One century after Chagas disease was first described, research has provided better understanding of the disease-causing parasite (shown under magnification). However, more activities and partnerships are needed in order to develop and deliver better-adapted diagnostics and treatments for this and other neglected diseases.
Major progress towards addressing the most neglected diseases with better medicines, including DNDi’s 1st treatment for sleeping sickness.

DNDi has made significant progress in establishing a well-balanced pipeline for the 3 diseases of our current primary focus: sleeping sickness (Human African trypanosomiasis; HAT), visceral leishmaniasis (VL), and Chagas disease; and in addressing issues on access to these essential medicines.

Promising developments can be seen in each of the disease-specific and discovery portfolios:

- **Discovery phase**: new commitments from pharmaceutical partners like Anacor and GlaxoSmithKline, as well as key academic groups, such as the Drug Discovery Unit at the University of Dundee, and Institute Pasteur Korea
- **HAT**: positive Phase III results and inclusion of NECT onto the WHO Essential Medicines List, advancement of lexitinidazole towards clinical development, and promising lead series from Scynexis and Anacor
- **VL**: combination studies in Asia and Africa are progressing, with new sites and studies added; development of combination strategy for Latin America; excellent progress seen from lead optimisation consortium
- **Chagas disease**: agreement with LAPEPE to develop the only available compounds suitable for therapeutic switching, or for further improvements via alternative or new formulations

Short-term objectives of making existing drugs available in broader geographic areas and developing better treatments from existing drugs; examples include conducting necessary studies to register drugs not yet available in selected regions, developing fixed-dose combinations, and identifying combinations of existing drugs to reduce treatment duration, improve tolerability and lower the risk of resistance development.

By this balanced approach of portfolio-building, DNDi is able to address patient needs in the near and long term, while also ensuring that a sustainable pipeline is established.

With the aim to deliver improved treatments for patients with neglected diseases, DNDi manages a spectrum of skilled partners with unique and varied expertise in the research and development of improved treatments for patients with neglected diseases. Discovery efforts are consolidated to allow the maximum efficiency for uncovering compounds with potent antiparasitic activities.

### DNDi’s R&D Projects – Filling the Gaps

<table>
<thead>
<tr>
<th>Gap 1</th>
<th>Gap 2</th>
<th>Gap 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Long-term projects</strong></td>
<td><strong>Medium-term projects</strong></td>
<td><strong>Short-term projects</strong></td>
</tr>
<tr>
<td>New compounds</td>
<td>Therapeutic switch ‘Rediscovered’ compounds</td>
<td>New formulations (PDC) Geographical extensions</td>
</tr>
<tr>
<td>Existing compounds</td>
<td></td>
<td>Co-administration</td>
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<tr>
<td>&gt; 6 years</td>
<td>3-6 years</td>
<td>≤ 3 years</td>
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and clinical development activities are organised by disease area, and each is focused on the ultimate goal of developing new treatments which reach patients and contribute to improved disease control.

**STRENGTHENING AND STREAMLINING THE PORTFOLIO**

Into 2009, DNDi’s portfolio continues to be strengthened and streamlined. Within the drug research and development process, milestones are defined for each project. Each year, a number of projects reach completion, and resources are reallocated to new projects.

We’d like to acknowledge our partners’ contributions to the following projects that have reached completion in the past year. DNDi continues to work with many of these partners on other projects:

- **COMPOUND SCREENING WITH CDRI (HAT), Stage: Discovery; Partner: Central Drug Research Institute (CDRI), India.**
- **MICROTUBULE INHIBITORS (HAT), Stage: Discovery; Partners: Murdoch University, Australia; Epichem, Australia; Centre for Drug Candidate Optimisation, Monash University, Australia.**
- **AMPHOTERICIN B POLYMER (VL) Partners: Imperial College, UK; London School of Pharmacy, UK; LSHTM, UK.**

The R&D portfolio represents a collection of projects that are in-sourced at all stages along the drug R&D process, from early discovery through clinical development, with the objective to bring new, field-relevant tools to patients in the shortest time and most efficient way possible. DNDi utilises a target product profile (TPP) which is a hypothetical “package insert” that guides the development process. The TPP plays a key role in guiding lead optimisation of drug candidates, decision-making within the team, design of clinical research strategies, and constructive communication with regulatory authorities. TPPs can be found for each of DNDi’s target diseases in the following pages.

Sound knowledge of patient needs is essential to a credible TPP. Our clinical project managers have in-depth knowledge about the patients in the field. They solicit input from healthcare workers, patients, health regulators, and policymakers in disease-endemic countries where the drug will ultimately be made available. Input from key opinion leaders and the R&D landscape for each disease area are also important and influential in shaping the TPPs.

With dozens of partners spanning the globe and crossing various sectors related to neglected diseases and drug development, DNDi is firmly on its way to meeting its objectives. However, additional support, from new research partners to governments and other donors, is needed in order to fully deliver the best science for the most neglected.

### CHARACTERISTICS OF A TPP

**Indication**
- Which diseases?

**Population**
- Which patients and where?

**Clinical Efficacy**
- Does it kill the parasite effectively?

**Safety and Tolerability**
- What kind and how many adverse events?

**Stability**
- How long can it be stored in the field?

**Route of Administration**
- How is it given to patients?
- How often and how long must it be given?

**Cost**
- Will it be affordable to target population?

**Time to Availability**
- How long will it take to develop?
Consolidated efforts in discovery are feeding a pipeline that will deliver

Discovery research – a three-stage process consisting of screening, lead selection, and lead optimisation – is the one of the earliest stage of drug research and development, and contributes to bringing forward novel drugs that are significantly better than current therapies. DNDi continues its screening efforts into 2009 by consolidating and strengthening activities to ensure a robust pipeline that will deliver.

Many molecular targets or chemicals with therapeutic potential never make it into the drug development process. Although a lot of research has been conducted on the kinetoplastid parasites over the past century, culminating in the publishing of sequencing of its genomes and proteomes in 2005, basic research has yet to translate into new therapeutic tools.

DNDi is working to overcome this gap in the discovery stage by: (1) accessing broad chemical diversity through a number of different sources and partnerships such as a natural products screening network and collaborations with pharmaceutical companies, (2) evaluating antiparasitic activity of compounds in vitro and in vivo according to standard operating procedures to ensure that screening at different sites and with different groups are comparable, and (3) increasing screening capacity for the kinetoplastid diseases. A resourceful and pragmatic approach, with a variety of strategies and partnerships, is used to feed the pipeline and deliver suitable leads to the lead optimisation (LO) programme.

Oxaboroles, now a promising lead series being optimised as part of the HAT lead optimisation consortium, have a unique boron-based chemistry that allows researchers at Anacor to use rational drug design in creating compounds with unique properties beyond traditional small-molecule drugs. As shown above, boron’s reactive P-orbital allows it to form a tetrahedral structure under certain conditions.

Into 2009, important developments within DNDi’s discovery efforts include:

■ a high-throughput screening (HTS) assay for the intramacrophagic Leishmania parasite, with the goal to have HTS for all 3 kinetoplastid diseases by end of 2009 – this is already available for T. brucei (the parasite causing human African trypanosomiasis), but remains a rate-limiting step for both Leishmania and T. cruzi

■ agreements with pharmaceutical and biotechnology companies – GSK, Anacor, Merck, and many others in discussion

■ streamlining/sharing with other PDPs [MMV, TB Alliance], new research agreements with the Drug Discovery Unit at the University of Dundee, and information sharing with the Consortium for Parasitic Drug Development at the University of North Carolina.

DNDi has taken efforts in the past year to consolidate its activities with strategic focus on proactive compound mining, improved throughput of screening intracellular parasites, and general phenotypic screening. The following projects are part of DNDi’s discovery activities but are by no means comprehensive as DNDi continues to take on new exploratory activities.

