

INNOVATIVE APPROACHES FOR NEGLECTED DISEASES DRUG DISCOVERY

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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



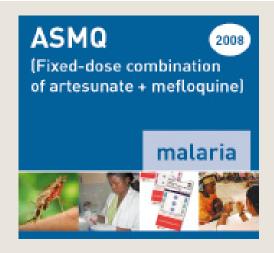
Filaria

Published Target Product Profiles to meet patients' needs
 See: www.dndi.org



6 New Treatments Developed Since 2007

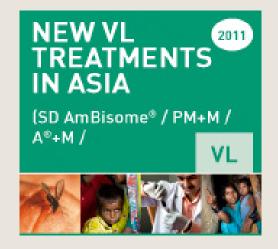






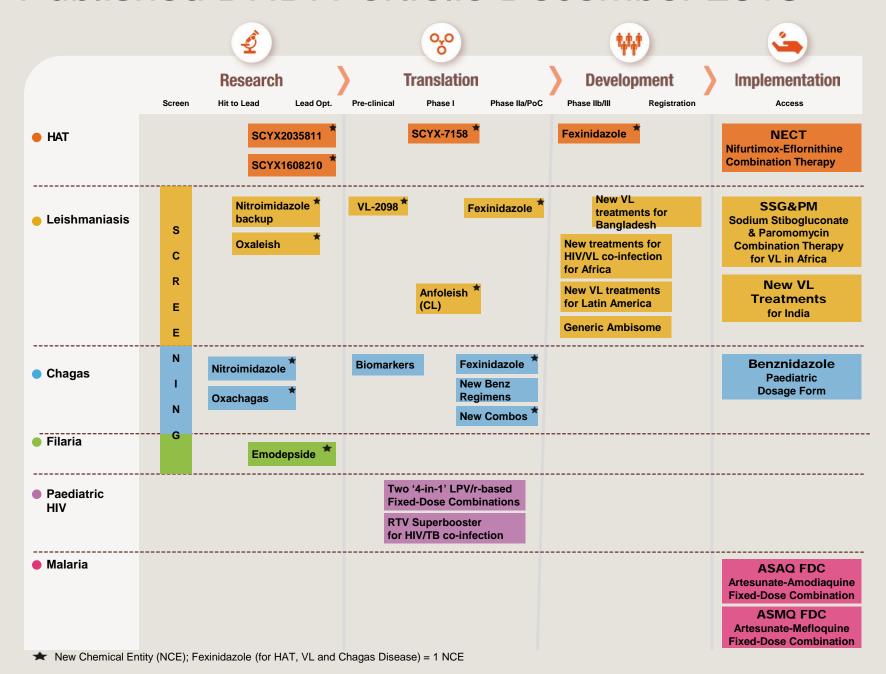
☑ Easy to Use ☑ Affordable ☑ Field-Adapted ☑ Non-Patented







Published DNDi Portfolio December 2013



Share and use open data





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

The parasitic disease huma also known as sleeping sich condition endemic in sub-5 treated with medicines that

easy-to-use treatments are imidazoles possess antibact and examples such as trichomoniasis and guardis including genotoxicity limi a 2-substituted 5-nitroimid

a 2-substituted 5-nitroimid for Neglected Diseases in compound mining of publi databases, has the potentia and effective oral treatmen HAT. This paper descrif fexindazole and its two a and suffone derivatives, mutagrafic in the Salmoned high is, either attenuate, tither attenuates

nicity is either attenuate strains that lack one or me

that these enzymes can ni

redox potentials, whereas redox potentials, whereas parts cannot, under morm its metabolites have low re lian cell assays to detect ge study either in vitro (micre cytes) or in vitro (ex vitro rats; home marrow micr negative. Thus, Fexinidan hazard to patients and camdidate for HAT, Fexinid Il clinical trials in 2012.

II clinical trials in 2012

An estimated 60 million countries are at risk for hun especially poor and neglec-areas (1,2). In west and ce

Tripanosoma brucei pand

© The Author 2012 Published by All tichs mored. For personne

Els Torreele^{1*}, Bernadette Bourdin Trunz¹, David Tweats^{1,2}, Marcel Kaiser^{3,4}, Reto Brun^{3,4}, Guy Mazué¹, Michael A. Bray1, Bernard Pécoul1

Drugs for Neglected Diseases initiativ (DND), Geneva, Switz Tropical and Public Health Institute.

