# HAT Platform

## Fexinidazole update

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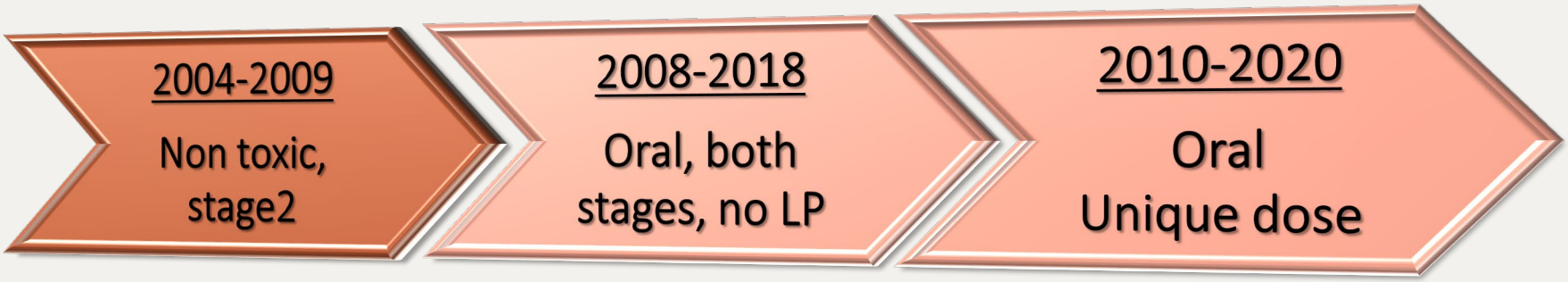
Kampala, October 2018


# What were our objectives? How far are we?




| Parasite confirmation<br>Staging | Parasite confirmation<br>No staging | No parasite confirmation<br>No staging |
|---|---|---|

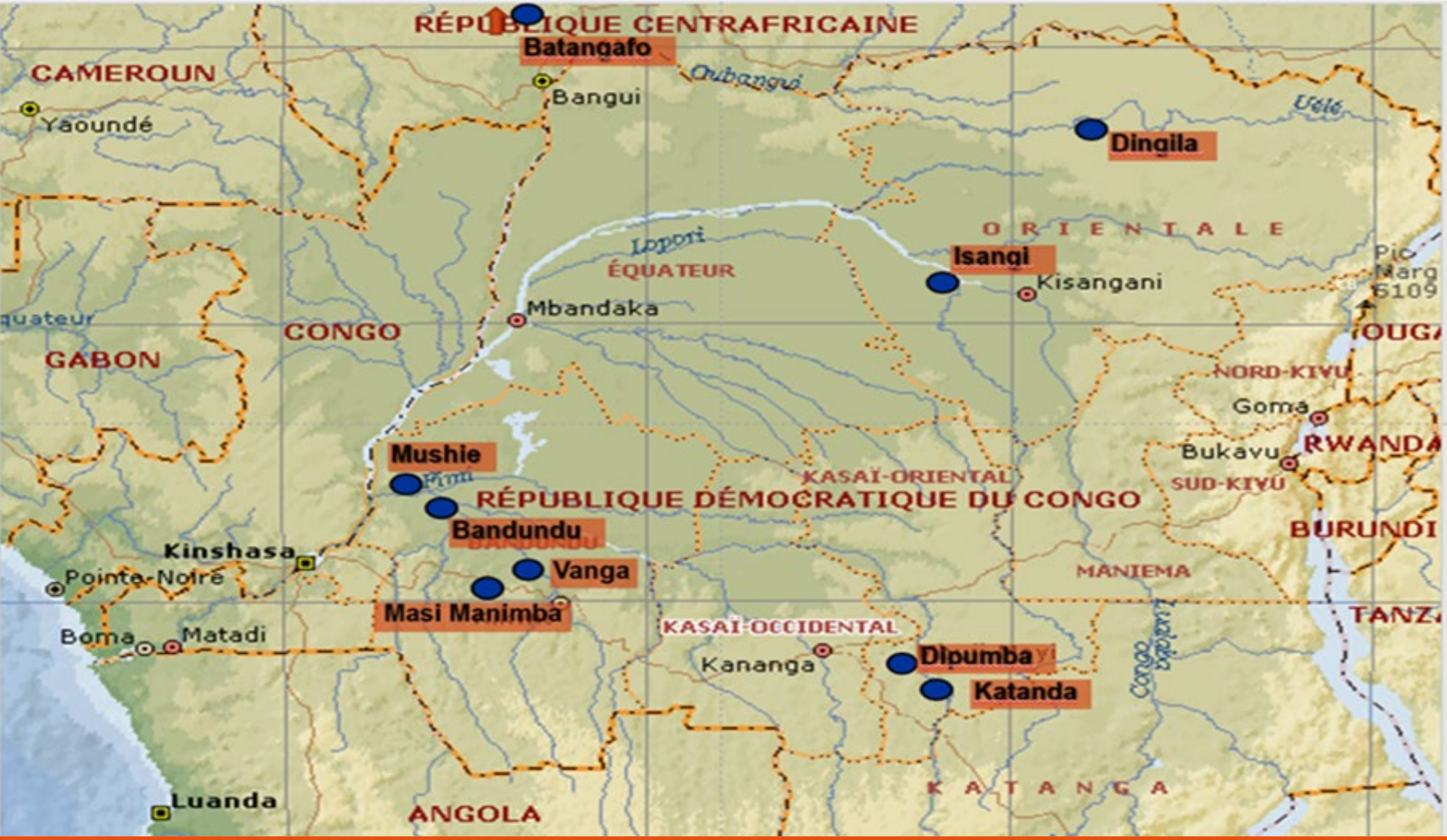
We are here !!!

