Single-dose Safety and Pharmacokinetics of Fexinidazole in Healthy Subjects

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Nb 1.3-034

ABSTRACT

Background
Fexinidazole is a 2-substituted 5-nitroimidazole, which exhibits activity against *Trypanosoma brucei rhodesiense* and *T.b. gambiense* parasites, the causative agents of human African trypanosomiasis (HAT). This first in man study investigated the safety, pharmacokinetics (PK) and pharmacodynamics of single doses in healthy male volunteers of sub-saharan african origin.

Methods:.
72 subjects were randomized in 9 cohorts of 8 subjects (6 active +2 placebo) to receive single ascending doses of 100, 200, 400, 800, 1200, 1800, 2400, 3000 and 3600mg FEXINIDAZOLE oral suspension. Assessment included clinical and laboratory safety and ECG recordings. Fexinidazole, fexinidazole sulfoxide(M1) and fexinidazole sulfone(M2) were quantified in plasma and urine by LC-MS/MS.

Results:.
All subjects completed the study (mean ±SD age 27±5.9 years). There were no clinically relevant abnormalities in laboratory parameters, ECGs or vital signs. Adverse events (AEs) were rare and nor severe or serious AEs were reported. Fexinidazole and M1 exhibited similar kinetic pattern *i.e.* rapid absorption and elimination process (median T_{max} 3.00 h - 4.00 h and geometric mean (Gmean) $T1_{/2}$ 9 to 15 h for fexinidazole *vs.* median T_{max} 2.00 h -5.00 h and Gmean $T_{1/2}$ 8 to 15 h, but slower for the second metabolite (M2) (median T_{max} 18.00 h - 24.00 h and Gmean $T_{1/2}$ 18 h to 25 h).There was no saturation of the metabolism of fexinidazole and metabolites.

Conclusion:
Fexinidazole was generally well tolerated up to the maximum orally administered dose 3600 mg OAD. Within the dose range 100 mg to 3600 mg, the dose proportionality was not demonstrated for C_{max} and AUCs neither for fexinidazole nor M1 nor M2. The elimination route of fexinidazole and metabolites M1 and M2 was almost entirely extra-renal.

OBJECTIVES AND METHODS

Objectives

- To assess safety and tolerability of fexinidazole after single oral administration of increasing doses of oral suspension of fexinidazole in healthy male volunteers compared to placebo
- To determine PK parameters of fexinidazole and its metabolites

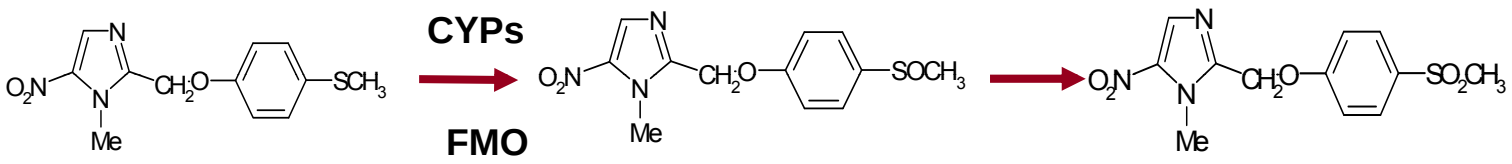
Design

- Randomized, double-blind, placebo-controlled, single ascending dose with fexinidazole administered as an oral suspension.
- 9 cohorts of 8 subjects were dosed.(6 A, 2 placebo
- Single dose of : 100 mg to 3600 mg
- Hospitalization from D-1 to D8
- PK profile + urine collection : H0 to H168 post dose (16 samples)
- 12 leads ECG recording + vital signs at H0, and 1, 2, 3 ,4 ,6, 9, 12, 16, 24 h post dose

Demographic characteristics

		Placebo	All
	N	18	72
	Mean (SD)	25.0 (5.6)	27.0 (5.9)
Age (years)	Min-Max	19-37	19-45
	Mean (SD)	74.68 (12.74)	75.86 (10.83)
Weight (kg)	Min-Max	53.2- 99.9	53.2-99.9
	Mean (SD)	179.7 (7.6)	179.2 (6.4)
Height (cm)	Min-Max	168-193	163-193
	Mean (SD)	23.06 (2.92)	23.57 (2.57)
BMI (kg/m²)	Min-Max	18.0-28.0	18.0-28.5

