Nifurtimox Eflornithine Combination Therapy Phase IIIb Field Trial (NECT Field): Final Effectiveness and Safety Results

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Introduction and purpose *Trypanosoma brucei* (*T.b.*) *gambiense* Human African trypanosomiasis (HAT, sleeping sickness) is a fatal disease. In 2014, 3796 cases of HAT were diagnosed in Sub-Saharan Africa, 87% of which were in the Democratic Republic of Congo. Until 2009, available treatments for 2nd stage HAT were complicated to use (eflornithine monotherapy) or toxic and with low efficacy (melarsoprol). Nifurtimox-eflornithine combination therapy (NECT) was an improvement on this; shown to be non inferior to eflornithine therapy,[1] it presented safety advantages in a randomised controlled trial and was added to the World Health Organization (WHO) List of Essential Medicines (EML) for adults in 2009 and for children in 2013. Other advantages included a reduced treatment duration, with fewer IV infusions and a reduction in the cost of 50%. The NECT Field trial documents its overall safety and effectiveness at 24 months after treatment.

1. *Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial* by Priotto, G et al. *Lancet*. 2009 July; 374:56-64

Objectives The primary objective was to assess the clinical response of NECT under field conditions (discharged alive from the hospital). Secondary objectives included an assessment of the incidence and type of adverse events (AE) and the capacity of the treatment centers to deal with these, the feasibility of the implementation of NECT by the health center and the effectiveness of NECT at 24 months after treatment.

Methods A multicentre, open label, single arm, phase IIIb study of the use of NECT for 2nd stage *T.b. gambiense* HAT. All patients who had given signed informed consent and who could take oral medication were treated with NECT. Inclusion criteria were extended to children and pregnant women. Follow-up visits were done every 6 months until 24 months after end of treatment. The target sample size was 620 patients, a DSMB was appointed and ethical clearance was obtained from Basel and Kinshasa Ethics Committees.

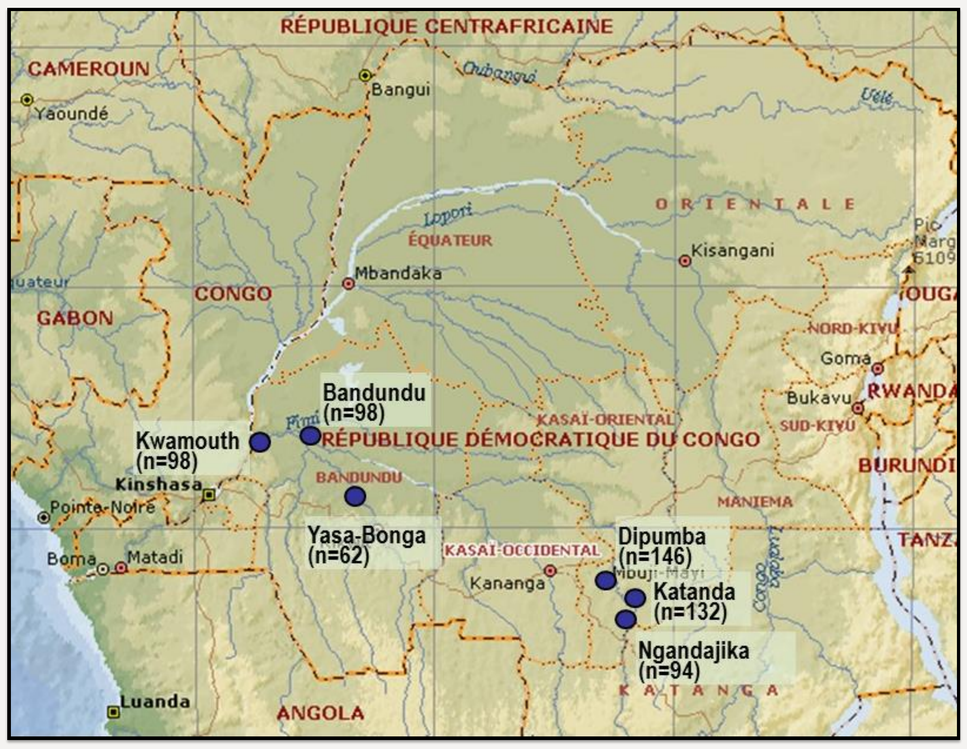
Results Between May 2009 and May 2010, 630 patients were included, but 1 died before receiving the first dose; 16 patients were completely lost to follow-up (2.6%). Out of 613 patients included in the final modified intention to treat analysis (mITT), 577 were considered cured, showing 94% effectiveness. Final safety results brought 28 deaths (11 related to the treatment or HAT) and a total of 67 serious adverse events (SAE) in 58 patients. 92% of patients showed at least one adverse event during treatment. No new safety signal was detected compared to the phase III randomized controlled trial.

