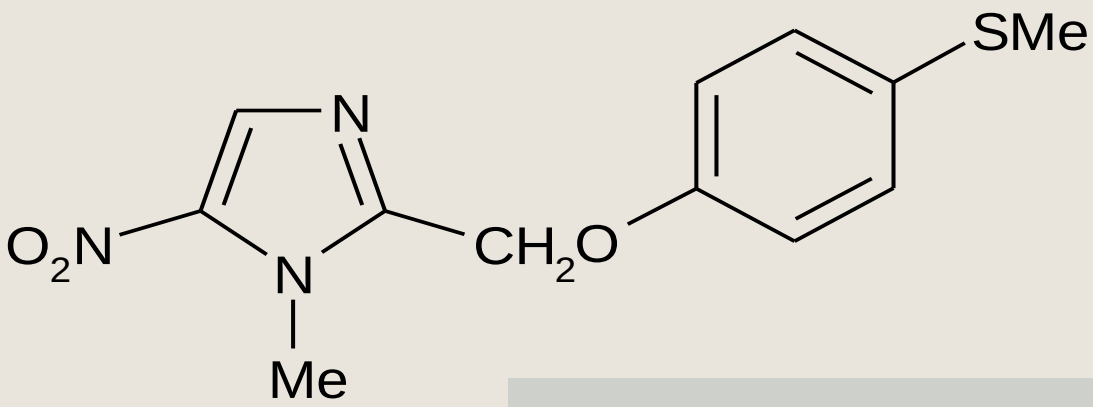

FEXINIDAZOLE FOR HAT

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ICTMM RIO Sept 2012
Dr Antoine Tarral, Head of HAT Clinical program

Fexinidazole for HAT

- Preclinical reslts
- Multiple ascending dose in fasted conditions
- Food interaction
- Therapeutic dose regimen assessment

Fexinidazole preclinical results

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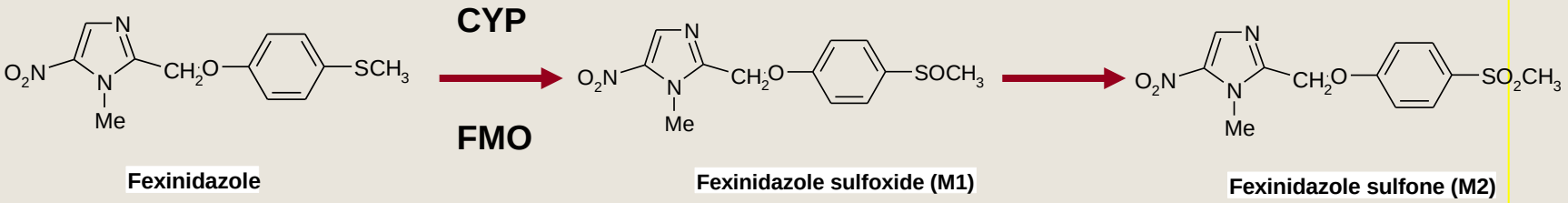
Fexinidazole

- Discovery : 1970 HOE 239, discontinued 1980
- Chemical Name: 1H-imidazole,1-methyl-2-[[4-methylthio) phenoxy] methyl] 5-nitro-imidazole
- Metabolism



Fexinidazole **Fexinidazole sulfoxide (M1)** **Fexinidazole sulfone (M2)**

- PM FEXI = 279 g/mol
- PM M1 = 295 g/mol
- PM M2 = 311 g/mol

- pKa-value = very weak base
- $logD_{pH\ 7.4}$ = 2.8

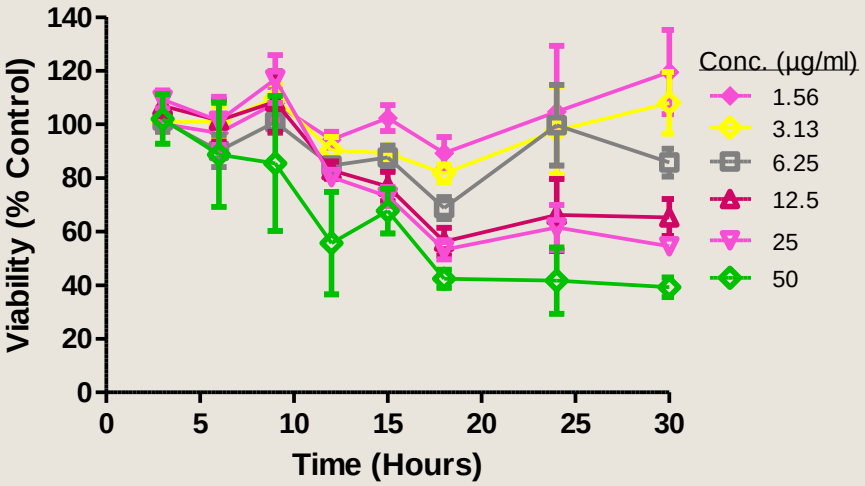
In vitro activity of fexinidazole

Compound Tested	***T.b. rhodesiense**** **(IC_{50} µg/ml)**	***T. b. brucei**** **(IC_{50} µg/ml)**	***T. b. brucei**** **(IC_{90} µg/ml)**
Fexinidazole (Batch 1)	1.265	2.86	5.00
Fexinidazole (Batch 2)	0.719	ND	ND
Fexinidazole sulfoxide	0.487	1.96	4.74
Fexinidazole sulfone	0.354	0.89	2.20

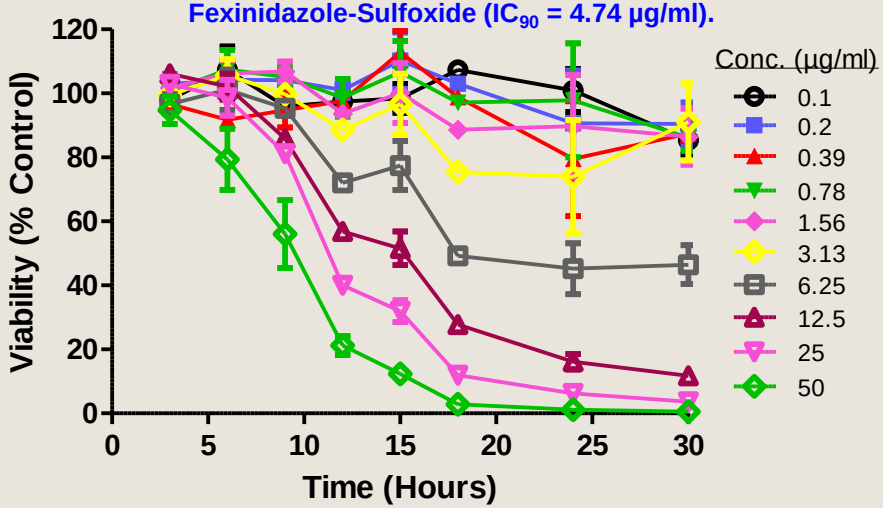
*Data from STI
**Data from SCYNEXIS

Time to Kill Assays - Fexinidazole and Metabolites

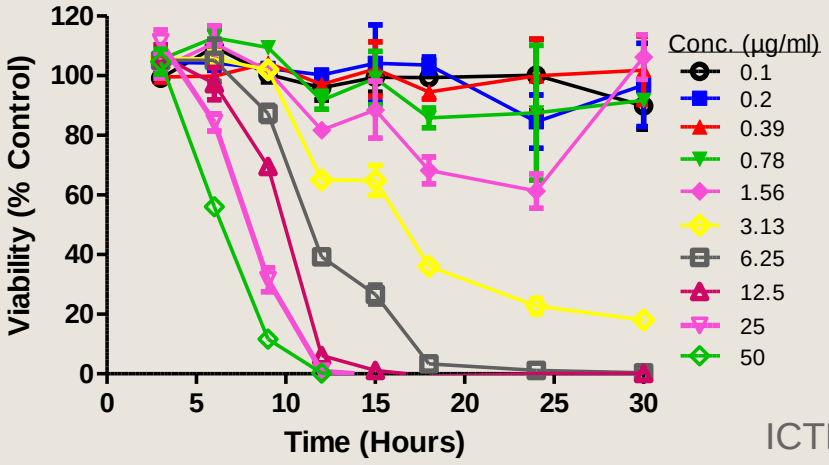
Fexinidazole (IC_{90} = 5.00 µg/ml)

