HAT
DNDi program progress and evolution in the path to elimination

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HAT Platform,
Kampala
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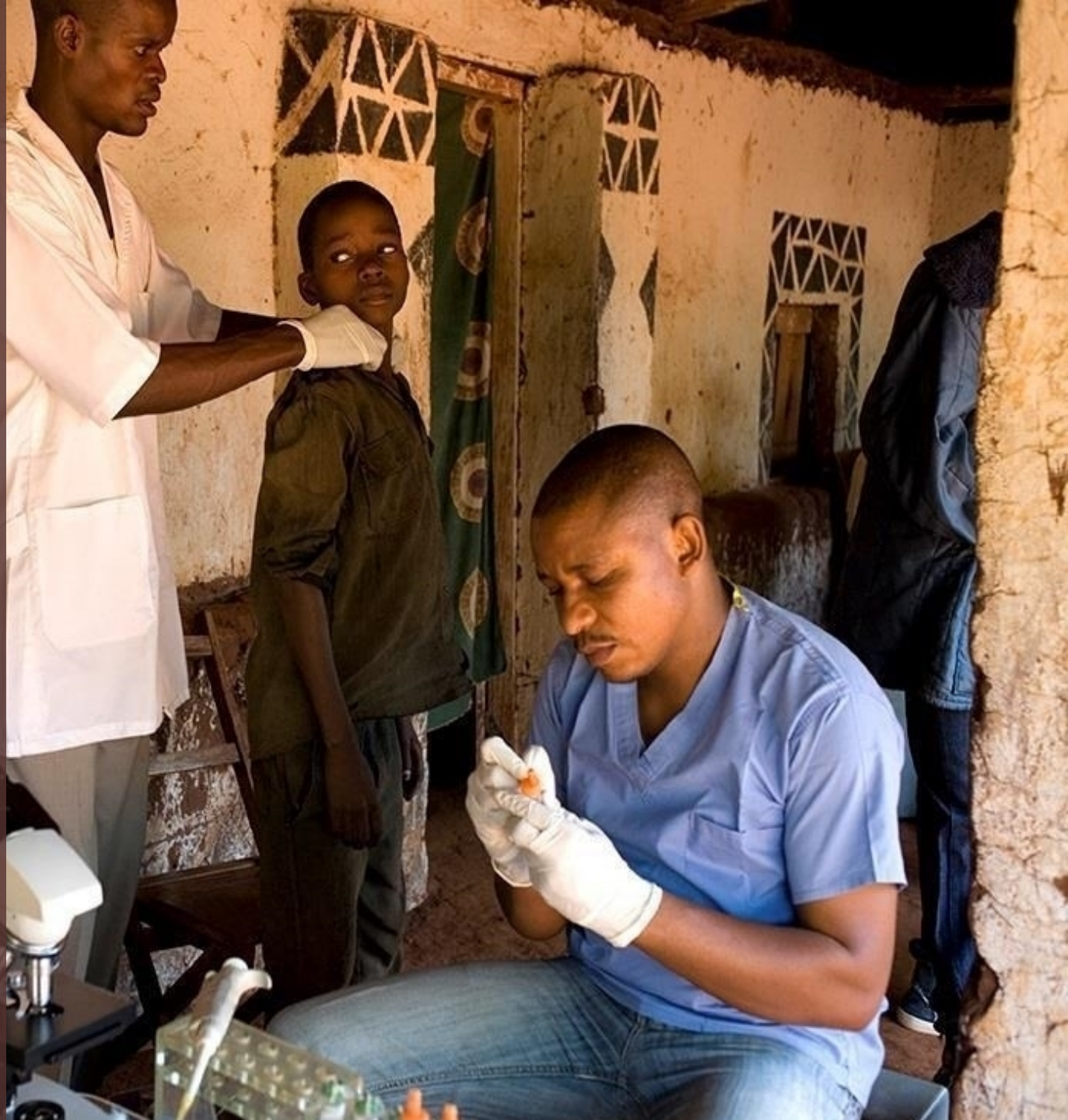


DND*i*'s Mission

- To develop new drugs or new formulations of existing drugs for **people suffering from neglected diseases**.
- To develop drugs for the **most neglected diseases** (such as sleeping sickness, leishmaniasis, and Chagas disease), while considering engagement in **R&D projects for other neglected patients** (e.g. malaria, paediatric HIV, filarial infections)
- To **strengthen capacities in a sustainable manner**, including through know-how and technology transfers in the field of drug R&D for neglected diseases.
- To adopt **a dynamic portfolio approach**

