Product – Development - Partnership

- Non-profit drug research & development (R&D) organization founded in 2003
- Addressing the needs of the most neglected patients
- Harnessing resources from public institutions, private industry and philanthropic entities

8 regional offices working close to patients in:
Brazil, Democratic Republic of Congo, Kenya, South Africa, Malaysia, India, Japan, USA

Founding Partners
Indian Council for Medical Research (ICMR), Kenya Medical Research Institute (KEMRI), Malaysian MoH, Oswaldo Cruz Foundation Brazil, Médecins Sans Frontières (MSF), Institut Pasteur France, WHO/TDR (permanent observer)
8 new treatments delivered since 2007

- **2007 ASAQ**
  - Malaria
  - >500 million patients reached

- **2008 ASMQ**
  - Malaria
  - Used in Africa and Asia

- **2009 NECT**
  - Sleeping sickness
  - 100% of stage-2 patients

- **2010 SSG&PM**
  - Visceral leishmaniasis in E Africa
  - Now 1st line in all countries

- **2011 PAEDIATRIC BENZNIDAZOLE**
  - Chagas disease
  - Two sources developed

- **2011 NEW VL TREATMENT ASIA**
  - Visceral leishmaniasis in Asia
  - Support to disease elimination

- **2018 FEXINIDAZOLE**
  - Sleeping sickness
  - Approved by European Medicines Agency, first all-oral treatment

- **2019 4-in-1 Pediatric Formulation**
  - Paediatric HIV
  - Quadrime under Review by FDA, under 1 USD
New tools to eliminate onchocerciasis

Where are we?
Mass Drug Administration (MDA, ivermectin)
Ivermectin does not kill the adult worms
Sustainable Development Goals cannot be met with current tools

Common strategic goals:
Expanding coverage of MDA programs
Adopting Test-and-Treat approaches in affected areas
Developing new drugs with superior efficacy to ivermectin

Over **20 million** people infected
About **200 million** people at risk
**4 million** people suffer from severe itching or dermatitis
**1.34 DALY’s** lost in 2017
Use Case for a Macrofilaricide

Case 1: TNT - Programmatic approach
• Test-and-Treat strategies (TNT), for treatment of patients in endemic areas outside MDA campaigns when diagnostic tools are available, especially in “mop up” campaigns after the disease burden has been reduced by MDA programs and is no longer cost effective, or in areas that are difficult to treat
• Test-and-not-Treat (TaNT) campaigns in areas where Loa loa is co-endemic, when the macrofilaricidal drug also has rapid microfilaricidal activity

Case 2: TNT - Case Management
• Symptomatic patients
• Patients diagnosed positive for onchocerciasis

Case 3: MDA
• MDA, if safety and tolerability profile is suitable, in order to drastically reduce the number of MDA cycles from 10-15 years as currently required.
R&D: A long and risky road

Source: Pharmaceutical Research and Manufacturers of America
Filarial Landscape

Direct acting

Research
- Screen
- Hit to Lead

Translational
- Pre-clinical
- Phase I
- Phase IIa / PoC
- Bayer Emodepside
- Oxfendazole
- Celgene CC6166

Development
- Phase IIb / III
- Regist
- Implement
- TDR/MGHI
  Moxidectin

Anti-Wolbachia

LSTM / FSAI
- AbbVie / AWOL
  ABBV-4083

Uni Bonn
- Corallopyronin A

Uni Bonn
- Rifapentin / Moxifloxacin
- Doxycycline

DNDi projects
Filarial Landscape

Direct acting

Research
- Screen
- Hit to Lead

Translational
- Pre-clinical
- Phase I
- Phase IIa / PoC

Development
- Phase IIb / III
- Regist°
- Implem°

- Celgene CC6166
- Bayer Emodepsid
- Oxfendazole
- DOLF IVM / DEC / ALB (Oncho)

- LSTM / FSAI
- Uni Bonn Corallopyronin A
- Uni Bonn Rifapentin / Moxifloxacin
- Uni Bonn Doxycycline
- AbbVie/AWOL ABBV-4083
- TDR/MDGH Moxidectin

DNDi projects
DNDi Macrofilaricide program

Project activities:
- Development of macrofilaricidal drugs against Onchocerciasis.

