NEW MECHANISMS TO ACCELERATE DRUG DISCOVERY FOR NEGLECTED TROPICAL DISEASES (NTDs)

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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 artemesunate + amodiaquine) 2007
- **ASMQ** (Fixed-dose combination of artemesunate + mefloquine) 2008
- **NECT** (Nifurtimox-eflornithine combination therapy) 2009
- **SSG&PM** (Sodium stibogluconate & paromomycin combination therapy) 2010
- **NEW VL TREATMENTS IN ASIA** (SD AmBisome® / PM+M / A®+M / VL) 2011
- **Benznidazole** 12.5 mg Pediatric dosage form of benznidazole 2011

- Easy to Use
- Affordable
- Field-Adapted
- Non-Patented
**DNDi Portfolio June 2014**

**HAT**
- SCYX2035811
- SCYX7158
- SCYX1608210
- Fexinidazole

**Leishmaniasis**
- Nitroimidazole backups
- Oxoleish
- VL-2098
- Fexinidazole
- New VL treatments for Bangladesh
- Cpg-D35 (CL)
- Anfoleish (CL)
- New VL treatments for Latin America
- Generic Ambisome

**Chagas**
- Nitroimidazole
- Oxachagas
- Biomarkers
- Fexinidazole
- New Benz Regimens
- New Combinations

**Filaria**
- Emodipside

**Paediatric HIV**
- Two '4-in-1' LPV/r based FDC granules
- RTV Superbooster for HIV/TB co-infection

**Malaria**
- ASAQ FDC
- Artesunate-Atovaquone Fixed-Dose Combination
- ASMQ FDC
- Artesunate-Mefloquine Fixed-Dose Combination

**NECT**
- Nifurtimox-Eflornithine Combination Therapy

**SSG&PM**
- Sodium Stibogluconate & Paromomycin Combination Therapy for VL in Africa

**New VL treatments**
- for Bangladesh
- for Latin America
- for India

**New treatments for HIV/VL co-infection**
- for Africa

**New Chemical Entity (NCE); Fexinidazole (for HAT, VL, and Chagas disease) = 1 NCE**
Chagas Disease (CD)

- 100 million at risk in Latin America
- Transmitted by triatomine insects, blood transfusion, organ transplantation, congenitally or orally

- 7.6 million people affected by CD
  - Largest parasitic cause of death in western hemisphere
  - Leading cause of cardiomyopathy
  - Kills more people in region than malaria
  - Patient number growing in non-endemic, developed countries
  - Majority of patients undiagnosed until late stage

- To date, geographical separation of CD and VL has led to little co-infection
Drugs for Chagas Disease

*Limited options in one class*

<table>
<thead>
<tr>
<th></th>
<th>MW 260, clogP 0.90</th>
<th>MW 287, clogP 0.02</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benznidazole</strong></td>
<td><strong>Nifurtimox</strong></td>
<td></td>
</tr>
<tr>
<td>po</td>
<td>po</td>
<td></td>
</tr>
<tr>
<td>5-7 mg/kg/day</td>
<td>8-10 mg/kg/day, TID, 12-20 mg/kg/day in children</td>
<td></td>
</tr>
<tr>
<td>10 mg/kg/day in children</td>
<td>60-120 days</td>
<td></td>
</tr>
<tr>
<td>40-80 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>variable efficacy</td>
<td>variable efficacy</td>
<td></td>
</tr>
</tbody>
</table>

- GI toxicity
- dermatological

- GI toxicity
- dermatological
- dizziness
- headache

- Long treatments & variable efficacy
- Serious toxicities resulting in 20-30% discontinuations
- Urgent need for new effective, safe, and convenient treatments
# Chagas Disease – Target Product Profile

