Multicenter clinical trial of nifurtimox-eflornithine combination therapy for second-stage sleeping sickness

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Treatment of HAT in second-stage

- Melarsoprol:
  - High toxicity, treatment failure rates rising
- Eflornithine (DFMO):
  - Less toxic, efficacious, but resource-intensive
- Nifurtimox:
  - Cheap, easy to use, but limited efficacy in monotherapy & not registered for HAT

No new drugs under clinical development

Drug combinations can be avenues of improvement

Initial studies on drug combinations

Northern Uganda, MSF-France, 2001-2004

- Trial comparing 3 combinations (n=54):
  - Melarsoprol - Nifurtimox (M+N)
  - Melarsoprol - Eflornithine (M+E)
  - Nifurtimox - Eflornithine (N+E)

  High toxicity and fatality
- Nifurtimox – Eflornithine case-series (n=31)

Observations in both studies:
- Safety: acceptable
- Efficacy: 100% at 24 months

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N+E Combination Therapy (NECT)

- Started in Rep. of Congo, MSF-Holland, 2003
- Two-arms comparative trial
  - E: Eflornithine 400 mg /kg/d, QID, 14 d
  - N+E: Nifurtimox 15 mg/kg/d, 10 d
    Eflornithine 400 mg /kg/d, BID, 7 d
- Primary objective: To compare the efficacy
- Secondary objective: To evaluate the safety

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NECT methodology

- Randomized, parallel, open, non-inferiority trial
- Sample size planned = 280 patients
- Common Toxicity Criteria
- Hematology & Biochemistry
- Pharmacology
- 18-months active follow-up
- Primary outcomes:
  - Efficacy: Cure rate at 18 months
  - Safety: Proportion of patients suffering major (grade 3 & 4) related adverse events

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Enrollment criteria

- Confirmed case: parasites seen
- Stage 2, >20 leukocytes/uL in CSF
- Naive of second-stage treatment
- ≥15 yrs of age
- Non-pregnant
- Reasonable chances of follow-up

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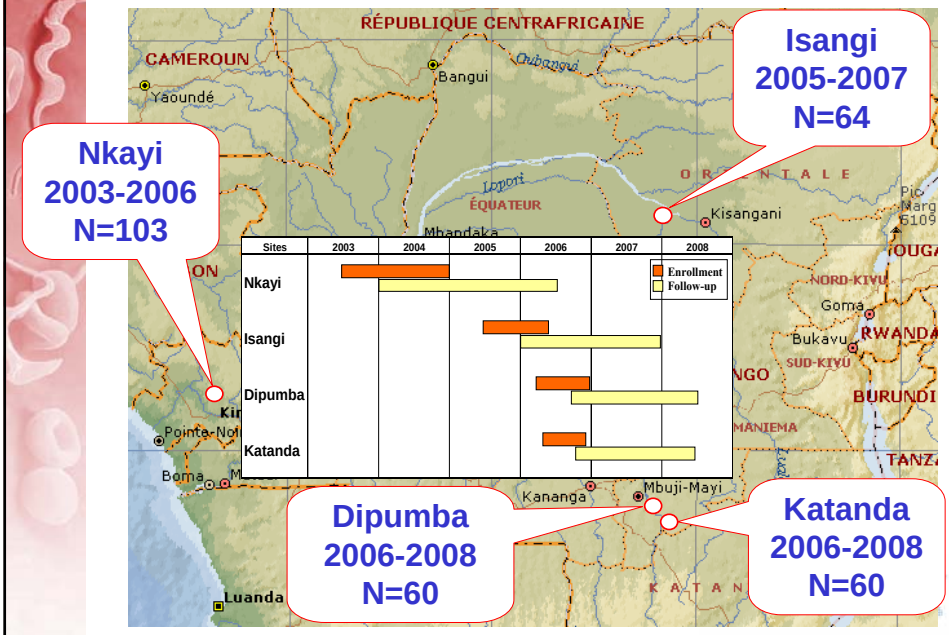
NECT multicentre: study sites



Results: Efficacy follow-up

- Excellent follow-up
  - 99% at least one assessment
  - 93% completed the follow-up

	E (n=143)	N+E (n=143)
No follow-up	1 (0.7%)	2 (1.4%)
Partial follow-up	8 (5.6%)	9 (6.3%)
Complete follow-up until endpoint	134 (93.7%)	132 (92.3%)
Death due to AE	3	1
Relapsed	8	2
Cured	123	129