# Our roots: the Target Product Profile developped by the HAT Platform

TPP
*(Target Product Profile)*

| | Desirable | Minimally acceptable |
|---|---|---|
| Indication | Stage 1 **and** 2 HAT caused T. by b. gambiense and T.b. rhodesiense | Stage 1 **and** 2 HAT caused by T.b. gambiense |
| Target Population(s) | adults, children, pregnant and lactating | adults, children |
| Route of Administration | **oral** | parenteral |
| Product Presentation | oral tablet/capsule/suspension | intramuscular, intravenous |
| Dosage form and schedule | once a day for 7 days | once a day for 10 days |
| Expected Efficacy | 95% parasitolgical cure at 18 month follow-up - | 90% parasitological cure at 18 months follow-up |
| Contraindications, Warnings, Precautions, Interactions, and Use during Pregnancy and Lactation | AE/SAE profile better than existing therapy. No drug related mortality- Can be used in all trimesters of pregnancy and in lactating women | AE/SAE profile no worse than existing therapy |
| Coadministration | No interaction with anti-retrovirals, anti-TB drugs | |
| Shelf-Life | Greater than 4 years in zone 4 - | Greater than 2 years in zone 4 - |
| Cost of Goods | < 30€/course | < 100€/course or < 200€/course if high efficacy |
| Storage | no cold/cool chain | no cold chain |
| Product registration /WHO PQ | | dossier to ICH or equivalent st. |

# From 2012 to 2016 in DRC & CAR



# HAT Phase II/III Clinical Development plan

HAT Plan discussed with EMA (art58) during 2 Scientifc Advice meetings (2011 and 2014)

| Study number | design | population | Dose | N | Country |
|---|---|---|---|---|---|
| FEX004 | OL [(i)], randomised, non-inferiority, vs NECT | Adults inpatients Stage 2 g-HAT | Day 1-4: 1800mg/day qd - Day 4-10: 1200mg/day QD | 394 | DRC[(ii)], CAR[(iii)] |
| FEX005 | OL, cohort | Adults inpatients Stage 1, early stage 2 g-HAT | Same as FEX004 | 230 | DRC[(iv)] |
| FEX006 | OL, cohort | Children ≥ 6-14 years All stages, g-HAT, inpatients | *> 35kg*: same as FEX004 *≥ 20kg to < 35kg* 1200mg/day, QD 4days 600mg/day, QD 6 days | 125 | DRC[(iv)] |
| FEX009 | OL, cohort | All the above, in- or outpatients | As above | 91 | DRC and Guinea |

**A total of 710 patients treated with fexinidazole**

(i) Sponsor blinded (ii) Democratic of Republic of Congo (iii) Central African Republic (iv) same sites as FEX004

