

# Pharmacokinetic interaction of riociguat and antiretroviral combination regimens in HIV-1-infected adults

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## Abstract

Riociguat, a first-in-class soluble guanylate cyclase stimulator, is approved for the treatment of pulmonary arterial hypertension (PAH), a serious potential complication of human immunodeficiency virus (HIV) infection. This open-label study investigated the pharmacokinetic drug–drug interaction potential of antiretroviral therapies on riociguat exposure in HIV-infected adults. HIV-infected adults without PAH on stable antiretroviral regimens (efavirenz/emtricitabine/tenofovir disoproxil, emtricitabine/rilpivirine/tenofovir disoproxil, elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil, abacavir/dolutegravir/lamivudine, or a ritonavir-boosted triple regimen) for  $\geq 6$  weeks received a single riociguat dose (0.5 mg). Riociguat pharmacokinetics and safety were assessed; pharmacokinetics was compared with historical healthy volunteer data. Of 41 participants treated ( $n = 8$  in each arm, except  $n = 9$  in the ritonavir-boosted triple regimen arm), 40 were included in the pharmacokinetic analyses. Riociguat median  $t_{\max}$  was 1.00–1.27 h, with comparable maximum concentration ( $C_{\max}$ ) across the five background antiretroviral groups. Riociguat exposure was highest with abacavir/dolutegravir/lamivudine, followed by elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil > emtricitabine/rilpivirine/tenofovir disoproxil > ritonavir-boosted triple regimen > efavirenz/emtricitabine/tenofovir disoproxil; riociguat area under the plasma concentration versus time curve (AUC) was approximately threefold higher with abacavir/dolutegravir/lamivudine than efavirenz/emtricitabine/tenofovir disoproxil. Compared with historical data, riociguat exposure in HIV-infected adults was similar when co-administered with efavirenz/emtricitabine/tenofovir disoproxil, slightly increased when administered with ritonavir-boosted triple regimen and increased by approximately threefold when administered with abacavir/dolutegravir/lamivudine. Riociguat was well tolerated, with no new safety findings. Riociguat was well tolerated in adults with HIV on stable background antiretroviral therapy although an apparent increase in AUC of riociguat was observed in patients receiving abacavir/dolutegravir/lamivudine. Patients should be monitored closely during riociguat initiation and dose adjustment for signs and symptoms of hypotension.

## Keywords

HIV, soluble guanylate cyclase, pulmonary arterial hypertension, drug exposure

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## Introduction

By the end of 2017, around 36.9 million people were infected with the human immunodeficiency virus type 1 (HIV-1).<sup>1</sup> Although not curative, the use of modern antiretroviral therapy (ART) has led to a significant reduction in the incidence of acquired immune deficiency syndrome (AIDS) and mortality from HIV-1 infection.<sup>2,3</sup> However, while the incidence of opportunistic infections is decreasing in individuals

with HIV-1, non-AIDS HIV-related complications, including pulmonary arterial hypertension (PAH), are emerging as new causes of mortality.<sup>4,5</sup>

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PAH is an underdiagnosed and potentially fatal complication of HIV infection.<sup>6,7</sup> It is estimated to affect approximately 0.5% of adults with HIV,<sup>8,9</sup> which is much higher than the estimated prevalence of 1–2 per million for PAH in the general population.<sup>10</sup> PAH associated with HIV (HIV-PAH) is characterized by increased pulmonary vascular resistance due to progressive remodeling of the pulmonary vasculature, which can ultimately lead to death due to right heart failure.<sup>11–14</sup> As the pathogenesis of HIV-PAH appears to involve similar processes as seen in idiopathic PAH, the response to PAH-targeted therapies is anticipated to be similar.<sup>15,16</sup> Current PAH treatment guidelines therefore recommend using the same treatment algorithm for patients with HIV-PAH as for those with idiopathic PAH, while taking into consideration co-morbidities and potential drug–drug interactions with ART.<sup>12</sup> A retrospective review of 77 patients with HIV-PAH treated at a French reference center for pulmonary hypertension (PH) found that the addition of PAH-targeted therapy to ART improved patients' hemodynamics and exercise capacity compared with ART alone.<sup>17</sup> A number of different classes of PAH-targeted therapies are indicated for idiopathic PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase type 5 inhibitors (PDE5i), prostacyclins, and a soluble guanylate cyclase stimulator (riociguat). However, there have been no randomized controlled trials to date that have specifically investigated the treatment of HIV-PAH with PAH-targeted therapies; current therapy recommendations are based on case reports, cohort studies, case-control studies, and case series. As such, no specific therapy of choice for HIV-PAH has yet been established.<sup>10,12,18</sup>

Pharmacokinetic interactions between antiretroviral drugs and concomitant medications are common and complex; several of these agents are both inducers and/or inhibitors of cytochrome P450 (CYP) enzymes. Of note, the protease inhibitor ritonavir is a strong inhibitor of CYP3A4 and is often included in ART regimens to “boost” the plasma concentrations of other protease inhibitors in the regimen that are metabolized via this isoenzyme; it can, however, cause increased exposure to other concomitant medications that are also metabolized by CYP3A4. Several PAH-targeted agents, including the PDE5i sildenafil and tadalafil and the ERA bosentan, have warnings or contraindications for their use with ritonavir or other strong CYP3A4 inhibitors in the treatment of PAH, which can lead to increases in their exposure.<sup>19–24</sup> While the effect of ritonavir on the pharmacokinetics of the ERA macitentan has not been assessed, it is expected to increase macitentan exposure.<sup>25,26</sup>

