Drug-Drug Interaction Study of Benznidazole and E1224 in Healthy Male Volunteers

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Abstract

E1224 is a prodrug of ravuconazole (RVZ), an antifungal drug with promising anti-
*Trypanosoma cruzi* activity, the causative organism of Chagas disease (CD). This study was
designed to assess the pharmacokinetics (PK) and safety interactions of benznidazole (BNZ),
the drug of choice for treatment of CD, and E1224 in healthy volunteers.

This open-label, single-centre, sequential, single and multiple oral dose study enrolled 28
healthy male subjects. These subjects received BNZ (2.5 mg/kg) once daily on Day 1 and Day
9 and twice daily from Day 12 to Day 15, and E1224 once daily from Day 4 to Day 15
(loading dose of 400 mg for 3 days and maintenance dose of 100 mg for 9 days).

The maximum concentration (C\text{max}) and area under the concentration curve from zero to
infinity for BNZ were comparable whether BNZ was given alone or with E1224 at steady-
state, with the ratios of geometric means for BNZ-RVZ/BNZ of 0.96 and 0.83, and
corresponding 90\% confidence intervals (CI) of [0.91-1.10] and [0.80-0.87], respectively.
However, RVZ C\text{max} and area under the concentration curve from zero to 24 h increased by
about 35\% when concomitantly administered with BNZ at steady-state (ratio of geometric
means for RVZ-BNZ/RVZ of 1.31 and 1.36, and corresponding 90\% CI [1.23-1.39] and
[1.31-1.41], respectively). Both compounds were well tolerated. There were no clinically
relevant safety interactions between E1224 and BZN. Given these results, co-administration
of RVZ and BNZ should not require any adaptation of E1224 dosing.

Keywords: E1224, benznidazole, Chagas disease, *Trypanosoma cruzi*, pharmacokinetics
Introduction

Chagas disease is an important global neglected tropical disease caused by *Trypanosoma cruzi* (*T. cruzi*). Significant mortality and morbidity are observed in 20–30% of those chronically affected, with development of cardiac and digestive organ involvement decades after initial infection. Treatment is mainly based on benznidazole (BNZ) and nifurtimox, two nitro-aromatic compounds developed in the 1960s and 70s (1,2,3).

BNZ, a nitroimidazole derivative, is the drug of choice for treating adults and children with Chagas disease in most countries. After a single administration of 100 mg, the time to maximum plasma concentration (*t*\(_{\text{max}}\)) is about 3.5 h and maximum plasma concentration (*C*\(_{\text{max}}\)) is between 2.2 and 2.6 µg/mL (4). BNZ half-life (*t*\(_{1/2}\)) is about 12 h (ranging from 10.5 h to 13.6 h) (5). Food effect and drug-drug interactions have not been studied and little is known about the metabolism and absorption of BNZ, therefore its interaction with other drugs cannot be easily anticipated. BNZ metabolism is likely to occur via a cytochrome P450 (CYP); CYP1A2, CYP2E1, and CYP2A6 are suspected but the isoenzyme responsible has not yet been clearly identified(6, 7).

This treatment is constrained by safety and tolerability (8,9) issues and there is limited robust data on efficacy in chronic disease (7). BNZ is poorly tolerated, frequently resulting in an interruption of treatment (7,8,9). New, better-tolerated therapeutic options and new treatment regimens are needed.

The prodrug (BF) E1224 is a monolysine form of ravuconazole (RVZ), an inhibitor of ergosterol biosynthesis, more specifically a C14-alpha-demethylase inhibitor. E1224 and ravuconazole showed promising *in vitro* and *in vivo* activity against *T. cruzi* (10, 11, 12). The minimum inhibitory concentration of ravuconazole for *T. cruzi* epimastigotes and amastigores was 300 nmol/L (221 ng/mL) and 1 nmol/L (7.4 ng/mL), respectively (11). No *in vitro* studies have been performed to evaluate the antiprotozoal activity of E1224 itself, as the latter
is readily and completely converted into ravuconazole by plasma dephosphorylase enzymes (e.g., alkaline phosphatase) and would not be expected to demonstrate any intrinsic antiprotozoal activity in assays without metabolic enzymes. E1224 was shown to be curative in murine models of T. cruzi infection (with 71.5% (20 mg/kg and 40 mg/kg), 85.7% (30 mg/kg and 50 mg/kg) and 100% (10 mg/kg) animals cured at the end of a 6-month follow-up period, versus 87.5% for benznidazole at 100 mg/kg) (12). Following single oral administration of E1224, plasma concentrations of RVZ attain peak levels at approximately 2 to 4 h. RVZ has a long t1/2, ranging from a mean of 157 to 221 h (6.6 to 9.2 days) (13). Cmax and area under the concentration curve (AUC) values of RVZ in the plasma increase almost dose-proportionally. After multiple oral dosings, RVZ accumulates over time, but with selection of loading and maintenance doses it is possible to attain steady-state on Day 7. Based on in vitro and in vivo assays, E1224 appears to have a moderate inhibitory effect on CYP3A4, but it showed no clinically important effect on the metabolism of probe drugs mediated by CYP2C19, CYP2D6, and CYP1A2, and no effect on the metabolism of drugs mediated by CYP2C9 (14).