Responding to the needs of patients suffering from neglected diseases

DND*i*'s PRIORITY:
Neglected Patients

…from bench to bedside

+ incubation with WHO of:

GARDP
Global Antibiotic Research & Development Partnership

Sleeping Sickness

Search for a simplified and improved treatment

Two new treatments in development to achieve and sustained elimination

15 years ago

Melarsoprol:

Toxic, resistant

Eflornithine:

Unavailable

Since 2009

NECT

Improved therapy

2018

Fexinidazole

Oral treatment (10 days)

Future objective

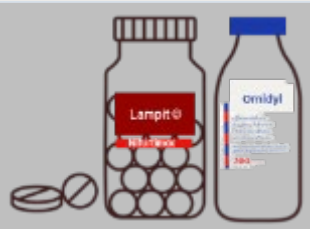
Acoziborole

Single-dose, oral treatment

A better, simpler treatment for sleeping sickness

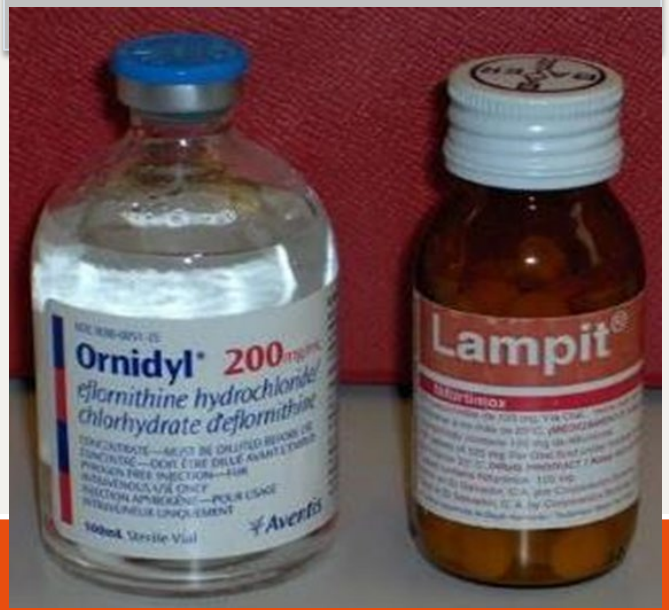
Implementation

Access



Nifurtimox-eflornithine combination therapy

Objective: Develop and implement a safe, effective, and adapted treatment for stage 2 *gambiense*



- 2003: single study by MSF and Epicentre in Congo
- 2004: additional sites in DRC by DND*i* in collaboration with Epicentre, MSF, STI (now Swiss TPH), and DRC National Control Programme (PNLTHA)
- 2008: multi-centre clinical study comparing efficacy and safety in 287 patients finds **NECT as well-tolerated as eflornithine monotherapy**
- 2009: NECT included in WHO Essential Medicines List
- 2010-2012: **Implementation study** including adults, pregnant and breastfeeding women, and children
- Ongoing: DND*i* continues to support access to NECT in endemic countries

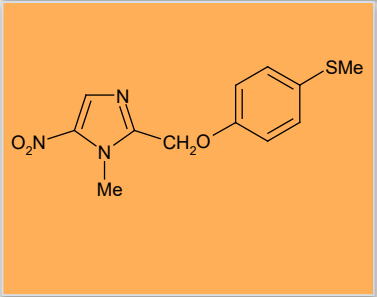
DND*i*'s First NCE to Reach Phase II/III

DEVELOPMENT

Phase IIb/III | *Registration*

Fexinidazole

Objective: Develop and register fexinidazole as a new drug for the treatment of stage 2 *T.b. gambiense*, ideally also for stage 1 and for children between 6 and 14 years old



PARTNERS: *BaseCon; Bertin Pharma; Venn Life Sciences (previously Cardinal Systems); Cardiabase; Médecins Sans Frontières, and other HAT Platform members; Phinc Development; National Control Programmes of the Democratic Republic of Congo and the Central African Republic; RCTs; Sanofi; Swiss Tropical and Public Health Institute (Swiss TPH); SGS; Theradis Pharma*

