FIGHTING NEGLECTED TROPICAL DISEASES

Over one billion people are at risk of or affected by tropical diseases that the international community considers to be "neglected." Very often these diseases affect communities in remote rural areas, urban slums and conflict zones with poor living conditions and hygiene.

I. BACKGROUND

Neglected Tropical Diseases (NTDs) are very low on the list of international public health priorities and health agendas. NTDs refer to a group of parasitic, bacterial, fungal and viral diseases that cause substantial illness for more than one billion people globally, affecting the world's poorest communities. Funding for research and development to find new treatments is typically limited, given that the potential return on investment is either very small or nonexistent. Consequently, most of the medicines available today were developed years ago and are not always adapted to the needs of patients and caregivers. There is also a real risk that resistance to these treatments will develop, making them ineffective.

The support of endemic countries and increased awareness within the international community are fundamental to eliminating and controlling these diseases.

There are 149 countries and territories where NTDs are endemic. In at least 100 of them, two or more of these diseases are endemic.

For more information, see: http://www.who.int/neglected_diseases/en/

II. SANOFI GLOBAL HEALTH

Sanofi Global Health, formerly Access to Medicines department, is dedicated to conduct, in collaboration with its partners, initiatives for the most vulnerable populations in low and middle income countries, to provide sustainable solutions to unmet medical needs in malaria, neglected tropical diseases, tuberculosis, diabetes, cardiovascular diseases, mental health and epilepsy.

III. POLICY

Sanofi's commitment to NTDs is demonstrated by the company's corporate social responsibility, as well as our expertise, developed since 1946, in the research and production of treatments for sleeping sickness (Human African Trypanosomiasis, or HAT) and leishmaniasis.

Sanofi and the World Health Organization (WHO) have joined forces in the fight against NTDs since 2001, and their collaboration continues to grow in a concerted effort to combat HAT, leishmaniasis, Chagas disease and Buruli ulcer.

- **2001-2005:** An initial collaboration is formed to combat HAT.

- **2006-2010:** The collaboration is expanded to include other NTDs: leishmaniasis, Buruli ulcer, Chagas diseaseand yaws
- **2011-2015:** The collaboration is renewed for an additional five years, with the goal of eliminating sleeping sickness as a public health concern by 2020 and improving control of leishmaniasis, Buruli ulcer and Chagas disease.
- **2016:** the collaboration was renewed and is now renewed every year until 2020
- **2012:** Sanofi signed the London Declaration, an initiative gathering the WHO, the Bill & Melinda Gates Foundation, several governments and 13 pharmaceutical companies, including Sanofi, in an effort to eliminate or control 10 neglected tropical diseases by 2020

Since 2001, the company has contributed US$5 million per year in financial support and drug donations to the WHO for the treatment of sleeping sickness, Chagas, leishmaniasis, Buruli ulcer and yaws.

Thanks to this support, the WHO, working with the national disease control programs, is able to ensure that all patients with sleeping sickness, no matter how disadvantaged they are or how remote their dwelling place, are able to receive complex parenteral treatment at no cost. This is a major achievement considering the logistics challenge it represents.

IV. SLEEPING SICKNESS

Sleeping sickness or Human African Trypanosomiasis (HAT) is a parasitic disease transmitted by the bite of an infected tse-tse fly. It affects mostly poor populations living in remote rural areas of sub-Saharan Africa. Left untreated, sleeping sickness is usually fatal.

1. Committed to providing treatments for sleeping sickness as long as needed

Five medicines are available to treat sleeping sickness. Sanofi manufactures three of them (pentamidine, eflornithine and melarsoprol) and provides them to the WHO at no cost, within the remit of their partnership.

The company is committed to providing drugs for the treatment of sleeping sickness for as long as necessary. In addition, Sanofi is collaborating with the Drugs for Neglected Diseases initiative (DND*i*) to develop a promising new oral treatment, fexinidazole. In October 2017, during the 10th European Congress of Tropical Medicine and International Health (ECTMIH) held in Antwerp, Belgium, our partner DND*i* presented the results of a clinical trial showing efficacy and safety of fexinidazole. Between 2012 and 2016, an open-label randomised pivotal Phase II/III clinical trial was conducted to compare the efficacy and safety of the new treatment, fexinidazole, with NECT (nifurtimox-eflornithine combination treatment), the current standard of care, in patients with stage 2 sleeping sickness. 394 patients were recruited across 10 sites in the Democratic Republic of Congo and the Central African Republic. The results, which have been published in The Lancet on November 4th 2017, met the pre-defined non-inferiority criteria in terms of efficacy and safety compared to NECT. Being the first oral treatment, circumventing all potential complications associated with intravenous catheter use, *"Fexinidazole may be a key asset in the elimination of this fatal neglected disease"*, as stated by the investigators in The Lancet publication. Two additional studies confirmed the efficacy of fexinidazole in different stages of the disease, in adults and in children.

