been the subject of debate. Conflicting evidence about the benefit of remdesivir to reduce hospitalization duration and mortality in COVID-19 patients has been published (3–5). More insights into the pharmacokinetics of remdesivir in COVID-19 patients might help to understand these results.
Remdesivir is a prodrug and predominantly metabolized by carboxylesterase-1 to GS-704277 and subsequently to the parent nucleoside analogue GS-441524 (6). The antiviral efficacy of remdesivir is determined by the intracellular concentration of the triphosphate metabolite GS-443902. Metabolism from remdesivir to GS-443902 can occur via two routes, one in which remdesivir is transported into the target cells and intracellularly phosphorylated to GS-443902 and the other in which remdesivir is metabolized to GS-441524 extracellularly and GS-441524 is transported into the cell and phosphorylated to GS-443902. GS-443902 is incorporated into viral RNA where it causes chain termination, resulting in the inhibition of viral replication. The extent to which each route contributes to the antiviral effectiveness of remdesivir is currently unknown (7). The metabolism of GS-441524 to GS-443902 was previously assumed to be rate limited, and therefore, the efficacy of remdesivir was considered a result of metabolism from remdesivir directly to GS-443902 (8). However, more evidence is emerging that GS-441524 is also effectively metabolized to GS-443902 in in vitro lung cell models and could also contribute to the antiviral effect of remdesivir (7, 9, 10).

A contribution of GS-441524 to clinical effectiveness would be beneficial since the half-life of remdesivir in healthy individuals is short (1 h), while the half-life of GS-441524 is much longer (24 h) (11). Remdesivir is excreted mainly by renal clearance, with 74% (10% as unchanged remdesivir and 49% as the metabolite GS-441524) excreted in the urine (6, 11). The main clinical toxicity of remdesivir is suggested to be a concentration-dependent increase in liver transaminases, which has been attributed to remdesivir and not GS-441524 (11). The threshold concentration for hepatotoxicity is assumed to be approximately 1.3-fold higher than the peak concentration reached after a 200-mg administration (12, 13). The optimal dose leading to the maximal antiviral efficacy of remdesivir in humans is currently unknown, but modeling and simulation studies suggest that the current dosing regimen might be suboptimal (14, 15). These studies were performed using pharmacokinetic data from healthy individuals, whereas studies regarding the pharmacokinetics of remdesivir in COVID-19 patients are limited to case series with scarce sampling schedules and a single pharmacokinetic study with only GS-441524 concentrations (16–21).

The primary objective of this study was to develop a population pharmacokinetic model for remdesivir and the metabolite GS-441524 in adults with COVID-19. This model can be used to investigate the influence of patient characteristics on the pharmacokinetics of remdesivir and GS-441524 and to evaluate dosing regimens for remdesivir and GS-441524 in hospitalized COVID-19 patients.

RESULTS
In total, 17 patients were included, and 84 blood samples were obtained. The most common reason for missing plasma samples was the transfer of patients to another hospital, as was routinely done in The Netherlands during the COVID-19 pandemic to balance the COVID-19 burden across hospitals. The median age was 55 years, and the median body weight was 92 kg. One of the included patients was female. The severity of disease could be classified as score 5 on the WHO COVID-19 ordinal scale for all patients (22). Other and more detailed patient characteristics are presented in Table 1. Thirty-four percent of the remdesivir concentration measurements were below the limit of quantification (LOQ), and 25% were below the limit of detection (LOD). No concentrations below the LOQ or LOD were found for GS-441524. See supplemental material for the measured remdesivir and GS-441524 concentrations.

Pharmacokinetic modeling. An integrated pharmacokinetic model including remdesivir and GS-441524 concentrations was developed. A one-compartment model best described the pharmacokinetics of remdesivir and GS-441524. The addition of more compartments for remdesivir or GS-441524 did not improve the parameter estimates. Nonmetabolic clearance of remdesivir was fixed to 10% of the total remdesivir clearance because previous reports showed that 10% of the administered remdesivir was excreted unchanged in the urine. Interindividual variability (IIV) was identified for
the volume of distribution, metabolic clearance of remdesivir, and on the volume of distribution and clearance of GS-441524. Data below the LOQ for remdesivir were modeled using the all-data method described previously by Keizer et al. (23) An additive-error model was used to describe the residual error.