- 2007: Selection of fexinidazole as pre-clinical candidate for HAT
- 2008: Pre-clinical development completed. Prototype tablets available
- 2009: Phase I starts in France
- 2010: Phase I completed
- 2012: Phase II/III starts in DRC and CAR. Sanofi industrial partner. Comparing fexinidazole *vs* NECT in patients with stage 2
- 2015: Phase II/III completed. Inclusion of 394 patients. 2 additional studies for stage 1 and early stage 2 (230 p.) and children (125 p.) patients also completed recruitment.
- 2016: follow-up for the 3 studies + start of an implementation study in outpatients
- 2017: **Phase II/III results: 91.2% efficacy** + **submission to EMA** in December 2017
- 2019: EDCTP funded Trial for *Tb rhodesiense* to start

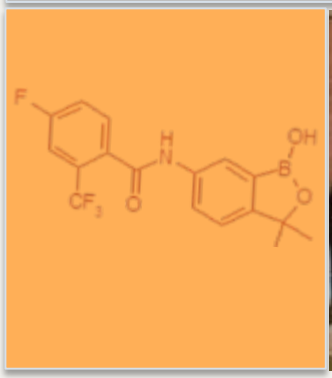
Promising Oral-only Single Dose Treatment for Sleeping Sickness to Enter Phase II/III Clinical Study

DEVELOPMENT

Phase IIb/III

ACOZIBOROLE

Objective: Develop and register acoziborole as a new drug for the treatment of stage 2 *T.b. gambiense,* ideally also for stage 1.



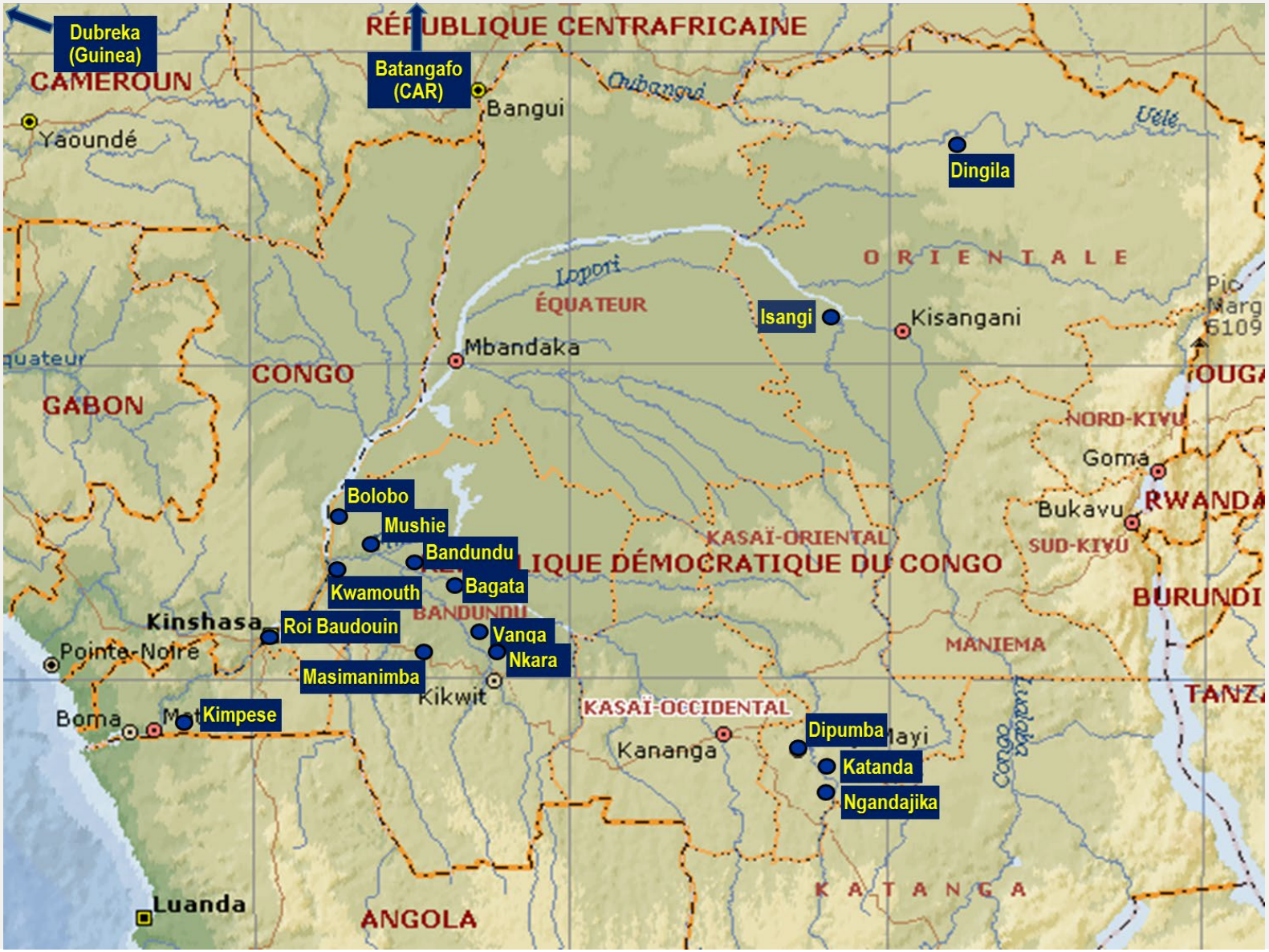
- Identified as hits against *T.b. brucei* at Sandler Center, University of California San Francisco
- Innovative partnership with 2 biotechs (Anacor, Scynexis) and 1 university (Pace) in the US
- End 2009: First NCE resulting from DND*i* lead optimization programme
- 2011: Pre-clinical development
- 2012: Phase I study in France
- June 2016: Start of Phase II/III clinical study in DRC in adults with stage 2 HAT
- May 2017: inclusion of adults with stage 1 HAT
- Jan 2019: Inclusions to be completed

