Results from the pivotal trial of fexinidazole in sleeping sickness patients

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DNDi
Drugs for Neglected Diseases *initiative*

FEX004 study design

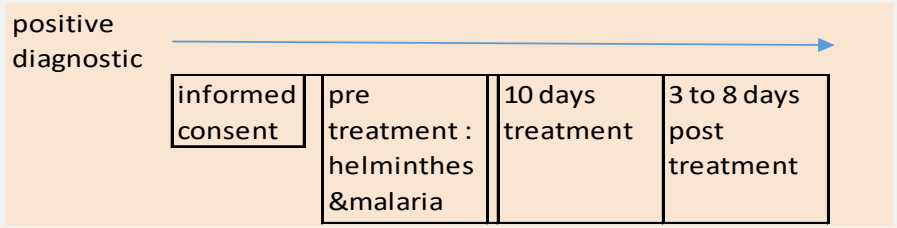
FEX004: Pivotal phase II/III in adults late Stage 2 HAT patients

FEXINIDAZOLE versus NECT, open–labeled randomised (2/1) (n=394)

Fexinidazole : 600mg tablet oral dosing OD with food for 10days :3 tablets D1-D4 + 2 tablets D5-D10

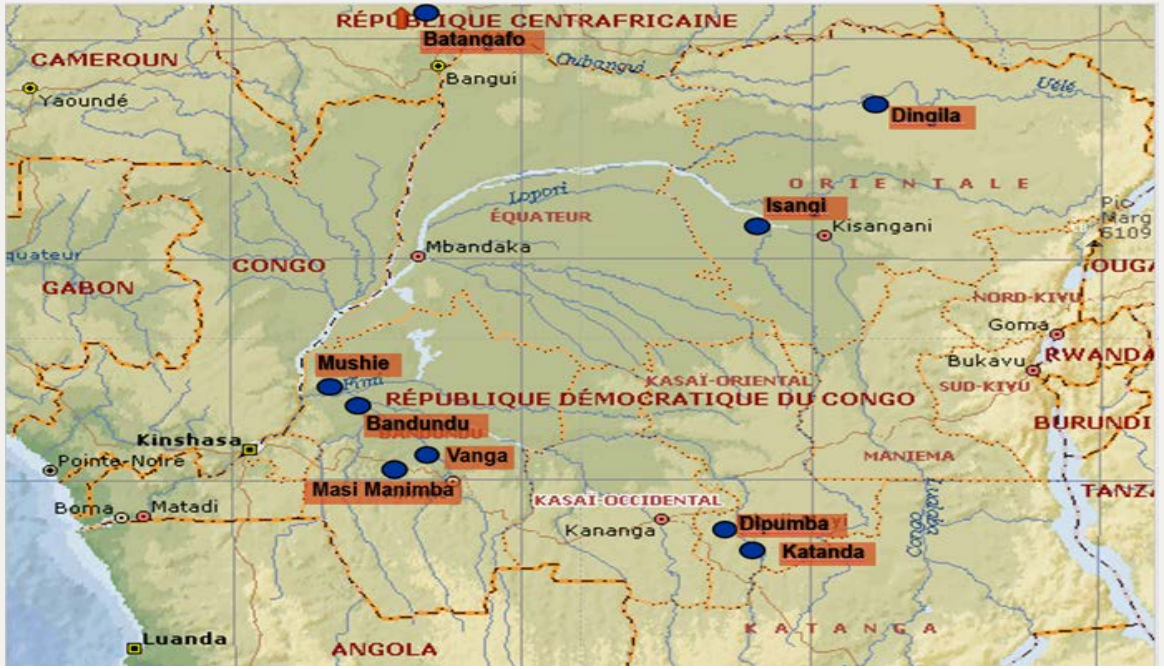
NECT: eflornithine IV infusion (2hours) 2*/day for 7 days + Nifurtimox oral dosing 3*/Day for 10days

PERIOD 1: HOSPITALIZATION



- Signs and symptoms of HAT,
- Physical examinantions,
- Neurological examinations
- Clinical adverse events
- Haematology & biochemistry
- ECG recording with online review
- PK sampling (DBS) blood and CSF

