



Results From Drug–Drug Interaction Studies In Vitro and In Vivo Investigating the Inhibitory Effect of Finerenone on the Drug Transporters BCRP, OATP1B1, and OATP1B3

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Abstract

Background and Objectives In vitro and in vivo studies were performed with the novel, selective, nonsteroidal mineralocorticoid receptor antagonist finerenone to assess the relevance of inhibitory effects on the transporters breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1), and OATP1B3. These transporters are involved in the disposition of a number of drugs, including statins. Statins are also a frequent comedication in patients receiving finerenone. Therefore, inhibitory effects on BCRP and OATPs are of potential clinical relevance.

Methods The effect on the transport of specific substrates of BCRP and OATP1B1/1B3 was assessed in cell-based in vitro assays with finerenone or its metabolites. A fixed-sequence crossover study in 14 healthy male volunteers investigated the effects of finerenone (40 mg once daily) on the pharmacokinetics of the index substrate rosuvastatin (5 mg) administered alone, simultaneously with, or approximately 4 h before finerenone. The effect of finerenone on the endogenous OATP substrates coproporphyrin I and III was also assessed.

Results Based on in vitro findings and threshold values proposed in regulatory guidelines, finerenone appeared to be a potentially relevant inhibitor of all three transporters. Relevant inhibition could also not be ruled out for the finerenone metabolites M1a (OATP1B1) and M3a (OATP1B1 and OAT1B3), which prompted an investigation into the relevance of these findings in vivo. After administration on a background of finerenone 40 mg, all point estimates of area under the curve ratios (114.47% [rosuvastatin], 99.62% [coproporphyrin I; simultaneous], and 105.28% [rosuvastatin; 4 h separation]) and maximum concentration ratios (111.24% [rosuvastatin], 101.22% [coproporphyrin I], 89.14% [coproporphyrin III; simultaneous], and 96.84% [rosuvastatin; 4 h separation]) of the investigated substrates were within 80.0–125%. In addition, the 90% confidence intervals of the ratios were within the conventional no-effect boundaries of 80.0% and 125% for rosuvastatin after temporally separated administration, and for coproporphyrin I and III.

Conclusion Administration of finerenone 40 mg once daily confers no risk of clinically relevant drug–drug interactions with substrates of BCRP, OATP1B1, or OATP1B3. The potential for relevant inhibition of these transporters suggested by in vitro findings was not confirmed in vivo.

Plain Language Summary

Finerenone is a drug that is used to reduce the risk of adverse kidney and cardiovascular outcomes in patients with chronic kidney disease associated with type 2 diabetes mellitus. Taking more than one medicine, and often several at the same time, is common in these patients; therefore, it is important to investigate the drug–drug interaction potential of finerenone. These studies were carried out to assess the interaction potential of finerenone and its metabolites in both laboratory experiments

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and healthy volunteers. Initial laboratory experiments indicated that finerenone and its metabolites could inhibit transporters used by other drugs. A study in healthy volunteers was performed and demonstrated that finerenone is not associated with any clinically meaningful changes to drugs that are substrates for the transporters. The study in healthy volunteers demonstrates that medications that are substrates of these transporters can be safely co-administered with finerenone.

Key Points

A potential pharmacokinetic interaction was identified in vitro for finerenone and its metabolites as perpetrators with sensitive substrates of breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1), and OATP1B3 transporters.

A phase I study in healthy volunteers was performed to investigate the clinical relevance of this potential drug–drug interaction (DDI). Simultaneous co-administration of rosuvastatin (a reference substrate of both BCRP and OATPs) with finerenone indicated no evidence of a clinically relevant DDI in vivo. Administration of finerenone 4 h after rosuvastatin was also not associated with a meaningful change in rosuvastatin exposure. Finally, there was no effect of finerenone on the exposures of endogenous substrates of OATP1B1 and OATP1B3 (coproporphyrin I and coproporphyrin III).

As there was no clinically relevant effect of finerenone on substrates of both BCRP and OATPs in vivo, the results of this DDI study indicate that medications that are substrates of these transporters can be safely co-administered.

1 Introduction

Finerenone is a novel, selective, and nonsteroidal antagonist of the mineralocorticoid receptor (MR) that blocks the binding of the MR ligands aldosterone and cortisol more potently than spironolactone and eplerenone [1]. Finerenone reduced the urinary albumin-to-creatinine ratio in phase II studies in patients with chronic kidney disease (CKD) while having smaller effects on serum potassium levels than spironolactone [2, 3]. A phase III study (FIDELIO-DKD) in patients with CKD and type 2 diabetes mellitus (T2DM) met both its composite primary renal endpoint and its composite key secondary cardiovascular endpoint [4]. In a second phase III study (FIGARO-DKD), finerenone improved cardiovascular outcomes in patients with T2DM and stage 2–4 CKD with moderately elevated albuminuria or stage 1 or 2 CKD with severely elevated albuminuria as compared with placebo [5]. Finerenone has been approved in the United States to reduce the risk

of a sustained estimated glomerular filtration rate decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adults with CKD associated with T2DM [6]. Currently, the drug is also approved in several other countries for the treatment of CKD, while regulatory assessments of the indication for heart failure are ongoing in these regions.

The pharmacokinetics of finerenone in phase I clinical studies were described in healthy volunteers [7–12] and in subjects with renal or hepatic impairment [13, 14]. In addition, the pharmacokinetics in patients and their relationships with pharmacodynamic parameters or clinical endpoints were assessed in phase II and III studies [15, 16].

In summary, finerenone is rapidly and completely absorbed after oral administration (time to maximum plasma concentration [T_{max}] of 0.5 to 1.25 h), has dose-linear pharmacokinetics, and is rapidly eliminated (terminal half-life of 2 to 3 h). About 80% of the administered dose is excreted in urine (<1% is unchanged) and approximately 20% in feces (<0.2% is unchanged). Finerenone's absolute bioavailability is 43.5% due to first-pass metabolism in the gut wall and liver. The metabolites of finerenone are not pharmacologically active. Cytochrome P450 (CYP) 3A4 is responsible for about 90% of the metabolic clearance of finerenone, with the remainder attributable to CYP2C8. Mild, moderate, or severe renal impairment and mild or moderate hepatic impairment have no relevant effect on the pharmacokinetics of finerenone.