PARTNERS: *Anacor Pharmaceuticals; Advinus Therapeutics; SCYNEXIS; Swiss Tropical and Public Health Institute; Institute of Tropical Medicine – Antwerp; Institut de Recherche pour le Développement; Institut National de Recherche Biomédicale*

The challenge of conducting Phase II/III trial

- Site selection oriented by epidemiology
- Infrastructure
  - Patient wards, Laboratory, Pharmacy, Invest. office
  - Telecommunication, electricity, cold chain
  - Water, sanitation and waste disposal
- Staff training
  - GCP, Clinical, Nursing, Lab procedures, electronic data transfert
- Equipment
  - Microscopy with camera (video),
  - HAT diagnosis, Biochemistry, haematology, digitalised ECG recording,PK/PD sample collection

DNDi HAT Clinical trial sites



The challenge of recruitment:
support to case detection in 2017-18

- Active case detection
  - Support 10 NSSCP Mobile teams
    - 1.000.000 examined persons
    - 110 detected HAT cases
- Passive case detection
  - 10 hospitals (study sites)
  - Since 2018 additional centers at the peripheral level:
  - 9 able to do serological + parasitological testing
  - 22 only serological testing + trypanolisis sampling to send to INRB
  - Reactive screening of those serologically identified previously
  - Additional PNLTHA active case detection with ITM collaboration

