A well-balanced and robust pipeline in order to develop new needs-driven treatments for neglected patients.
n 2010, DNDi’s drug portfolio continues to be enriched with the engagement of private and public partners who share DNDi’s vision and commitment, and who bring complementary capabilities. DNDi’s virtual R&D model allows for the outsourcing of R&D activities with active management by DNDi personnel experienced in different aspects of pharmaceutical development. This model cuts costs while providing flexibility. Most importantly, it has allowed DNDi to establish a well-balanced and robust pipeline in order to develop new treatments for sleeping sickness (HAT), visceral leishmaniasis (VL), Chagas disease, and malaria. One of DNDi’s unique characteristics is its R&D scope of diseases: four diseases until 2010, plus two new disease areas as of 2011 (see page 2). According to each specific disease strategy, DNDi’s activities range from discovery to pre-clinical and clinical phases, to implementation and access.

TPPs: ENSURING THE DEVELOPMENT OF NEEDS-DRIVEN TREATMENTS

As a guiding principle for building each disease portfolio, the desired key features for these new drugs/treatments are defined in the target product profiles (TPPs). Each R&D project in the portfolio is selected, progressed, and managed with decision matrices that ensure products will meet these TPPs, thus ensuring that patient needs are met. TPPs are defined with input from disease experts, representatives of Ministries of Health, of National Control Programmes in endemic countries, WHO representatives, and specifically from leading clinicians and researchers, as well as with health workers who deal with each disease on a daily basis. DNDi’s TPPs are reviewed and revised annually, and shared with other investigators openly. In 2010, for instance, the TPP for HAT was revised to reflect the change of the latest reference treatment (NECT; previously melarsoprol).

By implementing this strategy, DNDi has delivered four treatments – for sleeping sickness, visceral leishmaniasis, and malaria – the latest of which is a combination therapy for visceral leishmaniasis in Africa [SSG&PM, see page 28]. In 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for VL in East Africa, and it was recommended and implemented in Sudan during the year. For the three treatments previously launched, DNDi has continued its efforts to facilitate access to these essential medicines.

In 2010, DNDi projects continue to progress well in the pipeline. Thanks to the vital engagement of its partners, the following DNDi projects have reached important milestones in the past year:

**Overall Portfolio:** One additional treatment made available, DNDi’s first treatment for VL reaching this milestone; successful advancement of new leads and optimized leads in the discovery and pre-clinical phases in order to guarantee a robust pipeline for the coming years; clinical projects progressing successfully towards future implementation.

- **Discovery:** Increased and strengthened collaboration with pharmaceutical partners in order to ensure access to their compounds and expertise, as well as enhanced screening capacity through high-throughput screening [e.g. IPK]. See page 15 for a list of these partners.

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**BY KEEPING THE FOCUS ON THE PATIENTS AND THEIR NEEDS, DNDI’S PROJECT PORTFOLIOS BALANCE LONG-, MEDIUM- AND SHORT-TERM PROJECTS.**

- **Long-term projects** - to develop innovative medicines with new chemical entities.
- **Medium-term projects** - to identify existing pre-clinical or clinical stage compounds suitable for therapeutic switching, or for further improvements via improved formulations.
- **Short-term projects** - to make existing drugs available in broader geographic areas and to develop better treatments, including combinations, from existing drugs.

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**DNDI’S R&D PROJECTS – FILLING THE GAPS**

<table>
<thead>
<tr>
<th>Gap 1</th>
<th>Gap 2</th>
<th>Gap 3</th>
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<tbody>
<tr>
<td><strong>Discovery</strong></td>
<td><strong>Preclinical</strong></td>
<td><strong>Clinical</strong></td>
</tr>
<tr>
<td>Lacking basic research and preclinical research due to lack of funding</td>
<td>Validated drug candidates don’t enter clinical development</td>
<td>Patient can’t access drugs due to cost, availability, adaptability...</td>
</tr>
</tbody>
</table>

- **Long-term projects**
  - New compounds
  - Existing compounds
  - > 6 years

- **Medium-term projects**
  - Therapeutic switch
  - “Rediscovered” compounds
  - 3-6 years

- **Short-term projects**
  - New formulations
  - IFDC Geographical extensions
  - Co-administration
  - ≤ 3 years
**DNDi PORTFOLIO (as of December 2010)**

<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical</th>
<th>Clinical</th>
<th>Implementation</th>
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<td>S</td>
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**Discovery Activities**
- Compound mining
- Chemical classes
- Target-based
- Screening

**Pre-clinical**
- Nitroimidazole backup (HAT)
- Oxaborole (HAT)
- Alternative formulations Amphotericin B (VL)
- Nitroimidazole (VL)
- Drug combination (Chagas)
- K777 (Chagas)
- Exploratory

**Clinical**
- Fexinidazole (HAT)
- Combination therapy (VL in Asia)
- Combination therapy (VL in Africa)
- AmBisome®
- Miltefosine
- Combination therapy (VL in Latin America)
- Exploratory

**Implementation**
- ASAQ (Malaria) Fixed-Dose Artesunate/Amodiaquine
- ASMQ (Malaria) Fixed-Dose Artesunate/Mefloquine
- NECT (Stage 2 HAT) Nifurtimox - Eflornithine Co-Administration
- Combination therapy (VL in Africa) SSG&PM

**Major Collaborators**
- Sources for hit and lead compounds: GSK, Anacor, Merck, Pfizer, Novartis (GNF, NITD), TB Alliance, ...
- Screening Resources: Eskitis, Institut Pasteur Korea, Univ. Dundee, ...
- Reference screening centres: LSHTM, Swiss Tropical & Public Health Institute, University of Antwerp

**Target Product Profile (TPP)**

- **Indications:** which diseases?
- **Population:** which type of patients and where?
- **Clinical Efficacy:** does it treat the parasitic infection effectively?
- **Safety and Tolerability:** what level of acceptability for adverse events?
- **Stability:** how long is the shelf life of the drug(s), and storage conditions?
- **Route of Administration:** how is it administered to patients?
- **Dosing Frequency and Treatment Duration:** how often and how long must it be given?
- **Cost:** will it be affordable to the target population?
- **Time to Availability:** how long will it take to develop?

Projects completed in 2010 (End of contract period)

- **HAT:** NECT available in 10 countries; fexinidazole progressing in Phase I; the SCYX-7158 oxaborole, identified in lead optimization, in pre-clinical phase, as well as promising nitroimidazoles in lead optimization.
- **VL:** SSG&PM, recommended by WHO Expert Committee on the Control of Leishmaniasis for East Africa, now available and implemented in Sudan; increasing number of sites for combination studies in Africa and Asia, with results of a large Phase III study in India with drug combination; one project in pre-clinical phase and promising leads in lead optimization.
- **Chagas disease:** Two projects in clinical phase: one pediatric treatment for which DNDi and its partners prepare the dossier for registration, one in Phase II; one project in pre-clinical phase and promising perspectives in lead optimization.
- **Malaria:** Implementation phases for both ASAQ and ASMQ. Over 80 million treatments of ASAQ have been delivered in 21 countries [registered in 28] and a pharmacovigilance plan developed with sanofi-aventis and MMV; ASMQ: technology transfer from Brazil to India completed, preparation of submission dossiers for registration in Asia, preparation of clinical studies in Africa.
- **Platforms:** DNDi is a founding partner of regional platforms for capacity strengthening and clinical research. One platform per kinetoplastid disease is now operational: HAT Platform for sleeping sickness, LEAP for VL, and the CCRP for Chagas disease [see pages 40-41].
In 2010, DNDi has continued to remodel its discovery activities from a hunter-gatherer approach – identifying projects mostly based on networking interactions – to a fully integrated process-oriented platform in partnership with pharmaceutical and biotechnology companies. The sourcing of compounds is based on a clear strategy combining compound mining, access to specific chemical classes, extension of chemical diversity and target based approaches supported by high-throughput screening capacity for all three kinetoplastids.

**DISCOVERY AND THE ‘S’ RULE**

Discovery research – a three-stage process consisting of sourcing and screening compounds, lead selection, and lead optimization – is the earliest stage of drug research and development (R&D), helping to identify novel drugs that offer significant improvements over current therapies. Since 2003, DNDi has built up a well-balanced and robust pre-clinical pipeline to develop new treatments for sleeping sickness, visceral leishmaniasis, and Chagas disease. To proceed, DNDi has recently transitioned from a hunter-gatherer approach – identifying projects mostly based on networking interactions – to a more pragmatic and structured discovery strategy relying on partnerships with public (universities, academia, etc.) and private partners (pharmaceutical and biotechnology companies). Those partnerships include Sourcing and Screening of compounds followed by the Selection of Series to optimize.

**A pragmatic strategy for more efficient R&D**

This discovery platform takes advantage of a dedicated and improved capacity for phenotypic screening as well as of lead optimization consortia funded by DNDi. The nomination of SCYX-7158 as pre-clinical candidate for sleeping sickness is the first success achieved through this new model (see pages 21-22).

