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

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INTRODUCTION

Chagas disease (CD) is an important global neglected tropical disease, where new, better tolerated, therapeutic options are needed. Benznidazole (BNZ) is the drug of choice for treating adults and children with CD. E1224 (ravuconazole ([RVZ]) prodrug) is an antifungal drug with promising anti-T. cruzi activity, but unsatisfactory clinical results in monotherapy. Combination treatment is a well-recognised treatment modality, with potential in CD to improve efficacy and safety and reduce putative risk of resistance. Little is known about the metabolism and absorption of BNZ, therefore its interaction with other drugs cannot be easily anticipated. An in vivo interaction study in healthy volunteers was designed to assess the pharmacokinetics (PK) and safety interaction of BNZ and E1224.

OBJECTIVES

Primary Objectives

- To investigate the potential effect of multiple oral doses of BNZ to alter the PK of E1224 in healthy male subjects at steady-state,
- To investigate the potential effect of multiple oral doses of E1224 to alter the PK of BNZ in healthy male subjects after single dose.

Secondary Objective

- To assess the safety and tolerability of multiple oral doses of BNZ and E1224 given in healthy male subjects.

STUDY ENDPOINTS

Primary Endpoints

- PK parameters of BNZ following single dose: Cmax, tmax, AUC0-t, AUC0-∞ and t1/2 (Day 1 and Day 9)
- PK parameters of E1224 following multiple dose: Cmax, tmax, AUC0-24, (Day 8 and Day 15), morning pre-dose (Day 6, 7, 8, 13, 14, and 15)

Secondary Endpoints

- Monitoring for the occurrence of adverse events (AEs).
- Changes in physical examination, vital signs (blood pressure and pulse rate), 12-lead ECG, and clinical laboratory tests (clinical chemistry, hematology, and urinalysis).

STUDY POPULATION - 28 healthy male volunteers

Inclusion criteria

- Male healthy volunteers 18 to 45 years of age;
- Light smokers (< 5 cigarettes per day) or subjects who are non-smokers;
- Male subjects with a body weight of at least 50 kg and a body mass index (BMI) calculated as weight in kg/height (in m^2) from 18 to 28 kg/m^2 at screening;
- Able to communicate and to comply with study requirements;
- Signed and dated informed consent form;

STUDY DESIGN

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
BNZ	X								X			X	X	X	X
E1224				X	X	X	X	X#	X	X	X	X	X	X	X

#: steady-state assumed to be reached, based on simulation; **X: BID; X: QD**

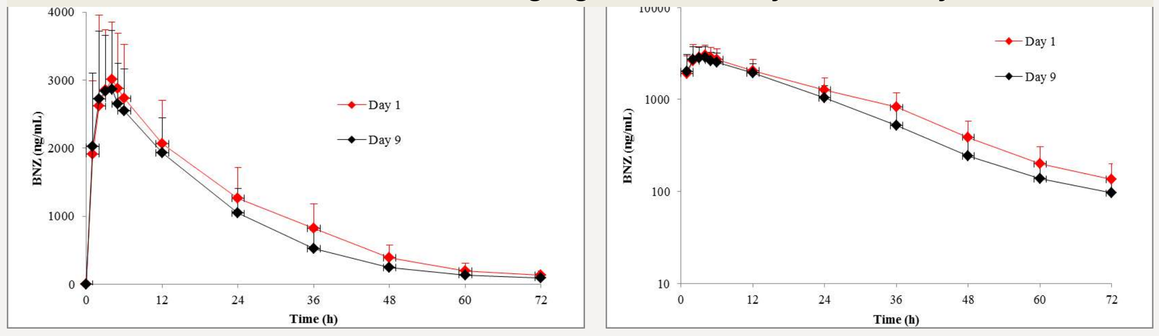
- □ **Day 1** BNZ single dose (2.5 mg/kg)
- □ **Day 4 to Day 15** E1224 multiple dose 400 mg loading dose **once** daily for 3 days followed by maintenance dose 100mg once daily for 9 days (from Day 7 to Day 15)
- □ **Day 9*** BNZ single dose (2.5 mg/kg)
- □ **Day 12* to Day 15** BNZ multiple dose (2.5 mg/kg twice daily)

On Day 9 and from Day 12 to Day 15, E1224 and BNZ will be given concomitantly.