Riociguat is a first-in-class guanylate cyclase stimulator approved for the treatment of PAH and chronic thromboembolic pulmonary hypertension, at doses of up to 2.5 mg three times daily (t.i.d.) (individually dose-adjusted from a starting dose of 1.0 mg).<sup>12,27,28</sup> In the pivotal, randomized controlled phase 3 trial, PATENT-1, riociguat was well tolerated and significantly improved exercise capacity,

functional status, and hemodynamics compared with placebo in patients with PAH.<sup>29</sup> In addition, the benefits of riociguat therapy on exercise capacity and functional status were sustained at two years, with no new safety signals identified, in the long-term extension study, PATENT-2.<sup>30</sup> However, patients with HIV were excluded from PATENT-1 as the potential for drug–drug interactions between riociguat and antiretroviral was unknown at the time. Riociguat is mainly metabolized by CYP1A1, CYP3A4, CYP3A5, and CYP2J2, with CYP1A1 primarily responsible for formation of the major active metabolite M1, which has one-tenth to one-third the biologic activity of riociguat.<sup>31</sup> In general, riociguat is considered to have a relatively low risk of clinically relevant drug interactions due to its clearance by multiple CYP enzymes and excretion by the transporter proteins P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and a lack of effect on major CYP isoforms at therapeutic levels.<sup>31</sup> Riociguat has a high bioavailability (> 90%),<sup>31</sup> a mean half-life of approximately 7 h in healthy individuals, and approximately 12 h in patients with PAH, and is excreted via both renal and biliary/fecal routes.<sup>31</sup>

This study evaluated the pharmacokinetic drug–drug interaction potential of commonly used ARTs on riociguat exposure in adults with HIV and compared the riociguat pharmacokinetic parameters with those obtained from historical pharmacokinetic studies of riociguat alone in healthy volunteers.

## Methods

### Study design and participants

This was a single-dose, open-label, non-blinded, non-placebo-controlled study (NCT02556268) conducted in two centers in the USA between 23 February 2016 and 7 December 2016. Adults aged 18–64 years with a confirmed diagnosis of HIV receiving a stable fixed-dose antiretroviral combination regimen of efavirenz/emtricitabine/tenofovir disoproxil fumarate (ATRIPLA<sup>®</sup>, Gilead Sciences, Inc.), emtricitabine/rilpivirine/tenofovir disoproxil fumarate (COMPLERA<sup>®</sup>, Gilead Sciences, Inc.), elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (STRIBILD<sup>®</sup>, Gilead Sciences, Inc.), or abacavir/dolutegravir/lamivudine (TRIUMEQ<sup>®</sup>, ViiV Healthcare), or a ritonavir-boosted triple regimen for  $\geq 6$  weeks, with no clinical evidence of PH (i.e. non-PAH patients), were eligible for inclusion. Adults with a diagnosis of PH, coronary artery disease, symptomatic postural hypotension (or systolic blood pressure < 100 mmHg), history of asthma or other airway disease, severe hepatic or renal (creatinine clearance < 15 mL/min or on dialysis) impairment, or a condition likely to affect the pharmacokinetics of riociguat were excluded. In addition, participants were not allowed to receive nitrates/nitric oxide donors within 48 h before to 24 h after riociguat administration, PDE5i within four days before to 24 h after riociguat administration, antacids within 2 h before

and 1 h after riociguat administration, and broad-spectrum CYP inhibitors/charcoal dishes/grapefruit juice/St John's Wort within two weeks before to 48 h after riociguat administration. No more than two participants in each group could be current smokers. All participants provided written informed consent. The study protocol was approved by the institutional review board of the Boston University School of Medicine and was conducted in accordance with local legal and regulatory requirements and the Declaration of Helsinki guidelines for Good Clinical Practice.

Participants received a single oral dose of riociguat 0.5 mg in addition to their background ART in the morning following a fasting period of  $\geq 10$  h, followed by a further 4-h fast. A low riociguat dose of 0.5 mg was selected for this study (compared with the recommended starting dose of 1.0 mg t.i.d. in idiopathic PAH) based on the potential for a decrease in systemic blood pressure in the event of drug–drug interaction resulting in increased riociguat exposure (0.5 mg was the suggested starting dose for patients on strong CYP inhibitors or those who may not tolerate the hypotensive effect of riociguat).<sup>28</sup> Following riociguat administration, participants were monitored for two days.

### Pharmacokinetic evaluations

Blood samples for pharmacokinetic analyses were taken at baseline, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 24, and 48 h after administration. Riociguat and M1 plasma concentrations were analyzed by high-pressure liquid chromatography and tandem mass spectrometric detection, using internal standards. The calibration range for both riociguat and M1 was from 2  $\mu\text{g/L}$  (the lower limit of quantitation [LLOQ]) to 500  $\mu\text{g/L}$  (the upper limit of quantitation). Quality control samples were determined in the range of 6–400  $\mu\text{g/L}$  (for both analytes), with an accuracy of 100.0% and 99.6–102.0% and a precision of 2.49–2.70% and 2.28–2.62% for riociguat and M1, respectively.

The primary pharmacokinetic parameters, area under the concentration versus time curve from 0 to infinity after single dose (AUC) and maximum drug concentration in plasma after single-dose administration ( $C_{\text{max}}$ ), were calculated for riociguat and its main metabolite, M1. Additional pharmacokinetic parameters assessed included AUC from time 0 to the last data point  $>$  LLOQ (AUC[0– $t_{\text{last}}$ ]), time to reach  $C_{\text{max}}$  ( $t_{\text{max}}$ ); in case of two identical  $C_{\text{max}}$  values, the first  $t_{\text{max}}$  was used, half-life associated with the terminal slope ( $t_{1/2}$ ), apparent total clearance of study drug from plasma (CL/F), apparent volume of distribution during terminal phase ( $V_z/F$ ), AUC divided by dose per body weight (AUC<sub>norm</sub>), and  $C_{\text{max}}$  divided by dose per body weight ( $C_{\text{max, norm}}$ ). Pharmacokinetic parameters were calculated using a model-independent (compartment-free) method and the computer program WinNonlin v5.3 (Pharsight Corporation) with the Automation Extension v2.90 (Bayer AG).