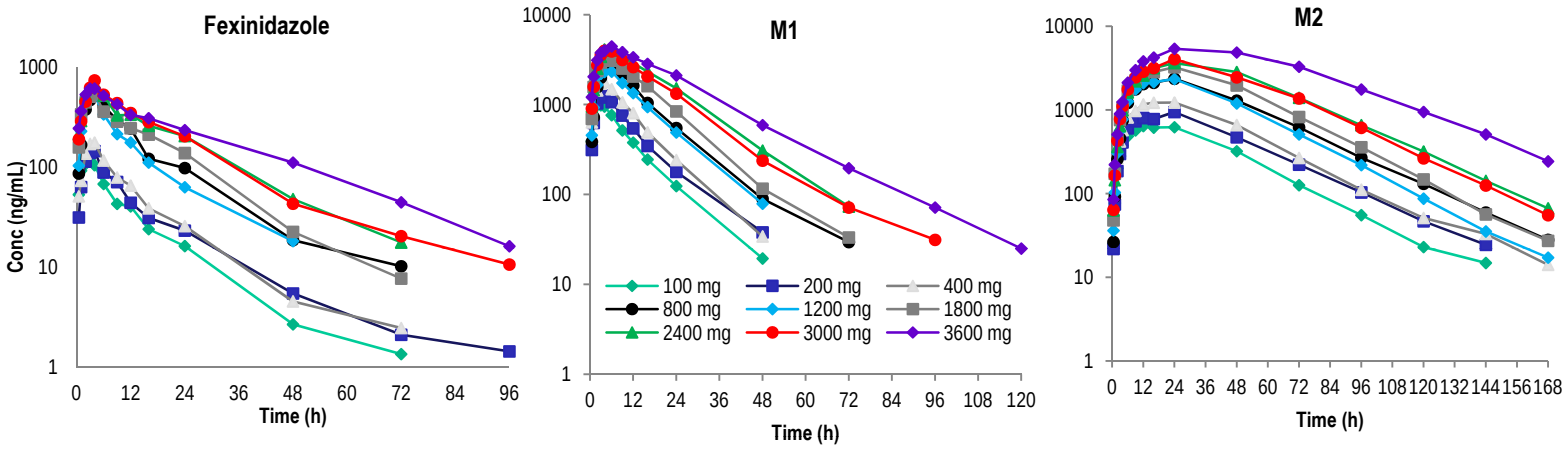
CHEMICAL STRUCTURE



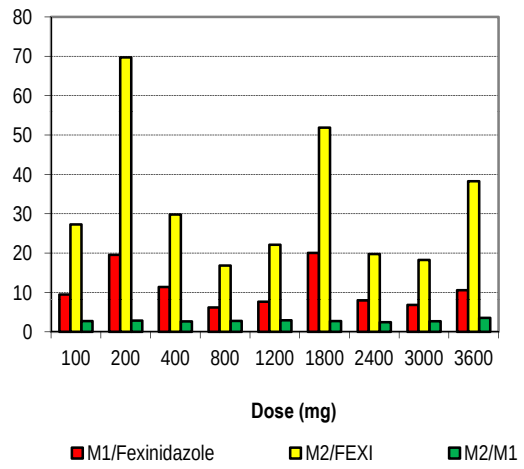
Fexinidazole — Fexinidazole sulfoxide (M1) — Fexinidazole sulfone (M2)

RESULTS

PHARMACOKINETICS



AUC Metabolic ratios



FEXINIDAZOLE was rapidly absorbed with a median Tmax of 3-4 h. Plasma concentrations exhibited a multiphasic decline, with a comparable elimination for all dose levels (T1/2 of 9-15h). M1 exhibited a PK profile consistent with fexinidazole: (median Tmax 2–5 h and T1/2 of 8-15 h). By contrast, M2 plasma concentrations increased slowly with a Tmax of 18-24 h post-dose and T1/2 of18-25h. Pharmacokinetics of fexinidazole and both metabolites were not linear with dose (less than dose proportional over the studied dose range 100 to 3600 mg). Indeed when the dose increased by 2-folds, Cmax, AUC0-t and AUC0-∞ increased by 1.46, 1.64 and 1.65 respectively for fexinidazole, by 1.33, 1.53 and 1.65 for M1 and 1.47 and 1.55 for M2. Overall, there was no saturation of the metabolism of fexinidazole to M1 or for M1 into M2 or for M2 metabolism/elimination.

