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TITLE PAGE

A study of the effect of cyclosporine on fevipiprant pharmacokinetics and its absolute bioavailability using an intravenous microdose approach¶

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RUNNING TITLE PAGE

Cyclosporine effect on fevipiprant oral and IV PK

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Nonstandard abbreviations (in alphabetical order)

ADME: absorption, distribution, metabolism and excretion

AE: adverse events

SAE: serious adverse event

$Ae_{0\text{-}24h}$: Amount of drug (or metabolite) excreted into the urine from time zero to 24h]

AG: acyl-glucuronide

ALT: alanine aminotransferase

$AUC_{inf:}$ area under the plasma concentration–time curve from time zero to infinity

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AUC_{last}: area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration

BMI: body mass index

CI: confidence interval

C_{max}: maximum plasma concentration

CL: clearance

CLr: renal clearance

CRTh2: chemoattractant receptor-homologous molecule expressed on Th2 cells

DP_2: prostaglandin D_2 receptor 2

ECG: electrocardiogram

F: absolute bioavailability

IV: intravenous

LC-MS/MS: liquid chromatography–tandem mass spectrometry

LLOQ: lower limits of quantification

MDR1: multidrug resistance protein 1

M/P: metabolite-to-parent

OAT: organic anion transporter

OATP: Organic anion transporting polypeptide

PGD_2: prostaglandin D_2

P-gp: P-glycoprotein

PK: pharmacokinetics

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po: *per os* (oral administration)

R^2: coefficient of determination in regression analysis

$T_{1/2}$: terminal half-life

T_{max}: time to reach peak or maximum concentration following drug administration

UGT: uridine 5'-diphospho-glucuronosyltransferase

V: volume of distribution

Vz/F: the apparent volume of distribution during the terminal phase following extravascular administration

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Abstract

This drug-drug interaction (DDI) study determined the effect of cyclosporine, an inhibitor of OATP1B3 and P-gp, on the pharmacokinetics (PK) of fevipiprant, an oral, highly selective, competitive antagonist of the prostaglandin D_2 receptor 2 and a substrate of the two transporters. The concomitant administration of an intravenous (IV) microdose of stable isotope-labeled fevipiprant provided the absolute bioavailability of fevipiprant, as well as mechanistic insights in its PK and sensitivity to drug interactions. Liquid chromatography–mass spectrometry/mass spectrometry was used to measure plasma and urine concentrations. Geometric mean ratios (90% CI) for oral fevipiprant with or without cyclosporine were: for C_{max}, 3.02 (2.38, 3.82); for AUC_{last}, 2.50 (2.17, 2.88); and for AUC_{inf}, 2.35 (1.99, 2.77). The geometric mean ratios (90% CI) for fevipiprant IV microdose with or without cyclosporine were: for C_{max}, 1.04 (0.86, 1.25); for AUC_{last}, 2.04 (1.83, 2.28) and for AUC_{inf}, 1.95 (1.76, 2.16). The absolute bioavailability for fevipiprant was approximately 0.3–0.4 in the absence and 0.5 in the presence of cyclosporine. The IV microdose allowed differentiation between systemic and pre-systemic effects of cyclosporine on fevipiprant, demonstrating a small (approximately 1.2-fold) pre-systemic effect of cyclosporine and a larger (approximately 2-fold) effect on systemic elimination of fevipiprant. Uptake by OATP1B3 appears to be the rate-limiting step in the hepatic elimination of fevipiprant while P-gp does not have a relevant effect on oral absorption.

Significance statement: The drug interaction investigated here with cyclosporine, an inhibitor of several drug transporters, provides a refined quantitative understanding of the role of active transport processes in liver and intestine for the absorption and elimination of fevipiprant, as well as the basis to assess the need for dose adjustment in the presence of transporter inhibitors. The applied IV microdose approach presents a strategy to maximize learnings from a trial, limit the number and duration of clinical trials, and enhance mechanistic DDI understanding.

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Introduction

Fevipiprant (QAW039) is an oral, competitive antagonist of the prostaglandin D_2 (PGD_2) receptor 2 (DP_2, previously called chemoattractant receptor-homologous molecule expressed on TH2 cells [CRTh2]) that dissociates slowly from this receptor (Sykes et al., 2016). In Phase II trials, fevipiprant significantly decreased sputum eosinophil counts, and reduced airway smooth muscle mass in patients with asthma (Erpenbeck et al., 2016a; Gonem et al., 2016; Bateman et al., 2017; Saunders et al., 2019) but Phase III results [ClinicalTrials.gov numbers: NCT02555683; NCT02563067; NCT03215758; NCT03226392] did not support submission in this indication.

One aspect of drug development is to build a detailed understanding of the processes underlying the pharmacokinetics (PK) of the drug in order to determine if, and to what extent, co-medications or other factors can affect its PK. In this context, regulatory authorities encourage obtaining intravenous (IV) PK data of drugs in development (European Medicines Agency, 1987). PK parameters requiring IV data (such as absolute bioavailability and systemic clearance), can increase the predictability of physiologically-based modeling of PK and are generally important for any quantitative estimation of exposure change with, for example, change in formulation, age, partial inhibition of a clearance pathway by DDIs, or organ impairment.

Renal clearance and hepatic elimination via glucuronidation and/or biliary secretion contribute to the elimination of fevipiprant; IV PK data can help to estimate the contributions of these clearance pathways more quantitatively. In a human absorption, distribution, metabolism and excretion (ADME) study of fevipiprant the fraction of the oral dose absorbed from the intestine was estimated to be at least 43.5% (42.1% of the total radioactive dose recovered from urine and 1.4% as metabolites in feces) (Pearson et al., 2017). However, the absolute bioavailability,

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i.e. the fraction of the oral dose reaching the systemic circulation unchanged, could be higher or lower than this minimal estimate of absorption. *In vitro* data indicate that fevipiprant is taken up via organic anion transporting polypeptide 1B3 (OATP1B3) into the liver, followed by formation of an acyl glucuronide (AG) metabolite by several uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes. Of note, the AG metabolite is the only major circulating metabolite of fevipiprant and is not pharmacologically active (Pearson et al., 2017). Organic anion transporter 3 (OAT3) is responsible for the active renal excretion of fevipiprant (Pearson et al., 2017). Because fevipiprant is a substrate of P-glycoprotein (P-gp or multidrug resistance protein 1; MDR1) and UGT enzymes, intestinal efflux and metabolism could have an impact on its absorption and first-pass metabolism, respectively (Pearson et al., 2017). In addition, the hepatic first-pass extraction by OATP1B3-mediated uptake may influence the bioavailability of fevipiprant.