Given the need to maintain ART in HIV-infected participants, a crossover design to compare pharmacokinetic parameters for riociguat plus ART versus riociguat alone was not possible. Therefore, a pre-specified integrated pharmacokinetic analysis was conducted to compare the pharmacokinetic data from this study with historical pharmacokinetic data for a single dose of 0.5 mg riociguat alone in two previously published studies of riociguat in healthy volunteers: (1) Study 1 investigated the pharmacokinetics of a single oral dose of 0.5 mg riociguat when co-administered with ketoconazole versus 0.5 mg riociguat alone in 16 healthy male individuals;<sup>32</sup> and (2) Study 2 was a five-way crossover study in 24 healthy male individuals to investigate the dose proportionality of riociguat pharmacokinetics given as single oral doses of 0.5, 1.0, 1.5, 2.0, and 2.5 mg.<sup>33</sup> These studies were selected because of the availability of exposure data for a riociguat 0.5 mg dose, including in fasted state for Study 2, and because their study populations had comparable baseline characteristics to the current study, including smoking status.

### Safety and tolerability

Safety was assessed as occurrence of treatment-emergent adverse events (AEs) and readings for vital signs, electrocardiogram, and laboratory parameters. Supine and/or sitting blood pressure readings were taken regularly, at times generally corresponding with blood sampling.

### Statistical analyses

**HIV-infected adults.** The planned sample size was eight patients per background antiretroviral group to give 80% power to detect an increase in AUC of riociguat (one-sided t-test of mean ratio with log-normal data,  $\alpha=0.05$ ,  $N_2=16$ ). This was estimated based on the mean historic coefficient of variation (CV) of AUC for riociguat of 97% from Studies 1 and 2, and a true mean AUC ratio of 2.5 for background antiretroviral group/riociguat alone.

The riociguat pharmacokinetic analysis set comprised all participants who completed the study with valid pharmacokinetic profiles of riociguat. For pharmacokinetic analyses, participants were stratified into five groups according to background ART. Statistical analyses were performed using the software package SAS release 9.2. Summary pharmacokinetic statistics are presented as geometric mean and percentage CV unless otherwise stated.

**Integrated pharmacokinetic analysis.** In the integrated pharmacokinetic analysis, the impact of background antiretroviral on AUC and  $C_{\text{max}}$  of riociguat and M1 was analyzed assuming log-normally distributed data. An analysis of variance (ANOVA) was performed on the logarithms of AUC and  $C_{\text{max}}$  for riociguat and M1. Data were calculated as point estimates (least squares [LS] means) and exploratory 90%

confidence intervals (CI) for the ratios “background antiretroviral group/riociguat alone.” Study 1 was excluded from the historical comparison for  $C_{max}$ , since in this study riociguat was administered 20 min after a standard breakfast (while food has minimal impact on the AUC of riociguat, it has been shown to decrease  $C_{max}$ ).<sup>32,33</sup> LS mean ratios with 90% CIs are presented as forest plots.

## Results

### Participants

Of 47 individuals screened, 41 met the eligibility criteria and received a single dose of 0.5 mg riociguat ( $n=8$  patients in each of the fixed-dose combination groups and  $n=9$  in the ritonavir-boosted triple regimen group). All 41 participants completed the study and are included in the safety evaluation; 40 participants were evaluable for pharmacokinetic analysis.

Baseline characteristics were generally comparable between the five background antiretroviral groups (Table 1). The overall study population had a mean age of 40.8 years (age range = 24–62 years) and was predominantly male (78%). Participants in the group “ritonavir-boosted triple regimen” received stable dose combinations of atazanavir or darunavir with ritonavir and emtricitabine and tenofovir disoproxil.

### Pharmacokinetic analyses

Riociguat plasma concentration–time profiles for the five background antiretroviral groups are shown in Fig. 1.

Mean plasma concentrations of riociguat were calculated up to 8 h after administration for all background antiretroviral groups, with at least two-thirds of individual values above the LLOQ. Riociguat was rapidly absorbed; median  $t_{max}$  was in the range of 1.00–1.27 h across the five background antiretroviral groups (Table 2).  $C_{max}$  for riociguat was broadly comparable across all five background antiretroviral groups (range = 14.2–20.4  $\mu\text{g/L}$ ) (Table 2). There were large differences between the regimens studied in terms of the effect on riociguat AUC. Riociguat exposure was highest with abacavir/dolutegravir/lamivudine, followed by elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil > emtricitabine/rilpivirine/tenofovir disoproxil > ritonavir-boosted triple regimen > efavirenz/emtricitabine/tenofovir disoproxil. The AUC for riociguat was approximately threefold higher with background abacavir/dolutegravir/lamivudine than with background efavirenz/emtricitabine/tenofovir disoproxil (Table 2, Fig. 1).