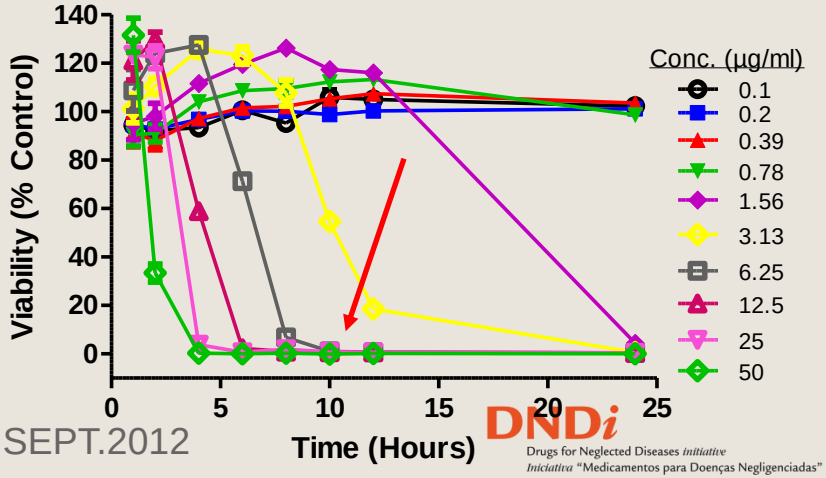


Fexinidazole-Sulfoxide (IC_{90} = 4.74 µg/ml).



Fexinidazole sulfone (IC_{90} = 2.20 µg/ml)





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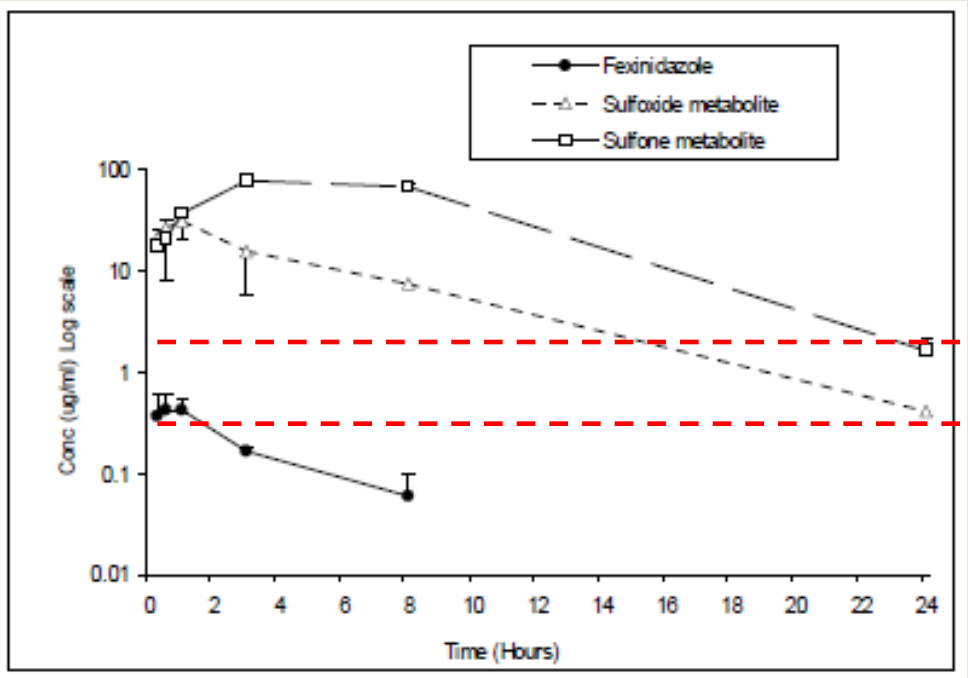
Fexinidazole mice PK profile at 200 mg/kg)

- Mice PK profile (at the efficacious dose of 200 mg/kg)



IC_{99} Fexi-sulfone

IC_{50} Fexi-sulfone

- Concentration of Fexi-sulfone is above IC_{90} for 22 hrs

Key preclincal Data (1)

- The most active metabolite is M2: Fexinidazole sulfone
- No drug interaction expected as several CYP P450 involved
- IC_{90} of M2 is 2.200 ng/mL
- Killing curve test:
  - Time dependent: 24h if concentration ≥ 3X MIC
  - Killing rate (irreversibility) 12h if concentration ≥ 3X MIC

Key preclincal Data (2)

- Chronic Infection Mice model for HAT
  - Dose 200mg/kg for 5 days 7/8 mice cured
  - plasma concentration ~8-10.000 ng/mL (mice data)

- No toxicological target organ
  - NOAEL = 200 mg/kg
  - ADME Rat brain concentration:

Met ID	Collection time	
	8 h	24 h
fexinidazole	3.3 %	nd
M1	36.1 %	12.3 %
M2	56.1¨%	76.2 %

Fexinidazole Clinical Studies

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Phase I studies

118 /154 subjects have been exposed to Fexinidazole

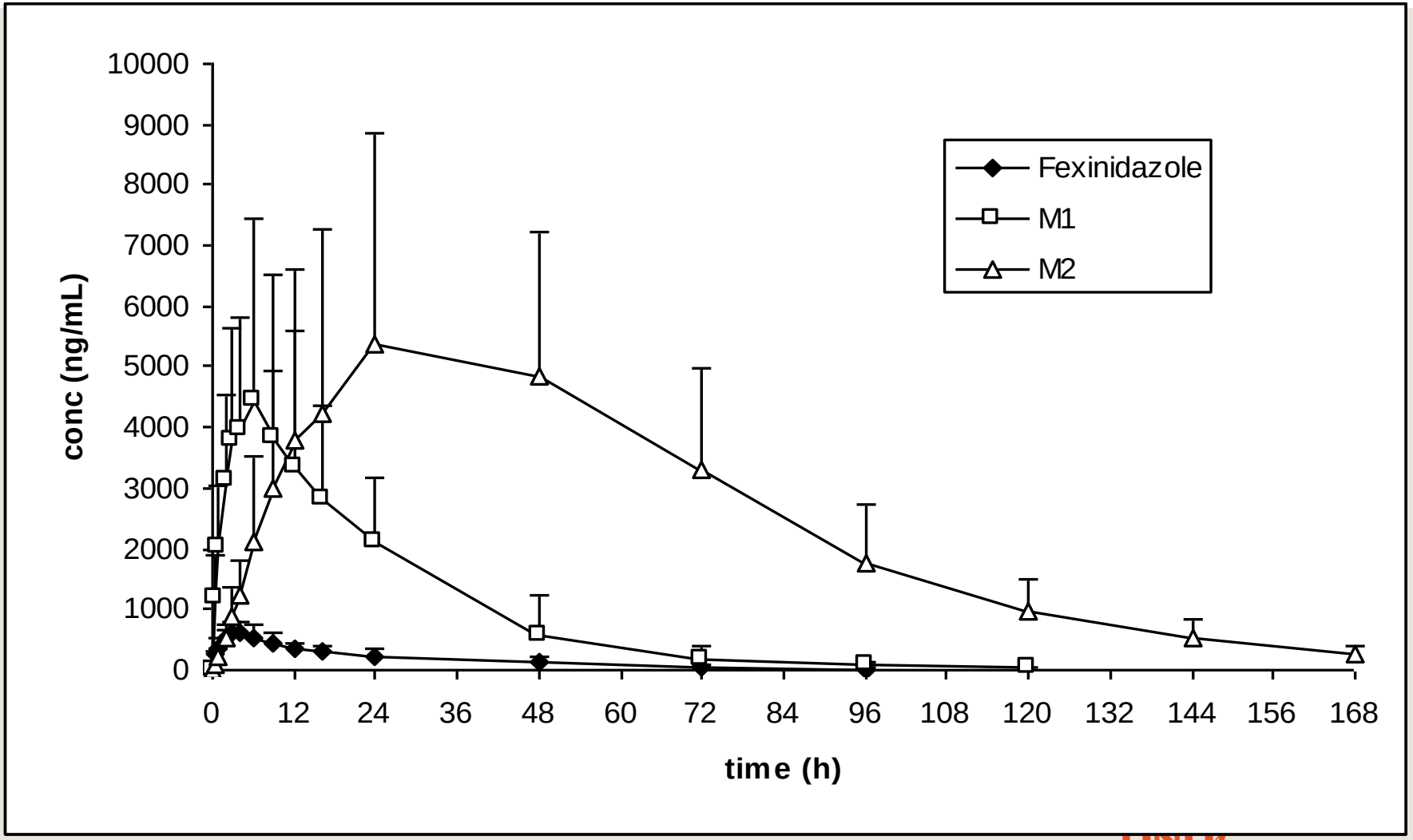
- **Tolerability study**
  - *Part 1 (SAD) Study Design*

