Vision & Objectives

- **Vision:**
  A collaborative, patients’ needs-driven, virtual, non-profit drug R&D organisation to develop new treatments against the most neglected communicable diseases

- **Objectives:**
  - Deliver **11 to 13 new treatments by 2018** for sleeping sickness, Chagas disease, leishmaniasis, malaria, paediatric HIV and specific helminth infections
  - Establish a **robust pipeline** for future needs
  - Use and strengthen existing **capacity in disease-endemic countries**
Responding to the Needs of Patients Suffering from Neglected Diseases…

- Malaria
- Leishmaniasis
- Paediatric HIV
- Sleeping Sickness (HAT)
- Chagas Disease
- Filaria

- Published Target Product Profiles to meet patients’ needs
  See: www.dndi.org
6 New Treatments Developed Since 2007

- ASAQ (Fixed-dose combination of artesunate + amodiaquine)
- ASMQ (Fixed-dose combination of artesunate + mefloquine)
- NECT (Nifurtimox-eflornithine combination therapy)
- SSG&PM (Sodium stibogluconate & paromomycin combination therapy)
- NEW VL TREATMENTS IN ASIA (SD AmBisome® / PM+M / A®+M / VL)
- Benznidazole (12.5 mg Pediatric dosage form of benznidazole)

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
Published DNDi Portfolio December 2013

**HAT**
- SCYX2035811
- SCYX7158
- Fexinidazole
- NECT: Nifurtimox-Eflornithine Combination Therapy

**Leishmaniasis**
- Nitroimidazole backup
- Oxaleish
- VL-2098
- Fexinidazole
- Anfoleish (CL)
- New VL treatments for Bangladesh
- New VL treatments for Latin America
- Generic Ambisome

**Chagas**
- Nitroimidazole
- Oxachagas
- Biomarkers
- Fexinidazole
- New Benz Regimens
- New Combos
- Benznidazole: Paediatric Dosage Form

**Filaria**
- Emodepside

**Paediatric HIV**
- Two ‘4-in-1’ LPV/r-based Fixed-Dose Combinations
- RTV Superbooster for HIV/TB co-infection

**Malaria**
- ASAQ FDC: Artesunate-Amodiaquine Fixed-Dose Combination
- ASMQ FDC: Artesunate-Mefloquine Fixed-Dose Combination

★ New Chemical Entity (NCE); Fexinidazole (for HAT, VL and Chagas Disease) = 1 NCE
Antitrypanosomal Activity of Fexinidazole, a New Oral Nitroimidazole Drug Candidate for Treatment of Sleeping Sickness

Moneel Kaner1,2, Michael A. Byard2,3, Patricia Cala4
Eli Tornesella5, and Raúl Isac6

Fexinidazole – A New Oral Nitroimidazole Drug Candidate Entering Clinical Development for the Treatment of Sleeping Sickness

Moneel Kaner1,2, Michael A. Byard2,3, Patricia Cala4
Eli Tornesella5, and Raúl Isac6

Abstract

Background and objectives: Fexinidazole is a 3-nitroimidazole recently included in a clinical efficacy trial as an oral drug for the treatment of human African trypanosomiasis (HAT). Preclinical studies showed it to be a pharmacologically active pro-drug with low toxicity and efficacy in in vitro cell culture, mouse models, and a long-term efficacy in rodent models. The present study aimed to determine the best dose regimen for the treatment of stage II sleeping sickness patients, which would normally also treat stage I patients. Methods: Fexinidazole was assessed in 13 healthy volunteers and eight volunteers with asymmetrical sub-Saharan African origin. These initial phase I studies and two additional studies assessed a single ascending dose and multiple dosing doses with a burning drug regimen under fast conditions.