# The 3 fexinidazole studies

- FEX004 pivotal study
  - Open-label for site but blinded for Sponsor (including data management)
  - Based on a binary endpoint: success or failure measured after 18 months follow-up. Failure is defined as below:
    - trypanosome in any body fluid after EOH
    - or WBC > 20/µl in CSF or
    - or rescue treatment,
    - or death,
    - or Lost To Follow Up.
  - Non-inferiority test with a 13% acceptability margin
  - Primary analysis on mITT (excluding patients who fled due to civil war and were LTFU due to this)
- FEX005
  - Adults – Stage 1 Working hypothesis: success rate greater than 80%.
- FEX006
  - Children - Working hypothesis: success rate greater than an unacceptable rate of 80% and compatible with a target rate of 92%.

EOH: End of Hospitalisation CSF : cerebrospinal Fluid mITT: modified intention-to-treat

# results

DNDi
Drugs for Neglected Diseases *initiative*

# Patient disposition in HAT studies

| | FEX004 [a] | | FEX005 [b] | FEX006 [b] | All Fexi |
|---|---|---|---|---|---|
| | NECT | Fexinidazole | | | |
| N | | | | | |
| ITT | 130 | 264 | 230 | 125 | 619 |
| mITT | 127 | 262 | | | |
| LTFU | | | | | |
| ITT | 3 | 4 | 0 | 0 | 4 |
| mITT | 0 | 2 | | | |
| Treatment discontinuation (N) | 0 | 2 | 0 | 0 | 2 |
| Gender (%) | | | | | |
| Male | 61,5 | 61 | 50 | 53,6 | 55,4 |
| Female | 38,5 | 39 | 50 | 46,4 | 44,6 |
| Age (years) | | | | | |
| Mean | 35,32 | 34,48 | 34,38 | 10,86 | 29,68 |
| Min-Max | 15 - 68 | 15 - 71 | 15 - 73 | 6 - 15 | 6 - 73 |

(a) 18 months follow-up - (b) 12 months follow-up

# Primary efficacy analysis

| | FEX004 | FEX005 | FEX006 |
|---|---|---|---|
| N | (394) mITT 389<br>262 fexi – 127 NECT | 230 | 125 |
| Efficacy based on S.R ( success rate**) | S.R. = 91.2% (fexi) vs 97.6% (NECT) | S.R. = 98.7%<br>[96.2% - 99,7%] | 97.6%<br>[93.1% - 99.5%] |
| | Difference (effect size) = -6.61%<br>C.I. of difference = [-11.2%; -1.61%] | p < 0.0001<br>($H_0$: S.R. ≤ 80%) | p < 0.0001<br>($H_0$: S.R. ≤ 80%) |
| | P = 0.0029*<br>$H_0$: $\Delta_{S.R.} \leq -13\%$) | | |

*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.

** Success defined as absence of failure

Failure is defined as follows:

- Presence of trypanosomes in any body fluid
- WBC in CSF >20 /µl at 12-18 months
- Rescue treatment
- Death
- Lost to follow up

# Success rate according to number of WBC and presence of tryps in CSF at baseline

EP population, n = 608*, fexinidazole group, 3 studies pooled, [95% C.I.]

| CSF parameter | No tryps | Tryps | Overall success rate |
|---|---|---|---|
| WBC ≤ 5 | **99.6%** (253/254), [98.2%, 99.9%] | **100%** (2/2), [33.3%, 100%] | 98.1% (255/256), [98.2%, 99.9%] |
| 6 ≤ WBC ≤ 20 | **100%** (59/59), [95.8%, 100%] | **100%** (3/3) [46.4%, 100%] | 100% (62/62), [96.0%, 100%] |
| 21 ≤ WBC ≤ 100 | **98.6%** (72/73), [85.5%, 97.3%] | **97%** (32/33), [86.7%, 99.7%] | 98.1% (104/106), [94.1%, 99.6%] |
| WBC > 100 | **91.7%** (22/24), (75.9%, 98.2%] | **88.1%** (140/159), [82.3%, 92.4%] | 88.5% (162/183), [83.3%, 92.5%] |
| Overall success rate | 99.0% (406/410), [97.7%, 99.7%] | **89.8%** (177/197), [85.1%, 93.5%] | 96.0% (583/607), [94.3%, 97.4%] |