PERIOD 2: FOLLOW-UP



Operational challenges

Logistical support to clinical sites

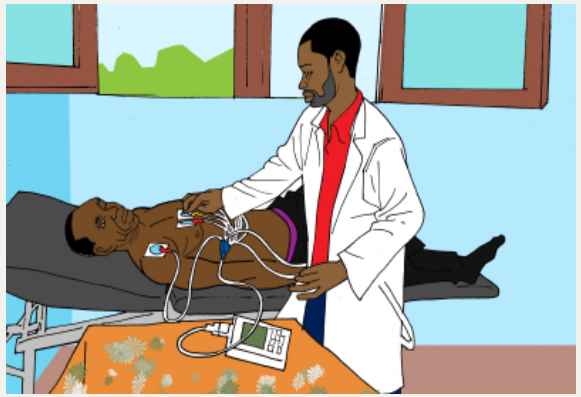
- Upgrading each clinical site infrastructure
  - Renovation of ward
  - Creating a laboratory room
  - Hygiene and waste disposal equipment and infrastructure
  - Provision of clinical equipment for biological testing, ECG recording, emergency care devices
- Energy supply (Solar and generators)
- Installation of internet connection

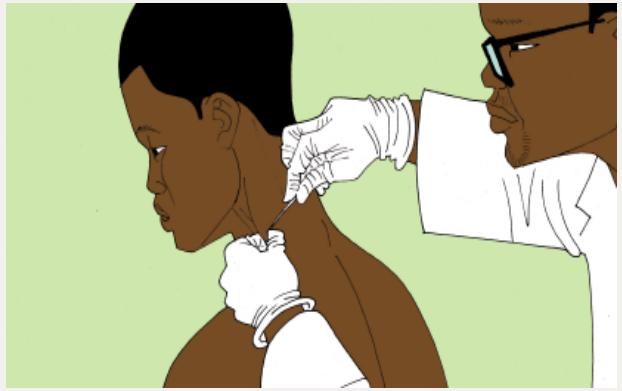
Study related support

- Support of screening to the mobile teams + equipment
- Informed consent for illiterate patients (pictures ICF)
- Local coordination support team (medical, logistic and technic)
- Training of medical, nursing and lab staff
  - Regular updates of clinical staff

Monitoring:

- conducted by SwissTPH





Statistical methods

- **Primary objective:** non inferiority versus NECT @ M18
- Based on success/failure (binary)
- Expected NECT efficacy: 94%
- Expected fexinidazole efficacy: 89%
- Expected difference NECT-fexinidazole: 5%

- Acceptable margin set @ 13%
- Primary analysis on mITT
  - excluding patients who fled due to civil war and were LTFU due to this

Success defined as absence of failure
failure was conservatively defined as:

- Trypanosome in any body fluid any time after EOH
- rescue treatment (any time),
- or death (any cause),
- or WBC > 20/µl in CSF at 18M
- or Lost To Follow Up.

Patient disposition in FEX004

Study dates: October 2012 to November 2016
Screening involved mobile teams and study sites ,
In total around 500.000 individuals were screened
419 people were detected positive
395 patients had parasite positive CSF and met the inclusion criteria
394 were randomized (1 patient committed suicide before randomization)

		NECT	FEXINIDAZOLE
		N= 130	N= 264
Gender %	Male	61.50%	61.00%
	Female	39%	39%
Age (years)	Mean	35.32	34.48
	Min-Max	15-68	15-71

Efficacy results

Statistical results		NECT	FEXINIDAZOLE	difference between proportion and 97.06% CI	p-value*
Primary Efficacy Analysis	mITT	97.64% (n=127)	91.22% (n=262)	-6.42(-11.22; -1.62)	0.0029
Sensitivity analysis	ITT	95.38% (n=130)	90.53% (n=264)	-4.85(-10.40 ; 0.76)	0.0016

*Note: the two-sided p-value presented here is from a Blackwelder test (with a non-inferiority margin of -13%). It should be compared to 0.0294 (two-sided). The confidence interval is adjusted for multiplicity of testing.