Concentrations of M1 were below the LLOQ in many samples and plasma concentration versus time curves could only be calculated up to 8 h for the background efavirenz/emtricitabine/tenofovir disoproxil and ritonavir-boosted triple regimen groups, with plasma concentrations above LLOQ rarely measured at 24 h after administration in

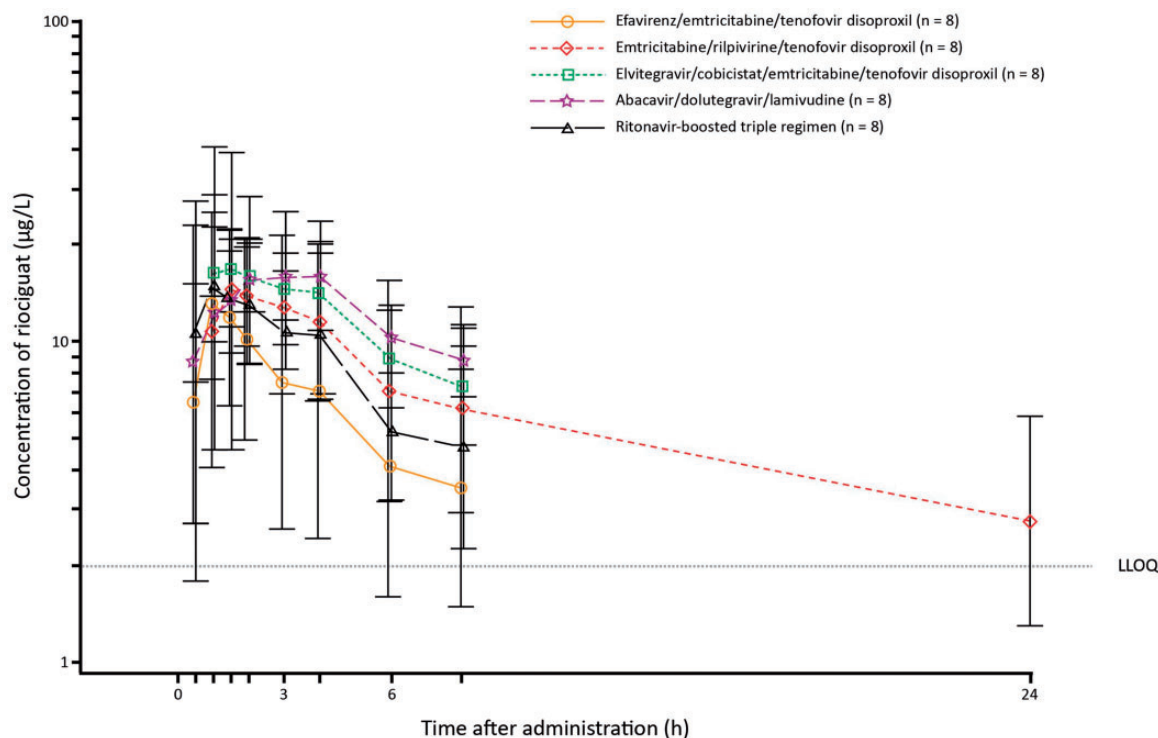
**Table 1.** Demographics, according to background ART (safety analysis population).

Characteristic	Background antiretroviral regimen					Total ( $n=41$ )
	Efavirenz/ emtricitabine/ tenofovir disoproxil (ATRIPLA <sup>®</sup> ) ( $n=8$ )	Emtricitabine/ rilpivirine/ tenofovir disoproxil (COMPLERA <sup>®</sup> ) ( $n=8$ )	Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil (STRIBILD <sup>®</sup> ) ( $n=8$ )	Abacavir/ dolutegravir/ lamivudine (TRIUMEQ <sup>®</sup> ) ( $n=8$ )	Ritonavir-boosted triple regimen ( $n=9$ )*	
Age (years), mean (range)	44.6 (32–57)	38.3 (24–50)	37.8 (27–49)	34.5 (26–54)	47.9 (33–62)	40.8 (24–62)
Male	6 (75)	7 (88)	7 (88)	6 (75)	6 (67)	32 (78)
Race						
White	5 (63)	4 (50)	6 (75)	5 (63)	4 (44)	24 (59)
Black/African American	3 (38)	3 (38)	2 (25)	2 (25)	5 (56)	15 (37)
American Indian/Native Alaskan	0	1 (13)	0	0	0	1 (2)
Weight (kg), mean (SD)	84.9 (11.2)	95.7 (33.7)	95.1 (22.1)	77.7 (17.3)	88.6 (20.6)	88.4 (22.1)
Height (cm), mean (SD)	171.8 (6.5)	178.0 (11.3)	177.8 (10.9)	171.1 (8.6)	176.1 (9.9)	175.0 (9.6)
BMI ( $\text{kg/m}^2$ ), mean (SD)	28.9 (4.6)	29.7 (8.9)	29.9 (5.3)	26.4 (4.5)	28.5 (5.7)	28.7 (5.9)
Smoking history						
Never	4 (50)	7 (88)	7 (88)	5 (63)	4 (44)	27 (66)
Former	3 (38)	1 (13)	1 (13)	1 (13)	4 (44)	10 (24)
Current	1 (13)	0	0	2 (25)	1 (11)	4 (10)

Values are presented as  $n$  (%) unless otherwise specified.

\*Pharmacokinetic (PK) data are not reported for one patient in this group. Percentages may not add up to 100% due to rounding.

BMI, body mass index; SD, standard deviation.



**Fig. 1.** Riociguat plasma concentration vs. time curve following a single 0.5 mg dose of riociguat in adults with HIV on background ART. ART, antiretroviral therapy; HIV, human immunodeficiency virus; LLOQ, lower limit of quantitation; SD, standard deviation.

**Table 2.** Summary of riociguat pharmacokinetics parameters following a single 0.5 mg dose of riociguat in adults with HIV on background ART.