  - oral suspension escalation from 100 up to 3600 mg
  - *Part 2 Cross-over bioequivalence and food effect* Study

  - 1200 mg single dose
  - *Part 3 (MAD) Study Design*

  - Three cohorts of 8 subjects (6 active, 2 placebo)
  - Oral tablet (600 mg) once a day for 14 days 1200mg,2400mg &3600mg
- **Field food interaction study (3way cross-over study ,12 subjects)**
- **Multiple dose in fed condition**
  - Randomized , double- blind versus placebo
  - Two cohorts of 18 subjects (12 active, 6 placebo/ cohort)
- **POP PK analysis**

Mean (+SD) plasma concentration of fexinidazole, (M1) (M2) *vs.* time profiles - 3600 mg fexinidazole



PK Results SAD

- Bioavailability
  - Fexinidazole: median Tmx:3 – 4 H; mean T1/2: 9-15H
  - M1 : median Tmx: 2-5 H; mean T1/2: 18-20H
  - M2 : median Tmx: 18-24 H; mean T1/2: 18-25H
- Exposure increased linearly, but not proportional to dose administered
- No saturation of the metabolism
- Steady state : D4 for fexi and M1, D9 for M2

Multiple ascending dose fasting

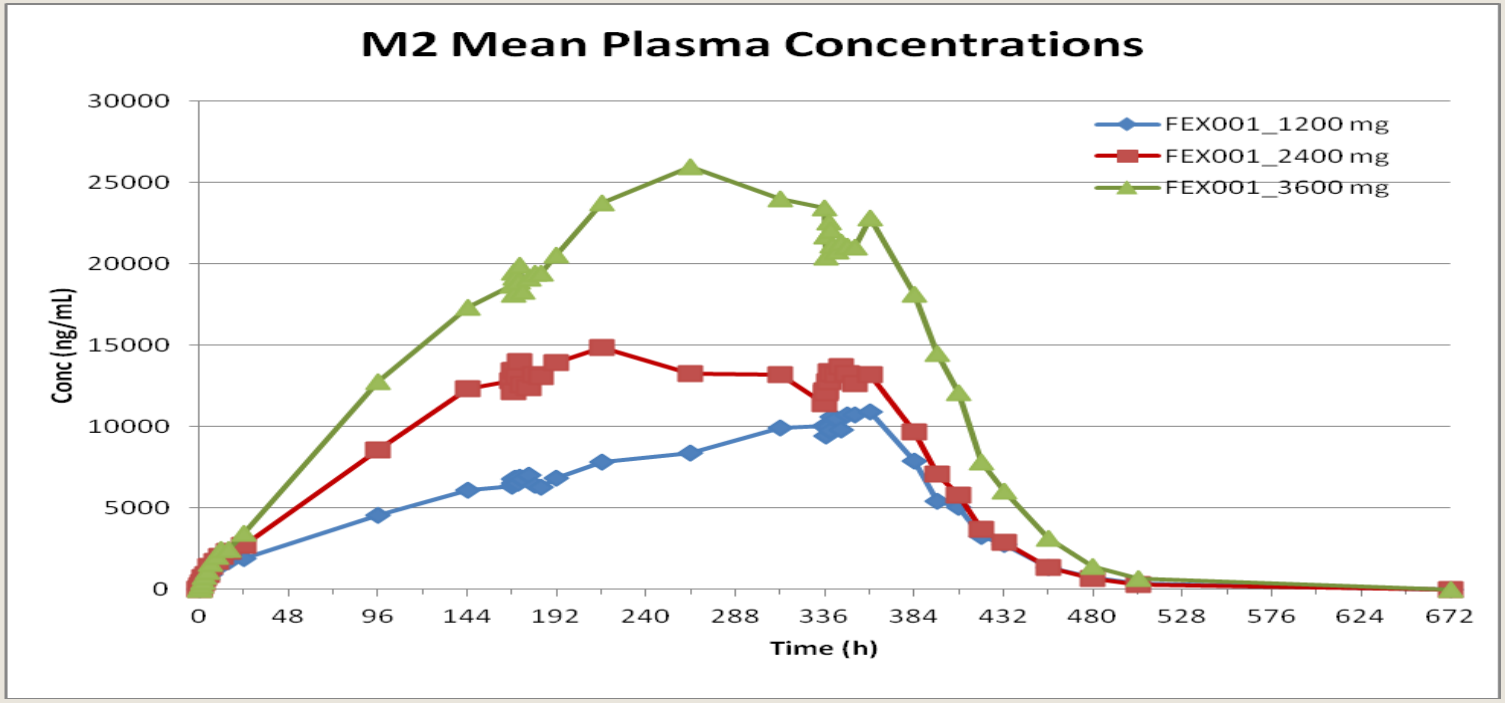
- Randomized, double-blind, placebo-controlled design
- cohorts of 8 subjects (6 A, 2 P) sub-Saharan origin
- Oral fasting tablets of 600g - once daily for 14 days
- Ascending dose levels: 1200mg ; 2400mg ; 3600mg.

Multiple ascending dose fasting

- Subjects hospitalized from D-2 through D16
- Ambulatory visit D17- D21 morning (EOS)
- Standard safety lab, ECGs, AEs, PK
- 24h ECG holter
- Validation DBS method for PK

Multiple dose – Fasting - M2 PK Summary

Fexinidazole was administered once daily for 14 d



Frequency of ALT/AST increases/FEX001

ALAT	cohort 1	cohort 2	cohort 3
dose	1200 mg	2400 mg	3600 mg/
nb volunteers	9	9	9
≤1N	4	6	7
1N<x≤2N	4	1	
2N<x≤3N	1	1	1
3N<x≤30N		1	
30N<x≤40N			1

ASAT	cohort 1	cohort 2	cohort 3
dose	1200 mg	2400 mg	3600 mg
nb volunteers	9	9	9
≤1N	7	6	7
1N<x≤2N	1	2	1
2N<x≤5N			
5N<x≤6N		1	
6N<x≤9N			
9N<x≤10N	1		
10N<x≤30N			
30N<x≤40N			1