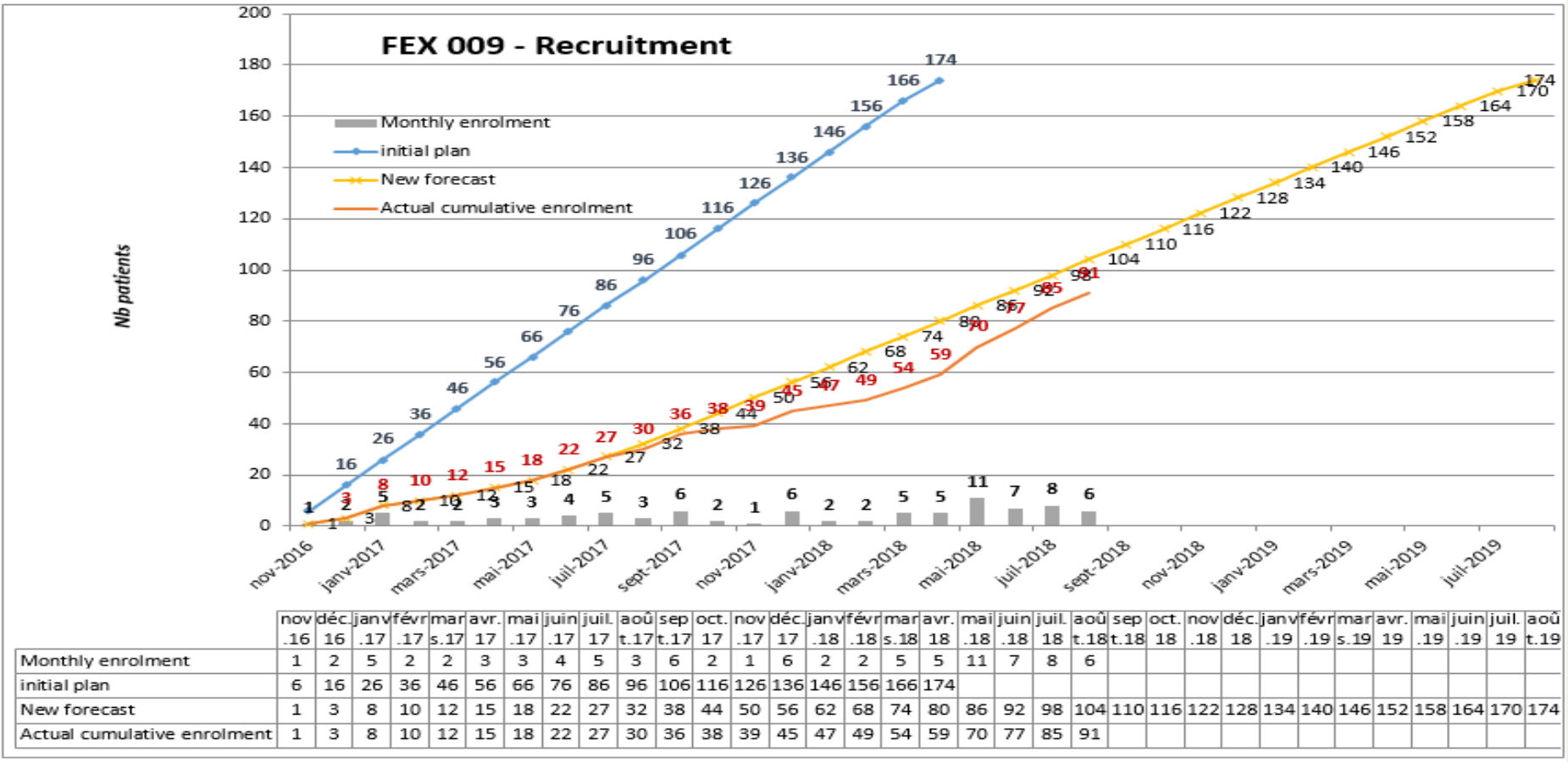
FEX009 STUDY UPDATE

→ Recruitment status as of 31-August

Sceened Patients	Screen Failures	In screening	Included	D11	M3	M6	M12	M18	Withdrawals, LFU, death
106	15	3	91	86	70	48	26	9	1

Patient disposition:

- 67 in- / 24 out-patients
- 61 stage 2 and 30 stage 1

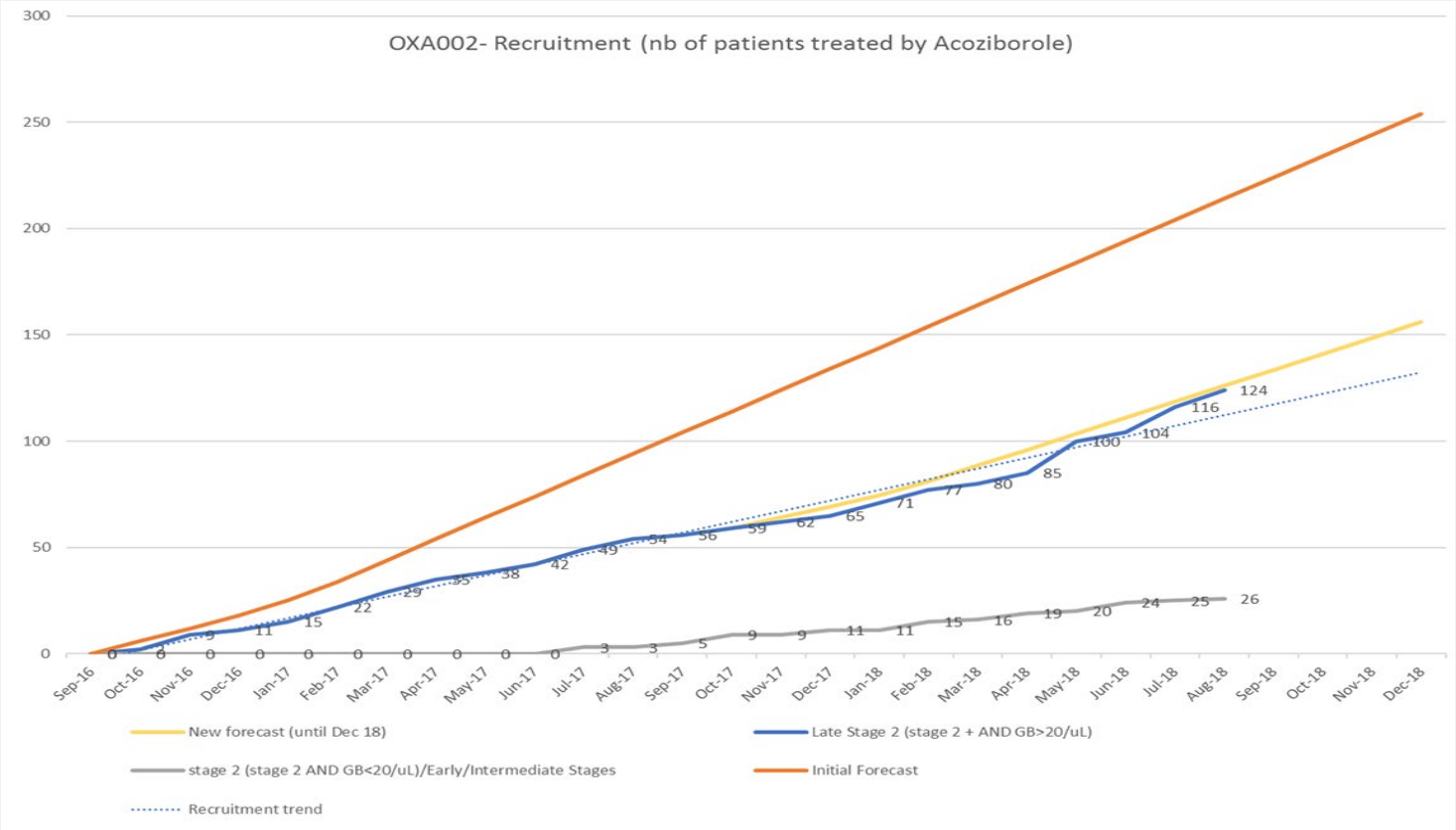


	nov .16	déc. 16	janv .17	févr .17	mars.17	avr. 17	mai .17	juin .17	juil. 17	aoû t.17	sept.17	oct. 17	nov .17	déc. 17	janv .18	févr .18	mars.18	avr. 18	mai .18	juin .18	juil. 18	aoû t.18	sept.18	oct. 18	nov .18	déc. 18	janv .19	févr .19	mars.19	avr. 19	mai .19	juin .19	juil. 19	aoû t.19
Monthly enrolment	1	2	5	2	2	3	3	4	5	3	6	2	1	6	2	2	5	5	11	7	8	6												
initial plan	6	16	26	36	46	56	66	76	86	96	106	116	126	136	146	156	166	174																
New forecast	1	3	8	10	12	15	18	22	27	32	38	44	50	56	62	68	74	80	86	92	98	104	110	116	122	128	134	140	146	152	158	164	170	174
Actual cumulative enrolment	1	3	8	10	12	15	18	22	27	30	36	38	39	45	47	49	54	59	70	77	85	91												

OXA 002 recruitment update

- Recruitment by August 31, 2018

Screened patients	Screen Failures	On Screening	Stage 2 patients > 20Cells in CSF	M3 FU	M6 FU	M12 FU	M18 FU
201	46	1	124	123	93	58	23



Conclusion: Sustained disease elimination requires new tools

- A **paradigm shift** in diagnosis and treatment is needed:
  - Treatment effective for stage 1 and 2 and for *T.b. gambiense* and *rhodesiense* => could avoid the need for staging lumbar puncture
  - Oral simplified treatment
  - Patients screened and diagnosed close to their village
- Efforts in **control and surveillance** (mobile teams, passive case-detection centres, sentinel surveillance sites) need to be sustained to avoid re-emergence of the disease.

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

ANACOR PHARMACEUTICALS
BAYER
SANOFI
SCYNEXIS
AVISTA PHARMA
ADVINUS

DONORS

AFD
Norad
giz Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) GmbH
Federal Ministry of Education and Research by KFW
Ministry of Foreign Affairs of the Netherlands
BILL & MELINDA GATES foundation
Liberté • Égalité • Fraternité RÉPUBLIQUE FRANÇAISE MINISTÈRE DES AFFAIRES ÉTRANGÈRES ET EUROPÉENNES
UKaid
UBS Optimus Foundation
UBS
Schweizerische Eidgenossenschaft Confédération suisse Confederazione Svizzera Confederaziun svizra
Swiss Agency for Development and Cooperation SDC
REPUBLIQUE ET CANTON DE GENEVE
POST TENEBRAS LUX
medicor foundation Liechtenstein
aecid

DNDi

Drugs for Neglected Diseases *initiative*