Background: Human Afric trypanosomes. Current tre bite of infected t trypanosomes. Current tre particular for the advanced are urgently needed. Here Neglected Diseases initios nitroheterocycles, could be of the disease in risk for HAT, an could be implemented at requirements before initi toxicological profile of fex ported HAT case

Human Africas ing sickness, is

16), with over 95 Methods and Findings: S experimental models for international regulatory gu in vitro against African try 0.93 µg/mL) and oral adm cured mice with acute and There are for sleeping sickness the bemolympha oprol and efforn disease when parasites hadministration and readil the disease, when vous system (CNS)

fexinidazole was 41% in m least two biologically activ the therapeutic effect. Key sulfone metabolites are a 0 drugs currently in poor oral bioavail mL respectively. Essential pharmacology and 4-week No Observed Adverse Eve both species, with no is nitroheterocycles, is mutag in vitro or in vivo as asset micronucleus test, and an

Conclusions: The results effective oral drug candida human phase I studies in treating advanced-stage s

Editor: Marieen Sociaers, Institut Received April 29, 2010; Accept Copyright: 0 3010 Tomede et al. unrestricted use, distribution, and e Funding: All studies in this pap analysis leven if performed by or

Competing Interests: DT, GM is

(G), www.plosntds.org

Mutagenesis Advance Access published April 26, 2012 Genotoxicity profile of fexinidazole-a drug candidate in clinical development for human African trypanomiasis (sleeping sickness)

David Tweats^{1,2,1}, Bernadette Bourdin Trunz³ and Els Torrecle³ sleeping sickness, whereas in eastern and southern Africa, T. b.

ORIGINAL RESEARCH ARTICLE

DOI 10.1007/s40262-014-0136-3

Determination of an Optimal Dosing Regimen for Fexinidazole, a Novel Oral Drug for the Treatment of Human African Trypanosomiasis: First-in-Human Studies

Antoine Tarral · Séverine Blesson · Olaf Valverde Mordt · Els Torreele - Daniela Sassella - Michael A. Bray - Lionel Hovsepian Eric Evène - Virginie Gualano - Mathieu Felices - Nathalie Strub-Wourgaft

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Backermed and Objectives Fexinidazole is a 5-nitroimidazole recently included in a clinical efficacy trial as an oral drug for the treatment of human African trypanosomiasis (HAT). Preclinical studies showed it acts as a pharmacologically active pro-drug with two key active metabolites: sulfoxide and sulfone (the most active metabolite). The present studies aimed to determine the best dose regimen for the treatment of stage 2 sleeping sickness tients, which could eventually also treat stage 1 patients Methods Fexinidazole was assessed in 154 healthy adult male subjects of sub-Saharan African origin. Three initial first-in-human studies and two additional studies assessed a single ascending dose and multiple ascending doses (both under fasted conditions), tablet versus suspension formu-lation and food effect (fasted vs. high-fat meal and fieldsdapted food), and multiple ascending doses with a loading dose regimen under fed conditions.

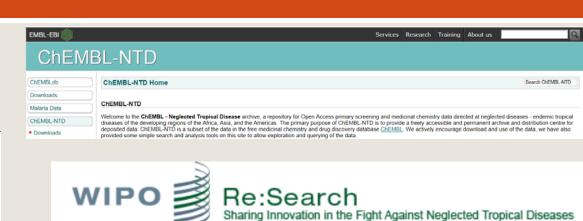
The studies were registered with ClinicalTrials.gov under the following numbers: NCT00982904, NCT01340157 and NCT0148370.

Electronic supplementary material. The online version of this material, which is available to authorized users

Results Fexinidazole was well-tolerated in a single dose from 100 to 3,600 mg, with quick absorption of the parent drug and rapid metabolism into sulfoxide [time to maxi mum concentration (t_{max}) 2–5 h] and sulfone (t_{max}) 18–24 h). The tablet formulation was approximately 25 % loss bioavailable than the suspension, and food intake increased drug absorption and plasma concentrations of fexinidazole and its two metabolites by approximately 200 %. Fourteen-day multiple ascending dosing administered up to 3,600 mg/day in fasted conditions showed that fexinidazole was generally well-tolerated (mild to moderate, spontaneously reversible drug-related adverse events) Following the high-fat food effect finding, another study was conducted to evaluate the impact of a low-fat regimen closer to that of the target population, showing that the type of meal does not influence fexinidazole absorption. The last study showed that a loading dose of 1,800 mg/day for 4 days followed by a 1,200 mg/day regimen for 6 days with a normal meal provided the desired exposure of fex inidazole and its metabolites, particularly sulfone, with good tolerability. Based on preclinical evidence from a chronic infection mouse model, systemic drug concentrations obtained are expected to be clinically effective in stage 2 HAT.