The aim of this study was to determine the effect of oral cyclosporine, an inhibitor of OATP1B3 (Shitara et al., 2012) and P-gp (Kovarik and Koelle, 1999), on the PK of fevipiprant, and also to increase the overall understanding of fevipiprant PK. Cyclosporine has no inhibitory effects on the other elimination pathways of fevipiprant, that is, UGTs [no inhibition was reported at time of survey in the Metabolism and Transport Drug Interaction Database (DIDB®)] and OAT3 (El-Sheikh et al., 2013). An IV microdose of stable (i.e. non-radioactive) isotope-labeled fevipiprant ([$^{13}C_2{}^{15}N_2$]fevipiprant) (Figure 1) was co-administered with unlabeled oral fevipiprant to determine its absolute bioavailability and systemic clearance, both in the absence and presence of cyclosporine. Labeled and unlabeled fevipiprant are identical biologically, i.e. their interaction with e.g. the target or drug transporters is not expected to differ, but they can be distinguished analytically by mass spectrometry. This allows IV and oral data to be obtained on the same drug, from the same study participant, at the same time without the risk of a bias of the IV-PK data due to the microdose in case of PK non-linearity (Lappin et al., 2006). In the context of the DDI assessment this allowed determination of systemic (from fevipiprant IV administration) as

well as 'pre-systemic plus systemic' (from fevipiprant oral administration) effects of cyclosporine, adding mechanistic granularity.

Materials and methods

Study objectives

The primary objective was to determine the effect of cyclosporine on the three key PK measures of orally administered fevipiprant in healthy volunteers: (i) the area under the plasma concentration–time curve from time zero to the time of the last quantifiable concentration (AUC_{last}); (ii) the area under the plasma concentration–time curve from time zero to infinity (AUC_{inf}); and (iii) the maximum plasma concentration (C_{max}).

The secondary objectives were to determine: (i) the absolute bioavailability (F) and the absolute disposition parameters of fevipiprant, i.e. clearance (CL) and volume (V) of distribution, by administering an IV microdose of stable isotope-labeled fevipiprant concomitantly with the oral dose; (ii) the effect of cyclosporine on the PK of the IV microdose of fevipiprant (V, CL, AUC_{last}, and AUC_{inf}); (iii) the safety and tolerability of fevipiprant administered both orally and intravenously, with and without co-administration of cyclosporine; and (iv) the effect of cyclosporine on the PK of the major AG metabolite of oral fevipiprant. The study protocol was approved by the Institutional Review Board for the study center and the study was conducted according to the ethical principles of the Declaration of Helsinki.

Study design

This was an open-label, single-sequence, two-period, crossover study with two treatment periods separated by a washout period of 7–14 days (Figure 2). The study was carried out at IQVIA (formerly QuintilesIMS), Overland Park, KS, USA. The investigational drug, fevipiprant 150 mg film-coated tablets and fevipiprant 100 µg labeled IV microdose ([$^{13}C_2{}^{15}N_2$]fevipiprant)

(Figure 1), were prepared and released by Novartis Technical Research and Development. Cyclosporine 100 mg and 25 mg soft gelatin capsules (Neoral® Novartis Pharma AG, Basel, Switzerland) were commercially available and sourced locally by the site.

In Treatment Period 1, study participants were admitted to the clinic on Day −1 for baseline evaluations at least 12 hours before dosing. On Day 1, they received a single oral dose of fevipiprant 150 mg, followed by an IV microdose of labeled fevipiprant (100 µg) 1 hour (± 5 minutes) later. Participants fasted for 8 hours before the oral dose administration and continued to fast for 2 hours afterwards, and were confined to the clinic for approximately 28 hours following the oral study drug administration during which time blood and urine samples for PK analysis and safety assessments were taken. On Days 3-5, participants returned to the study site for outpatient safety and PK visits. They returned to the clinic for Treatment Period 2 following a washout period; overall 7-14 days separated Day 1 in Treatment Period 1 from nominal Day 16 in Treatment Period 2. Anyone that prematurely discontinued from Treatment Period 1 was required to complete an early termination visit (Day 15 visit).

In Treatment Period 2, participants were admitted to the clinic on Day 15 for baseline evaluations at least 12 hours before dosing. On Days 16 to 19, they received oral doses of cyclosporine 175 mg bid and on Day 20, a single oral dose of cyclosporine 175 mg in the morning. On Day 17, participants received a single oral dose of fevipiprant 150 mg in parallel with the morning cyclosporine dose (± approximately 3 minutes), followed by administration of an IV microdose of labeled fevipiprant (100 µg) 1 hour (± 5 minutes) later. On all dosing days participants fasted for 8 hours before the oral drug administration in the morning and continued to fast for 2 hours thereafter. Samples were taken for PK analysis on Days 16-21. Participants fasted for 2 hours before the evening doses of cyclosporine and continued to fast for 1 hour thereafter and were confined to the clinic until study Day 21. On Day 23, participants returned to

the study site for safety assessments; end of study safety assessments were completed on Day 25.

The sample size (16 participants so that at least 12 would complete the study) was selected to control the width of the confidence interval for the geometric mean ratio for fevipiprant AUC and C_{max} when given with and without cyclosporine. Further details may be found in the Online Data Supplement.