Demographics

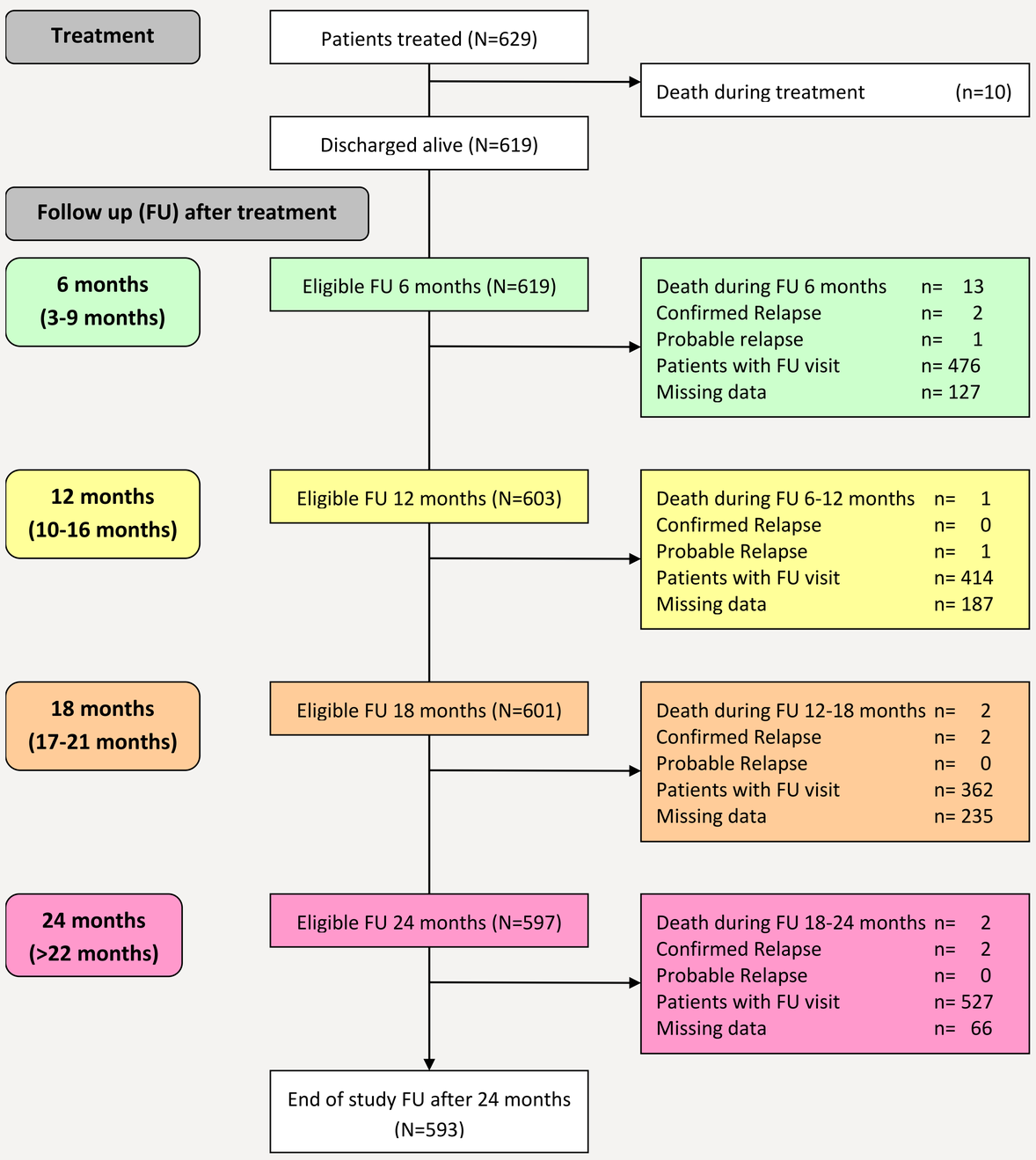
Characteristics Number of patients by centre n (%)	All (N=629)
Adults*	529 (84)
Children 0-11 years	100 (16)
0-23 months	8 (1)
2-4 years	27 (4)
5-11 years	65 (10)
Sex	
Male	354 (57)
Female	275 (43)
Women	
Breastfeeding	33 (5)
Pregnant	14 (2)
Missing status	43 (7)
Age, mean (SD) years	30 (16)
Median	28
Range (min-max)	0.5 - 77
Previous HAT	
All	135 (22)
within 2 years of admission	84 (13)