Description of failures by category (primary analysis)

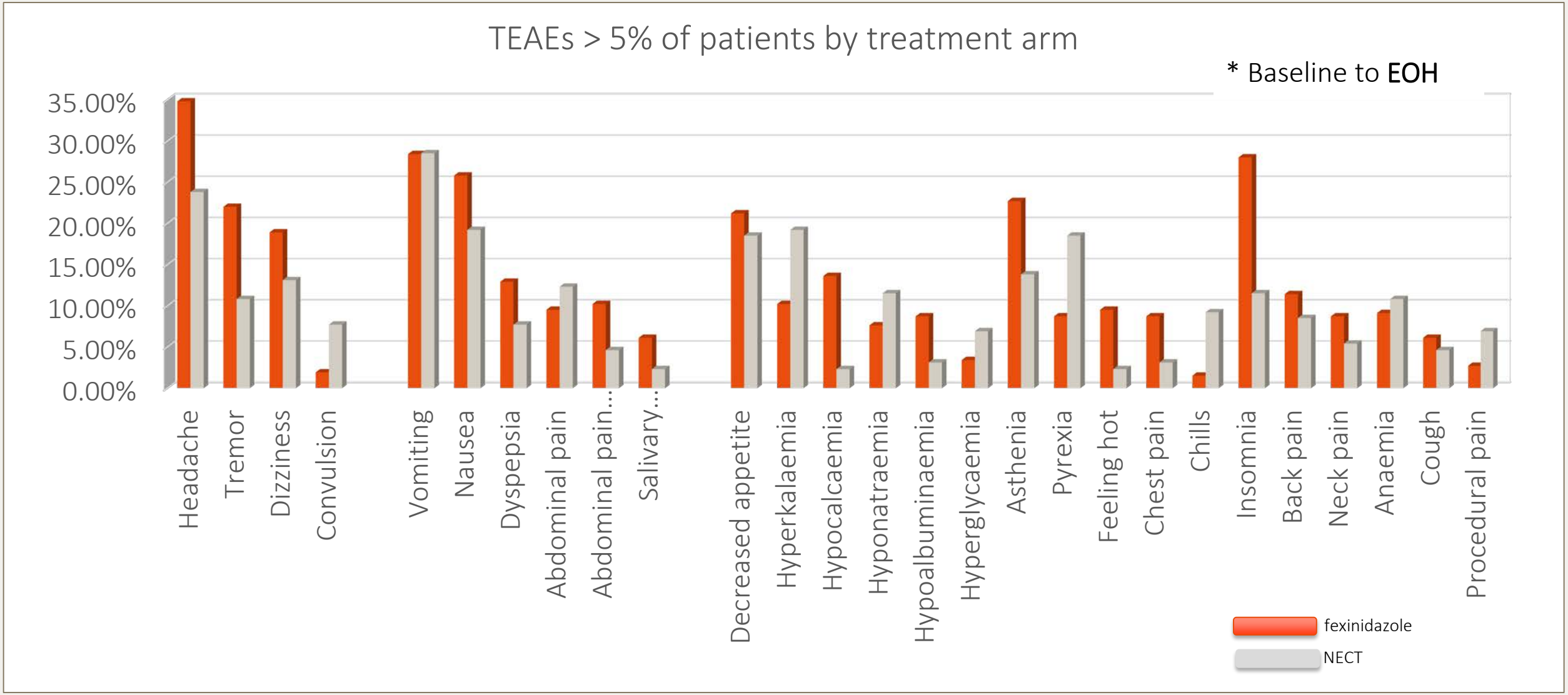
	NECT (N= 127)	Fexinidazole (N=262)
Success rate	97.6%	91.2%
Failures N (%)	3 (2.4%)	23 (8.8%)
Disease relapse N (%)	0	15 (5.7%)
Death N (%)	2 (1.6%)	6 (2.3%)
LTFU N (%)	0	1 (<0.1%)
No Lumbar Puncture N (%)	1 (<0,1%)	0
Consent withdrawal N (%)	0	1 (<0.1%)

Safety summary

	FEX004 NECT (N=130)	FEX004 Fexinidazole (N=264)
TEAEs	121 (93%)	247 (94%)
Serious TEAEs	13 (10%)	31 (12%)
Severe	23 (18%)	52 (20%)
Deaths	2 (2%) *	9 (3%)*
Possibly Related	103 (79%)	215 (81%)
Permanent treatment discontinuation	0	2 (<1%)