In the covariate analysis, the addition of the glomerular filtration rate (eGFR) on the clearance of GS-441524 using a power model significantly improved the model fit (decrease in the objective function value [OFV] of 20 points) and explained 66% of the IIV. The final model code is presented in supplemental material. Parameter estimates of the final model are shown in Table 2.

The model was evaluated using nonparametric bootstrapping, prediction-corrected visual predictive checks (pcVPCs), and goodness-of-fit (GOF) plots. The GOF plots and pcVPCs (Fig. S1) show that the model predictions are in agreement with the observed remdesivir and GS-441524 concentrations. Bootstrap medians and 95% confidence intervals (CIs) are shown in Table 2 and confirmed the parameter values.

**Pharmacokinetics.** Using the final model, an average elimination half-life of approximately 0.48 h for remdesivir was found. For GS-441524, the maximal concentration was reached after 3.7 h and was on average 173 mg/L during the first 24 h. The elimination half-life of GS-441524 was 26.6 h.

**Monte Carlo simulations.** The Monte Carlo simulations are presented in Fig. 1. For patients with eGFR values at the median level (94 mL/min/1.73 m²), the probability of target attainment (PTA) at a 50% effective concentration (EC₅₀) of 1,406 µg/L was 0.7%, and that for an EC₅₀ of 50.22 µg/L was 100% for remdesivir using the standard dosing regimen. Results were the same for dosing regimens 2 and 3. For dosing regimen 4, the PTAs were 0.0% and 100%, respectively.

For GS-441524, the simulations are visualized in Fig. 2. Using dosing regimen 1, the

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**TABLE 1 Baseline and clinical characteristics**

| Parameter                                      | Value                       |
|-----------------------------------------------|-----------------------------|
| No. of patients                               | 17                          |
| No. of female patients (%)                    | 1 (5.9)                     |
| Median age (yrs) (range)                      | 55 (31–74)                  |
| Median WHO ordinal scale score (range)        | 5 (5–5)                     |
| Median oxygen requirement at admission (L/min) (range) | 4 (1–15)                   |
| Median no. of days of complaints prior to admission (range) | 9 (4–22)                   |
| Median time from start of complaints to remdesivir (days) (range) | 10 (4–22)                  |
| Median time from hospitalization to start of remdesivir (days) (range) | 0 (0–1)                    |
| Median hospitalization durationh (days) (range) | 4 (1–64)                   |
| No. of patients with ICU admissionh (%)       | 3 (17.6)                    |
| No. of patients with mortality during hospitalizationh (%) | 1 (5.9)                    |
| Median body wt (kg) (range)                   | 92 (65–122)                 |
| Median BMI (kg/m²) (range)                    | 30.86 (21.72–41.21)         |
| Median body surface area (m²) (range)         | 2.11 (1.77–2.52)            |
| Median creatinine concn (µmol/L) (range)      | 75 (46–573)                 |
| Median eGFR (CKD-EPI) (mL/min/1.73 m²) (range) | 94 (8–119)                  |
| Median albumin concn (g/L) (range)            | 37 (30–47)                  |
| Median total bilirubin concn (µmol/L) (range) | 8 (2–18)                    |
| Median hemoglobin concn (mmol/L) (range)      | 8 (6.6–11.1)                |
| Median white blood cell count (10³/L) (range) | 6.8 (3.4–15.1)              |
| Median urea concn (mmol/L) (range)            | 4.9 (2.4–17.6)              |
| Median CRP concn (mg/L) (range)               | 147 (6–346)                 |
| Median ALT concn (U/L) (median)               | 36 (20–150)                 |
| Median D-dimer concn (mg/L) (range)           | 0.37 (0.17–1.45)            |

No. of comorbidities (%)

| Cardiovascular disease | 5 (29) |
| Diabetes mellitus     | 6 (35) |
| Asthma                | 1 (5.9) |
| Malignancy            | 1 (5.9) |

*aICU, intensive care unit.