Parameter	Background antiretroviral regimen				
	Efavirenz/ emtricitabine/ tenofovir disoproxil (ATRIPLA®) (n = 8)	Emtricitabine/ rilpivirine/ tenofovir disoproxil (COMPLERA®) (n = 8)	Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil (STRIBILD®) (n = 8)	Abacavir/ dolutegravir/ lamivudine (TRIUMEQ®) (n = 8)	Ritonavir-boosted triple regimen (n = 8)
AUC (µg*h/L)	95.5 <sup>†</sup> /105 (22.5–415)	185/103 (29.2–429)	185/74.1 (90.4–538)	255/65.8 (115–662)	116/74.6 (39.8–281)
AUC <sub>norm</sub> (kg*h/L)	16.3 <sup>†</sup> /108 (3.85–76.1)	33.4/155 (3.56–109)	34.5/73.4 (15.6–92.0)	38.8/75.3 (15.0–94.4)	20.6/82.3 (5.68–46.8)
AUC(0–t <sub>last</sub> ) (µg*h/L)	51.8/175 (5.90–280)	125/97.6 (21.1–322)	148/79.1 (72.0–461)	170/43.5 (96.0–298)	90.6/75.5 (32.5–231)
C <sub>max</sub> (µg/L)	14.2/56.3 (5.34–27.4)	16.3/23.0 (11.8–21.6)	20.4/25.9 (15.0–34.5)	20.0/46.4 (8.82–39.9)	15.8/41.0 (8.94–35.7)
C <sub>max, norm</sub> (kg/L)	2.39/60.1 (0.823–5.03)	2.94/41.1 (1.44–4.63)	3.78/26.7 (2.46–5.90)	3.05/48.8 (1.26–4.92)	2.82/47.5 (1.28–5.94)
t <sub>max</sub> * (h)	1.00 (0.550–2.00)	1.03 (0.500–3.03)	1.03 (0.500–4.05)	1.27 (0.533–6.00)	1.03 (0.550–1.50)
t <sub>1/2</sub> (h)	4.12 <sup>†</sup> /69.7 (2.54–16.2)	9.22/120 (1.80–24.6)	6.69/101 (2.33–19.0)	8.72/136 (2.64–50.6)	5.00/78.1 (2.25–11.6)
V <sub>z</sub> /F (L)	31.1 <sup>†</sup> /50.1 (17.9–81.5)	35.9/35.5 (18.6–47.6)	26.0/32.2 (13.7–35.9)	24.7/48.0 (13.1–55.1)	31.1/28.9 (20.3–44.8)
CL/F (L/h)	5.23 <sup>†</sup> /105 (1.21–22.2)	2.70/103 (1.17–17.1)	2.70/74.1 (0.930–5.53)	1.96/65.8 (0.756–4.35)	4.32/74.6 (1.78–12.6)

Data are presented as geometric mean /%CV (range).

\*Median (range).

<sup>†</sup>n = 7.

AUC, area under the concentration vs. time curve from 0 to infinity after single (first) dose; AUC<sub>norm</sub>, AUC divided by dose per body weight; AUC(0–t<sub>last</sub>), AUC from time 0 to the last data point >lower limit of quantitation; CL/F, apparent total clearance of study drug from plasma; C<sub>max</sub>, maximum drug concentration in plasma after single dose administration; C<sub>max, norm</sub>, C<sub>max</sub> divided by dose per body weight; CV, coefficient of variation; HIV, human immunodeficiency virus; t<sub>1/2</sub>, half-life associated with the terminal slope; t<sub>max</sub>, time to reach C<sub>max</sub> (in case of two identical C<sub>max</sub> values, the first t<sub>max</sub> was used); V<sub>z</sub>/F, apparent volume of distribution during terminal phase.

any background antiretroviral group. As a result, reliable pharmacokinetic parameters for M1 could not be calculated and a reasonable estimate of M1 exposure was not possible in this study.

### Comparison with historical pharmacokinetic data in healthy volunteers

The integrated riociguat pharmacokinetic analysis included data from 40 participants with HIV on background antiretroviral in the current study and 40 healthy volunteers in the historical studies (Study 1,  $n=16$ ; Study 2,  $n=24$ ). Baseline characteristics of age, sex, race, weight, body mass index (BMI), and smoking status were generally comparable across the studies (Table S1). Most individuals (83%) were non-smokers.