**No statistical difference between NECT and fexinidazole on relative risk of death p>0.05*

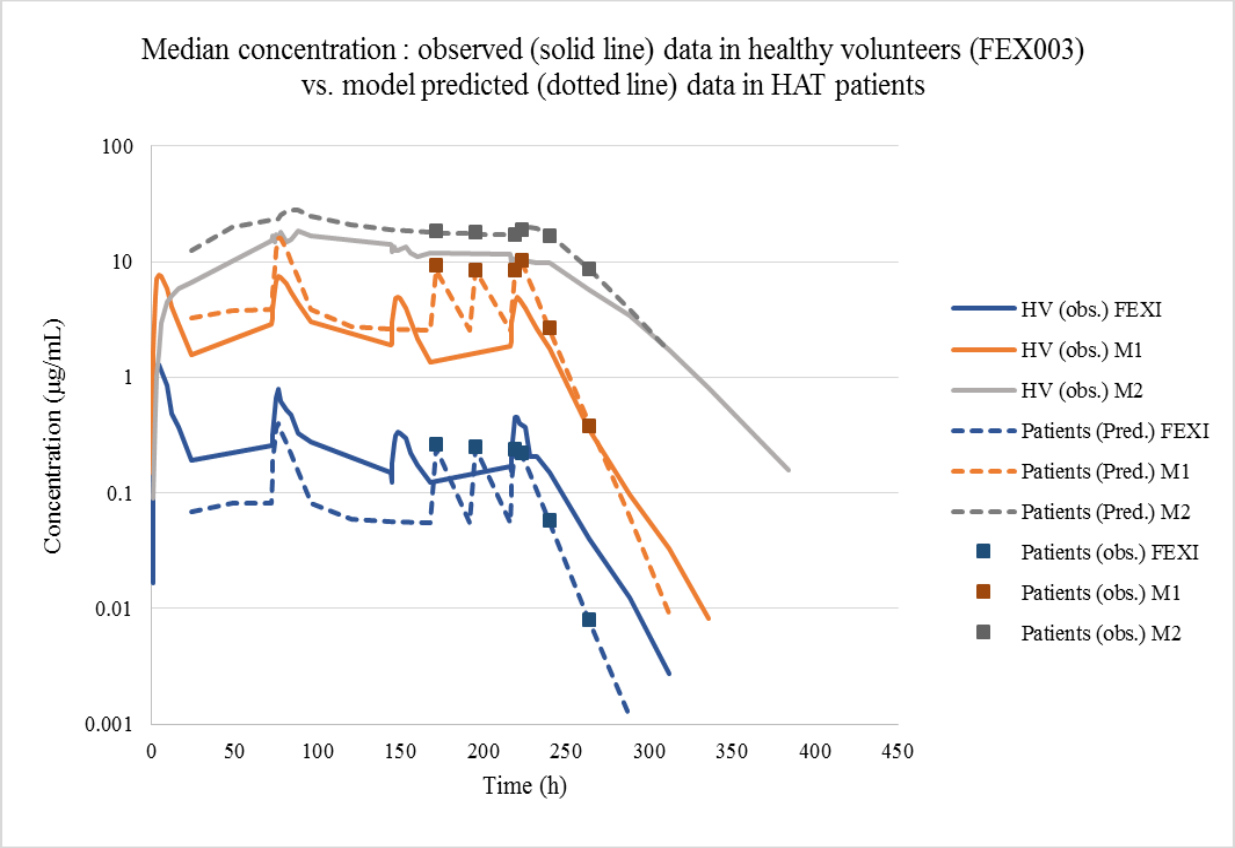
Safety* per Treatment Emergent Adverse Events