In human studies, E1224 and another ergosterol biosynthesis inhibitor, posaconazole, demonstrated a rapid, but transient suppressive effect on parasite clearance, whilst BZN showed early and sustained efficacy until 12 months (13, 15). Model-based calculations with the maximum observed average concentrations show that if E1224 dose was increased and treatment duration prolonged to e.g. 12 weeks, the probability of relapse would fall below 20%. Since one of the main limitations of BNZ treatment relates to safety, tolerability, and the long duration of treatment, it was hypothesized that combination treatment regimens could potentially impact overall treatment effectiveness and compliance. In addition, depending on the choice of regimen, combination therapy could be used to improve efficacy and potentially reduce the risk of resistance to BNZ (12). In vivo combination studies in murine model
demonstrated that concomitant treatment with E1224 and benznidazole was more effective in reducing circulating parasite levels and inducing parasitological cure than either of the drugs given alone, even against highly drug-resistant organisms (12). BNZ is at least partially metabolised by CYP3A4 and a weak inhibition of BNZ metabolism could therefore be expected with E1224. As no relevant in vivo or in vitro data were available and since BNZ and E1224 are intended to be administered concomitantly in patients with Chagas disease, an in vivo interaction study in healthy subjects was needed. This interaction study in healthy volunteers was designed to assess the pharmacokinetic (PK) interaction of BNZ with E1224. Upon review of the safety and tolerability profiles of these two drugs, the key safety concern was the potential of concomitant administration of these compounds to cause drug-induced liver injury. Indeed, both E1224 and BNZ cause dose-related increases in serum markers (11,13) for hepatocellular injury (alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT)) in a subset of treated patients. Elevations may be consistent with observations with other drugs in their respective classes. It was, therefore, important to examine the impact of interactions between the two compounds, BNZ and E1224, on safety.

Results

The very long half-life of RVZ (more than 200 h) did not allow a classical randomized cross-over design with two successive periods of treatment. With the design chosen, it was possible to study the effect of E1224 on the PK disposition of BNZ and the effect of BNZ on the PK disposition of E1224. The effect on E1224 was studied at steady-state and the effect on BNZ was studied after a single dose.

Subject disposition: Between November and December 2014, a total of 28 healthy male subjects were randomized at one study site in Argentina. All the subjects received BNZ 2.5 mg/kg once a day on Day 1 and Day 9 and then 2.5 mg/kg twice a day (12 h apart) from Day 12 to Day 15, and E1224 once a day from Day 4 to Day 15 with a loading dose of 400
mg once daily from Day 4 to Day 6 followed by a maintenance dose of 100 mg once daily from Day 7 to Day 15. All the subjects completed the study.

**Baseline characteristics**

Subjects were aged from 18 to 45 years (mean, 29 years) and with BMI of 18.3-28.0 kg/m² (Table 1). Some minor abnormalities were reported in baseline levels of laboratory (biochemistry and haematology) parameters. Three study subjects had ALAT levels above the normal upper limit, with values between 41 and 53 IU/L, for a normal upper limit <40 IU/L, while only one subject had elevated ASAT with value of 69 IU/L for a normal upper limit <40 IU/L.