The phase I program included studies investigating finerenone as a victim [8] or potential perpetrator [10] of drug–drug interactions mediated by enzymes of the CYP system. The systemic exposure of finerenone as a victim of drug–drug interactions is increased by inhibitors of CYP3A4. From the perspective of being a potential perpetrator, finerenone has no relevant effect on CYP enzymes and the pharmacokinetics of substrates metabolized by these enzymes.

In vitro experiments suggested that finerenone could inhibit the activities of the drug transporters breast cancer resistance protein (BCRP), organic anion transporting polypeptide 1B1 (OATP1B1), and OATP1B3, which are involved in the absorption and disposition of potential comedications, such as statins [17]. Subsequently, an in vivo study was performed to assess the clinical relevance of these findings. The results of both the in vitro experiments and the in vivo study are presented in this paper.

2 Methods

2.1 In Vitro Investigations

The assessment of the inhibitory potential of finerenone and its metabolites towards drug transporters was conducted using cell-based in vitro assay systems. For the detailed assay protocols, please see Supplementary Methods S1.

2.2 Clinical Study

The study protocol was reviewed and approved by the Independent Ethics Committee of the North-Rhine Medical Council (Düsseldorf, Germany) and by the Federal Institute for Drugs and Medical Devices (Bonn, Germany). Informed consent was obtained from all participants before study commencement. The studies were conducted in accordance with the Declaration of Helsinki and adhered to the International Conference on Harmonization Good Clinical Practice guideline, European Union Clinical Trial Directive 2001/20/EC, and German drug law.

2.2.1 Participants

Participants were eligible for inclusion if they were healthy Caucasian males 18–45 years of age with a body mass index of 18.0–29.9 kg/m², a systolic blood pressure (BP) of 100–140 mmHg, a diastolic BP of 60–90 mmHg, and a resting heart rate (HR) of 50–90 beats per minute.

Key exclusion criteria were: relevant diseases evident from medical histories or pre-study examinations; contraindications for rosuvastatin; a relevant deviation from the normal range in clinical chemistry, hematology, or urinalysis parameters; history of severe allergies, non-allergic drug reactions, or multiple drug allergies; regular use of therapeutic or recreational drugs; regular consumption of more than 20 g of alcohol per day; use of foods or medications (especially those affecting CYP3A4) within the 2 weeks or 5 half-lives (whichever was longer) preceding the study that could interfere with finerenone metabolism; participation in another clinical trial within the previous 3 months; history of coronavirus disease 2019 (COVID-19) or contact with a patient who tested positive for COVID-19 within the past 4 weeks or a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test.

2.2.2 Study Drug

Both study drugs—finerenone 40 mg (Bayer AG, Leverkusen, Germany) and rosuvastatin 5 mg (Crestor[®],

AstraZeneca GmbH, Wedel, Germany)—were administered as a film-coated tablet.

2.2.3 Safety and Tolerability

The safety of finerenone 40 mg and the co-administered drug rosuvastatin was monitored by physical examinations and regular measurements of systolic/diastolic BP, HR in the supine position, and the 12-lead electrocardiogram (ECG) after a rest of 15 min before and 1, 2, 3, 4, 6, 12, and 24 h after same-time dosing and 1, 2, 4, 5, 6, 12, and 24 h after the temporally separated administration of finerenone and rosuvastatin. BP, HR, and ECG were measured before and 1, 2, 4, 5, and 6 h after the dosing of rosuvastatin alone. Blood samples for the analysis of standard hematological and clinical chemistry laboratory parameters, including serum electrolytes, were taken the morning before and 24 and 48 h after dosing (but not for temporally separated dosing). Tolerability was assessed by asking subjects regularly about their well-being and any adverse events (AEs) using non-leading questions from pre-dose to follow-up 1, 2, 4, 6, and 12 h after rosuvastatin alone, 1, 2, 4, 6, and 12 h after same-time treatment, and 1, 2, 4, 6, and 12 h after separated finerenone and rosuvastatin treatment. The intensity of AEs (mild [not interfering with everyday activities], moderate [sufficient discomfort to interfere with normal everyday activities], or severe [prevents normal everyday activities]) and any causal relationship between study drugs and AEs were assessed by the investigator, based on criteria predefined in the study protocol.

2.2.4 Pharmacokinetic Sampling

Blood samples for the determination of plasma concentrations of the respective analyte(s) were taken pre-administration and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 15, 24, 36, 48, 60, and 71.5 h thereafter (rosuvastatin; 3.0 mL per sample) or 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 15, and 23.5 h after administration (finerenone and its metabolites M1, M2, and M3; 1.5 mL per sample). Blood samples for the determination of coproporphyrin I (CP-I) and CP-III (1.2 mL) were collected across an interval of 24 h at relative times of 0, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 15, and 24 h, where the '0 h' sample was taken at approximately 8 a.m., immediately before the administration of rosuvastatin. Plasma was prepared by centrifugation at approximately 2000×g for 10 min at ambient temperature or at approximately 4 °C (rosuvastatin). Blood and plasma samples were not exposed to sunlight. Samples were stored in temperature-controlled freezers at ≤ −20 °C (finerenone and metabolites, and rosuvastatin) and at −85 ± 10 °C (CP-I and CP-III), respectively.

2.2.5 Study Design and Treatment

The effect of finerenone on BCRP and OATP1B1 and OATP1B3 was investigated in a single-center, open-label, fixed-sequence interaction study with three subsequent periods. Single doses of rosuvastatin 5 mg in the fasted state were administered on three occasions, alone (period 1) and on a background of finerenone at steady state (periods 2 and 3). The first dose of rosuvastatin was administered alone on day 1 of period 1, followed by the collection of pharmacokinetic samples over 71.5 h. On day 4, after collection of the last pharmacokinetic sample for rosuvastatin, a regimen of multiple doses of finerenone 40 mg once daily for 10 days was started. On the third day of administration of finerenone, the second dose of rosuvastatin 5 mg was given (at the same time as finerenone), again followed by the collection of pharmacokinetic samples for rosuvastatin over 71.5 h (period 2). On the eighth day of the finerenone once-daily regimen, the third single dose of rosuvastatin was administered (temporally separated, 4.25 h before finerenone), and pharmacokinetic samples for rosuvastatin were collected over the following 71.5 h (period 3).

In period 1 (rosuvastatin alone) and period 2 (rosuvastatin and finerenone simultaneously), pharmacokinetic samples were also collected over 24 h to determine CP-I and CP-III plasma concentrations.