REFERENCE SCREENING CENTRES

Dedicated research groups at the London School of Hygiene and Tropical Medicine (LSHTM), Swiss Tropical Institute (STI), and the University of Antwerp serve as reference screening centers for DNDi in our efforts to harness existing expertise as well as to help ensure that screening results are comparable and standard for in vitro and in vivo assays at different sites and with different groups.
SCREENING OF PROMISING CHEMICAL CLASSES

GSK - CYSTEINE PROTEASE INHIBITORS AND PYRIDONES
- Target diseases: HAT, Chagas, and VL
- Partners: GlaxoSmithKline, Spain; Swiss Tropical Institute, Switzerland
- DNDi project manager and coordinator: Denis Martin, Jean-Robert Ioset
- Project start: March 2008

In early 2008, GSK and DNDi formalized an ambitious collaboration which makes available a large GSK library of new cysteine protease inhibitors and a library of pyridone compounds to DNDi in order to examine their specific activities against kinetoplastid parasites as both compound libraries have shown good parasitic activity. Cysteine proteases (CP) are nearly ubiquitous in protozoan parasites, play a number of key roles in parasite survival (from nutrition to immune evasion), and have well-known structure-activity relationships. Pyridones have demonstrated potent in vitro and in vivo antimalarial activity. In 2009, over 500 compounds have been screened in vitro, and a number of compounds have been selected for further pharmacokinetic and in vivo efficacy testing.

NITROIMIDAZOLES – PROACTIVE COMPOUND MINING
- Target diseases: HAT, Chagas, and VL
- Partners: Swiss Tropical Institute, Switzerland; Fiocruz, Brazil; Ouro Preto University, Brazil; Covance, UK; Absorption Systems, USA; BioDynamics, UK; and a range of worldwide collaborators who have made compounds of interest available for testing, including ENH Research Institute, USA; Tehran Univ of Medical Sciences, Iran; Silesian Univ of Technology, Poland; LaSapienza Univ, Italy; Univ of Alberta, Canada; Univ of Tennessee, USA; Tokushima Univ, Japan; Univ of Auckland, Australia; sanofi-aventis, France; Roche, Switzerland; Novartis/NITD, USA-CH-Singapore; Alkern, India; TB Alliance, USA; Sigma-Aldrich, USA
- DNDi project manager: Els Torreele
- Project start: January 2005

Nitroimidazoles are a well-known class of anti-infective compounds; however, the risk for genotoxicity linked to the nitro-group has been a concern for drug development. An extensive, proactive compound mining effort was undertaken by DNDi to ‘revive’ nitroimidazoles as drug leads against the kinetoplastid parasites. Over 700 existing compounds from 15 different sources were identified, accessed, and tested for in vitro and in vivo activity. Active compounds underwent extensive drugability profiling, including possible mutagenic activity, ADME, and pharmacokinetics. This approach has led to the discovery and characterization of fexinidazole as a promising drug candidate for HAT [see page 18] and with promising activity against T. cruzi [the parasite causing Chagas disease]. Additionally, N-aryl-4-nitroimidazoles have been identified as a new lead series for HAT as a possible back-up for fexinidazole, should it fail in the clinic. Other nitroimidazoles have shown promising activity against Leishmania and T. cruzi, and are being assessed for their potential for further development. This research shows that it’s possible to select non-mutagenic nitroimidazoles with good antiparasitic activity.

ESKITIS SCREENING OF NATURAL PRODUCTS
- Target disease: HAT
- Partners: Eskitis, Australia; Griffith University, Australia
- DNDi project manager and coordinator: Eric Chatelain, Jean-Robert Ioset
- Project start: November 2007

As part of early exploratory activities, DNDi accessed the natural products’ wealth and drug discovery expertise of Eskitis Institute for Cell and Molecular Therapies to examine the in vitro trypanocidal activity of 64,000 natural products from a diverse screening li-
library of over 200,000 extracts. This unique lead-like peak library of natural products, which possess well-characterized physicochemical properties optimised for drug development, includes representatives of 60% of global plants and 9,500 marine invertebrates. The proprietary lead-like enhancement technology used by Eskitis is a two-step process which enriches extracts in lead-like and drug-like components prior to pre-fractionation; this process maximizes the chance of a positive outcome, i.e., detecting a ‘hit’. In 2008, the first ‘hit’, a marine invertebrate, was identified. As the project continues through 2009, the remaining 136,000 compounds have been screened, and hit expansion with 2 series is due to begin later in the year.

KITASATO SCREENING OF NATURAL SUBSTANCES
• Target disease: HAT
• Partners: Kitasato Institute (KI), Japan
• DNDi/project manager and coordinator: Eric Chatelain, Jean-Robert Ioset
• Project start: April 2005

Natural products from microbial and plant resources, such as avermectin and artemisinin, have played an important role in the history of parasitic chemotherapy. Likewise, KI has a long history in the research and discovery of anti-infectious drugs from natural products, such as microbial metabolites and plant products. The objective of this specific project is to discover new types of antitrypanosomal molecules from KI natural products via in vitro and in vivo screening. Through March 2009, over 25,000 natural products and their synthetic derivatives have been screened, with 9 compounds having been identified as having high activity. These compounds are now being evaluated for possible lead optimisation at Scynexis, where researchers are currently undertaking hit expansion on one of the compounds, malonomycine; at the same time, KI will continue searching for further ‘hits’ to feed the pipeline.

INSTITUT PASTEUR KOREA (IPK)

Developing a technological breakthrough: IPK visual high-throughput screening (HTS)
• Target disease: Visceral leishmaniasis (VL)
• Partners: Institut Pasteur Korea (IPK)
• DNDi/project manager and coordinator: Eric Chatelain, Jean-Robert Ioset
• Project start: December 2007

A cell-based, high-throughput visual screening system for Leishmania parasites offers the possibility to quickly generate new hits against novel targets. Utilising both the intellectual and technological capacity of the Institute Pasteur Korea, this project seeks to develop a major methodological advance in antileishmanial drug development as this will be the first HTS visual screening assay for the clinically relevant intracellular form of the parasite: intracellular Leishmania amastigotes in macrophages.

Having operationally begun in May 2008, the project first sought to develop and validate the visual assay in the first year so as to then use it in the second year of the project to test confirmed ‘hits’ against Leishmania. The project is now at a stage where a 200,000 compound library is being screened, with results expected later in 2009.

When the methodology is validated with the current screening run, this assay will be the first of its kind in the world, and it will then be expanded to include testing against other intracellular parasites such as T. cruzi. Such a visual screening would represent a huge advance for antitrypanosomal screening as well. Highlights of the ongoing research efforts were presented during the World Leishmaniasis Congress in February 2009, and the presentation is available on the DNDi website.
At the forefront of DNDi’s efforts to develop new treatments is the need to understand the realities and treatment needs of patients and health care staff in the field. The ultimate goal for human African trypanosomiasis (HAT) is a truly simplified treatment which can be orally administered, implemented at the primary health care level, and effective against both stages of the disease. Currently, both diagnosis and treatment require a complicated series of tests and trained medical supervision. A key issue with HAT is that it affects hard-to-access communities in regions with poor health infrastructure; as a result, there is probably considerable underreporting of the condition. Poor access to medical facilities, a lack of resources and skills, and misdiagnosis all contribute to underreporting. Due to the resource-poor areas where the disease occurs, control efforts are often mobilised into vertical programmes. Consisting of a series of specifically equipped and trained diagnosis and treatment centres and mobile teams in endemic areas, but these programmes are not integrated into regional health centres.

There is an immediate need to improve current treatment options, particularly for patients with advanced stage of the disease where the few drugs that are available are toxic, increasingly ineffective in killing the parasite, and difficult to use. Ideally, a treatment will be safe enough to be used in the first stage of the disease and effective enough in the second stage of the disease. In addition to lead optimisation programmes, DNDi has conducted proactive compound mining activities to identify existing compounds with potential against kinetoplastid diseases. The compound mining activities of DNDi have led to the revival of the nitromidazole class as potential drug candidates: the most notable example is fexinidazole, upon which DNDi has begun clinical development for HAT.