*bFour patients were transferred to another hospital during COVID-19 treatment due to hospital bed occupancy.
PTAs at EC\textsubscript{50}s of 152.6 \text{ \(\mu\)}g/L and 184.3 \text{ \(\mu\)}g/L were 74.8% and 51.9%, respectively. Dosing regimen 2 led to PTAs of 93.8% and 81.6%; dosing regimen 3 led to PTAs of 99.3% and 94.7%; and dosing regimen 4 led to PTAs of 89.0% and 78.7%, respectively. However, it takes up to 38 h to reach a PTA above 50% for an EC\textsubscript{50} of 184.3 \text{ \(\mu\)}g/L using dosing regimen 4.

The influence of the eGFR on GS-441524 pharmacokinetics is visualized in Fig. 3. Compared to the PTA of 51.9% for a median eGFR for the highest EC\textsubscript{50} of 184.3 \text{ \(\mu\)}g/L, the PTA was low (35.9%) for patients with an eGFR of 120 mL/min/1.73 m\textsuperscript{2} and high (99.4%) for patients with a severely reduced eGFR (<30 mL/min/1.73 m\textsuperscript{2}). Figure 3 also shows that GS-441524 accumulates in patients with a reduced eGFR.

**DISCUSSION**

In this study, we present for the first time a population pharmacokinetic model based on both remdesivir and GS-441524 concentrations in hospitalized COVID-19 patients. We found that the population pharmacokinetics were best described by an integrated one-compartment model. The eGFR was significantly related to GS-441524 clearance. Simulations with the final model showed that decreasing the remdesivir dosing interval would lead to an increase in the PTA for GS-441524.

Previously, a more complex structural pharmacokinetic model (two compartments for remdesivir and three compartments for GS-441524) using data from healthy individuals was reported (24). Efforts to fit more complex models to the data resulted in parameter estimates with high residual errors, which could be a result of the limited sample size in this study. Nevertheless, the developed one-compartment model showed good resemblance between the predicted and measured concentrations of remdesivir and GS-441524 and is in line with the results of Sukeishi et al. for GS-441524 (21).

Remdesivir clearance was higher than that previously reported for healthy individuals, resulting in a lower remdesivir elimination half-life (0.48 versus 1 h) (6). A potential explanation for this observation is the upregulation of carboxylesterase-1 activity and thereby the increased metabolism of remdesivir as a result of dexamethasone therapy, obesity, or diabetes. In our patient population, all patients used concomitant dexamethasone, diabetes was present in 35% of the patients, and the median body mass

### TABLE 2 Population pharmacokinetic parameters of the final model\textsuperscript{a}

| Parameter       | Value | Final model | 1,000 bootstrap runs |
|-----------------|-------|-------------|----------------------|
|                 | Mean  | RSE (%)     | Shrinkage (%)        | Bootstrap median | 95% CI     |
| Remdesivir      |       |             |                      |                   |            |
| Metabolic CL (L/h) | 207   | 13          |                      | 209               | 152–279    |
| Renal CL (L/h)  | 20.7 fixed |           |                      | 164               | 98.9–259   |
| V (L)           | 157   | 19          |                      |                   |            |
| GS-441524       |       |             |                      |                   |            |
| CL (L/h)        | 27.6  | 17          |                      | 28.1              | 20.7–38.9  |
| eGFR on CL      | 1.76  | 22          |                      | 1.68              | 0.31–2.91  |
| V (L)           | 1,060 | 11          |                      | 1,062             | 834–1,270  |
| Interindividual variability (%) |       |             |                      |                   |            |
| Remdesivir nonrenal CL | 38.9 | 22          | 12                   | 37.9              | 18.9–51.5  |
| Remdesivir V    | 47.9  | 23          | 24                   | 44.9              | 17.1–62.3  |
| GS-441524 CL    | 47.4  | 29          | 28                   | 41.7              | 17.5–57.8  |
| GS-441524 V     | 42.9  | 17          | 0                    | 41.8              | 14.6–56.7  |
| Residual variability |     |             |                      |                   |            |
| Remdesivir      | 0.0294| 12          |                      | 0.0269            | 0.0091–0.0468 |
| GS-441524       | 0.0140| 11          |                      | 0.0136            | 0.0083–0.0189 |