Key inclusion and exclusion criteria

Men and women were admitted as study participants if they were aged 18–55 years and in good health, as determined by past medical history, physical examination, vital signs, electrocardiogram (ECG), and laboratory tests at screening and/or at first baseline visit. Further details on vital sign measurement are provided in the Online Data Supplement. Participants had to weigh between 60 and 90 kg and to have a body mass index (BMI) within the range of 20–30 kg/m^2. Study participants gave written informed consent before any assessment took place, had to be able to communicate well with the investigator, and to understand and comply with the requirements of the study. Exclusion criteria details are provided in the Online Data Supplement.

Pharmacokinetic analyses

PK blood and urine samples were taken at prespecified time points from all participants and acidified pending analysis to avoid back-conversion of the AG metabolite to fevipiprant (details are provided in the Online Data Supplement). Validated liquid chromatography–mass spectrometry/mass spectrometry (LC-MS/MS) methods were used to measure the plasma concentrations of unlabeled fevipiprant (given orally) and labeled fevipiprant (given as IV microdose) using the transitions of m/z (mass to charge ratio) 427 to m/z 145 and of m/z 431 to

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m/z 149, respectively. The MS/MS transition used for the acyl glucuronide metabolite of (unlabeled) fevipiprant was m/z 603 to m/z 427. The MS/MS transition used for the measurement of cyclosporine was m/z 1219.9 to m/z 1202.9. Further details of the LC-MS/MS methods may be found in the Online Data Supplement. The plasma concentrations of the AG metabolite of unlabeled fevipiprant and the blood concentrations of cyclosporine were measured by validated LC-MS/MS methods. The concentrations of unlabeled fevipiprant and its major AG metabolite in urine were determined using qualified LC-MS/MS methods. Concentrations below the lower limits of quantification (LLOQ) were reported as "zero" and missing data were labeled as such in the bioanalytical data reports.

The following PK measures of fevipiprant were determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4): C_{max}, T_{max} (time to reach peak or maximum concentration following drug administration), AUC_{last}, AUC_{inf}, $T_{1/2}$ (terminal half-life), Vz/F (the apparent volume of distribution during the terminal phase following extravascular administration), CL, F and CL/F from the plasma concentration time data. For the AG metabolite, C_{max}, T_{max}, AUC_{last}, AUC_{inf} and $T_{1/2}$ were determined using non-compartmental analysis only after oral administration. The amount excreted into the urine ($Ae_{0–24h}$) of unlabeled fevipiprant and its AG metabolite was determined from the urine concentration and volume–time data. The renal clearance (CLr) of fevipiprant and its AG metabolite was determined as Ae/AUC from the same time period. The absolute oral bioavailability (F) was estimated as a ratio of the dose-normalized AUCs following oral (po) and intravenous administration ($F=[AUC_{po}*DOSE_{iv}]/[AUC_{iv}*DOSE_{po}]$). The linear trapezoidal rule was used for AUC calculation. Regression analysis of the terminal elimination phase for the determination of $T_{1/2}$ included at least three data points after C_{max}. If the adjusted R^2 (coefficient of determination) value of the regression analysis of the terminal phase was less than 0.75, no values were reported for $T_{1/2}$, AUC_{inf}, CL, V or CL/F.

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Key safety and tolerability assessments

Safety assessments consisted of collecting all adverse events (AEs), serious AEs (SAEs), with their severity and relationship to study drug. Laboratory evaluations included hematology, biochemistry and urinalyses. Vital signs, physical condition, body weight and standard 12-lead ECG were also assessed.

Statistical analyses

Participants' data were analyzed according to the study treatments received for all analysis sets. The safety analysis set included all participants who received any study drug. The PK analysis set included all participants with at least one available valid PK concentration measurement, who received any study drug and with no protocol deviations that had an impact on PK data. For the primary endpoints, the log-transformed fevipiprant PK measures (AUC_{last}, AUC_{inf} and C_{max}) were analyzed separately by a mixed effects model, with treatment as a fixed effect and participant as random effect. The estimated mean and 90% confidence interval (CI) for treatment difference (fevipiprant plus cyclosporine versus fevipiprant alone) were back-transformed to obtain a geometric mean ratio and 90% CI of the ratio. SAS software was used for all statistical analyses. Statistical analysis of the secondary endpoints is provided in the Online Data Supplement.

Results

Participants

Sixteen participants entered the study, of whom 13 (81.3%) completed Treatment Period 1. Fourteen participants were male and two were female; 11 were Caucasian, four were black with one of another race (not specified). Their mean age was 32.5 years (range: 20–52) with a mean weight of 77.7 kg (range: 64.5-88.7) and mean BMI of 25.6 kg/m^2 (range: 21.6–30.0). Three

participants discontinued for the following reasons: because of an AE (n=1), being lost to follow-up (n=1), or physician decision (positive drug screen on Day 15; n=1). All 13 participants who completed Treatment Period 1 entered Treatment Period 2 and completed the study. All 16 participants were included in the PK and the safety analysis sets.

Effect of cyclosporine on the PK of fevipiprant (oral and IV doses)

Peak concentrations of oral fevipiprant were seen 1.5 h after the fevipiprant dose and 3 hours after the cyclosporine plus fevipiprant dose (Figure 3; Table 1). The mean concentration-time data for fevipiprant with and without cyclosporine are provided in Supplemental Table 1. For C_{max}, the geometric mean ratio (90% CI) was 3.02 (2.38, 3.82) (Supplemental Table 2) indicating an approximately three-fold increase in peak exposure of fevipiprant when co-administered with cyclosporine. The geometric mean ratios (90% CI) were 2.50 (2.17, 2.88) for AUC_{last} and 2.35 (1.99, 2.77) for AUC_{inf} (Supplemental Table 2), indicating that the effect of cyclosporine on fevipiprant total exposure is smaller than the effect on peak exposure. Oral clearance and volume of distribution of fevipiprant were reduced by approximately 50% upon co-administration with cyclosporine, whereas $T_{1/2}$ was similar (Table 1).