Several groups worldwide have specific established expertise and knowledge in drug discovery that are readily applicable to the discovery of new antitrypanosomal drugs. In this context, DNDi has established:

- Partnerships with pharmaceutical / biotechnology / academic groups for interaction and access to natural product as well as synthetic chemical libraries, chemistry, HTS, biological models, and drug design
- A network of key international laboratories to support discovery efforts with pharmacokinetic, pharmacodynamic, and toxicological expertise, and defined synergy between these laboratories.

At the clinical stage of development, DNDi is working to both investigate new medicines and to also strengthen capacity for clinical research on HAT. With the recent inclusion of NECT onto the WHO Essential Medicines List, DNDi is well on its way to meeting its short-term objective to bring a new, short-course, co-administration treatment for stage 2 HAT to the patients. Through this project, DNDi has also built important relationships with other groups involved in HAT clinical research as well as with the WHO, national HAT control programmes and NGOs working to control HAT.
SLEEPING SICKNESS – Human African Trypanosomiasis (HAT)

60 million people at risk in sub-Saharan Africa

WHAT IS THE ANNUAL IMPACT OF HAT?
50,000-70,000 cases (1)
48,000 deaths (2)
1,525,000 DALYs (2) (3)
Large proportions of communities can be affected by HAT, with serious social and economic consequences. Epidemics at the end of the 20th century infected up to 50% of population in several villages across rural Africa.

WHERE DOES HAT OCCUR?
Of the 36 countries considered endemic for HAT, the 7 most affected countries represent 97% of all reported cases (see map).
The Democratic Republic of the Congo (DRC) alone accounts for 2/3 of reported cases (4).
HAT primarily occurs in the poorest, most rural areas in Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term: better use of existing treatments
– Nifurtimox-eflornithine combination therapy (NECT), a simplified treatment for stage 2 HAT, now ready for use

Medium term: rediscovered compounds
– Fexinidazole: first drug candidate entering clinical development from nitroimidazoles project
– Back-up nitroimidazoles

Long term: new compounds and improved research capacity
– New drugs developed from compounds identified (i.e. oxaboroles) in discovery research and progressed through HAT lead optimisation consortium
– Multi-country, multi-partner HAT Platform to strengthen regional research capacity (see Section 3).

WHAT ARE THE SYMPTOMS/PRESENTATIONS?
HAT occurs in two stages:
– stage 1 - the haemolymphatic phase – includes non-specific symptoms like headaches and bouts of fever (generally goes undiagnosed) without active HAT surveillance.
– stage 2 - the later, neurologic phase – occurs when the parasite crosses the blood-brain barrier (BBB) and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and, ultimately, results in death without effective treatment.

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– New drugs developed from compounds identified (i.e. oxaboroles) in discovery research and progressed through HAT lead optimisation consortium
– Multi-country, multi-partner HAT Platform to strengthen regional research capacity (see Section 3).

By 2014, DNDi aims to deliver from its HAT-specific portfolio:
– 1 new combination therapy recommended by WHO
– 1 new drug registered
– A robust pipeline

3) DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. (4) Simarro PP, Jannin J, Cattand P, PLoS Med. 2008;5:e55.
**LEAD OPTIMISATION CONSORTIUM**

- **Partners:** Scynexis, USA; Pace University, USA
- **DNDi project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** April 2007

With an objective to develop optimised leads by progressing 'hit' molecules with a good safety profile and activity against *T. brucei* parasites, these consortia bring together expertise in chemistry, biology, screening, and pre-formulation. Optimisation focuses on the molecule’s capacity to be absorbed into the bloodstream, be distributed effectively to the infection, survive in the body, kill the parasite and not harm the patient. With two full lead optimisation teams in place (a total of 18 scientists), a number of hits identified from DNDi screening partners are undergoing hit expansion. Scientists within the consortia use advanced techniques to study how the selected molecules interact with the therapeutic target (ie. a protein or an enzyme) and optimise the drug-like characteristics of these molecules to ensure that they comply with the target product profile. This phase requires a close, highly interactive collaboration between the biologists and chemists, who form a feedback loop: the biologists test the biological properties of compounds on biological systems while the chemists perfect the chemical structure of these compounds based on information obtained by the biologists. Two compound series have been chosen as lead series:

- **Oxaboroles**, provided by Anacor and possessing a unique boron-based chemistry, were identified as hits against *T. brucei* at the Sandler Centre of the University of California San Francisco, and have shown in vivo activity.
- **Kinase inhibitors**, of which approximately 300 analogs have been synthesized to date. Significant in vitro potency has been developed but only moderate in vivo activity, so further study is ongoing. These two series will continue to be optimised, with the goal to enter preclinical development in 2010 and 2011.

This strategy and the promising early results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

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**SAMPLE COMPOUND STRUCTURE OF OXABOROLES AND KINASE INHIBITORS**

- **Oxaboroles**
- **Kinase inhibitors**
- **Pyrimidines**
- **Thiazoles**
- **Ongoing collaboration with Dundee University**

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**CLINICAL**

**FEXINIDAZOLE**

- **Stage:** preclinical moving clinical development
- **Partners:** Accelera, Italy; Aptuit, UK; Axyntis, France; Covance, UK; Drugabilis, France; Labor für “Pharma and Umweltanalytik”, Germany; Germany sanofi-aventis, France; Swiss Tropical Institute, Switzerland
- **DNDi Project Manager:** Els Torreele
- **Project start:** February 2007

Fexinidazole as a drug candidate for stage 2 HAT is the first success of the proactive compound mining efforts DNDi has pursued in particular in the nitroimidazoles project (see page 13).
A 5-nitroimidazole that was in preclinical development as a broad-spectrum anti-protozoal by Hoechst in the early 1980s, fexinidazole was rediscovered by DNDi after being an abandoned compound. Extensive profiling by DNDi has shown that fexinidazole is orally active, and readily distributes to the brain and cures mouse models for both acute and chronic infection with African trypanosomes. Importantly, fexinidazole is not mutagenic in a panel of in vitro and in vivo mammalian genetic toxicology tests, confirming its favorable activity/toxicity profile as a drug candidate.

In 2007, a full preclinical programme was established to enable first-in-human studies. This included process chemistry and GMP-manufacturing of the active pharmaceutical ingredient, its preclinical formulation, extensive ADME-PK profiling and confirmatory studies in animal models of HAT, and the regulatory toxicology package (4-weeks repeated dose toxicokinetics in rat and dog, safety pharmacology, and an extensive genetic toxicology package). In June 2008, a full review of the data by DNDi concluded that fexinidazole is suitable for progression into clinical development.

Preparation for first-in human phase I studies are underway, including clinical tablet formulation considered a promising development candidate for HAT. Fexinidazole will enter into Phase I clinical studies in 2009, which would make it the only new drug candidate in clinical development for HAT, and the regulatory toxicology package. In 2008, a full review of the data by DNDi concluded that fexinidazole is suitable for progression into clinical development.

This project and the preclinical results were presented during the 2008 meeting of American Society of Medicine & Tropical Hygiene, and are available at www.dndi.org.

Now available for use after being added to the WHO Essential Medicines List as treatment against stage 2 sleeping sickness

- **Stage**: clinical
- **Partners**: Epicentre, France; MSF; the national HAT control programmes of the Democratic Republic of the Congo (DRC) and the Republic of the Congo; SCIH/STI, Switzerland
- **DNDi/project manager**: Els Torrelee
- **Project start**: April 2004

With the ultimate goal to enable a WHO recommendation on the use of the nifurtimox-eflornithine combination therapy (NECT), the NECT project has shown that the combination is as effective and safe as standard eflornithine monotherapy, but easier to use, and safer than melarsoprol (toxic though still widely used in ~70% of patients with stage 2 HAT).

