15 November 2018
EMA/CHMP/843546/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fexinidazole Winthrop

International non-proprietary name: fexinidazole

Procedure No. EMEA/H/W/002320/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

(c)GMP	(current)Good Manufacturing Practices
3T3 NRU-PT	3T3 neutral red uptake phototoxicity test
ADME	Absorption, Distribution, Metabolism, and Excretion
ADRs	Adverse drug reactions
AE	Adverse events
Ae	Absolute excretion
ALP	Alkaline phosphatase
Alu	Aluminum
API	Active Product Ingredient
AQ	Absorption Quotient
AQL	Acceptable quality limit
AR	assessment report
ASMF	Active Substance Master File
AST	Aspartate aminotransferase
AUC	Area under time-concentration curve
b.i.d.	Two times a day
BBB	Blood-brain barrier
BC	Buffy-coat
BCS	Biopharmaceutics Classification System
BID	Twice a day
BMI	Body mass index
BSA	Bovine Serum Albumin
BUN	Blood urea nitrogen
BW	Bodyweight
CAR	Central African Republic
CD	Chagas disease
CFU	Colony Forming Unit
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval

Clint	Intrinsic clearance
Clr	Clearance
C_{max}	Maximum observed plasma concentration
CMH	Cochran Mantel Haenszel
CNS	Central nervous system
CNS	Central nervous system
Cpk	Process capability
CQAs	Critical Quality Attributes
C-R	Concentration-Response
CRF	Case report form
CS	Clinically significant
CSF	Cerebrospinal fluid
CSR	Clinical study report
CTAB	Cetyl Trimethyl Ammonium Bromide
CTC	Capillary tube centrifugation
CTD	Common Technical Document
DALA	Dependence and drug abuse liability
DART	Development and reproductive toxicology
DBL	Database lock
DBS	Dried blood spot
DDI	Drug-drug interactions
DFMO	α-difluoromethylornithine
DNA	Deoxyribonucleic acid
DND*i*	Drugs for Neglected Diseases initiative
DRC	Democratic Republic of the Congo
DSC	Differential scanning calorimetry
DSMB	Data and Safety Monitoring Board
EC	European Commission
ECG	Electrocardiogram
eCRF	Electronic case report form
EDx	Effective dose; dose of drug which kills a percentage(subscript) of parasites

	within a defined period of time
E_H	Hepatic extraction
EMA	European Medicines Agency
E_{max}	Maximal effect
EOH	End of hospitalisation
EOT	End of treatment
EP	European Pharmacopea
EP	Evaluable patients
ESI/LCMS	electrospray ionization mass spectrometry
EU	European Union
F	Female
FaSSIF	Fasted state simulated intestinal fluid
fe	Fractional excretion
FeSSIF	Fed state simulated intestinal fluid
FIH	First in human
FMO	Flavin-containing monooxygenase
GC	Gas chromatography
GCP	Good Clinical Practice
GLP	Good laboratory practice
GM	Geometric mean
GMP	Good manufacturing practice
GOF	Goodness-of-fit
HAT	human African trypanosomiasis
HED	Human Equivalent Dose
HEK 293	Human embryonic kidney cells
hERG	Human ether-a-go-go related gene
HMBC	heteronuclear multiple bond correlation spectroscopy
HPBL	Human peripheral blood lymphocytes
HPLC	High performance liquid chromatography
HPLC-MS	High performance liquid chromatography-mass spectrometry
HR	Hazard ratio

HS-GC	Head-space Gas Chromatography
HSQC	Heteronuclear single quantum coherence spectroscopy
IC_{50}	Half-maximal effective concentration
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
ICx	Concentration of drug which kills x % of parasites within a defined period of time
IEC	Independent ethics committee
IMP	Investigational medicinal product
INN	International non-proprietary name
INRB	Institut National de Recherche Biomédicale
IR	Infrared
IRB	Institutional review boards
IV	Intravenous
KF	Karl Fischer titration
L. donovani	*Leischmania donovani*
L. infantum	*Leischmania infantum*
LC	Liquid chromatography
LC-MS/MS	Liquid chromatography coupled to mass spectrometry
LDPE	Low density polyethylene bags
LFTs	Liver function tests
LLN	Lower Limit of Normal
LOD	Loss on drying
LP	Lumbar puncture
LPLV	Last patient last visit
M	Months
M	Male
M1	Fexinidazole sulfoxide
M2	Fexinidazole sulfone
MAD	Maximum Administered Dose
mAECT	Minianion exchange centrifugation technique
MDCK	Madin-Darby canine kidney

MDR1	Multi-Drug Resistance 1 gene
Methocel	Methyl cellulose
MIC	Minimum inhibitory concentration
mITT	modified Intention-to-treat
MO	Major objection
MoA	Mechanism of action
MS	Mass spectrometry
MSC	Modified single centrifugation
MSF	Médecins Sans Frontières
MTD	Maximum tolerated dose
NADH	Nicotinamide adenine dinucleotide
NCA	Non-compartmental analysis
NECT	Nifurtimox eflornithine combination therapy
NF	National Formulary
NMR	Nuclear magnetic resonance
NMRI	Naval Medical Research Institute
NMT	Not more than
NOAEL	No-observed adverse effect level
NSSCPs	National Sleeping Sickness Control Program
NTR	Nitroreductase
NZW rabbits	New Zealand White rabbits
OPA	Oriented polyamide
OR	Odds ratio
P_{app}	Apparent permeability
PACMP	Post-approval change management protocol
PD	Pharmacodynamics
PDA	Photodiode Array
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopea
PI	Product information
PK	Pharmacokinetic

POS	Powder for oral suspension
PP	Per protocol
PPK or popPK	Population pharmacokinetic
PSD	particle size distribution
PT	Preferred term
PV	Pharmacovigilance
PVC	Polyvinyl chloride
q.d.	Once a day
QT	QT interval
QTc	Corrected QT
QTcB	QT interval corrected according to Bazett
QTcF	QT interval corrected according to Fridericia
QTPP	Quality target product profile
RH	Relative humidity
RMP	Risk Management Plan
rpm	Revolutions per Minute
RSE	Root square error
S9	Metabolic activation system
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SD	Standard deviation
SDS	Sodium dodecyl sulfate
SD rats	Sprague-Dawley rats
SLS	Sodium lauryl sulfate
SmPC	Summary of Product Characteristics
SOC	System Organ Class
T. b	*Trypanosoma brucei*
T. b. gambiense	*Trypanosoma brucei gambiense*
T. b. rhodesiense	*Trypanosoma brucei rhodesiense*
T. cruzi	*Trypanosoma cruzi*
$t_{1/2}$	Terminal half-life

TAMC	Total Aerobic Microbial Count
TC	Treatment completers
TEAE	Treatment emergent adverse event
TEER	Transepithelial/transendothelial electrical resistance
TGA	Thermogravimetric analysis
TK	Toxicokinetics
t_{max}	Time to reach maximum plasma concentration
ToC	Test-of-Cure
TSE	Transmissible Spongiform Encephalopathy
TYMC	Total Yeast and Mold Count
UDS	Unscheduled DNA synthesis
ULN	Upper Limit of Normal
USAN	United States Adopted Name
USP	United States Pharmacopea
UV	Ultraviolet
VL	Visceral leishmaniasis
WBC	White blood cell
WHO	World Health Organization
WMA	World Medical Association
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant sanofi-aventis groupe submitted on 14 December 2017 an application in accordance with Article 58 of (EC) No Regulation 726/2004 to the European Medicines Agency (EMA) for a scientific opinion in the context of cooperation with the World Health Organisation for Fexinidazole Winthrop.

The eligibility by the World Health Organisation was agreed upon on 30 April 2010. The eligibility for an application for a CHMP scientific opinion in accordance with Article 58 Regulation (EC) No 726/2004 was agreed upon by the EMA/CHMP on 26 May 2010 and reconfirmed on 23 April 2015.

Fexinidazole Winthrop will exclusively be intended for markets outside the Union.

The applicant applied for the following indication:

Fexinidazole Winthrop is indicated for the treatment of both first-stage (hemo-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.

The legal basis for this application refers to:

This application is submitted under Article 58 of Regulation (EC) No 726/2004 and includes a complete and independent dossier, by analogy to Article 8(3) of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Not applicable

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

Scientific Advice

The applicant received scientific advice from the CHMP:

Scientific advice	date	Area
EMA/CHMP/SAWP/18787/2011	20 January 2011	Clinical aspects
EMA/CHMP/SAWP/343867/2014	26 June 2014	Clinical aspects

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Fátima Ventura Co-Rapporteur: Nithyanandan Nagercoil

- The application was received by the EMA on 14 December 2017.
- Accelerated Assessment procedure was agreed-upon by CHMP on 14 September 2017.
- The procedure started on 25 January 2018.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 28 March 2018. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 March 2018. By analogy to Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 29 March 2018
- The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on 12 April 2018
- During the meeting on 24 April 2018, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 April 2018.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 24 May 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 18 June 2018
- The Rapporteurs circulated an Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 22 June 2018
- During the CHMP meeting on 26 June 2018, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant. In addition, the accelerated assessment timetable was reverted to a standard timetable.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 July 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 August 2018
- The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on 6 September 2018.
- The Rapporteurs circulated an Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 14 September 2018
- During the CHMP meeting on 20 September 2018, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- An expert consultation (Scientific Advisory Group meeting) was organised on 25 September 2018.
- The applicant submitted the responses to the CHMP 2nd List of Outstanding Issues on 15 October 2018.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of

Outstanding Issues to all CHMP members on 2 November 2018

- The Rapporteurs circulated an Updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 8 November 2018
- During the meeting on 12-15 November 2018, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive scientific opinion to Fexinidazole Winthrop on 15 November 2018.

2. Scientific discussion

2.1. Introduction

2.1.1. Disease or condition

The therapeutic indication claimed by the applicant is the treatment of first-stage (hemo-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.

Human African trypanosomiasis (HAT), or sleeping sickness, is a life-threatening, neglected tropical disease that is endemic in sub-Saharan Africa. Two subspecies of the protozoan parasite *Trypanosoma brucei* (*T. b.*) are pathogenic for humans:

- *T. b. gambiense*, responsible for the chronic form of the disease (average duration of approximately 2 years) and located in western and central Africa;

- *T. b. rhodesiense*, responsible for a more acute form of the disease (lasting from few weeks to 6 months) and located in eastern and southern Africa.

Both parasites are transmitted by the tsetse fly and it is generally accepted that humans constitute the epidemiologically important reservoir of the *T.b. gambiense*, parasite.

2.1.2. Epidemiology

T. b. gambiense is responsible for 97% of HAT cases and evolves to a fatal outcome in 2 to 3 years after infection.

At the time of the initiation of the pivotal clinical study (October 2012), 7216 annual cases of *T. b. gambiense* HAT had been reported worldwide. However, with the increased efforts of control programmes and availability of combination therapy with eflornithine and nifurtimox (NECT), this number reduced to 2184 HAT cases worldwide in 2016 (WHO data). Despite of this encouraging number it is suspected that incidence may be under reported considering the difficult diagnosis in particular of the stage 2 of the disease, which requires lumbar puncture, allied with difficulties related with the access of health care professional to very remote areas where the disease is endemic. The Democratic Republic of the Congo (DRC) presents the majority of disease cases reported (83-84% in 2012, 2015 and 2016), with the remainder cases located in bordering central African countries.

Facing this recent success in the control of the disease, *T. b. gambiense* was included in WHO's "roadmap eradication for elimination and control of neglected tropical diseases" with a target date for global elimination of

HAT as a public health problem (<1 case/10 000 inhabitants at least 90% of endemic foci) set for 2020 and complete interruption of transmission in Africa targeted for 2030.

No precise data are available in respect to age distribution of the disease. Based on a HAT database of Médecins Sans Frontières (MSF) and maintained by Epicentre, and in 18 programmes in 6 African endemic countries the treated HAT population included 23.7% of children aged <15 years.

Transmission of gambiense HAT depends on the site, intensity and frequency of contact between tsetse flies and humans. The risk of transmission has been associated with daily activities developed along water locations and increases when tsetse habitats are restricted, as it occurs during the dry season. Transmission in urban areas is associated with travels of the locals or suburban locations closer to areas that constitute a suitable tsetse habitat with few alternative hosts.

It has been described potential protective immunity exists against new infections in humans after suffering from the disease and self-cure and asymptomatic carriage.

2.1.3. Aetiology and pathogenesis

Both *T. b. gambiense* and *T. b. rhodesiense* are transmitted by the tsetse fly and it is generally accepted that humans constitute the epidemiologically important reservoir of the *T.b. gambiense* parasite.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The criteria for staging HAT due *T. b. gambiense* and that was used in the fexinidazole clinical development programme is based on the WHO modified criteria and comprehends basically a Stage 1 (hemo-lymphatic), and Early Stage 2 and a Late Stage 2 (meningo-encephalitic). The qualification for late stage 2 relies on the presence of trypanosomes in the CSF independently of the WBC count in the CSF, or by WBC count >20 cells/µL in the CSF in the absence of trypanosomes in the CSF and presence of trypanosomes in the blood or lymph.

Table 1: Criteria for staging human African trypanosomiasis due to T.b. gambiense

FEX (004-005-006) stage terminology	WHO stage terminology	HAT stage guidance	Trypanosomes in blood or lymph	Trypanosomes in CSF	WBC in CSF
Stage 1	Stage 1	Stage 1	Positive	Negative	≤5 cells/ µL
Early stage 2	Intermediate stage 2	Early stage 2	Positive	Negative	[6 to 20] cells/ µL
Late stage 2	Intermediate stage 1	Early stage 2	Positive	Positive	≤5 cells/ µL
Late stage 2	Intermediate stage 2	Late stage 2	Positive	Positive	[6 to 20] cells/ µL
Late stage 2	Second stage	Late stage 2	Positive	Negative or positive	>20 cells/ µL

CSF = cerebrospinal fluid; HAT = human African trypanosomiasis; WBC = white blood cells

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The selection of the treatment for *T b. gambiense* HAT is based mainly on the disease stage, which currently requires the performance of a lumbar puncture and requires logistics for direct microscopy for parasitological diagnosis (evidence of parasites in CSF and/or significant pleocytosis) in the context of any other serologic (generally: “card hemaglutination”) or direct examination diagnostic test for trypanosomiasis.

2.1.5. Management

Disease staging determines the treatment that will be required, i.e., whether or not the treatment is required to penetrate the BBB.

The current treatment options for HAT are as follow:

Table 2: Summery of current treatment options for HAT

HAT	Drug (Introduction into market)	Mode of administration/Associated problems
Stage 1 (haemo-lymphatic) treatment	Pentamidine (1940)	7-10 IM (preferred) or IV injections; effective in stage 1 gambiense HAT
	Suramin (1920s)	Test dose then weekly IV injections for 5 weeks; primarily for stage 1 rhodesiense HAT; rarely used for gambiense HAT
Stage 2 (meningo-encephalitic) treatment	Melarsoprol (1949)	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.
	Eflornithine monotherapy (1990)	Difficult administration (4 IV infusions/day for 14 days); mainly used as a second line treatment for stage 2 gambiense HAT
	NECT = Nifurtimox Eflornithine Combination Therapy (2009)	Simplified but not ideal regimen (7 days eflornithine [2 infusions/day] and 10 days oral nifurtimox); First-line treatment for stage 2 gambiense HAT

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

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

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Pentamidine is currently the drug of choice for the treatment of Stage 1 HAT caused by *T. b. gambiense*. It must be administered by the intramuscular route or, when possible, IV in saline over 2 hours, daily, for 7-10 days, at a dose of 4 mg/kg up to a maximum of 300 mg for both adult and children. Intramuscular injections of pentamidine are reported to be painful and may induce sterile abscesses. Pentamidine may not be as effective in intermediate stages and is not adequate for the treatment of the second stage of disease.

Few therapeutic options are available to treat meningo-encephalitic stage HAT. Until recently, available products were parenteral, toxic, painful, or difficult to manage. The introduction of eflornithine, or α -difluoromethylornithine (DFMO), initially as monotherapy and later in combination with nifurtimox (NECT), has improved the prognosis of treated patients and, since 2010, NECT has become the first-line therapy for stage 2 *T. b. gambiense* HAT. However, NECT treatment requires a minimum health infrastructure and personnel to administer 2 slow infusions every day for 7 days on top of an oral treatment every 8 hours for 10 days.

Melarsoprol, an organo-arsenic drug, has been used for the rescue treatment of Stage 2 disease by *TBG* in resource poor regions, being more affordable than eflornithine and allowing for high cure rates with a 10 day course of daily parenteral administration (86% after two years, although the evidence is limited, Schmid et al J Infect Dis 2005; 191:1922–3) (Brun, Blum, Chappuis, Lancet 2009).

Melarsoprol + nifurtimox combination has also been tested in a small number of patients but with high success rates. It is reported that increased treatment-failure rates with melarsoprol have been reported in Angola, Uganda, and Sudan, and primary resistance may occur (Bisser et al J Infect Dis 2007; 195:322–9). Encephalitis may arise as a limiting adverse reaction with melarsoprol. There is no vaccine available for HAT.

In this scenario, there is an unmet need for a treatment that may be equally effective in both stages of the disease, thus avoiding the need for the pre-treatment definition of disease stage. There is also a need for a treatment that may be fully administered by the oral route, provided an acceptable safety profile is demonstrated.

The disease course is essentially similar in adults and children, as are the current treatment options with proper dose adjustment. Any new treatment option should be also available for the paediatric population. The applicant has addressed this need in the development programme of fexinidazole.

2.1.6. About the product

As a member of the 5-nitroimidazole group of compounds, fexinidazole belongs to antiparasitic class. Fexinidazole development has begun during the 1970s decade and is claimed to show *in vitro* activity against *T. brucei gambiense* and *T. brucei rhodesiense* at levels which may be obtained in humans through oral administration. The mechanism of action, although not clearly demonstrated likely involves the role of fexinidazole and its metabolites M1 and M2. As all have low redox potentials, it was suggested that they could act as electron acceptors disturbing the parasites' electron transport chain. Nevertheless, recent non-clinical studies indicate that fexinidazole, M1 and M2 may act through bioactivation by nitroreductase (NTR) enzyme thereby generating reactive amines that can react with biomolecules that are both toxic and mutagenic affecting the parasite viability.

Fexinidazole Winthrop 600 mg tablet is intended for oral administration once a day for 10 days during the main meal of the day with the proposed posology:

- Patients weighing ≥ 35 kg: 1800 mg (3 tablets) once a day for 4 days followed by 1200 mg (2 tablets) once a day for 6 days.
- Children ≥ 6 years old and weighing ≥ 20 and <35 kg: 1200 mg (2 tablets) once a day for 4 days followed by a single tablet once a day for 6 days.

2.1.7. Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the following reasons:

Considering the wide geographic distribution of the population at risk for disease caused by *T. brucei gambiense*, the potentially fatal prognosis of the disease and the current lack for an exclusively oral pharmacologic antiparasitic regimen for the treatment of the second meningo-encephalitic stage, the disease may be regarded as a medical condition that is not addressed adequately by an existing therapy, thus configuring an unmet medical need.

Also, the availability of a highly effective and safe alternative for the treatment of HAT caused by *T. brucei gambiense* which may be effective irrespective of the disease stage may have a positive impact on the need for technically challenging diagnostic methods, including lumbar puncture, thus rendering the management of the disease simper and safer and more adapted to the available health resources in the geographic regions where the disease is endemic.

However, during assessment the CHMP concluded that it was no longer appropriate to pursue accelerated assessment, as the assessment identified major objections, which could not be satisfactory resolved within an

accelerated timetable.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as tablets containing 600 mg of fexinidazole as active substance.

Other ingredients are: lactose monohydrate, microcrystalline cellulose, povidone, croscarmellose sodium, sodium lauryl sulfate and magnesium stearate.

The product is available in aluminium/aluminium foil blisters placed in a cardboard wallet as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The fexinidazole (or HOE 239) active substance is a achiral, weakly basic nitroimidazolic compound, with the chemical name 1-methyl-2-[(4-methylsulfanylphenoxy)methyl]-5-nitro-imidazole corresponding to the molecular formula $C_{12}H_{13}N_3O_3S$. It has a relative molecular mass of 279.3 g/mol and the following structure:

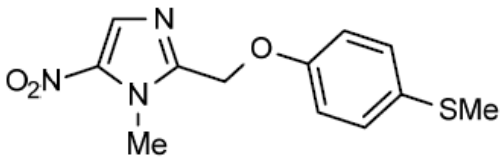


Figure 1: active substance structure

The chemical structure of fexinidazole was elucidated by a combination of infrared spectroscopy (IR), ^{1}H- and ^{13}C-NMR spectroscopy, heteronuclear single quantum coherence spectroscopy (HSQC), heteronuclear multiple bond correlation spectroscopy (HMBC), two dimensional NMR spectroscopy (COSY) and mass spectrometry (MS). Fexinidazole is a yellow non hygroscopic powder. It is practically insoluble in water, sparingly soluble in acetone and acetonitrile, very slightly soluble in ethanol and slightly soluble in methanol.

Fexinidazole has a non-chiral molecular structure.

A polymorph screening was carried out using various solvents, supersaturation, temperature and water activity. Solids were analysed using X-Ray (Powder) Diffraction (XRPD), Differential Scanning Calorimetry (DSC), and/or Thermo-Gravimetric Analysis (TGA). The only polymorphic form observed was called Form 1. No additional fexinidazole polymorphs were identified. In addition to Form 1, the appearance of different solvates was found in the presence of methanol, ethanol or ethyl acetate. These solvates were not stoichiometric solvates, main part of the solid remained Form 1.

Manufacture, characterisation and process controls

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

Fexinidazole is synthesized in a telescoped synthetic process comprising mesylation of the starting material; Coupling; Salt and base formation; Recrystallization; and Micronization of fexinidazole. Details from the

manufacturing process of the active substance, namely process controls, have been provided in the restricted part of the ASMF and were considered satisfactory.

The proposed manufacturing process is a very short synthesis with chemical transformation steps, mesylation and coupling, taking place in a one-pot reaction with no isolated intermediates. Following a major objection (MO) raised in the restricted part of the ASMF in respect to one of the starting materials, the applicant recognized the concern on potential risks from future changes to the starting material synthesis. A post approval change management protocol (PACMP) was presented for the future redefinition of this starting material. The applicant's proposal is acceptable in terms of the proposed steps and timeline. Moreover, the applicant declared that the first four commercial batches from fexinidazole API were manufactured by the same process (described above) and that the analytical results of the acceptance tests for the batches of that particular starting material received from the current supplier, and used in the synthesis of four batches of active substance, as well as the results already obtained for three of these API batches are consistent and within the updated, proposed specifications. In addition, the applicant commits not to purchase additional starting material batches or manufacture new fexinidazole API until the redefinition of that starting material is completed.

In addition, during the procedure, upon request from the CHMP, the applicant included additional impurities in the starting material specifications and tightened the limits for some impurities initially included in the starting material specifications. This was critical due to the limited chemical transformations between the introduction of the starting material into the manufacturing process and the final active substance. The revised acceptance criteria for each impurity are justified and are considered as acceptable. Overall, the action taken by the applicant indicates that impurities in that starting material are adequately controlled. The MO and all the other concerns previously raised in the restricted part of the ASMF in respect to impurities and validation of the analytical procedures for the starting materials have been solved.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate product, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regard to their origin and adequately characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified.

The active substance is packaged in double, low-density, sealed polyethylene bags, inserted into fiber drum. Confirmation that the primary packaging is suitable for packaging foods for human use and that it complies with Ph. Eur. 3.1.3 and Commission Regulation (EU) No. 10/2011, as amended was provided. Secondary packaging (fibre drum) helps to protect fexinidazole from light and to keep the integrity of the packages. Stability results demonstrate the compatibility with the packaging material.

Specification

The active substance specification includes tests for appearance (visual), identification (IR, LC), loss on drying, sulphated ash (Ph. Eur.), chloride content (potentiometric titration), related substances (LC), residual solvents (HS-GC), assay (potentiometric titration), microbiological purity (TAMC, TYMC, *E.Coli*) (Ph. Eur.), and particle size distribution (laser diffraction).

The absence of a test for heavy metals has been adequately justified. Nevertheless in order to ensure the finished product complies with the ICH Q3D guideline, elemental impurity screening was performed on

fexinidazole batches. None of the studied elemental impurities were found to be above 30% of the corresponding ICH Q3D limit.

Related substances of fexinidazole are tested by an LC method. This method is selective and capable of separating identified and unidentified impurities and has been shown to be stability indicating. To detect potential genotoxic impurities at an adequate level, another LC method was developed. The LC method for genotoxic impurities was used for process development and evaluation studies. Process development studies showed that none of those impurities are present in the final active substance, therefore this method is not proposed to be routinely used during the qualification of the final fexinidazole. The applicant has however committed to apply the LC method, developed for genotoxic impurities, to the analysis of the first 6 production scale batches as part of the validation of the manufacturing process.

Taking into account the maximum daily dose of fexinidazole (1800 mg / day), there are no specified impurities in fexinidazole. These specification limits for related substances for fexinidazole are consistent with the ICH Q3A guideline.

Due to the poor solubility of the active substance, it is required to be micronized. Particle size is therefore a critical parameter. The test for particle size was originally based on a single test point only; being a critical parameter, upon request of the CHMP, the applicant introduced a three-point acceptance criterion. The specification is based on appropriate batch results including the validation batches that are representative of production scale manufacture.

The analytical methods used have been adequately described and (the non-compendium methods) appropriately validated in accordance with ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurity identification testing has been presented.

Batch analysis data from three consecutive production validation batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data were provided from five commercial scale (two development and three validation) batches of active substance from the proposed manufacturer, stored in packaging simulating that intended for the market for up to 36 months (60 months for the two development batches) under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines.

The following parameters were tested during stability studies: appearance, loss on drying, related substances, assay, microbial purity and particle size distribution. The analytical methods used were the same as for release and have been shown to be stability indicating. The results showed minimal change in loss on drying, assay or impurities at 25°C/60% RH or 40°C/75% RH and all tested parameters were within the specifications.

For the demonstration of the stability indicating power of the LC related substances method used for the control at release and stability of the fexinidazole active substance and also to better understand fexinidazole degradation profile, stress studies were performed. Samples from one validation batch were exposed to acidic, alkaline, oxidative, elevated temperature and light conditions. In acidic conditions, a very slight degradation was detected. In alkaline media, degradation of the active substance was observed. In the presence of oxidizing agents main degradants were identified. No significant degradation was observed at elevated temperature. During photostability studies, degradation of the active substance was detected. Based on the HPLC results from the degradation studies it was concluded that significant degradation occurs under alkaline, oxidative and sun-light exposure conditions.

Stability to light was initially investigated using exposure to sunlight only and formal photostability testing of the active substance was not provided. Upon request of the CHMP, results from a photostability study performed as per the ICH Q1B guideline were provided. Samples were tested for appearance, assay and related substances. Results showed significant degradation. Therefore fexinidazole should be stored in its original container and protected from light.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 24 months stored at 25±2°C in the proposed container protected from light.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Fexinidazole Winthrop 600 mg tablets are presented as pale yellow, round biconvex tablets with no debossing. Each tablet contains 600 mg fexinidazole, lactose monohydrate, microcrystalline cellulose, sodium lauryl sulfate, povidone, croscarmellose sodium and magnesium stearate.

Fexinidazole is an achiral, weakly basic active substance developed for the treatment of Human African Trypanosomiasis (HAT). An immediate release uncoated tablet was selected for the delivery of fexinidazole as the compound is orally active. The Quality Target Product Profile (QTPP) for the tablets is summarized in

Table 3: Quality target product profile of the finished product.

Elements	Attribute	Target
Administration	Route/Dosage form	Oral dosage form
		Tablets preferred as capsule not optimized for climatic zones IVa and IVb or high dose
Container / Closure	Primary Packaging Materials	Suitable packaging for endemic countries
		Blister packaging required for compliance
		Opaque material required for light protection
Specification quality attributes	Identity, Assay, Content Uniformity, Impurities, microbial limits and dissolution	Meets pharmacopoeial requirements for Identity, Assay, Content Uniformity, impurities and microbial limits. In-vitro dissolution should conform with requirements for an immediate release dosage form
Stability		Minimum 2 years in zone IVb

Fexinidazole is a compound practically insoluble in water, having satisfactory bioavailability and a single polymorphic form. Since it is a weak basic compound with an estimated pKa value of 1.3, the solubility increased slightly with decreasing pH in aqueous buffer solutions. The low solubility of fexinidazole in water prompted the drug development efforts to ensure adequate dissolution of the tablet is achieved.

Fexinidazole is a lipophilic compound with a logD value of around 2-3. The permeability of fexinidazole was characterized using a Caco-2 cell monolayer model in both apical-basolateral (A-B) and the reverse (B-A) direction. The data show that fexinidazole has high permeability. Due to low aqueous solubility and high permeability observed in Caco-2 model, fexinidazole can be characterized as a BCS Class II compound.

In view of the low solubility, particle size is considered a critical quality attribute (CQA) as this had an effect on dissolution and the hardness of the tablet. Therefore, the active substance particle size is controlled to ensure adequate dissolution of the product. Drug development activities support the particle size characteristics chosen for fexinidazole, and this particle size was used for all clinical, bioequivalence and primary stability batches and will be used for the commercial finished product as well. The excipients were selected based on their functionalities and compatibility with the active substance as well as their compliance with the Ph. Eur and the United States Pharmacopoeia/National Formulary (USP/NF). The chosen excipients are typical for a wet granulated tablet and their functionality is as follows:-Lactose monohydrate - brittle compression filler- and microcrystalline cellulose - ductile compression filler- are used as the principal diluents. A milled grade of lactose monohydrate is used due to its smaller particle size tending to result in superior tablet crushing strength.

-Povidone (polyvinylpyrrolidone) is used as a binder in the formulation to assist integrity of the tablet.

-Croscarmellose sodium is used as a disintegrant. It is employed intra- as well as extra-granularly to promote initial rapid disintegration into granules followed by further erosion of the granules themselves until complete disintegration occurs.

-Sodium lauryl sulphate (SLS) is used as a wetting agent to optimize the dissolution rate.

-Magnesium stearate is used as lubricant.