2. Resuming the downward trend in the number of new cases

Since 2001, more than 36 million people have been screened for sleeping sickness and over 210,000 patients have received treatment for this disease. Thanks to improved detection and disease management, the annual number of patients being treated fell below 10,000 in 2009 for the first time in 50 years and below 3,000 in 2015 to reach 2,184 cases in 2016. This is the lowest number of new cases recorded since the implementation of a reliable monitoring system 75 years ago.

3. Preparing countries for sleeping sickness elimination

Today, mobile medical teams provide diagnosis and treatment in areas of high endemicity, which are invariably remote. The mobile teams are specially trained and equipped to detect the disease and to manage treatment. Their goal is to help provide screening and diagnosis at the earliest stage possible. If sleeping sickness is not treated it is usually fatal, whereas if treatment is administered during the first stage of illness, the patient's life can be saved.

Patients who are diagnosed with stage one sleeping sickness can be treated by the local healthcare professional at the primary care center. Those who are diagnosed with stage two of the disease are taken to the nearest hospital for treatment, which may be several hours away by car or boat.

As sleeping sickness becomes less widespread, mobile teams can no longer be justified. Consequently, a surveillance system must be set up within the healthcare system to ensure that the rare cases of sleeping sickness that do arise are quickly diagnosed and treated.

The WHO is running training programs in countries where the incidence of sleeping sickness is low, and setting up sentinel sites that offer the necessary skills to diagnose and treat sleeping sickness. Today1445 fixed health facilities in endemic countries can diagnose and treat HAT.

4. The future

In December 2015, Sanofi renewed its collaboration with the WHO for a new term. The company continues to uphold its commitment to provide drugs for the treatment of sleeping sickness, until the disease is eliminated—a commitment that was made public in the London Declaration, in January 2012.

The clinical trial to demonstrate the safety and efficacy of fexinidazole has proved positive, as presented during the 10th European Congress of Tropical Medicine and International Health (ECTMIH) held in Antwerp, Belgium, in October 2017 and published in the Lancet in November 2017. The dossier has been submitted to EMA under art 58[1] for a Scientific Opinion.

V. LEISHMANIASIS

Leishmaniasis is caused by protozoan parasites and transmitted by the bite of infected sand flies. It exists in two forms: a visceral form, affecting notably the liver and spleen; and a cutaneous form, affecting the skin. It is estimated that 700,000 to one million new cases and 20,000 to 30,000 deaths occur annually (WHO).[2]

1. The challenge of a complex disease

Sanofi's commitment to combat leishmaniasis takes several forms:

- Collaboration with the WHO since 2006 to improve epidemiological surveillance and treatment centers for this disease, especially in the Middle East region
- Providing meglumine antimoniate for developing countries at a single, discounted price
- Forming research collaborations to find new treatments that are better adapted to patients' needs
- Supporting physician education programs, particularly in Latin America.

In October 2015, Sanofi and the Institut Pasteur of Tunis signed a partnership agreement to launch a program aiming to educate on cutaneous leishmaniasis in the school environment. This leishmaniasis awareness program distributed 40,000 comic books (available in both French and Arabic) to schoolchildren in seven governorates where leishmaniasis is endemic. The program was launched in May 2016. The knowledge on the disease was evaluated before and after the comic was read by the pupils in 11 schools, showing an improvement, mainly in those with lower knowledge at baseline, concluding that comics are an appropriate tool for disseminating awareness on endemic diseases.

[1] EMA has accepted the application under a special procedure called "Article 58" which allows the EMA to give a scientific opinion, in co-operation with the World Health Organization (WHO), for the evaluation of medicinal products that are intended exclusively for markets outside of the European Union. Fexinidazole was previously granted accelerated assessment by the EMA.

[2] WHO, Fact sheet N°375, updated April. 2017: http://www.who.int/mediacentre/factsheets/fs375/en/

VI. BURULI ULCER

Buruli ulcer is a chronic necrotizing skin disease caused by infection with a mycobacterium, which may lead to extensive destruction of the skin and soft tissues, usually on the arms or legs. The scarring of which can produce severe deformities and mechanical limitations

Moving toward earlier, simplified treatment

This disease has been reported in over 33 countries, primarily in sub-Saharan Africa. Although the vast majority of the 5,000 patients reported to have the disease each year live in West Africa, there are also small outbreaks in Australia. Most African patients are children under the age of 14.

Early diagnosis and treatment with antibiotics can prevent the appearance of large ulcers, which take long periods to heal and may require hospitalization.

Through our partnership with the WHO, we are working to facilitate earlier treatment of the disease and develop antibiotic therapy that is only administered orally, as opposed to the current treatment, which requires one drug to be administered by intra-muscular injection.

VII. CHAGAS DISEASE

Chagas disease, also known as American trypanosomiasis, is a parasitic chronic infection transmitted by the feces of a bug, the triatome or kissing bug. This disease affects 10 million people worldwide, especially in Latin America, but due to mass migration, today patients are found outside of traditional endemic areas. In the chronic phase of the disease, 30% of patients will develop cardiac disorders (arrhythmias and heart failure).

Through our collaboration with the WHO, Sanofi contributes to developing epidemiological surveillance of Chagas disease to the reduction of intradomiciliary vector transmission as well as the implementation of control measures to eliminate Chagas disease transmission through blood transfusions.