C_{max} values of the fevipiprant IV microdose were similar in the presence and absence of cyclosporine (Figure 4; Table 2), with a geometric mean ratio for C_{max} (90% CI) of 1.04 (0.86, 1.25) (Supplemental Table 4). The mean concentration-time data for the fevipiprant IV microdose with and without cyclosporine are provided in Supplemental Table 3. T_{max} was typically at the first sampling time i.e. 2 min after IV dosing. A terminal half-life and volume of distribution (V) for fevipiprant are not reported, since the terminal phase was not sufficiently covered in the concentration–time data, which is required to derive V. The terminal half-life after IV administration is expected to be identical to that derived from the oral data. AUC_{inf} and CL were estimated by non-compartmental analysis (Table 2), despite the limitations in describing

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the terminal phase. Since the captured concentration–time profiles cover a 1000-fold range in concentrations, the bias resulting from the incomplete representation of the AUC after concentrations dropped below the LLOQ of 20 pg/mL is considered to be small. Both AUC_{last} and estimated AUC_{inf} for fevipiprant IV microdose were approximately 2-fold higher in presence of cyclosporine (Table 2), with geometric mean ratios (90% CI) of 2.04 (1.83, 2.28) and 1.95 (1.76, 2.16), respectively (Supplemental Table 4).

Absolute bioavailability of fevipiprant

The combination of oral and IV microdose fevipiprant PK data was used to estimate its absolute bioavailability. Because of the limitations to deriving AUC_{inf} for the IV profiles, the absolute oral bioavailability for fevipiprant was based on comparison of dose normalized AUC_{last} (mean ± SD), and was 0.43 ± 0.09 and 0.53 ± 0.16 in the absence and presence of cyclosporine, respectively. These values are expected to be slightly higher than the real values since the covered time interval is longer for the oral data. The absolute bioavailability of fevipiprant was also estimated based on comparison of $AUC_{0–11h}$, because most IV profiles could be measured up to 11 h post dose. Estimates based on this comparison were (mean ± SD) 0.28 ± 0.05 and 0.48 ± 0.16 in the absence and presence of cyclosporine, respectively. Using this method, a larger fraction of the fevipiprant oral profile is ignored; therefore, this value is a minimal estimate of the real value, which is expected to be in the range defined by the assessments based on AUC_{last} and $AUC_{0–11h}$, i.e. approximately 0.3–0.4 in the absence and 0.5 in the presence of cyclosporine.

Effect of cyclosporine on the PK of the major AG metabolite of fevipiprant

No relevant change in exposure of the AG metabolite of oral fevipiprant was seen in the presence of cyclosporine (Table 3). Consequently, the metabolite-to-fevipiprant ratio of AUC_{last} decreased from 1.5 to 0.59 in presence of cyclosporine. The mean concentration-time data the

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AG metabolite with and without cyclosporine are shown in Supplemental Table 1. Geometric mean ratios for PK measures for the AG metabolite are shown in Supplemental Table 5.

Effect of cyclosporine on the urinary excretion of fevipiprant and its AG metabolite

Co-administration with cyclosporine did not result in any relevant changes in the renal clearance of oral fevipiprant (Table 1) and its AG metabolite (Table 3). However, consistent with the higher exposure, the fraction of the dose excreted as unchanged fevipiprant into urine within 24 h increased by 2.5-fold from 16.7 ± 3.55% to 40.9 ± 7.50% when co-administered with cyclosporine. There was only a slight increase in the amount of AG metabolite excreted into urine from 31.7 ± 6.08 mg to 37.3 ± 4.79 mg in the presence of cyclosporine (corresponding to approximately 15 or 18% of the fevipiprant dose).

Effect of fevipiprant on the PK of cyclosporine and concentration-effect relationship of cyclosporine

No relevant change in mean trough blood concentrations of cyclosporine was observed from Day 17 in the morning (before administration of fevipiprant) to any time point after fevipiprant administration (mean trough blood concentrations were in the range of 45–54 ng/mL cyclosporine). This indicates the absence of a major effect of fevipiprant 150 mg on the PK of cyclosporine and that cyclosporine steady state had been achieved at the time of fevipiprant dosing.

The relationship of trough concentrations of cyclosporine to the observed change in oral fevipiprant C_{max} was explored graphically (Figure 5). There was no apparent trend for an increasing effect on fevipiprant C_{max} with increasing trough concentrations of cyclosporine.

Safety and tolerability

Overall, administration of fevipiprant alone and fevipiprant plus cyclosporine showed no major or novel safety signals. There were 20 AEs reported in nine patients: headache (n=3); nausea (n=2); alanine aminotransferase (ALT) elevation (n=1); back pain (n=1); catheter site hematoma (n=1); contact dermatitis (n=1); dizziness (n=1); dysgeusia (n=1); flushing (n=1); muscle fatigue (n=1); pharyngitis (n=1); upper respiratory tract infection (n=1); chlamydial urethritis (n=1); vessel puncture site pain (n=1); and vomiting (n=1). A breakdown of the safety data by treatment period may be found in the Online Data Supplement (Table S6).

Ten AEs were suspected to be related to study medication: eight were suspected to be related to cyclosporine; one was suspected to be related to fevipiprant (mild postural dizziness); and one was suspected to be related to one or other or both study treatments (mild headache); it was not possible to distinguish which. All reported AEs were of mild intensity, except one AE (pharyngitis) which was of moderate intensity. The participant who experienced increased ALT discontinued the study, this AE was not suspected to be related to study drug. Apart from the elevation in ALT in one participant, no clinically significant changes were seen in laboratory parameters, vital signs or ECG parameters. There were no serious AEs or deaths.

Discussion

The aim of this study was to assess how cyclosporine, by inhibiting OATP1B3-mediated liver uptake and P-gp-mediated efflux in the intestine and liver, affects the PK of oral fevipiprant. The inclusion of an IV microdose of stable isotope-labeled fevipiprant provided major additional learnings without the need for more participants, or a longer study duration: the absolute bioavailability of fevipiprant was derived, and the mechanistic DDI understanding increased, by the ability to differentiate between systemic and pre-systemic effects of cyclosporine. These learnings would be reflected in a potential future fevipiprant drug label in two sections: 1) the absolute bioavailability and dependence on active transport as part of the PK section and 2) the

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assessment of the need for dose adjustment in presence of OATP1B3 or P-gp inhibitors in the drug interaction section.