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Primary efficacy analysis

One-sided non-inferiority test

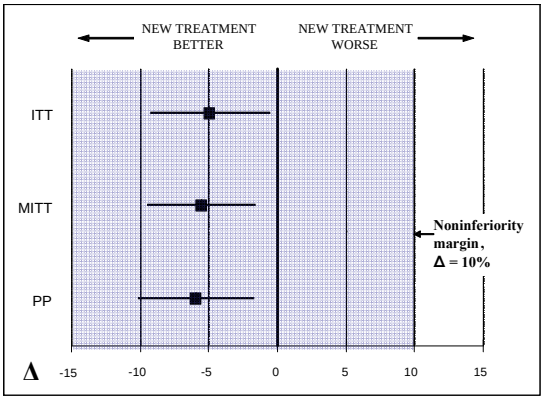
Difference in cure rate:

E minus N+E = Δ

91.6% - 96.5% = -4.9%

92.3% - 97.9% = -5.6%

91.7% - 97.7% = -6.0%



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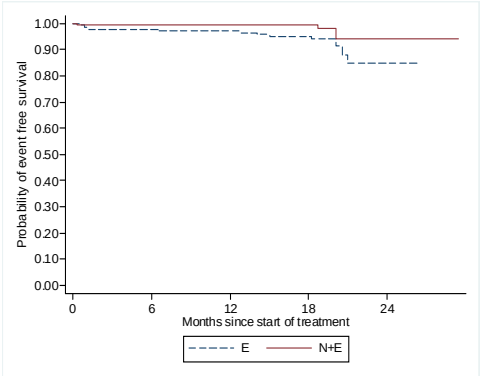
Secondary efficacy analysis:
Method: Survival analysis

Failure events: relapses and deaths (treatment-or HAT-related)



Probability of event-free survival:

	E	N+E	Log-rank
ITT:	84.8%	94.3%	p= 0.0497
MITT:	84.8%	94.3%	p= 0.0497
PP :	83.5%	94.1%	p= 0.0460

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Secondary efficacy indicators

Treatment outcome - MITT analysis	E (n=142)		N+E (n=141)		p-value
	n/N	%	n/N	%	
Treatment failure rate	11/142	7.7	3/141	2.1	0.027
Relapse rate at 12 Months	5/139	3.6	0/140	0	0.030
Relapse rate at 18 Months	8/139	5.8	2/140	1.4	0.060
Parasitologically confirmed relapse rate	5/139	3.6	0/140	0	0.030
Fatality rate (within 30 days)	3/142	2.1	1/141	0.7	0.622
Overall cure rate at 12 months	133/142	93.7	137/141	97.2	0.256
Treatment response rate	141/142	99.3	140/141	99.3	1.000

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Overview of safety data

- 1754 adverse events reported
  - 1262 Clinical events (351 multiple events)
- 153 laboratory events
- Overall frequency = 4.9 events/patient

- Difficult to establish causality:
  - Disease/s vs. Treatment

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Principal safety results

N° of patients presenting:	E (n=143)		N+E (n=143)		
	n	%	n	%	p- value
At least one AE	138	96.5	136	95.1	0.555
At least one Serious AE	6	4.2	1	0.7	0.120
Treatment pauses	9	6.3	1	0.7	0.019
Deaths	3	2.1	1	0.7	0.622
PRIMARY SAFETY OUTCOME:					
At least one Major AE	41	28.7	20	14.0	0.002

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Major adverse events

Major AE	E (n=143)		N+E (n=143)	
	n	%	n	%
Seizures	6	4.2	6	4.2
Coma	3	2.1	1	0.7
Confusion	1	0.7	2	1.4
Hallucinations	1	0.7	1	0.7
Other neurological	2	1.4	3	2.1
Gastrointestinal	2	1.4	2	1.4
Fever	18	12.6	7	4.9
Infection	5	3.5	1	0.7
Hypertension	3	2.1	0	0.0
Headache	2	1.4	1	0.7
Acute Respiratory Distress	1	0.7	1	0.7
Other clinical AE	2	1.4	2	1.4
Anemia	1	0.7	2	1.4
Leucopenia	0	0.0	0	0.0
Neutropenia	10	7.2	2	1.4
Total	65		31	

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Most frequent clinical events (selected)

	E (n=143)		N+E (n=143)	
	n	%	n	%
NEUROLOGICAL				
Seizures	13	9.1	18	12.6
Anxiety/agitation	11	7.7	4	2.8
Dizziness	24	16.8	26	18.2
Inner ear disturbance	7	4.9	10	7.0
Insomnia	14	9.8	14	9.8
GASTROINTESTINAL				
Abdominal pain	42	29.4	35	24.5
Anorexia	20	14.0	36	25.2
Diarrhea	41	28.7	9	6.3
Nausea/Vomits	29	20.3	69	48.3
CARDIOVASCULAR				
Arrythmia	31	21.7	27	18.9
Hypertension	19	13.3	6	4.2
OTHER				
Fever	61	42.7	37	25.9
Infection	32	22.4	18	12.6