Following the last (tenth) dose of finerenone, pharmacokinetic samples were collected over 24 h to determine finerenone and metabolites. On the following day, the subjects were discharged from the ward. Follow-up procedures were performed not less than 7 days after the last dose of finerenone. The duration of the in-house period was 15 days, with 14 overnight stays.

The study protocol included an optional study part 2 investigating the effect of the lower dose of finerenone 20 mg once daily according to the above design. However, the study was closed after the completion of part 1, as predefined criteria to conduct part 2 (i.e., an increase in rosuvastatin area under the concentration–time curve from zero to infinity [AUC] or maximum plasma concentration [C_{\max}] by > 25% after administration of finerenone 40 mg) were not met.

2.2.6 Bioanalysis

Rosuvastatin was determined in plasma after the addition of a stable-isotope–labeled internal standard (triple-deuterated rosuvastatin) and subsequent liquid–liquid extraction with methyl *tert*-butyl ether. Separation and detection were achieved by high-performance liquid chromatography–tandem mass spectrometry (HPLC–MS/MS). Calibrators (0.0200–10.0 $\mu\text{g/L}$ [lower to upper limit of quantification (LLOQ–ULOQ)]) and quality control (QC) samples

(0.0600–7.50 $\mu\text{g/L}$) were analyzed with study samples in a batchwise fashion. QC samples were determined with an accuracy and precision of 98.9–100.3% and 2.47–4.55%, respectively ($n = 32$ per QC concentration level).

Determination of CP-I and CP-III concentrations in plasma was conducted using HPLC–MS/MS after protein precipitation with methanol containing the internal standards (fourfold ^{15}N -labeled CPs). The calibration range of the procedure was 0.100 $\mu\text{g/L}$ (LLOQ) to 100 $\mu\text{g/L}$ (ULOQ) for both analytes (CP-I and CP-III). QC samples (0.300–75.0 $\mu\text{g/L}$) were determined with an accuracy and precision of 95.0–98.0% and 3.3–7.6% (CP-I) and 93.0–96.7% and 3.4–5.6% (CP-III) ($n = 10$ –12 per QC level), respectively.

Plasma concentrations of finerenone and its metabolites M1, M2, and M3 (the structures of the metabolites are given in [9]) were determined using HPLC–MS/MS, based on [11]. The respective stable-isotope–labeled compounds were used as internal standards for the quantification of the four analytes. The working range was 0.100 $\mu\text{g/L}$ (finerenone) or 0.500 $\mu\text{g/L}$ (metabolites) to 500 $\mu\text{g/L}$ (all analytes). QC samples contained analyte concentrations of 0.300 $\mu\text{g/L}$ to 375 $\mu\text{g/L}$ (finerenone) and 1.50 $\mu\text{g/L}$ to 375 $\mu\text{g/L}$ (metabolites). The accuracy and precision for the QC samples were 93.3–99.5% and 1.7–2.2% (finerenone; $n = 7$ –8 per QC level), 96.5–100.3% and 2.6–6.7% (M1; $n = 9$ –10), 97.9–104.3% and 4.7–6.6% (M2; $n = 5$ –6), and 102.4–107.8% and 3.4–7.1% (M3; $n = 5$ –6), respectively.

All method validations and analyses of the study samples were performed in compliance with the pertinent guidelines on bioanalytical method validation [18, 19]. Assays were sensitive and selective for the respective analytes, as stated above, and were fully validated. No mutual effects on ionization or chromatographic interference between analytes and/or internal standards were observed in validation experiments conducted prior to starting the analysis of study samples.

2.2.7 Pharmacokinetic and Statistical Evaluation

Pharmacokinetic parameters were calculated by non-compartmental analysis using Phoenix WinNonlin 8.1 (Certara, Princeton, NJ, USA). They are presented as geometric mean values and the geometric coefficient of variation, except for the time to reach C_{\max} (T_{\max}), for which the median and range are reported. Summary statistics of plasma concentration values at any time were calculated if at least two-thirds of the individual data points were measured and were greater than the LLOQ. Values below the LLOQ were substituted by $0.5 \times \text{LLOQ}$ if this condition was met. The parameters $T_{1/2}$ ($T_{1/2,\text{md}}$ after multiple dose administration) and CL/F denote the half-life associated with the terminal slope and the apparent oral clearance, respectively. The areas under the curve from zero to infinity (AUC), from zero to the time

of the last quantifiable concentration ($AUC_{(0-t)}$) (both after single dose administration), and within a dosing interval ($AUC_{\tau,md}$) (after multiple dose administration) and the maximum plasma concentration (C_{max} [single dose], and $C_{max,md}$ [multiple dose]) were analyzed assuming log-normally distributed data. The logarithms of pertinent pharmacokinetic parameters for rosuvastatin and CP-I and CP-III were subject to analysis of variance (ANOVA), and treatments were compared by calculating point estimates (least-squares [LS] means) and explorative 90% confidence intervals (CIs) for treatment ratios after re-transformation of the logarithmic data using the intraindividual standard deviation of the ANOVA. The pharmacokinetic parameters of finerenone and its metabolites were summarized by descriptive statistics.

$N = 15$ subjects were included to meet the required minimum sample size of subjects valid for pharmacokinetics, $N = 12$. Based on previous knowledge of the intraindividual pharmacokinetic variability of rosuvastatin, and assuming a point estimate for the treatment ratio of rosuvastatin AUC and C_{max} of unity, this sample size was adequate to show no interaction within the no-effect boundaries (90% CI) of 80.0–125%.

3 Results

3.1 In Vitro Assessment of Inhibitory Potential Towards Drug Transporters

The potential of finerenone to act as a perpetrator for various transporter-mediated drug–drug interactions (DDIs) was investigated in vitro. The results for finerenone, both atropisomers of metabolite M1 (M1a and M1b), and the a-series of atropisomers for M2 and M3 [9] regarding the inhibition of BCRP, OATP1B1, and OATP1B3 are summarized in Table 1 and will be discussed here.

Finerenone inhibited BCRP-mediated transport with a half-maximal inhibitory concentration (IC_{50}) of 17.4 μ M. Furthermore, it was identified as an inhibitor of OATP1B1, with an IC_{50} of 3.2 μ M. Both atropisomers of M1, M1a, and M1b did not relevantly inhibit BCRP; however, inhibition of OATP1B1 and OATP1B3 was observed with IC_{50} values of 3.8 μ M and 3.9 μ M for OATP1B1 and 7.6 μ M and 7.3 μ M for OATP1B3, respectively. For M2a, no inhibition > 50% was apparent for any of the tested transporters, whereas, for M3a, an IC_{50} of 3.4 μ M was established for OATP1B3. If no exact IC_{50} value could be determined for a certain transporter (less than 50% inhibition at the highest tested assay concentration), the IC_{50} is indicated to be above the highest tested assay concentration in Table 1 (e.g., > 20 μ M).