Project stage:
- Currently, emodepside, ABBV-4083 (TylAMac®) and have passed the First-In-Human study (Phase 1) and will be tested for efficacy and safety in infected humans.
- Oxfendazole has passed the First-In-Human study (Phase 1)

Countries:
- Ghana, DRC to start with proof of concept for emodepside and ABBV-4083

Duration (emo/ABBV-4083):
- Complete development: until 2032
- For proof of concept 2022/2023

Reducing Development Time Lines & Costs
- Repurposing of drugs
- Liase with veterinary drug developers
- Bayer Pharma, Bayer Animal Health
- AbbVie
ABBV-4083 - TyIAMac

• Synthetic derivative of tylosin A (common veterinary macrolide antibiotic)

• Highly potent against *Wolbachia* (>200-fold more potent than doxycycline)

✓ Tox-package completed
✓ IND (Investigational New Drug) application 11/2017
✓ Phase 1 Single Ascending Dose study completed
✓ Scientific advice meeting held with FDA
Emodepside - Profender

Emodepside
- Cyclooctadepsipeptide
- Veterinary anthelminthic with broad activity

Active against
- different nematode species
- different larval stages
- gastrointestinal and tissue parasites
- micro- and macrofilaricidal activity on filarial parasites

- preclinical studies completed
- Veterinary toxicology package available
- First-In-Human clinical studies completed
- Scientific advice meeting held with FDA
Study Endpoints

Proof-of-Concept Endpoints:
- Absence of microfilaridermia
- Embryogenesis inhibition
- Adulticidal effect
- *Wolbachia* depletion (surrogate)

Proof-of-Concept Design:
- Dose range

Regulatory Endpoint:
- Absence of microfilaridermia after 24 months
  - Long term sterilizing, clinical benefit
Oxfendazole

- broad spectrum benzimidazole anthelmintic
- Veterinary anthelminthic with broad activity

**Active against**

- roundworm, strongyloides and pinworms
- macrofilaricidal activity on filarial parasites

- preclinical studies completed
- First-In-Human clinical studies completed (ODG)
- Scientific advice meeting held with FDA
<table>
<thead>
<tr>
<th>Direct acting drugs: Emodepside</th>
<th>Direct acting drugs: Oxfendazole</th>
<th>Indirect-acting drugs (anti-wolbachial): ABBV-4083</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Activity:</strong> Macrofilaricide + microfilaricide (Oncho only areas)</td>
<td><strong>Activity:</strong> Macrofilaricide (Oncho-Loa coinfected areas)</td>
<td><strong>Activity:</strong> Macrofilaricide (Oncho-Loa coinfected areas)</td>
</tr>
<tr>
<td><strong>Advantage:</strong> Proven target in veterinary medicine Fast-killing (micro+macro), morbidity management Rapid reduction in transmission window Potentially useful for multiple nematodes</td>
<td><strong>Advantage:</strong> Proven target in veterinary medicine Slow decrease of skin mf -&gt; No side effects in loiasis infected individuals Potentially useful for multiple nematodes</td>
<td><strong>Advantage:</strong> Slow-killing (slow antigen release) Reduction of inflammation due to removal of <em>Wolbachia</em> Slow decrease of skin mf -&gt; No side effects in loiasis infected individuals MOA supported by doxycycline data</td>
</tr>
<tr>
<td><strong>Disadvantage:</strong> Risk of AE due to microfilaricidal activity</td>
<td><strong>Disadvantage:</strong> Compound class with reprotoxicity risk</td>
<td><strong>Disadvantage:</strong> Long time to death of the adult parasite May need combination treatment (i.e. IVM; MOX) for symptomatic patients</td>
</tr>
</tbody>
</table>
Develop a new safe and field-adapted drug with long-term sterilizing / macrofilaricide activity

• To implement in TNT/TaNT, case management

• DNDi candidates passed Phase 1

• Emodepside and ABBV-4083 will be tested for safety and efficacy

• No healthy drug discovery pipeline exists

• Similar challenges in other helminth areas
Partners
## SWOT Analysis for helminth control

<table>
<thead>
<tr>
<th><strong>Strength</strong></th>
<th><strong>Weakness</strong></th>
</tr>
</thead>
</table>
| - Elimination programs have reduced morbidity due to helminth infections  
- Abrogation of transmission in some areas and countries  
- Awareness for neglected patient groups increases | - Relies on extremely limited number of (sub-)optimal tools  
- Current drugs do not kill/eliminate adult worms (Oncho, Trichuriasis)  
- Transmission unbroken in many areas  
- No sensitive diagnostics available |

<table>
<thead>
<tr>
<th><strong>Opportunities</strong></th>
<th><strong>Threats</strong></th>
</tr>
</thead>
</table>
| **MDA** | - Potential spread of drug resistance  
- Compliance issues with drug treatment  
- Migration of infected individuals into post-control regions  
- Vulnerable populations often not targeted |
| - Transfer of successful programs  
- Collaborations national level  
- Common targets in various helminth species  
- Large body of knowledge on the animal health market  
- Advanced compounds available that have a complete tox package or have already been used in humans, but have no registration |