* One patient was not included in this table because of one missing data

Effect of number of WBC ($Log_e$ WBC): $p < 0.0001$

Effect of tryps: $p < 0.0001$

Effect of tryps in addition to WBC: Not Significant due to correlaon between tryps and WBC

N.B. WBC > 20 = late stage 2 (adults and children)



WBC cut-off at 100 differentiates higher and lower success rates

# Link between presence of high WBC and clinical symptoms in all fexinidazole studies

| Symptom occurrence | WBC ≤100 69.7% | 101 ≤WBC ≤400 16.5% | WBC >400 13.8% | P-value association | Occurrence rate |
|---|---|---|---|---|---|
| | | | % (n/N) | | |
| Headache | 63.5 (273/430) | 71.6 (73/102) | 75.3 (64/85) | 0.0531 | 66.5 (N = 616) |
| Weight loss | 38.5 (165/429) | 61.8 (63/102) | 57.6 (49/85) | <0.0001 | 45 (N = 616) |
| Asthenia | 27.0 (116/429) | 60.8 (62/102) | 67.1 (57/85) | <0.0001 | 38.1 (N = 616) |
| Pruritus | 25.6 (110/430) | 52.0 (53/102) | 81.2 (69/85) | <0.0001 | 37.6 (N = 617) |
| Sleepiness | 16.3 (70/429) | 70.6 (72/102) | 78.8 (67/85) | <0.0001 | 33.9 (N = 616) |
| Fever | 28.4 (122/429) | 47.1 (48/102) | 34.1 (29/85) | 0.0014 | 32.3 (N = 616) |
| Anorexia | 15.3 (66/430) | 19.6 (10/102) | 12.9 (11/85) | 0.4266 | 15.7 (N = 617) |
| Insomnia | 16.3 (70/430) | 34.3 (35/102) | 43.5 (37/85) | <0.0001 | 23.2 (N = 617) |
| Tremor | 7.4 (32/430) | 34.3 (35/102) | 51.8 (44/85) | <0.0001 | 18.0 (N = 617) |
| Walking disability | 3.3 (14/430) | 20.6 (21/102) | 30.6 (26/85) | <0.0001 | 9.9 (N = 617) |
| Nausea | 9.5 (41/430) | 8.8 (9/102) | 5.9 (5/85) | 0.5578 | (N = 617) |
| Language disability | 1.4 (6/429) | 14.7 (15/102) | 21.2 (18/85) | <0.0001 | (N = 616) |
| Success rate (%) | 99.3 | 91 | 85.7 | | |

**Legend**: P-values are linked to the null hypothesis of equality of success rate in presence and absence of each symptom.
Occurrence rate is the percentage of patients presenting the symptom at entry in the evaluable set of patients treated with fexinidazole.

# Management of failures

| ITT set of patients | Fexinidazole N (%) | NECT N (%) | Cumulated relapses fexinidazole N (%) | Cumulated relapses NECT N (%) | Excess relapse rates |
|---|---|---|---|---|---|
| Randomized | 264 | 130 | 0 | 0 | |
| Relapse at M3 | 0 | 0 (0%) | 0 | 0 | 0% |
| Relapse at M6 | 3 (1.14%) | 0 (0%) | 3 (1.14%) | 0 (0%) | 1.14% |
| Relapse at M12 | 7 (2.65%) | 0 (0%) | 10 (3.79%) | 0 (0%) | 3.79% |
| Relapse at M18 | 3 (1.14%) | 0 (0%) | 13 (4.92%) | 0 (0%) | 4.92% |
| Relapse at M24 | 2 (0.76%) | 0 (0%) | 15 (5.68%) | 0 (0%) | 5.68% |

**Abbreviations: CSF,** cerebrospinal fluid**; ITT**, intention-to-treat; **LTFU**, lost-to-follow-up; **M**, month; **NECT**, nifurtimox-eflornithine combination therapy; **WBC**, white blood cells