Begun originally as a single centre study by MSF-Holland and Epicentre in the Republic of Congo (Brazzaville) in 2003, this study was extended, as of 2004, to additional sites in the DRC by DNDi in collaboration with Epicentre, MSF, STI and the national HAT control programmes of the DRC.

This multi-centre clinical study, which enrolled 287 patients and was completed in 2008, compared the safety and efficacy of NECT, a coadministration of the oral drug nifurtimox and the intravenous drug eflornithine, with eflornithine monotherapy, the current first-line treatment for stage 2 T. b. gambiense HAT. As is requisite to establish efficacy in this disease, patients were actively followed up for 18 months after treatment.

The study conclusively demonstrated that NECT is as well-tolerated and efficacious as eflornithine. At the end of 2008, the final efficacy and safety results of the Phase III study were available and led to DNDi’s submission of NECT for inclusion on the WHO Essential Medicines List (EML). The final results are in the process of being published, and were presented by Epicentre during the 2008 meetings of American Society of Medicine & Tropical Hygiene and the HAT Platform, and are available at www.dndi.org. The EML application and support statements of the HAT community are available on the website of the WHO Essential Medicines List.

In May 2009, MSF, Epicentre, and DNDi announced that NECT had been included on the EML. According to the WHO, NECT can now be used in patients and will provide an opportunity to improve the management of HAT cases. The WHO has already made preparations for the arrival of this improved therapeutic opportunity and is working to ensure that patients have access to NECT by providing appropriate training and supplying the drugs and necessary equipment to disease-endemic countries.

DNDi and partners are conducting a field study, which began enrolling patients in April 2009, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children.

Recognised as “Project of the Year in 2008”
Based on the current R&D landscape, the realities in VL-endemic regions, the limited treatment options, DNDi and partners have determined that the ideal product should be oral, safe, effective, low cost, and short course (≤10-day). Ideally, this treatment will be effective against all forms of the disease and is adequate for use in rural health settings.

As it can take five to ten years to bring a compound through the preclinical and clinical phases of development, DNDi is currently building on previous research by extending the registration and availability of current drugs, while maximizing their potential and minimizing their drawbacks.

Combination therapies of these new treatments represent a critical path forward because they could offer the following important advantages: shorter course of treatment, better tolerability, reduction in the work load on the health systems in resource-limited areas, better affordability, and potential to prevent or retard resistance development and prolong the life span of these drugs.

DNDi has three clinical (active) projects: one examining combination treatments (AmBisome®, paromomycin, miltefosine) in India and two ongoing studies in East Africa. In addition to completing these projects, DNDi will conduct further work to improve combination treatments. Several products including new oral formulations of amphotericin B, 8-aminoquinolines, and potential compounds at late preclinical phase are considered and could be made available to patients as early as possible. In addition, DNDi has a lead optimisation programme which will bring new candidates into clinical development over the next few years. All of these new drugs will also be considered for combination therapy.

Using a multi-disciplinary approach, DNDi will bring practical, safe and effective treatments to VL patients that will be a significant step in helping to control the disease in South Asia, East Africa, and Latin America.
KALA-AZAR — Visceral Leishmaniasis (VL)

200 million people at risk worldwide

WHAT IS THE ANNUAL IMPACT OF LEISHMANIASIS?

- 500,000 cases of VL; 1.5 million cases of CL
- 51,000 deaths
- 2,357,000 DALYs

A lack of surveillance systems and frequency of misdiagnosis means that it is difficult to estimate the true incidence and case-fatality rate of VL.

HOW IS LEISHMANIASIS TRANSMITTED?

Diversity and complexity mark the disease of leishmaniasis: more than 20 species of the kinetoplastid protozoan parasite Leishmania are transmitted to humans by ~30 species of phlebotomines sandflies.

WHAT IS LEISHMANIASIS?

Leishmaniasis is a disease with several forms. The two most common are:
- VL: fatal without treatment
- cutaneous leishmaniasis (CL): has a spectrum of presentations: typically with self-healing or chronic lesions on the skin.

VL is the primary disease target for DNDi, whereas CL is secondary, mainly because it is typically not life-threatening.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?

The number of treatment options has increased in the past decade, but each treatment has numerous drawbacks, such as difficulty to administer, length to treat, toxicity, cost, and increasing parasitic resistance to treatment:
- Pentavalent antimonials: toxic & increasingly ineffective due to resistance; 30-day, hospital-based parenteral treatment
- Amphotericin B: dose-limiting toxicity; 15-20 day, hospital-based IV treatment
- Liposomal amphotericin B (Ambisome®): effective, but expensive
- Paromomycin: registered in India, but efficacy in Africa not yet determined
- Miltefosine: first orally available drug registered in India, but expensive and teratogenic.

WHAT ARE THE CURRENT PATIENT TREATMENT NEEDS?

Patients need a treatment which is oral, safe, effective, low cost, and short course (≤10-day course).

WHERE DOES LEISHMANIASIS OCCUR?

Leishmaniasis infects approximately 12 million people in 88 countries. VL affects poor, remote populations in 70 countries across Asia, East Africa, South America, and the Mediterranean region (see map).

The 7 most affected countries – Bangladesh, Brazil, India, Ethiopia, Kenya, Nepal, and Sudan – represent over 90% of new cases.

WHAT ARE THE SYMPTOMS/PRESENTATIONS OF VL?

VL is characterised by prolonged fever, enlarged spleen & liver, substantial weight loss, and progressive anemia. These symptoms occur progressively over a period of weeks or even months. Coinfection with other infectious diseases is an increasing concern. HIV-VL coinfection has been reported in 35 countries worldwide. Almost all clinically symptomatic patients die within months if untreated.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?

Short term: Better use of existing treatments through geographical extension and new combinations.
- Combination in Africa: Registration of paromomycin in 2010, recommendation of combination including paromomycin + sodium, stibogluconate (SSG), registration of Ambisome® in 2011, registration of miltefosine, development of combination with short-course Ambisome®
- Combination in India: Recommendation in India, Bangladesh and Nepal by 2011
- Combination in Latin America: Recommendation in 2013

Medium term: Registration of one new drug through new formulations of existing treatments and therapeutic switching
- Alternative formulations of amphotericin B – DNDi is evaluating an oral formulation developed by BioDelivery Sciences International (BDSI)
- 8-aminoquinolines – DNDi is in discussion with GlaxoSmithKline (GSK) about rafenoquine and sitamaquine for clinical development
- Potential compounds in-sourced at late preclinical phase – DNDi is actively pursuing potential candidates ready for clinical development in the short term

Long term: New compounds and improved research capacity
- New drugs developed from compounds identified (i.e. 2-quinolines) in discovery research and progressed through VL lead optimisation consortium
- Multi-country, multi-partner LEAP to strengthen regional research capacity (see Section 3).

By 2014, DNDi aims to deliver from its VL-specific portfolio:
- 1 new drug registered
- 1-3 geographical extensions in endemic regions outside India by 2014
- 1-3 coadministrations recommended by WHO
- A robust pipeline
LEAD OPTIMISATION CONSORTIUM
- Partners: Advinus, India; CDRI, India
- DNDi project manager and coordinator: Denis Martin, Delphine Launay
- Project start: November 2007

With a full team in place, including 12 team members at the two primary partner sites, assessment of three series of synthetic compounds has been conducted and chemistry-biology activities have begun to bear fruit, with the promising lead series of 2-quinolines. Partners at the "Institut de Recherche et Development" (IRD) originally isolated the 2-quinolines from Bolivian plants, which are used in traditional medicine to treat cutaneous leishmaniasis and malaria. After some promising early results, the DNDi-managed LO consortium has synthesised more than 250 diverse analogues of 2-quinolines. These modified quinolines were significantly more effective than the parent compounds and a few compounds have shown >90% parasite killing at <1.0 μM. Metabolic stability, which is a known liability of this series, has been improved through the introduction of halogen substituents in more than ten compounds. Further studies of the most promising compounds are underway to confirm the druggability and in vivo efficacy and safety. More hits from the other chemical series, including oxaboroles and licochalcones, provided by DNDi screening partners will be continue to be examined by Advinus. This strategy and the promising early results were presented during the World-Leish4 meeting in February 2009 and are available at www.dndi.org.