There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

A compatibility study between fexinidazole and excipients typically used for solid oral dosage forms was performed. Binary mixtures of the excipients and fexinidazole were prepared and stored for 8 weeks in open glass and closed glass vials respectively. The results obtained demonstrate the stability of fexinidazole in the presence of the chosen excipients and the suitability of the excipients used in the tablets.

Several formulations were used in the early development of fexinidazole. As per the QTPP, the objective was to develop an oral dosage form for a practically insoluble, hydrophobic active substance, suitable for administration within the target patient population. Based on early clinical trials, suitability of the fexinidazole formulation as an immediate release dosage form was established. Results for the first-in-man study were conclusive enough to pursue the development with a tablet formulation. Tablet preparation by direct compression of the dry blend was not successful Therefore, standard wet granulation tablet formulation was chosen to produce an acceptably sized tablet with top dose strength of 600 mg of fexinidazole. Initial development of the formulation was successful except for one problem related with the poor dissolution performance of the tablets due to poor solubility of fexinidazole.

The formulation was then modified to improve dissolution, and an appropriate rate of dissolution was obtained. This tablet formulation was used throughout development to commercial batches.

The microbiological quality of the tablet is controlled by a specification test to standard pharmacopoeial limits for non-sterile dosage forms and therefore no antimicrobial preservatives are required.

Forced degradation studies of the active substance (see stability section above) showed that fexinidazole can degrade under oxidative stress conditions and in the presence of light, and for this reason, precautions are taken during manufacturing of the tablets and suitable primary packaging of the finished product (alu/Alu blisters) was chosen. Nevertheless, should any formation of the oxidation degradant occur, it would be detected and quantified as an unspecified impurity using the standard HPLC methodology for release and stability testing.

With regard to the manufacturing process development, as indicated above, a wet granulation process was selected for the development of a manufacturing process for the tablets. The initial development of the process for fexinidazole tablets utilized traditional development concepts to produce finished product suitable for the clinical development phases. The transfer of the manufacturing process from the development site to the commercial site has been described and supported by suitable studies showing comparative dissolution profiles, bioequivalence and production batch data. A risk assessment of the process was undertaken utilizing the principles outlined in the ICH Q8 (R2) and Q9 guidelines to capture all the process knowledge generated and to frame the continuing development of the process at the final manufacturing site. In addition, some changes were made to the process to accommodate the equipment in use at the commercial manufacturing site and to optimize the process. The optimized manufacturing process was then scaled up to confirm the robustness of the process to produce finished product of consistent quality that met the specifications.

Since fexinidazole is practically insoluble in water, this posed a challenge during the development of the dissolution test method media. Given this and the fact that the dose of fexinidazole is 600 mg, a simple aqueous media with pH adjustment across the physiological range was not suitable. The solubility of fexinidazole in covering the physiological media containing surfactants [sodium layryl sulphate (SLS), polysorbate (Tween) 80 or cetyl-trimethyl ammonium bromide (CTAB)] was therefore assessed. Media containing SLS achieved sink conditions. Conditions based on this finding were subsequently used to further develop the dissolution test. Based on the studies conducted, a USP Apparatus II (paddle) and a dissolution medium of HCl with SLS were selected. Dissolution testing using this method was carried out on three batches of fexinidazole tablets prepared by the finished product manufacturer in comparison to one batch prepared by the development partner. The overall profiles were similar (f2>50). Tablets from the batches used in this study were also used in the bioequivalence study which concluded that the formulations are bioequivalent in the fed state. The dissolution method was shown to be discriminatory with respect to the hardness of the tablets (dissolution rate slows with increasing tablet hardness), overgranulation and with decreased disintegrant/increased binder. In addition, the dissolution study compared tablets produced with non-micronized active substance vs. micronized active substance. The results show the dissolution method is capable of distinguishing between product manufactured using non-micronized or micronized fexinidazole. The primary packaging is polyamide /aluminium / poly(vinyl chloride) – aluminium blister package (aluminium-aluminium blister package), which provides protection from light. Material of construction complies with appropriate pharmacopoeias and food additive regulations. The laminate complies with EC directives, EC 1935/2004, EC 2023/2006 and EC 94/62/EC art.11. The PVC film complies with EC Directive 2002/72/EC as amended relating to plastic materials and articles intended to come in to contact with food stuffs. The OPA/Alu/PVC with aluminum foil lidding blister package meets USP <671> Containers –Permeation, Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets criteria for Class A Pack and USP <661> Containers – Physiochemical Tests – Plastics suitable for packaging of dry oral dosage forms. The aluminum push through blister foil with lacquer complies with EC directives, EC 1935/2004, 1895/2005, 2023/2006, and EC 2002/72/EC. The blister foil does not contain any plastic layers, therefore it does not fall under the scope of EU Regulation No. 10/2011, 321/2011, 1282/2011, 1183/2012, 202/2014, or Ph. Eur. 3.1.11.

The PVC layer of blister forming material complies with Ph. Eur. Chapter 3.1.11.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of eight main steps: blending, wet granulation, wet milling, drying, milling, final blending, compression and primary packaging. As indicated above, the process is performed under

controlled conditions to prevent photodegradation as the active substance is light sensitive. The process is considered to be a standard manufacturing process.

The following in-process controls are performed during the fexinidazole finished product manufacturing process:-The tablet granulation is dried with heated inlet air to achieve an acceptable granulation moisture level.

-Tablet compression is controlled by monitoring the tablet weight, hardness, thickness, friability, disintegration and appearance.

Major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The manufacturing process for the tablets will be validated as per the process validation scheme provided. This is considered acceptable.

Product specification

The finished product release specifications include appropriate tests for of the proposed dosage form: appearance (visual), identification (HPLC- UV spectrum and retention time), assay (HPLC), related substances (HPLC), uniformity of dosage units by weight variation (Ph. Eur.), dissolution, microbial examination (TAMC, TYMC, *E. coli*- Ph. Eur.) and water content (KF).

The finished product is released on the market based on the release specifications, through traditional final product release testing.
The fexinidazole sulfoxide impurity is the main degradant primarily formed under oxidative conditions; fexinidazole sulfoxide is qualified toxicologically as it is a major metabolite. The test results of synthetic impurities or degradation products from analyses of the clinical and primary stability batches and from accelerated and long-term stability studies showed that impurities or degradation products arise specifically from the active substance. No impurities or degradation product arise specifically from the finished product itself.

Inorganic impurities are controlled in the active substance and no inorganic impurities are generated in the drug product manufacturing process.

The risk assessment carried out for elemental impurities in the tablets, demonstrated that the medicinal product complies with the ICH Q3D guideline requirements. For the 7 tested elements (As, Cd, Hg, Pb, Co, Ni, V), the elemental impurity level is in a range less than the limit of quantitation to the control threshold (30% of the PDE). As a consequence, the safety risk associated to the presence of elemental impurities in the medicinal product can be considered as negligible, close to nil. There is no risk to the patients. No additional controls (other than those implicit in the process and material controls already in place) are required to ensure that the medicinal product meets the requirements of the ICH Q3D guideline.

Residual solvents in the active substance, excipients and finished product are controlled in accordance with the ICH Q3C guideline.

Since dissolution is included as a parameter in the finished product specification, disintegration is not included in the specification.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data for a large number of batches of fexinidazole tablets manufactured during the development phase were presented. Batch release data for three fexinidazole 600 mg tablet batches manufactured at the commercial site using the proposed commercial process at production scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification were also provided.

Stability of the product

Stability data from three commercial scale batches of finished product stored for up to 36 months under long term conditions (30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the WHO/ICH guidelines were provided. The batches of Fexinidazole Winthrop tablets used in the stability studies are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for assay, appearance, dissolution, disintegration, related substances by HPLC and microbial examination. All the tests are performed at each timepoint and condition with the exception of the microbial limit test that will be performed annually. The analytical procedures used have been demonstrated to be stability indicating.

The data presented showed no significant effect on the physical and chemical characteristics of tablets stored in cold form foil (Alu/Alu) blisters at both long-term and at elevated temperatures and humidity conditions. Specifically, the assay for the tablets was within specification and no trend was observed. There was little or no change observed for the degradation products irrespective of the conditions studied and they remained below the unspecified (unknown) impurity specification. Therefore, the tablet stability is consistent with that of fexinidazole active substance. The dissolution profiles of all the three batches tested showed very little change on storage under both conditions. All results were within the specifications.

A photostability study was carried out on one primary stability batch according to the ICH Q1B guideline on the exposed drug product sample (bulk batch) and on the finished product in the proposed primary packaging. At the end of the exposure period, the samples were analysed for any changes in appearance, colour, assay and degradation products. The appearance of bulk tablets exposed directly to light did not conform to the specification for appearance. The light exposure did not affect the potency of the finished product and the results met the specification. Similarly, the impurity profile for the bulk and intermediate packaged tablets exposed to light were similar indicating that the light exposure does not affect the impurity profile of the drug product. The results met the specification for bulk drug product release. Overall, the photo stability study results demonstrated that the tablet remains stable in the proposed packaging upon exposure to light.

Considering the high humidity where the medicinal product is going to be used, a special precaution to protect the product against moisture was included in the product information as follows: “Do not store above 30ºC. Store in the original package in order to protect from light and moisture”. Confirmation was provided that the start of the shelf life of the drug product is set in accordance with the CPMP/QWP/072/96 guideline.

In respect to bulk tablets, no stability data have been presented and therefore holding times cannot exceed 30 days. Maximum holding time of the intermediates (dried sized granulate, final blend and bulk tablets) will be evaluated as part of the post-approval process validation studies and module 3.2.P.8 will be updated via variation.

Based on the available stability data, the proposed shelf-life of 36 months and proposed storage conditions ‘do not store above 30°C, store in the original package in order to protect from light and moisture’, as stated in the SmPC (section 6.3), are acceptable.

Adventitious agents

It is confirmed that lactose, used as an excipient of the finished product, is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. A description of the synthesis of fexinidazole from the proposed starting materials is given.

The major objection previously raised on the redefinition of one of the starting materials is considered to be solved subsequent to the revision of the specifications and the inclusion of a PACMP to redefine that starting material post-approval. The applicant also committed not to purchase additional starting material batches or manufacture new fexinidazole active substance until the redefinition of the starting material is completed. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data have been presented to give reassurance on TSE safety.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP notes that the applicant has agreed with the Committee's recommendation:

- to re-define starting material as per the submitted PACMP and to provide the relevant information via the appropriate post-approval variation within 24 months.

- to apply the LC method, developed for genotoxic impurities, to the analysis of the first 6 production scale active substance batches as part of the validation of the manufacturing process.

2.3. Non-clinical aspects

2.3.1. Introduction

GLP

Much of the data source is from the DNDi development program, except where other sources (e.g., Hoechst AG data and literature references) provide additional information considered to be relevant in the context of the current development program. As much of the early *in vitro* and *in vivo* reassessment of fexinidazole trypanocidal activity was conducted in a research setting at the Swiss Tropical and Public Health Institute (Swiss

TPH), formal reports as per ICH/GLP Guidelines have not been provided. However, key data have been published in a peer reviewed scientific journal (2011) and have been utilized to support the primary pharmacodynamic (PD) data. The applicant states that all recently completed safety and ADME studies were performed in accordance with the principles laid down in the current Declaration of Helsinki and/or ICH guidelines or to the standards required within the jurisdiction of the Health Authorities of the contracted laboratories.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The trypanocidal potency of fexinidazole and its two metabolites, fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2), has been assessed *in vitro* using a variety of T. brucei sub-species and strains, including sensitive and resistant wild-type strains, laboratory-induced melarsoprol- and pentamidine-resistant strains, and new field isolates. The studies showed that fexinidazole and both M1 and M2 had potent trypanocidal activity against all T. brucei sub-species and strains, with the metabolites being slightly more potent than the parent compound, and that there was no evidence of innate resistance to any of the compounds among any of the strains tested. The Minimum Inhibitory Concentration (MIC) for the M2 metabolite, which is considered to be responsible for most of the *in vivo* efficacy of fexinidazole, was 2.20 µg/mL.

Fexinidazole was shown to be effective in murine models of acute infection with T. b. gambiense and T. b. rhodesiense. C_{max} plasma levels of fexinidazole, M1 and M2 in these models were estimated to be around 0.457, 33.6 and 77.6 µg/mL, respectively, after repeat oral dosing with fexinidazole (200 mg/kg/day for 5 days), which are of a similar order to the concentrations found in humans treated with fexinidazole at the recommended dose regimen.

The applicant has not carried out studies to assess the trypanocidal mechanism of action (MoA) of fexinidazole beyond a report referenced in Toreelee et al indicating a strong effect on the microbial electron transport systems by acting as electron acceptor thus aborting the natural biological electron transport mechanism.

The applicant has theorised that metabolite M2 is the most likely responsible for the efficacy of fexinidazole as exhibited in preclinical animal models of HAT. In particular, the higher and more sustainable concentrations of M2 in the brain compared to that reported for the parent support the view that the proposed product is suitable for treatment of stage 2 HAT. With this in mind, the applicant was requested to explain the clinical relevance of the lower than expected M2 levels in the *in vitro* juvenile hepatocyte studies. The applicant explained that the unchanged drug levels in juvenile hepatocytes were in the range of 24% to 44% remaining after incubation for 120 minutes; with the main metabolite being M1 (56 to 74%) and no M2 detected due to a much slower rate of metabolism. It is theorised that a longer incubation period may have allowed for detectable levels of M2 to form. Reassuringly it was shown that the *in vitro* differences are not mimicked in the clinical context. Moreover, age was not shown to influence the popPK parameters.

Fexinidazole has shown cross-resistance in *in vitro* and *in vivo* studies using a nifurtimox-resistant *T. b. gambiense*, suggesting a common mode of resistance and action amongst nitro drugs based on the MoA of parasite killing. This is supported by data showing that the trypanocidal potency of fexinidazole is unaffected in *T. b. rhodesiense* strains which are resistant to non-nitro containing compounds such as pentamidine or melarsoprol. Thus, whilst it is unlikely that the use of fexinidazole monotherapy in the field is affected by the use of current non-nitro containing HAT therapies, the potential for the development of resistance to fexinidazole in patients previously treated with NECT cannot be fully discounted.

Secondary pharmacodynamic studies

The secondary PD data indicate that fexinidazole and its M1 and M2 metabolites can also be an effective treatment for Chagas disease (CD), as well as Leishmania, trichomonad, and E. histolytica infections. Fexinidazole was, however, shown to be more effective against Leishmania when used in combination therapy.

The receptor binding profile of fexinidazole suggests selectivity for the inhibition of binding at the muscarinic M1 and M2 receptors at a high concentration (10 µM = 2.8 µg/mL), which raised concerns about a possible interaction with other drugs acting as muscarinic antagonists. The DNDiFEX003 study, in which healthy subjects took fexinidazole according to the clinical dosing regimen, showed that the highest expected plasma levels of fexinidazole were around 1.5 µg/mL on day 1, and thereafter lower at 0.8 to 0.3 µg/mL on days 4 to 10. In the clinical study in adult patients, DNDiFEX004, treated with the clinical dosing regimen, dried blood samples (DBS) taken around the T_{max} (estimated between 3-4 hours post-dose) on days 8 to 10, were 0.26 to 0.29 µg/mL. Values for fexinidazole in DBS were similar on day 10 for paediatric patients (DNDiFEX006). Taken into account the DBS to plasma concentration ratio for fexinidazole of 0.6 (Study DOH0916), the maximum fexinidazole levels in plasma of patients would be estimated to be around 0.48 µg/mL. Further, it is remarked that the popPK analysis showed that the systemic levels of fexinidazole in patients was slightly lower than that seen in healthy subjects. Overall, in view of the predicted levels of fexinidazole in the CNS for patients treated under the recommended clinical dosing regimen of fexinidazole, and based on the actual findings from DNDiFEX004 and DNDiFEX006 trials with patients and the list of most likely muscarinic receptor antagonists that patients could receive, a potential pharmacodynamic interaction at the muscarinic M1 and M2 receptors is considered unlikely.

Safety pharmacology programme

Fexinidazole and its active metabolites have no significant effects on general behaviour, body temperature, or respiration parameters in conscious male SD (Sprague-Dawley) rats up to 1000 mg/kg fexinidazole. Further, no significant effects were noted on blood pressure, respiratory, or electrocardiogram parameters (including no effects on QT or QTc parameters), or on body temperature in telemetered conscious male dogs given single oral dose of fexinidazole up to 1000 mg/kg. There were no *in vitro* effects of fexinidazole or M1 on hERG currents in HEK 293 cells (performed at non-GLP conditions) at concentrations up to 30 µM (8.38 and 8.86 µg/mL, respectively). A weak inhibition (32.6%) of hERG current occurred with M2 at 30 µM (9.34 µg/mL). This effect may have clinical relevance, particularly if M2 metabolite levels are increased due to drug-drug interactions (DDIs). Because of the M2 alert in the hERG study, intensive ECG surveillance was implemented in each clinical trial, for both healthy volunteers and patients (mean 15 ECGs/patient during the treatment period), confirming potential for QT prolongation correlating with M2 plasma concentration (reports PH16052 and PH17016 in module 5.3.5.3). Overall, in all studies, QT prolongation never translated in any cardiac arrhythmia. With reference to DDIs and M2 prolongation, as M2 is the major circulating metabolite deemed responsible for the pharmacological and clinical effect of fexinidazole following oral administration to patients, the co-administration of CYP inducers with fexinidazole could affect the safety profile. Based on clinical findings, there was a risk for prolongation in the QTcF interval. Concentration-response analyses showed that the QTcF increase by M2 is best described by a saturable E_{max} model (PH17016 - safety report). This model predicts at the geometric mean maximum concentration of the therapeutic regimen a maximum increase (90% confidence interval) from baseline in QTcF of 18.0 ms (90% CI: 16.4 to 19.6) and 14.9 ms (90% CI: 12.8 to 17.1), respectively, in adult and paediatric patients suffering from HAT infection. Despite different E_{max} estimates between the adult and paediatric patient populations, the results showed that the effect on ΔQTcF converged towards the same maximal asymptotic effect (plateau) estimated between 27 and 30 ms. As the highest exposures in M2 with the regimens used in the studies were below the M2 levels necessary to reach the plateau,

the predicted ΔQTcF of 14.9 to 18.0 ms remained below these predicted theoretical maximum values. In view of this saturable E_{max}, and the generally good safety profile observed for fexinidazole in the treated populations, the risk on safety from strong inducers is therefore considered low. Nevertheless, special warnings and precautions for use concerning QT prolongation were introduced in the Summary of Product characteristics (SmPC).

Pharmacodynamic drug interactions

The combinations of fexinidazole or either of its metabolites with melarsoprol, eflornithine, or pentamidine resulted in an additive effect. These data indicate that there are no interactions between these compounds which would preclude their use in, albeit unlikely, combination therapies.

The *in vitro* assays used to evaluate the effects of fexinidazole, M1 and M2 metabolites on transporters as well as the respective enzymatic inhibitory/induction activity have been identified as having limitations and are not according to current guidelines. The applicant has not adequately justified that the methods used are sufficient or appropriate. Given that there are efficacy and safety concerns if the drug concentration is too low or too high, respectively, it is imperative to well characterise the transport, metabolism and elimination pathways for fexinidazole and its metabolites. It would be amiss to rely solely on *in vitro* studies with known limitations and clinical DDI interaction reports from the limited clinical studies prior to commercial use of the medicinal product, especially as the currently proposed SmPC contains cautions against some other medicines. Furthermore, regardless of the number of patients and their location of treatment, the pharmacology of a medicine and potential for DDIs should be well characterised, especially for a product with a potentially narrow therapeutic index such as fexinidazole. Until potential pathways for fexinidazole and its metabolites DDI have been characterised according to currently guidelines, the SmPC should be adjusted to contraindicate any concomitant medications. The applicant has committed to perform, - in accordance with the current guideline on the investigation of drug interactions-, *in vitro* CYP induction and transporter studies for fexinidazole, M1 and M2 using different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole and in particular the formation of fexinidazole sulfoxide (M1)and M1 enantiomers, the metabolism of M1 and M1 enantiomers, their further conversion to fexinidazole sulfone (M2) and the potential metabolism of M2. The final report for the CYP induction study is planned for Q1 2019.

2.3.3. Pharmacokinetics

The ADME characteristics of fexinidazole, and the M1 and M2 metabolites, as the latter are responsible for most of the *in vivo* activity, have been studied in NMRI and Swiss CD-1 mice, SD rats, Golden Syrian hamsters, NZW rabbits, and Beagle dogs. Additionally, a distribution study was conducted in Lister hooded (pigmented) rats, and brain penetration potential *in vivo* was specifically evaluated in NMRI and CD-1 mice. Mice were chosen to support pharmacodynamic models, whilst rats, rabbits and dogs were used to support toxicology studies. Hamsters were selected to support the use of fexinidazole in Visceral Leishmaniasis (VL) pharmacodynamic models. *In vitro* metabolism and protein binding studies were conducted in several species, including humans. Fexinidazole exposure was also determined in repeat-dose toxicity studies in the SD rat and Beagle dog, and in reproductive toxicity studies in SD rats and NZW rabbits. The single- and repeat-dose *in vivo* studies, performed by IV and/or oral routes in the various species, were conducted within the range of doses used for safety pharmacology evaluation.

Fexinidazole was rapidly absorbed after oral administration in all species. Oral bioavailability was low (<30%) in rat and dog, which was most likely due to an extensive first-pass metabolism of fexinidazole, to the active metabolites M1 and M2; in mice, oral bioavailability was better and moderate at around 50-60%. In general, the

plasma $t_{1/2}$ of the parent drug was 1 to 3 hours, whilst the M1 and M2 were 2 to 7 hours and up to 24 hours, respectively. M2 was the major metabolite following oral administration of fexinidazole across all species, being formed sequentially from M1, and showing a high and sustained systemic exposure. The exposure to metabolites greatly exceeded that of parent for all species. Specifically, the M1 AUC ranged from 25.7 (rat 10 mg/kg) to 690 (dog 600 mg tablet) times the fexinidazole AUC. The M2 AUC ranged from 22.5 (rat 10 mg/kg) to 5400 (dog 600 mg tablet) times the fexinidazole AUC. In terms of actual C_{max} values, levels ranged from BLQ (rabbit 40 mg/kg) to 1.15 µg/mL (hamster 300 mg/kg) for fexinidazole, 1.38 (rabbit 10 mg/kg) to 34.5 µg/mL (hamster 300 mg/kg) for M1, and 2.52 (rabbit 10 mg/kg) to 48.6 µg/mL (hamster 300 mg/kg) for M2.

Fexinidazole was shown to have a large volume of distribution in the mouse, rat and dog, suggesting extensive tissue distribution. This was confirmed in a quantitative whole body autoradiography study in rats following oral administration of ^{14}C-labelled fexinidazole, which importantly showed that ^{14}C-drug derived radioactivity could penetrate into the brain, spinal cord and lymph nodes. This brain penetration is essential for treating the Stage 2 human disease where there is CNS-involvement. Further, there was no specific melanin binding or retention of ^{14}C-drug derived radioactivity which was almost completely eliminated within 96 hours, in the faeces (58.8% of the administered dose) and urine (29.9% of the administered dose). No parent drug was recovered in urine and only minimal amounts were recovered in faeces, showing that fexinidazole was almost completely metabolized before elimination.

No significant gender differences were observed in dogs, but in rats, fexinidazole exposures in females generally exceeded male exposures by about 2- to 3-fold over the whole dose range on days 1, 14 and 28. M1 and M2 exposures in female rats also exceeded male exposures on days 14 and 28 at all doses. However, such differences have no clinical relevance, as no gender difference was observed in the pharmacokinetics of fexinidazole in human patients.

Brain (targeted tissue for late stage HAT indication) penetration of fexinidazole and the M1 and M2 metabolites was confirmed in *in vivo* studies using non-radiolabelled fexinidazole. The studies in mice showed that the PK profiles for fexinidazole, M1, and M2 in the brain tended to parallel their corresponding levels in plasma, following oral administration of fexinidazole, showing that all three analytes are able to cross the BBB, thus confirming the findings in *in vitro* permeability and brain penetration studies using MDR1 monolayers. The mouse brain exposure of the M1 and M2 metabolites generally exceeded those of fexinidazole, and increased with oral dose over the range 25 to 100 mg/kg of fexinidazole. Notably, at the latter dose of 100 mg/kg of fexinidazole, the M2 metabolite concentrations in the brain were maintained above 2.2 µg/mL, from 3 to 6 h post- dose, this level corresponding to the MIC evaluated for M2 in *T. b. brucei* 427 cell cultures (see 2.6.2, Study Scynexis-trypanosoma b. brucei). Interestingly, whilst it was shown that higher plasma and brain concentrations of M2 were obtained following oral administration of M2 itself to mice, rather than giving the same adjusted dose of fexinidazole, the pharmacology studies in late stage HAT mouse models clearly showed that fexinidazole was more efficacious than M2 alone by the oral route. This could in part be due to the slow formation of M2 after administration of fexinidazole combined with the long plasma half-life for M2 which results in both a high and sustained plasma and brain exposure. Alternatively, it could indicate that the combined trypanocidal effects of fexinidazole, M1 and M2 are important for *in vivo* efficacy.

The plasma protein binding of fexinidazole has shown to be high in all species (87.7 to 95.4%) whereas that of M1 and M2 was considerably lower (24% to 50% and 29% to 62%, respectively). Species differences were minimal.

In vitro and *in vivo*, fexinidazole rapidly converts to the M1 and M2 metabolites by oxidation. The major route was oxidation of the sulphur atom to form the M1 metabolite, and then sequentially the M2 metabolite. The rapid M1 formation involves a wide range of CYP450 enzymes with no preferred or exclusive CYP450 enzymes,

indicating a low risk of adverse drug interactions. Enzymes involved in the formation of M2 have not yet been identified. Demethylation, N-desmethylation and S-desmethylation, as well as hydroxylation and conjugation (with cysteine and mercapturic acid) in the imidazole moiety, were evident with a combination of these reactions also being present. As fexinidazole is rapidly metabolized after oral administration, the contribution of non-CYP metabolism was investigated. Additional studies showed that fexinidazole was also metabolized via the human flavin monooxygenase (FMO)-3 enzyme, though M1 was stable in the presence of (FMO)-3. The metabolite profile was similar between animal and human hepatocytes, with the monkey quantitatively showing faster oxidation than the other species. The metabolic profile was qualitatively similar between juvenile and adult hepatocytes (from rats, dogs and humans) with M1 as the major metabolite.

In vitro CYP inhibition assays showed that fexinidazole had a moderate or high risk of DDI with CYP1A2 and CYP2C19, respectively, whilst the metabolite M1 had a moderate risk of DDI with CYP2C19. The metabolite M2, which gave the highest and most prolonged systemic exposures after oral dosing of fexinidazole, showed no risk of DDI (IC_{50} >100 µM for all CYPs). The referred moderate or high risk of DDIs is adequately addressed in the SmPC.

Following oral dosing to rats, fexinidazole is almost completely metabolised before elimination in the faeces (58.8% of dose) and urine (29.9% of dose), over a 96 hour period. No parent drug was recovered in urine and only minimal amounts were found in faeces. The major metabolites in urine were M22/M23, M10, and M6 (each <12% dose), whereas M6 (<7% of dose) alone was the major metabolite in faeces. Milk excretion of radioactivity derived from ^{14}C-fexinidazole following oral dosing to lactating rats at 800 mg/kg was significant with a 7.4 hour half-life of radioactivity in milk, which parallels the 8.0 hour half-life in plasma. Radioactive material was present in milk through 48 hours after administration. Milk excretion is adequately addressed in the SmPC, section 4.6.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies, non-GLP and without a negative control group, have been conducted in mice, rats, guinea pigs and rabbits; all with administration by the oral route, using 2% potato starch mucilage as the vehicle. Although results from these studies suggest a low risk of acute toxicity at the intended therapeutic dose levels - on a weight per body weight comparison basis, the lowest determined LD_{50} [1414 mg/kg] is almost 50 times higher than the human doses, when considering the administration of 1800 mg to an adult with 60 kg body weight -, the studies are of limited value as they were non-GLP and were not accompanied by toxicokinetic data (neither concomitant nor from other studies conducted in the same species using the same vehicle). Taking into account that information on single dose toxicity can also be obtained from other studies, namely, repeated dose toxicity and safety pharmacology studies, it may be considered that no additional single dose toxicity studies are needed.

Repeat dose toxicity

Pivotal, GLP-compliant, repeated dose toxicity studies comprised studies in rats and dogs with daily oral administration of fexinidazole over 28 days followed by a 2-week recovery period. Effects observed in these studies were mostly limited to reductions in food consumption and body weight (rats and dogs). Additionally, rats showed increases in liver weight and hypertrophy of the centrilobular hepatocytes, which were considered to be adaptive in nature. The fexinidazole dose of 200 mg/kg/day was determined to be the NOAEL in rats in dogs. Without toxicokinetic data, the nature of the observed effects and comparison of animal and human dose levels on a weight per body weigh basis would suggest a low risk for toxicity. However, the toxicokinetic data

reveal that, at the rat NOAEL, the animal's systemic exposures (AUC_{0-24}) to fexinidazole, M1 and M2 metabolites were lower to identical to those expected in humans. At the dog NOAEL, the animal's systemic exposures to fexinidazole and its metabolites M1 and M2 were lower than those expected in humans. Furthermore, even at the maximum tested doses (800 mg/kg/day in both species), systemic exposures (AUC_{0-24}) to fexinidazole and its metabolites were still lower to identical to those expected in humans at the therapeutic dose levels.

Genotoxicity

A series of genotoxicity tests were conducted with fexinidazole (and M1, as formed in the presence of S9) or the M2 active metabolite. *In vitro*, fexinidazole did induce mutation in S. typhimurium strains TA98, TA100, TA1535 in the absence or presence of S9, and in strains TA1537 and TA102 in the presence of S9. The M2 active metabolite did induce mutation in strains TA98, TA100, TA1535, TA1537 and TA102 in the absence of S9. When performed under the same treatment conditions, parallel treatments of strains TA98NR, TA100NR, TA1535NR, YG7167 and YG7168 (NTR-deficient strains of TA98, TA100, TA1535, TA1537 and TA102, respectively) resulted in marked reductions in the mutagenic response seen in the corresponding parent strain. Bacterial nitroreduction enzymes were therefore shown to play a significant role in the mutagenicity of fexinidazole and of its active metabolite M2. Fexinidazole, M1 and M2 did not induce micronuclei in cultured human peripheral blood lymphocytes and fexinidazole *in vivo* did not induce micronuclei in the PE of mice bone marrow. Fexinidazole did not show genotoxicity activity through induction of UDS in Sprague-Dawley rat hepatocytes.