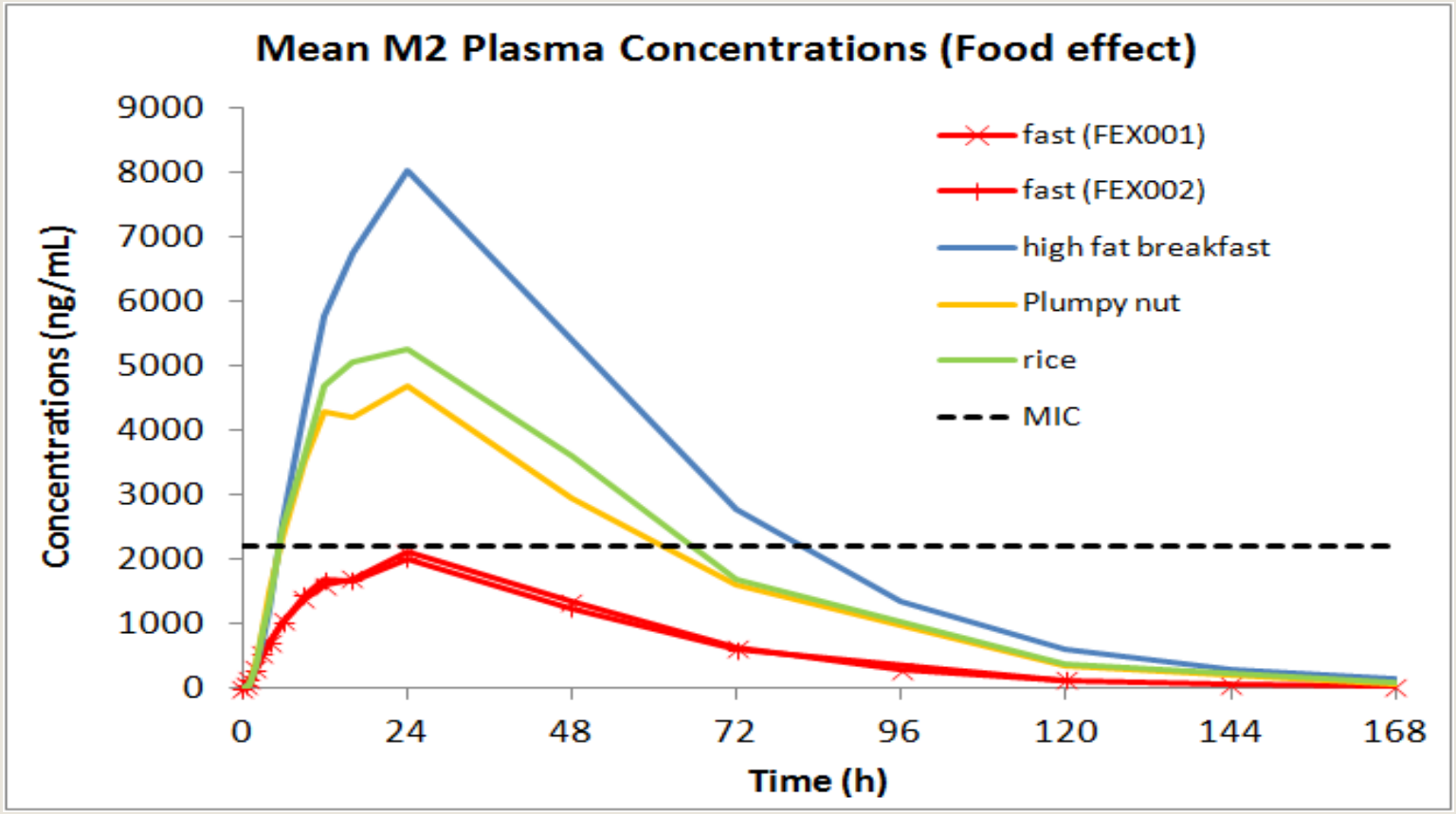
Food interaction studies

- 2 studies : open, 3 way cross-over design
  - 1200mg (2X600mg tablets) singe dose
- **1st study : high fat rich breakfast**
  - relative bioavailability Cmax and AUC_{0-t}:
    - 4 fold increase of absorption of fexinidazole
    - M1 & M2 increased proportionally
  - intra-individal variability
    - Cmax and AUC0-t markedly reduced (10 – 15%)

Food interaction studies

- **2nd study : Plumpy Nuts®(Fed1), rice and beans(Fed2)**
  - 3 way cross-over: fasted / fed 1/ fed2
  - Determination of free fraction
- Relative bioavailability Cmax and AUC_{0-t}:
  - 2.5 – 3 fold increase in of absorption of fexinidazole
  - M1 & M2 increased proportionally
- intra-individal variability
  - Cmax and AUC0-t markedly reduced (10 – 15%)
- Free fraction
  - Fexi:3%, M1:59%, M2: 43%

M2 fed : Mean Plasma levels



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Key Pharmacokynetic Data

➢ Human Clinical Pharmacology data

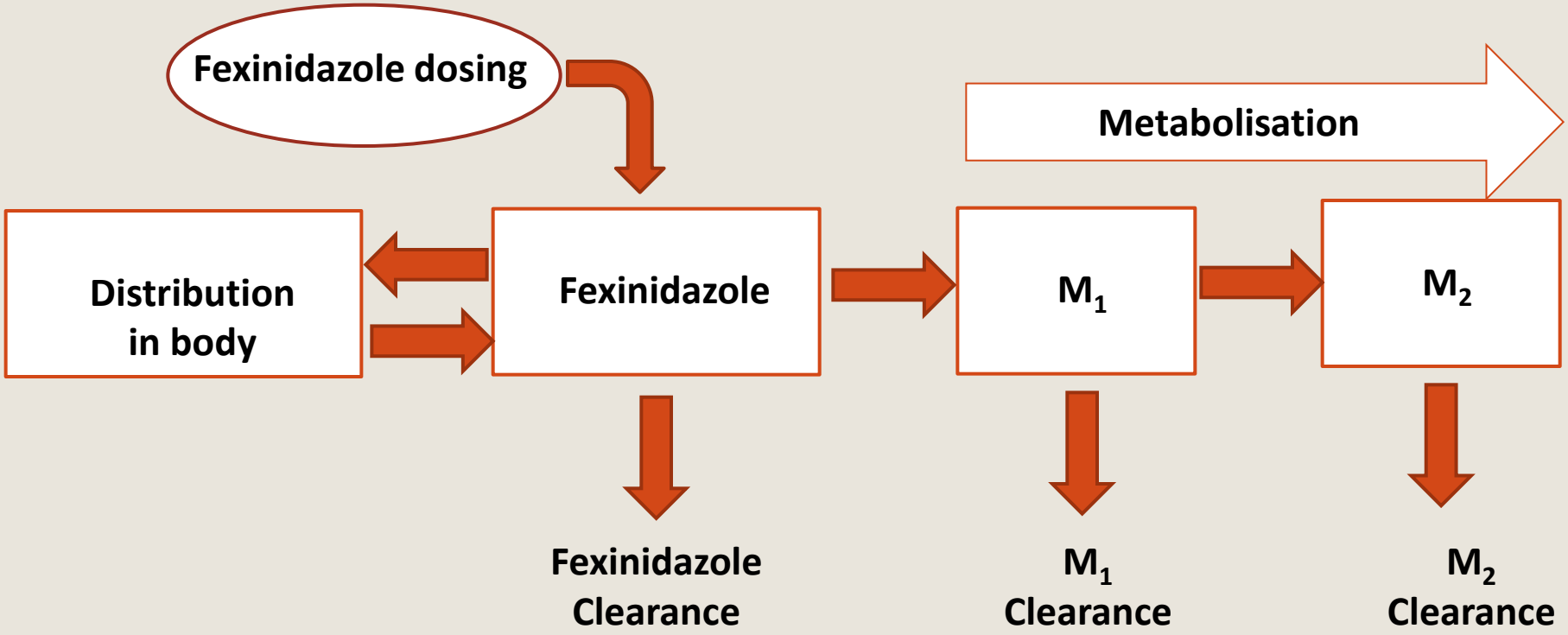
- Long Lag time to reach steady state of M2 in fasting dosing
- Food effect: 2-3 X increase in plasma concentration / fasting
- M2 $T_{1/2}$ ≥ 24h
- Free fraction of M1= 59% M2= 43%: prediction of high body diffusion
- Best Treatment duration should be less than 14 days

Rationale for population PK simulation

Targets:

- Simulate M2 plasma levels after multiple dosing over 10 days under fed conditions
- M2 concentrations 2-3 times > the IC_{90} (2200ng/mL)
- M2 plasma levels around 10.000 ng/mL for at least 72H (mice data)
- M2 plasma level should be reached within 2-3 days
- M2 C^2max plasma levels ≤ 20.000-25.000 ng/mL

Population PK model used for the simulations of several dosing regimens in patients



Winkelmann E, Raether W (1980). New chemotherapeutically active nitroimidazoles. Curr Chemother Infect Dis, Proc 11th Int Congr Chemother 2: 969-970.

