TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TITLE PAGE</td>
<td>1</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>2</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>4</td>
</tr>
<tr>
<td>LIST OF FIGURES</td>
<td>4</td>
</tr>
<tr>
<td>ABBREVIATIONS</td>
<td>5</td>
</tr>
<tr>
<td>1 SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION</td>
<td>6</td>
</tr>
<tr>
<td>2 RELEVANT WHO TECHNICAL DEPARTMENT AND FOCAL POINT (IF APPLICABLE)</td>
<td>7</td>
</tr>
<tr>
<td>NAME OF THE FOCAL POINT IN WHO SUBMITTING OR SUPPORTING THE APPLICATION</td>
<td>7</td>
</tr>
<tr>
<td>3 NAME OF ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION</td>
<td>7</td>
</tr>
<tr>
<td>4 INTERNATIONAL NONPROPRIETARY NAME (INN) AND ANATOMICAL THERAPEUTIC</td>
<td>7</td>
</tr>
<tr>
<td>CHEMICAL (ATC) CODE OF MEDICINE</td>
<td>7</td>
</tr>
<tr>
<td>5 DOSE FORM(S) AND STRENGTH(S) PROPOSED FOR INCLUSION, INCLUDING</td>
<td>8</td>
</tr>
<tr>
<td>ADULT AND AGE APPROPRIATE PAEDIATRIC DOSE FORMS/STRENGTHS</td>
<td>8</td>
</tr>
<tr>
<td>6 WHETHER LISTING IS REQUESTED AS AN INDIVIDUAL OR AS REPRESENTATIVE</td>
<td>9</td>
</tr>
<tr>
<td>OF A PHARMACOLOGICAL CLASS</td>
<td>9</td>
</tr>
<tr>
<td>7 TREATMENT DETAILS (REQUIREMENTS FOR DIAGNOSIS, TREATMENT AND</td>
<td>9</td>
</tr>
<tr>
<td>MONITORING)</td>
<td>9</td>
</tr>
<tr>
<td>7.1 THERAPEUTIC INDICATION</td>
<td>9</td>
</tr>
<tr>
<td>7.2 POSOLOGY AND METHOD OF ADMINISTRATION</td>
<td>9</td>
</tr>
<tr>
<td>7.2.1 Special populations</td>
<td>11</td>
</tr>
<tr>
<td>7.3 WHO GUIDELINES</td>
<td>11</td>
</tr>
<tr>
<td>8 INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE</td>
<td>12</td>
</tr>
<tr>
<td>8.1 EPIDEMIOLOGY</td>
<td>12</td>
</tr>
<tr>
<td>8.2 ASSESSMENT OF CURRENT USE</td>
<td>16</td>
</tr>
<tr>
<td>8.3 TARGET POPULATION</td>
<td>19</td>
</tr>
<tr>
<td>9 REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS</td>
<td>19</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1 - Posology of fexinidazole in adults and children ................................................................. 10
Table 2 - Summary of current treatment options for HAT ................................................................. 17
Table 3 - List of studies in the fexinidazole clinical development programme ...................................... 20
Table 4: FEX004 Primary Analysis: Success rate at M18 per randomized treatment group and Non-
inferiority test – mITT population ........................................................................................................ 21
Table 5: FEX005 Primary Analysis: Success rate at M12 ................................................................. 21
Table 6: FEX006 Primary Analysis: Success rate at M12 (ITT population) ........................................... 22
Table 7 – Efficacy outcome at 12 and 18 months after the end of treatment with fexinidazole or NECT
(secondary efficacy population, clinical efficacy studies in HAT) ..................................................... 22
Table 8 - Treatment success at 18 months according to baseline CSF-WBC count ......................... 23
Table 9 - Comparison between 18 and 24 months and between primary and follow-up analysis .......... 24
Table 10 - List of studies in the fexinidazole clinical development programme ..................................... 25
Table 11 - Adverse Reactions by decreasing frequency reported in at least 2 patients treated with
fexinidazole ............................................................................................................................................. 27

LIST OF FIGURES

Figure 1 - fexinidazole structure ......................................................................................................... 8
Figure 2 – Distribution of cases and risk of T. b. gambiense infection in Africa (2010-2014) ............ 15
ABBREVIATIONS

AE: Adverse event
ALP: Alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
ATC: Anatomical Therapeutic Chemical
BBB: Blood Brain Barrier
CD: Chagas disease
CI: Confidence Interval
CNS: Central Nervous System
CSF: Cerebrospinal fluid
DBL: Database lock
DNDi: Drugs for Neglected Diseases initiative
DRC: Democratic Republic of Congo
ECG: Electrocardiogram
EMA: European Medicines Agency
EOH: End of hospitalization
EOT: End of treatment
GCP: Good Clinical Practice
HAT: Human african trypanosomiasis
ICH: International Conference on Harmonization
ITT: Intent to treat population
IV: Intravenous
LFT: Liver function test
mITT: modified Intention to treat population
NECT: combination therapy with eflorentine and nifurtimox
NTD: Neglected Tropical diseases
PD: Pharmacodynamic
PK: Pharmacokinetic
QTc: QT interval corrected
QTcF: QT interval corrected according to Fridericia
SAE: Serious adverse event
SmPC: Summary of Product Characteristics
SOC: System Organ Class
TEADR: Treatment emergent Adverse Drug Reaction
TEAE: Treatment emergent adverse event
ULN: Upper limit of normal
VL: Visceral leishmaniasis
WBC: White Blood Cell
WHO: World health Organization
1 SUMMARY STATEMENT OF THE PROPOSAL FOR INCLUSION

Fexinidazole is a new chemical entity: a 2-substituted 5-nitroimidazole compound belonging to a wider class of nitroimidazole anti-infective agents that includes metronidazole and benznidazole.

The fexinidazole project has been developed in partnership between Drugs for Neglected Disease Initiative (DNDi), a non-profit drug research and development organization and Sanofi. DNDi was responsible for pre-clinical, clinical and pharmaceutical development and Sanofi is responsible for the industrial development, registration, production and distribution of the product.

The indication for use of fexinidazole is the oral treatment of both the first-stage (hemolympathic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense in adults and children ≥ 6 years old and weighing ≥ 20 kg. Fexinidazole should be used in line with official recommendations.

However, lower efficacy of fexinidazole as compared to NECT has been seen in a subgroup of patients. Patients with cerebrospinal fluid white blood count (CSF-WBC) > 100 / µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated.

Fexinidazole was intended to be developed for use in settings where the disease is endemic in which there is weak health system in terms of both, access and capabilities thus making challenging the current intravenous treatment. The objective of the development program was to provide an oral, stage-independent, safe and effective new therapeutic option that would enable patients to be treated closer to home.

HAT has been targeted for elimination in 2020 and interruption of transmission in 2030 by the WHO; in 2015 less than 2800 patients were reported to WHO for T.b. gambiense HAT, and in 2017 there were less than 1500 cases.

According to the indication, the targeted population to be treated with fexinidazole is gambiense HAT adults and children ≥ 6 years old and weighing 20 kg or more, with first-stage (hemolympathic) or second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT)1.

(see section 8.3)

Fexinidazole is expected to address key critical unmet medical needs in terms of:

- Availability of first oral and stage independent gambiense HAT treatment,
- Easier administration: tablets instead of existing parenteral drugs and a therapeutic option that will enable to manage patients in peripheral health facilities, closer to home as today majority of patients must be treated in hospitals because of the administration requirements of current treatments ,

1 Patients with cerebrospinal fluid white blood cells count (CSF-WBC) >100/µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated
And finally, fexinidazole aims to provide an easy to use tool for elimination of HAT as part of the WHO roadmap.

Fexinidazole is intended to be listed in the essential medicines core list (EML).

As fexinidazole is indicated for children of 6 years old and above and weighing more than 20kg, the inscription on the Essential Medicines List for Children (EMLc) is as well requested.

2 RELEVANT WHO TECHNICAL DEPARTMENT AND FOCAL POINT (IF APPLICABLE) - NAME OF THE FOCAL POINT IN WHO SUBMITTING OR SUPPORTING THE APPLICATION.

The application is supported by NTD WHO Department and more specifically by the HAT Control and surveillance programme in Intensified and innovative disease management Unit (IDM) (Jose Ramon Franco Minguell, Gerardo Priotto)

3 NAME OF ORGANIZATION(S) CONSULTED AND/OR SUPPORTING THE APPLICATION

DNDi: Drugs for Neglected Diseases initiative.

The fexinidazole development project is a partnership between the independent, not-for profit Drugs for Neglected Diseases initiative (DNDi) and Sanofi. Under the signed agreement, DNDi is responsible for preclinical, clinical and pharmaceutical development; Sanofi is responsible for the industrialization, production, registration and distribution of the drug.

4 INTERNATIONAL NONPROPRIETARY NAME (INN) AND ANATOMICAL THERAPEUTIC CHEMICAL (ATC) CODE OF MEDICINE

Fexinidazole is a new chemical entity: a 2-substituted 5-nitroimidazole compound (Figure 1) belonging to a wider class of nitroimidazole anti-infective agents that include metronidazole and benznidazole.
International Non-proprietary Name (INN): fexinidazole

The ATC code application has been submitted in January 2018. The classification of fexinidazole in the ATC 5th level P01CA03 is on the agenda for the 2019 March meeting and published temporary on WHO ATC code web page.

5 DOSE FORM(S) AND STRENGTH(S) PROPOSED FOR INCLUSION, INCLUDING ADULT AND AGE APPROPRIATE PAEDIATRIC DOSE FORMS/STRENGTHS

The dosage form of fexinidazole is a 600 mg oral tablet presented as pale yellow, round biconvex tablet with no debossing.

The selected excipients are compliant with the “United States Pharmacopoeia/National Formulary”(USP/NF) and Ph. Eur. The excipients list is: lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate, magnesium stearate.

Fexinidazole is to be administered orally once a day (QD) with food for 10 days during the main meal of the day to provide adequate therapeutic plasma and CSF concentrations.

2 dosing regimen are proposed for the treatment of *T. b. gambiense* HAT:

- **Adult**: 1800 mg (3 tablets) QD for 4 days followed by 1200 mg (2 tablets) QD for 6 days. The adult dose is proposed for use in children ≥6 years old who weigh ≥35 kg.

- **Children ≥6 years old and weighing between 20 and <35 kg**: 1200 mg (2 tablets) QD for 4 days followed by 600 mg (1 tablet) QD for 6 days.

The tablets are packaged in Aluminium/Aluminium foil blisters and into specific wallets according to the dose regimen adult or children ≥6 years old and weighing between 20 and <35 kg.

- For adults: wallet of 24 tablets
- For children: wallet of 14 tablets
6 WHETHER LISTING IS REQUESTED AS AN INDIVIDUAL OR AS REPRESENTATIVE OF A PHARMACOLOGICAL CLASS

The application for listing of fexinidazole in the Essential Medicines lists adult and children is requested as an individual medicine.