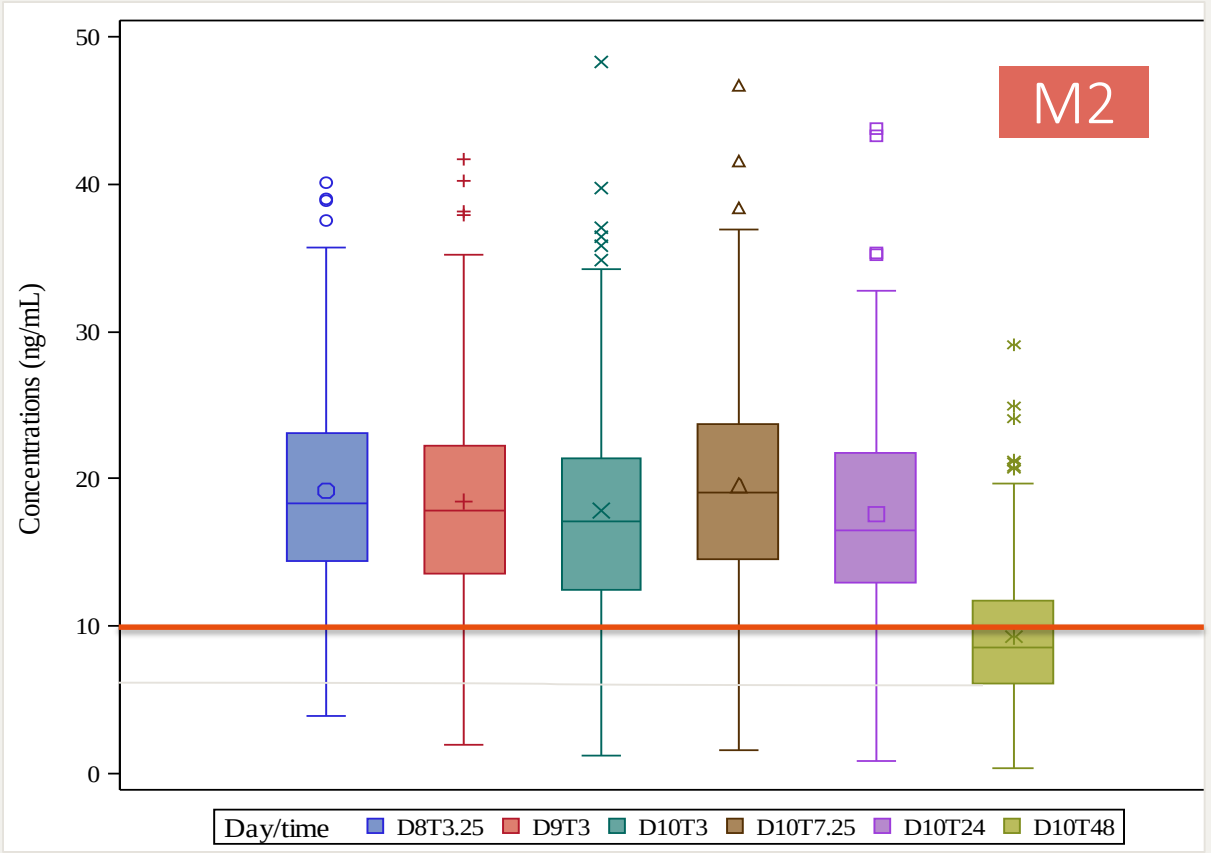


Death cases

Patient ID	Preferred term	Causality as assessed by the Investigator	Start – End date	Failure in primary analysis
FEXINIDAZOLE GROUP (FEX004)				
01_009	Ameloblastoma	Unrelated	Days 474 – 701	NO
01_023	Alcohol poisoning	Unrelated	Day 675	NO
01_046	Poisoning	Unrelated	Day 8	YES
02_040	Pneumonia + Influenza	Unrelated	Day 82	YES
02_042	Poisoning	Unrelated	Days 21 – 22	YES
02_060	Starvation + Hypoglycemia	Unrelated	Day 352	YES
02_064	Pneumonia aspiration	Unrelated	Day 5	YES
05_008	Inguinal hernia Strangulated	Unrelated	Day 594	NO
06_006	Death (cause unknown)	Unrelated	Day 94	YES
NECT GROUP (FEX004)				
02_023	Hypoglycaemia	Unrelated	Day 19	YES
07_008	Cardio-respiratory arrest	Unrelated	Day 197	YES

Pharmacokinetic results





- No covariates were found to influence the population PK parameters.
- There was no difference in popPK parameters between the adults patients (<50 kg or >50 kg)

Fexinidazole has demonstrated high efficacy and acceptable tolerability

Efficacy:

- The primary efficacy endpoint at 18 months was met: 91.22% success
- The difference between fexinidazole and NECT is within an acceptable pre-set margin

Safety:

- No patient discontinued treatment due to a related adverse event
- Safety profile did not reveal any unexpected finding
- Digestive (nausea, vomiting) and CNS (headache, insomnia) disorders were the most frequently observed adverse events.

Fexinidazole will simplify the way HAT is managed,
with benefits for the patients,
the healthcare professionals and public health

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including nurses, lab technicians and any other staff at the site

NSSCP mobile teams

MSF:

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