BUPARVAQUONE
- Partners: Advinus Therapeutics, India; Drugabils, France; University Sains, Malaysia; LSHTM, UK
- DNDi project manager: Denis Martin
- Project start: January 2008

Buparvaquone has been shown to exhibit antileishmanial activity in vitro and in vivo. However treatment of dogs infected with visceral leishmaniasis failed to halt disease progression. It was postulated that the disappointing in vivo data, when compared to in vitro potency may be a result of low plasma levels in the experimental animals. Preliminary animal studies at the Universiti Sains, Malaysia, and DNDi-commissioned studies at Advinus Therapeutics have shown that oral absorption of buparvaquone is dissolution-rate limited and that a self-emulsifying drug delivery system (SEDDS) can increase absolute oral bioavailability to greater than 60%. Such an increased bioavailability should be reflected by an improved efficacy. Buparvaquone efficacy was further tested...
The Kala Azar Medical Research Centre is one of the clinical research partners for the VL combination studies in Asia.

ALTERNATIVE FORMULATION OF AMPHOTHERICIN B POLYMER

- **Partners:** Polyscience, UK; London School of Pharmacy, UK; Imperial College, UK; LSHTM, UK; BioDelivery Sciences International (BDSI), United States
- **DNDi Project Manager:** Denis Martin
- **Project start:** September 2006

The goal of this project is to identify an amphotericin B-based formulation which shows the most promise in terms of in vivo efficacy, safety, low cost, and heat stability. Amphotericin B, under various formulations, has become one of the most efficient treatments for VL. The standard formulations (oily suspension) have limitations related to side effects. AmBisome®, a liposomal formulation has overcome these limitations, but its cost and stability are serious limits to its wide-spread use. There has been very limited use in VL-endemic regions of Africa and Asia, where disease burden is greatest, because of its high cost. Recently, new formulations have emerged and are approved or under clinical development in India. However, their intravenous route of administration is still a barrier for appropriate use in the field. Studies aimed at replacing the lipid-based component with a narrow molecular weight polymer are ongoing, with the goal of developing a soluble complex, cheaper, and exhibiting increased thermal stability. Polymers can also prevent the systemic toxicity of amphotericin B to which they are conjugated, still allowing the drug intracellular delivery. The team in the UK has been investigating a less expensive, modified metacrylic polymer; efforts to establish adequate in vivo efficacy in a disease model while optimizing key characteristics of the polymer did not yield promising results, so this part of the project was concluded in early 2009. Recently, two new formulations of amphotericin B – phospholipid-based cochleates and a lipid-based form with enhanced gastrointestinal tract absorption – have been reported to show activity as antifungals when administered orally in animal models. Early reports suggest that they also exhibit activity in murine models of visceral leishmaniasis. BDSI has developed an oral formulation that is currently in Phase I, targeting fungal infections. DNDi is conducting an exploratory preclinical evaluation of this oral formulation for VL and, if successful, will proceed to clinical development.

CLINICAL COMBINATION THERAPY FOR VL IN ASIA (INDIAN SUBCONTINENT)

- **Partners:** ICMR, India; Kala Azar Medical Research Centre, India; Rajendra Memorial Research Institute of Medical Sciences, India; GVK BID, India
- **DNDi project manager and coordinator:** Farrokh Modabber, Sally Ellis
- **Project start:** December 2006; revised protocol approved October 2007

With the objective to identify a safe and effective short-course combination therapy using existing drugs which could be easily deployed in control programmes, this four-armed, definitive Phase III combination therapy study is using drugs already registered in the region: AmBisome®, miltefosine, and paromomycin. Three arms with a combination of 2 drugs/arm for a maximum of 15-day treatment will be compared with the standard 30-day therapy using amphotericin B. In June 2008, the first patient was enrolled into the study. Enrolment should be completed in June 2009, and results are expected by early 2010. The study has been designed to provide data for authorities in India, Bangladesh and Nepal to make informed recommendations for combination treatment which can be used in the elimination programme. Discussions are ongoing to initiate bridging trials in Bangladesh and Nepal to evaluate the safety of the same combinations, followed by larger trials for further evaluation of safety and efficacy. It is anticipated that these combination treatments will be shorter, safer and cheaper than the standard treatment.
In the next year, DNDi and LEAP will embark on additional clinical research to examine new potential combination therapies, including a geographical extension study on miltefosine, one of the few oral drugs effective against leishmaniasis.

**PAROMOMYCIN FOR AFRICA**

- **Partners:** LEAP (Leishmaniasis in East Africa Platform) group including Kenya Medical Research Institute, Kenya; Addis Ababa University, Ethiopia; Gondar University, Ethiopia; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; Ministries of Health in LEAP countries; Médecins Sans Frontières (MSF); I+ Solutions, the Netherlands; LSHTM, UK; University of Nairobi, Kenya; Institute for OneWorld Health, USA
- **DNDi project manager & coordinator:** Manica Balasegaram; Sally Ellis
- **Project start:** November 2004

In Africa, visceral leishmaniasis is difficult to treat with existing drugs due to various issues, such as toxicity, emerging resistance, difficulty of use, and cost. Paromomycin (PM), an aminoglycoside antibiotic that was identified as an antileishmanial in the 1960s, has the potential to be an improved treatment at a lower cost when combined with the standard treatment of sodium stibogluconate (SSG).

Currently being made available throughout the Indian subcontinent by fellow PDP; Institute for One World Health (IOWH), paromomycin is being studied in parallel by DNDi and the Leishmaniasis East Africa Platform (LEAP) in Ethiopia, Kenya, Sudan, and Uganda. The aim is to register paromomycin as a new treatment in each region, to have it adopted in national treatment guidelines, and to evaluate the shorter course combination of PM+SSG as an alternative treatment for VL.

After early results showed the initial dosage of paromomycin did not work as well in Africa as it did in India, LEAP decided to increase the dose and is now examining a higher-dosage regimen to determine if it is more effective. Over 1000 patients have been recruited so far into the various arms of the study.

In 2008, the study is continuing to recruit patients at sites where infrastructure has been improved or built (see section 3). Initial data was presented during the 2007 RSTMH symposium, and final results of the early part of the study were presented during the World Leish meeting in February 2009; are in the process of being written up for publication, and are available at www.dndi.org. The study is due to complete in 2009, with final results being ready by the spring of 2010.

**AMBISOME® FOR VL IN AFRICA**

- **Partners:** LEAP (Leishmaniasis in East Africa Platform) group including Addis Ababa University, Ethiopia; Gondar University, Ethiopia; LSHTM, UK; Ministry of Health, Ethiopia; Kenya Medical Research Institute, Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; University of Makarere, Uganda; Ministries of Health in LEAP countries; I+ Solutions, the Netherlands; LSHTM, UK; Gilead, USA
- **DNDi project manager & coordinator:** Manica Balasegaram; Sally Ellis
- **Project start:** Approved in May 2006; study start in May 2009

AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, has been used with increasing frequency to treat VL, especially in Europe, over the past decade. Unfortunately, in Africa and Asia, where disease burden is high, drug access is poor because of the high cost of the drug. With recent preferential pricing offered by the manufacturer to patients in the public sector in East Africa, it is possible that AmBisome® could become economically feasible for treatment, even in resource-poor countries.