In the absence of cyclosporine, the PK properties of fevipiprant including exposure to its major metabolite were consistent with earlier studies (Erpenbeck et al., 2016b; Erpenbeck, 2017; Pearson et al., 2017). Co-administration of cyclosporine increased the C_{max} of oral fevipiprant 3-fold and the AUC_{inf} by 2.35-fold. While fevipiprant concentrations shortly after IV-dosing were similar, the AUC of IV administered fevipiprant was 2-fold higher in the presence of cyclosporine, corresponding to a 2-fold decrease in systemic clearance. The approximately 1.2 fold stronger effect on oral as compared to IV exposure (2.35/2 i.e. ~1.2) can be attributed to the effect of cyclosporine on absorption and/or first-pass elimination of fevipiprant. This combined effect was small and indicates that the inhibition of intestinal P-gp has only a minor or no impact. Early clinical investigations in healthy participants indicated a dose-proportional PK of fevipiprant over a 2-fold dose range (Erpenbeck et al., 2016b), while later more comprehensive data in patients demonstrated dose-proportional PK over a 10-fold dose range (unpublished observations). Therefore, the magnitude of drug interaction observed here is also relevant for other oral fevipiprant dose levels such as 450 mg, which was also tested in patient trials.

Despite the approximate 2-fold reduction in clearance, no increase in the terminal half-life of fevipiprant was observed with co-administration of cyclosporine. The likely explanation is a reduced distribution in the presence of cyclosporine as the terminal half-life depends on the ratio of distribution to clearance. Since cyclosporine reduced CL/F and Vz/F to a similar extent, the terminal half-life of fevipiprant remained largely unchanged. Mechanistically, the reduced hepatic uptake due to inhibition of OATP1B3 can explain the lower volume of distribution of fevipiprant in the presence of cyclosporine. In a rat ADME study with radiolabeled fevipiprant the liver showed the highest exposure to drug-related radioactivity (unpublished observations),

suggesting that liver uptake may be a major determinant of the distribution of fevipiprant. This change in distribution points to inhibition of liver uptake by OATP1B3 as the predominant mechanism for the effect of cyclosporine.

While in the presence of cyclosporine, fevipiprant exposure was increased; little change in exposure to the AG metabolite was observed and consequently, the metabolite:fevipiprant ratio for AUC_{last} was decreased 2.5-fold from 1.5 to 0.59 by cyclosporine (Table 3). Again, this suggests that reduced uptake into the liver, the major site of fevipiprant glucuronidation, is the primary mechanism of the observed cyclosporine effect. Otherwise, the metabolite:fevipiprant ratio would not decrease so strongly, because glucuronidation, as a high-capacity system, is not easily saturated (Williams et al., 2004).

The renal clearance of oral fevipiprant and its AG metabolite were not affected by cyclosporine. However, because of the higher systemic exposure to fevipiprant in the presence of cyclosporine, renal excretion contributed 2.5-fold more to the elimination of fevipiprant (40.9% vs. 16.7% of the dose excreted into urine).

There was no apparent relationship between the change in oral fevipiprant C_{max} and trough concentrations of cyclosporine, i.e. within the covered range, higher cyclosporine trough concentrations were not linked to a stronger drug interaction (Figure 5). Therefore, the degree of drug interaction may not be greater at higher cyclosporine oral doses that provide larger exposures than investigated in this study.

The terminal half-life of the IV microdose could not be derived since concentrations dropped below the LLOQ of 20 pg/mL by 23 hours post dose for most profiles. Concentrations shortly after dosing were approximately 1000-fold above LLOQ, suggesting that most of the AUC of the

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IV microdose was captured (extrapolated fraction of AUC_{inf} based on mean data was ≤ 6% both with and without cyclosporine).

The disposition of transporter substrates such as fevipiprant is complex, making prospective predictions of exposure changes with inhibitors of transporter activity challenging (Poirier et al., 2009b; Poirier et al., 2009a; Jamei et al., 2014; Taskar et al., 2020). Part of the challenge is that active transport processes influence absorption, clearance and tissue distribution, making it difficult to derive clean PK input parameters for modeling from oral data only. Combined IV and oral data obtained in this study in the presence and absence of a transporter inhibitor allow differentiation between systemic and pre-systemic processes and provide more robust parameters. This supports the development of more reliable physiologically-based PK models. These can be used to predict untested case scenarios, such as transporter DDI effects at steady state, and in case of fevipiprant the impact of other OATP1B3 inhibitors on its PK.

There was no effect of fevipiprant 150 mg on the trough concentrations of cyclosporine, which is consistent with expectations, based on available drug interaction data for fevipiprant as a perpetrator (Poller et al., 2019). Overall, administration of fevipiprant alone and fevipiprant plus cyclosporine was well tolerated with no unexpected or novel AEs. Most AEs suspected to be drug-related were attributed to cyclosporine. These findings are consistent with previous studies showing that fevipiprant was safe and well tolerated at single and multiple oral doses up to 1800 mg/day (Erpenbeck, 2017). The exposure change observed in this study will guide fevipiprant dosing recommendations in presence of OATP1B3 inhibitors in the context of the safety profile of fevipiprant in any potential future drug label.

The addition of a labeled IV microdose in this study allowed investigation of the absolute bioavailability and absolute clearance without the need to conduct an IV toxicology program and

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a separate IV clinical trial. Conventionally, absolute bioavailability studies are crossover studies involving 6–12 participants; the microdose approach negates the need for a separate study with the further advantage that IV and oral dose data from the same participants at the same time avoids variability. Furthermore, use of a microdose simplifies formulation work because of the small amounts involved, and there are fewer potential safety concerns.

