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
Quadrimune 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

Research
- Screen
- Hit to Lead

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

Development
- Phase IIb / III
- Regist
- Implem

Direct acting
- DOLF
- IVM / DEC / ALB (Oncho)
- Celgene
  - CC6166
- Bayer
  - Emodepside
- Oxfendazole

Anti-Wolfia
- LSTM / FSAI
- Uni Bonn
  - Rifapentine / Moxifloxacin
- Uni Bonn
  - Doxycycline
- AbbVie / AWOL
  - ABBV-4083

DNDi projects
DNDi Macrofilaricide program

Project activities:
• Development of macrofilaricidal drugs against Onchocerciasis.

Project stage:
• Currently, emodepside, ABBV-4083 (TyIAMac®) 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
• Adultiциdal 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 anthelmintic 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
Summary

*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>
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<tbody>
<tr>
<td>• Elimination programs have reduced morbidity due to helminth infections</td>
<td>• Relies on extremely limited number of (sub-) optimal tools</td>
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<tr>
<td>• Abrogation of transmission in some areas and countries</td>
<td>• Current drugs do not kill/eliminate adult worms (Oncho, Trichuriasis)</td>
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<tr>
<td>• Awareness for neglected patient groups increases</td>
<td>• Transmission unbroken in many areas</td>
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<tr>
<td>• No sensitive diagnostics available</td>
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<table>
<thead>
<tr>
<th><strong>Opportunities</strong></th>
<th><strong>Threats</strong></th>
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<tr>
<td><strong>MDA</strong></td>
<td>• Potential spread of drug resistance</td>
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<tr>
<td>• Transfer of successful programs</td>
<td>• Compliance issues with drug treatment</td>
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<td>• Collaborations national level</td>
<td>• Migration of infected individuals into post-control regions</td>
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<td><strong>R&amp;D</strong></td>
<td>• Vulnerable populations often not targeted</td>
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<td>• Common targets in various helminth species</td>
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<td>• Large body of knowledge on the animal health market</td>
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<td>• Advanced compounds available that have a complete tox package or have already been used in humans, but have no registration</td>
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