Additional genotoxicity studies (Ames test) were conducted to assess the potential genotoxicity of fexinidazole impurities. As conducted with fexinidazole and the active metabolite M2, bacterial mutagenicity of the potential impurities also containing a nitro group was evaluated in Salmonella strains expressing or deficient in nitroreductase enzymes. With all tested potential impurities mutagenicity was significantly reduced in nitroreductase deficient strains. It was therefore concluded that bacterial nitroreduction enzymes play a significant role in the mutagenicity of all tested impurities, suggesting bacterial-specificity. In addition, the MHI impurity did not induce micronuclei in cultured human peripheral blood lymphocytes following treatment in the absence and presence of S9. CI impurity did induce small increase in micronuclei in cultured human peripheral blood lymphocytes following treatment in the presence of S9. As a matter of fact, the Chloromethyl-fexinidazole was not detected in representative batches of fexinidazole API – obtained with current commercial synthesis process - although the detection limit for this compound was 2.5 ppm. Consequently, the daily dose of Chloromethyl-fexinidazole remained below 1.4 µg/day. The exposure to any genotoxic metabolite of Chloromethyl-fexinidazole would be even lower and would not be expected to represent a genotoxic risk to patient.

Carcinogenicity

No carcinogenicity studies were conducted with fexinidazole, M1 or M2 as the intended indication is for short-term treatment (less than one month).

Reproduction Toxicity

The potential effects of fexinidazole on reproduction and development were evaluated in a standard battery of studies: a fertility study in male and female rats, two embryo-foetal toxicity studies (one in rats and another in rabbits, with corresponding range-finding studies in both species), and a pre- and postnatal study in rats (with a range-finding evaluation performed along with the one supporting the embryo-foetal toxicity study in rats). Juvenile animal studies have not been conducted.

No effects were observed on fertility or embryonic development and effects on the parental generation were limited to reductions in food consumption. In the rat embryo-foetal development study, reproductive toxicity

effects were limited to reductions in foetal and placental weights and a delay in the degree of skeletal ossification in the foetuses. These have occurred at a dose level (the maximum tested dose) which caused maternal toxicity (reduced food consumption and body weight gain). In the rabbit study, reproductive toxicity was limited to abortions in combination to marked maternal toxicity (reduction in food consumption and body weight). Finally, in the prenatal and postnatal development study, reproductive toxicity/effects on the F1 generation were limited to reductions in pup weight and food consumption and to retardation of postnatal development. These have occurred at a dose level (the maximum tested dose) which caused maternal toxicity (reduced food consumption and body weight gain).

Overall, the results indicate lack of teratogenicity and occurrence of effects on embryo-foetal or postnatal development (abortions, reductions in foetal and placental weights, delay in the degree of skeletal ossification in the foetuses, reductions in pup weight and food consumption and retardation of postnatal development) only at maternal toxic dose levels.

Toxicokinetic data

Considering the available toxicokinetic data (TK), these reveal a lack of safety margins though: (i) for the fertility study, extrapolation of TK data from the 28-day repeated dose toxicity study in rats suggests that, up to the maximum tested dose (600 mg/kg/day), systemic exposures (AUC_{0-24}) to fexinidazole and its metabolites M1 and M2 may have been lower to identical to those expected in humans; (ii) for the rat embryo-foetal development study, at the NOAEL (200 mg/kg/day) both for the mother and embryo-foetal development, systemic exposures (AUC_t) to fexinidazole and its metabolites M1 and M2 were lower than those expected in humans and at the maximum tested dose (800 mg/kg/day), systemic exposures were still only up to approximately 3-4 times higher (for metabolite M1); (iii) in rabbits, systemic exposures to fexinidazole's metabolites M1 and M2 at the maximum tested dose in the pivotal study (40 mg/kg/day) may be estimated to have been lower than those expected in humans, as based on the results from the dose range finding study and (iv) also for the prenatal and postnatal development study, at the NOAEL for the F0 and F1 generations (200 mg/kg/day), systemic exposures to fexinidazole and its metabolites may be estimated to have been, during gestation, lower than those expected in humans.

Other toxicity studies

Fexinidazole was not found to have any phototoxic effect *in vitro*, whereas M1 and M2 exhibit a phototoxic potential in BALB/c mice 3T3 cells based on differential cytotoxicity with and without UVA irradiation. The relevance of these findings is provided on Section 5.3 of the SmPC.

2.3.5. Ecotoxicity / environmental risk assessment

An environmental risk assessment (ERA) was not submitted by the applicant.

ERA omission is accepted taking into account that:

- The medicinal product will be used to treat patients with Human African Trypanosomiasis, a rare tropical disease (<3000 cases per year);
- Following oral administration, fexinidazole has been shown to be rapidly and highly metabolized and only a small fraction (<3.15%) of the dose administered is recovered in the urine;
- The logD (pH 7.4) is 2.8, a value under the screening limit for Persistence, Bioaccumulation and Toxicity (3.2.S.1.3. – General properties).

2.3.6. Discussion on non-clinical aspects

The applicant has concluded that metabolite M2 is most likely responsible for the efficacy of fexinidazole as exhibited in preclinical animal models of HAT. In particular, the higher and more sustainable concentrations of M2 in the brain compared to that reported for the parent drug support the view that the proposed product is suitable for treatment of stage 2 HAT. The applicant explained that the unchanged drug levels in juvenile hepatocytes were in the range of 24% to 44% remaining after incubation for 120 minutes; with the main metabolite being M1 (56 to 74%) and no M2 detected due to a much slower rate of metabolism. It is theorised that a longer incubation period may have allowed for detectable levels of M2 to form.

Brain penetration (targeted tissue for late stage HAT indication) of fexinidazole and the M1 and M2 metabolites was confirmed in *in vivo* studies using non-radiolabelled fexinidazole. The studies in mice showed that the PK profiles for fexinidazole, M1, and M2 in the brain tended to parallel their corresponding levels in plasma, following oral administration of fexinidazole, showing that all three analytes are able to cross the BBB, thus confirming the findings in *in vitro* permeability and brain penetration studies using MDR1 monolayers. The mouse brain exposure of the M1 and M2 metabolites generally exceeded those of fexinidazole, and increased with oral dose over the range 25 to 100 mg/kg of fexinidazole.

No animal drug-drug interaction studies have been carried out, though studies were conducted to determine if fexinidazole, M1 and/or M2 would serve as cytochrome P450 enzyme substrates, inhibitors and inductors, or as substrates for the Multi-Drug Resistant 1 gene (MDR1) and P-glycoprotein (P-gp). The applicant has committed to perform, *in vitro* CYP induction and transporter studies for fexinidazole, M1 and M2 using different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole and in particular the formation of fexinidazole sulfoxide (M1) and M1 enantiomers, the metabolism of M1 and M1 enantiomers, their further conversion to fexinidazole sulfone (M2) and the potential metabolism of M2.

In safety pharmacology, no hERG current inhibition was observed with fexinidazole or M1, but an inhibition (32.6%) was noted with M2. There were no related effects on ECG parameters in telemetered conscious dogs at fexinidazole doses of up to 1000 mg/kg. Further, there were no relevant untoward effects on physiological CNS (behaviour and body temperature), cardiovascular or respiratory parameters in preclinical studies.

Fexinidazole exhibited low toxicity in regulatory preclinical safety studies. In 28-day repeated dose oral toxicology studies, fexinidazole was overall well tolerated in rats and dogs at doses up to 800 mg/kg/day, and effects were essentially limited to decreases in body weight gain and food consumption. The NOAEL was set at 200 mg/kg/day in both species. Systemic exposures (AUCs) at this dose level were nevertheless low as compared to clinical exposure.

No carcinogenicity studies were carried out based on the intended short duration of treatment in humans. There were no effects on fertility parameters in adult male or female rats after repeated oral doses up to 600 mg/kg/day. Effects observed in embryo-fetal and pre- and post-natal development were regarded as secondary to maternal toxicity, and not as direct developmental effects of fexinidazole. In both the rat and rabbit embryofetal developmental studies, effects on fetal development were observed but only at dose levels which were toxic to the dams (800 and 20 mg/kg, respectively). In the pre- and post-natal development study in the rat, slightly reduced pup weights and delayed sexual maturation occurred at the highest maternal dose of 600 mg/kg/day with no impact on reproductive performance in the F1 generation. In all reproductive toxicity studies, systemic exposures were shown or predicted to be low as compared to clinical exposures.

Fexinidazole and the M2 metabolite were shown to be mutagenic in the Ames test. These results are consistent with the nitroheterocyclic structure of these compounds which can be nitro-reduced by bacterial nitroreductases

to form bacterial mutagens, as confirmed by the reduced signal in Ames tests conducted in nitroreductase deficient-strains. In addition, no genotoxic potential was evidenced in a series of *in vitro*, *in vivo* or *ex vivo* tests in mammalian cells. Overall, fexinidazole and its active metabolites are not expected to pose a genotoxic risk to humans.

Both the M1 and M2 metabolites of fexinidazole carry a signal for phototoxicity in the 3T3 test at high concentrations, indicating a potential for phototoxicity reactions in subjects treated with fexinidazole and exposed to sunlight or artificial UV-A light. However, the risk is considered to be low, as the tissue distribution study in rats provided no evidence of fexinidazole and/or its metabolites showing a higher affinity for the skin or the eyes – the two critical tissues for phototoxicity as exposed to light, or binding to melanin.

2.3.7. Conclusion on the non-clinical aspects

A generally acceptable non-clinical testing methodology was followed in the development of fexinidazole. The applicant has committed to perform, *in vitro* CYP induction and transporter studies for fexinidazole, M1 and M2 using different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole and in particular the formation of fexinidazole sulfoxide (M1) and M1 enantiomers, the metabolism of M1 and M1 enantiomers, their further conversion to fexinidazole sulfone (M2) and the potential metabolism of M2. The final report for the CYP induction study is planned for Q1 2019.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the European Union were carried out in accordance with the ethical standards of Directive 2001/20/EC.

There are no identified major concerns about compliance with ethical requirements. It is acknowledged that the applicant took notable efforts, both in terms of equipment and training, in order to replicate adequate experimental conditions in an environment where the clinical resources may have deficiencies.

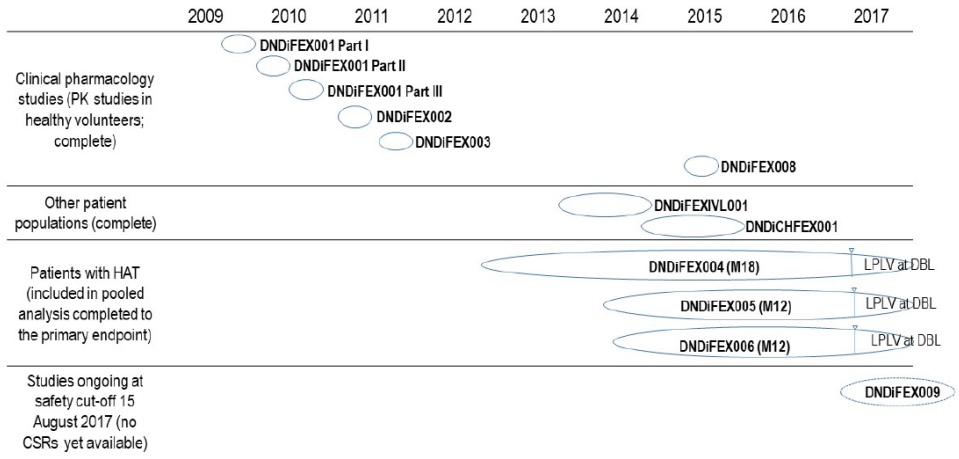
A considerable effort has been taken in order to ensure that the ethical issues have been respected for all patients included and that technical support has been obtained from recognized national and international entities prior to the local conduction of the studies. There is also detailed information on how the technical problems that are expected to arise in geographical regions with scarce clinical resources have been tackled by the applicant, with the help of local and international medical and other health personnel teams. The provision of technical material and training of trial personnel are well described. Taken together, these considerations provide reassurance that the investigational team has made sure that the quality of care and observation of good scientific standards have been maximized in the adverse condition in which the studies have taken place.

A number of GCP inspections have been already performed regarding different aspects of the process and are duly listed by the applicant. There are no imperative reasons for the need for a GCP inspection.

Tabular overview of clinical studies

Several *in vitro* and *in vivo* studies were conducted to investigate the clinical PK and PD of fexinidazole and its active metabolites, M1 and M2. The clinical development programme for fexinidazole includes data from Phase

I pharmacology studies in healthy subjects and Phase II/III efficacy and safety studies in adult and paediatric patients (≥6 years) with varying stages of HAT. The following figure and table resume the performed and ongoing *in vivo* studies contributing to the characterization of the clinical pharmacology profile of flexinidazole.



CSR=clinical study report; DBL=database lock; HAT=human African trypanosomiasis; LPLV=last patient last visit; M=month; PK=pharmacokinetic

Figure 2*:* Studies contributing to characterize the clinical pharmacology profile of fexinidazole

Table 4: Summary of studies contributing to characterize the clinical pharmacology profile of fexinidazole.

Study number	**Study objectives** **Study design**	**Population** **Number of subjects (randomized/completed)**	**Formulation** **Oral Dosage regimen** **Number of evaluable subjects**
DNDiFEX001 Part I	Safety, tolerability and PK profile of fexinidazole and its metabolites after single oral administration of increasing doses of oral suspension of fexinidazole Randomized, double-blind, single ascending dose, placebo-controlled	Healthy male subjects 72/72	**Fexinidazole extemporaneous suspension** - 100, 200 and 600 mg for extemporaneous suspension - Single escalating doses of 100,200,400,800, 1200,1800, 2400,3000, and 3600 mg **Placebo extemporaneous suspension**
DNDiFEX001 Part II	Compare the relative bioavailability of fexinidazole administered as a tablet with oral suspension; and assess the impact of concomitant food intake after single oral dose. Randomized, double-blind, placebo-controlled 3-way crossover study	Healthy male subjects 13/12	**Fexinidazole tablets** - 600 mg tablets - 2 × 600 mg tablets (1200 mg) **Fexinidazole extemporaneous suspension** - 600 mg tablet - 2 × 600 mg tablets (1200 mg) **Placebo tablets** **Placebo extemporaneous suspension**

DNDiFEX001 Part III	Safety, tolerability and PK profile of fexinidazole and its metabolites after multiple oral administration of increasing doses of tablets of fexinidazole Randomized, double-blind, multiple ascending dose, placebo-controlled	Healthy male subjects 27/23	**Fexinidazole tablets** - 600 mg tablets - 2 × 600 mg tablets (1200 mg) **Fexinidazole extemporaneous suspension** - 600 mg tablet - 2 × 600 mg tablets (1200 mg) **Placebo tablets**
DNDiFEX002	To assess the relative bioavailability of fexinidazole tablets administered as a single oral dose with concomitant food intake using 2 different types of meals in healthy male subjects compared with fasting conditions. Randomized, open study, 3-way crossover.	Healthy male subjects 12/11	**Fexinidazole tablets** - 600 mg tablets - 2 × 600 mg tablets (1200 mg)
DNDiFEX003	Safety, tolerability and PK profile of fexinidazole and its metabolites for 2 different dosing regimen of repeated administration under fed conditions Randomized Double-blind, placebo controlled multiple ascending dose	Healthy male subjects 30/22	**Fexinidazole tablets** - 600 mg tablets - 3 x 600 mg tablets tablets (Day 1 to 4), then 2 x 600 mg tablets (Day 5 to 10) or - 4 x 600 mg tablets (Day 1 to 4), then 2 x 600 mg tablets (Day 5 to 10)
DNDiHATFEX008	To assess the bioequivalence of the clinical trial 600 mg tablet formulation versus the proposed market 600 mg tablet formulation under fed condition after single oral administration Open-label, 2-treatment, 2-sequence, 4-period, single-dose, replicate crossover study, fed conditions	Healthy male subjects 30/30	**Fexinidazole tablets (for clinical trial and marketing)** - 600 mg tablets - 2 × 600 mg tablets (1200 mg) **Placebo tablets**

Bioanalytical methods using liquid chromatography and tandem mass spectrometry (LC/MS/MS) were developed to quantify fexinidazole and its active metabolites in plasma, dried blood spots (DBS) and urine and to quantify the two metabolites only in dried CSF spots. Fexinidazole and its M1 and M2 metabolites showed in DBS a linear relationship to plasma concentrations.

The initial formulations tested were tablets (200 and 600 mg) and powder for oral suspension (100, 200 and 600 mg). Early results led to selection of the 600 mg tablet for further study. The clinical trial formulation manufactured by Aptuit and the proposed commercial formulation manufactured by Alcami were compared in the DNDiFEX008 study.

All Phase 1 studies were conducted in France in adult male subjects of sub-Saharan ethnicity and BMI ~19-27 kg/m^2.

Summary of the clinical studies

DNDiFEX001 Part III involved daily dosing of 1200, 2400 or 3600 mg for 14 days in the fasted state. For the two highest doses, plasma fexinidazole levels suggested that steady-state was reached on Day 4. Across the cohorts, there was a slight accumulation after 7 days with geometric mean C_{max} ratio vs. day 1 of about 1.2 and $AUC_{0-\tau}$ ratio of 1.5. Respective ratios on day 14 were 1.3 and 1.7 indicating little accumulation from days 7-14. One subject dosed with 1200 mg/day had unusually low plasma levels through day 14 (e.g. AUC on day 14 was 1027.63 h*ng/mL vs. a mean value of 10499.21 h*ng/mL for the cohort on day 14).

Table 5: Geometric mean (CV%) of PK parameters of fexinidazole after single and repeated oral administration of increasing doses of fexinidazole between 1200 and 3600 mg

		Dose (mg)	t_{max}# (h)	C_{max} (ng/mL)	$AUC_{0-\tau}$* (h.ng/mL)	AUC_{0-t} (h.ng/mL)	CLss/F (L/h)
Day 1	N=6	1200	3.00 (3.00-4.00)	264.70 (45)	2444.49 (48)	-	*243.77** *(54)*
	N=6	2400	3.50 (1.00-4.00)	511.66 (34)	5334.89 (39)	-	*220.52** *(39)*
	N=5	3600	3.00 (0.50-4.00)	452.92 (29)	5605.34 (18)	-	*284.14** *(49)*
Day 7	N=6	1200	4.00 (3.00-4.00)	302.95 (50)	3718.37 (49)	-	322.72 (159)
	N=6	2400	4.00 (3.00-6.00)	516.06 (16)	7085.26 (24)	-	338.73 (24)
	N=5	3600	4.00 (3.00-4.00)	653.44 (19)	9625.12 (18)	-	374.02 (18)
Day 14	N=6	1200	3.00 (3.00-12.00)	385.40 (39)	4773.34 (54)	7448.56 (72)	251.40 (113)
	N=6	2400	3.00 (0.00-6.00)	485.69 (24)	7604.98 (23)	12602.31 (35)	315.58 (27)
	N=5	3600	4.00 (3.00-4.00)	635.05 (12)	9300.62 (16)	18956.46 (25)	387.07 (19)

#Median (min-max) - *$AUC_{0-\tau}$=AUC_{0-24} - * in italic CL/F data determined in study part I (using formula Dose/$AUC_{\grave{a}-\infty}$) ¶

M1 was formed rapidly with plasma PK profiles at each dose level that paralleled those of the parent drug but with much higher AUCs than for parent drug. For the two highest doses, steady-state was reached on Day 4. The geometric mean C_{max} and $AUC_{0-\tau}$ accumulation ratios were 1.8 and 2.1 on Day 7 and 2.2 and 2.5 on Day 14, indicating little accumulation from days 7-14.

Table 6: Geometric mean (CV%) of PK parameters of M1 after single and repeated oral administration of increasing doses of fexinidazole between 1200 and 3600 mg

		Dose (mg)	t_{max} [#] (h)	C_{max} (ng/mL)	$AUC_{0-\tau}$ [*] (h.ng/mL)	AUC_{0-t} (h.ng/mL)
Day 1	N=6	1200	4.00 (2.00-4.00)	2020.44 (21)	25245.55 (27)	-
	N=6	2400	3.00 (2.00-6.00)	3097.38 (27)	41996.81 (31)	-
	N=5	3600	3.00 (2.00-4.00)	3215.90 (17)	47742.35 (9)	-
Day 7	N=6	1200	4.00 (2.00-6.00)	2891.85 (34)	43112.55 (37)	-
	N=6	2400	4.00 (3.00-6.00)	5385.14 (23)	82907.50 (23)	-
	N=5	3600	4.00 (3.00-6.00)	7236.67 (19)	124546.99 (21)	-
Day 14	N=6	1200	3.50 (3.00-4.00)	4468.99 (29)	66811.12 (34)	102163.85 (53)
	N=6	2400	3.00 (3.00-4.00)	5602.67 (32)	87095.66 (28)	138243.51 (29)
	N=5	3600	4.00 (4.00-4.00)	7912.16 (15)	129269.80 (18)	244110.19 (29)

[#]Median (min-max) - *$AUC_{0-\tau}$=AUC_{0-24}

¶

Plasma M2 concentrations increased slowly over 24 h after the first dose. From Day 4 to Day 14 mean values were 8575-11425 ng/mL for 2400 mg and 2925-3735 ng/mL for 3600 mg cohorts but steady-state did not seem to be completely attained for the lowest dose. Geometric mean C_{max} and $AUC_{0-\tau}$ accumulation ratios were 5.2 and 7.3 on Day 7 and 6.2 and 8.4 on Day 14, indicating little accumulation from days 7-14.

Mean M2/fexinidazole ratios for C_{max} were consistently higher (26.87-29.49 on Day 7 and 28.99-34.77 on Day 14) than the M1/fexinidazole ratios (9.94- 11.18 on Day 7 and 11.09-12.44 on Day 14). The same pattern applied to AUC_{0-t} ratios (40.36-58.71 on Day 7 and 36.84-60.61 on Day 14 vs. 11.14-18.00 on Day 7 and 10.97-17.94 on Day 14). It was concluded that there was no saturation of the metabolism of fexinidazole to M1 or M1 into M2 and that the high exposure to M2 was related to the $t_{1/2}$ of about 20 h, associated with a possible saturation of M2 elimination after repeated administration of fexinidazole.

Table 7: Geometric mean (CV%) of PK parameters of M2 after single and repeated oral administration of increasing doses of fexinidazole between 1200 and 3600 mg

		Dose (mg)	t_{max}[#] (h)	C_{max} (ng/mL)	$AUC_{0-\tau}$[*] (h.ng/mL)	AUC_{0-t} (h.ng/mL)
Day 1	N=6	1200	24.00 (16.00-24.00)	1826.63 (36)	29858.36 (37)	-
	N=6	2400	24.00 (16.00-24.00)	2696.59 (32)	41973.16 (27)	-
	N=5	3600	24.00 (24.00-24.00)	3405.04 (9)	50030.01 (8)	-
Day 7	N=6	1200	4.00 (0.50-9.00)	7374.89 (29)	153130.41 (31)	-
	N=6	2400	2.50 (1.00-12.00)	14677.69 (31)	307563.31 (27)	-
	N=5	3600	16.00 (0.00-24.00)	21257.22 (8)	465415.25 (8)	-
Day 14	N=6	1200	5.50 (0.00-24.00)	10956.81 (43)	235399.81 (39)	708847.38 (49)
	N=6	2400	9.00 (0.00-48.00)	14758.27 (33)	302745.66 (31)	904734.98 (32)
	N=5	3600	2.00 (0.00-24.00)	24428.65 (16)	512220.72 (14)	1750815.38 (9)

[#]Median (min-max) -*$AUC_{0-\tau}$=AUC_{0-24}

DNDiFEX003 evaluated 10 days of treatment with one of the two loading and maintenance regimens using once daily dosing in the fed state (due to food effect studies; see below) as follows:

Cohort 1: 1800 mg fexinidazole or placebo days 1-4 and 1200 mg or placebo days 5-10

Cohort 2: 2400 mg fexinidazole or placebo days 1-4 and 1200 mg days 5-10

On each administration day, a light standard breakfast was served before dosing followed by other standard meals.

The study was stopped due to unacceptable tolerability (due to a high frequency of AEs rather than one specific AE type) after the inclusion of 6 subjects into Cohort 2. Of these 6 patients, 4 completed the study of which 2 received fexinidazole and 2 received placebo.

In Cohort 1 six (6) subjects dropped out (5 withdrew consent; 1 had an AE) and were replaced. Fexinidazole was measurable in plasma throughout the dosing interval with mean pre-dose levels of 250, 158 and 167 ng/mL on Days 4, 7 and 10, respectively. At 48 h after the last dose, fexinidazole was measurable in all subjects (14 to 140 ng/mL), in four subjects at 120 h but in none of the subjects by 168 h.

Table 8: Summery of fexinidazole PK parameter in Cohort 1

Day		t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	CL/F (L/h)	V/F (L)	$t_{1/2}$ (h)#
1	N	12	12	12	11	11	11	11
	GM	4	1519	14404	14105	128	1627	8.84
	(CV%)	(2-9)	(24)	(20)	(18)	(19)	(39)	(22)
4	N	12	12	12	8	8	8	8
	GM	4	777.3	10094	11410	158	3046	13.38
	(CV%)	(0-9)	(35)	(27)	(19)	(23)	(37)	(32)
7	N	12	12	12	5	5	5	5
	GM	4	335.5	4593	6285	191	3529	12.81
	(CV%)	(0-6)	(50)	(41)	(18)	(17)	(51)	(51)
10	N	12	12	12	12	12	12	12
	GM	4	485.5	9846	6596	182	3768	14.36
	(CV%)	(2-9)	(40)	(43)	(36)	(36)	(37)	(39)

M1 was measurable in plasma from all subjects throughout the dose interval with mean pre-dose levels of 3030, 1887 and 1951 ng/mL on Days 4, 7 and 10, respectively. At 72 h after the last dose it was still measurable in all subjects (19 to 301 ng/mL), in 6 patients at 120 h and in 2 patients at 168 h.

Table 9: Summery of M1 PK parameter in Cohort 1

Day		t_{max}* (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	AUC_{0-24} (h*ng/mL)	$t_{1/2}$ (h)#
1	N	12	12	12	12	12
	GM	4	7818	97617	98511	8.01
	(CV%)	(3-6)	(27)	(28)	(28)	(16)
4	N	12	12	12	11	11
	GM	4	7768	119141	119963	11.97
	(CV%)	(0-6)	(29)	(37)	(38)	(40)
7	N	12	12	12	10	10
	GM	4	3999	55141	52501	12.00
	(CV%)	(0-6)	(43)	(42)	(47)	(55)
10	N	12	12	12	12	12
	GM	3.5	5574	106825	77263	15.20
	(CV%)	(2-6)	(36)	(44)	(43)	(38)

M2 was measurable in plasma from all subjects throughout the dosing interval with mean pre-dose levels of 16430, 13590 and 11330 ng/mL on Days 4, 7 and 10, respectively. It was still measurable in all subjects at 168 h after the last dose (65 to 442 ng/mL). At pre-dose, 7 to 11 of 12 subjects had plasma M2 >10000 ng/mL (>4 times MIC) from Day 4 to Day 10. Levels were >20000 ng/mL in 4 subjects on days 4 and 5. Levels >10000 ng/mL for at least 3 consecutive days were observed in 9 subjects and in 7 patients the levels were above this threshold for the complete duration of treatment.

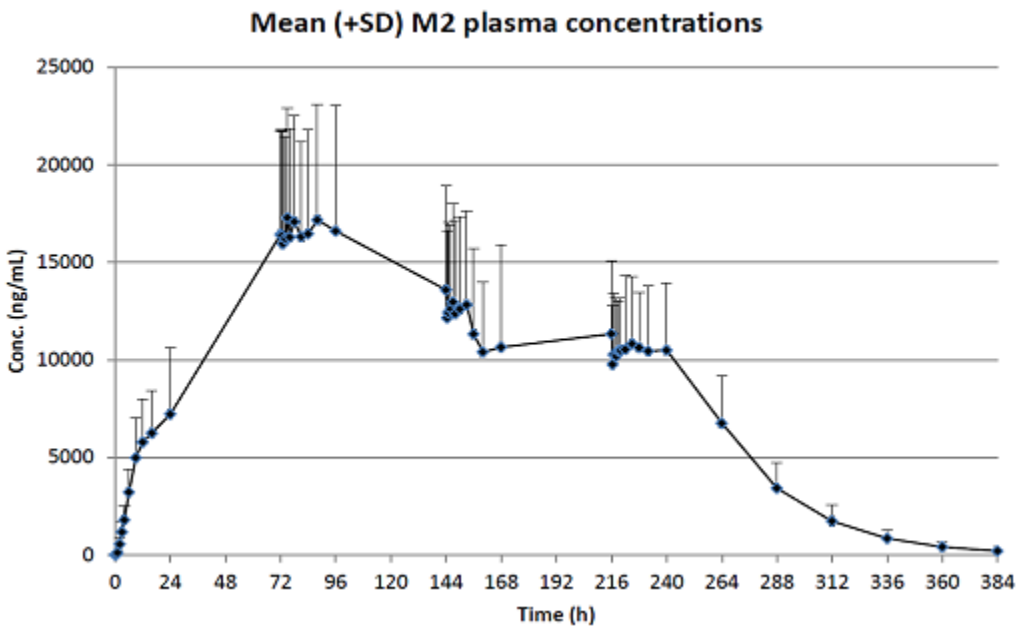


Figure 3: Mean + SD M2 plasma concentrations (ng/mL) measured in plasma samples collected after 1800 mg fexinidazole from Days 1 to 4, then 1200 mg fexinidazole from Days 5 to 10.