Concomitant oral dosing of unlabeled and IV microdosing of labeled compound in humans has previously been used to determine the absolute bioavailability, as well as the oral and IV PK of the HIV protease inhibitor nelfinavir (Sarapa et al., 2005), dabrafenib, a BRAF inhibitor (Denton et al., 2013), saxagliptin, a dipeptidyl peptidase-4 inhibitor, and dapagliflozin, a sodium glucose co-transporter-2 inhibitor (Boulton et al., 2013). In all these studies, the compound given as IV microdose was radiolabeled with ^{14}C and quantified by accelerator mass spectrometry. Furthermore, a double tracer technique using oral ^{14}C-radiolabeled tofogliflozin simultaneously administered with ^{13}C-stable isotope labeled tofogliflozin has been used successfully in an oral human ADME study to obtain additional information on the IV-PK of the compound (Schwab et al., 2013). IV microdosing for PK analysis has been accepted as a method by major health authorities (FDA Center for Drug Evaluation and Research, 2012; Boulton et al., 2013).

Administering the microdose after the oral dose circumvents the potential problem of PK non-linearity at microdose levels (Lappin et al., 2006) as the (labeled) microdose enters the body while the unlabeled compound given orally is present in the therapeutic drug concentration range. We observed little variability in the IV microdose data suggesting good data quality.

Analytical interferences between the unlabeled 1500-fold higher oral dose and the labeled microdose were avoided by careful selection of the positions of labeling (Figure 1) and the transitions used in the LC-MS/MS analyses. With the MS/MS transitions given in the

experimental part, the spill-over of the unlabeled compound into the signal of the labeled compound was reduced to only 3 ppm of the unlabeled signal (Gu et al., 2012) which is negligible in the present context. The internal standard used in the LC-MS/MS analyses was fevipiprant labeled with five deuteriums and one ^{13}C in the 4-methanesulfonyl-2-trifluoromethylbenzyl-part of the molecule; no interference with the IV-dosed labeled fevipiprant is expected.

In this study a single-sequence design without randomization was used. This is common in DDI studies and accepted by health authorities since the risk for bias of PK endpoints is considered small when investigated drugs do not display changes in clearance with time.

In conclusion, co-administration of cyclosporine increased oral fevipiprant AUC_{inf} and C_{max} by 2.35- and 3-fold, respectively. The use of an IV microdose allowed estimation of the absolute bioavailability of fevipiprant (0.3-0.4) and to differentiate between a small (approximately 1.2-fold) pre-systemic effect of cyclosporine and a larger (approximately two-fold) effect on systemic elimination of fevipiprant. The effect seems to be mainly by inhibition of OATP1B3-mediated hepatic uptake of fevipiprant. Additional mechanistic learnings from the IV data did not require any extra study participants, or a separate trial. Although significant DDI was observed, administration of fevipiprant alone and fevipiprant plus cyclosporine was well tolerated with no novel AEs observed.

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Many dedicated scientists have been involved in defining the best labeling strategy as well as a synthesis and release process for the stable isotope-labeled IV dose: the authors would like to thank Carsten Bauer, Harry Tiemessen, Philipp Lustenberger, Valerie Diart, Albrecht Glänzel, Joel Krauser and Caroline Steib-Lauer for their committed work.

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Data sharing statement

Novartis will not provide access to patient-level data, if there is a reasonable likelihood that individual patients could be re-identified. Phase 1 studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase 1 studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may preclude granting access under these provisions. Where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

Authorship contributions

Markus Zollinger, Veit Erpenbeck, Meredith Cain, Janardhana Vemula, Walid Elbast and Markus Weiss participated in the research design. Walid Elbast conducted the experiments. Janardhana Vemula, Ken-Ichi Umehara and Markus Weiss performed data analysis. All authors contributed to the writing of the manuscript.

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Footnotes

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Legends for Figures

Figure 1 Structure of fevipiprant showing the positions of the stable isotope-labeling ($^{13}C_2{}^{15}N_2$) used for the IV microdosing

Figure 2 Study design.

Figure 3 Mean (SD) plasma concentration–time profiles of oral fevipiprant 150 mg in the presence (closed squares; n=13) and absence (open circles; n=16) of cyclosporine 175 mg b.i.d., linear view and semi-logarithmic view (inset).

Figure 4 Mean (SD) plasma concentration–time profiles of labeled fevipiprant after IV dosing of 100 µg in the presence (closed squares; n=13) and absence (open circles; n=16) of cyclosporine 175 mg b.i.d., linear view and semi-logarithmic view (inset).

Figure 5 Scatter plot of oral fevipiprant ratio (Treatment Period 2/ Treatment Period 1) for C_{max} with different cyclosporine concentrations.
On the X-axis is the trough cyclosporine concentration on Day 17, before the co-administration with fevipiprant. Only study participants with data from both study periods are included.

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Tables

Table 1 Pharmacokinetic measures for oral fevipiprant with and without co-administration of cyclosporine

Measure (unit)	Fevipiprant 150 mg oral n=16	Cyclosporine 175 mg b.i.d. + fevipiprant 150 mg oral n=13
C_{max} (ng/mL)	724 ± 207 (28.5) [n=16]	2270 ± 809 (35.7) [n=13]
AUC_{last} (h*ng/mL)	3210 ± 601 (18.7) [n=16]	8110 ± 1980 (24.4) [n=13]
AUC_{inf} (h*ng/mL)	3330 ± 718 (21.5) [n=15]	7900 ± 1980 (25.1) [n=10]
T_{max} (h)[#]	1.50 (0.50–4.50) [n=16]	3.00 (0.92–4.50) [n=13]
CL/F (L/h)	47.0 ± 10.3 (22.0) [n=15]	20.2 ± 5.71 (28.2) [n=10]
Vz/F (L)	1090 ± 585 (53.6) [n=15]	446 ± 256 (57.4) [n=10]
$T_{1/2}$ (h)	17.5 ± 13.5 (77.1) [n=15]	14.9 ± 6.46 (43.4) [n=10]
CL_r (L/h)	9.49 ± 1.25 (13.2) [n=16]	8.45 ± 2.39 (28.3) [n=13]

Data are arithmetic means ± SD (CV%) [n]. CV% = Coefficient of variation (%) = SD/mean*100.

[#]For T_{max}, data are median (min–max) [n].