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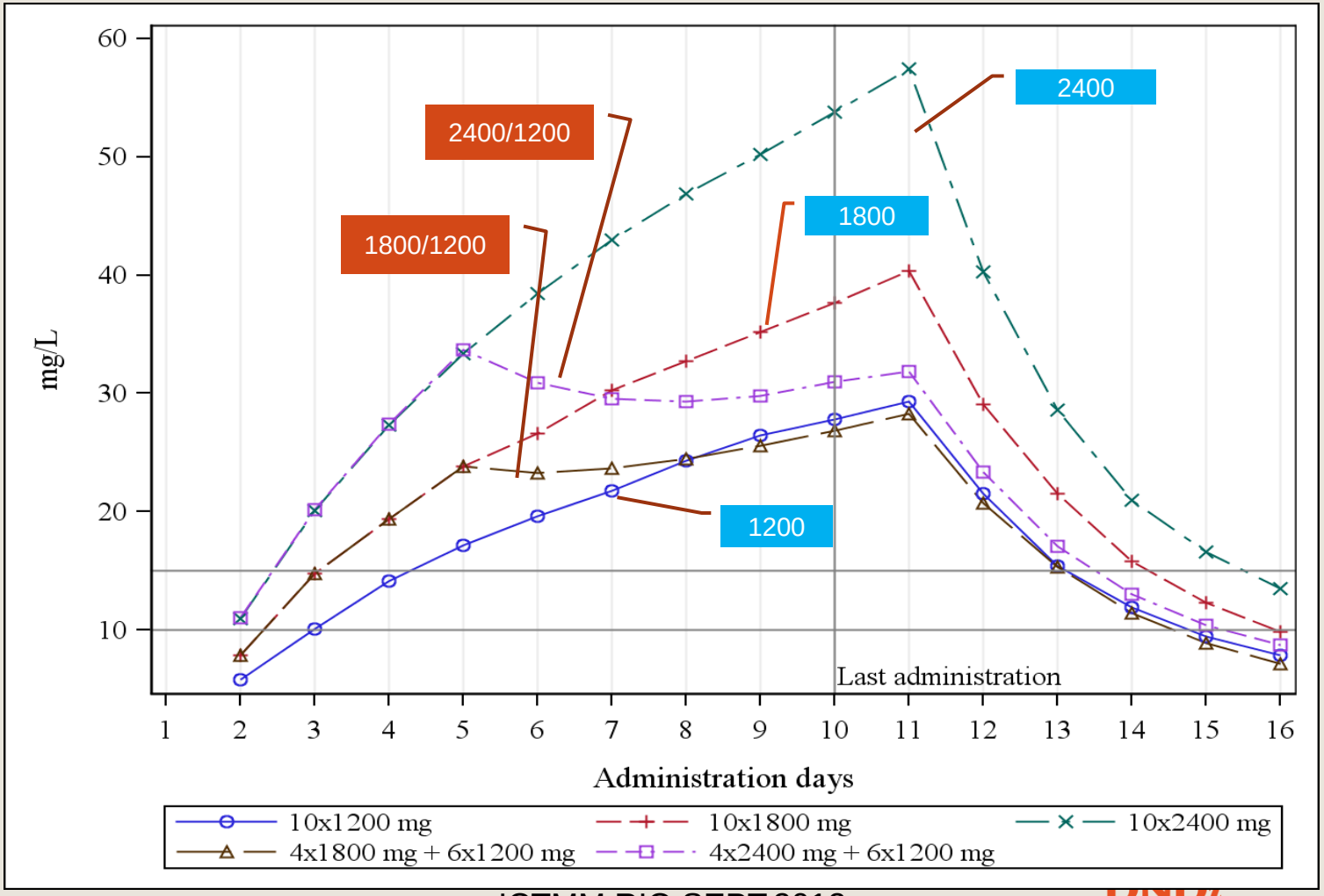
Population PK scenarii tested

Tested 5 Scenarii

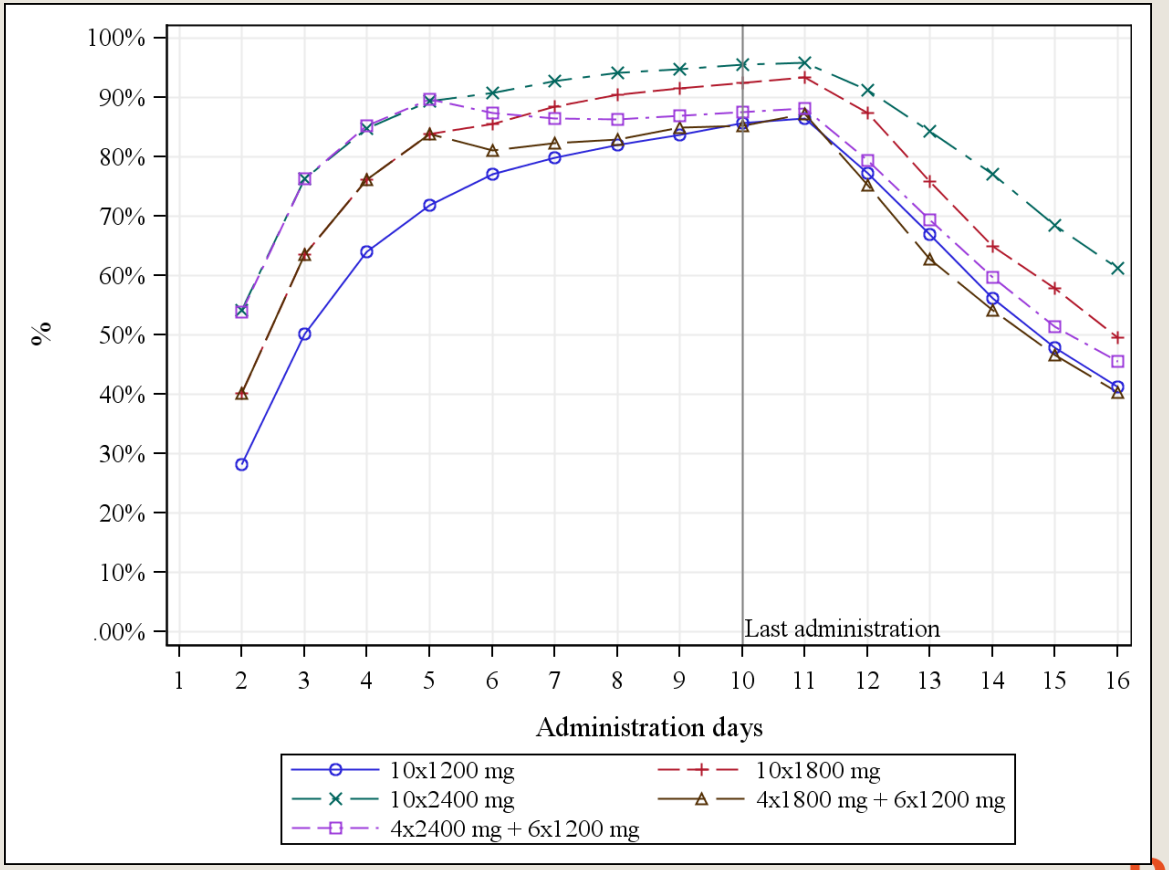
- **1200** mg once daily for 10 days with food
- **1800** mg once daily for 10 days with food
- **2400** mg once daily for 10 days with food
- **1800** mg for 4 days followed by **1200** mg for 6 days once daily with food
- **2400** mg for 4 days followed by **1200** mg for 6 days once daily with food