Table 1 Inhibitory potential of finerenone and metabolites M1a, M1b, M2a, and M3a towards drug transporters BCRP, OATP1B1, and OATP1B3 in vitro

Test item	IC_{50} (μ M)		
	BCRP	OATP1B1	OATP1B3
Finerenone	17.4	3.2	> 10
M1a	> 20	3.8	7.6
M1b	> 30	3.9	7.3
M2a	> 20	> 10	> 10
M3a	> 20	> 10	3.4

BCRP breast cancer resistance protein, IC_{50} concentration corresponding to half-maximal transporter inhibition, OATP1B1 organic anion transporting polypeptide 1B1, OATP1B3 organic anion transporting polypeptide 1B3

3.2 Calculation of the DDI Risk Based on In Vitro Results

The assessment of whether the in vitro results on transporter inhibition would necessitate clinical studies (i.e., the evaluation of the DDI risk from finerenone and its metabolites towards sensitive BCRP, OATP1B1, and OATP1B3 substrates) was performed according to pertinent regulatory guidelines (as issued by the US Food and Drug Administration [FDA] and European Medicines Agency [EMA]) [20, 21]. Input parameters for, and the results of, the calculations are summarized in Table 2. If no IC_{50} could be determined, the highest tested assay concentration was used for calculations, which represents the most conservative approach to DDI risk assessment.

Applying a cutoff value of $[I]_{gut}/IC_{50} \geq 10$, a risk for a clinically relevant interaction towards intestinal BCRP was identified for finerenone, as $[I]_{gut}/IC_{50}$ amounted to 24.3 for a 40-mg dose. By contrast, a risk for inhibition of systemic BCRP by finerenone and its metabolites did not emerge when taking cutoff values of $C_{max,tot}/IC_{50} \geq 0.1$ (FDA) or $C_{max,u}/IC_{50} \geq 0.02$ (EMA) into consideration.

For hepatic uptake transporters OATP1B1 and OATP1B3, regulatory guidelines describe varying approaches to assess a potential DDI risk. The 2020 FDA DDI guideline [21] states that a detailed investigation of the clinical DDI risk is warranted once $[I]_{inlet,max,u}/IC_{50} \geq 0.1$ (stated as $R = 1 + [I]_{inlet,max,u}/IC_{50} \geq 1.1$), where $[I]_{inlet,max,u}$ is the estimated maximum unbound plasma inhibitor concentration at the inlet to the liver. The EMA guideline [20] applies a stricter threshold, requiring further investigation of the risk of potential DDIs once the inhibitory constant (K_i) or $IC_{50} \leq 25 \times [I]_{inlet,max,u}$ (which can also be expressed as $[I]_{inlet,max,u}/IC_{50} \geq 0.04$). For finerenone-mediated inhibition of OATP1B1 and OATP1B3,

Table 2 Calculation of the risk to increase the exposure of substrates of BCRP, OATP1B1, and OATP1B3 for finerenone and metabolites M1a, M1b, M2a, and M3a

Dose (mg)	M_w (g/mol)	$C_{\max, \text{tot}}^a$ ($\mu\text{g/L}$)	f_u	C_p/C_p	k_a^c (min ⁻¹)	$F_a \times F_g^d$	$ I _{\text{gut}}/IC_{50}^e$	BCRP		OATP1B1		OATP1B3	
								$C_{\max, \text{tot}}/IC_{50}^f$	$C_{\max, \text{tot}}^f/IC_{50}^g$	$ I _{\text{inlet, max, u}}/IC_{50}$	$C_{\max, \text{u}}/IC_{50}^g$	$ I _{\text{inlet, max, u}}/IC_{50}^h$	$C_{\max, \text{u}}/IC_{50}^g$
Finerenone	40	378.42	0.0833	0.935	0.153	0.575	24.3	0.049	0.004	0.182	0.022	< 0.058	< 0.007
M1a	–	376.41	0.0582	–	–	–	–	< 0.080	< 0.005	–	0.025	–	0.012
M1b	–	376.41	0.0388	–	–	–	–	< 0.011	< 0.0004	–	0.003	–	0.002
M2a	–	392.41	0.174	–	–	–	–	< 0.039	< 0.007	–	< 0.013	–	< 0.014
M3a	–	406.39	0.678	–	–	–	–	< 0.017	< 0.012	–	< 0.023	–	0.068

BCRP breast cancer resistance protein, C_p/C_p blood-to-plasma concentration ratio, $C_{\max, \text{tot, u}}$ total/unbound maximum plasma concentration, *DDI* drug–drug interaction, *EMA* European Medicines Agency, $F_a \times F_g$ fraction absorbed and fraction escaping gut wall metabolism, *FDA* US Food and Drug Administration, f_u fraction unbound in plasma, IC_{50} concentration corresponding to half-maximal transporter inhibition, $|I|_{\text{gut}}$ applied dose/250 mL, $|I|_{\text{inlet, max, u}}$ maximum unbound concentration at the liver inlet, k_a absorption rate constant, K_i inhibitory constant, M_w molecular weight, *OATP1B1* organic anion transporting polypeptide 1B1, *OATP1B3* organic anion transporting polypeptide 1B3, Q_h hepatic blood flow rate

^aThe plasma exposure used for *DDI* assessment was scaled up linearly to a 40-mg dose based on the exposure measured following a 10-mg dose in patients with moderate renal impairment

^bThe maximum plasma concentrations of M1a and M1b were calculated based on the measured C_{\max} of M1 (i.e., the sum of both atropisomers) and the atropisomer ratio of M1a and M1b in human plasma, as published in [9]

^c k_a was determined in population pharmacokinetics analyses of concentration data from single dose escalation phase 1 studies (data on file)

^d F_a (= 1) and F_g (= 0.575) were determined in the mass-balance study [9] and absolute bioavailability study [8], respectively

^eLowest regulatory cutoff: $|I|_{\text{gut}}/IC_{50} \geq 10$ (based on EMA and FDA guidelines)