Conclusions These studies show that fexinidazole can be

medicines patent pool



WORLD INTELLECTUAL PROPERTY ORGANIZATION

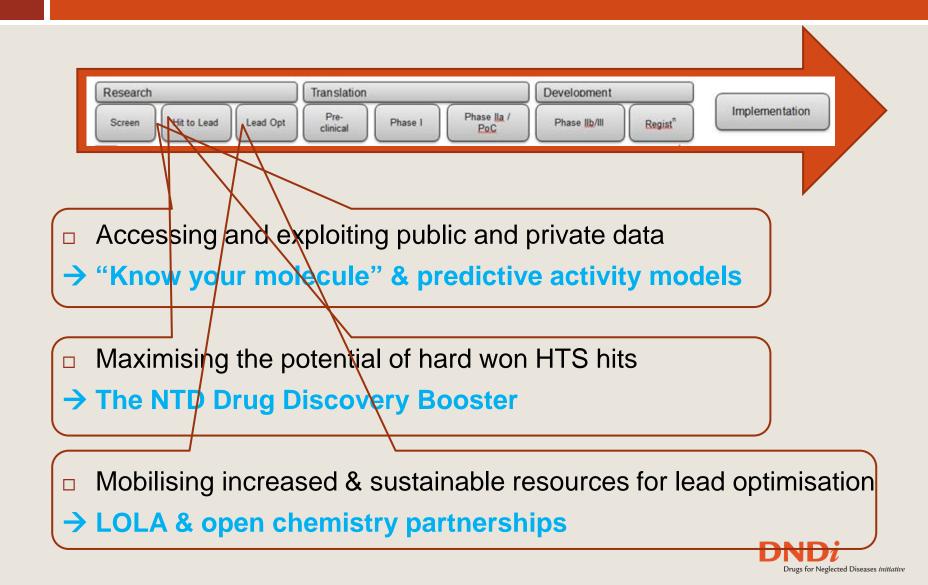


Share and use open data

- 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 focussed on bottlenecks most impactful
 - Some current examples for Research...



Some Drug Discovery challenges for DNDi Innovative collaborations and open source approaches can help

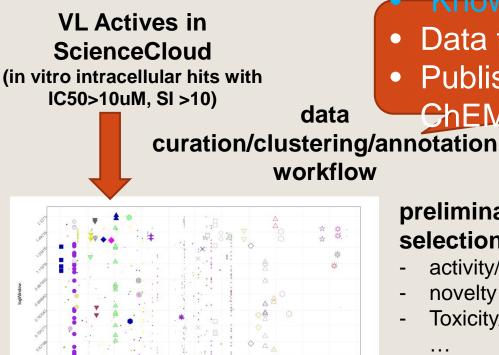


The changing discovery landscape

- 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**



Know your molecules'

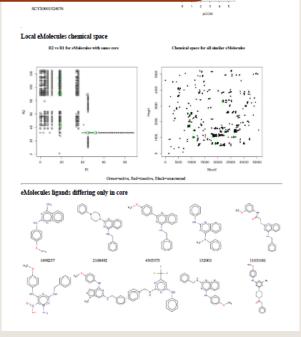
- Data from collaborations
- Published data from

ChEMBI

preliminary selection

- activity/selectivity
- novelty
- Toxicity/reactivity





ongoing

Hit analog purchase followed by confirmatory screening

6 priority series





Q2 2014



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) √
- \rightarrow in silico prediction of activity using commercial libraries (compound list) $\sqrt{}$
- In vitro screening to validate models ongoing
 Data available end Q2 2014
- Sharing of models with partners to select compounds from their libraries next



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

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



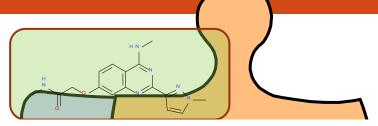
The changing discovery landscape

- 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 crosscollaboration 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