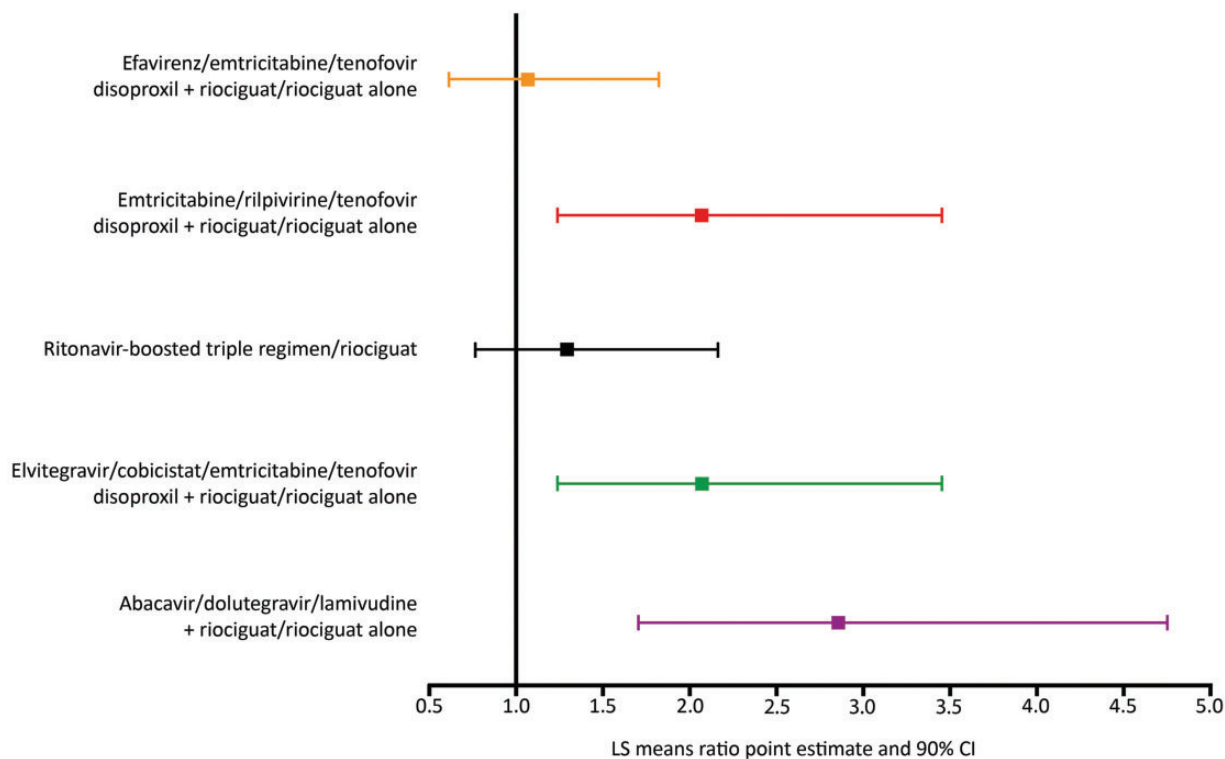
Compared with historical healthy volunteers, riociguat exposure in adults with HIV was similar when co-administered with efavirenz/emtricitabine/tenofovir disoproxil, slightly increased when administered with the ritonavir-boosted triple regimen, and increased by approximately threefold when administered with abacavir/dolutegravir/lamivudine (Fig. 2). Mean  $C_{max}$  values were in a similar range across the groups studied, with large overlaps in 90% CIs (Fig. 3). For M1, pharmacokinetic parameters could not be reliably calculated due to many samples having concentrations below the LLOQ.

### Safety

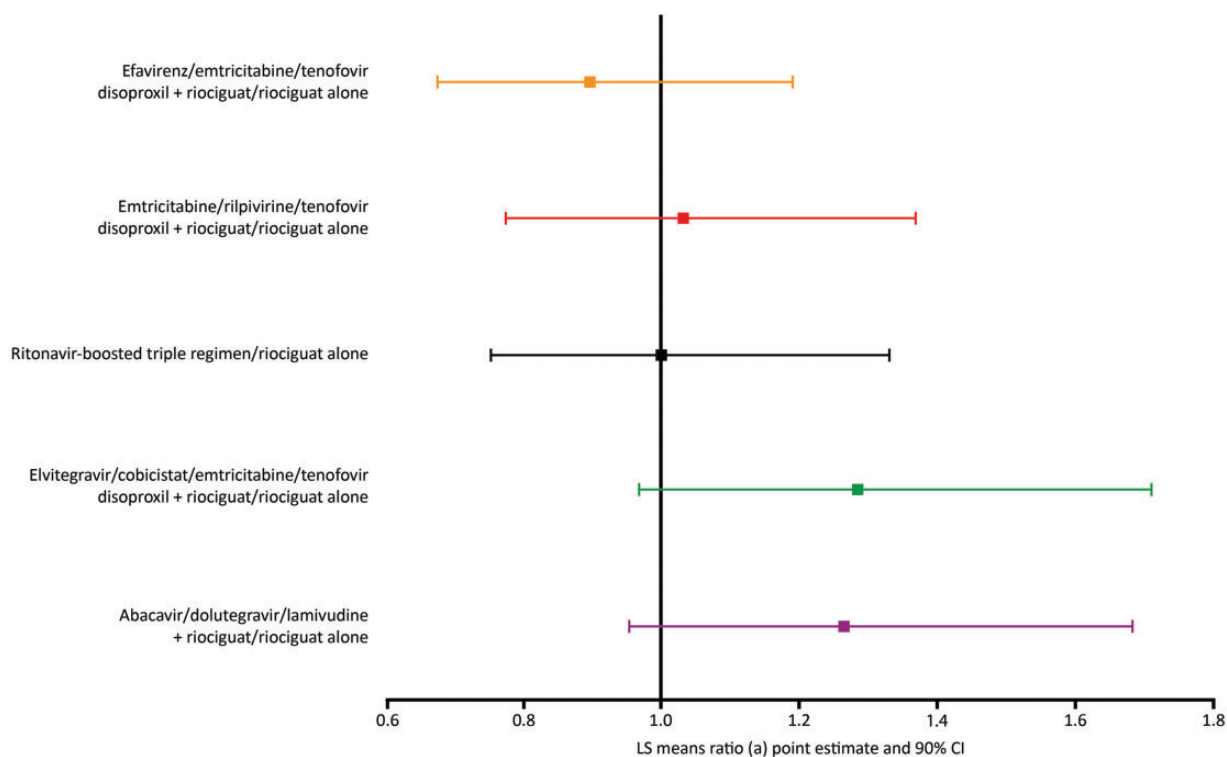
Overall, riociguat was well tolerated, with no serious AEs, AEs leading to discontinuation, or deaths reported in the study. Ten participants (24%) experienced a treatment-emergent AE during the study, most commonly headache (four participants, 10%) and fatigue (two participants, 5%). The incidence of AEs for riociguat was comparable among the five background antiretroviral groups (Table 3). All AEs were mild or moderate in intensity. Four AEs were considered related to riociguat in three participants: headache (one participant on background emtricitabine/rilpivirine/tenofovir disoproxil and two participants on background ritonavir-boosted triple regimen) and stomach cramps (one participant on background ritonavir-boosted triple regimen). All riociguat-related AEs were resolved by study end. No clinically significant changes were observed in vital signs, electrocardiogram, or laboratory parameters. No AEs related to decreased blood pressure or hypotension were reported.