<table>
<thead>
<tr>
<th></th>
<th>Acceptable</th>
<th>Ideal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Target population</strong></td>
<td>Chronic</td>
<td>Chronic and Acute (Reactivations)</td>
</tr>
<tr>
<td><strong>Strains</strong></td>
<td>Tcl, TcII, TcV and TcVI (according to new 2009 classification)</td>
<td>All according to new classification (2009)*</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>All areas</td>
<td>All areas</td>
</tr>
<tr>
<td><strong>Adult/children</strong></td>
<td>Adult</td>
<td>All</td>
</tr>
<tr>
<td><strong>Clinical efficacy</strong></td>
<td>Non inferior to benznidazole in all endemic regions (parasitological)</td>
<td>Superiority to benznidazole to different phases of disease (acute and chronic) (parasitological)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Superiority to benznidazole ** 3 CE plus 2 standard LE or ECG during treatment</td>
<td>Superiority to benznidazole or nifurtimox No CE or LE or ECG needed during treatment</td>
</tr>
<tr>
<td><strong>Activity against resistant strains</strong></td>
<td>Not necessary</td>
<td>Active against nitrofuran- and nitroimidazole-resistant <em>T. cruzi</em> strains</td>
</tr>
<tr>
<td><strong>Contraindications</strong></td>
<td>Pregnancy/lactation</td>
<td>None</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>No genotoxicity; No pro-arrythmic potential</td>
<td>No genotoxicity; No teratogenicity; No negative inotropic effect; ; No pro-arrythmic potential</td>
</tr>
<tr>
<td><strong>Interactions</strong></td>
<td>No clinically significant interaction with anti-hypertensive, anti-arrythmic and anticoagulants drugs</td>
<td>None</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td>Oral</td>
<td>Oral</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>3 years, climatic zone IV</td>
<td>5 years, climatic zone IV</td>
</tr>
<tr>
<td><strong>Dosing regimen</strong></td>
<td>Comparable to systemic antifungal treatments</td>
<td>Once daily/ 30days</td>
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Lessons for Discovery from DNDi'S first 10 years

- An evolving Discovery model
  - Switch from awarding grants to building focused consortia
  - Increased engagement with Pharma companies

- Phenotypic focus
  - Paucity of well validated drug targets
  - Success with phenotypic approach

- Compound sources
  - Access to large, high quality Pharma libraries - AbbVie, Astellas, AZ, Eisai, GSK, Merck, Pfizer, Sanofi,…
  - Re-purposing & large diverse collections

- Screen platforms
  - Huge leaps in screening through application of new technologies and industrial approaches – HCS, logistics and data management

- H2L & LO consortia
  - Successful biotech/academic/pharma/consultant collaborations yielding NCEs
The Science(s) of Lead Optimization

- Screening
  - Hits
    - 3-4 scaffolds

- Hit Expansion
  - 1 scaffold
    - Reiterative cycles of medicinal chemistry
    - Parallel assessment of DMPK Tox and Potency

- Lead Optimization
  - Pharmaceutical chemistry
  - GLP Toxicology

- Lead to Candidate
  - Drug Candidate
  - Parasitology
    - Biology / targets
    - Pathology / targets
    - Chemistry / targets

- Drug Discovery (Product Development)
  - Absorption, Distribution, Metabolism, Excretion
  - Pharmacokinetics
  - Toxicology
  - Pharmacodynamics
Lead Optimization Consortia
From Hit to Potential Pre-Clinical Candidate

- Continued evolution
  - 3 Consortia (1 in endemic country, LOLA)
  - Shared resources
- VL and Chagas are priority
- Access to series from Pharma
- New candidates already issued from:
  - Oxaboroles series (Anacor, USA)
  - Nitroimidazoles (Univ. of Auckland, NZ)
- Further chemical series in optimization
- Translational challenges being tackled
  - New tools/assays developed
  - Better understanding of PK/PD relationship for these diseases

Key partners:
CDCO/Monash University, Epichem, Griffith University, WuXi, iThemba, Sandexis, LMPH, LSHTM, Swiss TPH, UNICAMP, Anacor, Pfizer, Sanofi, AbbVie, GSK

A global network:
Australia, Belgium, Brazil, China, South Africa, Spain, Switzerland, UK, USA
Oxaborole SCYX-7158 for HAT
From Lead Optimization to Clinical Candidate

- Identified as hits against *T. brucei* at Sandler Center, showed activity in animal models of HAT
- Innovative US partnership with 2 biotechs and 1 university
- First candidate issued from DNDi Lead Optimization Programme
- Clinical Phase I study nearly complete

Key partners:
Scynexis, Anacor, Pace University,
Sandler Center UCSF, Swiss TPH
Future directions for discovery

- Build on progress of last 10 years

- Increased number of contributors in NTD drug Discovery
  - e.g. GSK, DDU, GNF, …

- Bilateral and multilateral collaborations with pharma companies
  - NTD Drug Discovery Booster

- New technologies, open innovation & exploiting more of the data
  - Identification of new series and more rapid optimisation

- Harnessing scientific expertise & capacity in endemic regions
  - Lead Optimisation Latin America (LOLA)