**Pharmacokinetics**

The mean BNZ concentration-time profiles after BNZ administration in the absence or presence of E1224 are shown in Figure 1. The summary statistics for BNZ PK parameters are shown in Table 2. Following administration of BNZ with E1224, the geometric mean (GM) of BNZ $C_{\text{max}}$ decreased by 4% (3221 ng/mL vs. 3,364 ng/mL) and the GM of the area under the concentration-time curve from time zero to infinity ($\text{AUC}_{0-\infty}$) and AUC from time zero to the last quantifiable concentration ($\text{AUC}_{0-t}$) decreased by 16% (61,162 and 59,299 ng.h/mL, respectively, vs. 72,720 and 70,559 ng.h/mL). Median $t_{\text{max}}$ was similar in both conditions (3 h). The GM of $t_{1/2}$ were also comparable when BNZ was administered alone or with E1224 (12 vs. 10 h). Formal statistical analyses supported the above observations since the 90% confidence intervals (CI) for $C_{\text{max}}$ [0.91-1.10] and $\text{AUC}_{0-\infty}$ [0.80-0.87] were within or very close to the reference range for bioequivalence [0.80-1.25](16). Corresponding point estimates were 0.96 for $C_{\text{max}}$ and 0.83 for $\text{AUC}_{0-\infty}$.

Following multiple dose administration of E1224, the pre-dose concentration of RVZ from Day 6 to Day 16 (*i.e.* from 2 days to 12 days of administration) is presented in Figure 2.
Mean (SD) pre-dose RVZ blood concentrations were 5217 (2707) ng/mL and 6976 (3127) ng/mL on Day 8 and Day 15, respectively. The mean RVZ concentration-time profiles at steady-state after E1224 administration in the absence or presence of BNZ are shown in Figure 3. The summary statistics for RVZ PK parameters are shown in Table 3.

Following administration of E1224 with BNZ, the GM of RVZ C\textsubscript{max} increased by 31% (8328 vs. 6366 ng/mL) and the GM of AUC from time zero to 24 h post-dose (AUC\textsubscript{0-24}) increased by 36% (151658 vs. 111851 ng.h/mL). Median RVZ t\textsubscript{max} was delayed after administration with BNZ (3 h vs. 1 h). Formal statistical analyses showed that the 90% CI for C\textsubscript{max} [1.23-1.39] and AUC\textsubscript{0-24} [1.31-1.41] were not fully included in the reference range for bioequivalence [0.80-1.25](16). The relative bioavailability of RVZ given concomitantly with BNZ resulted in an increase of about 35%, given the C\textsubscript{max} and AUC\textsubscript{0-24} point estimates of 1.31 and 1.36, respectively.

**Safety and tolerability**

No severe or serious adverse events were reported. A total of 13 drug-related treatment emergent adverse events (TEAEs) were reported by 9 out of 28 subjects. TEAEs were reported on days when E1224 was administered alone (3 TEAEs) or co-administered with BNZ (10 TEAEs). All of the reported events were of mild or moderate intensity. The most frequent TEAEs consisted of skin disorders (4 cases of rash, 1 case of pruritus and 1 case of erythema). Other TEAEs were laboratory result abnormalities (1 case of ASAT increase, 2 cases of non-clinically significant bilirubin increase and 2 cases of eosinophilia) and headache (2 cases). No subject discontinued treatment due to TEAE.

In electrocardiograms (ECG) or vital signs, only incidental, non-specific abnormalities were reported.

**Discussion**
E1224 is in development for the treatment of mycetoma and Chagas disease and is being investigated for use in combination with other treatments to improve efficacy. As BNZ is the current standard of care for Chagas disease, E1224 and BNZ are under consideration for concomitant administration.