### Discussion

There is an urgent need for well tolerated and effective treatment options for patients with HIV-PAH. Importantly, there needs to be a clear understanding of how PAH-targeted therapies interact with antiretrovirals. This study evaluated the potential drug–drug interaction between riociguat



**Fig. 2.** Forest plot of area under the concentration vs. time curve for riociguat following a single 0.5 mg dose of riociguat in adults with HIV on background ART compared with when given alone in healthy volunteers ( $n = 80$ ; historical data, including Study 1 individuals in the fed state and Study 2 individuals in the fasted state). CI, confidence interval; LS, least squares.



**Fig. 3.** Forest plot of maximum drug concentration in plasma after single dose administration for riociguat following a single 0.5 mg dose of riociguat in adults with HIV on background ART compared with when given alone in healthy volunteers (n = 64; historical data from Study 2, fasted state). HIV, human immunodeficiency virus; LS, least squares. (a) calculated by re-transformation of the logarithmic data.

**Table 3.** Adverse events (AE) following a single 0.5 mg dose of riociguat in adults with HIV on background ART.

AE	Background antiretroviral regimen					Total (n = 41)
	Efavirenz/ emtricitabine/ tenofovir disoproxil (ATRIPLA®) (n = 8)	Emtricitabine/ rilpivirine/ tenofovir disoproxil (COMPLERA®) (n = 8)	Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil (STRIBILD®) (n = 8)	Abacavir/ dolutegravir/ lamivudine (TRIUMEQ®) (n = 8)	Ritonavir-boosted triple regimen (n = 9)	
Any AE	1 (13)	3 (38)	2 (25)	2 (25)	2 (22)	10 (24)
Headache	0	1 (13)	0	1 (13)	2 (22)	4 (10)
Fatigue	0	0	1 (13)	1 (13)	0	2 (5)
Diarrhea	0	0	0	0	1 (11)	1 (2)
Dizziness	0	0	1 (13)	0	0	1 (2)
Lip swelling	0	0	1 (13)	0	0	1 (2)
Oral paresthesia	1 (13)	0	0	0	0	1 (2)
Oropharyngeal pain	0	1 (13)	0	0	0	1 (2)
Pain	0	1 (13)	0	0	0	1 (2)
Pyrexia	0	0	0	1 (13)	0	1 (2)
Upper abdominal pain	0	0	0	0	1 (11)	1 (2)
Urethritis	0	1 (13)	0	0	0	1 (2)

Values are presented as n (%).

and five different, commonly used antiretroviral regimens in HIV-infected adults, and compared riociguat pharmacokinetics with those previously reported in healthy volunteers. The findings showed that a single 0.5 mg dose of riociguat administered in combination with different antiretroviral regimens was well tolerated in HIV-infected adults. Riociguat exposures ranged from no apparent change when co-administered with efavirenz/emtricitabine/tenofovir disoproxil to an approximately threefold increase with abacavir/dolutegravir/lamivudine. These findings indicate a lack of interaction potential between riociguat and efavirenz/emtricitabine/tenofovir disoproxil and low potential for interaction with emtricitabine/rilpivirine/tenofovir disoproxil in terms of effect on riociguat exposure, supporting the combination of riociguat with these agents from a pharmacokinetic perspective in HIV-infected adults.

The interaction between riociguat and abacavir/dolutegravir/lamivudine had not been anticipated based on previous reports of the major biotransformation pathways for the components of this regimen.<sup>27,28,34–43</sup> Riociguat is mainly metabolized by *N*-demethylation, catalyzed primarily by CYP1A1 and, to a lesser extent, by CYP3A4, CYP3A5, and CYP2J2; ~27–71% of the riociguat dose is eliminated by oxidative biotransformation.<sup>31</sup> The potential for interaction between riociguat and abacavir/dolutegravir/lamivudine was considered low as the antiretroviral agents in this triple combination do not affect CYP3A at clinical concentrations.<sup>34–43</sup> However, the inhibitory potential of these agents on CYP1A1, the main metabolic enzyme for riociguat, is currently not reported in the literature. Following the findings of the current study, additional *in vitro* studies have been conducted to investigate the mechanisms by which antiretroviral regimens influence the metabolic clearance of riociguat, focusing on CYP1A1 and CYP3A4 isoenzymes; findings will be reported in a separate publication.