RESULTS

- Both compounds were well tolerated, in monotherapy and combination.
- There were no treatment discontinuations or serious adverse events.
- A total of 1,344 blood samples were obtained.
- Rate and extent of BNZ absorption was strictly comparable when given alone or with concomitant RVZ at steady-state.
- Overall RVZ exposure increased by about 35% when given with concomitant BNZ at steady-state.

Mean (+SD) BZN blood concentrations *vs.* time after a single oral dose administration of 2.5 mg/kg BZN on Day 1 and Day 9



Mean RVZ blood concentrations vs. time on Day 8 and Day 15

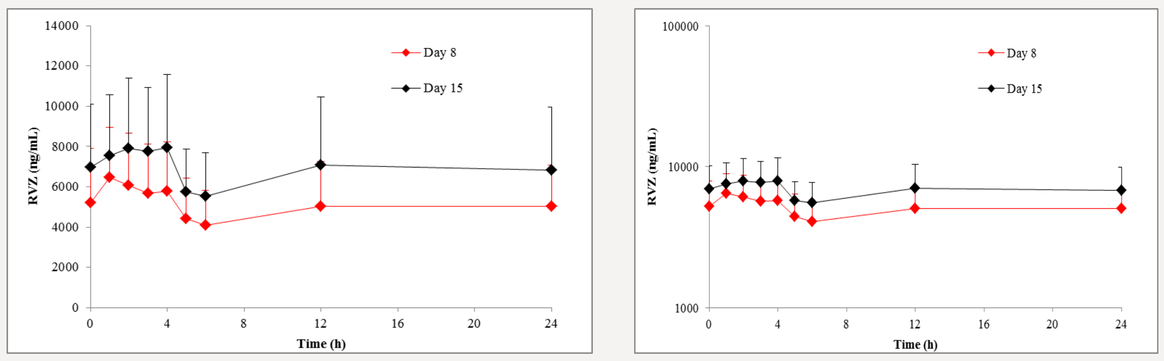


Table 1: Summary descriptive statistics of BNZ PK parameters on Day 1 and Day 9

Day		C_{max} (ng/mL)	t_{max}* (h)	AUC_{0-12} (h.ng/mL)	AUC_{0-t} (h.ng/mL)	$AUC_{0-\infty}$ (h.ng/mL)	$t_{1/2}$ (h)
1	N	28	28	28	28	28	28
	Mean	3477.36	3.00	29007.99	73892.61	76286.40	12.59
	CV%	26.41%	1.00-6.00	27.38%	32.04%	32.68%	25.19%
	GM	3363.85		28060.03	70559.49	72720.08	12.22
9	N	28	28	28	28	27	27
	Mean	3326.93	3.00	27804.23	61913.96	63874.79	10.16
	CV%	25.69%	1.00-6.00	23.49%	29.82%	29.78%	19.35%
	GM	3221.32		27071.03	59298.81	61162.38	9.99

Table 2: Summary descriptive statistics of RAV PK parameters on Day 8 and Day 15

Day		C_{max} (ng/mL)	t_{max}* (h)	AUC_{0-24} (h.ng/mL)
8	N	28	28	28
	Mean	6851.90	1.00	120893.09
	CV%	38.54%	0.00-12.00	41.31%
	GM	6365.74		111850.79
15	N	28	28	28
	Mean	9025.17	3.00	164271.60
	CV%	43.74%	1.00-12.00	43.24%
	GM	8328.26		151657.85

CONCLUSIONS

- There were no clinically relevant safety interactions between E1224 and BZN.
- Considering the lack of interaction of RVZ on BZN PK and the limited impact of BZN on RVZ PK, it appears that coadministration of RVZ and BZN may not require any E1224 dosing adaptation.

9th European Congress on Tropical Medicine and International Health (ECTMIH)
September 2015, Basel
PS2.065