No in vitro data were available on potential safety interactions. Evaluation of BNZ-ravuconazole interaction in vitro demonstrated a simple additive effect, based on the mean ΣFICs of 0.76 to 0.98 for the Y strain and 1.10 to 1.56 for the Colombian strain (12). As previously discussed, follow-up investigations of the E1224 and BNZ combination in murine models of T. cruzi (12) showed a positive interaction between E1224 and BNZ in the treatment of early infections by a multidrug-resistant strain, with a 100% cure rate and reductions in the period of patent parasitemia. It was considered necessary to investigate the effect of co-administering the two drugs on PK. Due to the very long half-life of RVZ, a sequential design was chosen to assess the effect of E1224 on the PK of BNZ and the effect of BNZ on the PK of RVZ. This design was consistent with guidelines for drug interaction studies (17,18). In this study, the effect of the interaction on E1224 was studied at steady-state and the effect on BNZ was studied after a single dose in healthy subjects. Following administration of BNZ at dose of 2.5 mg/kg, BNZ PK parameters ($C_{\text{max}}$: 3364 ng/mL, $t_{\text{max}}$: 3 h, $t_{1/2}$:12 h) were consistent with the results of previously published studies (4). When administered with E1224, a limited decrease in BNZ exposure was observed with a decrease in $C_{\text{max}}$ of 4% and a decrease in $\text{AUC}_{0-\infty}$ and $\text{AUC}_{0-t}$ of 16%. Other parameters ($t_{\text{max}}$ and $t_{1/2}$) were comparable for both conditions. The decrease in exposure was not clinically significant, with the 90% CIs for $C_{\text{max}}$ and $\text{AUC}_{0-\infty}$ within the reference range for bioequivalence. These results indicated that RVZ had no impact on the PK characteristics of a single oral dose administration of 2.5 mg/kg BNZ.
At steady-state, following concomitant administration of prodrug E1224 with BNZ, overall RVZ exposure significantly increased by about 35% with the 90% CIs for \( C_{\text{max}} \) and \( \text{AUC}_{0-24} \) slightly exceeding the reference range.

No clinically relevant safety interactions were documented from the perspective of safety. The skin disorders, in particular rash, that occurred after the first administration of E1224 with BNZ are consistent with common AEs observed for BNZ and previously reported for E1224 (6,7,9,13). Other AEs were in line with those previously reported following administration of E1224 (13). Under the conditions of this study, safety and tolerability may be considered to be good and no clinically relevant safety interactions were documented between BNZ and E1224.

**Conclusions**

Given the lack of impact of RVZ on BNZ PK and the significant 35% decrease in exposure of RVZ with BNZ, which was not anticipated to have clinical significance, it appears that co-administration of RVZ and BNZ does not require any adaptation of the E1224 dose. Concomitant administration of BNZ and E1224 was well tolerated.

**Materials and Methods**

**Study population**

Healthy male subjects in good health on the basis of medical history, physical examination, vital signs, ECG and routine laboratory safety tests, aged from 18 to 45 years, with BMI of 18-28 kg/m² and non-smokers or light smokers (≤5 cigarettes per day) were eligible.

The study was conducted in accordance with Good Clinical Practices and the ethical principles of the Declaration of Helsinki. The study was approved by an independent Ethics Committee in Argentina before the study start. All subjects provided written informed consent...
prior to participation. The subjects were enrolled from November 7, 2014 (first subject screening visit) to December 13, 2014 (last subject last visit).

Study design

This Phase I trial was an open-label, single-centre, sequential single and multiple oral dose drug-drug interaction study in healthy male subjects. A screening visit was performed within the 3 weeks preceding treatment initiation. Subjects were hospitalized from the evening of Day 1 to the morning of Day 2. Thereafter, ambulatory visits were planned on Day 2 (evening), Day 3 (morning and evening), and Day 4 (morning) and then on the morning of Days 5 to 7. Subjects were hospitalized from the evening of Day 7 to the morning of Day 10 for a second in-house period. Ambulatory visits were planned from the evening of Day 10 evening to the morning of Day 14. Subjects were then hospitalized for the third hospitalization from the evening of Day 14 to Day 16. Finally, the End-of-Study (EOS) visit was performed between 5 and 7 days after the last drug administration.

Dose administered

The therapeutic dose of BNZ was administered i.e., 5 mg/kg divided in two doses given with an interval of 12 h, corresponding to 2.5 mg/kg twice daily.

A multiple dose regimen was chosen for E1224 (a prodrug for the active ingredient RVZ). Subjects received a loading dose of 400 mg once daily for 3 days followed by a maintenance dose of 100 mg once daily for 9 days, to reach steady-state as soon as possible and to reduce the risk of liver enzyme increase.

BNZ and E1224 were administered to all subjects under fasted conditions according to the schema in Figure 4.

Study assessments
Safety assessments, including adverse events, clinical examination, vital signs, ECGs, clinical laboratory parameters and urinalysis, were performed at defined time points from screening to EOS.

Safety reporting period for this trial began upon subject enrolment in the trial (after signature of informed consent) and ended at 4 weeks after the last dose of study medications. Investigators were required to report all directly observed TEAEs and all TEAEs spontaneously reported by the trial subject. In addition, each trial subject was questioned about the occurrence of AEs in all study visits.

Information on AEs has to be evaluated by a physician at each patient visit. Each AE was classified by the investigator as serious or non-serious and regarding possible relationship to the study medication. AE intensity was graded using the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE, version 4.03).