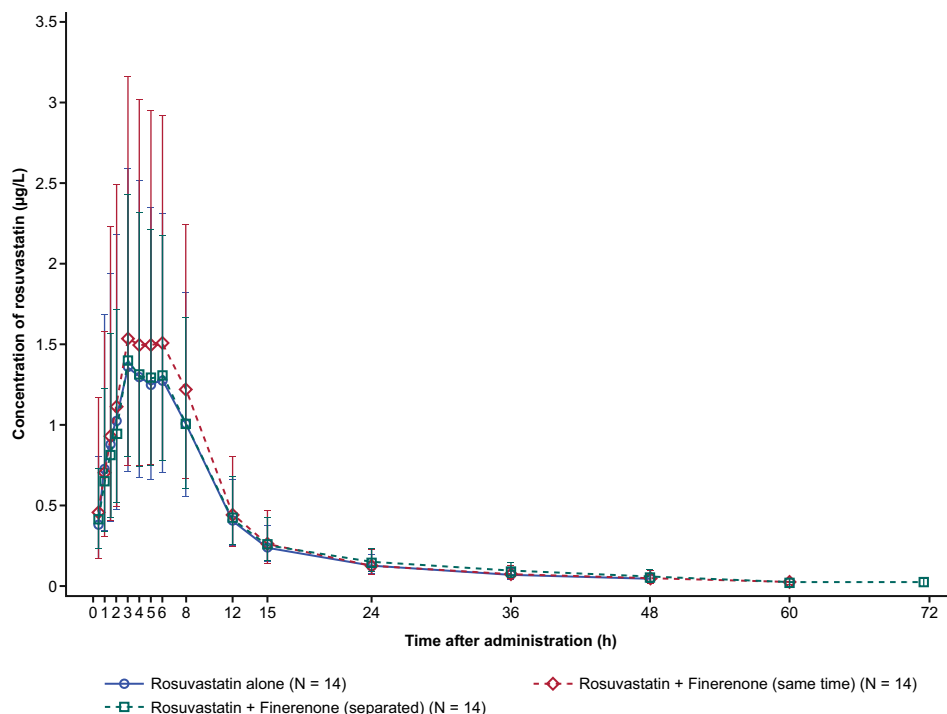
^fLowest regulatory cutoff: $C_{\max, \text{tot}}/IC_{50} \geq 0.1$ (based on the FDA guideline)

^gLowest regulatory cutoff: $C_{\max, \text{u}}/IC_{50} \geq 0.02$ (based on the EMA guideline)

^hLowest regulatory cutoff: $|I|_{\text{inlet, max, u}}/IC_{50} \geq 0.04$ (based on the EMA guideline, inferred from the cutoff indicated in the guideline of K_i (or IC_{50}) $\geq 25 \times |I|_{\text{inlet, max, u}}$)

$|I|_{\text{inlet, max, u}}$ was calculated according to $|I|_{\text{inlet, max, u}} = f_u \times (C_{\max} + (F_a \times F_g \times k_a \times \text{dose})/Q_h/C_p)$. For Q_h , a hepatic blood flow of 1.617 L/min was used

Fig. 1 Concentration of rosuvastatin ($\mu\text{g/L}$) in plasma by treatment (geometric mean/ SD ; pharmacokinetics set, $N = 14$). LLOQ = $0.02 \mu\text{g/L}$. LLOQ lower limit of quantification, SD standard deviation



$[I]_{\text{inlet,max,u}}/IC_{50}$ amounted to 0.182 for OATP1B1 and < 0.058 for OATP1B3. Hence, guideline cutoffs were exceeded for both transporters.

For metabolites, $C_{\text{max,u}}$ serves as relevant inhibitory concentration and guidelines recommend using $C_{\text{max,u}}/IC_{50} \geq 0.1$ (FDA) [21] and $C_{\text{max,u}}/IC_{50} \geq 0.02$ (EMA) [20] as thresholds. Metabolites M1a and M3a also displayed a potential for relevant transporter inhibition. Calculations of $C_{\text{max,u}}/IC_{50}$ resulted in values of 0.025 for M1a towards OATP1B1 and < 0.023 and 0.068 for M3a for OATP1B1 and OATP1B3, respectively. By contrast, no relevant inhibition of OATP1B1 or OATP1B3 was predicted for the remaining metabolites investigated.

3.3 Clinical Study

3.3.1 Patient Enrollment

Thirty-four subjects were enrolled and 15 successfully completed screening, one of whom withdrew from the study prior to any study medication due to family problems. Fourteen subjects were treated with rosuvastatin alone and in combination with finerenone and completed the treatment sequence and follow-up visit as planned. The mean (standard deviation) age, weight, and height of the 14 subjects were 29.6 years (5.4 years), 82.4 kg (7.8 kg), and 179.9 cm (4.9 cm), respectively.

3.3.2 Safety and Tolerability

The safety and tolerability of the study treatments were compared with baseline measurements by physical examinations and regular monitoring of systolic/diastolic BP and HR, measurements of ECGs, and blood sampling for hematology, clotting, and clinical laboratory parameters, including serum electrolyte levels. These parameters showed no clinically relevant changes in individual and mean values after dosing of finerenone 40 mg administered alone or in combination with rosuvastatin. Repeated finerenone doses were well tolerated and there were no drug-specific or mode-of-action-related clinically relevant side effects. In general, no serious or severe AEs were observed with finerenone 40 mg, no relevant changes in potassium levels were seen, and no premature terminations due to study-drug-related side effects occurred. Two cases of headache as an AE were, according to criteria predefined in the study protocol, judged to be treatment related, with one case occurring after the combination and the other after rosuvastatin alone. As these are events that were previously and are generally observed in phase I studies, they were not judged to be related to the drug's mode of action. Overall, the study treatments were well tolerated.