Table 10: M2 predose levels in Cohort 1

M2	Predose D2*	Predose D4	Predose D5*	Predose D7	Predose D8*	Predose D10	Predose D11*
1001	6060	13890	17770	12000	12130	11650	10820
1012	4450	13090	8148	7716	9387	7315	9446
1013	7238	11220	11630	13840	11740	10080	10120
1015	13640	24480	24830	15620	15220	19950	16680
1016	9547	22020	21820	21580	19700	11960	15490
1017	8577	23210	26440	16950	15160	12980	11470
1102	12870	21270	16990	21500	13000	12260	8444
1104	4269	13220	14030	11870	1596	9935	8981
1106	4121	13520	10970	7643	4984	6415	5762
1107	7825	16710	22810	15710	9896	15020	14100
1108	3389	7625	7169	4006	3273	6891	6603
1110	4618	16910	16660	14620	11730	11550	8019
N>10000 ng/mL	**2**	**11**	**10**	**9**	**7**	**8**	6
%	17%	92%	83%	75%	58%	67%	50%
N>20000 ng/mL	**0**	**4**	**4**	**2**	**0**	**0**	**0**
%	0%	33%	33%	17%	0%	0%	0%

The minor accumulation seen for fexinidazole and M1 appears consistent with the half-life of the drugs. The similar AUC_{0-24} on day 10 compared with day 7 for M2 indicates there is minimal accumulation and is consistent with its reported half-life.

DNDiFEX008 was a crossover bioequivalence study. The table in the Summary of Biopharmaceutics indicates that the study compared the Aptuit Italy 600 mg tablet used in the efficacy studies with the proposed commercial AAIPharma USA tablet. However, this is not stated in the CSR.

Single doses of test and reference tablets were given with a 2-week washout period. Based on inter-individual variability estimated from the 3-period cross-over results in **DNDiFEX002**, a replicate design was chosen. Dosing was under fed conditions using a field adapted meal (i.e. likely applicable to the target diseased population). Other meals during the residence period were standardised.

The primary analysis of bioequivalence was conducted based on the fexinidazole plasma levels.

Table 11: Summery statistics of PK parameters of fexinidazole calculated after single oral administration of 1200 mg of fexinidazole as two 600 mg Reference formulations (in period 1 or 2 for R1 or 3 or 4 for R2) or as two 600 mg Test formulations (in period 1 or 2 for T1 or 3 or 4 for T2) in healthy male volunteers under fed condition

Treatment		t_{max}# (h)	C_{max} (ng/mL)	AUC_{0-t} (h*ng/mL)	$AUC_{0-\infty}$ (h*ng/mL)	$t_{1/2}$ (h)
R1	N	30	30	30	30	30
	Mean (SD)	4.0 (2.0-8.0)	1120 (337)	13125 (4662)	13402 (4708)	12.6 (5.5)
	GM	3.92	1056	11427	11722	10.9
	CV%	33	30	36	35	44
R2	N	30	30	30	29	29
	Mean (SD)	4.0 (2.0-8.0)	1146 (499)	13395 (6209)	14061 (5923)	12.8 (5.6)
	GM	3.99	1014	11081	12190	11.2
	CV%	34	44	46	42	44
T1	N	30	30	30	30	30
	Mean (SD)	4.0 (2.0-6.0)	994 (315)	11747 (4437)	11959 (4491)	12.6 (6.1)
	GM	3.63	941	10292	10496	10.7
	CV%	32	32	38	38	49
T2	N	30	30	30	29	29
	Mean (SD)	4.0 (2.0-6.0)	1024 (402)	11675 (5300)	12312 (5020)	12.9 (6.0)
	GM	3.51	929	9543	10622	11.2
	CV%	34	39	45	41	47

Individual $t_{1/2}$ values ranged from 1.4 to 25 h after reference and from 1.7 and 29 h following test tablet administrations and were lowest (about 2 h) for 3 subjects with low fexinidazole plasma levels compared to the other subjects. Inter-subject variability in fexinidazole AUCs and C_{max} was moderate (30-46%) and comparable between formulations. There was a 10% decrease in GM C_{max} and 12% decrease in $AUC_{0-\infty}$ for the test compared to the reference tablet. Nevertheless, the lower bounds of the 90% CI were all above 80% while all upper bounds were <1.00.

Table 12: Summary of statistical comparisons of PK parameters of fexinidazole

Parameter	Reference GM	Test GM	GM Ratio (R/T)	GM ratio 90% CI	Reference Interval	Conclusion BE	CV#
C_{max} (ng/mL)	1035	935	0.9038	0.8341; 0.9793	0.7897; 1.2663*	accepted	31.8% *
AUC_{0-t} (h.ng/mL)	11253	9910	0.8807	0.8208; 0.945	0.8000; 1.2500	accepted	24.7%
$AUC_{0-\infty}$ (h.ng/mL)	11587	10204	0.8807	0.8209; 0.9448	0.8000; 1.2500	accepted	25.3%

For M1 the individual t1/2 values ranged from 4-28 h and 4-29 h for the two formulations. The lowest M1 values were seen for the same 3 subjects as for the parent drug. Inter-subject variability in AUCs and Cmax was low to moderate (15-33%) and comparable between formulations. The 90% CI indicated bioequivalence but upper bounds fell below 1.00.

Table 13: Summery of statistical comparisons of PK parameters of M1

Parameter	Reference GM	Test GM	GM Ratio (R/T)	GM ratio 90% CI	Reference Interval	Conclusion BE	CV#
C_{max} (ng/mL)	6973	6482	0.9296	0.8797; 0.9824	0.8000; 1.2500	accepted	20.1%
AUC_{0-t} (h.ng/mL)	107764	99335	0.9218	0.8674; 0.9796	0.8000; 1.2500	accepted	20.9%
$AUC_{0-\infty}$ (h.ng/mL)	108381	100881	0.9308	0.8777; 0.9871	0.8000; 1.2500	accepted	20.7%

For M2 the apparent $t_{1/2}$ ranged from 12.5-31 h for reference and 15.7-33 h for test tablets. Inter-subject variability in M2 AUCs and C_{max} was low to moderate (20-37%) and comparable between formulations. The 90% CI indicated bioequivalence but all upper bounds were <1.00.

Table 14: Summery of statistical comparisons of PK parameters of M2

Parameter	Reference GM	Test GM	GM Ratio (R/T)	GM ratio 90% CI	Reference Interval	Conclusion BE	CV#
C_{max} (ng/mL)	5405	4890	0.9048	0.8537; 0.959	0.8000; 1.2500	accepted	22.5%
AUC_{0-t} (h.ng/mL)	304888	276180	0.9058	0.8506; 0.9647	0.8000; 1.2500	accepted	23.8%
$AUC_{0-\infty}$ (h.ng/mL)	307287	278797	0.9073	0.8522; 0.9659	0.8000; 1.2500	accepted	23.7%

This slightly lower bioavailability of Test product (proposed commercial Alcami USA tablet) in comparison to the Reference product (Aptuit Italy clinical trial tablet) was also evident with mean M2 concentrations in Study DNDiFEX09 (efficacy and safety study with HAT patients with proposed commercial formulation), which appear to be lower than those obtained in the efficacy studies DNDiFEX004 and DNDiFEX006 with HAT patients performed with clinical trial formulation. Nevertheless, there is substantial overlap in the concentration ranges from Study DNDiFEX09, compared with the DNDiFEX004 and DNDiFEX006 studies.

DNDiFEX001 Part II and **DNDiFEX002** investigated the impact of food after a single dose of 1200 mg fexinidazole (2 x 600 mg tablets). Across the two studies, 3 types of meal were tested:

• Standard FDA high-fat breakfast (963 kcal): 2 eggs, a bacon equivalent, 1 slice of white toast with 10g of butter, 2 hash brown potatoes and 240 mL full fat milk (DNDiFEX001-Part II)

• Meal type 1 Plumpy'Nut® (500 kcal): 1 bag of Plumpy'Nut® (92 g) with peanut butter, dry skimmed milk, lactoserum, malto-dextrine, sugar, minerals and vitamins (DNDiFEX002)

• Meal type 2 Rice and Beans (393 kcal): rice (90 g) and red beans (50 g), no fat (DNDiFEX002); thought to be relevant to the diet of the target population for treatment.

Dosing with food increased bioavailability and reduced the variability in PK parameters. The shapes of the PK profiles were not affected and the ratios of metabolites to parent drug for C_{max} and AUCs obtained in fasting or fed conditions were not significantly affected. The magnitude of food effect on C_{max} and AUCs was similar for each type of meal, though meal type 2 (Rice and Beans) increased M2 C_{max} by about 20%. Levels above the MIC of M2 (2200 ng/mL) were only attained when fexinidazole was administered with food.

Table 15: Metabolites to parent drug ratios for the pharmacokinetic parameters after 1200 mg fexinidazole in fasting or fed conditions

Study (laboratory, country)	Fexinidazole dosage, form	Fasting/fed conditions	C_{max}			AUC_{0-t}			$AUC_{0-\infty}$			Study report location
			M1/fexi	M2/fexi	M2/M1	M1/fexi	M2/fexi	M2/M1	M1/fexi	M2/fexi	M2/M1	
			Mean (SD) [GM] *CV (%)*									
DNDiFEX001 Part II (SGS Aster, France) [a]	Treatment A 1200-mg oral suspension	Fasting	**5.58** (1.05) [5.48] *18.76*	**4.92** (0.95) [4.84] *19.36*	**0.90** (0.18) [0.88] *20.43*	**8.20** (2.47) [7.91] *30.09*	**23.03** (4.12) [22.69] *17.88*	**2.91** (0.52) [2.87] *17.83*	**8.00** (2.28) [7.74] *28.50*	**22.53** (3.81) [22.23] *16.90*	**2.91** (0.51) [2.87] *17.42*	5.3.1.1
	Treatment B 2 x 600-mg tablets	Fasting	**5.58** (1.32) [5.46] *23.74*	**4.89** (1.29) [4.74] *26.40*	**0.89** (0.20) [0.87] *22.65*	**9.25** (3.59) [8.82] *38.78*	**23.86** (6.04) [23.31] *25.32*	**2.68** (0.48) [2.64] *17.85*	**8.25** (1.76) [8.10] *21.32*	**21.48** (2.84) [21.31] *13.20*	**2.67** (0.47) [2.63] *17.44*	
	Treatment C 2 x 600-mg tablets	Standard FDA high-fat breakfast	**5.25** (1.57) [5.04] *29.88*	**4.66** (1.48) [4.42] *31.66*	**0.89** (0.17) [0.88] *18.79*	**7.64** (1.93) [7.43] *25.32*	**21.71** (4.25) [21.33] *19.58*	**2.90** (0.45) [2.87] *15.41*	**7.59** (1.92) [7.39] *25.23*	**21.73** (4.19) [21.36] *19.30*	**2.92** (0.45) [2.89] *15.36*	
DNDiFEX002 (SGS Aster, France) [b]	Treatment A 2 x 600-mg tablets	Fasting	**8.193** (1.484) [8.075] *18.1*	**7.388** (2.358) [7.081] *31.9*	**0.890** (0.154) [0.877] *17.3*	**10.483** (2.501) [10.227] *23.9*	**31.934** (9.262) [30.767] *29.0*	**3.090** (0.738) [3.008] *23.9*	**9.393** [c] (2.165) [9.199] *23.1*	**28.210** [c] (6.893) [27.484] *24.4*	**3.092** (0.749) [3.008] *24.2*	5.3.1.1
	Treatment B 2 x 600-mg tablets	Plumpy'Nut®	**6.091** (1.402) [5.946] *23.0*	**4.610** (1.215) [4.455] *26.4*	**0.778** (0.209) [0.750] *26.9*	**8.614** (2.082) [8.411] *24.2*	**27.885** (6.957) [26.923] *24.9*	**3.323** (0.928) [3.201] *27.9*	**8.500** (2.009) [8.308] *23.6*	**27.634** (6.908) [26.678] *25.0*	**3.335** (0.938) [3.212]] *28.1*	
	Treatment C 2 x 600-mg tablets	Rice + Beans	6.126 (0.879) [6.068] *14.3*	**5.437** (1.676) [5.199] *30.8*	**0.892** (0.257) [0.856] *28.9*	**8.451** (1.938) [8.272] *22.9*	**27.060** (6.926) [26.042] *25.6*	**3.284** (0.941) [3.149] *28.7*	**8.318** (1.857) [8.152] *22.3*	**26.745** (6.836) [25.752] *25.6*	**3.295** (0.949) [3.159] *28.8*	

Source: [Tables 14.4.2-10 to 12] in DNDiFEX001-Part II CSR (P080973) and [Table 14.4.3.1-4] in DNDiFEX002 CSR (PH10035).

Abbreviations: **AUC_{0-t}**, area under the curve from time zero to t; **$AUC_{0-\infty}$**, area under the curve from time zero to infinity; **C_{max}**, maximal concentration; **CV**, coefficient of variation expressed in percentages (%); **FDA**, Food and Drug Administration; **Fexi**, fexinidazole; **GM**, Geometric mean; **M1**, fexinidazole sulfoxide; **M2**, fexinidazole sulfone; **SD**, standard deviation.

a N = 12

b N =11

c N = 9

2.4.2. Pharmacokinetics

Absorption

The applicant has performed four *in vitro* permeability studies to assess the potential for intestinal and blood brain barrier permeability of fexinidazole and its metabolites sulfoxide (M1) and sulfone (M2).

The *in vitro* studies (6DNDiP2, 6DNDiP3, 068-10 and 9DNDiP2) were performed in accordance with the standard principles for permeability studies. Systems were validated through known markers. Results from these permeability *in vitro* studies showed a potential for a high intestinal permeability, a low potential for an efflux transport effect by P-gp, and a potential for a high permeability within the human blood brain barrier.

Considering the above, it can be concluded that the applicant is considering P-gp as the only transporter that is relevant to the pharmacology of fexinidazole, taking into account only CNS penetration. However, given that the metabolism and excretion of M1 and M2 are not fully characterised and the proposed SmPC that does not restrict the use of concomitant medications, it is imperative to understand if any other major transporters are involved in the PK of fexinidazole. Despite concomitant medication use may be low in the target population, it is nonetheless important to know which pathways and concomitant medications may contribute to a DDI. The applicant committed to perform *in vitro* studies with different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole, the formation of fexinidazole sulfoxide (M1), the formation of fexinidazole sulfone (M2) and the potential metabolism of M2. The final report is planned to be available in Quarter 1 2019. Considering the low aqueous solubility of fexinidazole (5.9 µg/mL) and its high-permeability, the compound can be considered as a Biopharmaceutic Classification System Class-II compound for biopharmaceutical and regulatory purposes.

The *in vivo* studies DNDiFEX001 Part I, DNDiFEX001 Part III and DNDiFEX003 are considered the first-in-man studies. Fexinidazole and matching placebo were formulated as oral tablets (200 mg and 600 mg of active ingredient) and powder for oral suspension (100 mg, 200 mg and 600 mg). The manufacturing process was developed at Aptuit (Scotland). *In vivo* absorption of fexinidazole following an oral single-dose of a suspension of fexinidazole was fast since the drug was detected in plasma at 0.5 hours (Study DNDiFEX001, Part I). Over the 100-3600 mg dose range, there was rapid biotransformation of fexinidazole into the active metabolite M1 (median t_{max} of fexinidazole was 3.0-4.0 hours and M1 was 2.0-5.0 hours). There was also fast biotransformation of M1 into the active metabolite M2 (median t_{max} of M2 18.0-24.0 hours), although the second biotransformation was slower than the first. Using a suspension formulation of fexinidazole, the mean maximal concentration (C_{max}) and total exposure (area under the curves [AUCs]) of fexinidazole and the 2 metabolites increased with dose in a non-linear manner (mostly less than dose proportionally, DNDiFEX001, Part I).

Study DNDiFEX003 performed in healthy adults showed that the selected dosing regimen of fed conditions with loading dose of 1800 mg/day for 4 days, followed by 1200 mg/day for 6 days allowed the target predicted plasma concentration (twice the MIC for M2) to be achieved after the start of the treatment (Day 2) and high concentrations to be maintained until Day 11 with a peak of 3-fold MIC level from Day 4 to Day 6.

The relative bioavailability of tablets in comparison to oral suspension was studied in study DNDiFEX001 Part II. In this study, it was shown that, regardless of the formulation, when fexinidazole is given in fasting condition, its plasma concentrations appeared rapidly with the first quantifiable sample measured at 0.5 h post-dose. The maximum plasma concentration was reached at a time point varying between 1 and 4 hrs post-dose in all subjects and thereafter mean plasma concentrations decreased according to a multi-exponential profile and remained quantifiable up to at least 24 h post-dose. Mean plasma levels obtained after administration of the tablet were about 20% lower than with the oral suspension.

When given in fed condition, a more important lag-time was observed, due to a delayed gastric emptying (usually 2h on fed state condition when compared to fasting state). The plasma concentrations reached maximum values at a time varying between 2 and 6 h post-dose in all subjects. Thereafter, plasma concentrations decreased according to a multi-exponential profile and remained quantifiable for a longer time than in fasting condition.

To be emphasized mean plasma levels obtained in fed condition were considerably markedly higher than those in fasting condition. In fasting condition, the mean C_{max} and AUC_{0-inf} of fexinidazole were respectively 23 and 24% lower than with the oral suspension. In fed condition, the mean C_{max} and AUC_{0-inf} of fexinidazole were about 200% higher, also showing a markedly reduced inter-subject variability. This food effect might be related to a higher dissolution of fexinidazole due to a higher concentration of bile acids released in this condition.

The safety data from study DNDiFEX001 Part II is in agreement with the proposed method of drug product administration in the SmPC: patients should take tablets with food (i.e., during or right after the main meal of the day and preferably at the same time each day) to ensure that efficacious concentrations are achieved.

Moreover, study results are also in agreement with section 5.2 in the proposed SmPC:

"Following oral administration of a single 1200 mg dose to fasted healthy adult male volunteers, fexinidazole was rapidly absorbed and extensively metabolised with exposures (C_{max}/AUC_{0-24h}) of metabolites which were 6.76/8.67 (M1) and 6.27/10.4 (M2) - fold higher than that of fexinidazole. Food intake increased markedly the bioavailability of fexinidazole, and subsequent both metabolites, by 2.4 to 3.0 fold".

Distribution

Protein binding of fexinidazole and its metabolites was studied *in vitro* (study 6DNDiP5R1, 9DNDiP2 and 401247-20150302) and *in vivo* (study DNDiFEX002). From the *in vitro* studies, it was concluded that fexinidazole is highly bound to plasma proteins (95.4%).

In **DNDiFEX002** the *in vivo* plasma protein binding of fexinidazole, M1 and M2 was estimated in human ultrafiltered plasma obtained after a single dose of 1200 mg following a high-fat meal (Plumpy'Nut®). The bound fraction of fexinidazole, M1 and M2 was constant regardless of sampling time, suggesting concentration-independent protein binding. Fexinidazole, M1 and M2 were bound to plasma proteins at 98%, 41% and 57%, respectively. These *in vivo* data indicated slightly higher binding of fexinidazole vs. *in vitro* estimates (90.7% to 95.4%) whereas binding of M1 and M2 appeared about 40% and 60% higher vs. *in vitro* data (25.9-33.9% for M1 and 33.7-41.6% for M2). The level of plasma protein binding appears to be independent of analyte concentration.

Volume of distribution

Using the popPK model applied to HAT patient PK data, the estimated fexinidazole V/F in adults in DNDiFEX004 was 4550 L, indicating extensive tissue distribution of parent drug, although the between-patient variance was 42%. In children with HAT in DNDiFEX006 the fexinidazole V/F (normalised to a 70-kg patient) was estimated at 6910 L.

CSF in adults (DNDIFEX004)

Using dried CSF from 79 patients, the mean M1 was 1.53±0.95 µg/mL (0.05 to 4.48 µg/mL) and mean M2 was 6.17±2.66 µg/mL (0.27 to 14.91 µg/mL) at 24 hours after the last dose. Compared to the IC_{50} (0.292 µg/mL [0.94 µM] for M1 and 0.270 µg/mL [0.91 µM] for M2), levels of M2 were above the IC_{50} in all 79 patients with

reportable results. The mean CSF to DBS concentration ratio was 0.32 for M2 (variability of 25%) and 0.51 for M1 (variability of 47%).

CSF in children (DNDiFEX006)

Dried CSF samples were collected from 27 children at 24 hours after the last dose.

- For children with a body weight ≥20-<35 kg, the mean M1 was 0.91 µg/mL (range 0.1 to 1.9 µg/mL) and mean M2 was 7.08 µg/mL (range 1.4 to 12.4 µg/mL). In addition, 23/24 (95.8%) children had M1 CSF concentrations >0.292 µg/mL and all had M2 CSF concentrations >0.270 µg/mL.
- For children with a body weight ≥35 kg, only 3 CSF concentrations were available. Concentrations were greater than IC_{50} values for both M1 and M2 concentrations.
- The mean CSF to DBS ratios were 0.54 and 0.47, for M1 and M2, respectively, and were quite comparable between-patients with a variability of about 15%.

Given a mean CSF/Plasma ratio of 0.47 in children and 0.32 in adults obtained in steady state at Day 10 of the treatment regimen (which corresponds to the lowest exposure), and assuming a rapid distribution of free M2 into CSF, the highest M2 concentration in CSF will be reached on treatment Day 4, which corresponds to highest M2 plasma concentration reached with the proposed treatment regimen (repeat oral doses of fexinidazole - 1800 mg/day for 4 days and 1200 mg/day for 6 days) with concomitant food. For adults, the mean target concentration of 2.2 µg/mL in CSF is obtained with a mean plasma concentration of approximately 7 µg/mL, which is reached after 24h after the first loading dose is administered.

Elimination

The applicant presented excretion data for fexinidazole and its metabolites sulfoxide (M1) and sulfone (M2) after oral administration of increased fexinidazole doses, as single (DNDiFEX001 Part I) and multiple (DNDiFEX001 Part III) administration, in fasting state.

After multiple dose administration, the mean estimate for the renal clearance of fexinidazole was between 2.68 mL/h and 6.64 mL/h. After single dose administration, the mean estimate for the renal clearance of fexinidazole was between 1.23 mL/h and 6.01 mL/h. Moreover, in DNDiFEX001part I, the cumulative total excretion amounts of fexinidazole, M1 and M2 account for a mean fraction excreted between 0.75% and 3.15%, assuming that the entire administered dose is totally bioavailable. In conclusion, based on this data, both bioavailability and total elimination pathways of fexinidazole are unknown, which can only be obtained through a mass balance study in humans, which has not been provided. The applicant justified the lack of a mass balance study based on available *in vitro* metabolism data for fexinidazole and metabolites, *in vivo* mass balance data in rats and excretion data in humans for fexinidazole after oral administration. Given the data available from these studies, it is plausible that fexinidazole is characterized by a high fraction absorbed from the gut. Moreover, the rat mass balance study also indicates a plausible biliary excretion of metabolites, as well as urinary excretion of other metabolites than M1 and M2, given the 30% of radioactivity found in urine and trace levels for fexinidazole, M1 and M2 found in urine.

Additionally, it is considered that plasma pharmacokinetics of M1 and M2 have been appropriately characterized in the PK studies performed by the applicant.

Based on the clinical data presented, and without an estimate of fexinidazole bioavailability, the applicant reworded the section 5.2 – Elimination from SmPC, as follows:

"In healthy subjects, after a single oral dose in fasted conditions, fexinidazole was rapidly metabolized to 2 major metabolites, fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2). Only a small fraction (<3.15%) of the fexinidazole dose administered was recovered in the urine. This fraction was mostly composed of M1 and M2 with only traces of the parent drug.The major proportion of M1 and M2 excretion occurred within the first 48 and 120 hours postdose, respectively, into faeces.

In healthy subjects, following the full 10 day treatment regimen, the mean plasma terminal half-life for fexinidazole, M1 and M2 were 14 hours, 15 hours and 23 hours, respectively."

Metabolism

In vitro metabolism studies using human hepatocytes, S9 subcellular fractions, liver microsomes and recombinant enzymes investigated the metabolism of fexinidazole. Based on the results, it was observed that:

- Fexinidazole was highly metabolised *in vitro* by CYP 1A2, 2B6, 2C19, 3A4 and 3A5 isoforms. The M1 and M2 metabolites showed little or no metabolism by the isoforms tested. However, the metabolic pathway responsible for the formation of M2 has not been identified.
- Fexinidazole presented an elevated rate of metabolism in human liver microsomes and a high hepatic extraction (EH) was predicted for humans. M1 and M2 underwent lower and minimal metabolism, respectively. M1 and M2 represented about 74% to 81% and 1% to 3% of fexinidazole loss, respectively. While M2 was derived from the metabolism of M1 (14% to 37% of M1 loss), the metabolism of M2 was not detected.
- Fexinidazole CL_{int} was high in human hepatocytes from Caucasian and African American adult donors while it was moderate in human hepatocytes from paediatric donors.

Table 16: In vitro intrinsic clearance (CL_{int}) for fexinidazole (1 μM) in human hepatocytes

Study (laboratory, country)	Origin of human hepatocytes	Average values of duplicates		Study report location
		$t_{1/2}$ (min)	CL_{int} (mL/min/kg)	
0141-2007 (Nerviano medical Sciences, Italy)	Caucasian	13.4	124	4.2.2.4
0327-2008 (Nerviano medical Sciences, Italy)	African American	6.5	257	5.3.2.2
0291-2011	Pediatric donors			5.3.2.2
(Nerviano medical Sciences, Italy)	3-month old	60.6	46.3	
	1-year old	37.3	78.7	
	2-year old	33.2	95.5	

Due to rapid conversion of fexinidazole to M1, the estimated *in vitro* $t_{1/2}$ and CL_{int} values of fexinidazole for recombinant human FMO-3 enzyme were 15 minutes and 0.93 mL/min/mg protein, respectively. The formation of M1 confirmed that M1 represents the major metabolite of fexinidazole through the activity of human FMO-3, while M2 was not detectable. Moreover, M1 was not metabolised by recombinant human FMO-3 in this experimental setting.

Overall, the studies showed that fexinidazole was metabolised very rapidly. After 120 minutes incubation with human hepatocytes M1 was the main metabolite, while very small amounts of M2 and M3 (N-des-methyl fexinidazole sulfoxide) were detected. A fourth metabolite (a cysteine conjugate of fexinidazole [M4]) formed through glutathione conjugate was identified in hepatocytes from juvenile rats. It is considered that the *in vitro* and non-clinical studies suggest that characterising fexinidazole, M1 and M2 accounts for nearly all the exposure observed. Other metabolites than M1 and M2, e.g. M3 and M4, were not assayed for in the human PK studies.

After being request, the applicant has used the PK data obtained in various races as evidence that there is minimal impact of genetic polymorphisms on fexinidazole metabolism, however given the difference in genotype both within and between different races this is a rather inexact approximation for the impact of genotype. Nevertheless, it is agreed that given the multiple pathways genotype may have minimal impact on the PK of fexinidazole and its metabolites.

Inter-conversion

There are 2 enantiomers of fexinidazole sulfoxide (M1). Selected incubate samples were taken during experiments with fexinidazole in the presence of hepatocytes from mouse, rat, dog, monkey and man (Caucasian, African-American and children) and analysed on a chiral column. The enantiomer of M1 with the shortest retention time was predominant (ratio ~2:1) in human hepatocytes of Caucasian origin (68% vs. 32% at t_0 and t_{120} and 63% vs. 37% at t_{30}). A similar profile of M1 enantiomers was found in hepatocyte samples of African American origin, with ~2:1 ratio of the enantiomer with the shortest retention time. After incubation of fexinidazole with hepatocytes from paediatric donors, different enantiomer profiles of M1 were observed. A 2:1 ratio of the enantiomer with the shortest retention time was found in hepatocytes from a 3-month-old donor at 30 and 120 minutes but a ratio ~4:3 was found with the other 2 lots of hepatocytes (1 and 2-year-old donors).

Dose proportionality

In DNDiFEX001 study after ascending single oral doses in the fasting state, the rate and extent of absorption of fexinidazole were less than dose proportional over the 100-3600 mg dose range such that a 2-fold dose increase gave increases in C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ by 1.46, 1.64 and 1.65, respectively.

The same applied to the metabolites. Doubling the dose would result in increases for respective parameters by 1.33, 1.53 and 1.65 for M1 and by 1.47 and 1.55 for M2.

After multiple dosing in the fasted state over 14 days, exposures to fexinidazole and its metabolites increased with dose but in a disproportional manner. While no formal conclusion was drawn M1 and M2 showed trends toward a slightly less than dose proportional increase of C_{max} and AUC_{0-t} in the dose range 1200 mg - 3600 mg/day. It was suggested by the applicant that this less than dose proportional absorption of fexinidazole behaviour could be due to its classification as a BCS class II drug (low solubility and high permeability).

Pharmacokinetics in target population

Population PK (popPK) models were developed, both on separate and pooled DBS data, to characterise the PK profiles of fexinidazole and its metabolites (M1 and M2) in HAT patients in DNDiFEX004 (adults) and 006 (children). Sampling design in these studies was optimized taking into consideration study environment and its efficiency to estimate properly the model parameters for fexinidazole and M2 C_{trough}, which were of primary interest for efficacy at the time of designing the study.

All three compounds were described by a 1-compartment model. For modelling purpose, the volume of distribution of the 2 metabolites was fixed to 1 L for adults and children since it was not possible to estimate the

volume for each metabolite independently. The applicant has justified the structure of model, with the 2-compartment model for fexinidazole not being fitted due to over-parametrization.

The popPK analysis allowed an estimation of all the PK parameters for fexinidazole, M1 and M2 in adult HAT patients. The general patterns of fexinidazole, M1 and M2 concentrations over time were correctly captured by the base model in HAT adult patients. Comparing the observed *versus* predicted parameters, there was a slight underestimation of the highest concentrations (identified in the GOF plots), but the bias was reduced for M1 compared to fexinidazole and for M2 compared to M1. However, the applicant considers that the predictive performance of the model is adequate and mostly superimposable on the observed data; the 95th percentile being slightly below the simulated band is also recognised. The applicant considers that bootstrapping has limited value. The pcVPCs are presented by study group in adults and children separately with reasonable agreement between the observed and the predicted data.

Fexinidazole PK was quite variable with a between-patient variance of 49% for clearance and 42% for apparent central volume of distribution.