In 2010, important developments among DNDi’s discovery efforts include:

- Committed support to strengthening the screening capacity against the parasites causing the three kinetoplastid diseases using high-throughput screening (HTS) assays, including *Trypanosoma brucei* (the parasite causing HAT) at the Institute Eskitis (Griffith University, Australia), and intracellular *Leishmania donovani* and *T. cruzi* assays at Institut Pasteur Korea (IPK).
- Agreements with pharmaceutical and biotechnology companies including Anacor, Merck, Pfizer.
- Streamlining and sharing with other Product Development Partnerships (PDPs) [Medicines for Malaria Venture, TB Alliance, and the Consortium for Parasitic Drug Development] and additional R&D industrial institutes and centres active in the field, such as the Novartis Institute for Tropical Diseases (NITD), Diseases of the Developing World at GlaxoSmithKline (GSK), the Drug Discovery Unit at the University of Dundee, the Genomics Institute of the Novartis Research Foundation (GNF) and the TI Pharma Consortium.

**DNDi’s discovery activities are dynamically evolving as DNDi continues to take on new exploratory activities.**

- **Target diseases**: HAT, VL, and Chagas disease
- **Partners**: Anacor, USA; Drug Discovery Unit (DDU) at the University of Dundee, UK; Eskitis Institute (Griffith University), Australia; Federal University of Ouro Preto, Brazil; Genomics Institute of the Novartis Research Foundation (GNF), USA; GlaxoSmithKline, Tres Cantos, Spain; Institut Pasteur Korea (IPK), South Korea; London School of Hygiene & Tropical Medicine (LSHTM), UK; Merck, USA; Novartis Institute for Tropical Diseases (NITD), Singapore; Pfizer, USA; SCYNEXIS Inc., USA; Swiss Tropical and Public Health Institute (Swiss TPH), Switzerland; TB Alliance, USA; TI Pharma, The Netherlands; University of Antwerp, Belgium; the UNDP/World Bank/WHO’s Special Programme for Research and Training in Tropical Diseases (TDR).
- **Management**: Discovery Manager, Jean-Robert Ioset

DNDi’s discovery strategy includes several approaches for compound sourcing:

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- **Management**: Discovery Manager, Jean-Robert Ioset

DNDi’s discovery strategy includes several approaches for compound sourcing:
### SOURCING

**Compound mining**
Proactive acquisition and investigation of compounds from selected series associated with a significant level of available information (biological activities, pre-clinical dossier, published data, safety profile, among others) in order to identify candidates with a potential for further development – ideally ready to enter into pre-clinical or later stage without further optimization – for the target diseases. An example of this approach is our compound mining effort undertaken in 2005 to explore new and old nitroimidazoles as drug leads against HAT. Over 700 compounds from 15 different sources were identified, accessed, and tested.

**Chemical classes**
Identification of promising chemical classes as sources for lead compounds. From libraries of collaborating pharmaceutical and biotech companies, promising compound classes can be identified by sampling a subset of representative compounds and testing them for antiprotozoal activities. Subsequent optimization from the selected classes would be more efficient as they result from existing know-how. Examples of interesting classes include oxaboroles (Anacor Pharmaceuticals), pyridones (GSK), and nitroimidazoles (TB Alliance).

**Chemical diversity**
Accessing diversity sets and libraries from various institutions and pharmaceutical companies (natural products, synthetic compounds, agriculture chemicals). This approach aims to mine new chemical territories to identify additional classes of molecules of potential interest in terms of drug development for DNDi target diseases. Illustrating this approach is the recent research collaboration with Pfizer to screen the Pfizer DGRS II set (representative of the entire Pfizer library in terms of chemical diversity, i.e., 150,000 compounds) against all three kinetoplastid diseases at the Eskitis Institute (HAT) and IPK (VL and Chagas disease).

**Target-based**
Screening compounds and assessing their activity against a specific target essential for parasite growth (e.g., Drug Discovery Unit at the University of Dundee, UK for VL; TI Pharma consortium for HAT and VL). This early discovery approach is used in combination with phenotypic screen of specific collections of compounds to allow the identification of inhibitors of targets essential to the growth of *Trypanosoma* and *Leishmania* pathogens.

### SCREENING

**High-throughput screening**
High-throughput screening (HTS) of large-size libraries for *Leishmania* and *T. cruzi* (IPK), and *T. brucei* (Eskitis) have been developed and are used to identify novel hit compounds. Screening capacity is a key element of our discovery strategy as it enables the screening of large libraries/series of compounds and therefore a quicker identification of hits/leads critical to our discovery programmes.

**Reference Screening Centres**
The Swiss Tropical and Public Health Institute (Swiss TPH), the University of Antwerp, and the London School of Hygiene & Tropical Medicine (LSHTM) serve as reference screening centres to ensure that screening methodologies are comparable and that in vitro and in vivo assays at different sites and with different groups meet the same standard. The centres also provide expert parasitology advice that ensures the quality of our data and work.
HIGH-THROUGHPUT SCREENING AT INSTITUT PASTEUR KOREA (IPK)

IPK on the cutting edge of technology in service of research for NTDs

- **Target disease**: Leishmaniasis and Chagas
- **Major Partners**: Institut Pasteur Korea (IPK)
- **Management**: Head of Chagas Discovery and Pre-clinical Programme, Eric Chatelain; Discovery Manager, Jean-Robert Ioset
- **Project start**: May 2008

The overall goal of this project was the identification of novel compounds for the treatment of leishmaniasis (but also Chagas and HAT). In collaboration with Institut Pasteur Korea (IPK) – a renowned translational research institute with funding from South Korea’s Ministry of Education, Science and Technology and the Gyeonggi Provincial Government – we have successfully developed and validated a unique HTS visual screening assay for Leishmania, and screened the IPK library. The main goal of this DNDi-IPK partnership has been to develop a method allowing the evaluation of thousands of compounds in a very short period of time. Until 2008, it was only possible to assess hundreds of compounds over a period of a few months. Combining the parasitology expertise to the screening and image-analysis technology and know-how of IPK, this project seeks to develop a major methodological advance in drug development. Additionally, we have also developed a HTS visual screening assay for *Trypanosoma cruzi*, taking advantage of the knowledge gained in the development of HTS for Leishmania.

IPK and DNDi have signed a broader collaboration agreement enabling the screening of third-party libraries at IPK for Leishmania and *T. cruzi* among others.

In November 2009, Pfizer Inc. and DNDi signed an agreement designed to facilitate advancements in the battle against human African trypanosomiasis (HAT), visceral leishmaniasis (VL), and Chagas disease. Under the agreement, DNDi obtained access to the Pfizer library of novel chemical entities and screened it for compounds that have the potential to be developed into new treatments. The screening of the Pfizer library at IPK against *L. donovani* is ongoing and completed for *T. cruzi* (over 150,000 compounds) using the newly developed assay.

IPK recently established the Center for Neglected Diseases Drug Discovery (CND3), affirming its commitment to neglected diseases. So far, a total of 210,000 compounds have been screened for VL from the compound libraries of IPK, Anacor, and the TB Alliance. With this new technology, the number of compounds screened for VL is probably higher than the total number of compounds that have ever been screened for this disease in the intracellular format. From this activity, one compound series has already shown very promising results — the aminothiazoles. This series is now in further development at the Indian pharmaceutical company, Advinus Therapeutics. The success of this new technology has allowed IPK and DNDi to develop high-throughput image screening for Chagas disease, leading to a broader collaboration between DNDi and IPK. Today, DNDi has access to compound libraries with a large number of compounds from different pharmaceutical companies that can now be screened with greater time efficiency than ever.

This collaboration will maximize the chances of identifying attractive starting points for a drug discovery programme, and marks an important step towards the fulfillment of DNDi’s objectives.

**Bringing it all together:**

- **Input image from screening**
- **Cell Counting**
- **Segmentation**
- **Parasite Counting**

Processing of *Leishmania donovani* High Content Screening (HCS) data: from image to determination of biological activity. Small dots are Leishmania parasites (intracellular amastigote form).
Human African Trypanosomiasis
Sleeping Sickness

Major progress in access to NECT treatment and promising new drug candidates

The year 2010 has seen the emergence of hope for elimination of sleeping sickness. According to WHO, the number of cases of human African trypanosomiasis (HAT) has substantially decreased. The current trend suggests that elimination of HAT is possible, and the efforts in the past decade by WHO and National Control Programmes, with MSF, sanofi-aventis, Bayer, DNDi, and others contribute to this. In addition, the introduction of NECT, an improved therapy option for stage 2 HAT, is accelerating this trend. However, it is important to bear in mind that HAT has known periods of decline in the past, which have been followed by re-emergence due to a lack of surveillance and control efforts in known endemic areas. While the decrease of reported cases is encouraging, some geographical areas are still not covered at all by surveillance and control efforts. Furthermore, one-third of HAT patients are women of childbearing age and one-fourth are children under 15 years of age. Currently available treatments are not adapted for these particularly neglected patients.