7 TREATMENT DETAILS (REQUIREMENTS FOR DIAGNOSIS, TREATMENT AND MONITORING)

7.1 THERAPEUTIC INDICATION

Following the article 58 procedure (EMA assessment in collaboration with WHO and relevant non-EU regulatory authorities of quality, safety and efficacy of a medicine intended for use only outside Europe), a positive opinion was given for the following indication:

**Treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense in adults and children ≥ 6 years old and weighing ≥ 20 kg.**

Fexinidazole should be used in line with official recommendations

Lower efficacy of fexinidazole as compared to nifurtimox-eflornothine combination therapy (NECT) has been seen in a subgroup. Patients with cerebrospinal fluid white blood cells count (CSF-WBC) >100/µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated.

7.2 POSOLOGY AND METHOD OF ADMINISTRATION

Fexinidazole should be taken orally once daily for 10 days with food each day at about the same time of the day.

The tablets should not be broken or crushed.

*Table 1* shows the recommended dosage regimens for children from the age of 6 years and adults according to body weight.
Table 1 - Posology of fexinidazole in adults and children

<table>
<thead>
<tr>
<th>Body weight</th>
<th>Posology (number of 600 mg tablets) to be taken once daily with food</th>
<th>Duration of dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 35 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading dose</td>
<td>1800 mg (3 tablets)</td>
<td>4 days</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>1200 mg (2 tablets)</td>
<td>6 days</td>
</tr>
<tr>
<td>≥ 20 and &lt; 35 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loading dose</td>
<td>1200 mg (2 tablets)</td>
<td>4 days</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td>600 mg (1 tablet)</td>
<td>6 days</td>
</tr>
</tbody>
</table>

If a dose is missed (not taken on the assigned day), normal dosing should resume the following day until the full course (10 days) of treatment has been completed. If a second dose is missed, the trained healthcare staff responsible of the treatment should decide how to continue the treatment based on the time point of occurrence within the scheduled dosing regimen.

In case of vomiting: During the clinical trials, vomiting occurred after fexinidazole administration. If a first event of vomiting occurs after receiving fexinidazole, do not re-dose. Patient should take the next dose the following day using the recommended treatment schedule. Pharmacokinetic data from clinical trials have shown that this should not impact the efficacy of the treatment. If a second event of vomiting occurs after administration of any other dose of fexinidazole, the healthcare staff responsible of the treatment should decide how to continue the treatment based on the timing of the vomiting after administration and the occurrence of the event in the scheduled dosing regimen.

The use of fexinidazole should be supervised by healthcare professionals trained in the management and treatment of patients with HAT. Administration of fexinidazole to all eligible patients should be done under the strict supervision of trained health staff, who needs to confirm that the patient is in fed condition and who directly observes each drug intake.

In patients where it is considered that the risk of poor compliance is low, outpatient administration should be done in hospitals or peripheral health facilities, and in particular situations, at home, but always under the strict supervision of trained health staff who ensures daily compliance of drug intake with food, for the total duration of treatment (10 days).
7.2.1 Special populations

Paediatric population
The safety and efficacy of fexinidazole in children aged less than 6 years and/or with less than 20 kg in body weight have not been established. No data are available.

Elderly population
No dose adjustment is required in patients aged ≥ 65 years.

Renal impairment
No dose adjustment is required for patients with renal impairment.

Hepatic impairment
No data are available in patients with hepatic impairment. Fexinidazole is contraindicated in patients with clinical signs of cirrhosis or jaundice.

In patients where there is risk of poor compliance to the recommended fexinidazole regimen, in children with a body weight lower than 35 kg and in patients with psychiatric disorders (history or acute) (see neuropsychiatric adverse reactions), hospitalized administration of fexinidazole should be done under the strict supervision of trained health staff. The same applies to the exceptional cases where severe patients with CSF-WBC > 100 / μL cannot be treated with any other adequate treatment (e.g. NECT).

As the risk of relapse is higher after fexinidazole treatment as compared to NECT patients should have follow-up monitoring at recurrence of symptoms suggestive of HAT, at 12 months and up to 24 months after treatment completion with fexinidazole. Patients should be made aware of the risk of relapse after therapy and instructed to contact healthcare worker in case of signs of relapse.

7.3 WHO GUIDELINES

Fexinidazole being recently given a positive opinion by EMA (15 November 2018) is not yet included in the WHO guidelines or any other national guidelines. However, sleeping sickness treatment WHO guidelines will be under revision in order to consider integration of fexinidazole as part of the therapeutic options to treat gambiense HAT.
8 INFORMATION SUPPORTING THE PUBLIC HEALTH RELEVANCE

8.1 EPIDEMIOLOGY

Human African trypanosomiasis (HAT), or sleeping sickness, is one of the most neglected tropical diseases. Without diagnosis and treatment, HAT is usually fatal as the parasites multiply in the body, cross the blood–brain barrier (BBB) and invade the central nervous system (CNS) at the late stage of the disease.

Human African trypanosomiasis takes two forms, depending on the parasite involved: Trypanosoma brucei gambiense HAT and Trypanosoma brucei rhodesiense HAT.

*T. b. rhodesiense* causes an acute, rapidly progressive and fatal disease and is present in 3% of HAT cases. *T. b. gambiense* is responsible for 97% of HAT cases (1) and evolves to a fatal outcome between 2 and 3 years after infection (2). According to a 2015 model based on survival analysis in Uganda and South Sudan, the estimated average duration of *T. b. gambiense* HAT is approximately 2 years and 2 months (95% CI 528–1232 days) with a median duration of 1 year and 6 months (95% CI 367–855 days), of which the mean duration of stage 2 was 252 days (95% CI 171–399) with a median duration of 175 days (95% CI 119–277) (3).

At the time of the initiation of the pivotal clinical study (October 2012), 7106 annual cases of *T. b. gambiense* HAT had been reported worldwide. With the increased efforts of control programmes and availability of combination therapy with efloornithine and nifurtimox (NECT) therapy, only 1420 gambiense HAT cases worldwide were reported to the WHO in 2017, the lowest level since the start of the systematic global data collection 75 years ago (4). However, the incidence is suspected to be under-reported due to different elements. The Democratic Republic of Congo (DRC) bears the majority of disease burden (83-84% of the reported cases in 2012, 2015(5) and 2016(4), (Figure 2).

In view of the success in control of the disease, *T. b. gambiense* was included in WHO's "roadmap for elimination and control of neglected tropical diseases". A target date was set for global elimination of HAT as a public health problem (<1 case/10 000 inhabitants in at least 90% of endemic areas) by 2020 with complete interruption of transmission in Africa targeted for 2030 (6).

Control of *T. b. gambiense* HAT has relied mainly on active case-finding surveys carried out by mobile teams in the field, passive case-finding performed in fixed health structures and treatment of detected cases. Control and surveillance data in DRC over a 12-year period (2000 to 2012) shows that a higher proportion of stage 1 HAT cases (64%) are determined through active screening and higher proportion of stage 2 HAT cases (77%) in passive surveillance (7). In 2012, in the DRC alone, of the 5968 new cases of HAT determined that year, 3311 (55.5%) cases were at stage 1 and 2579 (43.2%) cases were stage 2 HAT and 78 (1.3%) were of unknown stage.

No data appears to have been published in peer-reviewed journals specifically relating to age distribution of the disease. The biggest existing comprehensive database of HAT treated cases is the one set up by Médecins Sans Frontières (MSF) and maintained by Epicentre. In this data base,
from 18 programmes in 6 African endemic countries the proportion of the all treated HAT population (31467 patients) that were children aged <15 years was 23.7%, consisting of the following age subgroups: <5 years was 4.2%, ≥5 and <10 years was 6.6% and ≥10 and <15 years old was 12.8%

Transmission of gambiense HAT depends on the site, intensity and frequency of contact between tsetse flies and humans. The risk factors for *T. b. gambiense* transmission vary according to the different environmental settings and the characteristics of the vector in the different biotopes, and the activities carried out by human beings in the biotopes occupied by the tsetse flies (8). In humid forest, the tsetse flies are widely distributed, and human–fly contact is related to activities such as hunting, fetching firewood, timber-related activities, and forest clearing for farming. In the woodland savanna and riverine forest galleries, the fly is found close to rivers and streams. The risk of transmission has been associated with activities that are developed along these water bodies, such as fetching water, washing clothing or food (cassava), the artisanal extraction of palm oil, brewing, gold and diamond mining, and fishing. The risk of transmission increases when tsetse habitats are restricted, for example, during the dry season. In the transitional vegetation between forest and woodland savanna, the islands of vegetation provide a suitable habitat for tsetse, and these locations act as points from which hosts are sighted. These areas are often used for farming, making this activity a risk factor in these areas. In the mangrove areas, tsetse flies find a favourable habitat where a high risk of transmission is associated with fishing and crustacean collection, but the fly is also found in cleared areas used for rice cultivation. Pirogue jetties and fishing encampments are areas where human–fly contact can be intense. Cocoa, coffee, and also mango and banana plantations, where the original forest has been replaced, are also suitable habitats for tsetse flies, and these areas are related to transmission in plantation workers. Gambiense HAT is considered a rural disease, but the disease has also been occasionally diagnosed in urban settings. Nevertheless, HAT cases in urban areas is associated with travels to neighbouring rural areas for cultivating fields, however, transmission could occur in suburban outskirts closer to transitional vegetation areas, where agricultural activities are possible; these areas constitute a suitable tsetse habitat with few alternative animal suitable source of food.

It has been described that certain protective immunity exists against new infections in humans after suffering from the disease. Self-cure and asymptomatic carriage, ie, individuals who maintain a long term seropositivity but in whom parasites are not detectable by the most sensitive field methods, have been reported. These latent infections could contribute as cryptic reservoirs (9). Many different infection outcomes were observed during long-term follow-up (5 to 15 years) of patients parasitologically confirmed in first-stage HAT who refused treatment (10). While in this study the infection progressed to second-stage in most patients, as expected, a subset remained asymptomatic, became aparasitaemic by microscopy and polymerase chain reaction (PCR) and had a decreasing serological response, consistent with resolution of infection. A second subset of patients, although asymptomatic and aparasitaemic, showed continued seroreactivity and might be chronic carriers of infection. Additional data to support a chronic carrier state are the observations that aparasitaemic seropositive individuals are reactive in the highly specific immune trypanolysis test (11), and, although parasites cannot be found by microscopy, PCR gives intermittent positive results (12). Better understanding is needed of the immune response in these individuals to determine whether they play a role in maintaining transmission, so that appropriate strategies for sustainable control and elimination are used (6).
The risk associated with age- and sex-related factors pertains to the activities and behaviours made by the different age and gender groups. In general, *T. b. gambiense* HAT is predominately a disease of adults, mainly affecting young adults, as this is the group that is most involved in productive activities that facilitate contact with the vector. Children are usually less affected than adults, but in some areas (such as mangroves), teens present a higher rate of infection related to fishing and leisure activities in water areas. In areas where at-risk activities include mining, hunting, or fishing, the prevalence is higher in males. In transitional vegetation areas where the risk of infection is associated with agriculture and domestic activities at bodies of water, similar prevalence rates have been found in males and females.