14 out of the 15 patients received NECT

- 7 were cured
- 5 were LTFU
- 2 only had 6 months follow-up

→ High success rate after NECT rescue

# Summary of Safety

| | DNDiFEX004 NECT (N=130) | DNDIFEX004 Fexinidazole (N=264) | DNDIFEX005 Fexinidazole (N=230) | DNDIFEX006 Fexinidazole (N=125) | All Fexinidazole (N=619) |
|---|---|---|---|---|---|
| TEAEs | 121 (93%) [607] | 247 (94%) [1525] | 214 (93%) [1258] | 116 (93%) [583] | 577 (93%) [3366] |
| Serious TEAEs | 13 (10%) [22] | 31 (12%) [51] | 20 (9%) [32] | 10 (8%) [14] | 61 (10%) [97] |
| Severe | 23 (18%) [27] | 52 (20%) [68] | 23 (10%) [31] | 22 (18%) [25] | 97 (16%) [124] |
| Deaths | 2 (2%) [2] * | 9 (3%) [11] * | 4 (2%) [7] | 1 (<1%) [2] | 12 (2%) [17] |
| Possibly Related | 103 (79%) [345] | 215 (81%) [923] | 195 (85%) [859] | 103 (82%) [353] | 513 (83%) [2135] |
| Permanent treatment discontinuation | 0 | 2 (<1%) [2] | 0 | 0 | 2 (<1%) [2] |

Format is number of subjects (percent of subjects) [number of events]

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

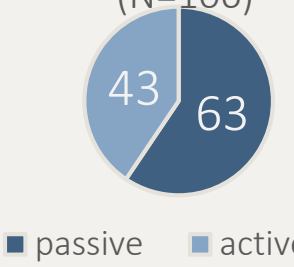
# Patients with AEs according to SOC by decreasing frequency (ITT)

| | DNDiFEX004 NECT (N=130) | DNDIFEX004 Fexinidazole (N=264) | DNDIFEX005 Fexinidazole (N=230) | DNDIFEX006 Fexinidazole (N=125) | All Fexinidazole (N=619) |
|---|---|---|---|---|---|
| Any TEAE | 121 (93%) | 247 (94%) | 214 (93%) | 116 (93%) | 577 (93%) |
| Gastrointestinal disorders | 64 (49%) | 157 (59%) | 179 (78%) | 98 (78%) | 434 (70%) |
| Nervous system disorders | 64 (49%) | 158 (60%) | 142 (62%) | 61 (49%) | 361 (58%) |
| General disorders and administration site conditions | 51 (39%) | 122 (46%) | 94 (41%) | 51 (41%) | 267 (43%) |
| Psychiatric disorders | 23 (18%) | 103 (39%) | 73 (32%) | 19 (15%) | 195 (32%) |
| Musculoskeletal and connective tissue disorders | 21 (16%) | 58 (22%) | 38 (17%) | 13 (10%) | 109 (18%) |
| Investigations | 10 (8%) | 7 (3%) | 42 (18%) | 21 (17%) | 70 (11%) |
| Blood and lymphatic system disorders | 18 (14%) | 29 (11%) | 13 (6%) | 20 (16%) | 62 (10%) |
| Infections and infestations | 8 (6%) | 22 (8%) | 13 (6%) | 12 (10%) | 47 (8%) |
| Respiratory, thoracic and mediastinal disorders | 11 (8%) | 32 (12%) | 9 (4%) | 6 (5%) | 47 (8%) |
| Vascular disorders | 9 (7%) | 24 (9%) | 18 (8%) | 1 (<1%) | 43 (7%) |
| Skin and subcutaneous tissue disorders | 8 (6%) | 22 (8%) | 13 (6%) | 7 (6%) | 42 (7%) |
| Eye disorders | 3 (2%) | 15 (6%) | 16 (7%) | 10 (8%) | 41 (7%) |
| Cardiac disorders | 7 (5%) | 18 (7%) | 17 (7%) | 4 (3%) | 39 (6%) |
| Renal and urinary disorders | 7 (5%) | 13 (5%) | 6 (3%) | 0 | 19 (3%) |
| Injury, poisoning and procedural complications | 14 (11%) | 15 (6%) | 0 | 2 (2%) | 17 (3%) |
| Reproductive system and breast disorders | 1 (<1%) | 5 (2%) | 5 (2%) | 0 | 10 (2%) |

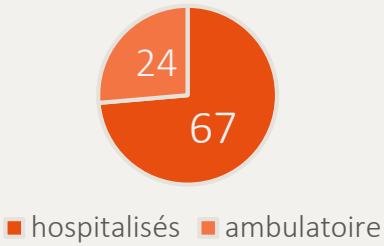
# FEX 009 – Patient Disposition and exposure to fexinidazole