Sustainable elimination necessitates maintaining and reinforcing current surveillance and control efforts in the known endemic areas. In addition, now more than ever, R&D investments to develop field-adapted diagnostic and treatment tools to reach and treat patients not accessed by current strategies have to be both boosted and secured.

Currently available treatments for HAT are complex regimens. In several regions, they have lost efficacy. Treatment is also stage-specific, with more toxic and more difficult-to-administer drugs for stage 2 disease. Taken together with the complicated and invasive diagnostic methods, the reality of HAT treatment has made it very challenging to integrate HAT control into already burdened health systems. There is an immediate need to improve current treatment options, particularly for patients with the stage 2 disease. Ideally, treatment should be orally administered and effective for both stages of the disease.

Since its inception in 2003, DNDi’s short-term strategy has been to develop a combination therapy of existing drugs to improve current treatment options. In September 2009, DNDi and its partners launched the first new treatment for sleeping sickness in 25 years: nifurtimox and eflornithine combination therapy (NECT). The combined use of these drugs has been included on the Essential Medicines List of the World Health Organization. As of December 2010, 10 HAT endemic African countries have signed the supply request with WHO and have been ordering this improved therapy option.

DNDi’s medium-term strategy was to initiate a proactive compound mining effort shortly after its inception to identify existing chemical compounds with potential against kinetoplastid diseases. This resulted in the rediscovery of fexinidazole in 2007, a drug that went through early pre-clinical assessment in the mid-1980s, but was shelved by the pharmaceutical company Hoechst. DNDi has since completed all necessary pre-clinical testing and has begun clinical development of fexinidazole for HAT as a potential oral drug to treat stage 2 disease.

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**IDEAL TARGET PRODUCT PROFILE FOR HAT**

- A new treatment for stage 1 + 2 HAT in adults and children
  - Active against *Trypanosoma brucei* (T.b.) *gambiense* and *T.b. rhodesiense*
  - Ideally requiring no monitoring
  - Ideally <0.1% drug related mortality
- Ideally safe during pregnancy and for lactating women
- Ideally >95% efficacy at 18 months follow-up
- Easy-to-use treatment
  - Short course (ideally <7 days, up to 10 days is acceptable)
  - Preferably oral or, if injectable, intramuscular
  - Preferably once-a-day treatment
- Affordable
- Stable in tropical climate (minimum 3-year shelf life)
WHAT IS THE IMPACT OF HAT?
The estimated number of actual cases is currently approximately 30,000. Fatal if untreated. Displacement of populations, war, and poverty lead to increased transmission, with severe social and economic consequences. Some areas are still not covered by surveillance and control efforts.

HOW IS HAT TRANSMITTED?
Transmitted by the parasite Trypanosoma brucei (T. b.) to humans through the bite of the vector tsetse fly, HAT is caused by two subspecies of the parasite: T. b. gambiense (West and Central Africa), T. b. rhodesiense (East Africa).

WHAT ARE THE SYMPTOMS?
HAT occurs in two stages:
• Stage 1 – the haemolymphatic stage – includes non-specific symptoms like headaches and bouts of fever (and generally goes undiagnosed without active HAT surveillance).
• Stage 2 – the later, neurologic stage – occurs when the parasite crosses the blood-brain barrier and can lead to serious sleep cycle disruptions, paralysis, progressive mental deterioration, and ultimately, without effective treatment, results in death.
A lumbar puncture is needed to differentiate between the 2 stages for the administration of proper treatment.

WHERE DOES HAT OCCUR?
Of the 36 countries considered endemic (i.e. countries that have presence of the tsetse fly) 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. HAT primarily occurs in the poor and rural areas of Africa, where difficulty of diagnosis, political instability, and lack of health surveillance make estimates of disease prevalence difficult to ascertain.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Available treatments are few, old, and stage-specific.
• Stage 1 treatments, pentamidine and suramin, are fairly well-tolerated but still require injections and are ineffective for stage 2.

• Stage 2 has three treatments available: melarsoprol, an arsenic derivative that is painful, toxic (killing 5% of those who receive it), and increasingly ineffective (up to 50% resistance and treatment failure in certain areas), eflornithine, which requires trained health staff and extended hospital stay (56 intravenous infusions taking 2 hours each to administer, over 14 days and four times each day); NECT (nifurtimox-eflornithine combination therapy) with only 14 injections of eflornithine over 7 days and 10 days of oral treatment with nifurtimox has been available since September 2009. NECT, developed by DNDi and its partners, is an improved therapy option for stage 2 sleeping sickness. While it is not the panacea for disease elimination, it provides an incremental improvement for case management in a hospital setting at the community level.

WHAT ARE THE PATIENT TREATMENT NEEDS?
A safe, effective, and orally administered stage 2 treatment is needed that improves and simplifies current case management. This drug should ideally work in both stages of the disease.

WHAT IS DNDI DOING TO ADDRESS UNMET TREATMENT NEEDS?
Short term: Nifurtimox-eflornithine combination therapy (NECT), the simplified treatment for stage 2 HAT, now in use.
Medium term: drug candidates identified through compound mining.
• Fexinidazole: first oral new drug candidate entered clinical development from the Nitroimidazoles Project
Long term: discovery of promising new drug candidates and improved clinical research capacity.
• New drugs developed from compounds identified (i.e. oxaboroles) in discovery research and progressed through HAT Lead Optimization Consortium to pre-clinical
• Multi-country, multi-partner HAT Platform to strengthen regional research capacity
• Back-up nitroimidazoles and oxaboroles

By 2014, DNDi aims to deliver from its HAT-specific portfolio:
• 1 new combination therapy recommended by WHO (delivered)
• 2 new drugs in development
• A robust pipeline

An agreement was signed in 2009 with sanofi-aventis as the industrial partner for this project.

To further build a pipeline for HAT drug R&D, DNDi has established the HAT Lead Optimization Consortium, and built additional partnerships with pharmaceutical, biotechnology, and academic groups for research collaboration and for access to natural products, synthetic chemical libraries, process chemistry high-throughput screening (HTS), and biological models. A network of expert advisors has been formed to guide DNDi’s discovery efforts with pharmacokinetic, pharmacodynamic, and toxicological expertise for selection and assessment of potential drug candidates.

One of the successful outcomes of the HAT Lead Optimization Consortium is the identification of one oxaborole as a promising lead series against the T. brucei parasite. SCYX-7158 oxaborole progressed steadily through pre-clinical development throughout the year.

In addition, DNDi is one of the founders of the HAT Platform (see page 41), launched in 2005 in the Democratic Republic of the Congo, that supports the clinical trials for NECT and, since May 2009, NECT-Field. The platform is also very active in strengthening existing capacities.

**DISCOVERY**

**HAT Lead Optimization Consortium**

- **Partners:** SCYNEXIS Inc, USA; Pace University, USA
- **Management:** Discovery & Pre-clinical Director, Robert Don; Project Coordinator, Ivan Scandale
- **Project start:** April 2007

With the objective of developing optimized leads by progressing ‘hit’ molecules with a good safety profile and activity against T. brucei parasites, this consortium brings together expertise in chemistry, biology, screening, and pre-formulation. Optimization efforts are focused on improving the molecule’s capacity to be absorbed into the bloodstream, to be distributed effectively to the infection sites, to survive in the body, to kill the parasite, and not to harm the patient. With two full lead optimization teams in place at SCYNEXIS (a total of 18 scientists), a number of hits identified from DNDi screening partners are undergoing hit expansion. Scientists within the consortium use advanced techniques to study how the selected molecules interact with the therapeutic target (i.e. a protein or an enzyme, if known) and optimize the drug-like characteristics of these molecules to ensure that they comply with the target product profile (TPP).

This phase of discovery work 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. Many compound series have been assessed. The current focus of the team is on the oxaborole series (see below). The nitroimidazole class is another chemical series that is promising. One of the compounds in this class, fexinidazole, has been advanced into clinical development. DNDi’s strategy for the Lead Optimization Consortium is to develop a back-up compound in each of the oxaborole and nitroimidazole series. In case of failure of one of the current developed compounds, the back-up should be able to replace it rapidly.
The nitroimidazoles are a well-known class of antibacterial and antiprotozoal drugs. Despite their widespread clinical and veterinary use, this family of drugs has been stigmatized, partly due to associated genotoxicity problems.

DNDi, through extensive compound mining efforts, was able to develop anti-trypanosomal active and non-genotoxic molecules belonging to a new class of nitroimidazoles: 1-aryl-4-nitro-1H-imidazoles. In parallel, DNDi accessed another very promising non-genotoxic nitroimidazole library from the Global Alliance for Tuberculosis Drug Development (TB Alliance). Approximately one thousand analogues belonging to this series have been tested at SCYNEXIS against T. brucei. Several active molecules have been identified and further assessments are ongoing at the University of Auckland, SCYNEXIS, and Pace University. Efforts for the identification of pre-clinical candidates within the nitroimidazole class will continue.