The clustering of cases and some familial aggregation has been described, as the risk of *T. b. gambiense* HAT for a child significantly increased when the mother also had HAT. It has been suggested that familial clustering was a consequence of similar exposure to the vector and shared behavioural risk factors, rather than of genetic susceptibility. Cases of congenital infection with *T. b. gambiense* have been reported within 5 days of birth and in children born to infected mothers who had left the endemic area before delivery. The rate of congenital transmission is not easily identifiable but in a programme of 200 to 400 new HAT patients treated annually, 1 or 2 congenital infections were diagnosed (13).

The risk of *T. b. gambiense* HAT infection in short-term travellers from nonendemic areas is very low, as tourists rarely visit the rural areas where gambiense HAT is endemic. Gambiense HAT cases that are occasionally diagnosed in nonendemic countries are mainly seen in immigrants and expatriate residents living in at risk areas for extended periods. Between 2000 and 2010, 26 cases of gambiense HAT were reported to WHO from non-endemic countries (14).

**Geographical distribution of cases and risk of infection**

The geographical distribution of both gambiense and rhodesiense HAT is uneven (Figure 2). The disease is confined in spatially limited areas called “foci”, which are located in Sub-Saharan Africa, mainly in remote rural areas. In the absence of environmental change, the foci of endemicity tend to remain spatially stable over time, the transmission intensity and geographical coverage waxing and waning. Environmental modifications and human or livestock population movements can, however, result in shifts in geographical location and extent. Disease mapping provides current, evidence-based estimates of populations at risk (15). The number of annually reported cases is based on annual figures reported to WHO by National Sleeping Sickness Control Programmes and non-governmental organisations. The tally is complemented by cases detected in nonendemic countries, concerning essentially travellers and migrants. These are linked to the location where they have most probably been infected. The geographic distribution of *T. b. gambiense* HAT is based on the data contained in the database of the Atlas of HAT (from 2000 to 2014) (1), for a total of 206 570 HAT cases (including 31 188 new cases reported in the latest 5-year period 2010–2014). The risk of *T. b. gambiense* HAT infection is expressed as the ratio of disease intensity (using the Atlas data which provided village-level mapping in 92.9% cases) and population intensity (using the Landscan database).

In the period 2010-2014, a total of 55 million people distributed over 1.08 million km² were estimated to be at risk for gambiense HAT (in the period 2005-2009, a total of 50 million people distributed over 1.22 million km² were estimated to be at risk) (1). The estimated population at
high and very high risk (defined as an annual incidence of at least 1 new case per 1000 people) was 1.2 million in the period 2010-2014 compared to 2.7 million in the period 2005-2009. The estimated population at moderate risk (defined as an annual incidence of 1 case per 1000 to 10 000 people) was 9.2 million in the period 2010-2014 compared to 13.7 million in the period 2005-2009. The estimated population at low and very low risk (defined as an annual incidence of 1 new case per 10 000 to 1 000 000 people and therefore meeting the objective set by WHO for the elimination as a public health problem) was 44.6 million in the period 2010-2014 compared to 33.4 million in the period 2005-2009. The DRC has the most people at risk (38 million in the period 2010-2014) and the largest area at risk (62% of the total area), but South Sudan, Congo and Angola also have sizeable populations at risk (1). In West Africa, the areas of greatest endemicity are classified as at moderate risk and are located in central Côte d’Ivoire and coastal Guinea (Figure 2).

**Figure 2 – Distribution of cases and risk of T. b. gambiense infection in Africa (2010-2014)**
Top figure: red circles (gambiense HAT cases) are plotted so as to overlay green circles (active screening campaigns in which no HAT case was detected). As a result, only the green circles that are at the fringes of gambiense HAT distribution are visible. Source: Franco 2017

8.2 ASSESSMENT OF CURRENT USE

Fexinidazole received on 15 November 2018 a positive scientific opinion from EMA for the oral treatment of both stages of the gambiense HAT disease in adults and children ≥ 6 years old and weighing ≥ 20 kg. Registration in DRC is ongoing but up to now the product has only been used in clinical trials (see section 9 and 10).

Current treatment options for patients with stage 1 and stage 2 HAT are shown in Table 2. Choice of therapy depends on the infecting subspecies of the parasite (ie, *T. b rhodesiense* or *T. b gambiense*) and on the disease stage.
Table 2 - Summary of current treatment options for HAT

<table>
<thead>
<tr>
<th>HAT</th>
<th>Drug (Introduction into market)</th>
<th>Mode of administration/Associated problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 (haemo-lymphatic) treatment</td>
<td>Pentamidine (1940)</td>
<td>7-10 IM (preferred) or IV injections; effective in stage 1 gambiense HAT</td>
</tr>
<tr>
<td></td>
<td>Suramin (1920s)</td>
<td>Test dose then weekly IV injections for 5 weeks; primarily for stage 1 rhodesiense HAT; rarely used for gambiense HAT</td>
</tr>
<tr>
<td>Stage 2 (meningo-encephalitic) treatment</td>
<td>Melarsoprol (1949)</td>
<td>10 (painful) daily IV injections; highly toxic with 5% treatment-related mortality; increasing numbers of treatment failures (up to 30% in some regions), restricted to cases refractory to NECT for stage 2 gambiense HAT; remains the only drug effective in stage 2 rhodesiense HAT.</td>
</tr>
<tr>
<td></td>
<td>Efflornithine monotherapy (1990)</td>
<td>Difficult administration (4 IV infusions/day for 14 days); mainly used as a second line treatment for stage 2 gambiense HAT</td>
</tr>
<tr>
<td></td>
<td>NECT = Nifurtimox-Efflornithine Combination Therapy (2009)</td>
<td>Simplified but not ideal regimen (7 days efflornithine [2 infusions/day] and 10 days oral nifurtimox); First-line treatment for stage 2 gambiense HAT</td>
</tr>
</tbody>
</table>

Source: WHO report, Control and surveillance of HAT, 2013

HAT=Human African trypanosomiasis; IM=intramuscular; IV=intravenous; NECT=nifurtimox-efflornithine combination therapy

Stage 1 HAT due to *T. b. gambiense* is currently treated with pentamidine, the most common dosing regimen being a single daily dose via intramuscular injection for 7 days. It is generally well tolerated, but adverse reactions of hypoglycaemia, injection site pain, diarrhoea, nausea and vomiting occur. The use of pentamidine is limited to stage 1 HAT as it does not reach curative levels in the CSF (16). Suramin, which is mainly used to treat first stage *T. b. rhodesiense*, is also effective against *T. b. gambiense*, but it is not often used because severe reactions occur in persons who are co-infected with *Onchocerca volvulus*.

Since 2009, NECT has become the first-line therapy for stage 2 HAT due to *T. b. gambiense* and has improved the prognosis of treated patients (17), replacing monotherapy with efflornithine (also known as α-difluoromethylornithine). Efflornithine as monotherapy against *T. b. gambiense* is given in 4 intravenous (IV) infusions daily for 14 days. Adverse effects of efflornithine include bone marrow suppression, gastrointestinal symptoms, and seizures. Efflornithine is highly effective, but the difficulty in administering 4 infusions daily in rural African facilities led to the use of efflornithine (dosed less frequently) in combination with nifurtimox (NECT). The efficacy of the combination regimen appears to be at least as high as efflornithine monotherapy. Fever, hypertension, and diarrhoea are less common following NECT therapy compared to efflornithine monotherapy, whereas, NECT more frequently provokes nausea and vomiting which tends to appear at least 1 hour after simultaneous administration of both drugs (18). NECT treatment requires a minimum health infrastructure and personnel to administer 2 slow infusions every day during 7 days, on top of an oral treatment every 8 hours for 10 days, requiring systematic hospitalisation as well as being resource-consuming for skilled health staff in the environment in which HAT patients live (remote, poor areas with little health infrastructure).
Second-line therapy for stage 2 HAT due to *T. b. gambiense* includes melarsoprol, an organoarsenic compound, which is highly toxic and to which resistance has developed (19). Adverse reactions to melarsoprol can be severe and life-threatening. An encephalopathic reaction occurs in 5-10% of patients with a case-fatality rate of approximately 50% when it occurs. Prednisolone is often given to patients who are being treated with melarsoprol to reduce the risk of encephalopathy. Other adverse reactions observed with melarsoprol include skin reactions, gastrointestinal upset, and peripheral neuropathy. Intravenous injections of melarsoprol are painful and can cause phlebitis. The drug has been administered by use of lengthy and complicated dosing schedules, however, an abbreviated 10-day regimen of melarsoprol has been developed.

The limitations associated with current HAT therapy include mandatory hospitalisation and need for skilled and trained health staff to administer IV infusions and/or injections. The medicines and the needed material to administer the treatment is provided by WHO free of charge in kits, according to the agreement signed by WHO and manufacturers (Bayer and Sanofi). Nevertheless, the distribution of treatment to remote health facilities due to heavy components (38 kg per box which includes 4 treatments consisting of drugs, solvents and equipment ([17]), is a costly logistical challenge (20). The repeated infusions needed with current HAT therapy are not only painful but increase the risk of infection for the patient. The complex treatment regimens, together with the drug toxicities, patient settings, make it important to develop new safe and effective drugs with a simpler dose, preferably as an oral tablet, and with efficacy in both stages of the disease. Currently, the standard treatment for late stage HAT due to *T. b. gambiense*, NECT, requires specific training of the health staff, hospitalization for slow infusions and has a non-negligible overall direct and indirect cost. Therefore, it is not recommended for early stage where patients are being treated with pentamidine that is administered via intramuscular injections.

The Target Product Profile of a new treatment has been defined by stakeholders of the HAT Platform and aims at developing a HAT treatment to be used with the same dose and duration for both late stage and early stages. This would allow treatment of patients in health care centres located closer to where they live and are being diagnosed (like primary health care centres) and with a simplified technical approach. It would consist of the same treatment given for the same duration with the same recommendation, regardless of the stage of disease.

To fulfil this unmet need, an oral formulation of fexinidazole (HOE239), a 2-substituted 5-nitroimidazole, has been developed which has in vitro and in vivo activity against both *T. b. gambiense* and *T. b. rhodesiense*. The ultimate objective of the fexinidazole development programme is to provide a short-course oral, stage-independent, safe and effective therapeutic option that will enable to improve the access of treatment of patients in need.
8.3 TARGET POPULATION

In line with its indication, the target population for fexinidazole is adults and children ≥ 6 years old and weighing ≥ 20 kg with first-stage (haemo-lymphatic) or second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei gambiense*.

Patients with cerebrospinal fluid white blood cells count (CSF-WBC) >100/µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated.

9 REVIEW OF BENEFITS: SUMMARY OF EVIDENCE OF COMPARATIVE EFFECTIVENESS

9.1 IDENTIFICATION OF CLINICAL EVIDENCE

Fexinidazole being a new oral treatment for sleeping sickness disease and not yet distributed, the demonstration of efficacy is based on data from 3 clinical efficacy and safety studies using data from 749 patients with HAT (from study sites in DRC and Central African Republic [CAR]) who completed to the primary endpoint (Table 3) out of which 619 were treated with fexinidazole.