3.3.3 Pharmacokinetics

Plasma concentration vs. time profiles of rosuvastatin are shown in Fig. 1, and results of the pharmacokinetic analysis are presented in Table 3. Plasma concentration vs. time

Table 3 Pharmacokinetic parameters of rosuvastatin in plasma after the administration of a single dose of rosuvastatin (5 mg) alone or on a background of finerenone (40 mg once daily) (geometric mean/%CV; all participants valid for pharmacokinetic analysis, $N = 14$)

Parameter	Rosuvastatin alone	Rosuvastatin + finerenone (at the same time)	Rosuvastatin + finerenone (separated ^b)
AUC, $\mu\text{g} \times \text{h/L}$	17.2 (55.7%)	19.6 (67.1%)	18.1 (52.0%)
AUC _(0-t) , $\mu\text{g} \times \text{h/L}$	16.3 (59.9%)	18.4 (70.6%)	17.2 (54.7%)
C_{max} , $\mu\text{g/L}$	1.48 (74.8%)	1.64 (77.6%)	1.43 (60.9%)
$T_{1/2}$, h	17.4 (31.6%)	19.9 (49.2%)	17.6 (21.1%)
T_{max} ^a , h	3.01 (1.00–6.02)	4.50 (2.98–8.00)	3.51 (3.00–6.00)
CL/F, L/h	291 (55.7%)	255 (67.1%)	277 (52.0%)

AUC area under the plasma concentration–time curve from zero to infinity, AUC_(0-t) area under the plasma concentration–time curve from zero to the last data point > lower limit of quantification, CL/F apparent oral clearance, C_{max} maximum plasma concentration, CV coefficient of variation, $T_{1/2}$ terminal half-life, T_{max} time to reach C_{max}

^aMedian (range)

^bRosuvastatin administered 4.25 h before finerenone

profiles of the endogenous OATP substrate CP-I are presented in Fig. 2, and pharmacokinetic parameters for both CP-I and CP-III are presented in Table 4. Concentration vs. time profiles for CP-III are not shown, owing to a large number of values below the LLOQ. The results of the statistical analysis (ANOVA) comparing treatment ratios for rosuvastatin, CP-I, and CP-III are given in Table 5.

The ANOVA demonstrated small increases in the exposure (AUC +14% [geometric coefficient of variation (CV) = 17%] and C_{max} +11% [geometric CV = 23%], based on point estimates) of rosuvastatin when administered simultaneously with finerenone (40 mg at steady state) compared with the administration of rosuvastatin alone. The 90% CI of the rosuvastatin C_{max} ratio included unity.

When rosuvastatin was administered 4.25 h before finerenone, there was no effect on its AUC and C_{max} compared with rosuvastatin alone. The point estimates for AUC and the C_{max} ratios were close to unity, and their corresponding 90% CIs fell within the conventional no-effect boundary (80.0–125%).

Finerenone did not show an effect on $C_{\text{max,md}}$ and AUC _{τ ,md} of CP-I and $C_{\text{max,md}}$ of CP-III. The point estimates for AUC _{τ ,md} and the $C_{\text{max,md}}$ ratios for CP-I and the $C_{\text{max,md}}$ ratio for CP-III were close to unity, and the corresponding 90% CIs of all ratios fell within 80.0–125%. The low plasma concentrations of CP-III, with observations frequently below the LLOQ, precluded an assessment of

Fig. 2 Concentration of CP-I ($\mu\text{g/L}$) in plasma by treatment (geometric mean/SD; pharmacokinetics set, $N = 14$). LLOQ = 0.1 $\mu\text{g/L}$. LLOQ lower limit of quantification, SD standard deviation

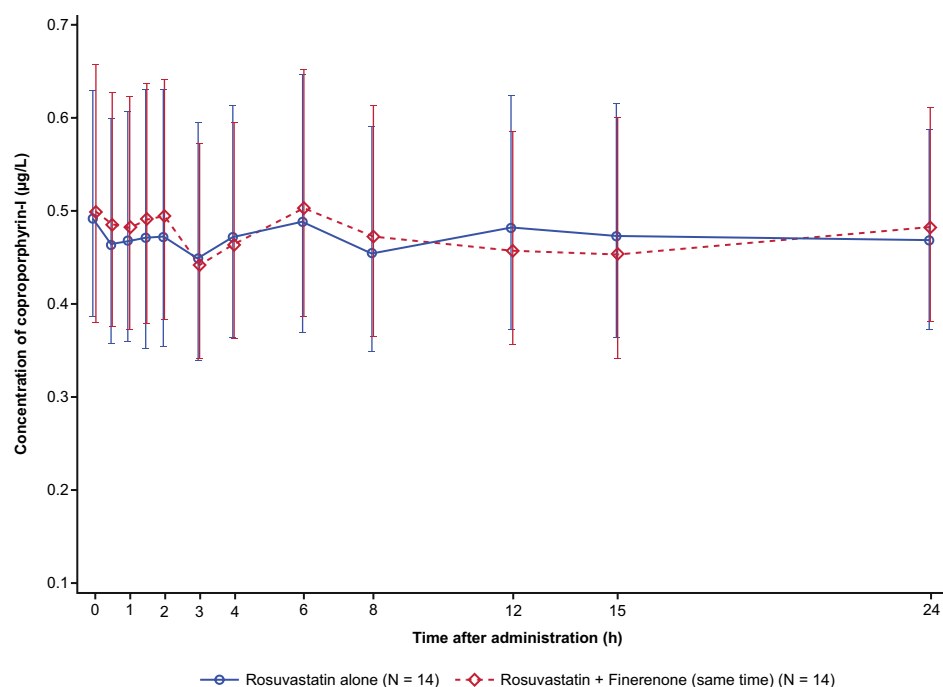


Table 4 Pharmacokinetic parameters of CP-I and CP-III in plasma after the administration of rosuvastatin (5 mg) alone or on a background of finerenone (40 mg once daily) (geometric mean/%CV; all participants valid for pharmacokinetic analysis, $N = 14$)

Parameter	CP-I		CP-III	
	Rosuvastatin alone	Rosuvastatin + finerenone (at the same time)	Rosuvastatin alone	Rosuvastatin + finerenone (at the same time)
	$n = 13$ (AUC), $n = 14$ (C_{max})	$n = 12$ (AUC), $n = 14$ (C_{max})	$n = 9$	$n = 6$
$AUC_{\tau,md}$, $\mu\text{g} \times \text{h/L}$	11.2 (26.4%)	11.3 (27.7%)	N.C.	N.C.
$C_{max,md}$, $\mu\text{g/L}$	0.530 (25.7%)	0.536 (25.8%)	0.118 (9.12%)	0.107 (7.84%)

AUC area under the plasma concentration–time curve from zero to infinity, $AUC_{\tau,md}$ area under the plasma concentration–time curve within a dosing interval after multiple dose administration, C_{max} maximum plasma concentration, $C_{max,md}$ maximum plasma concentration after multiple dose administration, CP coproporphyrin, CV coefficient of variation, $N.C.$ not calculated due to an insufficient number of observations above the lower limit of quantification

Table 5 Treatment ratios of the AUC and C_{max} of rosuvastatin and the $AUC_{\tau,md}$ and $C_{max,md}$ of CP-I and CP-III (all participants valid for pharmacokinetic analysis, $N = 14$)

Analyte	Parameter	N	Geometric CV (%)	Treatment ratio [LS means and 90% CI (%)]	
				Rosuvastatin + finerenone (at the same time)/rosuvastatin alone	Rosuvastatin + finerenone (separated ^a)/rosuvastatin alone
Rosuvastatin	AUC	14	17.06	114.47 (102.63, 127.68)	105.28 (94.39, 117.42)
	C_{max}	14	22.65	111.24 (96.30, 128.49)	96.84 (83.84, 111.97)
CP-I	$AUC_{\tau,md}$	13	5.14	99.62 (95.94, 103.44)	N.A.
	$C_{max,md}$	14	6.47	101.22 (96.94, 105.69)	N.A.
CP-III	$AUC_{\tau,md}$	N.A.	N.A.	N.C.	N.A.
	$C_{max,md}$	9	6.42	89.14 (82.73, 96.05)	N.A.