**Oxaborole**

**Partners:** Anacor Pharmaceuticals Inc., USA; SCYNEXIS Inc., USA; Pace University, USA

**Management:** Discovery & Pre-clinical Director, Robert Don; Project Coordinator, Ivan Scandale

**Project start:** December 2007

Oxaboroles, provided by Anacor – the originator of this unique boron-based chemical class – were identified as hits against T. brucei at the Sandler Center of the University of California San Francisco, and have shown activity in animal models of sleeping sickness. During the course of the subsequent 15 months, chemists at SCYNEXIS synthesized approximately 400 compounds and screened an additional 330 compounds from the Anacor libraries. Some compounds, in particular...
NECT (Nifurtimox-Eflornithine Combination Therapy)

- **Partners:** Epicentre, France; Médecins Sans Frontières (MSF); Swiss Tropical and Public Health Institute (Swiss TPH); National Trypanosomiasis Control Programmes of the Republic of Congo and the Democratic Republic of the Congo (DRC); HAT Platform partners
- **Management:** Medical Manager, Olaf Valverde Mordt; Project Coordinator, Séverine Blesson
- **Project start:** 2004

NECT (Nifurtimox-Eflornithine Combination Therapy) has been available to patients since the end of 2009 and is the first new treatment for sleeping sickness in 25 years. NECT consists of a simplified co-administration of oral nifurtimox and intravenous eflornithine. Developed by DNDi, Epicentre, Médecins Sans Frontières (MSF), the Swiss Tropical and Public Health Institute (Swiss TPH), and the National Trypanosomiasis Control Programmes of the Republic of Congo and the Democratic Republic of the Congo (DRC), NECT reduces the total number of infusions of eflornithine from 56 to 14, shortens hospitalization from 14 days to 10 and cuts the cost of treatment by half. Because NECT requires only two infusions a day that can be administered during daytime, it significantly reduces the burden on health staff, and makes the treatment far more adaptable for the resource-poor settings where HAT treatments take place.

Thanks to the inclusion in the WHO Essential Medicines List (May 2009), endemic countries have now begun ordering the new combination treatment through the WHO. As of December 2010, 10 countries – which together treat more than 97% of all HAT T.b. gambiense patients – have requested NECT as a treatment for HAT in their territories: Angola, Cameroon, Central African Republic, Chad, the Democratic Republic of the Congo, Equatorial Guinea, Gabon, Ivory Coast, South Sudan, and Uganda. Six of them have received the supplies from the WHO – nearly 6,000 treatments – and have begun to treat patients (2,176 patients treated with NECT by the end of 2010). Since the launch of NECT in the second half of 2009, melarsoprol and eflornithine in monotherapy are increasingly being replaced by NECT (see table below). The HAT Platform continues advocating for the use of NECT, which offers a safer and better field-adapted treatment for stage 2 sleeping sickness.

**NECT USE IN 2010, HAT PLATFORM COUNTRIES**

- **10 Countries**
- **97% of patients**

<table>
<thead>
<tr>
<th>T.b. rhodesiense</th>
<th>Approved</th>
<th>Pending</th>
<th>Not detected</th>
<th>Not endemic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NECT</strong></td>
<td>10.3%</td>
<td>2.1%</td>
<td>61.8%</td>
<td>25.8%</td>
</tr>
<tr>
<td><strong>Arsobal</strong></td>
<td>10.3%</td>
<td>2.1%</td>
<td>61.8%</td>
<td>25.8%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>10.3%</td>
<td>2.1%</td>
<td>61.8%</td>
<td>25.8%</td>
</tr>
</tbody>
</table>

DNDi and its partners are conducting a Phase IIIb ‘NECT-Field’ study, to further document the safety and ease of use of the combination in real-life field conditions and in special populations like children, pregnant women, and lactating women. The enrolment started in April 2009 and by December 2010, 638 patients had been enrolled for the study (including 100 children and more than 40 pregnant women). They will be followed up for 2 years.
A new combination therapy available in East Africa and clinical studies worldwide to develop field-adapted treatments

Leishmaniasis occurs in several forms, the two most common of which are visceral leishmaniasis (VL) and cutaneous leishmaniasis (CL). VL, also known as kala-azar or black fever, mainly occurs in poor, remote areas in South Asia, East Africa, and South America. Particularly affecting women and children, it is characterized by prolonged fever, enlarged spleen and liver, substantial weight loss, and progressive anaemia. VL is life threatening. CL is characterized by lesions on the skin, either self-healing or chronic. Another form of leishmaniasis is post-kala-azar dermal leishmaniasis (PKDL), a complication of VL, and is important as it serves as a parasite reservoir for VL, thus contributing to transmission of the disease.

DNDi, while focusing primarily on VL, also included cutaneous leishmaniasis (CL) in its portfolio and has ongoing exploratory activities to seek improved treatments.

There is a general agreement that chemotherapy remains one of the most important tools in the control of VL. Existing treatments have serious limitations such as potential of resistance development, low tolerability, long treatment duration, and difficulty in administration. Furthermore, they are high in cost. Established VL treatments include: pentavalent antimonials (given by injection, registered in East Asia and some African countries); amphotericin B (an intravenous treatment given over 30 days, registered in East Asia and some African countries); AmBisome® (a liposomal formulation of amphotericin B registered for VL in India, USA, and Europe); miltefosine (an oral drug registered in India in 2002, now in use as a monotherapy); and a low-cost parenteral (intramuscular) formulation of paromomycin, registered in India in 2007 by the Institute for OneWorld Health (iOWH).

In addition to developing novel therapies as a long-term goal, DNDi’s short-term approach is to develop new treatments involving either optimal monotherapy regimens or combination therapies of drugs that are already available. This offers the following important advantages: shorter course of treatment; better tolerability; reduction of the burden on health systems in resource-limited areas; greater affordability; and with combinations, the potential to prevent or delay resistance development and therefore prolong the life-span of these drugs. Another short-term objective pertains to extending registration and availability of current drugs to additional countries in need. The goal is to make drugs that are available in India, for example, also available to patients in Bangladesh, Nepal, East Africa, and other countries and regions, provided that a favourable efficacy/safety profile is also shown in these regions.

Over 2009 and 2010, DNDi and other partners made considerable headway in the development of new treatments for visceral leishmaniasis. In East Africa, the year 2010 saw the adoption of SSG&PM combination (sodium stibogluconate & paromomycin) - a new, improved treatment option which was recommended as first-line treatment for VL in the region by the World Health Organization (WHO) Expert Committee on the Control of Leishmaniases.

In India, significant progress was also made with the completion of two important Phase III clinical trials. One major study...
was completed by DNDi on three short-course combination therapies while another study, conducted by Sundar et al. on single-dose Ambisome® was published: both studies demonstrated the high efficacy (>95%) of these new treatment options.

**VL CLINICAL STUDIES ON THREE CONTINENTS**

The objective of the South Asia clinical project was to study short-course combination therapy using two of the three drugs registered in India: Ambisome®, paromomycin, and miltefosine (see Project of the Year, page 27). In parallel to this, another study was undertaken to develop an optimal single-dose regimen of Ambisome®. The goal is to have improved treatment options that can be implemented by National Control Programmes in India, Nepal, and Bangladesh.

The East Africa clinical projects, led by DNDi and the Leishmaniasis East Africa Platform (LEAP, see page 41), aim to geographically extend all currently available VL drugs to East Africa and to develop new therapies suitable for the region, of which SSG&PM is the first. DNDi is also participating in multicentre clinical trials in Latin America. These studies are sponsored by the Brazilian Ministry of Health to assess the safety and efficacy of the currently recommended treatments for VL in Brazil (Glucantime®, amphotericin B deoxycholate, Ambisome®), as well as to assess the combination of Ambisome® with Glucantime®. Furthermore, DNDi aims to accelerate the development and registration of new VL drugs by building on existing pre-clinical and early clinical data. In addition, DNDi has a lead optimization programme, which aims at bringing new candidates into clinical development.

The goal of this project is to generate new drug candidates that meet the target product profile for the treatment of VL. DNDi partnered in 2007 with Advinus Therapeutics, a drug discovery and development company based in Bangalore, India, and CDRI (Central Drug Research Institute), an Indian public institution located in Lucknow, India. Compounds showing activities (hits) are identified from DNDi’s ongoing screening projects carried out by our screening partners. The chemical structure of the best hits are then systematically modified, guided by a combination of medicinal chemistry, physicochemical properties, biological screening, and absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters, to ensure that the optimized compounds meet all the necessary drug-like criteria specified by the target product profile (TPP) for a new drug to treat VL. With a full team of eight chemists in place within the VL Lead Optimization Consortium, assessments of four series of synthetic compounds, provided by DNDi partners, have been carried out or are ongoing.

Recently, the thiazole series identified from a large screening campaign performed at Institut Pasteur Korea (IPK) has yielded potent lead molecules. Additional efficacy and pharmacokinetics studies are underway to identify pre-clinical candidates from this promising series.
WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS FOR VL?