Table 17: Fexinidazole and metabolites M1 and M1 popPK base model parameters and estimated exposure in HAT adult patients

Study (laboratory, country)	Study design	203 HAT patients mean age (range)	Analyte	Median AUC_{0-24h} (µg*h/mL) (range) *CV%*	Estimate (%RSE) [95%CI] *CV%*				Study report location
					D1 (h)	CL/F (L/h)	V/F (L)	k (h^{-1})	
DNDiFEX004 (SGS Life Science Services, Belgium)	R, OL, parallel-group, therapeutic doses Fed conditions	34.9±12.5 y (15-71)	Fexinidazole	**4.55** [a] (0.8-12.8) *43.8* **3.07** [b] (0.5-8.6) *44.1*	**3.60** (3.36) [3.36-3.84]	**364** (4.31) [333-395] *49.2*	**4550** (3.78) [4210-4890] *42.4*	-	5.3.5.1
			M1	**198.2** [a] (28.7-372.2) *27.1* **132.9** [b] (19.1-249.3) *27.4*	-	**1.08** [c] (7.06) [0.931-1.230]	1	**0.010** [d] (7.13) [0.009-0.012] *26.4*	
			M2	**580.2** [a] (74.7-1387.1) *35.0* **413.2** [b] (51.7-1010.3) *35.6*	-	**0.037** [c] (2.47) [0.035-0.038]	1	**0.110** [d] (3.48) [0.102-0.118] *27*	

Source: Appendix 16.2.5 of the DNDiFEX004 CSR (PH15035).

Abbreviations: **$AUC_{0-24 h}$**, area under the curve from time zero to 24 h; **CL/F**, total clearance; **CV**, coefficient of variation; **D1**, duration of absorption; **h**, hours; **HAT**, human African trypanosomiasis; **k**, rate of formation of M1 or M2; **M1**, fexinidazole sulfoxide; **M2**, fexinidazole sulfone; **OL**, open-label; **popPK**, population pharmacokinetics; **R**, randomized study; **RSE**, root square error calculated as percent relative to standard error; **SD**, standard deviation; **V/F**, distribution volume; **y**, years.

a AUC_{0-24h} at Day 4
b AUC_{0-24h} at Day 10
c Considering a fixed volume of distribution of 1 L
d k_{12} for M1 and k_{23} for M2

The AUC_{0-24} predicted on Day 4 (last loading dose) was 1.4-fold higher than that predicted on Day 10 (last day of treatment) for fexinidazole, M1 and M2. Based on median values of Day 10, the M1 to fexinidazole AUC ratio was 43 (vs. 12 in healthy subjects), while the M2 to fexinidazole AUC ratio was 134. The M2 to M1 ratio was about 3.

In children with HAT the adult dose was used for those ≥35 kg while those of ≥20-<35 kg received 1200 mg for 4 days and 600 mg/day for 6 days. Based on the observed data, 85/114 (74.6%) had M2 levels in DBS >10 µg/mL at 24 hours after the last dose on Day 10, including 65/93 [69.9%] in the lower weight group and 20/21

[95.2%] in the ≥35 kg group. In the ≥20-<35 kg weight group, the DBS levels of fexinidazole, M1 and M2 at 24 h after the last dose were 10% to 30% lower compared to the ≥35 kg group.

A popPK model was developed for children as for adults with HAT. An allometric approach was applied to scale all PK parameters to body weight of healthy adult with median weight of 70 kg except for D1 and for clearances the allometric exponent was fixed to 0.75. The estimated CL/F and V1/F for fexinidazole were 552 L/h and 6910 L, respectively, with high inter-individual variabilities for both parameters (CV [%] >65%).

As all model parameters except D1 were estimated for a 70-kg subject, these PK parameters were then expressed for a typical child weighing 26 kg.

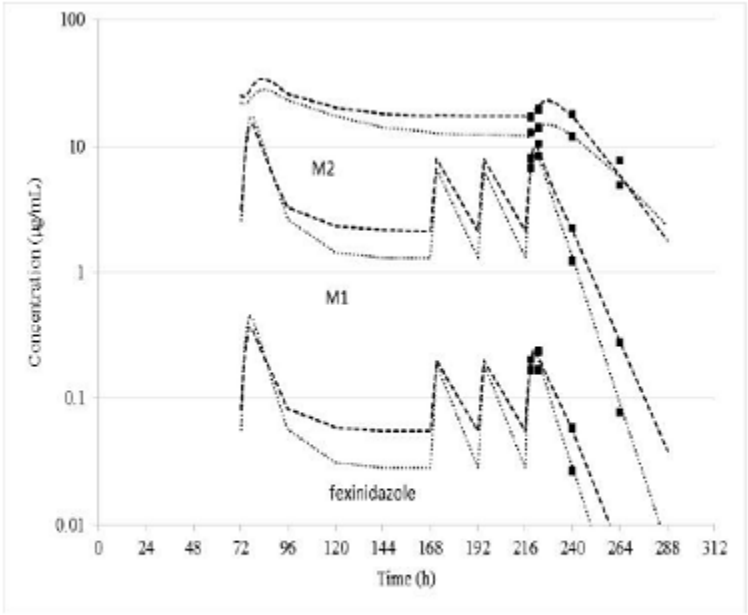
- The CL/F of fexinidazole in a child of 26 kg was 262.7 L/h with a between-patient CV of 74.4%. The V1/F was equal to 2566 L with a between-patient CV of 65%. The residual error CV for fexinidazole was 37%.
- For M1, the CL/F was 2 L/h. The V2/F was considered equal to 1 L and k12 was equal to 0.034 h^{-1} with a between-patient CV of 25.4%. The proportional residual error CV for M1 was equal to 31.9%.
- For M2, the CL/F was 0.039 L/h. The V3/F was considered equal to 1 L and k23 was 0.124 h^{-1} with a between-patient CV of 23.2%. The proportional residual error CV for M2 was equal to 18.1% and additive residual standard error was 0.868 mg/L.

However, the model appeared over parameterized and it was not possible to solve this problem, as all the parameters were structural elements and could not be eliminated.

The AUC_{0-24} predicted on Day 4 was 1.8-fold higher than that predicted on Day 10 for fexinidazole and M1, and for M2 it was 1.5-fold higher. AUC exposure showed high variability for fexinidazole about 60% against 26% to 36% for M1 and M2. The day 10 AUC_{0-24} was moderately increased in children from the highest dose group compared to the lowest dose group (+17% for fexinidazole and M1 and +34% for M2), and the applicant concluded that dose adjustment was adequate.

Based on median values of Day 10, the M1 to fexinidazole AUC ratio was 40 and M2 to fexinidazole AUC ratio was 140 while the M2 to M1 ratio was ~3 (i.e. similar to adults).

Overall, the general patterns of fexinidazole, M1 and M2 concentrations over time were correctly captured by the base model in HAT children. The observed DBS concentration in the 2 weight groups were in perfect agreement with the model predicted concentrations for the 3 compounds.



Square point = observed data, dotted line: simulated concentration in [20-35 kg[body weight group and dashed line simulated concentration in ≥35 kg body weight group. Complete profiles 24-hour on day 4 and 10, residuals between 96 and 216-hour, and one additional point at 3-hour postdoses between 192 and 216-hour postdoses.

Figure 4: Median concentration for fexinidazole and its 2 metabolites (M1 and M2): observed data versus model-predicted data in HAT children

The day 10 predicted AUC0-24 values of fexinidazole, M1 and M2 were comparable between adults and children ≥35kg but slightly lower for the children <35 kg.

Table 18: Model derived AUC_{0-24} (µg.h/mL) for fexinidazole, M1 and M2 based on individual model predicted concentrations on Day 4 and Day 10 in HAT patients

Time point	DNDiFEX004 5.3.5.1	DNDiFEX006 5.3.5.2	DNDiFEX006 5.3.5.2	Pooled data 5.3.3.5 PH16109
	Adults >15 y and ≥30 kg (N = 203) 14 400 mg (1800 x 4 d + 1200 x 6 d)	Children ≤15 y and ≥35 kg (N = 21) 14 400 mg (1800 x 4 d + 1200 x 6 d)	Children ≤15 y and [20-35 kg[(N = 93) 8400 mg (1200 x 4 d + 600 x 6 d)	All HAT patients (N = 317) 14 400 mg and 8400 mg
	Fexinidazole: median [min-max], geometric mean *(CV%)*			
Day 4	**4.62** [0.5-14.1]	**4.30** [1.6-12.8]	**4.56** [0.6-12.4]	**4.59** [0.5-14.1]
	4.46 *(45)*	4.65 *(58)*	4.15 *(59)*	4.38 *(50)*
Day 10	**3.10** [0.3-9.4]	**2.87** [1.0-8.5]	**2.28** [0.3-7.4]	**2.94** [0.3-9.4]
	2.98 *(45)*	3.07 *(59)*	2.10 *(61)*	2.69 *(51)*
	M1: median [min-max], geometric mean *(CV%)*			
Day 4	**197.50** [28.4-384.3]	**179.86** [119.2-283.7]	**193.49** [80.5-320.5]	**195.40** [28.4-384.3]
	190.69 *(28)*	187.20 *(21)*	186.77 *(27)*	189.30 *(27)*
Day 10	**131.80** [19.0-257.3]	**120.10** [79.5-182.2]	**96.90** [40.3-181.2]	**120.50** [19.0-257.3]
	127.58 *(28)*	123.58 *(19)*	94.41 *(28)*	116.54 *(31)*
	M2: median [min-max], geometric mean *(CV%)*			
Day 4	**569.00** [78.1-1386.7]	**525.00** [327.7-937.4]	**435.07** [170.2-863.3]	**528.32** [78.1-1386.7]
	547.99 *(34)*	544.12 *(29)*	443.21 *(33)*	514.67 *(35)*
Day 10	**421.70** [55.3-1039.4]	**403.60** [260.3-655.8]	**303.20** [122.9-620.8]	**390.40** [55.3-1039.4]
	409.76 *(35)*	416.05 *(27)*	301.98 *(35)*	375.04 *(37)*

Source: Table 11 in popPK analysis report PH16109.
Abbreviations: **AUC**, area under the curve; **CV**, coefficient of variation; **d**, day; **HAT**, human African trypanosomiasis; **M1**, fexinidazole sulfoxide; **M2**, fexinidazole sulfone

PK results obtained in the food effect study (study DNDiFEX002), where fexinidazole was administered with a meal composed of rice and beans representing similar field conditions, showed that Day 4-to-Day 10 AUC_{0-24} ratios are similar to the ones predicted by popPK model.

There was a clear trend for rate of transformation of M1 into M2 (k23) and body weight, such that k23 appeared to be lower in children patients with body weight ≥20 to <35 kg. The difference in exposure to fexinidazole was less than the difference in dosing regimen, such that the 2-fold difference in dose (600 mg *vs*. 1200 mg) resulted in ~25 % difference in exposure. The same holds true for M1, while M2 was ~20% lower in children with BW<35 kg.

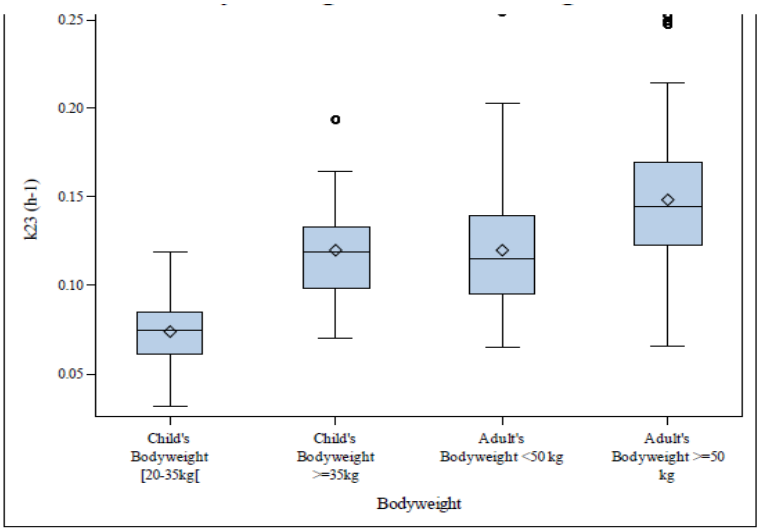


Figure 5:

The CSF to blood ratio was quite comparable between adults and children and was about 53% for M1 (CV of 40%) and 36% for M2 (CV of 30%) for all HAT patients (see below). Based on target levels for M2 in blood (10 µg/mL) and CSF (0.270 µg/mL), proportions with efficacious levels were between 70% and 100% at 24 hours after the last dose on day 10.

Table 19: Mean concentration of metabolites M1 and M2 om CSF of HAT patients and CFS to DBS ratios (DNDiFEX004 and DNDiFEX006 studies)

Parameters at Day 10 T24 h mean (SD), median [min-max] *CV%*	DNDiFEX004 5.3.5.1	DNDiFEX006 5.3.5.2	DNDiFEX006 5.3.5.2	Pooled data 5.3.3.5 PH16109
	Adults N = 79 [a] 14 400 mg (1800 x 4 d + 1200 x 6 d)	Children ≥35 kg N = 3 14 400 mg (1800 x 4 d + 1200 x 6 d)	Children [20-35 kg[N = 24 8400 mg (1200 x 4 d + 600 x 6 d)	All HAT patients N = 106 [a] 14 400 mg and 8400 mg
		M1		
Concentration in CSF (µg/mL)	**1.53** (0.95) **1.24** [0.05-4.48] *62*	ND [b] **1.20** [0.80-2.20]	**0.91** (0.50) **0.89** [0.10-1.9] *55*	**1.39** (0.89) **1.16** [0.00-4.50] *64*
CSF to DBS ratio	**0.51** (0.24) **0.50** [0.05-2.25] *46*	ND [b] **0.82** [0.60-0.90]	**0.54** (0.08) **0.53** [0.30-0.70] *15*	**0.53** (0.21) **0.51** [0.10-2.20] *40*
		M2		
Concentration in CSF (µg/mL)	**6.17** (2.66) **5.72** [0.27-14.91] *43*	ND [b] **8.26** [6.60-11.60]	**7.08** (2.94) **6.94** [1.40-12.40] *42*	**6.45** (2.75) **6.17** [0.30-14.90] *43*
CSF to DBS ratio	**0.32** (0.08) **0.30** [0.15-0.77] *25*	ND [b] **0.61** [0.40-0.70]	**0.47** (0.06) **0.47** [0.30-0.60] *13*	**0.36** (0.11) **0.33** [0.10-0.80] *30*

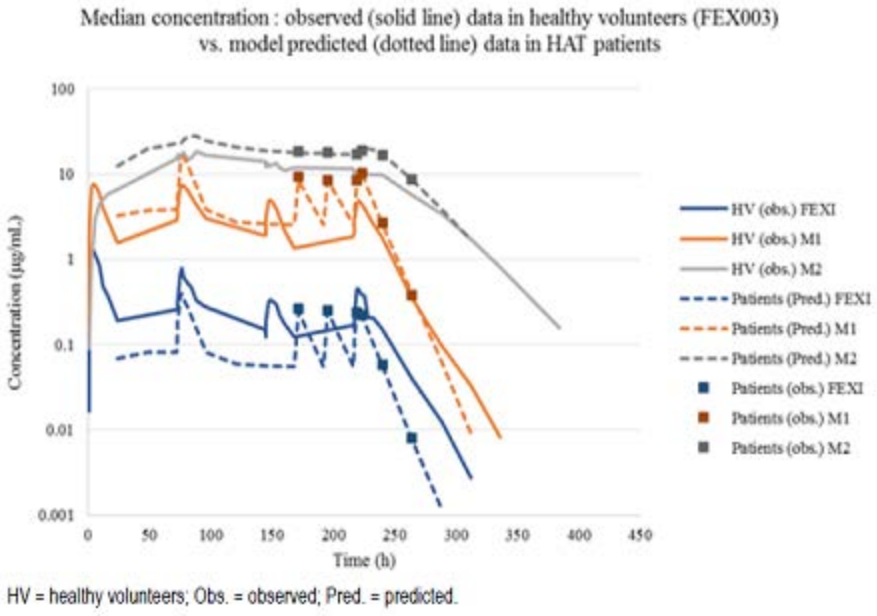
Source: Table 7 in DNDiFEX004 popPK report (PH15035), Table 8 in PH16109 pooled popPK analysis report and [Table 5] in Appendix I.

Abbreviations: **CSF**, cerebrospinal fluid; **CV**, coefficient of variation; **d**, day; **DBS**, dried blood spot; **h**, hour; **HAT**, human African trypanosomiasis; **M1**, fexinidazole sulfoxide; **M2**, fexinidazole sulfone; **ND**, not determined; **SD**, standard deviation.

a N = 70 for adults and N = 97 for all patients for CSF to DBS ratio values

b Not determined when N ≤3

A comparison between healthy subjects vs. HAT patients can be made only for adults since there are no healthy subject PK data other than in sub-Saharan African adult male subjects. The CSR for DNDiFEX004 reports that model-predicted levels of fexinidazole in patients were slightly lower than those measured in healthy volunteers (DNDiFEX003 i.e. same dose regimen in fed state). In contrast, the model-predicted levels of M1 and M2 were higher in HAT patients than in healthy volunteers. It is pointed out that different methods of blood collection and different assay methos were used in the healthy volunteers (plasma) and in the HAT patients (DBS), which could partly explain these findings. The two methods are comparable when measuring the concentration levels of M1 and M2 but there is an underestimation of fexinidazole levels when using DBS vs. plasma.



HV = healthy volunteers; Obs. = observed; Pred. = predicted.

Figure 6: Median concentration: observed data in healthy volunteers (DNDiFEX003, solid line) versus model-predicted data in HAT patients (DNDiFEX004, dotted line)

In the pooled popPK model, which included 317 patients (203 adults and 114 children), only 4 patients were aged over 65 years and 29 patients had a body weight above 60 kg. Results are summarized in the table below, as well as the cross-tabulation of body weight by age groups:

Table 20: Number of patients in each subgroup of age and body weight in DNDiFEX004 and DNDiFEX006

Age group (years)	Frequency	Percent (%)	Body weight group (kg)	Frequency	Percent (%)
[6 to 12[	62	19.5	[20 to 35[	97	30.6
[12 to 15[	50	15.8	[35 to 60[	191	60.2
[15 to 65[	201	63.4	≥60	29	9.20
≥65	4	1.30			

Table 21: Cross-tabulation with number of subjects between body weight and age subgroups in DNDiFEX004 and DNDiFEX006

Age group (years)	Body weight group (kg)			
	[20 to 35[	[35 to 60[	≥60	Total
[6 to 12[	62	0	0	62
[12 to 15[	31	19	0	50
[15 to 65[	4	168	29	201
≥65	0	4	0	4
Total	97	191	29	317

Overall, the concentrations of fexinidazole were similar in patients with body weight above 60 kg and between 35 and 60 kg. However, the concentrations of M1 and M2 were slightly lower in patients with body weight above 60 kg than in those weighing between 35 and 60 kg. Because of the limited number (N = 4) of patients aged above 65 years, the comparison with the other subgroups was not relevant.

Special populations

There were no studies conducted in special populations except for the efficacy study in children with HAT. Intrinsic or extrinsic sources of PK variability were investigated in the popPK analyses using data from HAT patients. None of the covariates tested (age, body weight, BMI, gender, liver function tests, haemoglobin and/or creatinine) had a significant impact on the exposure to fexinidazole, M1 and M2.

The applicant has provided the plasma concentrations for fexinidazole, M1 and M2 on Day 10 with bodyweight as continuous variable. It appears that M2 concentrations are lower for the children especially in the 30-35 kg band compared with other children suggesting potential underexposure in this sub-population. However, there is no apparent impact on efficacy and a recommendation has been included in the SmPC for patients <35 kg, where fexinidazole was considered as treatment of choice, to be hospitalised ensuring better compliance and best treatment option.

Only patients with mild and moderate hepatic renal impairment were evaluable for popPK analyses while the effect of severe impairment could not be assessed due to few patients. Mild or moderate renal impairment did not modify the PK of fexinidazole, M1 and M2. The effect of hepatic impairment using the Child-Pugh classification was not formally assessed. PopPK analyses showed that the liver function parameters tested (AST, ALT, ALP, total bilirubin, albumin, and total protein) were not significant covariates.

The demographic characteristics of the 2013 adults and 114 children who contributed data to the pooled popPK analysis indicate that few adults were aged >65 years, weighed > 60 kg or could be considered overweight based on BMI but exact numbers cannot be discerned from tables and the CSRs do not contain additional data by sub-groups. Females accounted for ~40% of total HAT patients.

Drug interactions

Drug transporter

The unidirectional permeability of fexinidazole, M1 and M2 and interaction potential with the P-gp efflux transporter were evaluated in MDCK-MDR1 cells. On average, the apparent permeability of all analytes was >5 x 10^{-6} cm/s (67.1 x 10^{-6} to 76.2 x 10^{-6} cm/s), indicating a high permeability potential in the apical to basolateral direction. These values were almost not altered in the presence of the P-gp inhibitor GF918 (71.1 x 10^{-6} to 80.2

x 10^{-6} cm/s), from which the applicant concluded that none of the analytes was a strong substrate for P-gp efflux.

The absorption coefficients of all analytes were <0.1, supporting a low propensity of efflux transport by P-gp. It was concluded that fexinidazole, M1 and M2 should be easily transported through the intestine membrane with little or no hindrance by P-gp. No other transporter studies are reported.

Drug metabolism

Fexinidazole, M1 and M2 as victim(s)

Based in the *in vitro* metabolism studies, it was showed that fexinidazole is metabolised to M1 by several CYPs (CYP1A2, 2B6, 2C19, 3A4 and 3A5) and by FMO-3, while M1 and M2 are not significantly metabolised by CYPs. The applicant committed to perform additional *in vitro* studies with different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole, the formation of fexinidazole sulfoxide (M1), the formation of fexinidazole sulfone (M2) and the potential metabolism of M2, however given the limited knowledge regarding the enantiomers of M1, these should be investigated as part of these studies. Moreover, the applicant has also agreed to perform a CYP induction study, for fexinidazole, M1 and M2, in accordance with the guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1). This study will also assess the potential of fexinidazole, M1 and M2 to induce CYP1A2, 2B6, and 3A using human hepatocytes. The reports for both studies are planned to be available in Quarter 1 2019. If the ADME pathways of the M1 enantiomers are different, this may impact safety and/or efficacy fexinidazole in certain sub-populations. The SmPC text has been updated to not recommend other concomitant medications with fexinidazole due to PK interactions, with caution suggested for CYP2D6 inhibitors and paracetamol. Various concomitant medications are contraindicated due to the potential for PD interactions. These adjustments to the SmPC are acceptable, given the limited knowledge regarding the metabolic pathways of fexinidazole and its metabolites.

To further evaluate the consequences of the drug-drug interactions (DDIs) of other drugs on the enzymatic pathways of fexinidazole clearance and M1 and M2 formation and exposures in patients, the applicant has performed popPK analysis of the effects on the fexinidazole PK of different groups of concomitant drugs taken during the 10-days of fexinidazole treatment in the Phase-III trial in adult patients (study DNDiFEX004).

The comparison of the base PK model investigating impact of CNS treatments is however considered as exploratory and does not resolve the outstanding question related to the possible impact that various inhibitors/inducers may have on the PK of fexinidazole. The applicant was unable to explore what impact antacid and cardiovascular treatments had on the PK of fexinidazole due to due to low number of subject taking these medications. The applicant has identified drugs co-administered with fexinidazole and performed a covariate analysis with the only medications given to a significant proportion of patients - CYP2D6 inhibitors and paracetamol. The population PK analysis report documenting the covariate analysis was not submitted. While such an analysis is not a substitute for dedicated clinical DDI studies, it does provide an insight into potential interactions. Neither CYP266 inhibitors nor paracetamol appeared to influence the exposure to fexinidazole, M1 or M2. The SmPC has been updated to caution their use during fexinidazole therapy.

It is stated that an interaction of fexinidazole with strong CYP inducers could decrease fexinidazole exposure and increase M1 and M2 exposures. The applicant concludes that co-administration of CYP inducers with fexinidazole is unlikely to modify its efficacy and appears to dismiss any concern regarding potential effects on cardiac safety related to M2 levels.

Fexinidazole, M1 and M2 as perpetrator(s)

Fexinidazole and M1 inhibited the activity of CYP2C19 and CYP1A2, which could increase exposure to drugs metabolised mainly by CYP2C19 (e.g. omeprazole, lansoprazole, diazepam, mephenytoin) or CYP1A2 (e.g. such as duloxetine, tacrine, tizanodine, theophylline). A DDI study to investigate the potential effects of fexinidazole on CYP2C19 and CYP1A2 is being initiated. No other clinical DDI studies have been conducted or are planned.

Fexinidazole, M1 and M2 induce CYP2B6 mRNA expression so that co-administration of fexinidazole with drugs mainly metabolised by CYP2B6 (buproprion, efavirenz) should be avoided.

Considering the target population for fexinidazole, the risk for DDI is considered low due to the expected low poly-medication. Regarding SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction), the applicant also emphasized the risks of unknown drug-drug interactions with traditional medicines, recommending avoiding the use of these traditional or herbal medicines during the entire treatment with fexinidazole.

2.4.3. Pharmacodynamics

Mechanism of action

The anti-protozoal's mechanism of action of fexinidazole or its two metabolites (fexinidazole sulfoxide – M1; fexinidazole sulfone – M2) is unknown, because no specific studies have been performed to assess the mechanisms of action. The trypanocidal activity is proposed to be related to the low redox potentials that can disrupt the parasite natural biological electron transport mechanisms. Nonclinical studies have suggested that nitro-containing drugs, such as nifurtimox and fexinidazole, have a common mechanism of action that involves bioactivation by NADPH-dependent bacterial-like type I (oxygen-insensitive) nitroreductase (NTR) enzymes found in Trypanosomatids but not in humans, with the production of reactive intermediates with toxic and mutagenic effects.

The possibility of cross-resistance of fexinidazole, M1 and M2 and other nitro-containing drugs, including nifurtimox, was estimated to be low based on the current incidence of stage-2 HAT and *in-vitro* studies investigating emergence of resistance. This cross-resistance can develop to all nitroheterocycles that require type I NTR for its activity like nifurtimox but not for nitro-imidazoles like metronidazole. The latter conclusion is supported by the lack of a signal for cross-resistance between nifurtimox and metronidazole.

It is likely that fexinidazole, M1 and M2 exert their anti-protozoal activity by the same mechanisms as other nitro-containing drugs, including nifurtimox. This being the case, cross-resistance between nifurtimox and fexinidazole could be expected. No in-human cross-resistance data was generated. This is a potential concern for any patient who fails fexinidazole since nifurtimox susceptibility testing cannot be expected to be readily available and NECT may effectively be reduced to eflornithine monotherapy if there is reduced susceptibility to nifurtimox.

It is currently unknown which fexinidazole/metabolite reduction product is responsible for the observed trypanocidal activity and the applicant's assumption that M2 is mostly responsible for efficacy appears to be based on *in vitro* activity (wt/wt) plus the higher plasma levels achieved vs. parent drug and M1. However, this is unproven, which must be borne in mind when considering the applicant's analysis of exposure vs. effect in patients. Moreover, it has been confirmed that fexinidazole and M2 do not have chiral centres/enantiomers. The PD models used a racemic solution (50% of each enantiomer present) of M1 to investigate anti-trypanosomal activity. The applicant has presented the non-clinical studies where the antitrypanosomal activity was assessed following administration of M1, given racemic mixture (50:50 ratio of each enantiomer), and M2. However,

these studies do not provide any information on the enantiomers of M1. The applicant does not propose to perform any further investigations to investigate the antitrypanosomal activity and metabolism of the 2 M1 enantiomers. However, if there is a difference in enantiomers of M1 this may only be apparent in certain sub-populations where the metabolism may be different, therefore further studies are warranted. M1 enantiomers should be investigated as part of the *in vitro* metabolism studies. Further information about the antitrypanosomal activity of fexinidazole M1 (enantiomers) should be pursued dependent on the results of these metabolism studies.

Primary and Secondary pharmacology

Primary PD is based mainly in non-clinical data, since no formal early dose-finding or confirmatory dose-response studies were conducted for the selection of doses. No clinical PD study was conducted in HAT patients apart from the concentration-response (C-R) analyses of electrocardiogram (ECG) records.

Using serial drug dilutions and several strains of *T. b. rhodesiense, T. b. brucei* and *T. b. gambiense* assay the fexinidazole IC_{50} or IC_{90} values were in the range of 0.76 to 3.31 µM (200 to 900 ng/mL) for all tested *T. b.* spp. The M1 and M2 metabolites were slightly more active than parent drug but IC values were of the same order of magnitude. Minimum inhibitory concentrations (MICs) were evaluated in *T. b.* spp. and were 5000, 4740 and 2200 ng/mL for fexinidazole, M1 and M2, respectively. There was no evidence of innate resistance to fexinidazole, M1 and M2 in any of the strains tested (IC_{50} values varied by less than a factor of 4).

In time-to-kill experiments with *T. b. brucei*, fexinidazole displayed poor activity with only 60% killing of parasites after exposure to 50 µg/mL for 30 h. A pulse exposure time of >12 h was needed to exhibit non-reversible effects on the parasites. In contrast, M1 and M2 showed >90% killing within 24 h following exposures to concentrations >3 times the reported MIC value and both exerted irreversible effects on trypanosomes after 6 to 8 h pulse exposures.

In non-clinical models of the disease (different stages of HAT), fexinidazole showed dose-related efficacy: 100% curative in 100 mg/kg oral dosing for four days and IP administration 100 mg/kg/day (2x50 mg/kg/day) for 5 days. 11/15 were cured by 200 mg/kg/day (2 x 100 mg/kg/day) for 5 days. However, M1 and M2 were less active than fexinidazole when administered IP or orally.

In a chronic HAT mouse model, fexinidazole was compared to nifurtimox when given by oral gavage for 5 days. Fexinidazole cured 2/8 mice at 100 mg/kg/day and 7/8 at 200 mg/kg/day while nifurtimox had no curative effects at any dose tested. Plasma levels after dosing on day 5 showed that both M1 and M2 appeared to have activity and the plasma and brain concentrations of non-infected mice where only M2 levels were seen to be above M2 MIC level. 200 mg/kg/day fexinidazole appeared appropriate to obtain a complete cure in this model of HAT and plasma and CSF concentrations of fexinidazole, M1 and M2 should be maintained at or above trypanocidal concentrations for at least 48 hours to achieve elimination.

The use of M2 MIC levels was shown to be appropriate in the clinical studies where good success rates were achieved and it was shown that M2 levels were likely to be above the MIC values.