AUC area under the plasma concentration–time curve from zero to infinity, $AUC_{T,md}$ area under the plasma concentration–time curve within a dosing interval after multiple dose administration, CI confidence interval, C_{max} maximum plasma concentration, $C_{max,md}$ maximum plasma concentration after multiple dose administration, CP coproporphyrin, CV coefficient of variation; LS means least squares mean point estimates, $N.A.$ not available, as CP concentrations were not assessed in this treatment, $N.C.$ not calculated due to an insufficient number of observations above the lower limit of quantification

^aRosuvastatin administered 4.25 h before finerenone

$AUC_{\tau,md}$ for this analyte. Therefore, the assessment for CP-III is based on $C_{max,md}$ alone.

Derived pharmacokinetic parameters for finerenone and its pharmacologically inactive metabolites M1, M2, and M3 are presented in Table 6.

4 Discussion

Finerenone has recently been approved by the FDA and EMA for the treatment of adults with CKD associated with T2DM [22] at doses of 10 mg and 20 mg. Currently, finerenone 40 mg is the highest dose investigated in patients with heart failure and left ventricular ejection fraction $\geq 40\%$ in an ongoing trial [23].

In vitro data, together with prediction algorithms, identified a potential DDI risk with sensitive substrates of BCRP, OATP1B1, and OATP1B3 for finerenone and its metabolites M1a and M3a at the highest clinically relevant dose.

More specifically, finerenone was identified as a potentially relevant inhibitor of all three transporters, whereas M1a exceeded cutoff values for OATP1B1 and M3a did so for both OATP transporters. It is noteworthy that the cutoff values currently stipulated in regulatory guidelines were not exceeded by a large margin (Table 2), raising the question as to whether these results would translate into a relevant effect in vivo.

For example, the threshold for finerenone-mediated inhibition of intestinal BCRP of $[I]_{gut}/IC_{50} \geq 10$ was exceeded at 24.3. Despite some successful attempts [24–26], there is no standardized procedure to quantitatively predict the exposure change of sensitive substrates for DDIs affecting intestinal efflux transporters. However, the threshold applied is set with the intention of avoiding false-negative predictions [27], which implies that it is rather conservative (a claim that was also substantiated by others; e.g., Costales et al. [25]).

The current FDA in vitro DDI guideline [21] utilizes the basic model [28, 29] to assess the potential for, and extent

Table 6 Pharmacokinetic parameters of finerenone and its metabolites M1, M2, and M3 in plasma after administration of finerenone 40 mg (day 10 of a 4-0mg once-daily regimen) (geometric mean/%CV; all participants valid for pharmacokinetic analysis, $N = 14$)

Parameter	Finerenone	M1 ^b	M2 ^b	M3 ^b
$AUC_{\tau,md}$, $\mu\text{g} \times \text{h/L}$	1090 (22.0%)	4940 (38.7%)	2800 (30.1%)	1040 (7.08%)
$C_{max,md}$, $\mu\text{g/L}$	332 (24.7%)	524 (22.9%)	226 (24.3%)	73.1 (14.7%)
$T_{1/2,md}$, h	2.77 (15.9%)	6.41 (23.7%)	7.99 (27.2%)	6.82 (23.1%)
$T_{max,md}$ ^a , h	1.00 (0.483–2.00)	2.00 (0.733–4.00)	4.00 (3.98–8.00)	5.97 (3.98–8.00)

$AUC_{\tau,md}$ area under the plasma concentration–time curve within a dosing interval after multiple dose administration, $C_{max,md}$ maximum plasma concentration after multiple dose administration, CV coefficient of variation, $T_{1/2,md}$ terminal half-life after multiple dose administration, $T_{max,md}$ time to reach $C_{max,md}$

^aMedian (range)

^bMetabolites were determined with a non-stereoselective analytical method. Results denote the sum of atropisomers a and b

of, transporter-mediated DDIs at the systemic level, including hepatic uptake transporters OATP1B1 and OATP1B3. The model allows the prediction of an increase in AUC (as the AUC ratio [AUCR]), according to $R = 1 + [I]_{inlet,max,u} / IC_{50}$ (or $C_{max,u} / IC_{50}$). As indicated in Table 2, AUCRs of 1.182, 1.025, and 1.068 were calculated for the inhibition of OATP1B1 or OATP1B3 for finerenone, M1a, and M3a, respectively. These calculations imply that the clearance of the hypothetical substrate is mediated only by the transporter of interest, which renders the substrate maximally sensitive to inhibition. Therefore, it appeared somewhat questionable as to whether the inhibitory effect of finerenone and its metabolites could lead to an exposure increase beyond the no-effect boundary for clinically relevant OATP substrates such as statins, which do possess multiple clearance mechanisms [30].