POP PK : Median of M2 simulation predose concentrations as fonction of dosing



Population PK probability calculations

% of subjects with M2 simulated predose concentrations >10 mg/L



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Dose regimens tested

- Based on the results, the 2 mixed dosing regimens were selected to be tested in healthy volunteers in ascending order
  - 1800 mg 4d, followed by 1200 mg 6d
  - 2400 mg 4d, followed by 1200 mg 6d

MAD in fed condition design selection of therapeutic dose

- Design: 10 Days MD, Randomized, Double-blind, Placebo controlled

- N= 18 subjects/ cohort (12 A + 6 Pl)
  - **1800 mg loading dose from D1 – D4 + 1200 mg D5 –D10,**
  - **2400 mg loading dose from D1 – D4 + 1200 mg D5 –D10,**

- Evaluations
  - **PK + Holter ECG at baseline D4; D7; D10**
  - **PK at D1; D4; D7; D10 + through levels D2, D5, D8, D9, D11 - D18**
  - **Safety LFT : D4; D7; D10 + follow up for 7 days**

MAD in fed condition Results

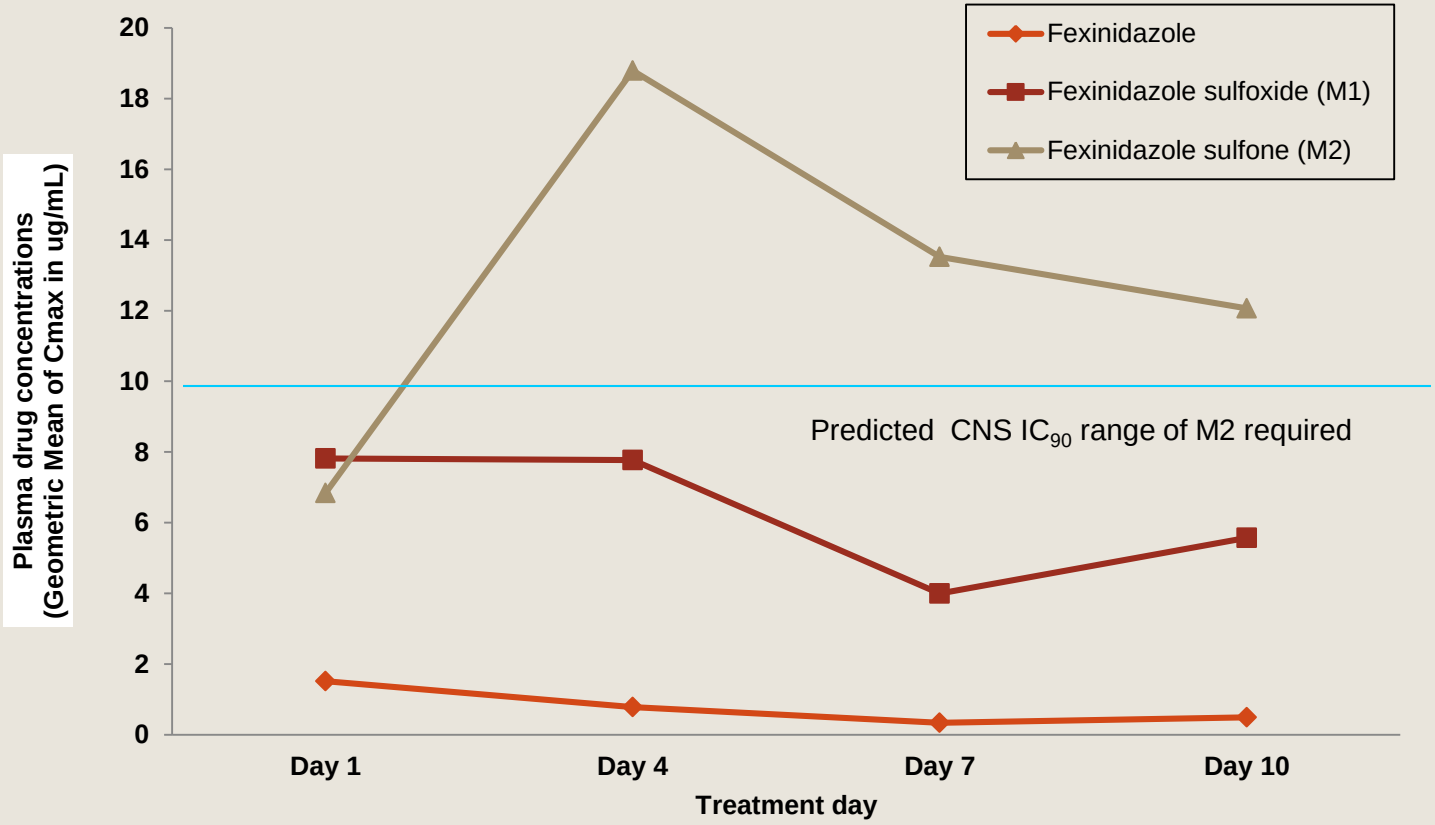
Overall results

- **1800mg D1-D4 + 1200mg D6 - D10 completed**
  - Detection of a safety group effect in 1srt sub-cohort of 9 subjects
  - All subject were replace
  - dosed in sub-groups of 3 no drop out
  - Total subjects N= 24 (n= 18 active + 6 placebo)
  - No biological safety concern
  - Majors Aes: Headache nausea vomiting at loading dose

- **2400mg D1-D4 + 1200mg D6 - D10**
  - 2 sub-groups of 3 subjects dosed
  - 1 subjects withdrawn in each dose for anxiety and episode of panic attack
  - Dosing stopped for safety reason