Clinical laboratory tests were performed during the study, including complete blood count (hemoglobin, red blood cell, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean cell hemoglobin concentration, white blood cell including differential, platelet counts), clinical chemistry (ALP, ALAT, ASAT, GGT, total bilirubin, total protein, creatinine, fasting glucose, albumin, urea, electrolytes (Na+, K+, Cl-), alcohol test and urine dipstick analysis. Assessments were performed at Screening, and D1, D4, D7, D9, D10, D12, D13, D14, D15, and EOS visits.

ECGs were performed at Screening, Visit D4, D7, D12 and end of study. Blood samples were collected for BNZ and RVZ PK analyses. For BNZ, blood samples were collected on Day 1 and Day 9 pre-dose, and at 1, 2, 3, 4, 5, 6, 12, 24, 36, 48, 60 and 72 h post-dose. For RVZ, PK samples were collected on Day 6, Day 7, Day 13 and Day 14 pre-dose and on Day 8 and Day 15 pre-dose, and at 1, 2, 3, 4, 5, 6, 12 and 24 h post-dose.
Bioanalysis

A liquid chromatography with tandem mass spectrometry method was developed, validated and used to analyse BNZ and RVZ dry blood spots in the laboratories of B & S INOVAÇÕES (Engenho do Meio, Recife, Brazil) in accordance with Good Laboratory Practice. The limits of quantification of these methods were 20 ng/mL for RVZ and 50 ng/mL for BNZ.

Pharmacokinetic analysis

PK parameters were determined by non-compartmental analysis using Phoenix WinNonlin® (Pharsight, Mountain View, USA). For BNZ, the following PK parameters were derived on Day 1 and Day 9: \( C_{\text{max}} \), \( t_{\text{max}} \), terminal rate constant estimated by log-linear regression analysis \( (k_e) \), \( \text{AUC}_{0-\infty} \) using a linear trapezoidal method, \( \text{AUC}_{0-\infty} \) and \( t_{1/2} \). For RVZ, the following PK parameters were derived on Day 8 and Day 15: \( C_{\text{max}} \), \( t_{\text{max}} \), \( \text{AUC}_{0-24} \) using a linear trapezoidal method.

Sample size estimation

The sample size was determined in order to achieve a power of at least of 80% at a type I error (\( \alpha \)) of 5%, in the case of reference bioequivalence margins (0.80 to 1.25), as recommended by US Food and Drug Administration guidance documents (16), and an intra-individual variability of 25%. A total of 28 subjects was deemed sufficient to demonstrate a lack of interaction between the two drugs.

Statistical analysis

All subjects who received at least one dose of the study medication were enrolled in the safety analysis set. All subjects who completed the study without events likely to bias the PK evaluation were included in PK analysis set.

Descriptive statistics were performed on demographic data, vital signs (temperature, blood pressure and heart rate), clinical laboratory parameters, ECG and AEs.
Descriptive statistics for individual blood concentrations and PK parameters were performed with Phoenix WinNonlin® 6.3 and were presented for each compound (i.e., BNZ and RVZ) by Day.

Statistical analysis was performed using SAS® software Version 9.4. The effect of BNZ on RVZ PK parameters and vice versa was evaluated based on AUC$_{0-\infty}$, AUC$_{0-t}$, and C$_{max}$ for BNZ and AUC$_{0-24}$ and C$_{max}$ for RVZ by analysis of variance (ANOVA) using a mixed-effect model applied to log transformed PK parameters with treatment as fixed effects and subjects as random effects. For each parameter, a point estimate for the ratio of geometric means (RVZ + BNZ [Day 15] / RVZ alone [Day 8]) and (RVZ + BNZ [Day 9] / BNZ alone [Day 1]) was obtained by calculating the difference of least square means on the logarithmic scale and subsequent back transformation using the anti-log function. Likewise, 90% CI for the ratios was obtained and a point estimate for the ratio of geometric means (RVZ + BNZ [Day 15] / RVZ alone [Day 8]) and (RVZ + BNZ [Day 9] / BNZ alone [Day 1]) was obtained by least square means. It was concluded that there was no interaction if the 90% CI for the ratio for all PK parameters fell entirely within the 0.80 to 1.25 reference interval.

The analysis of $t_{max}$ values was based on the non-parametric Wilcoxon signed rank.