*Age unknown for 2 patients

NECT Field trial sites and patients included



Flow of Patients



Effectiveness Measures

Summary of endpoints Number of patients (N)	All patients (n)	(%)	Confidence Interval
Treatment period (N=629)			
Treated	629	100.0	
Fatalities during treatment	10	1.6	
Discharged alive after treatment (1° endpoint)	619	98.4	[97.1 ; 99.1]
Follow up period (N=619)			
Fatalities during follow up*	18	2.9	
Relapses (Confirmed, Probable)*	8	1.3	
Lost during the follow up*	16	2.6	
Clinical Cure at 24 months (2° endpoint)			
mITT population[1] (N=613)	577	94.1	[91.8 ; 95.7]
PP2 population[2] (N=561)	525	93.6	[91.0 ; 95.3]
ITT CLTFU cure[3] (N=629)	593	94.3	[92.0 ; 95.8]
ITT CLTFU failure[4] (N=629)	577	91.7	[89.3 ; 93.8]

*percentages relate to the potential number of eligible patients for follow up after treatment;

[1]modified ITT: patients with at least one dose of study treatment and not lost to FU

[2]PP2: patients with at least one dose of study treatment and endpoint (death / relapse / 24 months FU examination) reached

[3]ITT CLTFU cure: patients with at least one dose of study medication and complete lost to follow up considered as cured

[4]ITT CLTFU failure: patients with at least one dose of study treatment and complete lost to follow up considered as failure

Adverse Events

Number (n) and frequencies (%)	Treatment period (safety population)	Follow up period (MITT population)	Total study
All patients	**629**	**613**	**629 (100)**
Adverse Events (AE)			
Patients with any AE (grades 1-5)	578 (91.9)	192 (31.2)	629 (100)
Patients with severe AE (grades 3-5)	79 (12.6)	na	na
Patients with serious AE (SAE)*	32 (5.1)	29 (4.7)	58 (9.2)
Patients who died (death; grade 5)	10 (1.6)	18 (2.9)	28 (4.5)

na: not available or not analysed *3 patients had SAEs during treatment and follow-up

Conclusion The use of NECT for treatment of second stage HAT is safe and effective in field settings and has since become the first line treatment for second stage gambiense sleeping sickness in all affected countries. Special subgroups did not show marked differences for either safety or effectiveness. The results are similar to those of the NECT Randomised Controlled Trial (2009). This trial supported inclusion of NECT treatment in the EML for Children 2013.

DNDi Drugs for Neglected Diseases *initiative*

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