Results from the pivotal trial of fexinidazole in sleeping sickness patients

ECTMIH OCTOBER 2017
Antoine Tarral, MD, Head of HAT Clinical program
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 10 days: 3 tablets D1-D4 + 2 tablets D5-D10
NECT: eflornithine IV infusion (2 hours) 2*/day for 7 days + Nifurtimox oral dosing 3*/Day for 10 days

PERIOD 1: HOSPITALIZATION

- Signs and symptoms of HAT,
- Physical examinations,
- 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

ECTMIH, October 2017
**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).

<table>
<thead>
<tr>
<th>Gender</th>
<th>NECT</th>
<th>FEXINIDAZOLE</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N= 130</td>
<td>N= 264</td>
</tr>
<tr>
<td>Male</td>
<td>61.50%</td>
<td>61.00%</td>
</tr>
<tr>
<td>Female</td>
<td>39%</td>
<td>39%</td>
</tr>
</tbody>
</table>

| Age (years) | NECT | FEXINIDAZOLE |
|            | Mean | Mean         |
|            | 35.32 | 34.48        |
|            | 15-68  | 15-71        |
**Efficacy results**

<table>
<thead>
<tr>
<th>Statistical results</th>
<th>NECT</th>
<th>FEXINIDAZOLE</th>
<th>difference between proportion and 97.06% CI</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Efficacy Analysis</td>
<td>mITT</td>
<td>97.64% (n=127)</td>
<td>91.22% (n=262)</td>
<td>-6.42 ( -11.22; -1.62)</td>
</tr>
<tr>
<td>Sensitivity analysis</td>
<td>ITT</td>
<td>95.38% (n=130)</td>
<td>90.53% (n=264)</td>
<td>-4.85 ( -10.40 ; 0.76)</td>
</tr>
</tbody>
</table>

*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)

<table>
<thead>
<tr>
<th>Category</th>
<th>NECT (N=127)</th>
<th>Fexinidazole (N=262)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Success rate</strong></td>
<td>97.6%</td>
<td>91.2%</td>
</tr>
<tr>
<td><strong>Failures N (%)</strong></td>
<td>3 (2.4%)</td>
<td>23 (8.8%)</td>
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<tr>
<td><strong>Disease relapse N (%)</strong></td>
<td>0</td>
<td>15 (5.7%)</td>
</tr>
<tr>
<td><strong>Death N (%)</strong></td>
<td>2 (1.6%)</td>
<td>6 (2.3%)</td>
</tr>
<tr>
<td><strong>LTFU N (%)</strong></td>
<td>0</td>
<td>1 (&lt;0.1%)</td>
</tr>
<tr>
<td><strong>No Lumbar Puncture N (%)</strong></td>
<td>1 (&lt;0.1%)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Consent withdrawal N (%)</strong></td>
<td>0</td>
<td>1 (&lt;0.1%)</td>
</tr>
</tbody>
</table>
## Safety summary

<table>
<thead>
<tr>
<th></th>
<th>FEX004 NECT (N=130)</th>
<th>FEX004 Fexinidazole (N=264)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAEs</td>
<td>121 (93%)</td>
<td>247 (94%)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>13 (10%)</td>
<td>31 (12%)</td>
</tr>
<tr>
<td>Severe</td>
<td>23 (18%)</td>
<td>52 (20%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (2%) *</td>
<td>9 (3%)*</td>
</tr>
<tr>
<td>Possibly Related</td>
<td>103 (79%)</td>
<td>215 (81%)</td>
</tr>
<tr>
<td>Permanent treatment</td>
<td>0</td>
<td>2 (&lt;1%)</td>
</tr>
<tr>
<td>discontinuation</td>
<td></td>
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</tr>
</tbody>
</table>

*No statistical difference between NECT and fexinidazole on relative risk of death p>0.05
Safety* per Treatment Emergent Adverse Events

TEAEs > 5% of patients by treatment arm

* Baseline to EOH

- Headache
- Tremor
- Dizziness
- Convulsion
- Vomiting
- Nausea
- Dyspepsia
- Abdominal pain
- Abdominal pain...
- Salivary...
- Decreased appetite
- Hyperkalaemia
- Hypocalcaemia
- Hypoalbuminaemia
- Hyperglycaemia
- Asthenia
- Pyrexia
- Feeling hot
- Chest pain
- Chills
- Insomnia
- Back pain
- Neck pain
- Anaemia
- Cough
- Procedural pain