- DNDiFEX004: the pivotal, prospective, randomised study compares fexinidazole tablets to the standard of care NECT treatment in HAT adult patients with late stage 2, ie, the most advanced form of the disease with CNS involvement.
- DNDiFEX005: the aim of this study is to evaluate, in first and intermediate stage HAT patients ≥ 15 years old, the efficacy, tolerability and safety of the same fexinidazole regimen used in the pivotal late stage HAT study, and to compare the fexinidazole safety profile with historical safety data of pentamidine (first-line treatment in early stage HAT due to *T. b. gambiense*).
- Study DNDiFEX006: the aim of this study is to evaluate the efficacy, tolerability and safety of an oral regimen of fexinidazole in all stages HAT pediatric patients (≥ 6 years old and ≥ 20 kg)

Study DNDiFEX009 is an ongoing, open-label study assessing effectiveness, safety and compliance with fexinidazole in patients with *T. b. gambiense* HAT at any stage to collect additional information on the efficacy and safety of fexinidazole under clinical conditions close to those in real life and thus also to confirm the feasibility of treating patients that could be for the first time outside the hospital setting. The target population includes patients who were excluded in the earlier studies, such as breastfeeding and pregnant women (after the 2nd trimester).
The studies were conducted in compliance with Good Clinical Practice (GCP), as required by the International Conference on Harmonization (ICH) E6 Guideline for Good Clinical Practice. The studies also meet with the requirements of the Declaration of Helsinki, standard operating procedures for clinical investigations and documentation of the Sponsor, applicable national laws and regulations and the ethical principles of the Directive 2001/20/EC.

### 9.2 SUMMARY OF AVAILABLE DATA

#### 9.2.1 Primary analysis for efficacy results

- **FEX004 study**

In adult patients (aged ≥15 years) with late stage 2 HAT, success rate was 91.2% for fexinidazole and 97.6% for the NECT combination. The primary objective of the study was met. Fexinidazole was considered an acceptable treatment as the difference in response compared to NECT was <13% in favour of NECT at 18 months after the End of Treatment (EOT) (Table 7). In the primary analysis, which included 262 patients in the fexinidazole group and 127 patients in the NECT group, the difference in success rate between groups (-6.4%, 97.06% CI [-11.2%; -1.6%]), remained within the margin of acceptable difference. Robustness of data was confirmed with
consistent analyses demonstrating the same trend, ie, fexinidazole was within the acceptable margin of difference to NECT.

Table 4: FEX004 Primary Analysis: Success rate at M18 per randomized treatment group and Non-inferiority test – mITT population

<table>
<thead>
<tr>
<th>Success at 18 M</th>
<th>Fexinidazole (N=262)</th>
<th>NECT (N=127)</th>
<th>Difference between Proportion and 97.06% CI</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>262</td>
<td>127</td>
<td></td>
<td>0.029 (S)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n (%) – No</td>
<td>23 (8.78)</td>
<td>3 (2.36)</td>
<td>-6.42 [-11.22 ; -1.61]</td>
<td></td>
</tr>
<tr>
<td>n (%) - Yes</td>
<td>239 (91.22)</td>
<td>124 (97.64)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* The P-value presented here is from a Blackwelder test (with a non-inferiority margin of -13%). It should be compared to 0.0294. The confidence intervals of the difference between treatment groups was adjusted for the multiplicity. In this analysis, a p-value equal to or above this is non-significant (NS), p-value below this is significant (S).

- FEX005 study

In 230 adult patients (aged ≥15 years) with stage 1 or early stage 2 HAT, success rate with fexinidazole at 12 months after the EOT (98.7%), was greater than an unacceptable rate of 80% (Table 7). The lower bound of the 95% CI for the success rate was 96.2%.

Table 5: FEX005 Primary Analysis: Success rate at M12

<table>
<thead>
<tr>
<th>Outcome at M12 (First Imputation Method)</th>
<th>N</th>
<th>230</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Success</td>
<td>227 (98.7%)</td>
<td>[96.2%;99.7%]</td>
</tr>
<tr>
<td>Failure</td>
<td>3 (1.3%)</td>
<td>[0.3%;3.8%]</td>
</tr>
</tbody>
</table>

- FEX006 study

In 125 children aged ≥6 years and <15 years, weighing at least 20 kg, with any stage HAT, success rate with fexinidazole at 12 months after the EOT (97.6%) was greater than an unacceptable rate of 80% and compatible with a target rate of 92% (Table 7). The lower bound of the 95% CI for the success rate (93.1%) was not only greater than 80%, the unacceptable rate, but also greater than the targeted 92%.
### Table 6: FEX006 Primary Analysis: Success rate at M12 (ITT population)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%) [95% CI] (binomial law)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>125</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>Success</td>
<td>122 (97.6%) [93.1%;99.5%]</td>
</tr>
<tr>
<td>Failure</td>
<td>3 (2.4%) [0.5%;6.9%]</td>
</tr>
</tbody>
</table>

### Table 7 – Efficacy outcome at 12 and 18 months after the end of treatment with fexinidazole or NECT (primary efficacy population, clinical efficacy studies in HAT)

<table>
<thead>
<tr>
<th>Description</th>
<th>Statistics</th>
<th>NECT (N=127)</th>
<th>Fexinidazole (N=262)</th>
<th>Fexinidazole (N=230)</th>
<th>Fexinidazole (N=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Success at 12 months</td>
<td>N</td>
<td>127</td>
<td>262</td>
<td>230</td>
<td>125</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>n (%) - Yes</td>
<td>125 (98.43)</td>
<td>239 (91.22)</td>
<td>227 (98.7%)</td>
<td>122 (97.6%)</td>
</tr>
<tr>
<td></td>
<td>95% CI (CP) - Yes</td>
<td>[94.4%;99.8%]</td>
<td>[87.1%;94.4%]</td>
<td>[96.2%;99.7%]</td>
<td>[93.1%;99.5%]</td>
</tr>
<tr>
<td>Success at 18 months</td>
<td>N</td>
<td>127</td>
<td>262</td>
<td>161</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Missing</td>
<td>0</td>
<td>0</td>
<td>69</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>n (%) - Yes</td>
<td>124 (97.64)</td>
<td>239 (91.22)</td>
<td>156 (96.9%)</td>
<td>83 (97.6%)</td>
</tr>
<tr>
<td></td>
<td>95% CI (CP) - Yes</td>
<td>[93.3%;99.5%]</td>
<td>[87.1%;94.4%]</td>
<td>[92.9%;99.0%]</td>
<td>[91.8%;99.7%]</td>
</tr>
</tbody>
</table>

CP=Clopper Pearson; NECT=nifurtimox-eflornithine combination therapy
Data source: 5.3.5.1 Study DNDiFEX004 (Table 20 and Table 36) (CIs calculated by statistician), 5.3.5.2 Study DNDiFEX005 (Table 17 and Table 25) and 5.3.5.2 Study DNDiFEX006 (Table 19 and Table 26)

### 9.2.2 Secondary analyses

In all studies, almost all sensitivity analyses confirmed the primary findings (except with the second imputation method in Study DNDiFEX004, which represents the most conservative approach since a failure was imputed in case of missing lumbar puncture at the primary timepoint).
• FEX004 study

In adult patients (aged ≥15 years) with late stage 2 HAT, the cumulative failure rate over time, without imputation and according to visit time point, was statistically significantly higher with fexinidazole than with NECT. The failure-free rate at 18 months was estimated at 93.1% for fexinidazole and 98.4% for NECT (based on proven failure, ie, death, rescue medication, presence of trypanosome in any body fluid or CSF WBC >20 cells/μL not followed by a CSF WBC count ≤20 cells/μL). A difference of 5.3% was confirmed between the 2 treatments. This represented a smaller treatment difference than with the primary analysis (6.4% difference between treatments).

In the fexinidazole group, failures up to the 18-month primary endpoint included disease relapse in 15 patients, death in 6 patients, lost to follow-up in 1 patient, and consent withdrawal in 1 patient. In the NECT group, failures up to the 18-month primary endpoint included death in 2 patients and 1 patient with no lumbar puncture at 18 and 24 months. In the fexinidazole group, 16/23 failures (69.6%) occurred within 12 months after the EOT compared to in the NECT group where 2/3 failures (66.7%) occurred within 12 months after the EOT.

The primary efficacy objective of FEX004 study was to demonstrate a non-inferior success rate of fexinidazole to NECT at 18 months after the end of treatment (EOT), with the margin of acceptable difference at 13%. Month 18 success rates were 91.2% for fexinidazole vs. 97.6% for NECT (difference fexinidazole-NECT -6.42%, 97.06% CI [-11.22; -1.61]). (see Section 9.2.1). However, in the subpopulation of patients with cerebrospinal fluid white blood cell count (CSF-WBC) > 100 /µL the efficacy was 86.9% in the fexinidazole arm versus 98.7% in the NECT arm, and therefore the risk of failure was higher in this subgroup with fexinidazole (See table 3).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>WBC count</th>
<th>N</th>
<th>Treatment failure n (%)</th>
<th>Treatment success n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>fexinidazole</td>
<td>≤100</td>
<td>102</td>
<td>2 (2.0)</td>
<td>100 (98.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
<td>160</td>
<td>21 (13.1)</td>
<td>139 (86.9)</td>
</tr>
<tr>
<td>NECT</td>
<td>≤100</td>
<td>49</td>
<td>2 (4.1)</td>
<td>47 (95.9)</td>
</tr>
<tr>
<td></td>
<td>&gt;100</td>
<td>78</td>
<td>1 (1.3)</td>
<td>77 (98.7)</td>
</tr>
</tbody>
</table>

Abbreviations: WBC: White blood cell; CSF: Cerebrospinal fluid; m ITT : modified intention to treat; NECT: nifurtimox-eflornithine combination therapy
FEX005 and FEX006 studies

The failure rate was low in Studies DNDiFEX005 and DNDiFEX006. In adult patients (aged \( \geq 15 \) years) with stage 1 or early stage 2 HAT (Study DNDiFEX005), 1.3% patients were considered failures at 12 months using the primary imputation method. All failures at 12 months were due to death: 1 patient was already a failure at 6 months due to death and 2 patients who died before 12 months and had no lumbar puncture at 6 months were also considered failures at 6 months. In children aged \( \geq 6 \) years and <15 years (Study DNDiFEX006), 2.4% patients were considered failures at 12 months using the primary imputation method. Failure was due to death between 3 and 6 months after the EOT, and due to CSF WBC count >20 cells/μL at 12 months; this latter patient was considered a success (<20 cells/μL) at the 6-month and 18-month time points.

9.2.3 Follow-up analysis

FEX004

The primary efficacy endpoint at 18 months was met, showing that the difference between fexinidazole and NECT is within an acceptable margin.

The follow-up analysis of the success rate at 24 months on the complete population (n=389) yielded similar findings to those with partial data for 24 months at the primary analysis timepoint (n=345) with only 2 new failures (1 in each group); See Table 9.

Table 9 - Comparison between 18 and 24 months and between primary and follow-up analysis

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Fexinidazole</th>
<th>NECT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time point</td>
<td>Primary</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>18 months</td>
<td>24 months</td>
</tr>
<tr>
<td>N</td>
<td>262</td>
<td>231</td>
</tr>
<tr>
<td>Successes</td>
<td>239 (91.2%)</td>
<td>205 (88.7%)</td>
</tr>
<tr>
<td>Failures</td>
<td>23 (8.8%)</td>
<td>26 (11.3%)</td>
</tr>
</tbody>
</table>

FEX005

No difference was seen in efficacy at 12 months according to the stage of the disease (stage 1 or early stage 2).