Conclusion

Fexinidazole was well tolerated in a single dose of 100 to 8,000 mg, with high absorptions of the parent drug and rapid transition into metabolites (to maximum concentrations of 12.4 to 88.7 mg/L and minimum 24.0 to 123.9 mg/L). The initial formulation was approximately 25% less bioavailable than the expansion, and final clinical results suggest that Fexinidazole is well tolerated. Its bioavailability and efficacy by approximately 20% reduction in adverse events and 25% to 30% for all volunteer treatments compared to standard treatment were established. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern. The study included two volunteers with asymptomatic sub-Saharan African origin. This study was conducted to evaluate the impact of a lower dose regimen closer to one of the population, showing that the type of dose is not an issue of concern.
Share and use open data

- Science works through sharing and collaborating
- A continuum of more or less ‘open’ approaches
  - What is shared?
  - When is it shared
  - With whom is it shared?
- Do not need to share everything, immediately & with everyone to have a useful impact!
- Innovations focused on bottlenecks most impactful
  - Some current examples for Research…
Some Drug Discovery challenges for DNDi

Innovative collaborations and open source approaches can help

- Accessing and exploiting public and private data
  → “Know your molecule” & predictive activity models

- Maximising the potential of hard won HTS hits
  → The NTD Drug Discovery Booster

- Mobilising increased & sustainable resources for lead optimisation
  → LOLA & open chemistry partnerships
The changing discovery landscape

- Screening for new leads against kinetoplastid parasites is evolving
  - Throughput increased & some new hits identified
  - But insufficient number and variety of starting points to give high confidence of delivering new clinical candidates

- Make best use of all the available data to
  - To better understand the hits we have
  - Construct computational models to guide further screening
Global review of HTS hits from DNDi VL discovery program

- VL Actives in ScienceCloud (in vitro intracellular hits with IC50>10uM, SI >10)
- Data curation/clustering/annotation workflow
- Preliminary selection:
  - activity/selectivity
  - novelty
  - Toxicity/reactivity
- 58 clusters

ongoing

Hit analog purchase followed by confirmatory screening

Q2 2014

6 priority series

Med Chem review

58 clusters

• “Know your molecules”
• Data from collaborations
• Published data from ChEMBL
Predictive activity models

**Objective:** Use existing data to identify novel active series for VL, Chagas disease & HAT

- 2- and 3-D model building (training sets of actives/inactives)
- *in silico* prediction of activity using commercial libraries (compound list)
- *In vitro* screening to validate models
- Sharing of models with partners to select compounds from their libraries

**Data sources:** IPK, GNF, DDU, AbbVie, GSK, ChEMBL, DNDi, PubChem

Sharing of selected data with key partner(s) can be enormously enabling

Data available end Q2 2014
The changing discovery landscape

- Screening for new leads against kinetoplastid parasites is evolving
  - Throughput increased & some new hits identified
  - But insufficient number and variety of starting points to give high confidence of delivering new clinical candidates

- The NTD Drug Discovery Booster will
  - Expand the hits from screening and enable scaffold-hopping to identify related series
  - Benefit from the pooling of structures and information from the consortium members to inform decision-making
  - Accelerate discovery and reduce costs
Growing a series from a seed

Consortium members add pieces

Seed from HTS
NTD Drug Discovery Booster

- The goal is faster, cheaper drug discovery for NTDs

- Rapid expansion of new screening hits through cross-collaboration with several Pharma

- DNDi would be able to generate additional SAR **before** commencing time consuming and expensive chemistry to make new analogues

- The expanded series produced could benefit from annotation by multiple partners
Annotations on the final ‘boosted’ series
- Inform decision to move into LO
- Highlight risks and benefits of series
- Guide medicinal chemistry strategy
- Accelerate lead optimisation and reduce costs
NTD Drug Discovery Booster: How Would it Work?
Moving from bilateral to multilateral collaborations

1 or 2 more round of analogue searching, seeded with **1 improved hit** of step « 3 »

**Consortium companies**

```
A → In silico Screening
```

Σ = ±10 million compounds

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B → DNDi + screening partners
```

~ 100 cpds

```
C → In vitro Screening
```

Σ = ±400 compounds + annotations

```
D → DNDi
```

Σ = ±5-10 compounds + annotations to build SAR

**DNDi + NTD-B**

Best hit series

Lead optimization (DNDi)

**Boost 1:**
12 to 18 months → 3 to 4 months

**Boost 2:**
24 months → 12 months

“Seed” compound = validated hit

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**Boost 1:**
12 to 18 months → 3 to 4 months

**Boost 2:**
24 months → 12 months
Drug Booster and Open Source innovations
→ faster, cheaper, sustainable & more efficient Research

- **NTD Drug Booster**
  - 2-3 years
  - €2-3m

- **Open chemistry partnerships**
  - 2-3 years
  - €3-4m

- **Pathogen box**
  - 4-5 years
  - €5-6m