(Cut-off date 31-Aug-18)

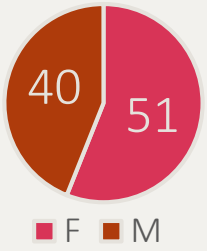
Type of diagnostic
(N=106)



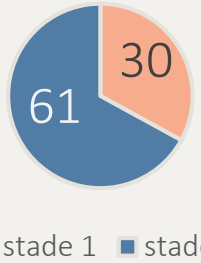

Treatment type
N=91



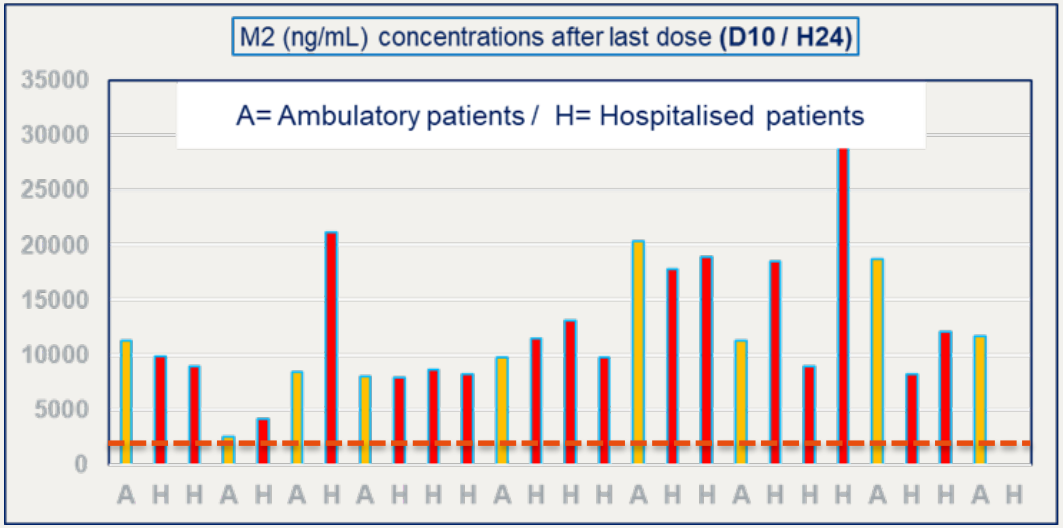

Demography
N=91




Stades
N=91




FEX09 CSF M2 concentration at 24hours post end of treatment




Good exposure at the end of treatment

# In summary

- A total of 710 patients have been treated with fexinidazole with 619 patients, both stages adults and children as part of the regulatory submission
- Fexinidazole has met the pre-set efficacy criteria as planned by protocol in all 3 studies
- In the overall population the efficacy was 96%
- Fexinidazole showed a favourable safety profile - No patient discontinued due to side effects – *this is confirmed in the ongoing study*
- Fexinidazole is under final review by EMA

# Fexinidazole – Industrial partner

- Joint development between sanofi/DNDi

DNDi
Drugs for Neglected Diseases *initiative*

responsible for preclinical, clinical, & pharmaceutical development

SANOFI

responsible for the industrial development, registration, production & DP distribution