pK result

Geomatric means of Cmax at D1,D4,D7,D10



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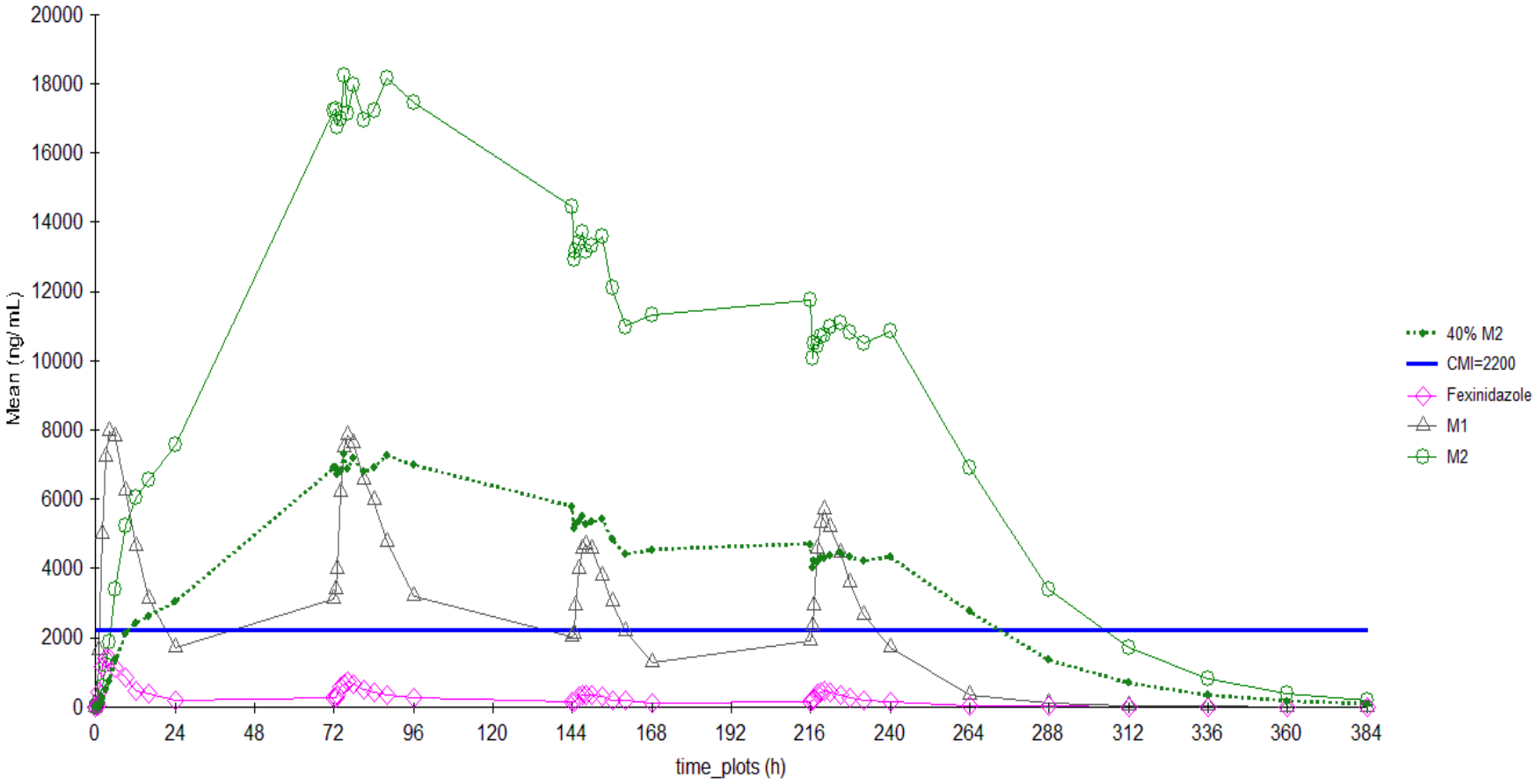
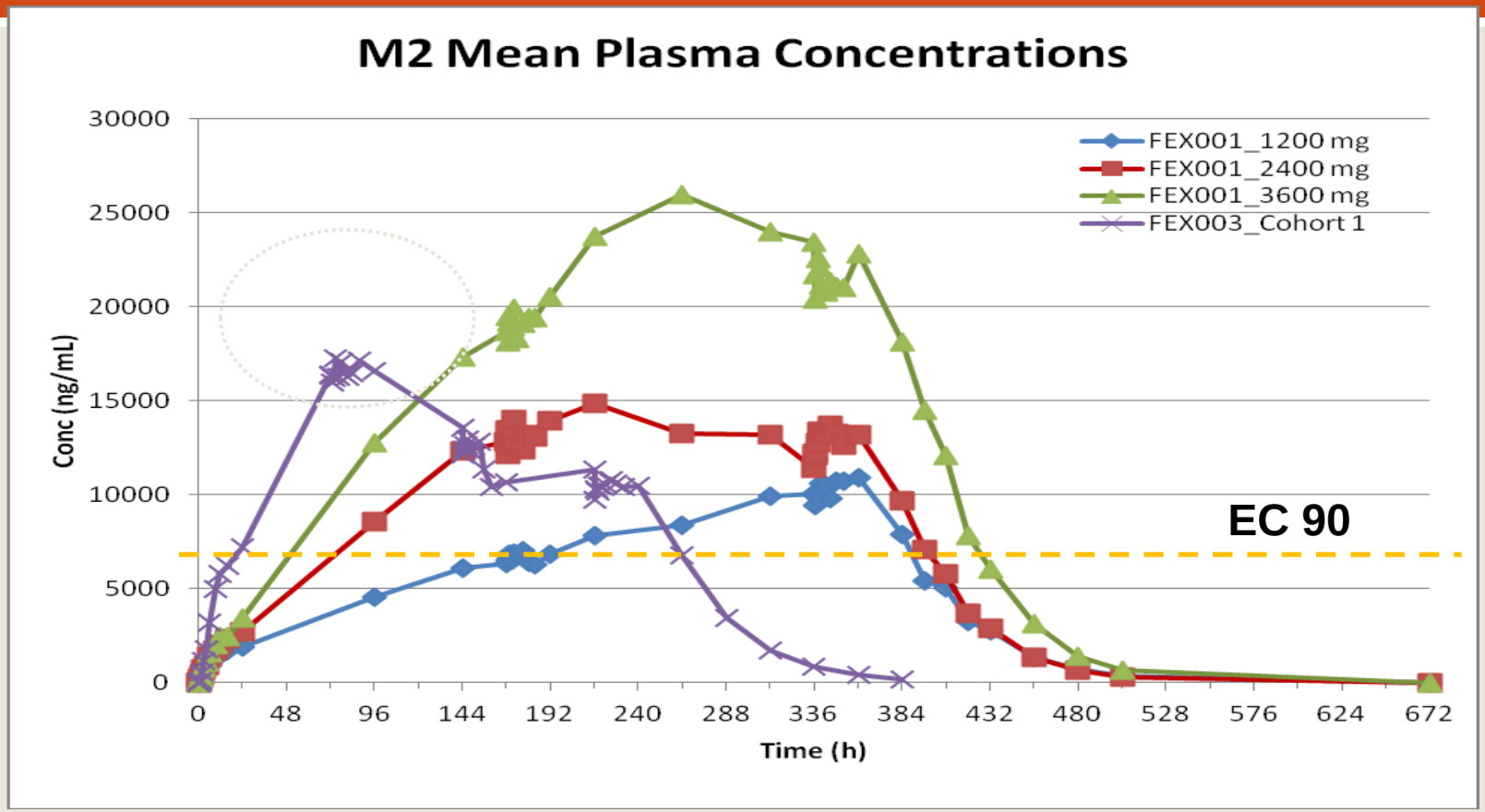
M2 Mean Plasma levels 1800/1200 mg



PK results : 1800/1200mg



Active metabolite M2 plasma concentration was reached rapidly and maintained for 3 to 4 days in all cases and more than 80% of the subjects had pre-dose plasma levels above 10 mg/L.