No dedicated early dose-finding or confirmatory dose-response studies were conducted for the selection of doses and the starting dose for initial Phase I clinical trials.

In **DNDiFEX003**, the selected dose regimens were based on the nonclinical PK/PD studies and the results of the first two Phase 1 studies. Since fexinidazole 3600 mg daily taken in the fasted state for 14 days had been well tolerated, the median plasma M2 C_{max} with the highest dose regimen was to be around 37 mg/L and the median AUC was not to exceed ~793 h.mg/L.

The plasma concentrations achieved with the tolerated cohort 1 regimen (1800 mg/day for 4 days, followed by 1200 mg/day for 6 days) were lower than those projected for fexinidazole, M1 and M2 but the M2 AUC_{0-t} on day 10 (665.9 µg.h/L) was near to that projected (701.6 µg.h/L). Using PK modelling it was concluded that this regimen would achieve the target M2 brain concentration on Day 2 and that concentrations would remain high until Day 11 with a peak of around 3- to 10-fold MIC from Day 4 to Day 6. This regimen was selected for the efficacy studies in HAT patients.

A dose regimen of fexinidazole 1200 mg/day for 4 days, followed by 600 mg/day for 6 days for children ≥20-<35 kg was derived based on dose per body weight considerations, noting that there were no major differences in the metabolism of fexinidazole and M1 and M2 metabolites between human, rat and dog hepatocytes from juveniles and adults.

The justification of the dose-regimen selection in children is based on a similar mg/kg dosing as that of adults in study DNDiFEX004 and the limitation of the available dose-strength (600mg) of fexinidazole formulation.

There is a risk that children in the upper range of 20-35 kg may be underexposed to the active M2, however in the limited data presented (n=93) there is limited evidence that this may lead to disease relapse. The applicant has proposed that children with a body weight<35 kg are hospitalised during treatment to ensure full compliance and best treatment options are made available.

A formal study to investigate the effective therapeutic plasma concentration range in patients with HAT was not conducted. The exposure-response relationships in relation to efficacy in adult HAT patients, were explored in the two C-R analyses of ECG. A similar analysis was not conducted for children with HAT due to the very few failures in DNDiFEX006.

In **DNDiFEX004**, the relationship between PK and effect was evaluated among 11/203 patients with HAT relapse who had PK data, DBS concentrations were similar to those of cured patients except for two patients (06001 and 06009) who had concentrations below the overall population 5th percentile for fexinidazole, M1 and M2. The possible reasons for these observations have not been discussed (see comment above on plasma levels in healthy persons). The M1 and M2 CSF concentrations were slightly lower in the 5/11 patients with relapse for whom there were CSF data compared to other patients. However, some patients who were cured had low CSF levels, with minimum values of M1 and M2 of 0.05 and 0.27 µg/mL respectively.

Secondary PD is based in the arrhythmogenic potential evaluation of fexinidazol, assessed as QTcF, in 2 concentration-response (C-R) analysis of electrocardiogram (ECG) records on pooled data from studies: DNDiFEX001 and DNDiFEX003 (healthy subject) and DNDiFEX004 and DNDiFEX006 (HAT patient).

QT prolongation with imidazole derivatives is documented in the literature (e.g. metronidazole and delamanid). Fexinidazole prolongs the QTc interval and raises heart rate (HR). M2 was shown to weakly inhibit (32.6%) the hERG current at 30 µmol/L (9.34 µg/mL), which was observed in plasma using the recommended dose regimen in HAT patients.

From studies DNDiFEX004 and DNDiFEX006 data, overall, there were 17 patients (8 adults [5 were located in an armed conflict zone], 9 children) with at least 50% of their measured M2 concentrations below the 5th percentile and no healthy subject. According to the applicant, these apparent low concentrations could not be explained by demographic characteristics, the stage of the disease, the lack of compliance or any adverse events reported during the treatment, except for 5 patients. However, these low exposures were not correlated with therapeutic failure, as only 2/17 (11.8%) patients had HAT relapse. Furthermore, the healthy subject with the lowest M2 concentrations remained above the 5th percentile of all patients at steady state (Day 10 at 3 hours).

Statistical C-R models were developed to compare ΔQTc as response variable and fexinidazole, M1 and M2 concentrations as dependent variables in 3 distinct models. The final models, linear and nonlinear, and estimations were different between studies and could not be directly compared for each compound but conclusions from the two C-R analyses were concordant, since both showed that QTc prolongation was strongly related to M2 levels being relatively stable due to a saturable E_{max} pattern. Hence, ΔΔQTcF increases were related to M2 concentrations with a relationship that flattened as exposure increased, towards a maximum effect of around 23 msec.

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

In **DNDiFEX004**, 19 (7.2%) patients in the fexinidazole group had a QTcF value of >450 msec vs. none in the NECT group and 72 (27.3%) vs. 9 (6.9%) in respective groups had a change from baseline between 30 and 60 ms. Three patients in the fexinidazole group had a recorded change from baseline in QTcF >60 msec and 3 had values > 480 msec. Two had a value exceeding 500 msec at 9 and 11 days after the EOT.

In **DNDiFEX006**, 3 patients treated with 1200/600 mg fexinidazole had a recorded change from baseline in QTcF >60 msec but none was >500 msec. The context of the QTc analyses (checks for heterogeneity and hysteresis and the topics pertinent to ICH E14) was considered acceptable. The exposure data of two children who had relapsed (one was a confirmed failure to respond and the other was a false failure as the month 18 data) established that these patients were exposed and successfully treated, confirming that failure in this study was not related to under-exposure.

Based on worst-case scenario effect on QTc and considering potential inter-individual variability, the model ensures that no further increase in QTcF would occur.

Analysis of data from these two studies gave an estimated ΔQTcF at highest M2 exposure of 18.0 msec for adults and 14.9 msec for children.

In healthy volunteers and in HAT patients, administration of fexinidazole resulted in a mean increase in heart rate (HR) of about 10 bpm, with quite narrow 90% confidence intervals around estimates. Rates for AEs of palpitations and tachycardia were not notably higher for fexinidazole vs. NECT in patients. The applicant's exposure-response analysis did not look at effect on HR. Nevertheless, it seems the effect on HR is modest and the safety data do not suggest clinically important effects.

An additive effect on QT interval prolongation of fexinidazole with other medicinal products that may prolong the QTc interval cannot be excluded and this potential risk is included in the proposed product information.

Regarding potential pharmacodynamics drug-drug interactions with fexinidazol, althought fexinidazole inhibited muscarinic M1 and M2 receptors, a potential PD interaction with muscarinic receptor antagonists is considered unlikely, based on the low levels of fexinidazole (below IC50) in the CNS for patients.

Because there is potential class effect PD interactions of fexinidazole with disulfiram (psychotic reactions with administration of other 5-nitroimidazoles like fexinidazol) and propylene glycol (5-nitroimidazoles interfere with the metabolism of propylene glycol), these potential interactions are included in the proposed product information.

2.4.4. Discussion on clinical pharmacology

Several *in vitro* and *in vivo* studies were conducted to investigate the clinical pharmacokinetics of fexinidazole and its metabolites sulfoxide (M1) and sulfone (M2). The applicant justified the lack of a mass balance study in humans was based on available *in vitro* metabolism data for fexinidazole and metabolites, *in vivo* mass balance data in rats, and excretion data in humans for fexinidazole after oral administration. Given the results from *in vitro* permeability studies with fexinidazole as well as the rat mass balance study, it is plausible that fexinidazole is characterized by a high fraction absorbed from the gut. Moreover, the rat mass balance study also indicates a plausible biliary excretion of metabolites, as well as urinary excretion of other metabolites than M1 and M2, given the 30% of radioactivity found in urine and trace levels for fexinidazole, M1 and M2 found in urine.

Moreover, the *in vitro* PD activity and *in vivo* PK studies suggested that M2 would probably be the most active metabolite in man. The *in vitro* MIC of M2 in *T. b.* spp. (2200 ng/mL = 2.2 µg/mL) was used to set the target brain exposure for this clinical trial following repeated administration of fexinidazole. Target levels in the brain were set at twice the MIC of M2, and these had to be maintained for at least 48 to 72 hours, in view of the *in vitro* time to kill studies with fexinidazole and metabolites. Using PK modelling of human plasma level data, it was shown that the target PK profile of M2 in the brain could be achieved by a loading dose (over 4 days) of fexinidazole followed by a maintenance dose (over 6 days), under fed conditions.

Further, high and sustained M2 levels would also be achieved in plasma. Two regimens using a loading and maintenance dose, under fed conditions, were tested in DNDiFEX003 study. The fexinidazole dose regimen of 1800 mg/day for 4 days, followed by 1200 mg/day for 6 days, had acceptable safety, and the systemic PK profiles obtained indicated that the target M2 brain concentration (twice the MIC) should be achieved quite early after the start of the treatment (Day 2) and should remain high until Day 11 with a peak of 3-fold MIC level from Day 4 to Day 6. Therefore, this same dose regimen was selected for the future Phase II/III clinical trials (DNDiFEX004 and DNDiFEX005) in HAT patients. A dose regimen with lower fexinidazole dose levels (1200 mg/day for 4 days, followed by 600 mg/day for 6 days) with the objective of having similar exposure was derived based on dose per body weight considerations for treating children in Phase II/III studies (DNDiFEX006), taking into account that non-clinical *in vitro* PK studies had shown that there were no major differences in the metabolism of fexinidazole and M1 and M2 metabolites between human, rat and dog hepatocytes from juveniles and adults. Even so, confirmation is needed related to the adequacy of the selected doses for paediatric patients. This is particularly required as it appears that more severe stage-2 HAT may fail to respond, and this could be potentially a greater risk in children if the exposures are not comparable to the adult population.

Apart from the Concentration-Response (C-R) analyses of ECG, no PD study was conducted in HAT patients. No specific studies have been performed to assess the MoA of fexinidazole and the M1 and M2 metabolites.

Nevertheless, C-R analyses showed that fexinidazole induced QTc prolongation and that this prolongation was strongly related to the extent of exposure to the metabolite M2 and unlikely to be directly related to either fexinidazole or M1 concentrations. Moreover, the C-R models built for M2 appeared more consistent than those built for fexinidazole and M1, in particular because the models addressed the cumulative effect on ΔQTcF after multiple-dosing, which was consistent with M2 accumulation, and that dissipation of effects on ΔQTcF were consistent with decreasing M2 concentrations after last administration.

Based on the findings of PD/PK modelling, the treatment of HAT patients with fexinidazole does not exhibit additional concerns regarding the cardiac safety of this compound with respect to dosing and duration of anti-infective treatment. Furthermore, in the clinical situation, there are no extrinsic factor risks that should modify (increase) the exposure to M2, and therefore the risk of QTc prolongation. In addition, it must be

emphasised that the anti-malaria treatment based on artemether-lumefantrine, a slight QT prolongator, administered before treatment with fexinidazole in HAT patients, did not increase the magnitude of the QT change from baseline.

2.4.5. Conclusions on clinical pharmacology

In healthy subjects, the systemic PK of fexinidazole and metabolites, M1 and M2, were investigated in plasma (DNDiFEX001, DNDiFEX002 and DNDiFEX003). The applicant commits to perform additional *in vitro* studies with different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole, the formation of fexinidazole sulfoxide (M1), the metabolism of M1 enantiomers, the formation of fexinidazole sulfone (M2), and the potential metabolism of M2. Moreover, the applicant has also agreed to perform a CYP induction study, for fexinidazole, M1 and M2, in accordance with the guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1). This study will also assess the potential of fexinidazole, M1 and M2 to induce CYP1A2, 2B6, and 3A using human hepatocytes. The reports for both studies are planned to be available in Quarter 1 2019 and have been included as post-opinion measures. The SmPC text has been updated to not recommend other concomitant medications with fexinidazole due to PK interactions, with caution suggested for CYP2D6 inhibitors and paracetamol. Various concomitant medications are contraindicated due to the potential for PD interactions. These adjustments to the SmPC are acceptable, given the limited knowledge regarding the metabolic pathways of fexinidazole and its metabolites.

There is limited evidence to support the potential risk that children in the upper range of 20-35 kg may be underexposed to the active M2, leading to potential disease relapse. Children with a body weight<35 kg, for whom fexinidazole was selected for treatment, must be hospitalized during treatment to ensure full treatment compliance.

2.5. Clinical efficacy

The main objective of the clinical development programme was to demonstrate that a 10 day, oral regimen of fexinidazole would allow acceptable rates of cure for both Stage 1 and Stage 2 HAT patients, thus avoiding the need for the mandatory pre-treatment disease staging, based on the parasitologic and cytologic result of CSF.

Description of the programme

Efficacy data in HAT patients were obtained in the following studies:

Study Category/ Identifier	Summary of key study information	Planned study duration	Number of patients/ subjects evaluated for safety
Patients with human African trypanosomiasis (included in pooled analysis completed to the primary endpoint)			
DNDiFEX004 HAT due to T.b. gambiense in the meningo-encephalitic stage (late stage 2)	Efficacy and safety of fexinidazole compared to nifurtimox-eflornithine combination therapy (NECT) in patients with late stage human African trypanosomiasis (HAT) due to *T.b. gambiense*: pivotal, non-inferiority, multicentre, randomised, open-label study	Patient participation for approximately 25 months	394 (264 fexinidazole; 130 NECT)
DNDiFEX005 HAT due to T.b. gambiense (stage 1 or early stage 2)	Efficacy and safety of fexinidazole in patients with stage 1 or early stage-2 human African trypanosomiasis (HAT) due to *T.b. gambiense*: a prospective, multicentre, open-label and single arm cohort study, plug-in to the pivotal study	Patient participation for approximately 19 months	230
DNDiFEX006 HAT due to T.b. gambiense (any stage)	Efficacy and safety of fexinidazole in children ≥6 years and <15 years old and over 20 kg body weight with human African trypanosomiasis (HAT) due to *T.b. gambiense*: a prospective, multicentre, open study, plug-in study	Patient participation for approximately 19 months	125

There is also one ongoing study (DNDiFEX009) in HAT:

Studies ongoing at safety cut-off 15 August 2017 (no Clinial Study Reports yet available)			
DNDiFEX09HAT (Phase IIIb) HAT	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	Patient participation for approximately 19 months	Planned to include 174 patients; 28 patients treated by 15 Aug 2017

The clinical efficacy program for fexinidazole for the treatment of trypanosomiasis caused by *T. brucei gambiense* included one pivotal study (DNDiFEX004) comparing fexinidazole tablets to existing NECT treatment (reference therapy) in adults with late stage 2 HAT. In addition, efficacy data are presented from 2 cohort 'plug-in' studies; these were initiated at the same study sites as the pivotal study (except for 2 sites in Study DNDiFEX004 that were not used in the plug-in studies) to increase the safety database and provide complementary data on efficacy for fexinidazole in adults with early stage 2 or stage 1 HAT (Study DNDiFEX005) and in children of ≥6 years with disease at any stage (Study DNDiFEX006).

The main pivotal study and supportive study DNDIFEX005 were considered as main studies, as they encompass the whole targeted spectrum of the disease, as proposed in the indication. Study DNDIFEX006 is considered as supportive data and as data in special populations.

2.5.1. Dose response studies

No dose-defining studies have been conducted. The relevant inhibitory concentrations of fexinidazole for use in the clinical development setting were derived from a few studies in healthy volunteers. However, no data regarding the distribution in CSF were obtained in humans prior to the conduction of Phase II studies and only limited data were ultimately available from the PK assessments included in the phase II/III clinical development programme.

In addition, even considering that the need for an initially higher exposure could improve the time-to-kill curve, the optimal duration of this period of increased exposure was not tested in dose finding studies.

The dose regimen of 1800 mg once daily, for 4 days, followed by 1200 mg once daily for 6 days, administered by the oral route, was selected for the phase-II/III clinical trials in adult HAT patients. For study DNDIFEX006, in paediatric patients aged 6 to 15 years or weighing more than 20 kg that were able to tolerate the tablets, the doses were adjusted according to body weight, as follows:

- Body weight ≥20 kg and <35 kg

- 1200 mg (2 x 600-mg tablets) once daily for 4 days (Days 1 through 4)

- 600 mg (1 x 600-mg tablet) once daily for 6 days (Days 5 through to 10)

- Body weight ≥35 kg (same as in adults)

- 1800 mg (3 x 600-mg tablets) once daily for 4 days (Days 1 through 4)

In children weighing less than 20 kg, the following dose regimen was administered:

- 600 mg from Day 1 to 10 if body weight <20 kg.

All participants were recruited in a geographic region with considerable endemicity for HAT and all had clinical and diagnostic elements compatible with the diagnosis of active HAT.

2.5.2. Main studies

- Study DNDiFEX004:

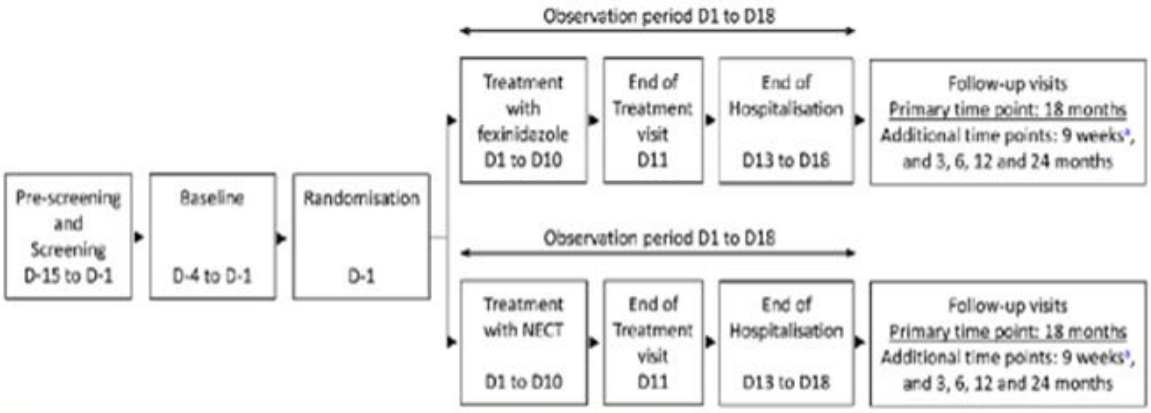
Efficacy and safety of fexinidazole compared to nifurtimox-eflornithine combination therapy (NECT) in patients with late-stage human African trypanosomiasis (HAT) due to T. b. gambiense: a pivotal, non-inferiority, randomised, open-label, multicentre study

The pivotal **study DNDIFEX004**, conducted between 2012-2016, selected only late stage 2 patients. In usual practice, patients are classified as being in stage 2 once they show a white blood cell (WBC) count >5 cells/µL in the CSF, but for the purpose of this study and to guarantee that the central nervous system (CNS) is attained by the disease, the lower limit of WBC in CSF was set at >20 cells/µL. Therefore, stage 2 patients were classified in two categories for the purpose of the clinical development programme of fexinidazole: early stage 2 and late stage 2. Early stage 2 patients were not eligible for the pivotal study, but they were for the subsequent studies DNDiFEX005 and DNDiFEX006.

This study (and the plug-in studies) was conducted at 9 sites in Democratic Republic of the Congo (DRC) and one site in Central African Republic (CAR). The sites were numbered from 01 to 10 according to their opening dates: in DRC. The CSR presents data collected through 18 months of follow-up and available data up to 24-months follow-up for patients who had reached this time point on the cut-off date.

At baseline, all participants had clinical and diagnostic elements that were compatible with the diagnosis of active HAT.

Study DNDiFEX004 was a randomised, open-label, multicentre, parallel-group study (see figure below) to assess the efficacy and safety of fexinidazole compared with NECT in patients with late stage 2 HAT due to *T. b. gambiense*



Note: For the purpose of the study, patients were hospitalised from their arrival at the investigational site (hospital/study site) until Day 18 (unless their clinical status was satisfactory, and they were permitted to leave from Day 13). Patients were to be followed for 24 months. Additional unscheduled visits could occur and were recorded in the eCRF.

a The Week 9 visit was performed in a subset of patients (the patients who reached this visit starting in mid December 2014), as per Protocol Amendment 3, release date 09 February 2015.

eCRF = electronic case report form; D = day; NECT = Nifurtimox-Eflornithine Combination Therapy.

Figure 7: Study design

Methods

Study Participants

Inclusion criteria for the pivotal study were:

1. 15 years of age or older

2. Male or female

3. Able to ingest at least one complete meal per day (or at least one sachet of Plumpy'Nut®)*

4. Karnofsky score >50

5. Late stage 2 HAT due to *T. b. gambiense* with confirmed evidence of parasite in the blood and/or lymph and/or CSF, certified by the report from the mobile team, with details on examinations performed and CSF WBC count, or performed at the investigational site. If testing for parasites in CSF was negative, a CSF WBC >20 cells/µL was required to confirm late stage 2 HAT. If testing for parasites in CSF was positive with a CSF WBC ≤20 cells/µL, the patient was considered as late stage 2 HAT. This deviates from the WHO recommendations.

Exclusion criteria were similar for all 3 studies, with only slight not relevant changes:

1. Severe malnutrition, defined as body mass index (BMI) <16 kg/m2

2. Unable to take medication by the oral route

3. Pregnancy or breastfeeding

4. Clinically significant (CS) medical condition that could, in the opinion of the Investigator, have jeopardised the patients safety or participation in the study, including, but not limited to significant liver or cardiovascular

disease, suspected or proven active infection, central nervous system trauma or seizure disorder, coma, or consciousness disturbances

5. Severely deteriorated general status, including as a result of cardiovascular shock, respiratory distress, or endstage disease

6. Any condition that affected the patient's ability to communicate with the Investigator as required to complete the study

7. Any contraindication to imidazole drugs, ie, known hypersensitivity to imidazoles, or to NECT, ie, known hypersensitivity to DFMO

8. Prior treatment for HAT

9. Prior enrolment in the study

10. Foreseeable difficulty complying with follow-up, including migrant worker, refugee status, itinerant trader

11. History of alcohol or drug addiction

Treatments

Patients were randomised centrally to receive fexinidazole (test drug) or NECT (active comparator) in a 2:1 ratio (fexinidazole:NECT). The treatment regimens were as follows (please see above for the justification of the fexinidazole adult dose regimen):

- Fexinidazole: fexinidazole 1800 mg (3 × 600-mg tablets) administered orally, once daily for 4 days (Days 1 through 4), followed by 1200 mg (2 × 600-mg tablets) administered orally, once daily for 6 days (Days 5 through 10), with food.

- NECT: nifurtimox tablets administered orally, three times daily at a dose of 15 mg/kg/day for 10 days (Days 1 through 10) + DFMO administered twice daily as a 2-hour intravenous (IV) infusion at a dose of 400 mg/kg/day for 7 days (Days 1 through 7), with food. The dose of nifurtimox was adjusted using quarters of 120-mg tablets as needed to achieve a dose as close as possible to 5 mg/kg TID. NECT was chosen as the comparator therapy because it was considered as the first-line treatment and had been added by WHO to its list of Essential Medicine (16th list, 2009) thus being adopted by National HAT Control Programmes as first-line treatment for late stage 2 HAT due to T. b. gambiense.

The total duration of treatment for both regimens was 10 days. Treatments (i.e., fexinidazole and NECT) were administered to patients at the investigational sites by site personnel during the period of hospitalization. Treatment compliance was recorded in each eCRF in such a way as to maintain the blind for the Sponsor and its representatives (no access to the treatment page in the eCRF Sponsor view).

Objectives

The primary (and relevant for the demonstration of efficacy in the proposed indication) **objective** for **study DNDIFEX004**, as initially projected, was to demonstrate that the success rate of the above mentioned 10 day regimen of oral fexinidazole in adult patients with Stage 2 HAT, was in favour of fexinidazole when compared to the currently recommended treatment, NECT, 18 months after the end of treatment (EOT).

Alternatively, the demonstration that the success rate of fexinidazole was "acceptable" was also a defined objective for the study. Fexinidazole was to be considered an acceptable treatment if the difference in response, as compared to NECT, was ≤13% in favour of NECT. Such a difference in response rate was considered acceptable by the applicant, in view of that the ability to administer fexinidazole orally would provide a

treatment advantage. The decision to accept a difference ≤13% in terms of a potential loss of efficacy, as compared to standard NECT, was based on a survey sent to HAT clinicians by email. A total of 19 clinicians (out of 20) completed the survey producing quite variable personal views on the acceptable limit. The retained margin of acceptable difference corresponds to the mid-point between the median response for the unacceptable difference (17%) and the median response for acceptable difference (9%). It also corresponds to the first tertile of the unacceptable difference (ie, 31.5% of the respondents had an unacceptable limit below 13%). In fact, the choice of the 13% margin may have been more based on personal clinical experience than on a statistical estimation. The choice of the value for this limit is relevant, particularly if efficacy comparison is not in favour of fexinidazole.

The secondary objectives included the assessment of a correlation between plasma and CSF concentrations of fexinidazole and its metabolites and the efficacy and safety of fexinidazole in patients with late stage 2 HAT due to *T. b. gambiense.*

Outcomes / endpoints

The **primary endpoint** was the outcome (success or failure) of the treatment and was assessed from the absence/presence of trypanosomes in body fluids and the WBC count in the CSF at EOT (adapted from WHO criteria) 3, 6, 12 and 18 months (except that CSF was tested at 3 months only if there were signs and symptoms of HAT). Testing was also performed at 24 months if relapse was suspected or according to local standard of care.

The CSF samples were also analysed to determine WBC count, as a test of brain inflammation, indirectly reflecting persistence of HAT infection. For each CSF sample, counting WBC was to be performed by 2 laboratory technicians. If the 2 readings were consistent, the first reading was entered in the eCRF. If the 2 readings were inconsistent, the head of the mobile team or the laboratory supervisor had to perform WBC counting from its initial step and his/her reading was entered in the eCRF. If the CSF WBC count was between 19 and 22 cells/ µL, inclusive, the WBC count had to be confirmed by the supervisor.

The chosen **secondary efficacy endpoints** were the outcome (either success or failure) of treatment as assessed at Day 11 (24 hours after EOT), and 3, 6, 12, and 24 months, after the EOT. The additional 24-month assessment visit was considered the late efficacy time point, the 18-month visit was considered the primary time point and the 12-month visit was considered an early efficacy time point. This time points were used respectively for the late endpoint (24 months), the primary endpoint (18 months) and the early endpoint (12 months). Earlier follow-up time points allowed detecting early relapse.

For the late efficacy endpoint at 24 months, the definitions of success and failure were the same as for the primary efficacy endpoint if a lumbar puncture was performed or if a definitive failure occurred before. In all other cases, the handling of missing lumbar puncture at 24 months gave more importance to the absence of signs and symptoms evoking a relapse.

Sample size

The epidemiology of HAT had a very favourable evolution over the last decade. At the time of study initiation (11 October 2012), 7216 annual cases had been reported worldwide. With the increased efforts of control programmes and availability of very effective combination regimen of eflornithine and nifurtimox (NECT) only 2804 HAT cases worldwide were reported to the WHO in 2015, the lowest level since the start of systematic global data collection 75 years ago.

The above mentioned notable change in incidence rate of HAT had a considerable impact on the design of the development programme. In fact, as enrolment of patients became slower, the applicant has successively

negotiated protocol amendments for the two studies in adults that conducted to an agreed reduction in sample size with the consequent increase in the risk of bias and uncertainty of the results.

In pivotal study 004, the initial approved version of the protocol had an overall sample size of 510 patients. Early on (2013), it was detected that the planned sample size would be difficult to reach. Based on these elements, a gathered Expert Committee recommended to reduce the sample size to 390 patients in total (260 in the fexinidazole group and 130 in the NECT group), with a subsequent reduction in study power from 87.8% to 80%. This sample size was calculated assuming a success rate of 89% for fexinidazole and 94% for NECT and a margin of acceptable difference of 13%, and using a global power of 80% for the final analysis, with a one-sided type 1 error rate of 0.025. The power refers to the probability that the 95% confidence interval (CI) of the difference in success rates between the two treatment groups would exclude the chosen limit of an unacceptable difference. This reduction was subsequently confirmed in meetings with the regulatory authorities and was implemented to the study conduct.

For study DNDIFEX004, a patient was considered as randomized as soon as a treatment was allocated by the eCRF.

Randomisation and blinding

In study DNDIFEX004 the methodology of randomization is well described by the applicant as are the measures taken in order to implement the study methodology. The allocation of randomized patients was blinded.

The open-label design for Pivotal study 004 was justified by the fact that the route of administration and dosing regimen were different for the two study treatments. The patients and Investigators (including Coordinating Investigator and Principal Investigator) were therefore aware of the treatment received. Other personnel/activities not blind to treatment included: the monitors, the eCRF support personnel, the independent statistician in charge of the interim analysis (introduced per Protocol Amendment 3, release date 09 February 2015) and the futility analyses (not performed), the IREC which assessed the 12-month interim analysis, and the personnel in charge of central reading of triplicate ECG. With regard to the personnel responsible for the bioanalytical PK laboratory, they were also not blind to treatment but did not have the clinical database information and were asked to generate a new random code in case of distribution of information for DSMB meetings.

All other personnel involved in the study, including the Sponsor, data management personnel, study statistician and statistical consultant, were kept blind to treatment until the final analysis at 18 months. Specifically, treatment compliance was recorded in the eCRF in a way that did not allow the Sponsor or his representative to identify the treatment received. The DSMB was kept blinded but had the possibility to break the code in case of safety concern.

Apparently, the blind was only broken for two patients during the study, for safety reasons.

Statistical methods

Analysis populations were defined as follows

The intention-to-treat (ITT) population comprised all randomized patients who received at least one dose of study treatment. This population was used to perform a sensitivity analysis on the primary efficacy endpoint. This population was also used to perform all safety analyses, as treated.

The choice to implement an mITT population in study DNDIFEX004 , defined by the exclusion of patients that had fled the region due to armed conflict, is prone to discussion, as, strictly, these patients are losses to follow-up. The method for replacement of these patients was provided and explained as an extension of the

inclusion. This decision was not pre-defined in the protocol, as it was made before the interim analysis, and therefore should be considered arbitrary. Furthermore, it may be considered that the decision to exclude these patients may be justified in light of the Guideline for Statistical Principles for Clinical Trials (CPMP/ICH/363/96), as the motives for the exclusion are discussed and, whereas it may be unclear that fleeing from the study region may not have been confirmed at all cases, all patients with similar characteristics were excluded from both arms and the ITT principle may not have been violated.