Short term: better use of existing treatments through geographical extension and new treatments schedules for VL
- Africa: Registration of paromomycin, AmBisome®, miltefosine, and development of an AmBisome® based combination. SSG&PM combination treatment now available.
- Asia: Recommendation and implementation of single-dose AmBisome® and combinations involving miltefosine, paromomycin, and Liposomal amphotericin B
- East Africa: sodium stibogluconate & paromomycin combination treatment (SSG&PM)
- Latin America: Liposomal amphotericin B monotherapy

Medium or long term: registration of one new drug through new formulations of existing treatments and therapeutic switching. Potential compounds in-sourced at late pre-clinical phase – DNDi is actively pursuing potential candidates ready for clinical development in the short term. New drugs developed from compounds identified through VL Lead Optimization Consortium. Multi-country, multi-partner LEAP to strengthen regional research capacity [see page 41].

By 2014, DNDi aims to deliver from its VL-specific portfolio:
- 1 new drug at late stage of clinical development
- 1-3 geographical extensions in endemic regions of currently available drugs
**Alternative formulations of amphotericin B**

- **Partners:** Polytherics, UK; Advinus, India; CDRI, India, LSHTM, UK; Auckland University, New Zealand
- **Management:** Head of Visceral Leishmaniasis Discovery and Pre-clinical Programme, Denis Martin
- **Project start:** September 2006

The goal of this project is to identify an improved formulation of amphotericin B that shows the most promise in terms of in vivo efficacy, safety, heat stability, and cost. Amphotericin B, under various formulations, is one of the most efficacious treatments for VL. The standard formulations (oily suspension) have side effects. AmBisome®, a liposomal formulation, has overcome these limitations, but its high cost and lack of heat stability limit its utility in disease-endemic countries. Recently, new formulations have emerged and have either been approved or are under clinical development in India. However, they are still not field-adapted and there is no safety and VL efficacy data available yet. DNDi and its UK partners are investigating improved polymer-based formulations to replace the lipid-based component with a narrow molecular weight range polymer. Ideally, the selected polymer can form an amphotericin B conjugate that is soluble, cheaper, better tolerated, and has increased thermal stability. Initial results show that reproducible in vivo activity could be achieved without signs of amphotericin-induced toxicity in test animals. Further characterization is in progress.

**Nitroimidazoles**

- **Partners:** TB Alliance, USA; Advinus, India; CDRI, India, LSHTM, UK; Auckland University, New Zealand
- **Management:** Head of Visceral Leishmaniasis Discovery and Pre-clinical Programme, Denis Martin; Project Coordinators, Delphine Launay, Anne-Sophie Bessis
- **Project start:** May 2010

Nitroimidazoles, a class of novel anti-bacterial agents, have great potential for addressing major unmet medical needs in TB therapy. PA-824, the first compound in the TB Alliance portfolio is currently undergoing Phase II clinical development for the treatment of TB. It has many attractive characteristics as a TB therapy. Through a contractual agreement with TB Alliance, DNDi was granted access to their nitroimidazole library. From the initially selected 70 nitroimidazoles belonging to 4 chemical subclasses, DNDi-VL-2098 was identified as a very potent and safe molecule and was selected for in-depth evaluation of its efficacy, pharmacokinetic, and early safety profile on the basis of these preliminary results. This compound is potent and selective in vitro and shows efficacy in acute and chronic VL animal models. Appropriate exposure is obtained after oral dosing in rodents and the compound does not induce toxicity after one-week administration at several times the efficacious dose. The objective is to perform all pre-clinical activities needed to meet regulatory requirements, and to file an Investigational New Drug (IND) by the end of 2011 if further pre-clinical data support advancement to clinical. A well-focused back-up programme is ongoing at Auckland University.

**Combination therapy (VL in Latin America)**

- **Major Partners:** René Rachou Research Institution – FIOCRUZ-MG, Brazil; Paediatric Hospital João Paulo II – FHEMIG, Brazil; Brasilia University, Brazil; Montes Claros State University, Brazil; Piáui Federal University, Brazil; Sergipe Federal University, Brazil; Tocantins Federal University, Brazil; Leishmaniasis Control Programme/Brazilian Ministry of Health, Brazil.
- **Management:** Head of Leishmaniasis Clinical Programme, Manica Balasegaram; Clinical Manager, Fabiana Piovesan Alves
- **Project start:** 2010

About 90% of VL cases in Latin America occur in Brazil, and most of them affect children. In 2007, Brazil reported around 3,500 new cases and a fatality rate of 5.4%. DNDi’s objective is to assist the Brazilian Ministry of Health to evaluate the safety and efficacy of Glucantime®, AmBisome®, and amphotericin B, and Glucantime® and AmBisome® combination to treat VL patients in Brazil. To this end, a feasibility assessment and VL site selection was performed over 2010, with potential study sites identified in different regions of the country. The broader objectives of the study, led by Dr Gustavo Romero of the University of Brasília, and sponsored by the Brazilian Ministry of Health, include the assessment of the effectiveness of currently recommended treatments for VL in Brazil. The project is conducted in several reference centres, involving a total of 600 adults and children. The recruitment of patients commenced in Q1 2011.
Good efficacy results in India for combination therapies

- **Major Partners**
  - **INDIA**: Indian Medical Research Council (ICMR), Delhi; Kala-Azar Medical Research Centre (KAMRC), Muzaffarpur; Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna.
  - **BANGLADESH**: International Centre for Diarrhoeal Disease Research (ICDDR, B), Dhaka; Shaheed Suhrawardy Medical College and Hospital (ShSMC), Dhaka; Community Based Medical College (CBMC), Mymensingh.
  - **NEPAL**: BP Koirala Institute of Health Sciences, Dharan.
  - **USA**: Institute for OneWorld Health, San Francisco.

- **WHO’s Special Programme for Research and Training in Tropical Diseases (TDR)**
- **Management**: Senior Advisor for Leishmaniasis, Farrokh Modabber; Head of Leishmaniasis Clinical Programme, Manica Balasegaram; Clinical Manager, Sally Ellis; Head of DNDi India, Bhawna Sharma.

- **Project start**: June 2008

DNDi’s objective is to identify a safe and effective short-course therapy using existing drugs, which could be easily deployed in control programmes and replace current treatment regimens which either lack efficacy (SSG in some regions), require long treatment courses (miltefosine, SSG, paromomycin) or are have some associated toxicity (conventional amphotericin B, SSG). Following preclinical and Phase II studies, an open label, randomized, prospective, non-inferiority Phase III trial was conducted to study the combination of drugs already registered in India: AmBisome®, miltefosine, and paromomycin. Three arms investigating the three possible 2-drug combinations with a maximum duration of 11 days were compared with the standard 30-day therapy (15 infusions every other day using amphotericin B). This study, involving a total of 634 patients, was completed in 2010. All three combination treatments were highly efficacious (>97.5% cure rate), and none was inferior to the standard treatment using amphotericin B.

This project has been developed in collaboration with ICMR, the Rajendra Memorial Research Institute of Medical Sciences (RMRIMS) in Patna and the Kala Azar Medical Research Centre (KAMRC) in Muzaffarpur.

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DNDi Project of the Year 2010

The complete results were published in *The Lancet* in January 2011.[1]

A two-step Phase III trial (first in hospital settings followed by treatment in primary healthcare centres) using the same combinations have also been initiated in Bangladesh, with recruitment commencing in July 2010. In December 2010, about 100 patients had been enrolled in the study. Discussions are ongoing with authorities and partners such as iOWH to initiate a trial in Nepal to evaluate the safety of one or more combinations with the same drugs. In addition, discussions are in progress with the Indian National Vector Borne Disease Control Programme.

In parallel to this work, Sundar et al. conducted another Phase III study that showed the efficacy of a single dose of 10mg/kg of AmBisome® (n=304) given as an i.v. infusion, which cured 95.7% of patients at 6 months (95% CI 93.40-97.90). The treatment was shown to be non-inferior in both safety and efficacy to the standard treatment of amphotericin B 1mg/kg i.v. given as 15 infusions on alternate days (n=108).

In March 2010, the WHO Expert Committee on the Control of Leishmaniasis met in Geneva and recommended that all 4 of the new treatments (the 3 combinations and single dose AmBisome®) be used preferentially to current established monotherapy treatments for VL in South Asia.

DNDi has actively developed a partnership with TDR and iOWH to facilitate the introduction of these new treatments for VL in South Asia. This will be done in collaboration with health authorities at state, national, and regional levels. DNDi and its partners intend to implement effectiveness studies in the region to demonstrate that such treatments can be feasibly and safely implemented in primary healthcare settings in both the public and private sectors.