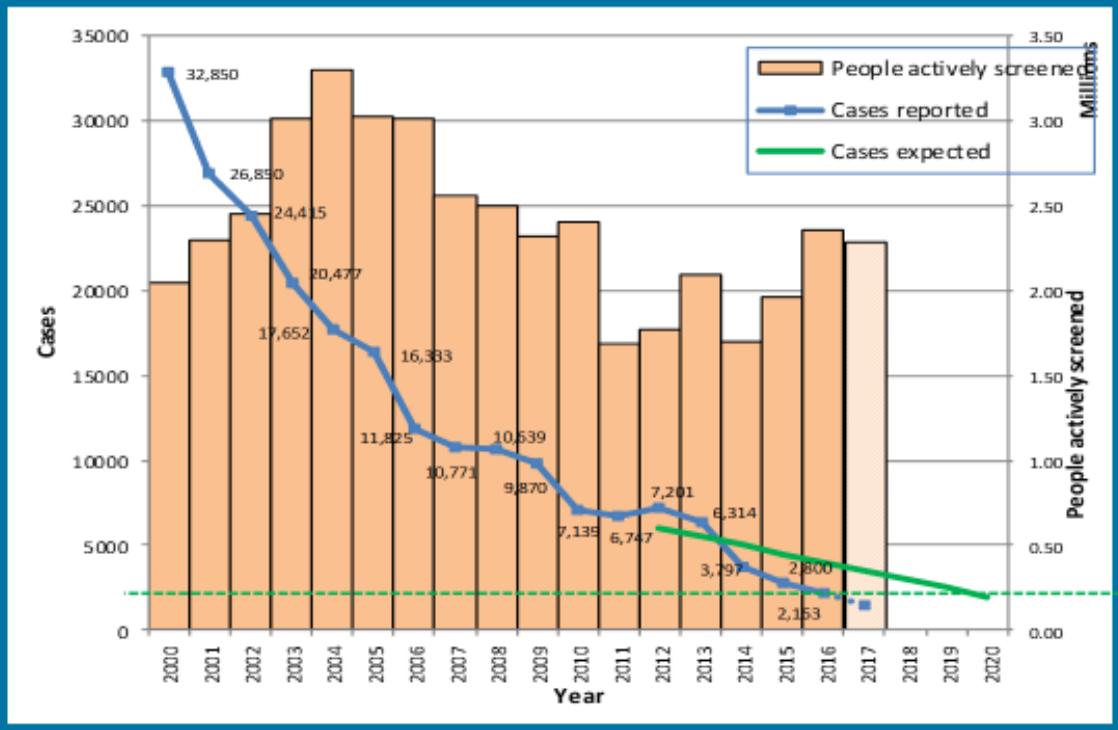
- Proposed indication:

*Treatment of both the first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis due to T.b gambiense in adults and children ≥ 6 years old and weighing 20 kg or more.*

# Measuring progress towards elimination

World Health Organization

Number of new cases reported and WHO benchmark



# Conclusion

Coupled with screening and diagnostic tools, the deployment of fexinidazole should support the programs to reach the last mile of the elimination goals, as set by the WHO roadmap.

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nurses, lab technicians and any other staff.

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DNDi
Drugs for Neglected Diseases initiative

# Partners on sleeping sickness R&D

## NGOs

epicentre
MEDECINS SANS FRONTIERES DOCTORS WITHOUT BORDERS
FIND Because diagnosis matters

## MoH & INTERNATIONAL ORGANISATIONS

World Health Organization
PNLTHA-RDC

## UNIVERSITIES

THE UNIVERSITY of EDINBURGH
MAKERERE UNIVERSITY
PACE UNIVERSITY Work toward greatness.
LMPH Laboratory of Microbiology, Parasitology and Hygiene University of Antwerp
UNIVERSITY OF JURA

## RESEARCH INSTITUTES

INSTITUTE OF TROPICAL MEDICINE ANTWERP
Swiss TPH
KARI
CIBAF
Institut Pasteur de Bangui
EANETT
Institut de Recherche pour le Développement FRANCE
Institut National de Recherche Biomédicale (INRB), DRC

## CLINICAL PARTNERS: REGIONAL PLATFORM FOR CLINICAL RESEARCH

- National sleeping sickness control programmes, research institutions and national laboratories of public health of the most affected endemic countries:

- Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; Institute of Tropical Medicine-Antwerp, Belgium; Institut National de Recherche Biomédicale (INRB), DRC; University of Makerere, Uganda; Kenya Agricultural Research Institute – Trypanosomiasis Research Centre (KARI-TRC), Kenya; Tropical Medicine Research Institute (TMRI), Sudan; Institut Pasteur Bangui, University of Juba, South Sudan; CAR; Médecins Sans Frontières (MSF); Foundation for Innovative New Diagnostics (FIND), Switzerland; Eastern Africa Network for Trypanosomosis (EANETT); Centre interdisciplinaire de Bioéthique pour l'Afrique Francophone (CIBAF); The National Sleeping Sickness Control Programme of Guinea; INZI Project of the University of Edinburgh. WHO Department of Neglected Tropical Diseases, as observer.

## INDUSTRIAL PARTNERS

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