Fexinidazole Safety results

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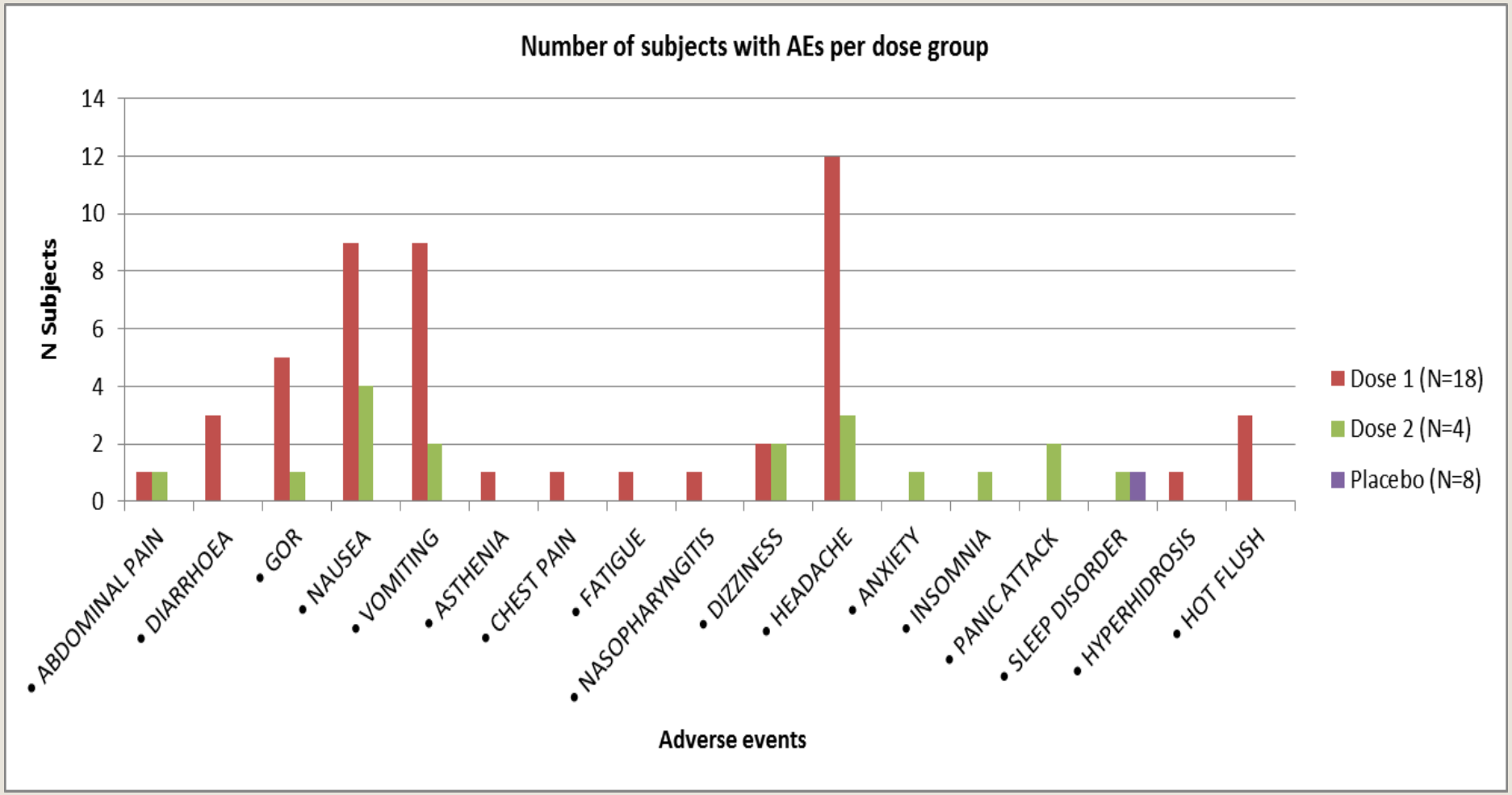
Safety Biology / FEXI003

Parameter	Placebo (N=8)			Dose 1 (N=18)			Dose 2 (N=4)		
	1N<x≤2N n	2N<x≤3N n	>3xN n	1N<x≤2N n	2N<x≤3N n	>3xN n	1N<x≤2N n	2N<x≤3N n	>3xN n
ALAT	1	0	0	1	0	0	0	0	0
ASAT	0	0	0	0	0	0	0	0	0
Alkaline phosphatase	0	0	0	0	0	0	0	0	0
Gamma-GT	0	0	0	1	0	0	0	0	0
Total bilirubin	0	0	0	6	1	2	1	0	0
Creatinine	0	0	0	11	0	0	3	0	0

Total bilirubin: abnormalities were present at screening and don't increased under treatment
liver function test: No abnormal values in liver function test
plasma creatinine: variation related to class abnormalities.

Adverse events /FEXI003



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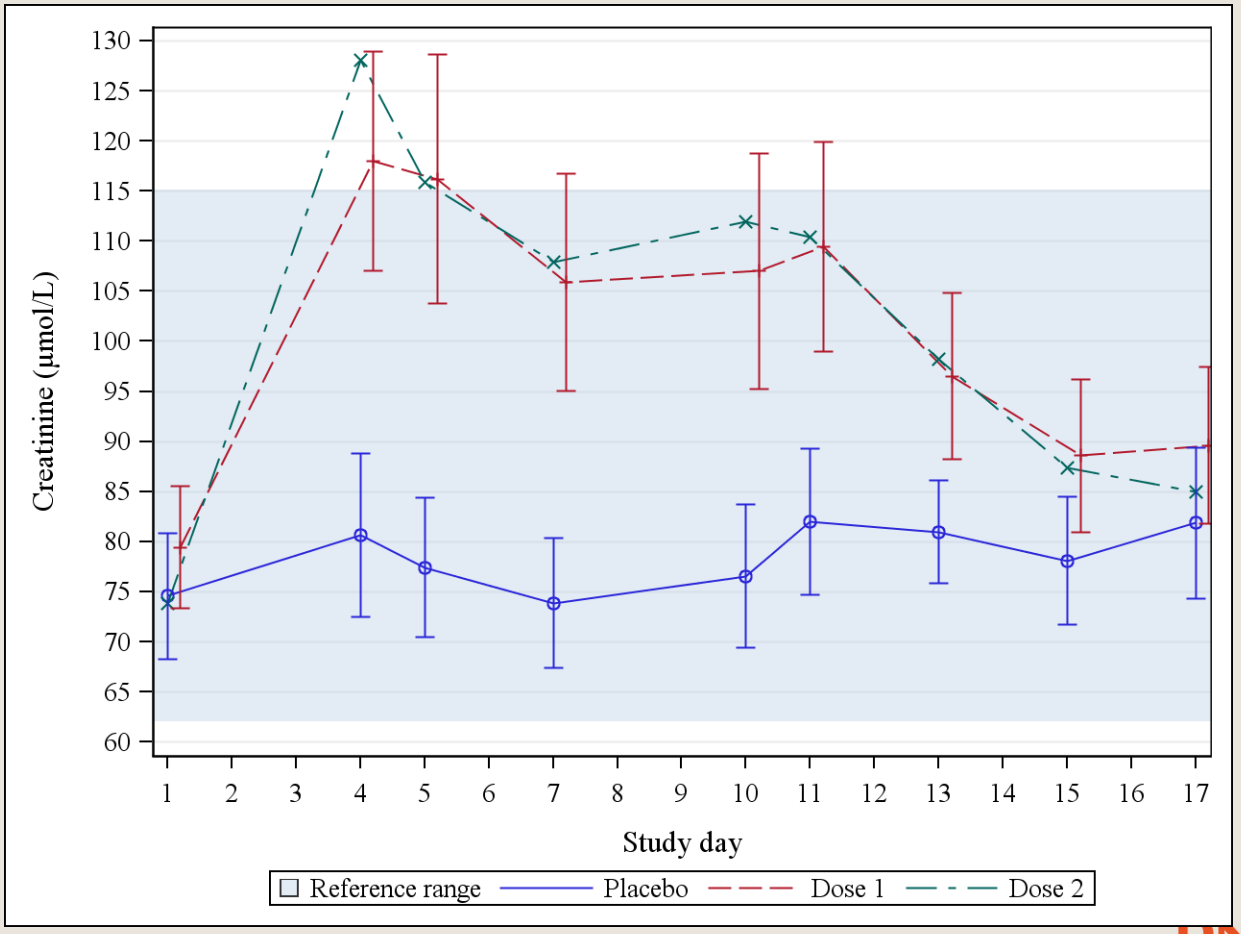
Creatinine Results FEX003



Conclusion

- Fexinidazole and its metabolites are activ againts *T brucei gambiense and rhodesiense*
- The most active metabolite is M2: Fexinidazole sulfone
- No drug interaction expected as several CYP P450 involved
- fexinidazole should be taken in fed conditions at once a day dosing
- The best regimen is 1800mg for 4 days followed by 1200mg for 6 days

THANK YOU

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