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COMBINATION THERAPY (VL IN AFRICA)

SSG&PM recommended for East Africa and further studies for new treatment options

- Major Partners
  Kenya Medical Research Institute (KEMRI), Kenya; Institute of Endemic Diseases (IED), University of Khartoum, Sudan; Addis Ababa University, Ethiopia; Gonder University, Ethiopia; University of Makerere, Uganda; London School of Hygiene and Tropical Medicine, UK; ASK (AMC, Slotervaart Hospital, KIT), The Netherlands; Ministries of Health of Ethiopia, Sudan, Kenya, and Uganda; Médecins Sans Frontières (MSF), + solutions, The Netherlands; Institute for OneWorld Health (iOWH), USA; LEAP (Leishmaniasis East Africa Platform)

- Management: Head of Leishmaniasis Clinical Programme, Manica Balasegaram; Clinical Manager, Sally Ellis

- Project start: November 2004

Due to various limitations such as toxicity, difficulty of use, and the high cost of existing drugs, VL is complex to treat in Africa. Sodium stibogluconate (SSG), a relatively toxic drug requiring a daily regimen of painful injections over 30 days, remains the mainstay of treatment. Other drugs, such as paromomycin (PM) and miltefosine, are neither registered nor available in the region. Since 2004, DNDi and the Leishmaniasis East Africa Platform (LEAP) have embarked on a clinical research programme with two specific objectives: to geographically extend all currently available VL drugs and to develop one to two new treatments. In 2010, the first – a combination therapy – came out of this clinical research programme: SSG&PM.

In addition to the LEAP 0104 study, DNDi also conducted two other clinical trials in the region during 2010 in order to develop a second treatment:

**AmBisome® / LEAP 0106 Study**

AmBisome®, a liposomal formulation of amphotericin B manufactured by Gilead, is approved to treat VL in Europe and USA. Gilead has worked with the World Health Organization and NGOs to provide AmBisome® at a preferential price for the treatment of leishmaniasis in resource-limited settings. Therefore, the goals of this project are 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 stays required, and to facilitate the registration and adoption of the drug in the region, in addition to its optimal use in combination therapies. Recruitment for the study was closed at the end of 2010. Results of this study will be presented in 2011.

**Miltefosine-AmBisome® / LEAP 0208 Study**

This study is to evaluate the safety and efficacy of miltefosine and AmBisome® combination treatment. Recruitment has started in Kenya and Sudan (Q2 2010). Miltefosine, a drug originally developed for the treatment of cancer, is the only orally administered drug against VL. Miltefosine is registered and used in India and in some countries in Latin America. The trial will collect safety, efficacy, and pharmacokinetic data on miltefosine to geographically extend the use of the drug into East Africa. In addition, combination treatments of AmBisome® with either miltefosine or SSG are evaluated. If the results are promising, it will be taken into Phase III development.

This project was initiated to register paromomycin in East Africa and evaluate its use in a shorter-course combination with SSG as an improved treatment for VL.

In 2010, the Leishmaniasis East Africa Platform (LEAP) completed this multi-centre, multi-country clinical trial sponsored by DNDi in Kenya, Ethiopia, Sudan, and Uganda. The LEAP 0104 study involved over 1,100 VL patients and showed that a short-course combination of PM (15mg/kg/day) and SSG (20mg/kg/day) had a similar safety and efficacy profile (efficacy at 6 months follow up post-treatment > 90%) as the standard SSG monotherapy treatment (SSG 20mg/kg/day for 30 days). The trial also demonstrated that the use of PM (15 or 20 mg/kg/day) alone for 21 days resulted in significantly lower efficacy. Thus the use of the combination will be critical to prolonging the use of both drugs in the region, particularly PM.

In March 2010, the WHO Expert Committee on the Control of Leishmaniases recommended SSG&PM as first-line treatment for visceral leishmaniasis in East Africa. A few months later, Sudan was the first country to apply the recommendation and implement SSG&PM to treat patients (end 2010). DNDi and LEAP will continue the process of ensuring the registration of paromomycin in the region in order to further implement the recommendation of SSG&PM as first-line treatment regimen for VL. These results were presented in PLoS (see publications, page 47).
Development of a paediatric treatment and of a new azole compound to treat adult chronic patients

After 40 years of scant clinical research on Chagas disease, DNDi launched three studies in Latin America, one of which to test a totally new compound against the \textit{T. cruzi} infection. Until recently, the primary focus for controlling Chagas disease was to interrupt transmission. This was done through vector control programmes and the screening of blood donors. In the Southern Cone of South America major initiatives began in 1991-92 and over the next decade most Central and South American countries joined the initiatives. The goal was to eliminate \textit{T. cruzi} infections by 2010 through a new Global Network for Chagas Elimination. While these programmes have significantly reduced the incidence of infection in children and have hindered blood-transfusion related transmission, Chagas disease still affects an estimated 8 million worldwide. In 2005, according to PAHO, 1.8 million women of childbearing age were infected and 14,000 children were born with the disease in the Americas.\(^1\)

Current therapy for Chagas disease is limited to two nitroheterocyclic drugs, nifurtimox and benznidazole. Both drugs require a long treatment duration (30-60 days), which increases the risk of patient noncompliance, and dose- and time-dependent toxicity is also frequent. Both are more effective in the acute form of the disease [mostly identified in children] than they are in the chronic phase. Unfortunately, most of the patients are diagnosed in the latter phase. Furthermore, no paediatric strength or formulation is currently available, meaning that caregivers are obliged to break and crush the only available adult formulation into small pieces for children, leading to potential errors in dosage.

The long-term goal is to develop new and effective treatments for chronically-infected patients. The near-term goal is to improve existing treatments through the development of new formulations that are better adapted to patients’ needs, especially for newborns who acquire the infection through mother-to-child transmission. DNDi currently has engaged in the development of a paediatric formulation of benznidazole, and in the clinical development of a new azole antifungal drug, E1224, against \textit{T. cruzi} in adult chronic patients bringing new hope to Chagas patients. In parallel, DNDi plans to evaluate selected biomarkers, which could shorten the patient follow-up for test of cure.

In the longer term, however, new chemical entities need to be developed that are safe and efficacious, as specified in DNDi’s target product profile. DNDi continues to identify and engage partners from private and public sectors to ensure that the goals in drug development for Chagas disease are met. Additionally, DNDi is committed to strengthening existing clinical research capabilities through a regional platform of experts, the Chagas Clinical Research Platform (see page 40), launched in 2009, that supports GCP-standard clinical trials.

\(^{(1)}\) PAHO, \textit{Estimación cuantitativa de la enfermedad de Chagas en las Américas}, 2006

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**IDEAL TARGET PRODUCT PROFILE FOR CHAGAS**

- \textbf{A new treatment for acute and chronic disease}  
  - Useful against most parasite species in all regions
- \textbf{Better safety profile than existing drugs}  
  - Ideally requiring little or no monitoring
- \textbf{Non inferior efficacy to benznidazole}
- \textbf{Easy-to-use treatment}  
  - Ideally once-a-day for less than 30 days  
  - Oral  
  - Preferably once-a-day treatment, ideally outpatient
- \textbf{Affordable}
- \textbf{Stable (3 years minimum) in tropical climates}
21 endemic countries and worldwide impact due to global migration

WHAT IS THE ANNUAL IMPACT OF CHAGAS DISEASE?
- 100 million people at risk(1)
- Approximately 8 million cases(2)
- 12,000 deaths(3)

HOW IS CHAGAS DISEASE TRANSMITTED?
Caused by the kinetoplastid protozoan parasite Trypanosoma cruzi. Chagas disease is primarily transmitted by large, bloodsucking reduvid insects widely known as ‘the kissing bugs’ in endemic countries. Other routes of transmission include blood transfusion, organ transplantation, as well as congenital and oral routes through ingestion of contaminated food or beverage.

WHAT ARE THE SYMPTOMS?
The disease has two clinical phases:
- **Acute phase** (fatal for 2-8% of children(4)), often asymptomatic or unrecognized due to its non-specific symptoms, such as fever, malaise, generalized lymphadenopathy, and hepatosplenomegaly, which spontaneously resolve in 4-6 weeks.
- **Chronic phase** can be divided into two stages:
  - The chronic asymptomatic ‘indeterminate’ stage, during which patients can transmit the parasite to others, especially through vertical transmission, while showing no signs of the disease, and which may last decades after infection.
  - The chronic symptomatic stage, which develops in up to 30% of infected patients and most often involves the heart or gastrointestinal tract. Chagas disease is the leading cause of infectious heart disease (cardiomyopathy) in the region.

WHERE DOES CHAGAS DISEASE OCCUR?
Endemic in 21 countries across Latin America, but through population migration the disease has spread to Australia, North America, Japan, and Europe.

WHAT ARE THE CURRENT TREATMENTS AND THEIR LIMITATIONS?
Current treatments have the highest efficacy in acute infection with limited evidence for efficacy in the chronic stages.
- **Benznidazole, nifurtimox** to treat acute and chronic phases:
  - Long treatment period (30-60 days)
  - Dose-dependent toxicity
  - High rate of patient non-compliance
  - No paediatric strengths
There is no treatment for chronic disease with target organ involvement.

WHAT ARE THE PATIENT TREATMENT NEEDS?
- A paediatric strength of benznidazole that is affordable and age-adapted.
- A new oral drug that is safe, efficacious, and adapted to the field, and ideally would work in both stages of the disease.

WHAT IS DNDi DOING TO ADDRESS UNMET TREATMENT NEEDS?
Short term: better use of existing treatments through the development of paediatric-strength benznidazole

Medium term:
1) **Azoles**: clinical assessment of known compounds already in development against fungal infections. Specifically, clinical studies of E1224, in collaboration with Eisai are being conducted.
2) **Development of new treatments** through combination therapy – in exploratory pre-clinical stage.