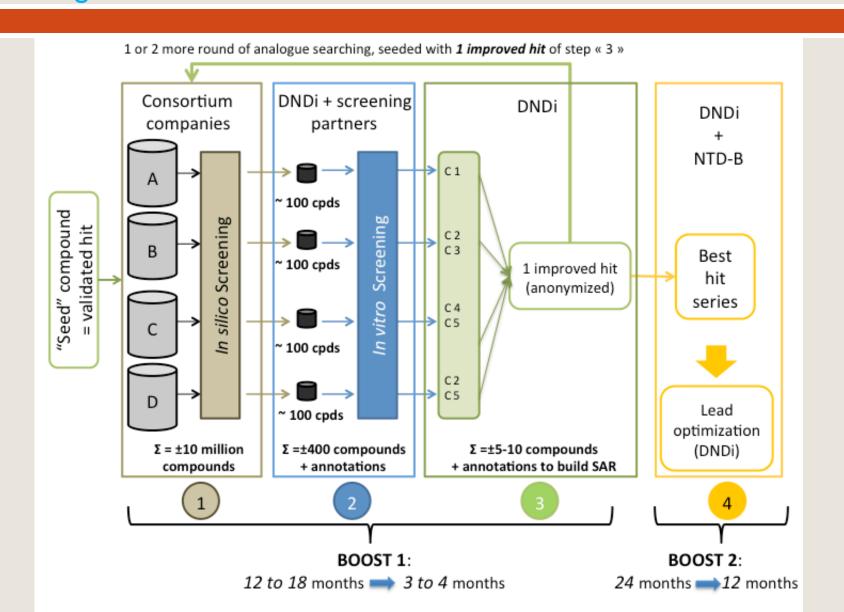
Annotations

- Annotations on the final 'boosted' series
 - Inform decision to move into LO
 - Highlight risks and benefits of series
 - Guide medicinal chemistry strategy
 - Accelerate lead otpimisation and reduce costs



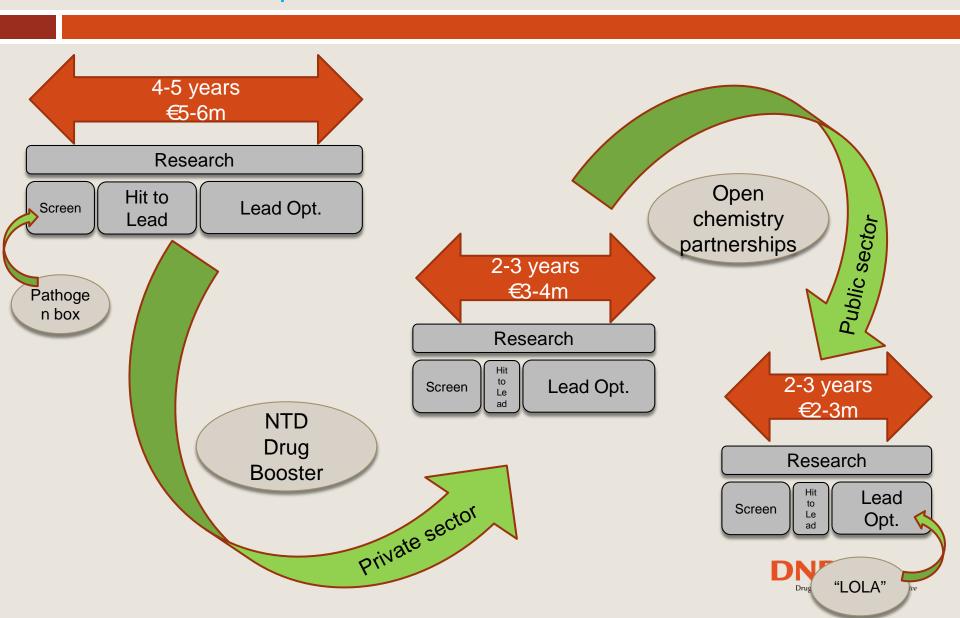
NTD Drug Discovery Booster: How Would it Work?

Moving from bilateral to multilateral collaborations



Drug Booster and Open Source innovations

→ faster, cheaper, sustainable & more efficient Research







THANK YOU

www.dndi.org