The additional 18-month data did not change the analyses of the primary efficacy endpoint since the number of failures at 12 months was confirmed.

The success rate at 18 months improved slightly between the initial and follow-up analysis due to the inclusion of the additional 69 patients in the follow-up analysis (all successes): 97.8% (95% CI [95.0; 99.3]) versus 96.9% (95% CI [92.9; 99.0]) in the initial analysis.
• FEX006

The additional 18-month data did not change the analyses of the primary efficacy endpoint since the number of failures at 12 months was confirmed. The success rate at 18 months improved slightly between the initial and follow-up analysis due to the inclusion of the additional 40 patients in the follow-up analysis (all successes): 98.4% (95% CI [94.3; 99.8]), versus 97.6% (95% CI [91.8%; 99.7%]) in the initial 12 month analysis.

10 REVIEW OF HARMS AND TOXICITY: SUMMARY OF EVIDENCE OF SAFETY

10.1 ESTIMATE OF TOTAL PATIENT EXPOSURE TO DATE

Up to now, across all studies in the fexinidazole clinical programme, a total of 932 patients or subjects have been exposed to fexinidazole across 10 studies: 619 patients with HAT in the 3 clinical studies completed to the primary endpoint, 107 patients with HAT in 1 ongoing study, 152 healthy subjects in the 4 clinical pharmacology studies, 14 patients in 1 study with visceral Leishmaniasis (VL) and 40 patients in 1 study with Chagas disease (CD) (Table 10).

Table 10 - List of studies in the fexinidazole clinical development programme

<table>
<thead>
<tr>
<th>Study Category/Identifier</th>
<th>Summary of key study information</th>
<th>Planned study duration</th>
<th>Number of patients/subjects evaluated for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with human African trypanosomiasis (included in pooled analysis completed to the primary endpoint)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNDIFEX004 HAT due to <em>T. b. gambiense</em> in the meningo-encephalitic stage (late stage 2)</td>
<td>Efficacy and safety of fexinidazole compared to niturrimox-eflornithine combination therapy (NECT) in patients with late stage human African trypanosomiasis (HAT) due to <em>T. b. gambiense</em>: pivotal, non-inferiority, multicentre, randomised, open-label study</td>
<td>Patient participation for approximately 25 months</td>
<td>394 (264 fexinidazole; 130 NECT)</td>
</tr>
<tr>
<td>DNDIFEX005 HAT due to <em>T. b. gambiense</em> (stage 1 or early stage 2)</td>
<td>Efficacy and safety of fexinidazole in patients with stage 1 or early stage-2 human African trypanosomiasis (HAT) due to <em>T. b. gambiense</em>: a prospective, multicentre, open-label and single arm cohort study, plug-in to the pivotal study</td>
<td>Patient participation for approximately 19 months</td>
<td>230</td>
</tr>
<tr>
<td>DNDIFEX006 HAT due to <em>T. b. gambiense</em> (any stage)</td>
<td>Efficacy and safety of fexinidazole in children ≥6 years and &lt;15 years old and over 20 kg body weight with human African trypanosomiasis (HAT) due to <em>T. b. gambiense</em>: a prospective, multicentre, open study, plug-in study</td>
<td>Patient participation for approximately 19 months</td>
<td>125</td>
</tr>
</tbody>
</table>

Other patient populations (complete)

<p>| DNDIFEX/IVL001 | Phase 2 proof of concept trial to determine the efficacy of | 10 days | 14 |</p>
<table>
<thead>
<tr>
<th>Study Category/Identifier</th>
<th>Summary of key study information</th>
<th>Planned study duration</th>
<th>Number of patients/subjects evaluated for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral Leishmaniasis</td>
<td>fexinidazole in visceral leishmaniasis patients in Sudan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNDICHFEXI001</td>
<td>Phase 2 multicentre study, testing different dosages in adult patients with chronic indeterminate Chagas disease</td>
<td>2 to 8 weeks</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(40 fexinidazole; 7 placebo)</td>
</tr>
</tbody>
</table>

**Clinical pharmacology studies (PK studies in healthy volunteers; complete)**

<table>
<thead>
<tr>
<th>Study Category/Identifier</th>
<th>Summary of key study information</th>
<th>Planned study duration</th>
<th>Number of patients/subjects evaluated for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNDIFEX001</td>
<td>Randomised, double-blind, placebo-controlled study of the tolerability, and pharmacokinetics of fexinidazole after single and repeated oral ascending doses, completed by a comparative bioavailability study of an oral suspension versus a tablet and an exploratory assessment of food effect, in healthy male volunteers</td>
<td>Single ascending dose 72</td>
<td></td>
</tr>
<tr>
<td>Part I</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNDIFEX001</td>
<td></td>
<td>3 way cross-over 13</td>
<td></td>
</tr>
<tr>
<td>Part II</td>
<td></td>
<td>3 single doses (14 day wash out) 112</td>
<td></td>
</tr>
<tr>
<td>DNDIFEX001</td>
<td></td>
<td>Multiple ascending doses 14 days 27</td>
<td></td>
</tr>
<tr>
<td>Part III</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNDIFEX002</td>
<td>Randomised, open study to assess the impact of 2 different types of food on the relative bioavailability of fexinidazole tablets after single oral dose in healthy male volunteers</td>
<td>3 single doses 12</td>
<td></td>
</tr>
<tr>
<td>DNDIFEX003</td>
<td>Double-blind, placebo controlled, randomised multiple ascending dose study in fed conditions for 10 days dosing regimen with a loading dose to evaluate the safety, the tolerability and the PKs of oral fexinidazole in 36 healthy male sub-Saharan volunteers</td>
<td>10 days 30</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(22 fexinidazole; 8 placebo)</td>
</tr>
<tr>
<td>DNDIHFEXFEX008</td>
<td>A bioequivalence study of the reference clinical fexinidazole tablet versus the proposed market formulation (600 mg tablet) in healthy male volunteers of African sub-Saharan origin: an open-label, randomised, 2-treatment, single dose, replicate design under fed condition</td>
<td>4 single doses 30</td>
<td></td>
</tr>
</tbody>
</table>

**Studies ongoing at safety cut-off 15 August 2017 (no Clinical Study Reports yet available)**

<table>
<thead>
<tr>
<th>Study Category/Identifier</th>
<th>Summary of key study information</th>
<th>Planned study duration</th>
<th>Number of patients/subjects evaluated for safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNDIFEX09HAT (Phase IIIb)</td>
<td>An open-label study assessing effectiveness, safety and compliance with fexinidazole in patients with human African trypanosomiasis due to T.b. gambiense at any stage</td>
<td>Patient participation for approximately 19 months 107 patients treated by Nov. 2018</td>
<td></td>
</tr>
<tr>
<td>HAT</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**10.2 DESCRIPTION OF THE ADVERSE EFFECTS/REACTIONS AND ESTIMATES OF THEIR FREQUENCY**

The most frequently reported adverse reactions (considered at least possibly related to treatment) in the pooled fexinidazole group (619 patients) were vomiting (38%), nausea (33%), asthenia
(20%), decreased appetite (17%), headache (16%), insomnia (15%), tremor (14%), and dizziness (14%).

Tabulated list of adverse reactions

Adverse reactions are presented by system organ class. Frequency categories are defined by using the MedDRA frequency convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000)

Table 11 - Adverse Reactions by decreasing frequency reported in at least 2 patients treated with fexinidazole

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very Common</th>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anaemia, neutropenia</td>
<td>Hypocalcaemia, hyperkalaemia, hyponatraemia, hypoalbuminaemia</td>
<td>Hypoglycaemia</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>Hallucination, agitation, logorrhea, abnormal behaviour, anxiety, psychotic disorder</td>
<td>Depression, nightmare, personality change, acute psychosis, delirium, euphoric mood, mental disorder</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Insomnia</td>
<td>Extrapyramidal disorder, paraesthesia</td>
<td>Convulsion, dysgeusia, cerebellar syndrome, dyskinesia, grand mal convulsion, motor dysfunction, psychomotor hyperactivity</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache, tremor, dizziness</td>
<td>Eye pain, photophobia</td>
<td>Eye pruritus, eyelid oedema</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Palpitations, QT interval prolongation</td>
<td>Hot flush, hypertension</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Cough</td>
<td></td>
<td>Dyspnoea, hiccups, oropharyngeal pain</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Vomiting, nausea, dyspepsia</td>
<td>Abdominal pain upper, salivary hypersecretion, abdominal pain, gastritis, constipation, dry mouth</td>
<td>Abdominal distension</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td>eructation, gastrointestinal sounds abnormal</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Hyperhidrosis</td>
<td>Pruritus, pruritus generalised</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Back pain, neck pain</td>
<td>Myalgia, arthralgia, muscle spasms, musculoskeletal pain, pain in jaw, sensation of heaviness</td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td>Nocturia, pollakiuria, urinary incontinence</td>
</tr>
</tbody>
</table>
10.3 SUMMARY OF AVAILABLE DATA

The safety of oral fexinidazole, administered once daily for 10 days for the treatment of *T. b. gambiense*, was assessed in HAT patients in the following 3 studies:

- Study DNDiFEX004, which compared the safety of fexinidazole to NECT treatment in late stage 2 adult HAT patients;
- Study DNDiFEX005, which assessed the safety of fexinidazole in stage 1 and early stage 2 HAT adult patients;
- Study DNDiFEX006, which assessed the safety of fexinidazole in children aged 6 years or older with any stage HAT.

These studies included a total of 619 HAT patients treated with fexinidazole; in addition to the individual study analyses, data from these 3 studies were pooled for the safety analyses. Pertinent SAE data from the ongoing study in HAT (DNDiFEX009) are also considered. The safety data from 2 studies were also considered in this document: 1 study in VL patients (similar dose regimen to HAT patients) and 1 study in CD patients (similar daily dose levels as for HAT treatment but longer duration of treatment of up to 8 weeks at the highest dose).

The pooled analysis in HAT patients did not include data from DNDiFEX009 as the study was ongoing when the pooled analysis was performed. The other patient populations (VL and CD) were not included in the pooled analysis as the indications and/or regional populations were considered too variable to pool with the data from patients with HAT, in addition to the small patient populations in the VL and CD studies which would not have increased the precision in signal detection. Furthermore, the dose schedules, duration and asymptomatic patients in CD differed. These studies were nevertheless analysed separately; Study DNDiCHFEXI001 was of particular interest following premature study interruption due to safety concerns. In this safety overview, areas of interest in terms of safety from the other patient population studies are discussed with the HAT patient data where pertinent.

10.3.1 Adverse events in clinical trials

An overview of AE data from the pooled analyses in HAT patients is presented with pertinent data from other disease populations where it contributes to the discussion of safety in HAT patients. An overview of the safety in VL and CD patients is also presented.
10.3.1.1 In HAT patients

Pooled analyses of data from Studies DNDiFEX004, DNDiFEX005 and DNDiFEX006 revealed findings consistent with observations from the individual study analyses, with regard to the incidence of Treatment Emergent Adverse Events (TEAEs), TEAEs that occurred between baseline and End Of Hospitalization (EOH), TEAEs that occurred after EOH, and TEAEs that were considered by the Investigator as possibly related to treatment. A total of 577 of 619 (93%) patients experienced TEAEs. One paediatric patient experienced a TEAE of vomiting that led to a temporary discontinuation of study treatment and 2 adult patients in Study DNDiFEX004 experienced fatal TEAEs during the treatment period that were considered unrelated to study treatment by the Investigator. There were no other TEAEs that led to interruption of fexinidazole treatment.