NECT
fexinidazole
## Death cases

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Preferred term</th>
<th>Causality as assessed by the Investigator</th>
<th>Start – End date</th>
<th>Failure in primary analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEXINIDAZOLE GROUP (FEX004)</strong></td>
<td></td>
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<tr>
<td>01_009</td>
<td>Ameloblastoma</td>
<td>Unrelated</td>
<td>Days 474 – 701</td>
<td>NO</td>
</tr>
<tr>
<td>01_023</td>
<td>Alcohol poisoning</td>
<td>Unrelated</td>
<td>Day 675</td>
<td>NO</td>
</tr>
<tr>
<td>01_046</td>
<td>Poisoning</td>
<td>Unrelated</td>
<td>Day 8</td>
<td>YES</td>
</tr>
<tr>
<td>02_040</td>
<td>Pneumonia + Influenza</td>
<td>Unrelated</td>
<td>Day 82</td>
<td>YES</td>
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<tr>
<td>02_042</td>
<td>Poisoning</td>
<td>Unrelated</td>
<td>Days 21 – 22</td>
<td>YES</td>
</tr>
<tr>
<td>02_060</td>
<td>Starvation + Hypoglycemia</td>
<td>Unrelated</td>
<td>Day 352</td>
<td>YES</td>
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<tr>
<td>02_064</td>
<td>Pneumonia aspiration</td>
<td>Unrelated</td>
<td>Day 5</td>
<td>YES</td>
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<tr>
<td>05_008</td>
<td>Inguinal hernia Strangulated</td>
<td>Unrelated</td>
<td>Day 594</td>
<td>NO</td>
</tr>
<tr>
<td>06_006</td>
<td>Death (cause unknown)</td>
<td>Unrelated</td>
<td>Day 94</td>
<td>YES</td>
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<tr>
<td><strong>NECT GROUP (FEX004)</strong></td>
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<tr>
<td>02_023</td>
<td>Hypoglycaemia</td>
<td>Unrelated</td>
<td>Day 19</td>
<td>YES</td>
</tr>
<tr>
<td>07_008</td>
<td>Cardio-respiratory arrest</td>
<td>Unrelated</td>
<td>Day 197</td>
<td>YES</td>
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</tbody>
</table>
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
<table>
<thead>
<tr>
<th>DNDi Geneva</th>
<th>DNDi Kinshasa</th>
<th>NSSCP Investigators:</th>
<th>NSSCP mobile teams</th>
<th>SwissTPH Kinshasa</th>
<th>NSSCP CAR:</th>
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<tbody>
<tr>
<td>Clelia Bardonneau</td>
<td>Thérèse Benyi</td>
<td>Franck Botalema</td>
<td>Francis Regongbenga (CAR)</td>
<td>Marcel Bananduenge</td>
<td>Sylvestre Mbadingaï</td>
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<td>Séréine Blesson</td>
<td>Alphonsine Bilonda</td>
<td>Médard Ilunga</td>
<td>Bruno Yonli Yakelendji (CAR)</td>
<td>Lucy Cadetti</td>
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<td>Beatrice Bonnet</td>
<td>Arthur Bongo</td>
<td>Lewis Kaninda</td>
<td>Jean Louis Lumaliza (RDC)</td>
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<td>Céline Bordbar</td>
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<td>Hanne Dam</td>
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<td>Sophie Delhomme</td>
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<td>Stephane Kuluta</td>
<td>Nines Lima</td>
<td>Stefan Schneitter</td>
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<td>Wendy Keller</td>
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<td>Nathalie Salichon</td>
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<td>Aurora Revuelta</td>
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<td>Nathalie Strub W.</td>
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<td>Willy Kuzienia Mindele</td>
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<td>Katia Salerno</td>
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<td>Dieudonné Mpoyi</td>
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<td>Antoine Tarral</td>
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<td>Guylain Mandula</td>
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<td>Olaf Valverde</td>
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<td>Tim Mayala</td>
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<td>Junior Mudji</td>
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<td>and any other staff</td>
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</tbody>
</table>

**NTD program DRC:**
- Victor Kandé (PI)

**NSSCP DRC:**
- Olivier Baka
- Espérand Bolimbo
- Patrice Kabangu
- Alain Fukinsia
- Crispin Lumbala
- Fifi Lwenda
- Wilfried Mutombo
- Pathou Nganzobo
- Digas Ngolo Tete
- Claude Nkongolo
- Julienne Tshowa

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- Médard Ilunga
- Lewis Kaninda
- Serge Kapongo
- Papy Kavunga
- Serge Kasongo
- Augustin Kukembila
- Stephane Kuluta
- Ismael Lumpumgu
- Fina Lubaki
- Steven Lumeya
- Florent Mbo
- Pathou Nganzobo
- Helène Mahenzin Mbembo
- Christian Mpiia
- Willy Kuzienia Mindele
- Félix Akwoso Masa
- Melchias Mukendi
- Dieudonné Mpoyi
- Guylain Mandula
- Tim Mayala
- Mathieu Matsho
- Junior Mudji
- Hérifiter Yalungu
- including nurses, lab technicians and any other staff at the site

**NSSCP mobile teams**
- SwissTPh
  - Julie Catusse
  - Lucia Cadetti
  - Angela Lazarova
  - Morgane Nusbaumer
  - Gabriele Pohlig
  - Marc Ulrich
  - Aita Signorell
  - Stefan Schneitter

**SwissTPH Kinshasa**
- Marcel Bananduenge
- Yves Lula
- Jerry Liwono
- Didier Kalemwa
- Clovis Mwamba Ilunga
- Pierre Mutantu Nsele
- Willy Mutangala
- Michel Mandro
- Ursule Samba Masika

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- Alberth Lari
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- Magalie Monnereau
- Aline Schindele

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- Pascal Voiriot

**Théradis**
- Chantal Raffy
- Nadime Vallomi

**Sanoﬁ**
- Benedict Blaynay
- Guillermo Doll
- Valérie Faillat-Proux
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