\textsuperscript{a}CL, clearance; V, volume of distribution; RSE, relative standard error.
index (BMI) was 30.8 kg/m² (25–27). However, the lower elimination half-life could also be related to differences in study populations or study procedures. GS-441524 clearance in COVID-19 patients was higher than that previously reported (27.6 L/h versus 11.8 L/h), a possible result of the higher median eGFR, differences in ethnicity or the severity of disease, or the lack of remdesivir concentration data in the study population (21). The volume of distribution was larger for remdesivir and GS-441524 than that in healthy individuals, which can be explained by the high BMI of the patients in the study population or potentially disease- or treatment-related factors. An influence of disease severity or treatment-related factors on remdesivir pharmacokinetics is also likely because of the high interindividual variation for both remdesivir and GS-441524 clearance and volume of distribution. This is in line with the results of the studies in COVID-19 patients by Corcione et al. and Sukeishi et al. and differs from the results of studies in healthy individuals (16, 21, 24).

GS-441524 clearance was found to be dependent on the eGFR, which confirms the observations by Choe et al. and Sukeishi et al. (20, 21). Our simulations show that accumulation as a result of reduced GS-441524 clearance leads to markedly higher GS-441524 concentrations in COVID-19 patients with severely reduced renal function. In
several observational studies investigating the safety of remdesivir in patients with reduced renal function, an eGFR of <30 mL/min/1.73 m² did not lead to increases in adverse events (28–31). Therefore, we do not recommend the dose reduction based on the eGFR suggested by Sukeishi et al. (21).

The simulation of three alternative dosing regimens showed that shortening the remdesivir dose interval, and thereby increasing the daily dose or increasing the remdesivir dose, leads to a higher GS-441524 PTA. Therefore, dosing regimens aimed at increasing the GS-441524 concentration might have the potential to improve the efficacy of remdesivir treatment, while safety concerns are unlikely as high concentrations of GS-441524 are generally well tolerated (28–31).

The PTA of remdesivir using the current dosing regimen would lead to sufficient exposure in plasma based on the EC₅₀ in human airway epithelial (HAE) cells but insufficient exposure in Calu3 2B4 cells. We did not simulate higher doses for remdesivir as previous studies indicated that higher remdesivir exposure could lead to hepatotoxicity (11–13). The differences in EC₅₀ have been suggested to be a result of the cell type-dependent capacity to metabolize remdesivir to GS-443902 and differences in the methods of in vitro research (8, 32). Studies connecting the plasma concentrations of remdesivir and GS-441524 in vivo and in vitro are needed to better understand the dose-response relationship and the potential for safety concerns.
remdesivir to clinical effectiveness are needed to determine the in vivo target range for remdesivir. This is important as the high interindividual variation seen in this study might result in subtherapeutic or toxic remdesivir concentrations in some of the patients.

Limitations of the study are its limited sample size and sampling on the first day of therapy. Nevertheless, nonlinear mixed-effects modeling (NONMEM) has been shown to accurately predict pharmacokinetic parameters in small and sparse data sets. The inclusion of only one female patient made it impossible to investigate sex differences in remdesivir pharmacokinetics and limits the generalizability of the results. We were unable to determine the lung tissue concentration of the intracellular active triphosphate form GS-443902. The concentrations measured in this study and the simulations are therefore a derivative of the clinical effective concentrations. Future studies are needed to verify these results. Finally, urinary concentrations of remdesivir and GS-441524 would have been beneficial for predicting the percentage of remdesivir converted into metabolites.