Overall, 506 of 619 (82%) patients reported a total of 2026 possibly related TEAEs between initiation of treatment and End Of Treatment (EOT), with most being mild or moderate. In study DNDiFEX004 in patients with late stage 2 disease, the overall incidence of TEAEs was comparable between the fexinidazole and NECT groups (93.6% with fexinidazole versus 92.3% with NECT, the current standard of care).

The most commonly reported TEAEs across all fexinidazole-treated patients (≥10% of patients) were vomiting (42%), headache (37%), nausea (35%), asthenia (27%), insomnia (23%), tremor (22%), decreased appetite (20%), dizziness (19%), dyspepsia (14%) and feeling hot (10%). Comparing overall TEAEs between fexinidazole and NECT in late stage 2 patients, there were notable differences between the 2 treatment groups; including higher rates in the NECT arm of pyrexia, chills, hyperkalaemia, convulsions and procedural pain; and higher rates in the fexinidazole arm of insomnia, tremor, headache, asthenia, nausea, dizziness, hypocalcaemia, feeling hot, hypoalbuminaemia, abdominal pain upper, chest pain and dyspepsia. Vomiting was reported in a similar percentage of patients. All other TEAEs occurred with similar frequency with NECT and fexinidazole in late stage 2 HAT patients, suggesting that the AEs were related to the underlying disease or that both treatments were associated with increased risk of the events to similar extents.

At the AE level there was a difference between the 2 fexinidazole age cohorts, with paediatric patients <15 years (Study DNDiFEX006) suffering a higher incidence of vomiting (68.8%) compared to adults (DNDiFEX005; 42.2% and DNDiFEX004; 28.4%).

Although there were no differences in the overall incidence of TEAEs in patients with stage 1 HAT (92%) compared to stage 2 HAT (94%), the overall incidence of TEAEs in the system organ classes (SOCs) of metabolism and nutritional disorders (43% versus 18%) and psychiatric disorders (37% versus 24%) was higher in patients with stage 2 HAT compared to stage 1 HAT. This profile is considered to reflect greater HAT symptomatology in patients with stage 2 disease than those with stage 1 disease. However, fexinidazole was well tolerated by the majority of patients independently of disease stage.

Adverse events of interest

Adverse events of special interest were selected for evaluation based on established class effects for nitroimidazoles or safety signals detected in pre-clinical and early clinical studies.
Risk of QT prolongation

In Study DNDiFEX004, more patients in the fexinidazole group had abnormal QTc values during the study when compared to the NECT group. Regarding QTcF, 19 (7.2%) patients in the fexinidazole group had a QTcF value of >450 ms versus none in the NECT group. Similarly, 72 (27.3%) patients in the fexinidazole group had a change from baseline in QTcF between 30 and 60 ms compared to 9 (6.9%) NECT patients. Three patients in the fexinidazole group had a recorded change from baseline in QTcF >60 ms and 3 patients had values for this variable exceeding 480 ms of whom 2 had a value exceeding 500 ms, 9 and 11 days after the EOT.

In Study DNDiFEX006, 3 patients (all in HAT stage 2 and receiving 1200/600 mg fexinidazole) had a recorded change from baseline in QTcF >60 ms but none had values for this variable exceeding 500 ms.

The QTc values in the VL patients in study DNDiFEXIVL001 mirrored changes seen in the HAT studies. QT changes (mean +22ms) were seen commonly to the same extent at each post-dosing timepoint, with only 1 patient exceeding a QTcF prolongation of 60 ms. No QTcF values >480 ms were measured.

Based on studies in healthy volunteers and HAT patients, a Concentration-Response model was built that appears, for M2 more consistent than those built for fexinidazole and its 1st metabolite M1, especially because it addressed the cumulative effect on ∆QTcF after multiple dosing, which was consistent with its 2nd metabolite M2 accumulation, and that dissipation of effects on ∆QTcF were consistent with decreasing M2 concentrations after last administration.

Despite different E_max estimates between the adult and paediatric patient populations, the results showed that the effect on ∆QTcF converged towards the same asymptotic E_max (plateau) estimated between 27 and 30 ms. As the highest exposures in M2 with the regimens used in these studies were below the M2 levels necessary to reach the plateau, the predicted ∆QTcF of 14.9 to 18.0 ms remained below these predicted theoretical maximum values.

The other relevant ECG finding observed in the clinical studies thus far performed with fexinidazole is the chronotropic effect. Both in healthy volunteers and in patients, administration of fexinidazole resulted in an increase in heart rate of about 10 bpm related to the TEAE of palpitations.

QT monitoring was performed in healthy subjects in Phase I studies. Based on these results, QT was closely monitored in HAT patients (Studies DNDiFEX004 and DNDi DNDiFEX006). QT prolongation with imidazole derivatives metronidazole (21)(22)(23) and delamanid (24)(25)(26) is documented in the literature. Data from the clinical studies suggest that fexinidazole treatment can be associated with this class effect. However, it appears not to exhibit a higher risk profile compared to other nitroimidazoles. QTcF does not approach or exceed values associated with adverse clinical sequelae. Additionally, the data do not indicate there to be a cumulative effect with the concomitant medications used in the HAT clinical trials. No consistent effects of treatment with fexinidazole on the PR interval and QRS duration were observed in healthy volunteers and patients. In addition, with fexinidazole, there were no TEAEs suggesting a life-threatening ventricular arrhythmia reported during the development programme.

Based on this data, the SmPC of the product stated that:
QT interval prolongation (section 4.4 of the SmPC)

In the pivotal clinical study, cases of QTcF interval increase were reported in patients treated with fexinidazole, with an average increase of 15.4 ms. Fexinidazole is contraindicated in at risk patients with known congenital prolongation of QT interval, uncorrected electrolyte abnormalities (e.g. hypokalaemia or hypomagnesaemia), history of symptomatic cardiac arrhythmia, clinically relevant bradycardia, severe congestive cardiac failure, or family history of sudden death, as this may lead to an increased risk for ventricular arrhythmias.

In order to compensate for potential hypokalaemia in a patient with malnutrition or diarrhoea/vomiting, the patient should receive potassium-rich foods or potassium chloride tablets.

Co-administration of fexinidazole is contraindicated with the following QT-interval prolonging medicinal products:

- anti-arrhythmics class IA and III
- tricyclic antidepressive agents
- certain antimicrobial agents
- certain antihistaminics
- others

In addition, co-administration of fexinidazole is contraindicated with medicinal products that can reduce potassium levels or are associated with clinically significant bradycardia.

If patients are, or need to be treated with medicinal products known to prolong QT interval or to induce bradycardia or hypokalaemia, either do not initiate fexinidazole until such medicinal products are eliminated from the body (allow a washout period of 5 half-lives), or do not start such medicinal products until fexinidazole and its active metabolites are eliminated from the body (allow a washout period of 7 days).

Hepatotoxicity disorders

Generally, any increases seen in Liver Function Test (LFTs) between baseline and EOT in the HAT studies were mild and transient. In the pooled analysis, changes in ALP, ALT, AST and bilirubin over time did not cause mean levels to stray outside of the normal reference ranges. In Study DNDiFEX004 a similar proportion of patients in the fexinidazole and NECT arms had increases in LFTs above the upper limit of normal (ULN). There was 1 case of transient ALT increased between 3x and 5xULN in Study DNDiFEX004 in the fexinidazole group versus none in the NECT group.

In the Phase I Study DNDiFEX001, there was 1 case of transient ALT increase up to 30xULN in a patient who received a high dose of 3600 mg/day for 14 days with mild clinical symptoms.

In CD patients, a statistically significant correlation between cumulative dose and AST/ALT transaminase peak was observed. The associations of persistent (>3 months) liver abnormalities and acute transaminase increase (3xULN) with cumulative dose of fexinidazole were also statistically significant.
A PK-PD model based on the data from CD patients was used to assess the likelihood of liver toxicity occurring in the recommended regimen for HAT. The analysis showed that the liver toxicity observed in CD Study DNDiCHFEX001 only predicts mild increases in ALT/AST levels for the HAT regimen (<3xULN). The actual increases observed in HAT studies DNDiFEX004, DNDiFEX005 and DNDiFEX006 (subgroups by body weight were imbalanced) were less than predicted from the CD study.

Based on the available data in the HAT programme, the use of fexinidazole is contraindicated in patients with clinical signs of cirrhosis or jaundice.

Haematological and neutropenia-related disorders

Twelve of 619 patients (2%) exposed to fexinidazole in the pooled population of the 3 HAT studies experienced TEAEs of neutropenia, with no apparent difference in frequency based on HAT stage. Of these, 4 experienced TEAEs of transient neutropenia that were considered by the Investigator as possibly related to fexinidazole (1 patient in Study DNDiFEX005 and 3 patients in Study DNDiFEX006), 1 of which was also severe in intensity but was not considered an SAE. There were no differences in the incidence of TEAEs related to haematological events and neutropenia based on the patients’ stage of HAT.

In the CD study DNDiFEXICH001, there were 8 cases of treatment-related, asymptomatic and transient neutropenia considered SAEs, amongst neutropenia reports in 13 patients. All cases remained asymptomatic and presented no infectious complications. The onset of neutropenia seems delayed and nadir occurs around 9 weeks after the start of treatment. Findings were reversible with no specific treatment, with return to grade 2 in most patients after approximately 1 week.

A PK-PD model was built based on the relationship between drug exposure and neutropenia in the CD study, and was used to assess the likelihood of severe neutropenia occurring in recommended regimen for HAT. Based on the available data, the Applicant concludes that there is minimal risk of severe neutropenia in HAT patients at the doses (<25.2 g) and durations (<14 days) used in the HAT clinical studies.

However, as a precaution, fexinidazole should be used with caution in patients with evidence, or history, of blood dyscrasia. Patients should return to the clinic if they develop a fever or clinical signs of suspected infection within 3 months of the end of treatment.

Neuropsychiatric disorders

The majority of patients, regardless of HAT stage, had normal results for all neurological/psychiatric examinations performed both at inclusion and EOT. Abnormalities present at inclusion included impaired balance (6.6%) and Glasgow scores of 13 (6.4%) and 14 (18.1%). When psychiatric symptoms were present at baseline the incidence tended to be higher in patients with stage 2 disease.

Any changes observed between inclusion and EOT were generally improvements.

During the HAT studies, TEAEs from the psychiatric disorders System Organ Class (SOC) in the ITT population were reported in 32% of patients treated with fexinidazole and included mainly
insomnia AEs (23%), the majority of which were considered related to treatment. The next most frequently occurring psychiatric AEs occurred far less frequently, eg, psychotic disorder (2%), hallucination (3%), agitation (3%) and logorrhoea (2%). Depression only occurred in 4 fexinidazole HAT patients, all in the pivotal study. There was no significant difference in incidence of psychiatric disorders between the different disease stages and across age categories, apart from a clear difference in insomnia between those 15 years of age and above (DNDiFEX004 28%; DNDiFEX005 25%) and those below 15 years of age (10%). In comparison to NECT, in adults and older adolescents with late stage 2 disease, fexinidazole was associated with a greater incidence of psychiatric disorders (18% versus 39% respectively).