The patients who were discarded from the mITT population were replaced in the ITT (not in the mITT) in which they were considered as failures. The replacement of patients excluded from the mITT analysis due to war conditions, was clarified by the applicant as not a real replacement as performed in many Phase I studies, and consisted in a small increase of sample size. An analysis with these patients excluded as failures, as per protocol, was provided showing that the difference in efficacy is still within the proposed acceptability margin.

The mITT population was used to perform the primary efficacy analysis and is therefore considered as the primary analysis set. This population was also used to perform multiple sensitivity analyses and secondary efficacy analyses. The analyses of efficacy performed on the mITT population were performed as treated, except for one sensitivity analysis on the primary efficacy endpoint that was performed as randomized.

The treatment completers (TC) population comprised all mITT patients who completed the treatment period and received all prescribed (protocol-planned) doses of study treatment. This population was used to perform a sensitivity efficacy analysis on the primary efficacy endpoint and safety analysis.

The EP population comprised all mITT patients, except (a) the patients who died for reasons clearly independent of treatment efficacy, treatment safety, or disease evolution, or (b) the patients who were not classified at 18 months due to insufficient information (patients lost to follow-up and patients with no post-treatment lumbar puncture). Exclusions were documented and decided during the blind data review meeting and when necessary, the cases subject to interpretation were submitted for adjudication to three independent experts from the DSMB committee.

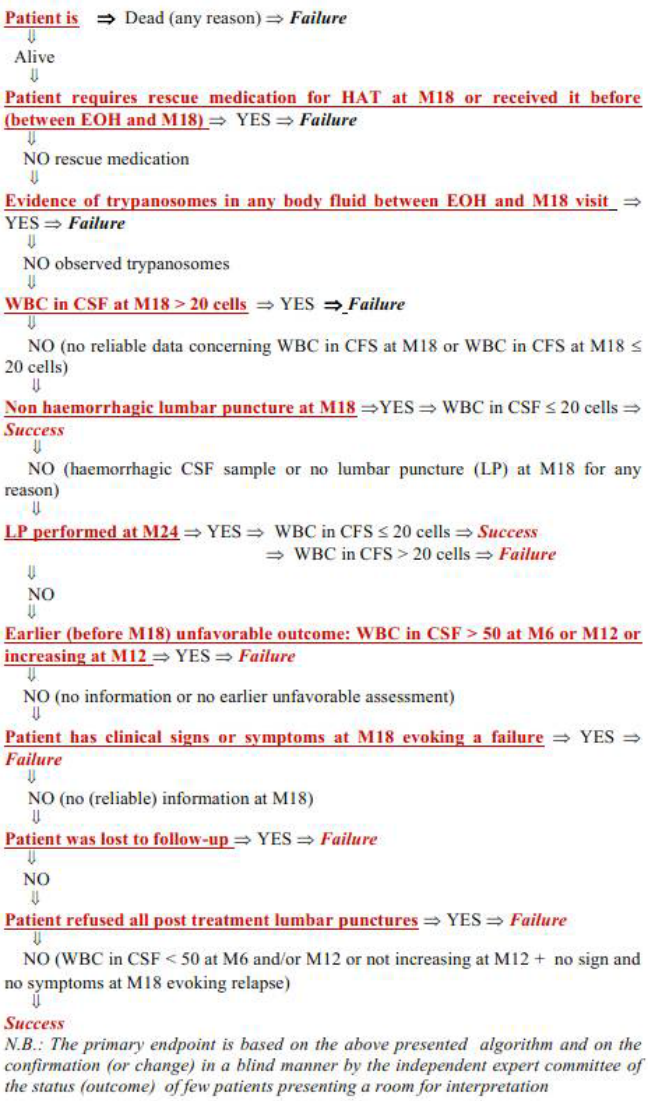
The definition of the EP population as stated above was finalized after the blind data review meeting.

The per-protocol (PP) population comprised all mITT patients (as treated) without major protocol deviations. Major deviations were documented for each patient, and exclusions were decided during the blind data review meeting.

The EP and PP populations were used to perform sensitivity efficacy analyses on the primary efficacy endpoint. Similar analysis populations, with the exception of the mITT (not included in the populations), have been defined for studies DNDIFEX005 and DNDIFEX006.

In general, the pre-defined populations did not show wide differences in number, indicating that the compliance with treatment and other study procedures and loss to follow-up for any reason were rather low.

The following algorithm was established for the definition of success or failure:



Using the algorithm provided by the sponsor, some patients had a questionable outcome due to the difficulty in interpreting signs and symptoms in the absence of lumbar puncture at 18 months. These cases were presented in a blind manner to three independent experts who confirmed or modified the patient's status using the algorithm. The primary analysis included the final adjudication decided by the experts.

The algorithm has not been strictly followed, as the need for the collection of a CSF specimen at the final evaluation time point, either at 18 or 24 months, has not been considered mandatory. Instead, the following final criteria applied:

Success at 18 months was defined as either:

Cure:

patient alive,

AND with no evidence of trypanosomes in any body fluid,

AND CSF WBC ≤20 cells/µL

Or Probable cure:

- Patient who refuses lumbar puncture OR whose CSF sample is haemorrhagic without trypanosomes
- AND with no parasitological evidence of relapse in blood and lymph
- AND whose clinical condition is satisfactory (without clinical symptom or signs) OR whose clinical status is unlikely to be due to HAT, a WBC count in CSF <50 cells/µL at 6 and/or 12 months, and not increasing at 12 months, as long as there was no indication of a relapse up to 24 months and if no definitive failure (presence of trypanosomes) had been observed before in any body fluid.

Some patients having refused to do the final lumbar puncture have been included in the final efficacy analysis, as per the adjudication of a group of three experts, who were unblinded to the treatment arm and for which the criteria for choice of the members is not presented. The summary narratives for these 5 patients (2 for fexinidazole, 3 for NECT) are presented, as well as the final decision of the expert group and it is acknowledged that all 4 patients (1 patient died 3 months after EOT) were negative for the blood parasitologic test at 18 months. An analysis excluding all 5 patients is presented below and shows quite similar results with the Primary analysis (see difference of success rate of -6.53 versus -6.42). All results are within the acceptability margin of 13% (after adjustment for multiplicity of testing due to interim analysis).

The outcome at 18 months was recorded as failure in the following cases:

- Death (for any reason)
- Relapse: evidence of trypanosomes in any body fluid
- Probable relapse: no evidence of trypanosomes in any body fluid but CSF WBC >20 cells/µL; no evidence of parasites in the blood or lymph and refusal to undergo lumbar puncture (or CSF sample was haemorrhagic), but required rescue treatment, in the opinion of the Investigator, because of a marked deterioration in his/her clinical status that was unlikely to be related to a disease other than HAT; patient refused lumbar puncture at 18 months and the outcome had been assessed as unfavourable at an earlier time point; or withdrawal from the study due to probable relapse at any time point earlier than 18 months.
- Patient lost to follow-up (except patients in an area of armed conflict)

A primary statistical analysis of the **primary efficacy endpoint**, to assess the difference in response rates between the two treatments groups (fexinidazole minus NECT), was performed using the Blackwelder non-inferiority test. The 2-sided Pocock adjusted CI for the difference associated with the Blackwelder test was also calculated. The margin of acceptable difference between the two treatment groups (i.e., acceptable margin of non-inferiority), in terms of the success rate, was set at 13% (at scientific advice a margin of 12% was agreed). The magnitude of the treatment effect was measured by the excess rate of success, which was calculated as the difference in success rate between groups (effect size = success rate in the fexinidazole group – success rate in the NECT group).

The success rate at 24 months is presented for the available subset of patients at the time of the database lock for the primary analysis and will be re-estimated once all patients had reached the 24-month visit and the final results presented in a subsequent report.

Additional inferential analyses (actuarial, regression) were performed as secondary analyses and will be presented along with their results.

The secondary efficacy analyses were performed on the mITT and TC populations.

A secondary analysis of the primary efficacy endpoint was stratified by site. The Breslow Day test was also conducted to test the interaction between treatment and sites.

Sensitivity analyses were performed on all the pre-defined populations. A sensitivity analysis of the same method of imputing success is provided in the ITT population, thus counting these patients as failures due to loss-to follow-up, indicating that the efficacy result is still within the accepted 13% margin for the difference in success rates.

Missing values were not replaced except for the primary efficacy variable. The classification of the primary efficacy variable was performed during the blind data review meeting. Cases subject to interpretation were submitted to 3 independent experts to determine the patient's status at 18 months and the adjudication from the 3 experts was used to perform the primary analysis. The different methods of imputation used in the absence of assessment at the 18-month visit are described in the following Table.

Table 22: Methods of imputation for missing data regarding the primary efficacy variable (outcome at 18 month)

Imputation method	Rules of imputation
Primary method	Probable success (considered as a success) if the patient refused the lumbar puncture at 18 months, showed no signs or symptoms of HAT at 18 months, did not report any sign of relapse later, and had a favourable evolution at the last available assessment. Otherwise, the outcome was considered as a failure. The outcome for any patient lost to follow-up at 18 months or before was also imputed as a failure except for patients who fled an area of armed conflict. The algorithm of classification provided the status at 18 months for all patients.
Primary method with experts' adjudication	The algorithm of classification was applied to all patients to classify them as success or failure (see primary method). The status of some patients was however subject to interpretation when signs and symptoms of HAT had to be interpreted in the absence of lumbar puncture at 18 months. These cases with possibly questionable outcome were detected during the blind data review meeting and presented in a blind manner to independent experts who confirmed or modified the patient's status.
Second method	Failure in the absence of lumbar puncture at 18 months.
Third method	No imputation of missing data. Any patient contributed to the estimate of the success rate at a given time point if the assessment was performed at that time point. In the case of a missing value (CSF WBC count) at an intermediary visit followed by a success or a failure at one of the following visit, the status at the latest visit prevailed on the status at the intermediary visit. In the Kaplan Meier approach, the observation was censored at the first missing outcome provided further assessments were all missing.
Fourth method	Imputation using the predicted probability of relapse. If the predicted probability of relapse at 18 months (given by logistic models[a] based on the MSF data of approximately 2000 patients, depending on the model) was above a cut-off which balanced the proportion of false positives and false negatives, the patient was classified as a probable relapse. Otherwise, the patient was a probable success.

a Three logistic models were fitted on MSF data, one using the baseline and 6-month CSF WBC counts as well as the age and sex of the patient (significant explanatory variables), another one using the 6- and 12-month CSF WBC counts, and the last one using the 12-month CSF WBC count, age and sex. For more information, please refer to Section 8.7.3.7.3.

CSF = cerebrospinal fluid; HAT = human African trypanosomiasis; MSF = Médecins Sans Frontières; WBC = white blood cells.

Source: Statistical analysis plan, Section 8.3.1.

In the end, as the number of patients that missed the final lumbar puncture was small (see above) the different methods of imputation do not significantly affect the final result for the primary endpoint (see below).

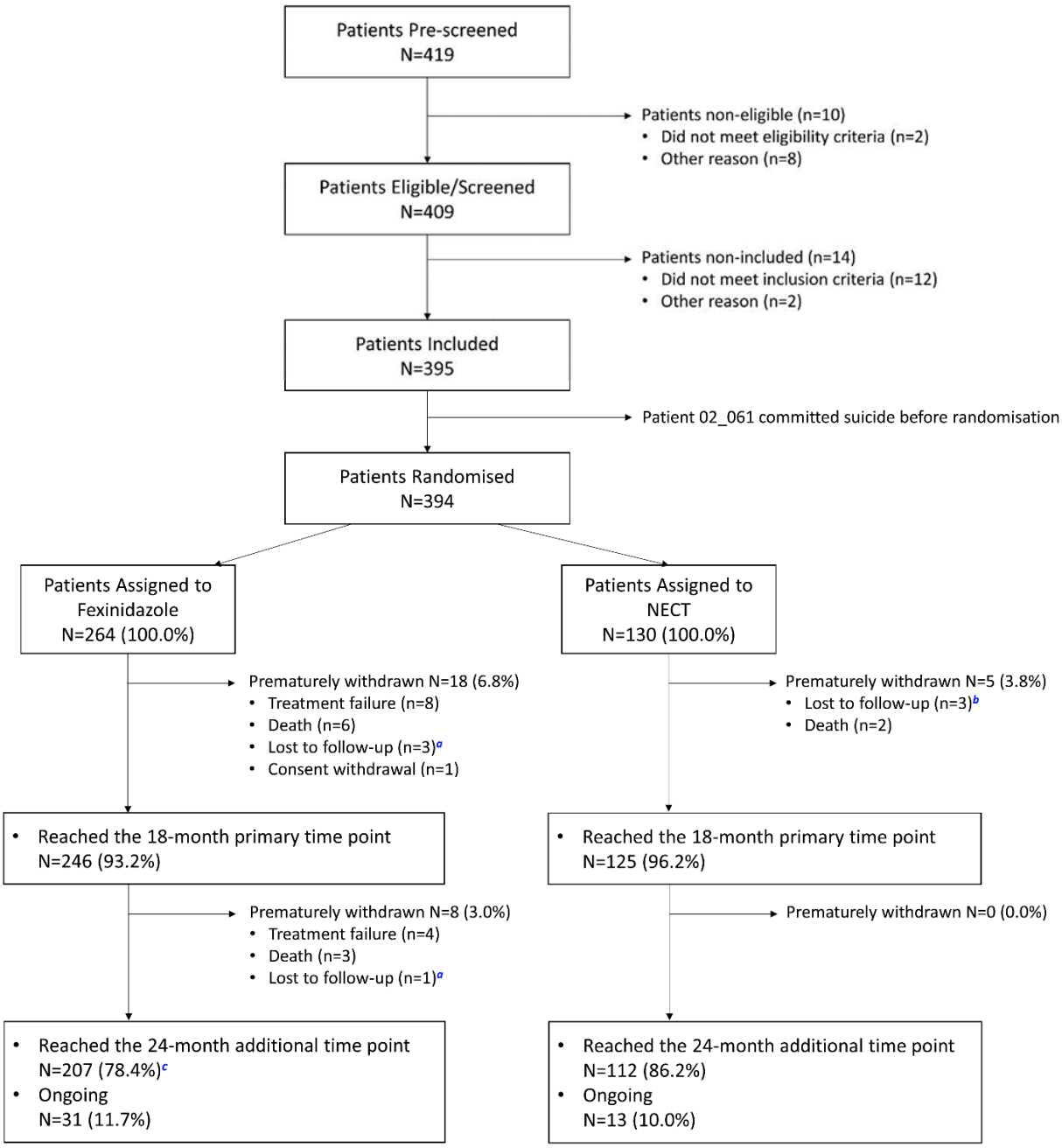
An interim analysis of the success rate was added in Protocol Amendment 3 and was performed on the first 195 randomised patients who had reached 12 months of follow-up. An adjustment of type 1 error for multiplicity for the interim efficacy and final efficacy analysis was made using the Pocock stopping boundaries method. From this method, the calculated critical Z-value for the primary endpoint of interim analysis and final analysis was 2.178. Therefore, the 2-sided significance level (alpha) was equal to 0.0294 for both the interim and final analyses.

Results

Participant flow

In study DNDIFEX004, there were 394 randomized patients included in the ITT population, of which 264 were assigned to fexinidazole and 130 were assigned to NECT, as per the 2:1 planned randomization schedule.

The patient flow is well documented and shown in the chart below:



A higher percentage (6.8% vs. 3.8%) of patients in the fexinidazole arm have died or presented as treatment failures, when compared to NECT. Of note, none of the patients randomized to NECT discontinued due to withdrawal of consent even though this treatment is apparently more complex and invasive. However, the involved numbers are small and may be due to chance alone, although a question of trust in the established treatment may also be at issue.

Fourteen patients in all HAT studies were reported as having received a rescue treatment with NECT. Data on the outcome were not recorded in the CRF but collected after unblinding. Among these patients, 7 were lost to

follow-up, 5 were considered cured and 2 had uncertain evolution as there was no post 6 months data. As part of updated guidelines, patients treated with NECT are not requested to come back for verification, only in case of symptoms. It can therefore be argued that the lost to follow-up patients could be inferred as potentially without symptoms, so that 12/14 patients treated with NECT seem to have resulted in a positive outcome after fexinidazole failure.

Overall, in the ITT population, the main reason for premature study withdrawal (before the 18-month visit) was treatment failure (n=12), death (n=11), lost to follow-up (n=7) and consent withdrawal (n=1) (total 31 ITT patients).

In the fexinidazole group, the reasons for premature study withdrawal (n=26, 9.8%) were treatment failure (n=13), death (n=9), lost to follow-up (n=4) and consent withdrawal (n=1).

In the NECT group, premature study withdrawal in the NECT group (n=5, 3.8%) was caused by the lost to follow-up (n=3) or death (n=2). None of the patients in the NECT group received rescue treatment due to treatment failure.

Conduct of the study

The successive amendments made to either study are well described and the major impact was on the sample size, already discussed.

In study DNDIFEX004 there was good compliance with treatment procedures in both arms. All patients received the correct dose of treatment. Regarding the attendance to follow-up visits, attendance at 3, 6, 12 and 18 months was comprised between 90% and 95% in each group.

A total of 2/394 patients (0.5%) did not complete the treatment. These 2 patients received fexinidazole but died before EOT. There were no more cases of permanent treatment discontinuation.

One NECT patient had no visit on Day 5 due to study staff evacuation from Site 6.

At the time of database lock for the current CSR (05 January 2017), 44 patients were still ongoing (had not reached the 24-month visit): 31 (11.7%) in the fexinidazole group and 13 (10.0%) in the NECT group.

Baseline data

Similar demographic characteristics were observed in the primary analysis population, the mITT population, and no differences were observed between groups with regard to gender, median age, height, weight, and BMI.

Male patients predominated (61.2% overall). The mean age was 34.8 years (range 15-71 years) and 27 patients (6.9%) were aged < 18 years (15 fexinidazole and 12 NECT). Mean BMI was 19.2 kg/m^2, with 75% having a BMI lower than 20.7 kg/m2 and 12 were <16 kg/m^2 at inclusion.

Regarding the characteristics of the most frequently reported signs and symptoms of HAT, pruritus, asthenia and sleepiness were experienced either continuously or intermittently by a similar percentage of patients. Time of onset was variable for all these frequently reported signs and symptoms. Headache for example appeared from less than 1 week to more than 6 months before the inclusion visit. Regarding the other frequently reported signs and symptoms (convulsion, diarrhoea, fever), they seemed to have appeared more than 1 month before the inclusion visit in the majority of patients. There were no differences between treatment groups for clinical picture at baseline.

However, the prevalence of some signs or symptoms at inclusion differed between sites. For example, asthenia was reported in 6.7% to 100.0% of patients assigned to fexinidazole and 0% to 100.0% of patients assigned to

NECT, depending which site was considered. A relatively large variability was also observed for impotence (0% to 69.2% in the fexinidazole group; 0% to 75.0% in the NECT group), shaking (0% to 57.1% in the fexinidazole group; 0% to 64.7% in the NECT group), weight loss in the NECT group (0% to 94.1%), fever in the NECT group (0% to 75.0%), sleepiness in the fexinidazole group (14.3% to 87.5%) and insomnia in the fexinidazole group (0% to 52.6%).

The **diagnostic and staging methods** were compared between sites by plotting the percentage of patients in whom trypanosomes were identified in each body fluid (lymph, blood, CSF) using the different methods (lymph node aspiration, CTC [WOO]/mAECT/mAECT-BC, and lumbar puncture).

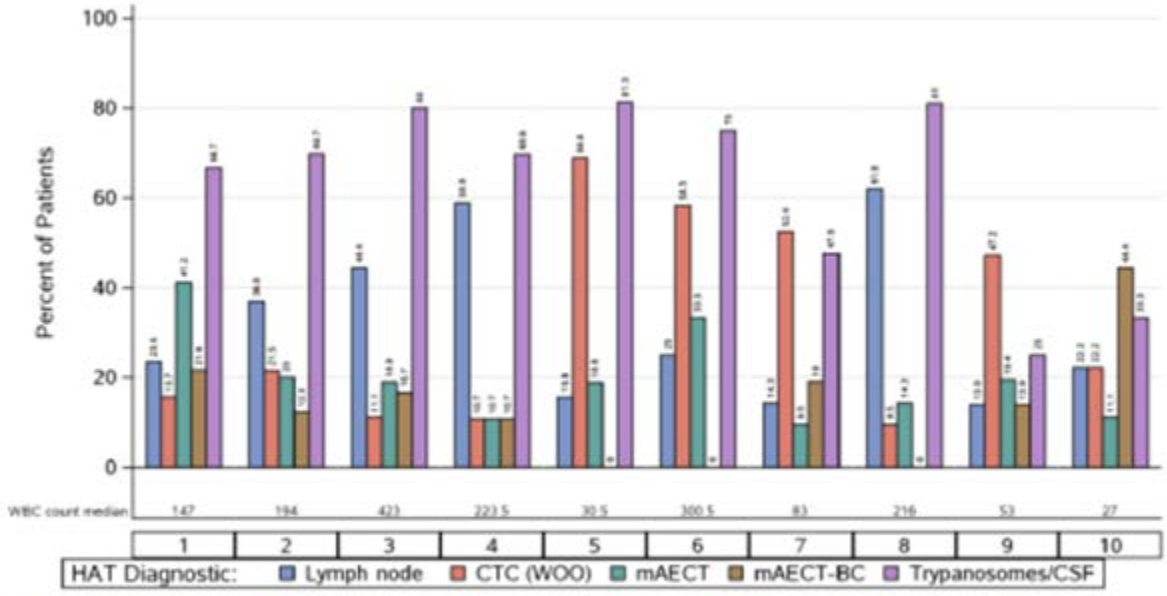
All patients tested positive for the entry serologic test, except 4 patients in the fexinidazole group: 3 tested negative and 1 did not do the test, but all 4 patients complied with the criteria for late stage 2 HAT by either presenting with trypanosomes in the CSF, or having CSF WBC count >20 cells/µL.

The tests performed to confirm the presence of trypanosomes revealed that parasites were detected in the lymph in 35.6% of patients, and in the blood in 13.5% to 25.2% of patients depending on the method used.

Examination of the CSF for the presence of trypanosomes was performed in all patients, except 1 patient assigned to fexinidazole, for whom the detection of parasites in the CSF was not done but who had a CSF WBC count of 110 cells/µL, therefore meeting the criteria for late stage 2 HAT. The test was positive in 175 patients (66.3%) assigned to fexinidazole group and 90 patients (69.2%) assigned to NECT.

A total of 11 patients had trypanosomes in the CSF but a CSF WBC count <20 cells/µL with 4 assigned to fexinidazole and 7 assigned to NECT. Although these patients were eligible for the present study, they would have been considered as intermediate stage 1 (if CSF WBC count ≤5 cells/µL) or intermediate stage 2 (if CSF WBC count >5 and ≤20 cells/µL) HAT patients according to the WHO classification.

Regarding signs and symptoms of disease, the reported profile seems to be compatible with the usual clinical description and supports the serologic and parasitologic diagnosis. This includes the signs and symptoms found at neurologic examination.



CATT = card agglutination test for trypanosomiasis; CSF = cerebrospinal fluid; CTC = capillary tube centrifugation; HAT = human African trypanosomiasis; mAECT = mini-anion exchange centrifugation technique; mAECT-BC = mini-anion exchange centrifugation technique – buffy coat; ITT = intention-ot-treat; WBC = white blood cell.

Figure 8: percentage of patients in whom trypanosomes were identified in each body fluid, and media WBC count per site (ITT population)

It has been noted that diagnosis of late stage 2 HAT at some study sites had gaps, which may be methodologically related as countries which might benefit from fexinidazole still do not have supporting infrastructure to identify the trypanosomes and to distinguish between *T.b.Gambiase* and *Rhodensiense*.

Two sites, and to a lesser extent a third one, were unusual in that less than half of patients had trypanosomes in CSF. Whilst these patients must have had the requisite of CSF WBC count to be eligible, it seems that evidence of trypanosomal infection in these patients was mainly based on blood tests. These sites also seemed to have lower median CSF WBC vs. all other sites, except for site 05.

The applicant confirmed that the inclusion of patients based on WBC count > 20 cells/µL with or without trypanosomes in CSF is in line with the recommended WHO criteria for a clinical trial in stage-2 HAT. The reason for the more number of cases without trypanosomes and lower median CSF WBC in sites 7,9 and 10 are explained by a temporal difference in the trial initiation at these sites which occurred more than a year later and resulted in less severe/advanced stage-2 HAT patients being recruited. Consequently, more number of patients had to be screened before fewer patients were found to be eligible. This is a plausible explanation and is accepted. But the fact remains that fexinidazole appears to be more successful in treating these less advanced stage-2HAT patients than the more severe/advanced stage-2 HAT patients.

It is seen that around 8% of the patients (18 in fexinidazole and 16 in NECT arm) had concomitant malaria and the rate was double in NECT than in fexinidazole due to the fewer total patients randomized to NECT. Further, it is confirmed that CSF WBC counts were measured prior to malaria treatment and therefore any confounding of the results due to erroneous diagnosis of stage-2 HAT in these patients is likely to bias the results in favour of NECT. Therefore, this is not likely to adversely affect the robustness of the results.

Numbers analysed

All 394 randomised patients were included in the ITT population, 264 assigned to fexinidazole and 130 assigned to NECT. The following table presents the allocation of patients to the pre-defined populations:

Table 23: Data sets analysed (Randomised population)

Description	Statistics	Fexinidazole (N=264)	NECT (N=130)	All (N=394)
ITT population	N	264	130	394
	n (%) - No	0 (0.0)	0 (0.0)	0 (0.0)
	n (%) - Yes	264 (100.0)	130 (100.0)	394 (100.0)
mITT population	N	264	130	394
	n (%) - No	2 (0.8)	3 (2.3)	5 (1.3)
	n (%) - Yes	262 (99.2)	127 (97.7)	389 (98.7)
TC population	N[a]	262	127	389
	n (%) - No	2 (0.8)	0 (0.0)	2 (0.5)
	n (%) - Yes	260 (99.2)	127 (100.0)	387 (99.5)
EP population	N[a]	262	127	389
	n (%) - No	4 (1.5)	2 (1.6)	6 (1.5)
	n (%) - Yes	258 (98.5)	125 (98.4)	383 (98.5)
PP population	N[a]	262	127	389
	n (%) - No	0 (0.0)	1 (0.8)	1 (0.3)
	n (%) - Yes	262 (100.0)	126 (99.2)	388 (99.7)

a For the TC, EP and PP populations, "N" corresponds to the number of patients in the mITT population since these populations are defined based on the mITT population.

EP = evaluable patients; ITT = intention-ot-treat; mITT = modified intention-to-treat; PP = per protocol; TC = treatment completers; NECT = Nifurtimox-Eflornithine Combination Therapy.

Source: Table 15.1.4.a and Table 15.1.4.b.

Outcomes and estimation

The measurement of the primary efficacy endpoint was based on the success rate at 18 months, using the primary imputation method (algorithm of classification at 18 months) and taking into account the adjudication by 3 independent experts for 5 patients.

As said above, the mITT population was used for most efficacy analyses, including the analysis of the primary efficacy endpoint. In practice, two patients for fexinidazole and 3 in NECT were not included in the mITT for this reason. The use of the expert's adjudication for the final attribution of success or failure to patients that had not done the lumbar puncture at the final 18-months (or alternative 24-month) time point, resulted in the allocation of two additional successes to fexinidazole but, apparently, none to NECT as one patient in NECT was a failure for not having the mandatory lumbar puncture but was considered a failure (or not reassessed by the expert committee).

Of note, the interim analysis of efficacy introduced after 195 patients had been included showed that the primary endpoint (difference in success rate at 12 months) was not met. The difference between groups was -9.41 (97.06% adjusted CI [-18.09;-0.73]) was not compatible with the limit of unacceptable difference.

The following final efficacy results for the pre-defined analysis sets at month 18 are reported for the primary efficacy endpoint, both in the mITT population and in the other pre-defined populations.

Table 24

DNDIFEX004	N (FEX/NECT)	FEX	NECT	Difference [97.06% CI]
Success rate at 18 months using the primary imputation method and experts' adjudication (mITT)	262/127	239 (91.22)	124 (97.64)	-6.42 [-11.22; -1.61]
Outcome at 18 months using the algorithm of classification (mITT)	269/127	237 (90.46)	124 (97.64)	-7.18 [-12.10; -2.26]
Success rate at 18 months using the primary imputation method and experts' adjudication (ITT)	264/130	239 (90.53)	124 (95.38)	-4.85 [-10.46; 0.76]
Success rate at 18 months using the primary imputation method and experts' adjudication (PP)	262/126	239 (91.22)	124 (98.41)	-7.19 [-11.71; -2.68]
Success rate at 18 months using the primary imputation method and experts' adjudication (TC)	260/127	239 (91.92)	124 (97.64)	-5.71 [-10.42; -1.01]
Success rate at 18 months using the primary imputation method and experts' adjudication (EP)	258/125	236 (91.47)	124 (99.20)	-7.73 [-11.89; -3.56]
Success rate at 18 months using the second imputation method and experts' adjudication (mITT)	262/127	226 (86.26)	119 (93.70)	-7.44 [-14.04; -0.85]
Success rate at 18 months and non-inferiority test, using the primary imputation method and taking into account the experts' adjudication, with the exact 95% CI (mITT)	262/127	239 (91.22)	124 (97.64)	-6.42 [-10.75; -1.21]

The success rate at 18 months was 91.2% in the fexinidazole group (89% expected) and 97.06% in the NECT group (94% expected). There were 23 patients (8.8%) considered as failures in the fexinidazole group, versus 3 patients (2.4%) in the NECT group.

The observed difference in success rate between groups (-6.4%, 97.06% CI [-11.2%; -1.6%]), despite being slightly larger than the -5% expected, remained within the margin of acceptable difference, set at -13% (p=0.0029, which is below the adjusted significance threshold). Consequently, the primary endpoint that was proposed by the applicant was met.