Conclusion. To the best of our knowledge, this study presents the first population pharmacokinetic model based on both remdesivir and GS-441524 concentrations in a cohort of hospitalized COVID-19 patients. In this cohort, remdesivir clearance was increased compared to that in healthy individuals, and the eGFR was identified as a relevant covariate on GS-441524 clearance. Since remdesivir is well tolerated in patients

**FIG 3** Simulated GS-441524 concentrations versus time for three different estimated glomerular filtration rates using the standard dosing regimen of 200 mg followed by 100 mg every 24 h. The blue line is the median concentration, and the shaded area is the 95% prediction interval. The red line represents the in vitro EC\textsubscript{50} in Calu3 2B4 cells, and the red dotted line represents the in vitro EC\textsubscript{50} in human airway epithelial cells.
with a reduced eGFR, we do not recommend lower dosing in patients with renal impairment. The simulations showed that a decreased dosing interval with an increased total daily dose led to an increase in GS-441524 exposure and thereby an increased PTA, which has the potential to improve remdesivir efficacy in hospitalized COVID-19 patients.

MATERIALS AND METHODS

Ethics. The study protocol was approved by the Medisch-Ethische Toetsingscommissie Leiden Den Haag Delft medical ethics review board (protocol 20-116) and the Institutional Scientific Review Board of the Haga Teaching Hospital. Written informed consent was obtained from all participants, and the study was carried out in accordance with International Council on Harmonisation (ICH) guidelines for good clinical practice.

Study design. A prospective observational pharmacokinetic study was performed on the general ward of the Haga Teaching Hospital between January and July 2021. Patients aged $\geq 18$ years were eligible for inclusion if they were hospitalized because of COVID-19 (confirmed by severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2] detection in a nasopharyngeal swab using reverse transcription-PCR) requiring supplemental oxygen therapy and in whom treatment with remdesivir was started.

Data on patient demographics, patient characteristics, medical history, medication use, laboratory values, and days of complaints prior to admission were collected at baseline. The baseline was defined as the day when the first dose of remdesivir was administered.

Remdesivir was administered as an intermittent intravenous administration in 1 to 2 h. On the first day, the patients received 200 mg, followed by four daily doses of 100 mg.

Sampling schedule and analytical methods. Blood samples for plasma concentration analysis were collected on the first day of therapy. Six samples were respectively drawn 0.5, 1.5, 2.5, 6, 12, and 23 h after the end of remdesivir administration. The blood samples were collected into EDTA tubes; directly after collection, the samples were kept on ice and processed within 4 h. Formic acid was added to the plasma samples to avoid carboxylesterase-induced degradation of remdesivir. The samples were stored at $-80^\circ$C until analysis.

The plasma samples were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method, which was derived from the method described previously by Xiao et al. (33). The method was optimized to analyze remdesivir and GS-441524 in a single run. The limits of quantification (LOQs) were 4 $\mu$g/L for remdesivir and 12 $\mu$g/L for GS-441524, and the limit of detection (LOD) was 1 $\mu$g/L for remdesivir. Uncertainties of measurement were 5.2% for remdesivir and 3.5% for GS-441524. All validation parameters were in accordance with European Medicines Agency bioanalytical method validation guidelines (34).