In the CD study, insomnia was also seen very commonly in fexinidazole patients (45.0%), as was depression (37.5%). One case of depression was considered serious and ended in suicide.

Of the psychiatric events occurring in fexinidazole administered HAT patients, 5 were considered by investigators and/or the Sponsor to be serious; 2 cases of personality change and 1 case each of acute psychosis, psychotic disorder and suicidal ideation. 4 of these events occurred in Study DNDiFEX004. No SAE in the psychotic SOC occurred in patients treated with NECT. The 5 psychiatric SAEs were considered resolved by DBL.

Adverse events in the nervous system disorders SOC also occurred frequently in fexinidazole-treated patients in the HAT programme (58%) and were made up mostly of AEs of headache (37%), tremor (22%) and dizziness (19%). However, these medical symptoms were also present at baseline in some patients, with baseline neurological symptoms also generally more common in patients with stage 2 (22.2%) than stage 1 disease (8.9%); which is in keeping with current knowledge of HAT disease stages. However, there was no evidence of a difference in disease stages within the neurological AE results. In DNDiFEX004 there was a tendency for neurological AEs to occur slightly less frequently in the NECT arm than in the fexinidazole arm. One neurological SAE occurred in fexinidazole treated patients - psychomotor hyperactivity; which was considered resolved at the time of database lock (DBL).

These results suggest that psychiatric symptoms, mostly insomnia in adults, occur commonly during treatment with fexinidazole. Most of these AEs were classed as mild or moderate. A small number of psychiatric SAEs occurred during treatment with fexinidazole which were considered possibly related to treatment. There is evidence to suggest that some patients with acute psychiatric symptoms had worsening of symptoms present at baseline. Then, caution should be exercised when using fexinidazole to treat HAT in patients with psychiatric disorders (history or acute) and it is recommended that these patients be hospitalised during the 10-day treatment period.

**Gastrointestinal disorders**

Data from the pooled analysis of Studies DNDiFEX004, DNDiFEX005 and DNDiFEX006 showed that gastrointestinal disorders were the most commonly reported TEAEs. At the event level, the most commonly reported gastrointestinal disorders were vomiting (258/619 [42%] patients), nausea (214/619 [35%] patients) and dyspepsia (87/619 [14%] patients); all other gastrointestinal events were reported in <10% of patients treated with fexinidazole.

The majority of these patients experienced gastrointestinal disorders considered as possibly related to fexinidazole. It is however worth noting that with the exception of 2 patients that experienced severe events of vomiting, all reported gastrointestinal disorders were of mild or
moderate intensity. Although 15/619 (2%) patients experienced gastrointestinal SAEs, none of these events were considered by the Investigator as possibly related to fexinidazole.

In Study DNDiFEX004, following fexinidazole treatment, the incidence of vomiting was <10% on any given day: ranging from 9.1% of patients (on Day 3) to 0.8% on Day 10. Following NECT treatment, the incidence of vomiting seemed to decrease from the first daily administration to the third daily administration of nifurtimox. Treatment had to be re-administered in the 13 (4.9%) patients who vomited within 30 minutes after fexinidazole and 4 (3.1%) patients after nifurtimox administration. No patient permanently discontinued treatment due to intolerable vomiting.

The trend to increased incidence of vomiting during the loading phase was also seen in studies DNDiFEX005 and DNDiFEX006. In DNDiFEX005, over the whole treatment period, 14 patients (6.1%) vomited within 30 minutes after treatment administration, 1 patient (0.4%) vomited between 30 and 60 minutes after treatment administration. Treatment was re-administered in all patients (6.5%) who vomited within the 60 minute period after administration.

In the paediatric Study DNDiFEX006, the incidence of vomiting was higher than seen in the adult studies. There are verbal reports from investigators which suggest that some children may have had problems swallowing the fexinidazole tablets causing them to vomit. During the 10 days of treatment incidence was highest on Day 2 of the loading phase (1200 mg or 1800 mg) (36.0%) and decreased over time during the maintenance phase (600 mg or 1200 mg), ranging from 11.2% (Day 5) to 4.8% (Day 10). Re-administrations were performed in a total of 27/125 patients (21.6%) in the first 2 hours after administration.

In most fexinidazole patients, treatment was re-administered once after vomiting.

The profile of vomiting during treatment with fexinidazole is in keeping with what is known of other agents in the nitroimidazole class, which is associated with gastrointestinal disturbances including nausea, vomiting, loose stools and abdominal pain (27)(28)(29)(30)(31). Vomiting is typically limited in severity and duration with nitroimidazoles, as was seen with fexinidazole. In DNDiFEX004, the incidence of early vomiting was higher in fexinidazole treated patients than in NECT treated patients.

Due to the observed frequency of vomiting seen during fexinidazole administration, particularly in the loading phase of treatment, guidance is provided in the SmPC advising physicians that patients who vomit once during the 10-day treatment course should not re-administer treatment but instead wait and administer the next day's treatment at the usual time. If the patient vomits a second time, the patient should be re-evaluated.

10.3.1.2 Other patient populations

The safety of fexinidazole was also assessed in patients with VL (Study DNDiFEXIVL001) and CD (Study DNDiCHFEXI001) with the following conclusions:

Patients with Visceral Leishmaniasis

Twelve of 14 (86%) patients with VL reported at least 1 TEAE, the majority of which were Grade 1 in severity and considered related to treatment. There were no SAEs, although 2 patients suffered transient grade 4 neutropenia which were not reported as SAEs.
The most common Treatment Emergent Adverse Drug Reactions (TEADRs) were vomiting (64% patients) and nausea (experienced by 43% patients). The only other TEADR occurring in ≥10% subjects was ECG QT prolonged, which did not require therapeutic interventions. (see AE of interest sections above).

**Patients with Chagas Disease**

Recruitment into the study was terminated for safety reasons after observation of delayed grade 4 asymptomatic neutropenia. It was initially planned to recruit 140 patients (ie, 7 groups of 20 patients). Patient recruitment was terminated early, resulting in a total sample size of 47 patients.

All patients with CD experienced at least 1 AE. Twenty-four SAEs were reported for 15 (37.5%) fexinidazole-treated patients; 1 patient on lower dose for 4 weeks died due to 2 SAEs (the patient experienced life-threatening depression, which was considered by the Investigator and Sponsor as related to fexinidazole, and committed suicide).

Of the fexinidazole-treated group, 10 (25.0%) patients experienced AEs that resulted in permanent study treatment discontinuation, in addition to 16 (40.0%) patients who experienced AEs that resulted in temporary interruption of treatment.

The most common TEADRs in fexinidazole-treated patients were headache (31 patients; 77.5%), nausea (26 patients; 65.0%), upper abdominal pain (21 patients; 52.5%), insomnia (18 patients; 45.0%), vomiting (15 patients; 37.5%), and ALT increased (15 patients; 37.5%).

Skin hyperpigmentation was reported in 10 fexinidazole-treated patients (25.0%) and was considered related to study drug. None of the events were classed as serious. No other signs of phototoxicity occurred frequently in CD patients. Hyperpigmentation and signs of phototoxicity did not commonly occur in the HAT or VL studies.

The majority of AEs, except skin hyperpigmentation, occurred rapidly after start of the treatment (within 10 days). In addition, there was a trend for AEs to occur more quickly in the 1800 mg dose group than in the 1200 mg dose group.

The most frequent SAE was neutropenia (8 fexinidazole-treated patients; 20.0%); all related to study medication and resolved without sequelae.

A statistically significant correlation between the cumulative dose of fexinidazole and AST/ALT transaminase peak ($r=0.6$) was observed. The associations of persistent (>3 months) liver abnormalities (odds ratio=0.81, 95% CI=[0.70;0.94]) and acute transaminase increase (3xULN) (odds ratio=0.88, 95% CI=[0.85;0.91]) with cumulative dose of fexinidazole were also statistically significant ($p<0.005$). A post hoc simulation also suggested an association of cumulative fexinidazole dose and neutropenia.

Overall, the safety profile of fexinidazole in patients with VL, based on observed TEAEs was comparable to that recorded for fexinidazole in the treatment of HAT. However, the safety of fexinidazole in patients with CD showed notable differences when compared to patients with HAT, particularly with regard to the incidence of liver abnormalities, but the cumulative fexinidazole dose used in CD was almost 2 times the cumulative dose administered in the HAT studies (14.4 g). There may also have been possible differences in the safety profile due to the different diseases characteristics of the HAT and CD populations. To note, a second study in
patients with CD has received regulatory approval in Spain (DNDiCHFEX012) and aims to evaluate efficacy and safety of lower doses.

10.3.2 Clinical laboratory data

Overall, in HAT patients administered fexinidazole, shifts in laboratory biochemistry parameters were balanced. The mean estimates at each time point and the shifts seen in the pooled fexinidazole cohort revealed some trends in biochemical parameters during the treatment period before EOT. These included:

- shifts in serum albumin towards normal values, likely reflecting an improved clinical condition in patients as a result of treatment and improving nutritional status (overall mean increases were observed in fexinidazole and NECT patients in Study DNDiFEX004), but equally shifts to a worsening of serum albumin were observed
- greater shifts towards a worsening in serum calcium with more individual shifts to low values (hypocalcaemia) in fexinidazole patients in DNDiFEX004 compared to NECT.
- a shift towards normalisation of sodium and potassium values, mainly from grade 1 and 2 abnormalities in individual patients over the 10-day treatment period, although when considering worst values over time, the individual shifts in sodium were balanced whereas there was a trend towards worsening in potassium values. However, in Study DNDiFEX004, shifts to life-threatening hyperkalaemia were more frequent in the NECT group (5 patients) than the fexinidazole group (1 patient).
- increases in blood glucose levels possibly also reflecting an improving clinical picture

Overall, no significant safety signals were raised for biochemical abnormalities. The relatively common occurrence of hypocalcaemia readings in serum biochemistry samples is noted. The contributing factors to this profile are unknown.

10.3.3 Pregnancy and lactation

Maternal exposure to fexinidazole before pregnancy was reported in 10 HAT patients (Study DNDiFEX005) and 7 CD patients (DNDiCHFEXI001); the shortest time between start of pregnancy and last dose was 61 days. In all patients, pregnancies were uncomplicated with normal outcome, except for the following 5 cases: 1 foetal death the day of delivery following foetal distress (conception was estimated to be 112 days after exposure; the mother was a HAT patient with a history of abortion and death of offspring); 1 child suffered a number of non-serious flu-like illnesses as an infant and fully recovered (conception occurred an estimated 74 days after last dose of fexinidazole; the mother was a HAT patient); 2 CD patients who suffered abortion spontaneous (both pregnancies started >300 days after the last treatment exposure); and 1 CD patient suffered threatened labour although pregnancy outcome was normal (the patient's last menstrual period was 5 months after the EOT and the SAE started 6 months into the pregnancy).