Long term: 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 Optimization Consortium.

By 2014, DNDi aims to deliver from its Chagas-specific portfolio
- 1 new paediatric-strength benznidazole
- 1 new drug registered for chronic Chagas disease

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(1) PAHO, Estimación cuantitativa de la enfermedad de Chagas en las Américas, 2006
In mid-2008, a Lead Optimization Consortium devoted to Chagas drug discovery was set up by DNDi. Members of this consortium are engaged in a complex, iterative process to optimize the efficacy and pharmacological properties of lead compounds while minimizing their toxicity. Rapid turnaround of compound assessment is achieved by a group of analytical and medicinal chemists (Epichem, Australia), pharmacologists (Monash University, Australia), and parasitologists (Murdoch University, Australia and Universidade Federal de Ouro Preto, Brazil). The objective is to develop at least one new optimized lead for Chagas disease by the first quarter of 2012 and to identify a new chemical series of interest. One of the current chemistry efforts is on the fenarimol series. Several high-potency compounds have been generated, and some have shown efficacy in vivo.

At the same time, the team is evaluating the oxaboroles series, taking advantage of the compounds generated from the lead optimization programme for human African trypanosomiasis (HAT). Over 2,000 oxaboroles have been screened for their activity against T. cruzi in vitro, and some have shown activity. Other series originating from DNDi screening efforts will serve as leads for further optimization in the future.
K777 is a vinyl sulfone cysteine protease inhibitor which irreversibly inhibits cruzain, a key protease required for viability of *Trypanosoma cruzi*, the parasite responsible for Chagas disease. A novel chemical entity originally characterized at University of California San Francisco (UCSF), K777 has since been shown to be safe and effective in models of acute and chronic Chagas disease in animals. The main objective of the project is to collaborate with the UCSF team in completing the pre-clinical drug development requirements to allow K777 to move into Phase I clinical trials.

**Paediatric benznidazole**

- **Major Partners:** Laboratório Farmacêutico do Estado de Pernambuco (LAFEPE), Brazil; Hospital de Niños Ricardo Gutierrez, Argentina; Instituto Nacional de Parasitología, Dr M Fatale Chabén, Argentina; Hospital de Niños de Jujuy, Argentina; Ministério de Salud, Provincia de Jujuy, Argentina; Hospital Público Materno Infantil – Salta, Argentina; Centro de Chagas y Patología Regional, Argentina; CONICET/INGEBI, Argentina; Centro Nacional de Diagnóstico e Investigación de Endemico-epidemias (CeNDIE), Ministry of Health, Argentina; University of Liverpool, UK; NUDFAC, Brazil; CRO - LAT Research, Argentina.
- **Management:** Head of Chagas Clinical Programme, Isabela Ribeiro; Clinical Trial Manager, Jayme Fernandes; Project Coordinator, Bethania Blum
- **Project start:** June 2008

Benznidazole, a nitroimidazole introduced by Roche in 1971, and licensed to the Brazilian LAFEPE, is one of the two products registered for Chagas disease treatment and is included in the WHO Essential Medicines List. It is supplied in 100 mg tablets and administered twice daily for 60 days at a dose of 5 mg/kg bodyweight/day for adults and 5-10 mg/kg bodyweight/day for children. Extemporaneous formulations and fractionation are needed for most children because no paediatric formulation of the drug exists. Fractionation of tablets is far from ideal because of the high risk of delivering improper dosages, thereby raising concerns about efficacy, safety, and decreased stability.

With the goal of developing an adapted dispersible tablet of benznidazole suitable for very young children, DNDi and LAFEPE signed a development agreement in July 2008.

Using current benznidazole dose recommendations, and data from dosing practices and patient age and weight profiles from reference centres that treat children with *T. cruzi* infections as a guide, the team has determined the most appropriate paediatric tablet formulation, strength, and associated dosing regimen (12.5 mg tablets). Biobatch production was carried out in early 2010 and submission for registration is planned for the first quarter of 2011. A population pharmacokinetics study is to start in 2011 in Argentina, involving 80 paediatric Chagas disease patients, to obtain additional information on pharmacokinetics, treatment safety, and efficacy for this targeted population.
AZOLES E-1224 & BIOMARKERS

A promising alternative treatment for Chagas disease

• Major Partners: Eisai Pharmaceuticals, Japan; Platform of Integral Care for Patients with Chagas Disease, Spain/Bolivia; Universidad Mayor de San Simon, Bolivia; Federal University of Ouro Preto, Brazil; CONICET, Argentina; MSF-Spain; Centre de Recerca en Salut Internacional de Barcelona (CRESIB), Spain
• Management: Head of Chagas Clinical Programme, Isabel Ribeiro; Clinical Manager, Fabiana Piovesan Alves; Project Coordinator, Bethania Blum
• Project start: June 2008

New antifungal azole derivatives offer a promising alternative treatment for Chagas disease. They potently inhibit T. cruzi ergosterol biosynthesis and possess desired pharmacokinetic properties (long terminal elimination half-life and large volume of distribution) suitable for the treatment of this disseminated intracellular infection. The current project evaluates E-1224, a new generation azole compound, as a new tool for the treatment of Chagas disease.

E-1224 is a water-soluble monolysine salt form of a pro-drug of ravuconazole, which is rapidly converted to ravuconazole in vivo. Ravuconazole has been evaluated extensively in animal models and in human trials, including Phase II safety and efficacy studies for fungal infections. E-1224, discovered and developed by Eisai Pharmaceuticals (Japan), has completed pre-clinical evaluation and five Phase I clinical studies. DNDi and Eisai Pharmaceuticals signed a collaboration and licensing agreement in September 2009. They will jointly conduct the safety and efficacy assessment of the compound in Chagas disease. DNDi is responsible for the clinical development to assess the safety and efficacy in patients with Chagas disease in endemic countries.

In partnership with Eisai Pharmaceuticals and the Platform of Integral Care for Patients with Chagas Disease - that brings together scientists from CRESIB, Spain and universities in Bolivia - DNDi will start a Phase II study to evaluate safety and efficacy of E-1224 in (adult) patients with chronic indeterminate Chagas infection. Sites will be located in Bolivia, where Chagas is highly endemic. They have been properly equipped and staff received appropriate training during 2010. The protocol has been approved by three different ethical committees and sites will be ready to start recruitment by second quarter of 2011.

Also in the scope of azoles compounds, DNDi will carry out, in partnership with the Federal University of Ouro Preto, Brazil, evaluations of the activity of ravuconazole in different strains of T. cruzi, in vivo and in vitro and in combination with benznidazole.

A study is ongoing to optimize procedures for the use of the polymerase chain reaction (PCR) blood test as a measure of treatment response in Chagas disease. This study is being conducted in collaboration with MSF Spain, with PCR assay support provided by the Universidad Mayor de San Simon (UMSS) in Bolivia and quality assurance from INGEBI-CONICET in Buenos Aires, Argentina.

In parallel, DNDi decided at the end of 2010 to start assessing biomarkers for Chagas disease with respect to their potential for application to clinical research (e.g. shortening of patient follow-up for test of cure, possible staging of the patients). This evaluation will be undertaken in 2011 in order to define a clear strategy for 2012 and years thereafter.
In 2002, the Fixed-Dose Artesunate-Based Combination Therapies (FACT) Consortium, created by DNDi started to develop two fixed-dose artesunate (AS)-based combination therapies (out of the four initially recommended by WHO) – ASMQ fixed-dose combination (artesunate and mefloquine) and ASAQ fixed-dose combination (artesunate and amodiaquine) – for the treatment of uncomplicated P. falciparum malaria to improve compliance and be available in all countries depending on their resistance profile. The development of the two fixed dose combinations (FDCs), ASAQ and ASMQ, registered respectively in 2007 and 2008, strengthened the existing ACT portfolio of fixed-dose combinations – adding to artemether-lumefantrine. The portfolio will be expanded by the addition of artesunate-pyronaridine FDC and dihydroartemisinin-piperaquine FDC under development by the Medicines for Malaria Venture (MMV).

Despite the substantial progress made worldwide over the past five years in the number of countries that have adopted and deployed ACTs as first-line treatment, their access is still limited in many parts of Africa and in some areas in Asia.

In 2010, the revised malaria treatment guidelines published by WHO strongly recommended the use of intravenous artesunate in place of quinine for the treatment of severe P. falciparum malaria in children and in adults.