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Table 2 Pharmacokinetic measures for labeled IV fevipiprant with and without co-administration of cyclosporine

Measure (unit)	Fevipiprant 100 µg IV n=16	Cyclosporine 175mg b.i.d. + fevipiprant 100 µg IV n=13
C_{max} (pg/mL) [#]	23600 ± 6030 (25.5) [n=16]	25000 ± 8500 (34.1) [n=13]
AUC_{last} (h*pg/mL)	5040 ± 774 (15.3) [n=16]	10300 ± 2160 (20.9) [n=13]
AUC_{inf} (h*pg/mL)	5360 ± 959 (17.9) [n=15]	10400 ± 2150 (20.7) [n=13]
CL (L/h)	19.2 ± 3.32 (17.3) [n=15]	9.97 ± 1.97 (19.7) [n=13]

Data are arithmetic means ± SD (CV%) [n]. CV% = Coefficient of variation (%) = SD/mean*100

[#]T_{max} was typically at the first sampling time i.e. 2 min (0.0330 hours) after IV dosing.

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Table 3 Pharmacokinetic measures for the AG metabolite of fevipiprant (unlabeled, derived from oral fevipiprant) with and without co-administration of cyclosporine

Measure (unit)	Fevipiprant 150 mg oral n=16	Cyclosporine 175 mg BID + fevipiprant 150 mg oral n=13
C_{max} (ng/mL)	1180 ± 333 (28.3) [n=16]	1330 ± 369 (27.7) [n=13]
AUC_{last} (h*ng/mL)	6650 ± 1450 (21.8) [n=16]	6720 ± 1470 (21.9) [n=13]
M/P*	1.5	0.59
AUC_{inf} (h*ng/mL)	6880 ± 1580 (22.9) [n=16]	6800 ± 1510 (22.3) [n=12]**
T_{max} (h)#	2.0 (0.92–6.0) [n=16]	3.0 (1.5–4.5) [n=13]
$T_{1/2}$ (h)	18.9 ± 13.0 (68.9) [n=16]	13.3 ± 6.96 (52.4) [n=12]**
CL_r	6.07 ± 1.02 L/h (16.7) [19.4]	6.29 ± 1.22 (19.4) [n=13]

Data are arithmetic means ± SD (CV%) [n]; CV% = Coefficient of variation (%) = SD/mean*100.

* Molar metabolite-to-parent (M/P) ratio for mean AUC_{last} considering the molecular weight difference (426 g/mol for fevipiprant and 602 g/mol for the AG metabolite). #For T_{max}, data are median (min-max) [n]. ** AUC_{inf} and $T_{1/2}$ were reported when R^2 (coefficient of determination in the regression analysis) adjusted value of the terminal elimination phase was > 0.75.