Not-related events are excluded

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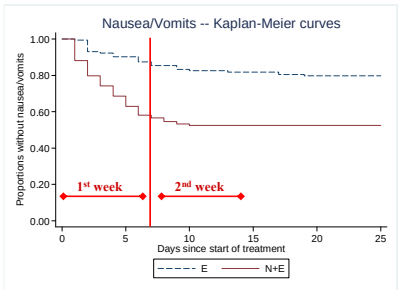
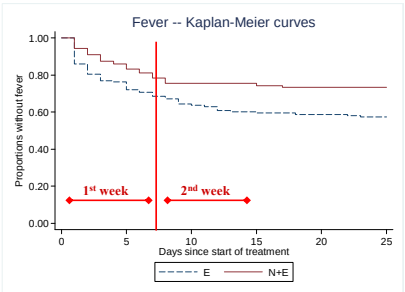
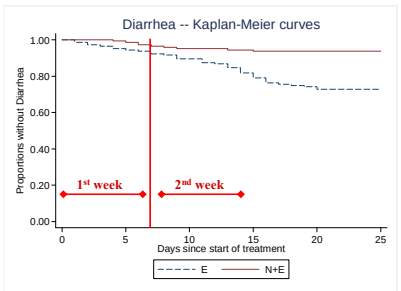
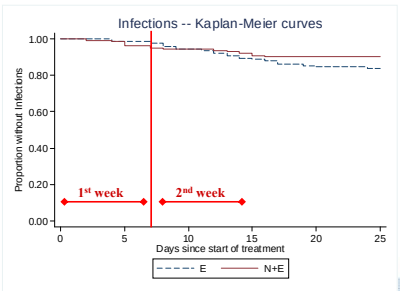
Onset time of adverse events









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Discussion: efficacy

- Non-inferiority of N+E cure rate
- Significant advantage of N+E in:
  - Probability of event-free survival
  - Other secondary indicators
- Excellent follow-up

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Discussion: safety

- In the context of second-stage HAT, both treatments were well tolerated
- Low fatality rate in both arms
- Significant advantages of N+E:
  - Lower risk of major adverse events
  - Lower risk treatment interruptions
  - Lower risk of infections, diarrhea, fever peaks, neutropenia
- Higher risk of nausea and vomiting with N+E

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Discussion: practical aspects

- Simpler regimen
  - More feasible than eflornithine
  - Fits the routine of health centers
  - Cheaper: staff, infrastructure, logistics
  - Short hospitalization
- Prevent the emergence of resistance

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Conclusion

- N+E combination can be used as first-line treatment for stage 2 HAT
  - Efficacy and safety comparable with eflornithine
  - Improved feasibility
  - Less toxic than melarsoprol

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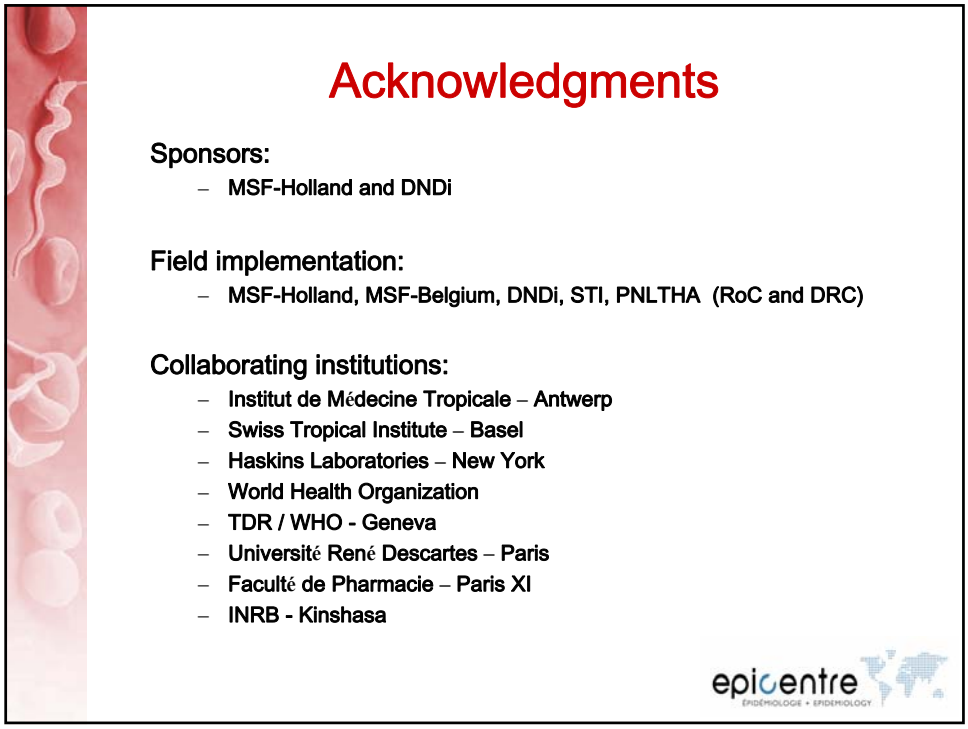
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