The goal of this project, therefore, is to determine the minimum dose of AmBisome® that is efficacious, safe, and cost effective in the treatment of VL in Africa, to reduce the length of hospital stay, and to facilitate registration and adoption of AmBisome® in the region. Identifying the minimum dose for monotherapy will be an important step in developing combinations for Africa and in preventing the development of drug resistance. Early in 2009, DNDi has received approval from both the national ethics committees and from the Ethiopian regulatory authority. The study began enrolling patients in May 2009.
Until recently, the primary focus for disease control has been interruption of transmission by vector control programmes and screening of blood donors. Major initiatives began in the Southern Cone countries in 1991 and 1992. Most central and southern American countries joined the initiative over the following decade. Despite these advances in reducing the incidence of T. cruzi infection, the burden of Chagas heart disease is expected to continue in the future since virtually all of the burden of Chagas heart disease comes from individuals already infected who progress from the indeterminate phase to the chronic phase.

Current therapy for Chagas disease is limited to two nitroheterocyclic drugs, nifurtimox and benznidazole. Unfortunately, these drugs are limited to treatment of acute infection in children with conflicting evidence for treatment of indeterminate disease and no evidence to support their use as therapy for symptomatic chronic disease. Even in children, who are more able to tolerate the considerable toxicity associated with treatment, the cure rate is only around 60%. No new anti-T. cruzi drugs are in the clinical development pipeline and only one class of drugs, the antifungal triazoles, have demonstrated potential for therapeutic switching to the treatment of Chagas disease.

The Chagas disease-specific portfolio is a balance of objectives. In the short- and midterm, the aim is for better use of existing treatments through new formulations, therapeutic switching and combination therapy. In the long term, new chemical entities must be developed. Another important element in DNDi’s strategy in Chagas disease is to address the methodological constraints that impact the design of clinical studies.

## Chagas Disease

### Prioritised Target Product Profile for Chagas

- **A new treatment** for adults and children for acute and early chronic disease
  - Priority is a pediatric formulation
  - Useful against both parasite species in all regions
- **Better safety profile** than existing drugs
  - Ideally requiring little or no monitoring
  - Suitable for immunocompromised patients
- **Equal or better efficacy** profile than existing drugs
- **Easy-to-use treatment**
  - Ideally less than 30 days
  - Oral
  - Preferably once-a-day treatment, ideally outpatient
- **Affordable**
- **Stable in tropical climate**
What is the impact of chagas disease?
Approximately 8 million cases (1)
14,000 deaths (2)
667,000 DALYs (2)(3)

Chronic Chagas disease results in significant disability with great social and economic impact including unemployment and decreased earning ability. In Brazil alone, losses of over US$ 1.3 billion in wages and industrial productivity were due to Chagas disease (4).

How is Chagas disease transmitted?
Caused by the kinetoplastid protozoan parasite Trypanosoma cruzi, Chagas disease is primarily transmitted by large, blood-sucking reduviid insects widely known as “the kissing bugs” in endemic countries. Other ways of transmission are blood transfusion, organ transplantation, as well as congenital and oral transmissions.

What are the current treatments and their limitations?
Current treatments can cure infected patients, but highest efficacy is seen early in infection.
- Benznidazole, nifurtimox to treat acute & early indeterminate disease:
  - Long treatment period (30-60 days)
  - Dose-dependent toxicity
  - High rate of patient non-compliance
  - No paediatric strengths
No treatment for chronic disease.

What are the priority patient treatment needs?
- A paediatric strength which is affordable, age-adapted, safe, and efficacious would cure patients early on in the disease.
- A new drug for chronic disease that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.

Where does Chagas disease occur?
Endemic in 21 countries across Latin America, Chagas disease kills more people in the region each year than any other parasite-born disease, including malaria.

Patient numbers are growing in non-endemic, developed countries, due to increased movement of unknowingly infected people unknowingly carrying the parasite in their blood (see map).

What are the symptoms/presentations?
The disease has two clinical stages:
- Acute (in which 5% of children die) - characterised by fever, malaise, facial oedema, generalised lymphadenopathy, and hepatosplenomegaly - often spontaneously resolves in four to six weeks
- Chronic disease has two phases:
  - Chronic asymptomatic “indeterminate” disease, during which patients can transmit the parasite to others while showing no signs of the disease, can last 10 years to life
  - Chronic symptomatic disease develops in 10% to 30% of infected patients and most often involves the heart or gastrointestinal tract.

Chagas disease is a leading cause of infectious heart disease (cardiomyopathy) worldwide.

What is DNDi doing to address unmet treatment needs?
Short term: better use of existing treatments through new formulations
- Paediatric strength of benznidazole: first treatment designed specifically for children

Medium term: development of new treatments through therapeutic switching and combination therapy
- Azoles: clinical development of a well-known compounds already developed against fungal infections for use as Chagas disease monotherapy and/or in combination with existing drugs

Long term: new drugs, and improved research & treatment capacity across region
- Nitroimidazoles: a well-known class of anti-infective compounds
- New drugs developed from promising compounds identified in discovery activities (such as GSK library of pyridones and cysteine protease inhibitors) and progressed through Chagas lead optimisation consortium.
- A multi-country, multi-partner Chagas clinical research platform in preparation (see Section 3).

By 2014, DNDi aims to deliver from its Chagas-specific portfolio:
- 1 new paediatric strength available
- 1 new drug registered
- A robust pipeline

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(3) DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability. (4) Moncayo A, Ortiz Yasmine M. Ann Trop Med Parasitol. 2006;100:1-15.
**DISCOVERY**

**CHAGAS LEAD OPTIMISATION CONSORTIUM**
- **Target disease:** Chagas disease
- **Partners:** Centre for Drug Candidate Optimisation (CDCO), Australia; Epichem, Australia; Murdoch University, Australia; Federal University of Ouro Preto, Brazil
- **DNDi project manager and coordinator:** Robert Don, Ivan Scandale
- **Project start:** July 2008

In 2008, a lead optimisation consortium was set up by DNDi so to engage in a critical, iterative process that helps to optimise the efficacy of a lead compound while minimizing its toxicity. This consortium includes institutions in Australia (Monash and Murdoch Universities and Epichem) and Brazil (Universidade Federal de Ouro Preto) and consists of a group of analytical and medicinal chemists, pharmacologists and parasitologists with rapid turnaround facilities or compound assessment. A full lead optimisation team has now been put in place to assure the speed of the highly iterative process. In 2009, five classes of compounds identified in DNDi screening programmes were further assessed in hit-to-lead studies. Work is ongoing to select a single series for lead optimisation by the end of the year.

**CLINICAL**

**AZOLES**
- **Partners:** Federal University of Ouro Preto, Brazil; and companies who will provide compounds of interest
- **DNDi project managers and coordinator:** Robert Don, Isabela Ribeiro, Bethania Blum
- **Project start:** 2007

A new generation of antifungal triazoles including posaconazole, voriconazole and ravuconazole show considerable promise as antitrypanosomal agents. The marketed antifungal drug posaconazole (Noxafil®, Schering-Plough), has previously been shown to induce parasitological cure in mice with acute and chronic infections, including benznidazole-resistant strains. It is considered the leading azole candidate for proof-of-concept evaluation. DNDi has been in discussion and negotiation with Schering-Plough since 2006. Two other triazole derivatives, ravuconazole (Eisai) and TAK-187 (Takeda) have shown encouraging in vitro and in vivo results. Both products have completed Phase I testing and are good candidates for further assessment as potential treatments. In 2009, DNDi continues to progress on the goal of advancing either posaconazole or another azole into clinical research on Chagas disease patients, if data and conditions are favorable, and to examine other molecules from the same family as potential drug candidates.
Chagas disease leaves a memorable impression in the areas where the disease is endemic.