Geometric mean (CV%) Pharmacokinetics

Dose (mg)		t_{max}# (h)	C_{max} (µg/mL)	AUC_{0-t} (h.µg/mL)	$AUC_{0-\infty}$ (h.µg/mL)	$t_{1/2}$ (h)
100	Fexi	3 (0.5-4)	0.130 (23)	1.26 (32)	1.29 (32)	9.07 (43)
	M1	2 (2-4)	1.01 (24)	11.9 (25)	12.2 (23)	7.82 (22)
	M2	18 (12-24)	0.656 (21)	31.9 (22)	32.3 (23)	19.25 (15)
200	Fexi	3 (1-4)	0.139 (44)	1.37 (56)	1.38 (56)	12.06 (58)
	M1	4 (3-6)	1.24 (27)	16.6 (27)	17.0 (27)	10.5 (50)
	M2	24 (16-24)	0.916 (28)	43.7 (27)	47.2 (27)	21.19 (15)
400	Fexi	3.5 (2-6)	0.171 (39)	2.06 (39)	2.08 (39)	14.75 (54)
	M1	4 (3-6)	1.82 (33)	23.0 (31)	23.3 (31)	9.33 (27)
	M2	14 (12-24)	1.29 (31)	60.9 (37)	61.4 (37)	19.5 (11)
800	Fexi	4 (3-6)	0.532 (31)	7.21 (23)	7.39 (22)	13.45 (47)
	M1	5 (4-6)	2.70 (31)	43.8 (24.3)	44.1 (24)	13.2 (60)
	M2	24 (16-24)	2.23 (39)	120 (32)	121 (31)	21.31 (24)
1200	Fexi	4 (3-6)	0.479 (77)	5.28 (54)	5.49 (52)	8.97 (29)
	M1	5 (4-6)	2.35 (36)	38.8 (22)	39.0 (22)	9.94 (39)
	M2	24 (12-24)	2.24 (43)	111 (28)	112 (38)	18 (5)
1800	Fexi	4 (1-4)	0.483 (54)	5.65 (56)	6.09 (54)	9.67 (20)
	M1	5 (1-6)	3.27 (26)	59.3 (34)	59.6 (34)	9.76 (33)
	M2	24 (16-24)	3.09 (34)	162 (35)	163 (35)	18.21 (13)
2400	Fexi	4 (3-9)	0.671 (32)	11.5 (43)	11.6 (43)	11.08 (46)
	M1	4 (4-9)	4.10 (26)	89.5 (29)	89.9 (28)	12.8 (46)
	M2	24 (16-24)	3.52 (31)	217 (36)	219 (37)	20.38 (17)
3000	Fexi	4 (3-4)	0.749 (19)	12.4 (24)	12.6 (24)	13.1 (41)
	M1	6 (4-6)	4.01 (8)	83.5 (9)	83.9 (9)	13.84 (38)
	M2	24 (24-24)	3.99 (20)	223 (14)	225 (14)	20.1 (16)
3600	Fexi	3.5 (1-6)	0.715 (20)	14.9 (45)	15.2 (44)	13.08 (45)
	M1	5 (2-6)	4.75 (59)	119 (47)	120 (47)	15.09 (44)
	M2	24 (24-48)	5.86 (55)	418 (51)	428 (50)	24.63 (18)

#median (Min-Max)

SAFETY RESUTLS

Adverse events	A total of 8 mild TEAEs were reported: 3 were related to fexinidazole 2 at 100 mg and 1 at 3600 mg
Laboratory parameters	No clinically relevant abnormalities
Vital signs: SBP, DBP, HR	No clinically relevant abnormalities
Respiratory Rate, Body Temperature	
12 leads ECG	No QTcB values over 450 ms No QTcB increase>30ms/baseline

CONCLUSIONS

- **Overall safety and tolerability of fexinidazole was very good up to 3600 mg and the MTD was not reached**
- **Pharmacokinetics of fexinidazole and both metabolites were not linear with dose (less than dose proportional over the studied dose range 100 to 3600 mg)**
- **There was no saturation of the metabolism of fexinidazole to M1 or for M1 into M2 or for M2 metabolism/elimination**

Torreele E, et al (2000) Fexinidazole – A New Oral Nitroimidazole Drug Candidate Entering Clinical Development for the Treatment of Sleeping Sickness. PLoS Negl Trop Dis 4(12):e923

Presented 7th ECTMIH Meeting, Barcelona, Spain, October 2011