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| Demographic data               | All subjects (N = 28) |
|-------------------------------|-----------------------|
| Age (years)                   | Mean (SD) 29.00 (7.93) |
| Min - Max                     | 18.00 - 45.00         |
| Height (cm)                   | Mean (SD) 172.36 (6.98) |
| Min - Max                     | 161.00 - 188.00       |
| Weight (kg)                   | Mean (SD) 73.55 (10.49) |
| Min - Max                     | 55.00 - 94.50         |
| BMI (kg/m²)                   | Mean (SD) 24.72 (2.95) |
| Min - Max                     | 18.30 - 27.97         |

SD: Standard deviation; Min: Minimum; Max: Maximum; BMI: Body mass index
Figure 1: Mean (+standard deviation) benznidazole (BNZ) blood concentrations versus time after a single oral dose administration of 2.5 mg/kg BNZ on Day 1 (BNZ alone) and Day 9 (BNZ+ravuconazole) (upper graph: untransformed scale; lower graph: semi-log scale)
### Table 2  Benznidazole pharmacokinetics parameters after single oral administration of 2.5 mg/kg BNZ alone or with E1224

| Treatment       | $C_{\text{max}}$ (ng/mL) | $AUC_{0-4}$ (ng·h/mL) | $AUC_{0-\infty}$ (ng·h/mL) | $t_{1/2}$ (h) | $t_{\text{max}}$* (h) |
|-----------------|---------------------------|------------------------|----------------------------|--------------|-----------------------|
| BNZ (N=28)      | 3364 (26.4)               | 70559 (32.0)           | 72720 (32.7)               | 12.2 (25.2)  | 3.0 (1.0-6.0)         |
| GM (CV%)        |                           |                        |                            |              |                       |
| BNZ+E1224 (N=28)| 3221 (25.7)               | 59299 (29.8)           | 61162 (29.8)#              | 10.0 (19.4)# | 3.0 (1.0-6.0)         |
| GM (CV%)        |                           |                        |                            |              |                       |
| BNZ+E1224 vs. BNZ PE (90% CI) | 0.96 (0.91-1.10) | 0.84 (0.81-0.88) | 0.83 (0.80-0.87) |              |                       |

$C_{\text{max}}$: Maximum concentration; $AUC_{0-4}$: area under the curve from time zero to the last measurement; $AUC_{0-\infty}$: area under the curve from time zero to infinity; $t_{1/2}$: terminal half-life; $t_{\text{max}}$: time of $C_{\text{max}}$; *: median and range (Min-Max)

BNZ: Benznidazole; GM: geometric mean; CV%: coefficient of variation; PE: Point estimate; CI: Confidence interval

# N = 27
Figure 2: Mean, minimum (Min), and maximum (Max) pre-dose concentration of ravuconazole (RVZ) from Day 6 to Day 16 (i.e. from 2 days to 12 days of administration)
Figure 3: Mean (+standard deviation) ravuconazole (RVZ) blood concentrations versus time on Day 8 (RVZ alone) and Day 15 (RVZ + benznidazole; upper graph: untransformed scale; lower graph: semi-log scale).
Table 3  Ravuconazole pharmacokinetics parameters after oral administration of E1224 alone or with 2.5 mg/kg benznidazole at steady-state

| Day     | C$_{\text{max}}$ (ng/mL) | AUC$_{0-24}$ (ng.h/mL) | t$_{\text{max}}$* (h) |
|---------|---------------------------|-------------------------|------------------------|
| E1224 (N = 28) GM (CV%) | 6366 (38.5) | 111851 (41.3) | 1.0 (0.0-12.0) |
| BNZ + E1224 (N = 28) GM (CV%) | 83286 (43.7) | 151658 (43.2) | 3.0 (1.0-12.0) |
| BNZ + E1224 vs. E1224 PE (90% CI) | 1.31 (1.23-1.39) | 1.36 (1.31-1.41) | |

C$_{\text{max}}$: Maximum concentration; AUC$_{0-24}$: area under the curve from time zero to 24h; t$_{\text{max}}$: time of C$_{\text{max}}$; *: median and range (Min-Max)

BNZ: Benznidazole; GM: geometric mean; CV%: coefficient of variation; vs.: versus; PE: Point estimate; CI: Confidence interval

Figure 4: Scheme of administration. BNZ: benznidazole; qd: once a day; bid: twice a day