Preclinical combination studies with azoles. A main treatment limitation in Chagas disease is the poor tolerability reported with currently available treatments. Side effects of benznidazole and nifurtimox are both time- and dose-dependent. Combination therapy could improve treatment efficacy, reduce dose, treatment duration and toxicity, and could also prevent the potential development of resistance to anti-infective drugs. Azole derivatives have shown synergistic anti-T. cruzi effects, in vitro and in vivo, with benznidazole and other compounds involved in the sterol biosynthesis pathway. Taking these results into consideration, DND, has begun preclinical studies with the objective of reducing the dose and duration of current Chagas treatments by systematically evaluating, in animal models, several azole compounds as monotherapy and in combination with the two existing drugs available for Chagas disease. Preliminary in vivo results demonstrated a clear synergistic effect for both combinations with posaconazole, with reduction of mortality and parasitaemia suppression observed in animals. These data will be confirmed in further studies, and will help to inform future clinical evaluation of the azole class.

currently, benznidazole tablets are fractionated by hand into 1/2 and 1/4 tablets (as seen at a health post in Honduras). Fractionation of tablets is not ideal - a paediatric formulation would improve the proper use of benznidazole.

### Meeting an acute patient need...

By developing and making available the only paediatric formulation for Chagas disease in the very young and malnourished, reduced efficacy (due to the addition of diluents) and stability concerns.

Benznidazole, one of only two products registered for Chagas disease, can be highly efficacious in children yet no paediatric formulation exists. For the majority of children, the 100-mg tablet must be fractionated (broken into pieces). A number of approaches have been examined to best meet the need of developing a new paediatric formulation which is affordable, age-adapted, and easy to comply with.

With the goal to develop an adapted, dispersible tablet of benznidazole, DNDi and LAFEPE signed a development deal in July 2008. Since then, the project team has been engaged in pre-formulation and analytical development activities. Using current benznidazole dose recommendations, dosing practices, and patient age and weight profiles from 10 centers which treat children with T. cruzi infections as a guide, the team has determined the most appropriate paediatric tablet formulation, strength and associated dosing regimen. Work is progressing, with batch production and stability testing planned for later in 2009.

### Stage: clinical

### Partners: Pharmaceutical Laboratory of Pernambucan State (LAFEPE), Brazil; Tulane University – Centro Nacional de Diagnostico e Investigacion de Endermo-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK

### DNDi project manager and coordinator: Isabela Ribeiro, Bethania Blum

### Project start: June 2008

Since the 1990s, there is consensus for early diagnosis and treatment of children and adolescents in the early indeterminate (chronic) phase of Chagas disease. Young children remain an important target population for treatment despite decreasing vectoral transmission, because congenital infection may remain an important mode of transmission for at least another generation.

This is not reflected in the current treatment options as current drugs are formulated as tablets for adults, not adapted to children weights. Tablet fractionation and extemporaneous formulations are needed to treat most children: these procedures increase the likelihood of improper dosages and raises safety concerns, particularly
Further progress made in fighting an old disease as FACT products gain ground in Africa and Latin America

The past year has seen efforts by DNDi and our industrial partners take further hold in the field of malaria treatment, particularly with the WHO prequalification of ASAQ, its growing use in the public market, and the proactive monitoring plan of ASAQ in “real-life” conditions, which includes the most ambitious proactive pharmacovigilance programme ever launched in Africa, for any drug. Important progress has also been seen with ASMQ as the first purchase was made by Brazilian authorities in April 2009, and plans for technology transfer to Asia and study of its possible use in Africa are afoot.

As we in the world malaria community move forward in meeting the needs of those suffering from malaria, one of the main strategies for malaria prevention and control is prompt and effective treatment. It has been well established that drug combinations are a strategic and viable option in improving efficacy, and in delaying development and selection of resistant parasites (after lessons learned with widespread resistance to chloroquine and SP).

Artemisinin-based combination therapy is nowadays the best therapeutic option for treating drug-resistant malaria and retarding the development or spread of parasite resistance. Since 2001, the WHO has recommended combination therapies containing an artemisinin derivative and, in 2006, strengthened its recommendations to say that fixed-dose combinations (FDCs) should be used wherever possible.

The advantages of using FDCs have been well documented in several disease areas, including malaria, tuberculosis and HIV/AIDS. FDCs offer several potential advantages: increasing patient adherence to treatment, delaying the development of parasite resistance, decreasing total treatment cost (including production, storage, and transport), reducing the risk of me-
What is the annual impact of Malaria?

350 to 500 million new cases (1)

Over 1 million deaths (1)

42,280,000 DALYs (2)

Malaria is the leading parasitic cause of morbidity and mortality worldwide, especially in developing countries where it has serious economic and social costs.

Malaria is thought to slow annual economic growth by 1.3% in endemic areas with high prevalence. The economic cost of malaria in Africa alone is estimated at US$12 billion every year (3).

How is Malaria transmitted?

Transmitted from person to person by the bite of anophele mosquitoes, malaria is caused by the Plasmodium parasite. Four species are involved: P. falciparum, P. malariae, P. vivax, and P. ovale. P. falciparum is the main cause of severe clinical malaria and death.

What are the current treatments and their limitations?

• Widespread drug resistance: chloroquine, one of the easiest to use and most available malaria treatments, is no longer effective, with parasite resistance at more than 90% in some parts of the world (4)

• Existing combination therapies, now adopted as first-line treatment in most malaria-endemic countries, can be expensive and have complicated treatment regimens

• Limited access of neglected patients to the few paediatric strength, fixed-dose ACTs which are available

• The countries suffering the most from malaria lack the necessary capacity and funding to deliver the drugs to the patients who need them.

What are the current patient treatment needs?

Patients in malaria-endemic countries need inexpensive, efficacious, and field-adapted drugs.

What is DNDi doing to address unmet treatment needs?

DNDi’s malaria-specific portfolio aims to facilitate the widespread availability of the two products delivered by its diverse partners in the Fixed-Dose Artesunate Combination Therapy (FACT) Project.

Because of numerous antimalarial R&D activities (e.g. Medecines for Malaria Venture), DNDi is phasing out its malaria activities to focus on the kinetoplastid diseases.

The FACT Project has produced 2 fixed-dose ACTs which are:

– Easy to use as given in a single daily dose of 1 or 2 tablets for 3 days

– A 2-in-1 fixed-dose combination (FDC) of drugs that ensures both drugs are taken together and in correct proportions

– Age-based dosing to facilitate proper dosing in rural, remote areas

• ASAQ – FDC of artesunate and amodiaquine for treatment of malaria in sub-Saharan Africa; now registered in 24 countries

• ASMQ – FDC of artesunate and mefloquine registered in Brazil in March 2008 and in use by Brazilian national authorities as part of ongoing intervention study

Through 2014, DNDi will support the proper use to work to facilitate access to these FACTs along with the other effective ACTs so as to maintain the effectiveness of artemisinin as a first-line treatment.

What are the symptoms/presentations?

Malaria begins as a flu-like illness 8 to 30 days after infection. Symptoms include fever (with or without other signs or symptoms such as headache, muscular aches and weakness, vomiting, diarrhea). Typical cycles of fever, shaking chills, and drenching sweats may then develop. Death may be due to brain damage (cerebral malaria), or damage to vital organs.

Where does malaria occur?

Malaria is present in over 100 countries and threatens half of the world’s population.

In sub-Saharan Africa, where it is the single largest cause of death for children under five, malaria kills one child every 30 seconds – approximately 3,000 children every day.

What are the current patient treatment needs?

Patients in malaria-endemic countries need inexpensive, efficacious, and field-adapted drugs.

Endemic
Chloroquine resistance
SP resistance


(2) DALYs are a measure of societal impact, being the sum of years of potential life lost due to premature mortality and the years of productive life lost due to disability.


dication errors by prescribers or patients themselves, and preventing the risk of medication given in combination to be taken only as monotherapy.

Following the recommendations of WHO and independent malaria experts, DNDi developed fixed-dose combination of ACTs (FDC-ACTs or ‘FACT’s) as part of its overall R&D efforts begun in 2003. In building partnerships with industrial partners – sanofi-aventis for ASAQ and Farmanguinhos/Fiocruz for ASMQ - from an initial network of public partners, DNDi has ensured that these products be developed as non-exclusive public goods and at cost so that the largest potential global health benefit could be attained.