According to the US label, riociguat should be started at a dose of 0.5 mg t.i.d. when co-administered with strong CYP inhibitors and P-gp/BCRP inhibitors, such as ketoconazole and HIV protease inhibitors; patients should be carefully monitored for signs and symptoms of hypotension.<sup>28</sup> Co-administration of ketoconazole with a single dose of 0.5 mg riociguat in 16 healthy volunteers resulted in an increase in mean  $AUC_{0-\infty}$  by 2.5-fold compared with controls.<sup>32</sup> The mechanism by which riociguat exposure is increased by abacavir/dolutegravir/lamivudine is currently unclear, but is likely to be different than with ketoconazole. Further differences between patients in the abacavir/dolutegravir/lamivudine group and the other groups possibly related to the increase in exposure could not be identified. Patients in the abacavir/dolutegravir/lamivudine group were younger and had lower BMI than the other groups; two were smokers compared with one each in the efavirenz/emtricitabine/tenofovir disoproxil and ritonavir-boosted triple regimen groups, and none in the emtricitabine/rilpivirine/tenofovir disoproxil and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil groups. Age or body weight do

not have a relevant influence on riociguat exposure,<sup>27,28,31</sup> while smoking reduces riociguat exposure via induction of CYP1A1.<sup>31</sup> These differences between populations therefore probably had no relationship to the higher exposure in the abacavir/dolutegravir/lamivudine group.

Regardless, the similar magnitude of increase in riociguat exposure seen with abacavir/dolutegravir/lamivudine as with ketoconazole suggests similar precautions would be advisable when initiating riociguat in HIV-infected adults receiving abacavir/dolutegravir/lamivudine. Riociguat doses should be individually dose-adjusted up to a maximum of 2.5 mg t.i.d., although reaching the maximum dose is not a prerequisite for achieving an optimal clinical response;<sup>44</sup> riociguat doses <2.5 mg t.i.d. may have a similar efficacy to higher doses in some patients, e.g. those with higher exposure to riociguat due to renal or hepatic impairment.<sup>45,46</sup> A therapeutic dose <2.5 mg t.i.d. may therefore be appropriate in some HIV-infected individuals receiving ART although, notably, riociguat was well tolerated in adults receiving background abacavir/dolutegravir/lamivudine, despite the increase in exposure.

Pharmacokinetic interactions have been reported between other PAH-targeted therapies, such as bosentan, sildenafil, and tadalafil, and antiretroviral agents, in particular the HIV protease inhibitor ritonavir.<sup>19–24</sup> For example, co-administration of ritonavir (500 mg twice daily) with sildenafil (100 mg single dose) resulted in a fourfold increase in sildenafil  $C_{max}$  and an 11-fold increase in sildenafil plasma AUC.<sup>47</sup> Based on these results, co-administration of sildenafil with ritonavir is not advised in the US and is contraindicated in the EU.<sup>19,20</sup> Ritonavir (200 mg twice daily) has been shown to increase the single-dose exposure to tadalafil 20 mg by 124% with no change in  $C_{max}$ ; it is expected that other HIV protease inhibitors would also increase tadalafil exposure.<sup>22</sup> As such, concomitant use of tadalafil and ritonavir requires close monitoring and dose adjustment in the US label and is not recommended in the EU label.<sup>21,22</sup> Experience with bosentan in patients with HIV-PAH is limited. An interaction study in healthy individuals showed increased plasma concentrations of bosentan when the drug was co-administered with lopinavir and ritonavir; patients requiring ritonavir-boosted protease inhibitors require dose adjustment and should be closely monitored during bosentan initiation and treatment due to the risk of hypotension and liver toxicity. In addition, due to its inducing effects on CYP, bosentan potentially may reduce the efficacy of ART and patients should be monitored carefully for worsening of their HIV infection.<sup>23,24</sup> While the effects of strong CYP3A4 inhibitors such as ritonavir on macitentan pharmacokinetics have not been studied, they are considered likely to result in an increase in macitentan exposure at steady state similar to that seen with ketoconazole, and co-administration is not recommended.<sup>25,26</sup>

There are limitations to this study. First, the study did not include a riociguat alone control arm, as this would not be ethically acceptable in HIV-infected individuals, and



hence the comparison with historical pharmacokinetic data for riociguat alone in healthy volunteers was necessary. The two healthy volunteer studies were pre-specified and carefully selected; they both assessed riociguat 0.5 mg, including in the fasted state for one study, and the study populations were comparable in terms of baseline characteristics with the current study in HIV-infected adults. Second, the relatively small group sizes may have led to the large variations seen in LS mean ratios for AUC. Finally, the dose of 0.5 mg riociguat used in this study was lower than the recommended starting dose of 1.0 mg t.i.d. in patients with idiopathic PAH;<sup>27,28</sup> this is in line with US prescribing recommendations for when riociguat is initiated in patients receiving strong CYP inhibitors and P-gp/BCRP inhibitors due to the potential for increased riociguat exposure and increased risk of hypotension.<sup>28</sup> The low dose of riociguat likely contributed to the low plasma concentrations of M1 and inability to obtain reliable M1 pharmacokinetic parameters. In addition, low plasma concentrations of riociguat beyond 8 h after administration resulted in the riociguat AUC being afflicted with a high extrapolated portion.

In conclusion, riociguat was well tolerated in adults with HIV receiving ART. Riociguat exposure, when co-administered with antiretrovirals, ranged from no apparent change with efavirenz/emtricitabine/tenofovir disoproxil to an approximately threefold increase with abacavir/dolutegravir/lamivudine. In patients on stable antiretroviral regimens, particularly abacavir/dolutegravir/lamivudine, riociguat should be initiated at a dose of 0.5 mg t.i.d. and individually dose-adjusted; patients should be monitored closely during treatment initiation and dose adjustment for signs and symptoms of hypotension. A maximum dose less than the recommended 2.5 mg t.i.d. may be appropriate in some patients receiving ART.

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### Conflict of interest

ED reports research grants from Gilead Science; advisory board membership with Gilead Science, Janssen Pharmaceutical, and Thera-Therapeutics; and speakers' bureaus with Gilead Science and Thera-Therapeutics. SC has nothing to disclose. SS, DvdM, CB, RF, SU, and WM are full-time employees of Bayer AG.

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