There are no data from the use of fexinidazole in pregnant women. In animals, effects of fexinidazole on embryo-fetal development were observed only at doses harmful to the dams. These effects were considered as secondary to maternal toxicity. Plasma concentrations of
fexinidazole and of its metabolites at these dose levels were low as compared to clinical exposures. As a precautionary measure, it is preferable to avoid the use of fexinidazole during the 1st trimester of pregnancy, and the benefit-risk of treatment with fexinidazole should be evaluated during the 2nd and 3rd trimesters.

There are no data from the use of fexinidazole in breast-feeding women. Available pharmacokinetic data in rats have shown that fexinidazole and its two active metabolites are excreted into breast milk. Effects on suckling rat pups were limited to transient development retardation at a sub-clinical exposure level. As a risk to the suckling child cannot be excluded, the decision to use fexinidazole during breast-feeding should take into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

10.3.4 Interactions

Drug-food interactions

In Study DNDiFEX001 Part II, it was concluded that although food increased the relative bioavailability of fexinidazole, the safety and tolerability of 1200 mg fexinidazole was very good, regardless of the formulation and the conditions of administration (ie, fed or fasting). Similarly, in DNDiFEX002, 1200 mg fexinidazole with 2 different food intakes and 1 treatment arm with fasting conditions presented a good safety and tolerability profile. In both studies the food and its metabolites appeared to have no impact on the overall safety and tolerability of fexinidazole.

Fexinidazole should be taken once daily for 10 days with food each day at about the same time of the day.

Drug-drug interactions

Since the pathways involved in the formation, metabolism and elimination of the active M2 metabolite are unknown and as no drug-drug interaction studies have been performed, it is recommended not to administer any other concomitant medications with fexinidazole. However, the following medicinal products have been concomitantly administered in a limited number of patients in the clinical trials without an effect on the pharmacokinetic parameters of fexinidazole and the M1 and M2 metabolites: paracetamol, and the following CYP2D6 inhibitors: chlorpromazine, metoclopramide, artemether-lumefantrine, chloramphenicol, chlorphenamine, cimetidine; this suggests that these medicinal products may be used with caution.

- In addition, due to pharmacodynamic interactions, the following concomitant uses are contraindicated:

Medicinal products that may prolong the QT interval: concomitant use of fexinidazole and the following medicinal products is contraindicated because the risk of an additive effect on QT interval prolongation cannot be excluded.

- anti-arrhythmics class IA (e.g. quinidine, hydroquinidine, disopyramide)
- anti-arrhythmics class III (e.g. amiodarone, sotalol, dofetilide, ibutilide)
- tricyclic antidepressive agents (e.g. imipramine, amitriptyline)
• certain antimicrobials including some antituberculosis agents (saquinavir, atazanavir, erythromycin IV, sparfloxacin, moxifloxacin, ofloxacin, levofloxacin, cloroquine, delamanid, pentamidine, certain antimalarials particularly halofantrine)

• certain antihistaminics (terfenadine, astemizole, mizolastine)

• others (cisapride, vincamine IV, diphenamid, lipid).

Antipsychotics could be used if required, in hospitalised patients under close monitoring.

Medicinal products that may lead to proarrhythmic events: Concomitant use is contraindicated with medicinal products that can reduce potassium levels (loop and thiazide diuretics, laxatives and enemas at high doses, corticosteroids, amphotericin B) or are associated with clinically significant bradycardia (beta-blockers, calcium channel blockers), as it may lead to an increased risk of proarrhythmic events.

If patients are, or need to be treated with drugs known to prolong QT interval or to induce bradycardia or hypokalaemia, either do not initiate fexinidazole until such drugs are eliminated from the body (allow a washout period of 5 half-lives), or do not start such drugs until fexinidazole and its active metabolites are eliminated from the body (allow a washout period of 7 days).

- Due to potential pharmacodynamic interactions, the following concomitant uses are not recommended:

Disulfiram: cases of psychotic reactions have been reported after the concomitant administration of 5-nitroimidazoles (benznidazole and metronidazole) with disulfiram. Because this effect cannot be ruled out for fexinidazole, disulfiram should not be used concomitantly with fexinidazole.

Alcohol: alcohol should not be consumed during treatment of fexinidazole or within 48 hours of the last dose.

Propylene glycol: as 5-nitroimidazoles interfere with the metabolism of propylene glycol, this effect could not be ruled out for fexinidazole. Medicinal products containing propylene glycol should not be used concomitantly with fexinidazole.

Traditional medicines: it is recommended to avoid the use of traditional or herbal medicines during the entire treatment with fexinidazole, as the potential interactions are unknown. In vitro interaction studies have shown that fexinidazole and the M1 metabolite inhibited the activity of CYP2C19 and CYP1A2, leading to potential risk of drug-drug interactions. Specifically, in the absence of fexinidazole drug-drug interaction studies in humans, it is predicted that fexinidazole and/or its M1 metabolite could increase the exposures of drugs mainly metabolised by CYP1A2 (such as caffeine, duloxetine, melatonin, tizanidine, theophylline) or CYP2C19 (such as omeprazole, lansoprazole, mephenytoin, diazepam). Because of the potential drug-drug interaction risk, caution is advised in case fexinidazole is co-administered with drugs which are metabolised by CYP1A2 or CYP2C19. Of note, fexinidazole and its 2 metabolites, M1 and M2, have shown no potential to inhibit CYP3A4, CYP2D6, and CYP2C9.

It was shown in vitro that fexinidazole and both M1 and M2 metabolites could induce CYP2B6 mRNA expression. Therefore, the coadministration of fexinidazole with drugs mainly metabolised
by CYP2B6 (bupropion, efavirenz) could result in a decreased exposure of those drugs and should therefore be avoided.

Drugs known to prolong the QT interval and/or induce bradycardia: caution is advised when fexinidazole is concomitantly used with drugs known to block potassium channels (such as antiarrhythmics, neuroleptics, fluoroquinolones, imidazole and triazole antifungals, pentamidine), prolong the QT interval (such as phenothiazines, tricyclic antidepressants, terfenadine and astemizole, IV erythromycin, antimalarials, and quinolone antibiotics) and/or induce bradycardia (such as β-blockers).

Caution is advised when fexinidazole is concomitantly used with traditional or herbal medicines, as the potential interactions are unknown. It is recommended to avoid the use of traditional or herbal medicines during the entire treatment with fexinidazole.

10.4 SAFETY CONCLUSIONS

Fexinidazole was overall well tolerated in HAT patients. Clinical safety manifestations were mostly mild and moderate in severity and did not result in treatment discontinuation.

Safety findings were consistent with the safety profile of the drug as established from previous studies conducted in healthy volunteers and patients with HAT and VL. Central nervous system/psychiatric events as well as emesis/vomiting were observed under fexinidazole treatment. Asymptomatic reversible neutropenia and elevated liver enzymes that were found at different dose regimens in CD patients were not reported in HAT patients with the treatment regimen used in the HAT studies. Asymptomatic QT prolongation induced by fexinidazole is moderate (predicted prolongation of 14-19 ms in adults and children), below the asymptotic E_{max} increase in QTc estimated for M2 (27-30 ms), and remained in the range of what is known from other imidazole derivatives. No ventricular arrhythmias have been observed.

No deaths related to fexinidazole according to the Investigator occurred during the entire HAT clinical development programme. Note that 1 event of suicide considered related to treatment occurred in a CD patient.

There were no major differences in the safety profile between disease stages.

Study DNDiFEX006 in paediatric patients showed a similar safety profile to that of the adult population except for more frequent “early” vomiting, as established in adults. TEAEs of vomiting were mostly mild to moderate in intensity and did not result in permanent treatment discontinuation.

The safety profile of fexinidazole in the treatment of HAT was generally consistent with other products of a similar class, as documented in the review of published literature.

In addition in the 6 months follow-up of the 3 key studies (FEX004, FEX005 and FEX006), no new safety issues were raised.
11 SUMMARY OF AVAILABLE DATA ON COMPARATIVE COST-EFFECTIVENESS OF THE MEDICINE

Drugs for HAT are provided free of charge to the WHO via a public/private partnership between WHO/Sanofi (pentamidine, melarsoprol and eflornithine) and WHO/Bayer AG (suramin, nifurtimox).

Sanofi signed an Agreement with WHO in 2001 which was renewed in 2006, 2011 and 2016 each time for five additional years. Drugs are donated to WHO, to be used exclusively for the treatment of HAT. Requests for supplies are made to WHO by governments of disease-endemic countries and organization working in association with these governments. Stock control and shipment of the drugs are undertaken by Médecins sans Frontières-Logistique according to agreement signed with WHO. Transport costs to countries are paid by Sanofi through its partnership with WHO.

In the same way as what is currently done for NECT or other HAT drugs, fexinidazole will be distributed free of charge through the World Health Organization (WHO) neglected tropical diseases (NTD) department to National Sleeping Sickness Control Programs (NSSCPs) and from there to the treatment centers. The product will not be available through wide logistic of pharmacies or out of the predefined distribution system. No return on investment is expected.

With NECT, indirect costs including transport to hospital, food and hospitalisation costs are born by the patients. They should be significantly reduced with fexinidazole when patients are not hospitalised and treated close to their home.

12 SUMMARY OF REGULATORY STATUS AND MARKET AVAILABILITY OF THE MEDICINE

This application for fexinidazole was submitted to European Medicines Agency (EMA) through Article 58 of Regulation (EC) No 726/2004. Article 58 is a mechanism whereby the EMA may give a scientific opinion, in co-operation with the WHO, for the evaluation of medicinal products intended to prevent or treat diseases of major public interest and exclusively intended for markets outside the European Community. A positive opinion from EMA was given on 15 November 2018 for the following indication:

“Fexinidazole Winthrop is indicated for the treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense in adults and children ≥ 6 years old and weighing ≥ 20 kg. Fexinidazole should be used in line with official recommendations”
However, lower efficacy of fexinidazole as compared to NECT has been seen in a subgroup of patients. Patients with cerebrospinal fluid white blood count (CSF-WBC) > 100 / µL should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated.

An application for this indication has also been submitted in RDC in August 2018 and the evaluation should start based on the EMA article 58 positive opinion. The dossier is also planned to be submitted in Uganda for registration.

Registrations in RDC and Uganda are scheduled. Further registrations in other endemic African countries are not planned due to the specific registration regulatory picture for Human African Trypanosomiasis products and ways of distribution. Actually, the current HAT drugs are not registered in all endemic countries but are registered in at least one Stringent Regulatory Authority (SRA). The stand-alone distribution system for these drugs is managed by WHO. It allows import and distribution in other endemic countries through a letter of interest ascertain the inclusion of fexinidazole in national HAT treatment policy from National authorities to WHO-NTD. The same distribution system will apply to fexinidazole.

13 AVAILABILITY OF PHARMACOPOEIAL STANDARDS (BRITISH PHARMACOPOEIA, INTERNATIONAL PHARMACOPOEIA, US PHARMACOPOEIA, EUROPEAN PHARMACOPOEIA

None available
14 REFERENCES


15 ANNEX

Annex I: Summary of Product Characteristics – 15 November 2018