As a result of these efforts, new, effective, easy-to-use and affordable FDC-ACTs are now available or under development. Through DNDi and its partners, artesunate-amodiaquine (ASAQ), and artesunate-mefloquine (ASMQ) are now available. In addition, efforts by Medicines for Malaria Venture (MMV), have led to the availability of a paediatric version of arteether-lumefantrine (AL), and the development of dihydroartemisinin-piperaquine (DHA/PQ), which is expected to become available in the second quarter of 2010.

Although the existing armamentarium of FDCs for the treatment of uncomplicated malaria is relatively limited nowadays, there are an increasing number of FDC-ACT manufacturers. With the April 2009 launch of the AMFm, DNDi joined MSF in its call for the exclusive use of FDC to further incentivise drug makers to enlarge the FDC-ACT pipeline.

Among the most studied ACTs is the three-day treatment with artesunate (AS) and mefloquine (MQ), which has shown to be a highly effective therapy against uncomplicated falciparum malaria. Used in the field for 16 years, the combination of AS and MQ has been one of four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated falciparum malaria.

ASMQ, the new co-formulation of AS and MQ, offers a simple regimen for children and adults that is as easy as 1-2-3: a single daily dose of one or two tablets over three days. This co-formulation was one of two malaria projects undertaken in 2002 by a number of public and private partners coordinated by TDR and MSF (who turned over the project to DNDi upon its foundation) as part of the FACT (Fixed-Dose, Artesunate-Containing Therapy) Project.

April 2008 marked an important milestone for ASMQ as the first public order was completed by Brazil. DNDi’s public industrial partner Farmanguinhos/Fiocruz successfully registered ASMQ in April 2008, and the co-formulation has been used by Brazilian national authorities as part of an intervention study, where preliminary results after one year show a greater than 70% drop in *P. falciparum* malaria cases and an approximate 65% reduction in malaria-related hospital admissions. The study has now treated over 23,000 patients with ASMQ. Work is ongoing to clean the data set and finalise the results.

In 2009, registration processes for ASMQ in 2 or 3 other countries in Latin America are being navigated; it will be submitted for PAHO pre-qualification; and Farmanguinhos/Fiocruz will continue its technology transfer to the Indian generics manufacturer, Cipla, in order to facilitate its future availability in Southeast Asia. Further clinical research with partners is in preparation to examine the potential therapeutic value of ASMQ in pregnancy and in Africa. A clinical study in India has recently been completed, with analysis ongoing, and a dossier for registration in India will be submitted by the end of 2009.

ASMQ is the only fixed-dose ACT available with a 3-year shelf life. Optimised for rural and remote settings. An innovative weight- and age-based dosing regimen, of ≳180,000 individuals, This work, as well as preliminary results from the Brazilian intervention study, was presented during the 57th American Society of Tropical Medicine & Hygiene in December 2008 and is available at www.dndi.org

ASMQ, FIXED-DOSE ARTESUNATE/MEFLOQUINE COMBINATION THERAPY

A public good developed and supported by public partners crosses continents

- **Stage:** Phase IV post-registration monitoring and access
- **Partners:** Farmanguinhos, Brazil; Epicentre, France; MSF International; Shoklo Malaria Research Unit, Thailand; University Sains Malaysia; Oxford University, UK; TDR, Cipla, India; Catalent, USA; ICMR, India; GVK BIO, India; Tanzania; Quintiles, USA
- **DNDi project managers and coordinator:** Jean-René Kiechel, Patrice Piola, Gwenaëlle Carn
- **Project start:** January 2002

The color-coded and age-based packaging of ASMQ provides clear information that is meant to facilitate proper use in the most remote of settings.
ASAQ, FIXED-DOSE ARTESUNATE/AMODIAQUINE COMBINATION THERAPY

More than 20 million of ASAQ treatments to be delivered for African malaria patients during 2009

- **Stage:** Phase IV post-registration monitoring and access
- **Target disease:** malaria
- **Partners:** sanofi-aventis, France; Medicines for Malaria Venture, Switzerland; National Centre for Research and Development on Malaria, Burkina Faso; University Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; MSF; Epicentre, France; TDR; Catalent, USA; KEMRI, Kenya; ICMMR, India; GVK BIO, India; Quintiles, USA; Cardinal Systems, France; Epicentre, France; MS; Komfo Anokye Teaching Hospital, Ghana
- **DNDi project managers and coordinator:** Jean-René Kiechel, Gwenaelle Carn
- **Project start:** January 2002.

ASAQ, the new fixed-dose combination (FDC) of artemisinin (AS) and amodiaquine (AQ), was the first drug to be made available by DNDi. Over 5.3 million treatments were distributed in 2008. Now available in 24 countries in sub-Saharan Africa, with over 20 million treatments to be delivered in 2009, the continuing focus of this post-registration project is to support sanofi-aventis the implementation of ASAQ for the treatment of uncomplicated falciparum malaria after its registration in endemic countries, mainly in sub-Saharan Africa, India, and Indonesia.

ASAQ provides a true innovation in patient treatment by being a tropical-stable bilayer co-formulation, which allows AS and AQ to be taken together and in the correct proportions in a simplified three-day dosing regimen where the most vulnerable population, children under the age of five, take one tablet per day.

To continue their pioneering efforts as the 1st public-private partnership to deliver a needs-adopted antimalarial medicine, sanofi-aventis and DNDi continue to work to enlarge the partnership by involving national malaria control programs and pharmacovigilance systems, as well as international organizations and agencies.

DNDi, sanofi-aventis and additional partners, in particular MMV and national malaria control programmes, are implementing a comprehensive “ASAQ Deployment Monitoring Plan” that aims to collect high-quality data on ASAQ effectiveness and safety profile in “the field”. This programme includes a series of proactive clinical studies conducted in several countries of sub-Saharan Africa with different levels of disease transmission. Some of the studies are underway while others are still in the design phase.

Key ongoing studies include two post-registration studies being done in collaboration with MSF, Epicentre, and the national malaria control programme in Liberia: 1300 patients have been enrolled in these studies, which will assess the tolerability and efficacy of ASAQ in comparison with artemether-lumefantrine (Coartem™). In Ivory Coast, two clinical studies are being set up in a collaboration between sanofi-aventis, MMV, and DNDi: these studies will collect relevant ‘real-life’ efficacy, effectiveness and pharmacovigilance data in over 15,000 patients at a district level.

Ultimately, more than 20,000 patients will be followed as part of this monitoring plan. These results will provide a comprehensive overview of the efficacy and safety of ASAQ in the long run and will also allow innovative pharmacovigilance methods to be developed, suited to the needs and resources of countries in sub-Saharan Africa.

The deployment monitoring plan as well as additional clinical data supporting the use of ASAQ has been presented over the past 6 months at international meetings such as ASTMH and the 3rd Annual East African Health Sciences Congress in March 2009. Highlights of these data and the plan can be found on www.actwithasaq.org.

- **Just published:** ASAQ is found to be efficacious and well-tolerated in pivotal Phase III field study carried out in Burkina Faso children: the study showed 28-Day PCR-corrected parasitological and clinical cure rates were ≥95% in both arms comparing the fixed-dose ASAQ combination with the non-fixed AS+AQ association in 750 children with uncomplicated P. falciparum malaria. Sirima SB, et al. Malaria J; 2009 8(1):48.

- A recent population pharmacokinetic analysis has shown that there is a pharmacological equivalence of ASAQ with the well-established separate products

- Meta-analyses – individual and aggregate – presented at ASTMH and in the process of publication

- Results published in Eur J Clin Pharmacol in May 2009 show that ASAQ is well-tolerated and with a comparable pharmacokinetic profile as the separate products

- A multi-center, non-inferiority trial comparing ASAQ with Coartem® (fixed-dose artemether-lumefantrine) in Cameroon, Madagascar, Mali, and Senegal, has shown that ASAQ is as efficacious and well-tolerated as Coartem® in a total of 941 patients including in 112 paediatric patients less than 5 years old. Nadiaye et al. Malaria J; 8 (125)