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Figures

Figure 1

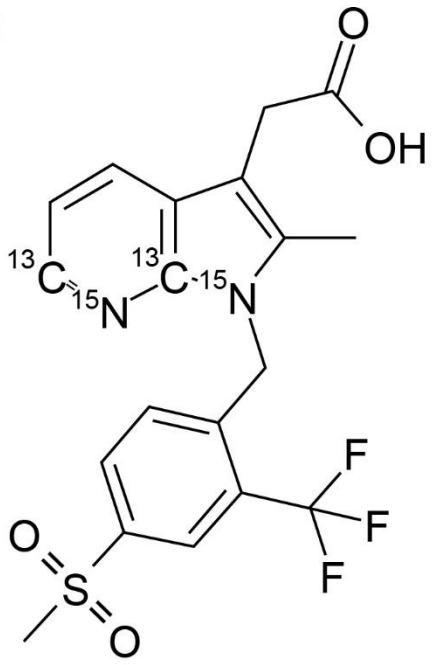

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Figure 2

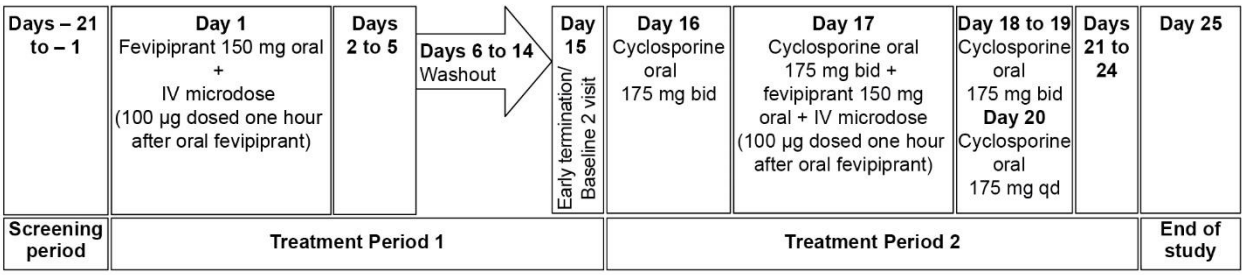

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Figure 3

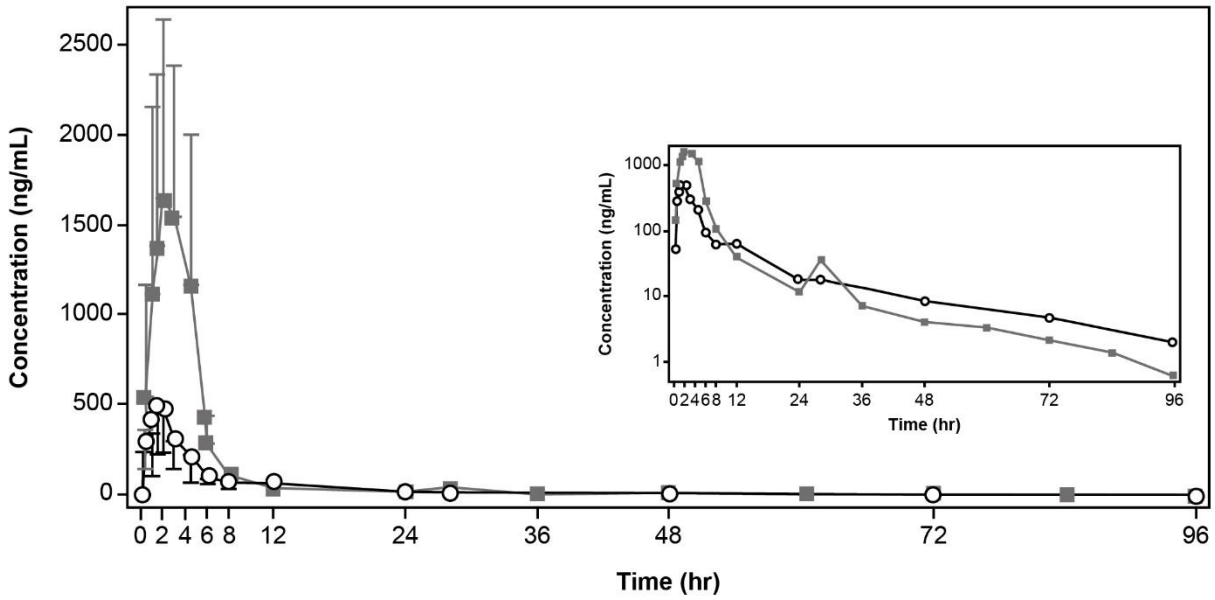

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Figure 4

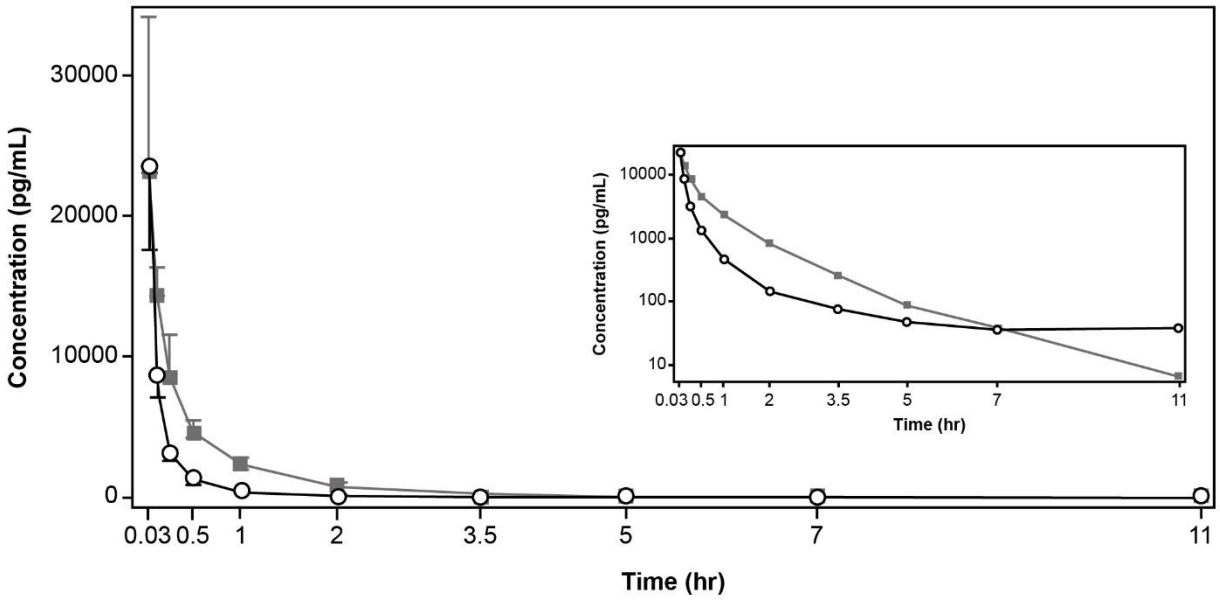

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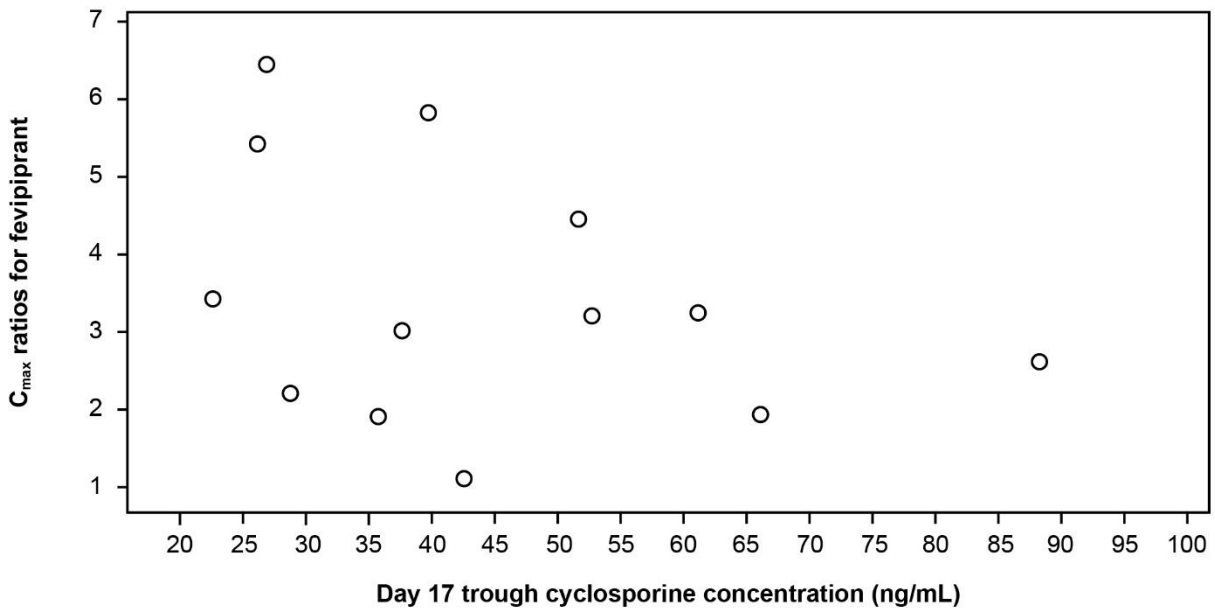
Figure 5



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