Within the landscape of increased availability of affordable ACTs and innovative financing mechanisms for antimalarials, DNDi in collaboration with National Malaria Control Programmes conducted market surveys in Ghana (2010), after Burundi and Sierra Leone (both in 2009). The three countries have adopted AS+AQ as first-line treatment for malaria. The main conclusions indicated that both the public and private sectors have actions to undertake to strengthen policies that lead to the replacement of loose blister packs with fixed-dose ACT products, develop strategies to ban inappropriate antimalarials and regulate those bans, and facilitate technology and knowledge transfer to scale up production of fixed-dose ACT products, which should be readily available and affordable to those patients who are in the greatest need of these medicines.71 Translating evidence into policy and then again into practice, improving quality supply, decreasing drug costs through various mechanisms put in place by the private and the public sectors and ensuring the availability of artesinin to also impact the cost of artesunate are the key components to facilitate access to new and available quality ACT treatments.
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 partnerships in the Fixed-Dose Artesunate Combination Therapy (FACT) Project.
DNDi will complete its malaria activities, including emphasis on technology transfer and sustained access, by shifting its malaria activities to other partners by 2014.

The FACT Project has produced two 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 proportion
- 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 30 African countries and in India
• ASMQ – FDC of artesunate and mefloquine registered in Brazil in 2008 and integrated in the national policy for treating uncomplicated malaria.
Through to 2014, DNDi will provide support to facilitate access to these combination therapies 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 is considered uncomplicated when symptoms are present without clinical or laboratory signs to indicate severity or vital organ dysfunction. The symptoms of uncomplicated malaria are non-specific and include fever. Infection with P. falciparum, if not treated, can quickly progress to severe malaria. The main symptoms include: severe breathing difficulties, low blood sugar, and low blood haemoglobin (severe anaemia), and coma. Children are particularly vulnerable as they have little or no immunity to the parasite. If untreated, severe malaria can quickly become life-threatening.

WHAT IS THE IMPACT OF MALARIA?
• One of the three most deadly diseases in Africa
• 225 million cases of malaria worldwide each year, with nearly 1 million deaths\(^1\)
• Every 45 seconds a child in Africa dies of malaria

HOW IS MALARIA TRANSMITTED?
Transmitted from person to person by the bite of Anopheles 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?
• In addition to the widespread resistance to chloroquine, the marketing of oral monotherapies, including artemisinin, threatens the continued efficacy of artemisinins
• Access to ACTs is still limited in many parts of Africa and in some areas of Asia, particularly for children, the primary victims of malaria worldwide, who do not have access to the paediatric strengths of fixed-dose ACTs
• Countries with the highest prevalence of 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, simple, safe, and field-adapted quality drugs
• Access to diagnostic testing needs to be expanded

WHERE DOES MALARIA OCCUR?
Malaria is endemic in 106 countries worldwide and threatens half of the world’s population. In sub-Saharan Africa, where it is the single largest cause of death for children under 5 years of age, malaria kills one child every 45 seconds. The disease accounts for 20% of all childhood deaths.

(1) World Malaria Report 2010, WHO.

Half of the world population at risk with 106 endemic countries
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 *P. falciparum* malaria. Used in the field for many years, the combination of AS and MQ is one of the four ACTs recommended by WHO since 2001 as first-line treatment for uncomplicated *P. falciparum* malaria.

ASMQ fixed-dose combination treatment (ASMQ FDC) was first developed in 2002 through an innovative partnership between the Brazilian government-owned pharmaceutical company, Farmanguinhos/Fiocruz and the FACT consortium, coordinated by WHO/TDR and MSF. The latter turned the project over to DNDi upon its foundation in 2003. ASMQ FDC was registered in Brazil in March 2008.

ASMQ FDC tablets (25/55 mg and 100/220 mg) offer an easy-to-use treatment regimen with one single daily dose of one or two tablets of two highly effective, combined products to be taken over three days. In addition, the three-year shelf-life of ASMQ FDC facilitates deployment and availability in rural health centres.

Following a major intervention study in Acre, a State of the of Amazon River Basin, sponsored by the National Malaria Control Programme, ASMQ FDC is now an alternative first-line treatment for uncomplicated *P. falciparum* malaria according to National Malaria Policy in Brazil. Over 180,000 treatments have been ordered by Brazilian government agencies.

In addition, the ASMQ FDC registration process is underway in three additional malaria-endemic countries in Latin America – Peru, Bolivia, and Venezuela, which have already adopted the combination of AS+MQ for treating uncomplicated *P. falciparum* malaria.

Following an agreement signed in 2008, the transfer of technology between Farmanguinhos in Brazil and the Indian generic pharmaceutical company Cipla was successfully completed in 2010. This technology transfer will facilitate and support the deployment of the treatment throughout the Indian sub-continent, in Central and Southeast Asia, as well as in other parts of the world.

Cipla, DNDi’s industrial partner, submitted the ASMQ registration file to regulatory authorities in India, Malaysia, and Myanmar. DNDi, in collaboration with National Malaria Control Programmes and other key malaria actors, is preparing the implementation of ASMQ FDC in countries where its...
registration is imminent. In order to render ASMQ eligible for international funds, DNDi and partners submitted a full dossier for WHO pre-qualification in 2010. According to WHO recommendations, AS+MQ could be considered for use in Africa. To provide additional information on the tolerability of ASMQ FDC, DNDi is sponsoring a multi-centre Phase IV study in Tanzania, Burkina Faso, and Kenya to assess efficacy, safety, and pharmacokinetics of ASMQ FDC as compared to that of artemether-lumefantrine treatment in children with uncomplicated *P. falciparum* malaria.

**ASQA – Artesunate-Amodiaquine fixed-dose combination**

80 million treatments distributed in Africa at the end of 2010

- Major Partners: sanofi-aventis, France; Medicines for Malaria Venture, Switzerland; National Centre for Research and Development on Malaria, Burkina Faso; Universiti Sains Malaysia; Oxford University, UK; Institute of Research for Development (IRD), Senegal; Université de Bordeaux Faculté de Pharmacie, France; Mahidol University, Thailand; Ellipse Pharmaceuticals, France; Médecins Sans Frontières; Epicentre, France; WHO/TDR; Kenya Medical Research Institute (KEMRI), Kenya; Indian Council of Medical Research (ICMR), India; National Malaria Control Programme, Ministry of Health, Burundi; WHO, Burundi; Ministry of Health, Sierra Leone; Komfo Anokye Teaching Hospital (KATH), Ghana
- Management: Senior Pharma Advisor & Product Manager, Jean-René Kiechel; Project Coordinator, Gwenaëlle Carn; Medical Coordinator FACT Project, Graciela Diap
- Project start: January 2002

ASAQ Winthrop, the fixed-dose combination (FDC) of artesunate (AS) and amodiaquine (AQ), was the first treatment made available by DNDi in 2007 through an innovative partnership with sanofi-aventis. ASAQ Winthrop was pre-qualified by WHO in October 2008. Over 80 million treatments were distributed by the end of 2010 throughout 29 African countries. It is estimated that an additional 55 million will be made available to malaria patients in Africa in 2011. First registered in Morocco, where it is manufactured, ASAQ is now registered in 30 African countries and India.

ASAQ truly represents an improvement for patients as it requires treatment regimens of once-a-day dosing. ASAQ is available at less than USD 0.5 for children and USD 1 for adults. In 2010, ASAQ Winthrop obtained WHO authorization for its three-year shelf life, giving the product the longest shelf-life of any pre-qualified FDC artemisinin-based treatment available for malaria. In partnership with MMV, DNDi, and National Malaria Control Programmes, sanofi-aventis is implementing an ambitious and comprehensive risk management plan for ASAQ, which aims at collecting high-quality data on ASAQ’s effectiveness and safety profile in the field. Being the first ever of its kind submitted to WHO, this risk management plan will ensure that appropriate post-marketing data is available as quickly as possible on safety and effectiveness of ASAQ in the field. The plan consists of several studies currently underway in West and East Africa, spanning from randomized, comparative, clinical trials in a limited number of patients treated under well-controlled conditions, to large-scale studies assessing the drug’s safety in ‘real-life’ conditions. Among these is a Phase IV efficacy and tolerability study conducted in Ivory Coast. The study recruited more than 1,800 patients in four different sites in the country by the end of 2010. Delays, however, are expected due to current instability in the country. Two additional clinical studies included in the above-mentioned plan have been managed by DNDi in collaboration with MSF, Epicentre, and the National Malaria Control Programme in Liberia, the results of which were made available in 2010. They show that ASAQ is highly efficacious, safe, and well tolerated in children and adults in Liberia.

In parallel, the evaluation and selection process of a second industrial partner for the production of ASAQ in Africa was conducted in 2010 by OTECI with the support of AEDES and Bertin Pharma, and technology will be transferred to Zenufa in Tanzania as of 2011.

Following the antimalarial market assessments conducted by DNDi in Burundi and Sierra Leone in 2009,(1) DNDi and its partner Komfo Anokye Teaching Hospital, Kumasi (KATH) are performing outlet surveys in Ghana, as part of the independent evaluation of the Affordable Medicines Facility–Malaria (AMFm) Phase I. This contribution, funded by the Global Fund to Fight AIDS, Tuberculosis, and Malaria, will provide data on the availability, affordability, use, and market share of ACTs in Ghana. The conclusions of the Burundi and Sierra Leone surveys, where ASAQ is the first-line treatment for malaria, were published in 2010 in *Malaria Journal* (2) and offered a set of recommendations at global, national, and community levels to facilitate broad implementation of ACTs.

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