Pharmacokinetic analysis. Population pharmacokinetic modeling using nonlinear mixed-effects modeling (NONMEM) was used to describe the pharmacokinetics of remdesivir and GS-441524. An integrated model containing both remdesivir and its metabolite GS-441524 was developed. One-, two-, and three-compartment models were considered as structural models for remdesivir and GS-441524. The structural model selection was based on the reduction of the objective function value (OFV) (approximation of a chi-square distribution for nested models, with a $\Delta$OFV of 3.84 corresponding to a $P$ value of 0.05), goodness-of-fit (GOF) plots, shrinkage, and precision of pharmacokinetic parameter estimates. Elimination from the compartments was modeled as first-order processes. Interindividual variability (IV) and residual variability were assumed to be log-normally distributed. Data below the LOQ were modeled using Beal's M1 and M3 methods and the all-data method described previously by Keizer et al. (23) Additive, proportional, and combined residual-error models were evaluated.

Demographic and clinical characteristics that were considered biologically plausible for affecting remdesivir pharmacokinetics were tested for inclusion as covariates. These included age, body weight, body surface area, body mass index (BMI), estimated glomerular filtration rate (eGFR), C-reactive protein (CRP), and alanine aminotransferase (ALT). Continuous covariates were modeled using linear, exponential, and power functions. For body weight, the allometric rule standardized to an average adult of 70 kg was also considered. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. A covariate was retained in the final model if its effect was biologically plausible, it produced a clinically relevant reduction in the interindividual variation of the parameter, and the OFV was decreased by at least 3.84 ($P < 0.05$) in the forward inclusion and 6.63 ($P < 0.01$) in the backward deletion.

The final model was evaluated using GOF plots and prediction-corrected visual predictive checks (pcVPCs). Parameter estimates and the confidence intervals were assessed using nonparametric bootstrapping using 1,000 resampled data sets. Population pharmacokinetic modeling was carried out using NONMEM (v.7.4; Icon Development Solutions, Ellicott City, MD, USA) and Perl Speaks NONMEM (v.4.8.1). Pirana (v.2.9.8) and R statistics (v.4.0.3) were used for interpretation and visualization of the pharmacokinetic models.

Probability of target attainment. Monte Carlo simulations ($n = 1,000$) were performed based on the final model to investigate the influence of the remdesivir dosing regimen and renal function on the probability of target attainment during a 5-day remdesivir treatment regimen. As the in vivo exposure required for remdesivir efficacy is currently unknown, the percentage of patients reaching an unbound plasma concentration above the in vitro EC$_{50}$ for remdesivir and GS-441524 was used as the best target for dose evaluation (35–37). We evaluated two target concentrations based on the EC$_{50}$ in different cell
Pharmacokinetics of Remdesivir line. Corrected for the protein binding of remdesivir (88%) and GS-441524 (2%), the EC$_{50}$ were 1.406 µg/L for remdesivir and 184.3 µg/L for GS-441524 in Calu3 2B4 cells (32). The EC$_{50}$ were 502 µg/L for remdesivir and 152.6 µg/L for GS-441524 in human airway epithelial (HAE) cells (32, 38). As the half-life of the intracellular active metabolite GS-443902 is 43.4 h in peripheral blood mononuclear cells, the assumption was made that reaching the EC$_{50}$ at any point during therapy was sufficient.

A typical virtual COVID-19 patient with an eGFR of 94 ml/min/1.73 m$^2$ was used to simulate the probability of target attainment (PTA) for four remdesivir dosing regimens. These regimens were (i) the currently used 5-day dosing regimen with a 200-mg loading dose followed by 100 mg once daily, (ii) a loading dose of 200 mg followed by 150 mg for 4 days, (iii) a 200-mg loading dose two times on day 1 followed by 100 mg every 12 h during 5 days in total, and (iv) a loading dose of 100 mg followed by 50 mg every 6 h during 5 days in total.

To investigate the influence of the eGFR on GS-441524 pharmacokinetics, three simulations were performed based on different eGFRs (30, 94, and 120 ml/min/1.73 m$^2$). The standard dosing regimen described in the paragraph above was used in these simulations.

**Data availability.** The data that support the findings of this study are available from the corresponding author upon reasonable request.

**SUPPLEMENTAL MATERIAL**

Supplemental material is available online only.

**SUPPLEMENTAL FILE 1, PDF file, 0.4 MB.**

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