A clinical phase I study was conducted to investigate finerenone as a potential inhibitor of BCRP and/or OATPs following the findings of the inhibition of these targets in vitro. Rosuvastatin was used as an index substrate of both BCRP and OATPs [17], similar to numerous previous studies with modulators of these drug transporters. Cyclosporine [31], an inhibitor of both BCRP and OATPs [17], increased rosuvastatin exposure in patients, with AUC and C_{max} ratios of 7.1 and 10.6, respectively, compared with historic control data for rosuvastatin alone. Less pronounced effects on rosuvastatin (AUC and C_{max} ratio of 1.55 and 2.03, respectively) were observed with eltrombopag [32], a BCRP inhibitor [17]. The OATP inhibitor gemfibrozil [17] increased the rosuvastatin AUC and C_{max} 1.88- and 2.21-fold, respectively [33]. In order to discern the mechanism behind potential effects of finerenone on rosuvastatin exposure, CP-I and CP-III as endogenous substrates of OATP1B1 and OATP1B3 were also measured in the present study, both in the absence and in the presence of finerenone. The utility of CP-I and CP-III in this context was confirmed in a study with the OATP inhibitor rifampicin and rosuvastatin in which the effect on rosuvastatin (AUC ratio of 5.0) was paralleled by increased exposure of CP-I and CP-III (AUC ratios of 4.0

and 3.3, respectively) [34]. It was concluded from studies with other OATP inhibitors that the magnitude of increase in plasma exposure of CP-I and CP-III is proportional to the strength of the applied inhibitor [35]. Thus, while increased rosuvastatin exposure could be the result of BCRP and/or OATP inhibition, the plasma concentrations of CP-I and CP-III would be a selective indicator for effects on OATP.

In order to maximize the potential for a systemic interaction, the substrate rosuvastatin was administered after finerenone and its metabolites had reached a steady state in plasma. The investigation of the effect of finerenone on CP-I and CP-III exposure was performed on a background of rosuvastatin administration, which has been shown to have no effect of its own on CP-I or CP-III exposure [34]. This study also assessed the possibility of avoiding an interaction during absorption by temporally separating the involved medications. Simultaneous co-administration was intended to separate the T_{max} values of finerenone and rosuvastatin, while temporal separation of intake (finerenone approximately 4 h after rosuvastatin, with the T_{max} of rosuvastatin expected at approximately 5 h [36]) was utilized for T_{max} alignment between the potential inhibitor and the substrate. Conversely, the potential for an effect of finerenone metabolite M3 (T_{max} of approximately 6 h, almost coinciding with that of rosuvastatin) on OATP1B3 was expected to be enhanced after simultaneous intake of finerenone and rosuvastatin.

After simultaneous co-administration with finerenone, the point estimate of the increase in rosuvastatin exposure (AUC +14%, C_{max} +11%) was < 25%; i.e., below the threshold of ‘weak inhibition’ defined in the context of metabolic pathways [37]. When rosuvastatin was administered approximately 4 h before finerenone, the point estimates for the AUC and the C_{max} ratios, together with their corresponding 90% CIs, fell within the no-effect boundary (80.0–125%). The complete absence of increased CP I and CP III exposure in both conditions suggests that finerenone does not affect OATP1B1 and OATP1B3. A previous study focusing on CYP2C8-mediated metabolism [10] had shown no effect of

finerenone (20 mg) on repaglinide, which is also an OATP substrate [17]. The observed not clinically relevant change in rosuvastatin AUC with finerenone (40 mg) is therefore believed to be due to an effect on BCRP.

Finerenone 40 mg is the highest investigated dose in patients [23] and was used to study the effect on rosuvastatin. An optional second part of the study with finerenone 20 mg, the highest approved dose in CKD associated with T2DM [6], was not performed after part 1 had shown no relevant effect of the 40-mg dose. The systemic exposure ($AUC_{\tau,md}$) of finerenone and metabolites in the present study following a dose of 40 mg once daily was consistent with published data (AUC) in healthy volunteers (20 mg [10, 11] for finerenone and 10 mg for the control group [13], finerenone and metabolites), applying dose-linear pharmacokinetics [7, 12].

5 Conclusions

In vitro investigations on the inhibitory potential of finerenone and its metabolites identified a potential DDI risk towards BCRP (for finerenone), OATP1B1 (for finerenone and M1a), and OATP1B3 (for finerenone, M1a, and M3a) by exceeding cutoff values established in pertinent regulatory guidelines. Accordingly, a clinical study was conducted to address these concerns by using rosuvastatin as the victim drug and substrate of all three transporters. Upon simultaneous co-administration with finerenone 40 mg, a 14% AUC and an 11% C_{max} increase was observed for rosuvastatin, indicating no clinically relevant effect in vivo, despite the potential risk indicated in vitro. When rosuvastatin was administered 4 h prior to finerenone to synchronize the maximum plasma exposure of rosuvastatin and the potential inhibitor M3a, the resulting effect fell completely within the no-effect boundary, demonstrating that M3a is also not a clinically relevant inhibitor of BCRP or OATP transporters. To identify the site of a potential interaction between finerenone and rosuvastatin, levels of CP-I and CP-III, which are endogenous substrates of OATP1B1 and OATP1B3, were measured. No effect on the exposure of CP-I or CP-III was observed, consistent with the claim that finerenone and its metabolites are not relevant inhibitors of OATP1B1 and OATP1B3. This finding also suggests that the observed minor increase in rosuvastatin exposure is likely due to an effect on BCRP rather than OATP transporters. In summary, we conclude that finerenone 40 mg is safe to be administered with substrates of BCRP and/or OATP1B1 and OATP1B3. As previously published by others (e.g., by Costales et al. [25]), the data presented here indicate that current regulatory guidelines apply rather strict cutoffs above which it is recommended that clinical transporter interaction studies should be conducted. This avoids false-negative findings on the one

hand, but, conversely, prompts additional in vivo studies in human subjects.

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Declarations

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Conflicts of interest RH, JN, RF, and SW are employees of Bayer AG. SL is an employee of Chrestos Concept GmbH & Co. KG, which received funding for this analysis from Bayer AG. In addition, RH, JN, RF, and SW have stock in Bayer AG, but are not paid in stock or stock options.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Consent to participate Informed consent was obtained from all individual participants included in the studies before study commencement.

Consent for publication Not applicable.

Availability of data Availability of the data underlying this publication will be determined later according to Bayer's commitment to the EFPIA/PhRMA principles for responsible clinical trial data sharing. This pertains to the scope, time point, and process of data access. As such, Bayer commits to sharing, upon request from qualified scientific and medical researchers, participant-level clinical trial data, study-level clinical trial data, and protocols from clinical trials in participants for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 1, 2014. Interested researchers can use www.clinicalstudydatarequest.com to request access to anonymized participant-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the study sponsor's section of the portal. Data access will be granted to anonymized participant-level data, protocols, and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that participant privacy is safeguarded.

Code availability Not applicable.

Author contributions RH, JN, and SL participated in the study concept and design of the phase I study and were involved in the acquisition, analysis, and interpretation of the respective data. RF was involved in the study concept and design of in vitro studies, their data acquisition, and analysis. RF and SW were involved in the interpretation of the in vitro results. All authors participated in preparing the manuscript.

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