Table 25: Primary analysis – Success rate at 18 months using the primary imputation method and experts' adjudication (mITT population)

Description	Statistics	Fexinidazole (N=262)	NECT (N=127)	Difference between proportions [97.06% CI]	P-value *
Success at 18 months mITT population	N	262	127		
	n (%) - No	23 (8.78)	3 (2.36)		
	n (%) - Yes	239 (91.22)	124 (97.64)	-6.42 [-11.22; -1.61]	0.0029 (S)

Note: * 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 CI of the difference between treatment groups was adjusted for multiplicity.
In this analysis, a p-value equal to or above 0.0294 is non-significant (NS), p-values below 0.0294 is significant (S).

The analysis of Outcome at 18 months using the algorithm of classification (mITT), i.e., excluding the patients adjudicated by the group of three experts, was a pre-defined sensitivity analysis for the primary efficacy

endpoint and is also within the range accepted for non-inferiority (see table below). However, the lower limit of the 95%CI is already below 12%, and would not support the primary analysis should the non-inferiority margin been placed at 12%.

The analysis of the success rate at 18 months and non-inferiority test performed on the ITT set of patients with only the use of the algorithm for establishing the outcome is considered by the applicant as probably the most objective analysis (no randomized patients discarded from the analysis and no clinical judgment in setting the outcome) even if it is not the most appropriate. This sensitivity analysis shows very similar results to the Primary analysis (excess rate of success of 5.61% in favour of NECT versus 6.42%). The difference in success rate is even a little more favourable to fexinidazole than in the mITT population using the algorithm only, with a difference of -5.61 versus -7.18. In both cases, the difference between treatments is still within the proposed acceptability margin of 13%.

The outcome at 18 months using the second imputation method, which consisted of imputing a failure in the absence of lumbar puncture at 18 months was assessed as a secondary analysis (see the overall result Table, above). Compared to the primary analysis, success rates were lower in each group, which was expected: 86.3% with fexinidazole and 93.7% with NECT. There were 13 more failures (5.0%) in the fexinidazole group (36 instead of 23) and 5 more failures (3.9%) in the NECT group (8 instead 3). Using this more stringent imputation method, the difference in success rate between groups (-7.4%, 97.06% CI [-14.0%; -0.8%]) did not remain within the margin of acceptable difference, since the lower bound of the adjusted CI was inferior to -13% (p=0.0664, which is above the adjusted significance threshold). According to this analysis, fexinidazole could not be considered as having an acceptable non-inferiority compared to NECT, when setting the margin of acceptable difference at 13%. This analysis is considered as a secondary and only supportive analysis. However, it should be considered relevant for the final assessment, as it may be the one which better represents the compliance with the efficacy algorithm, in which the failure to have a lumbar puncture at 18 or 24 months considered as a failure.

Using the exact 95% CI of the difference calculated using the Newcombe method based on the Wilson score to compared the **success rate at 18 months** between groups by using the same approach as the primary analysis (ancillary analysis), with the outcome at 18 months determined using the primary imputation method with the algorithm of classification and taking into account the experts' adjudication, the lower bound of the 95% CI of the difference in success rate between groups (-10.75%) was higher than -13%.

Table 26: Sensitivity analysis – Success rate at 18 months and non-inferiority test, using the primary imputation method and taking into account the experts' adjudication, with the exact 95% CI (mITT population)

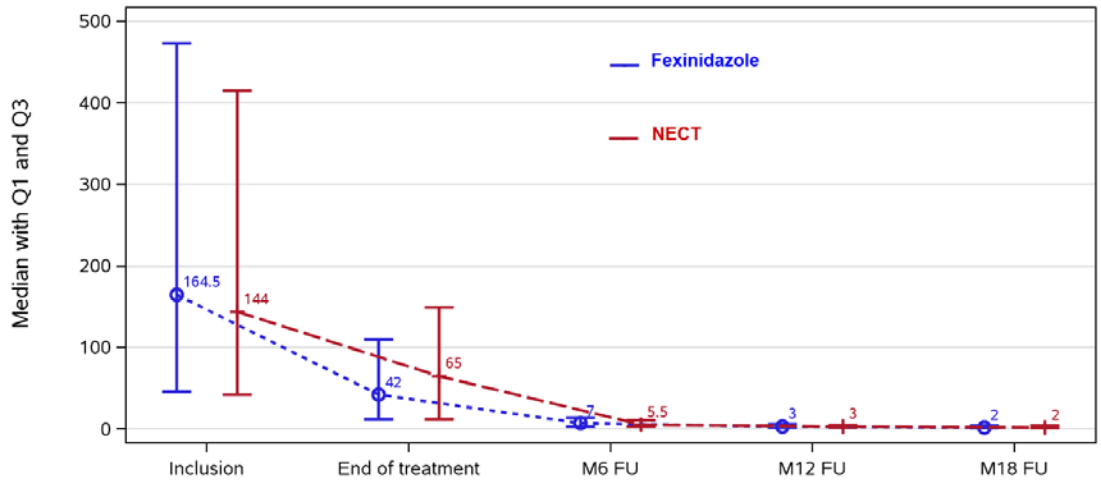
Description	Statistics	Fexinidazole (N=262)	NECT (N=127)	Difference between proportions [95% CI]
Success at 18 months mITT population	N	262	127	
	n (%) - No	23 (8.78)	3 (2.36)	
	n (%) - Yes	239 (91.22)	124 (97.64)	-6.42 [-10.75; -1.21]

Note: The 95% CI of the difference between treatment groups was calculated using the Newcombe method based on the Wilson score.
CI = confidence interval; mITT = modified intention-to-treat; NECT = Nifurtimox-Eflornithine Combination Therapy.
Source: Table 15.2.2.h

Regarding the clinical evolution of patients after treatment, there is an undeniable benefit, with most of the general signs and symptoms that could relate to the disease showing consistent and sustained improvement as

of the 3-month visit after EOT. A significant improvement in neurologic and psychiatric signs and symptoms was also consistent over time, although less evident.

The picture below shows the evolution of CSF WBC count over time in the two treatment arms:



Fexinidazole: Mean	378.04	90.36	16.96	10.80	5.42
Fexinidazole: Min,Max	4.0, 7545.0	0.0, 2400.0	0.0, 782.0	0.0, 586.0	0.0, 300.0
NECT: Mean	317.07	112.29	8.66	4.04	2.96
NECT: Min,Max	6.0, 2890.0	1.0, 812.0	0.0, 48.0	1.0, 20.0	0.0, 12.0

Figure 9

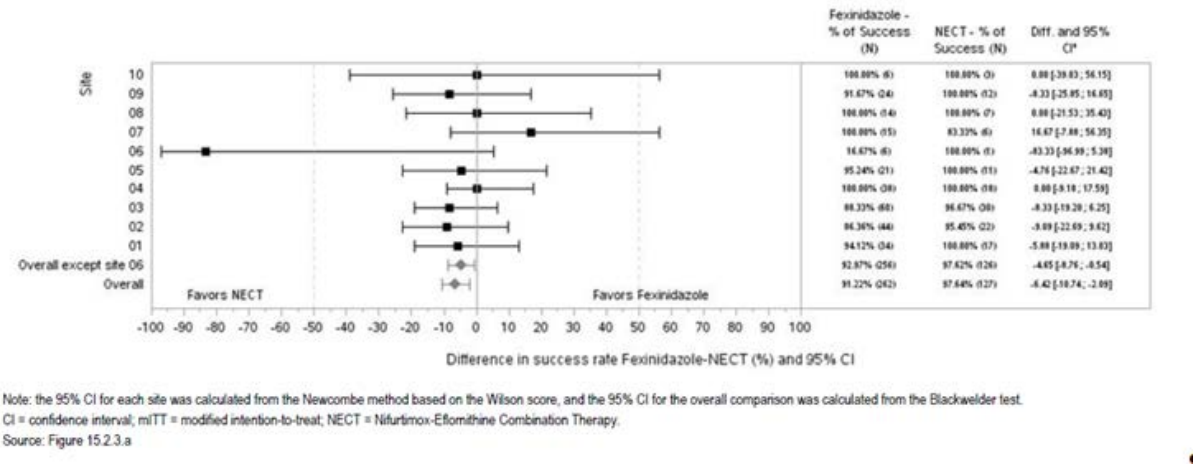
There were 13 more failures in the fexinidazole group (36 instead of 23) and 5 more failures in the NECT group (8 instead 3). Among the additional failures due to missing lumbar puncture at 18 months, 16/18 (88.9%) were successes at 24 months.

The predictors of treatment outcomes in the patients who were failures at 18 months using the primary imputation method (with or without experts' adjudication) were analysed for gender, age and baseline CSF WBC with findings suggesting diversity in characteristics as follows:

o Fexinidazole (N=27): 17 males and 10 females, age range 16-57 years, range in baseline CSF WBC count 14-7545 cells/µL

o NECT (N=6): 4 males and 2 females, age range 26-55 years, range in baseline CSF WBC count 18-938 cells/µL.

As shown in the forest plot, fexinidazole success rates ranged from 86.4% to 100.0%, except for Site 06. With NECT, success rate ranged from 83.3% to 100.0%.



Note: the 95% CI for each site was calculated from the Newcombe method based on the Wilson score, and the 95% CI for the overall comparison was calculated from the Blackwelder test.
CI = confidence interval; mITT = modified intention-to-treat; NECT = Nifurtimox-Eflornithine Combination Therapy.
Source: Figure 15.2.3.a

Figure 10: Forrest plots: Difference in success rate between fexinidazole and NECT, with 95% CI (mITT population)

Leaving Site 06 aside, the two highest enrolling sites had the lowest success rates for fexinidazole (86.4% and 88.3%, respectively) while the success rates for NECT were 95.5% and 96.7%, respectively. The three lowest enrolling sites (2 with 21 patients each and one with 9 patients) had 100% success rates for fexinidazole. The applicant recognizes the difficulty in explaining the success rate of individual sites due to their relatively small sample size. No relationship was found between the size of sites and the success rate (R^2 = 0.0678, p = 0.4672). Nevertheless, when excluding one site in Central Africa in region of conflict (clearly an outlier), there is a significant relationship between the size of sites and success rates per site (R^2 = 0.543, p = 0.0234). Sites with the largest recruitment were those with the smallest success rate and vice versa.

It was therefore next verified whether the size of sites was related to the severity of patients as measured by the number of WBC in CSF and as this was found to be associated with a higher risk of failure in a pooled analysis. A significant positive linear relationship was observed (R^2 = 0.641, p = 0.0095), suggesting that the largest sites, not only started the study at least an year earlier, but tended to have more severe patients (higher number of WBC) than sites with a small recruitment and therefore a larger proportion of patients at risk of failure, explaining the differences in fexinidazole success rates between sites.

Considering all sites, NECT performed better than fexinidazole (p=0.0283). After excluding Site 06, the difference in success rate between fexinidazole and NECT was no longer statistically significant (p=0.0573). A difference in excess rate of success across sites could not be completely excluded (Breslow day test: p=0.1282, which is <0.15). This could be due to Site 07, which is the only site where the success rate was higher with fexinidazole (100.0%) than with NECT (83.3%).

The CSF WBC count was significantly lower in one site both at diagnosis and EOT but the rate of identification of trypanosomes was as high, if not higher than in the other sites. Detailed investigations by the Sponsor, PNLTHA and MSF concluded that the discrepancy could be due to various technical and personnel errors and that these issues may have led to the over-diagnosis of some patients by the mobile team (essentially stage 1 patients being diagnosed late stage 2). The forest plot presenting the success rates in each site did not reveal any significant difference between Site 05 and the other sites so no further analysis was deemed necessary.

PK/PD

Another aim of the study was to reach high levels of M2 in the CSF since trypanosomes are present in the brain and need to be eliminated. No target levels were defined for this compartment as it was assumed that the CSF concentration of fexinidazole would correspond to 40% of its plasma concentration.

High M2 levels were reached in CSF, with 100.0% of patients (79/79 patients with reportable results) having CSF concentrations of M2 higher than 0.270 µg/mL at 24 hours after last administration on Day 10. Moreover, 96% patients (76/79) had CSF concentrations of M1 higher than 0.292 µg/mL at 24 hours after last administration on Day 10.

The in vitro trypanocidal activity against T. b. Gambiense, determined as the half-maximal effective concentration (IC50), was measured at 0.292 µg/mL for M1 and 0.270 µg/mL for M2. Compared to the in vitro results, the in vivo findings indicate that the therapeutic levels of M2 were obtained in all patients, with concentrations higher than the IC50 reaching the CSF.

The ratio of CSF to DBS concentration was quite comparable between patients and was about 0.30 for M2 (coefficient of variation (CV) =25%), and 0.50 for M1 (CV = 47%).

Of the 203 patients analysed for PK, 11 had a HAT relapse. These patients received fexinidazole as planned in the protocol. Overall, their laboratory tests values were normal, except for ALP (5 patients with values above ULN) and for albumin (9 patients with values under the LLN). There was no difference in their demographic characteristics and no correlation with any concomitant treatment or appearance of any AEs was elicited. Plasma concentrations in these patients were similar to those of other patients, except for Patients 06_001 and 06_009 who seemed to be underexposed. Indeed, their concentrations were under the overall population 5th percentile for fexinidazole, M1 and M. For CSF, values of concentration of M1 and M2 were slightly lower than those reported in the other patients (see Table 9 in the PK analysis report, 16-2-5-cdc-data [16.2.5.2.2]). However, CSF could only be measured in 5/11 patients with relapse. On the other hand, some patients who were cured experienced low CSF levels, as shown by the minimum values of M1 and M2 and 0.05 and 0.27 µg/mL respectively. Therefore, it is unlikely that the relatively low levels in CSF found in some patients who had a relapse could explain the treatment outcome.

In light of these results from a single open-label, randomized study, essentially unblinded and with limitations regarding the sample size, it should be considered that, even though the study performance and compliance with study procedures was good, the efficacy data does not support that fexinidazole, in the proposed oral 10 day regimen, is non-inferior to the standard recommended treatment of eflornithine and nifurtimox (NECT) for the treatment of adult patients with Stage 2 HAT. In fact, based only on data from study DNDIFEX004, the possibility that fexinidazole is inferior to NECT for the treatment of Stage 2 HAT cannot be excluded beyond a reasonable data. Also, the data fail to give assurance that difference in efficacy with regard to the WHO recommended treatment used as reference (NECT) is within the limit for acceptance of 13%.

Nonetheless, this does not mean that the data from study DNDIFEX004 indicates that the proposed regimen of fexinidazole is not effective for the treatment of second stage HAT in adults. Further analysis of the efficacy data shows that the impact of fexinidazole treatment on the course of disease and CSF WBC count was significant.

Ancillary analyses

Failure with Fexinidazole vs Rescue with NECT

Regarding patients who may fail on Fexinidazole, the applicant has discussed the impact of pre-treatment with Fexinidazole on subsequent chance of poor success with NECT. Based on this it is agreed that the risk of developing resistance to fexinidazole is low given the low number of late stage-2 HAT cases. Additionally, the risk of cross-resistance to both components of NECT due to prior treatment with fexinidazole is as well very low.

Furthermore, rescue treatment with NECT was provided to a small number of Fexinidazole failed patients (n=14). Five of these patients were considered cured, 7 were lost to follow-up and 2 had uncertain evolution as no data was available post-6 months of the treatment. However, this has to be interpreted in the context of current follow-up guidance where patients are requested to come back for verification only in case of symptoms. Under these circumstances, it is reassuring there is currently no evidence for any adverse impact on success of NECT due to prior treatment with fexinidazole.

The uncertainties due to the applied definition for late stage-2 HAT in the pivotal study have been adequately discussed and it is seen that there were very few patients recruited in the study who had trypanosomes in CSF but a WBC <20 (n=9; 3 patients for fexinidazole arm and 6 patients for NECT) and excluding these patients did not affect the conclusions. This is very reassuring, as the selection criteria recommended by the WHO for robust demonstration of an effect in stage-2 HAT (WHO/CDS/NTD/IDM/2007.1) is "Trypanosome negative or positive > 20 WBC/µl CSF". Therefore, it is reasonable to conclude that the pivotal study was positive and it robustly demonstrated that in the overall late stage-2 HAT population, treatment with fexinidazole did not breach the threshold of unacceptable difference (of 13%).

In respect to site 05

In respect to site 05 from the DNDiFEX004 study while not being one of the largest sites [considered by the applicant as a medium size site (N = 21)], this was the site with the highest rate of detection of parasites in the CSF (81.3%) while it was also the site with one of the lowest median WBC counts (30.5 cells/µL). Success rate for fexinidazole was high 95.24%. Three patients had less than 20 WBC/µL in CSF at screening but had trypanosomes in CSF. The applicant argued that such cases are not frequent but possible and anticipated in staging criteria according to the WHO. When looking for a possible link between the presence of trypanosomes and the number of WBC at baseline in CSF by site, no overall correlation is found (R^2 = 0.235, Figure 12). Furthermore, the site 05 appears to be outside of the general trend (blue arrow).

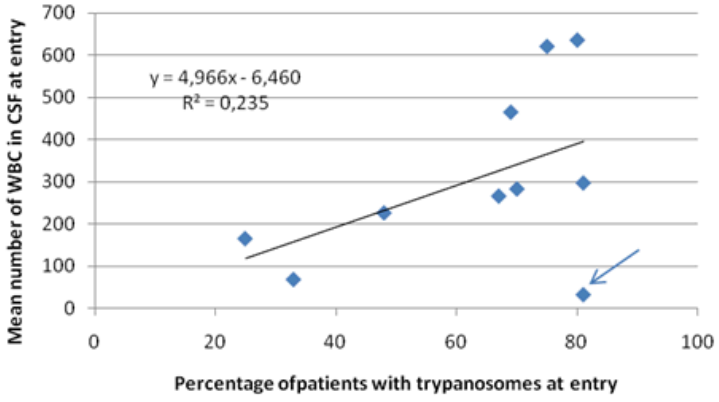


Figure 11: Relationship between percentage of patients with trypanosomes in CSF and mean number of WBC (cells/µL) in CSF per site (DNDiFEX004)

A sensitivity analysis was performed, upon CHMP request, excluding patients from site 05, to assess that fexinidazole efficacy is not significantly impacted by patients from this site, with low CSF WBC baseline values (table below).

Table 27: Analysis using algorithm classification and the independent expert committee adjudication at M18 and excluding patients from site 05 - Success rate at M18 per randomized treatment group and Non-inferiority test - mITT population (all data until follow-up M24)

Set	Success rate for fexinidazole	Success rate for NECT	Difference in success rate [97.06% CI]	Difference in success rate [95% CI]	p-value
mITT with adjudicated cases and Site 5 excluded (requested analysis)	90.87% (219/241)	97.41% (113/116)	-6.54% [-11.70; -1.38]	-6.54% [-11.19; -1.90]	0.0064 (S)
mITT with adjudicated cases (Primary analysis)	91.22% (239/262)	97.64% (124/127)	- 6.42 [-11.22; -1.61]	-6.42 [-10.74; -2.09]	0.0029 (S)

Abbreviations: CI, confidence interval; ITT, intention-to-treat; NECT, nifurtimox-eflornithine combination therapy; mITT, modified ITT

⇨ 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-values below this is significant (S)

The results are consistent with the overall success rate observed for fexinidazole and are within the -13% acceptance limit.

Analysis of success rate excluding site 06

The applicant provided an analysis of success rate with regard to study site recruitment, excluding site 06 (as an outlier). Taking into account the size of the site and excluding site 06, the 2 largest sites (site 02 and 03) in the DNDiFEX004 study had smaller success rate with fexinidazole (87.5%; 91/104 for both sites combined) than the 3 smallest sites (site 07, 08 and 10; success rate = 100%: 35/35). The difference of success rates between these sites is significant (p = 0.034, exact test). The applicant recognized that it is difficult to explain the success rate of individual sites due to their relatively small sample size. However, it verifies that there is no relationship between the size of sites and their success rate: when site 06 was taken into account the R^2 of the linear relationship was only 0.0678 (p = 0.4672, not shown), but, when removing site 06, there is a significant relationship between the size of sites and success rates per site (R^2 = 0.543, p = 0.0234, Figure 12).

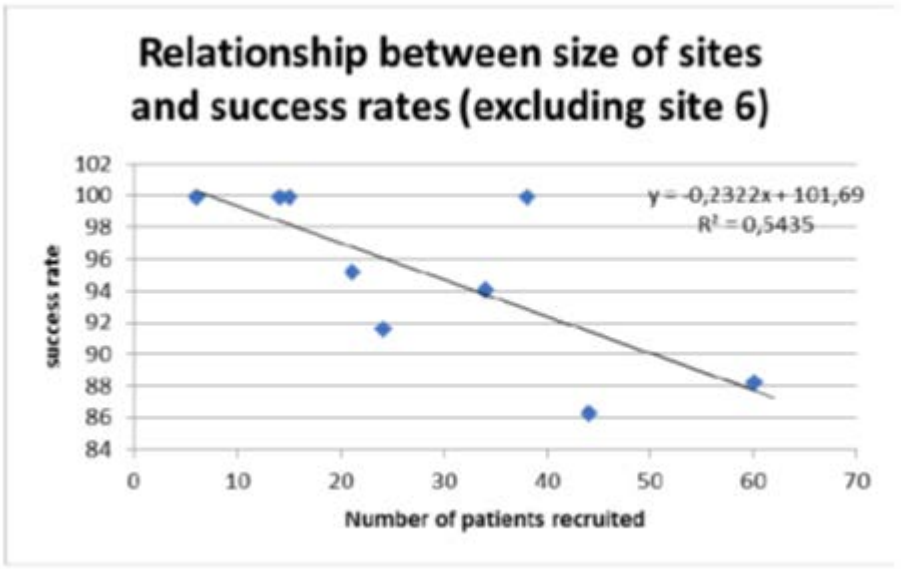


Figure 12: Relationship between the number of recruited patients and the success rate by site, excluding site 06 (DNDiFEX004)

Sites with the largest recruitment were those with the smallest success rate and vice versa. It was therefore next verified whether the size of sites was related to the severity of patients as measured by the number of WBC in CSF (Figure 9) and whether this was found to be associated with a higher risk of failure in a pooled analysis. A significant positive linear relationship was observed (R^2 = 0.641, p = 0.0095), suggesting that the largest sites tended to have more severe patients (higher number of WBC) than sites with a small recruitment.

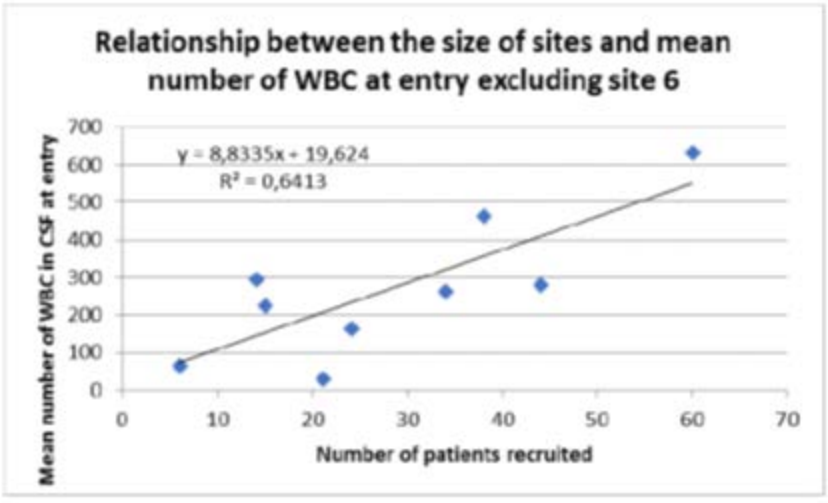


Figure 13: Relationship between the number of recruited patients and the mean number of WBC by site, excluding site 06 (DNDiFEX004)

Moreover, in the pooled efficacy analysis it was shown that patients with more than 400 WBC in CSF had a lower success rate (around 86%) than patients with 100 WBC or less (>98%). The relationship between the size of

sites (excluding site 06) and the proportion of patients with more than 400 WBC in CSF was thus explored showing a significant positive linear relationship (R^2 = 0.452, p = 0.0473, Figure 10) between both variables: the larger the recruitment, the larger the proportion of patients at risk of failure (WBC >400). The same type of relationship was tested between the size of sites and the proportion of patients with WBC≤ 100. A trend was found but the negative slope of the relationship was not significant (p = 0.1224, not shown).

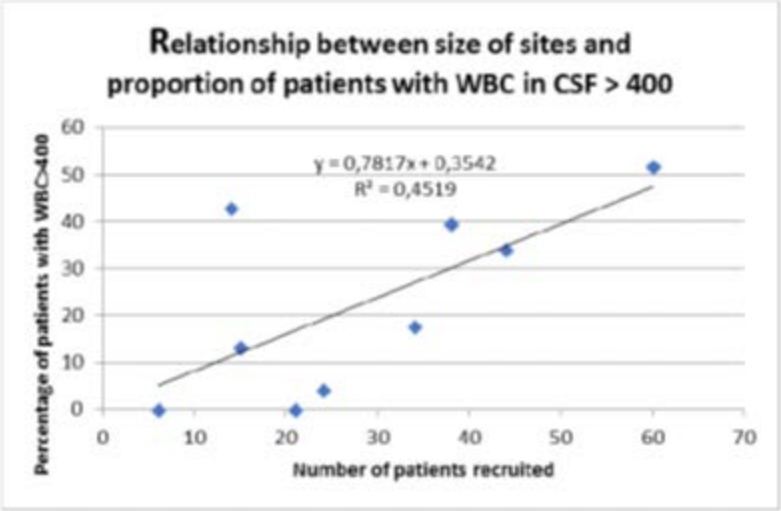


Figure 14: Relationship between the number of recruited patients and the success rate by site, excluding site 06 (DNDiFEX004)

The proportion of stage-2 patients with 100 WBC/µL in CSF or less, as well as the proportion of those with 400 WBC/µL at entry, are shown in Table below. These data show that the 2 largest sites (02 and 03, highlighted in bold in the Table) had 25% (26/104) of their patients with WBC ≤100 cells/µL and 44% (46/104) with WBC >400 cells/µL. On the other hand, the 3 smallest sites (07, 08 and 10, highlighted in bold italic in the Table) had 45.7% (16/35) of their patients with WBC ≤100 cells/µL and 22.8% (8/35) with WBC >400 cells/µL. The frequency of patients with a more severe disease was thus higher in the largest sites than in the smallest ones (44% versus 22.8%). This difference could possibly explain the difference in success rate, since less advanced patients (WBC ≤100 cells/µL) had a higher success rate as shown in the stratified analysis.

Table 28: Success rate in each site according to the WBC count in stage-2-HAT patients, in the fexinidazole arm of DNDiFEX004 study

Site	Proportions of patients with WBC ≤100 cells/µL at entry	Proportions of patients with WBC >400 cells/µL at entry	Success rate
	% (n/N)		%
Site 1	41.2% (14/34)	17.6% (6/34)	94.12
Site 2	**29.5% (13/44)**	**34.1% (15/44)**	**86.36**
Site 3	**21.7% (13/60)**	**51.7% (31/60)**	**88.33**
Site 4	23.7% (9/38)	39.5% (15/38)	100
Site 5	100% (21/21)	0% (0/21)	95.24
Site 6	0% (0/6)	50% (3/6)	16.67
Site 7	***60% (9/15)***	***13.3% (2/15)***	***100***
Site 8	***21.4% (3/14)***	***42.9% (6/14)***	***100***
Site 9	66.7% (16/24)	4.2% (1/24)	91.67
Site 10	***66.7% (4/6)***	***0% (0/6)***	***100***

Abbreviation: HAT, human African trypanosomiasis; WBC, white blood cells

The applicant has identified that the larger sites started the study at least one year earlier than other sites and tended to recruit the more severe patients. This is accepted as a plausible explanation, for the differences in fexinidazole success rates between sites. This analysis further supports the concerns with the efficacy of the proposed 10-day oral regimen in patients with late stage-2 HAT as compared to NECT. The provided analysis is relevant to the benefit-risk assessment.

Additional CRS for the 18 and 24-months results

A summary of the failures at 18 and 24 months in each treatment group, and between the primary and follow-up CSR is provided in the table below.

Table 29: Summery of the failures: comparison between 18 and 24 months and between primary and follow-up CSR (mITT population) – DNDiFEX004 follow-up CSR, Table 5

Analysis	Fexinidazole				NECT			
	Primary CSR		Follow-up CSR		Primary CSR		Follow-up CSR	
Time point	18 months	24 months	18 months	24 months	18 months	24 months	18 months	24 months
N	262	231	262	262	127	114	127	127
Successes	239 (91.2%)	205 (88.7%)	239 (91.2%)	235 (89.7%)	124 (97.6%)	112 (98.2%)	124 (97.6%)	124 (97.6%)
Failures	23 (8.8%)	26 (11.3%)	23 (8.8%)	27 (10.3%)	3 (2.4%)	2 (1.7%)	3 (2.4%)	3 (2.4%)
Reasons for failures:								
Rescue treatment	12	12	12	12	0	0	0	0
Death	6	9	6	9	2	2	2	2
CSF WBC >20 cells/µL	2	2	2	2	0	0	0	0
Trypanosomes in the blood	1	0	1	0	0	0	0	0
Lost to follow-up	1	2	1	3	1[a]	0[a]	1	1
Consent withdrawal	1	1	1	1	0	0	0	0

a Patient 03-088 was a failure at 18 months but was not included in the initial 24-month analysis because the 24-month visit was planned after the final database lock.

CSF = cerebrospinal fluid; CSR = Clinical study report; mITT = modified intention-to-treat; NECT = Nifurtimox-Eflornithine Combination Therapy; WBC = white blood cell.

Sources: Primary CSR, Table 15.2.1, 15.2.4.a, Listing 16.2.1.3, Listing 16.2.6.1, Listing 16.2.6.2, Listing 16.2.6.3.d, Listing 16.2.6.3.e, and Listing 16.2.9.7; Follow-up CSR, Table F-15.2.4.a, Listing F-16.2.1.3, Listing F-16.2.6.1, Listing F-16.2.6.2, Listing F-16.2.6.3.d, Listing F-16.2.6.3.e, and Listing F-16.2.9.7, and Data review report.

The follow-up analysis of the success rate at 24 months (N = 389) yielded similar findings to the initial 18 months analysis (N = 345, see primary CSR), with only 2 new failures (1 in each group). The success rate was 89.7% in the fexinidazole group (versus 88.7% initially) and 97.6% in the NECT group (versus 98.2% initially), and the observed difference between groups, despite being slightly larger than at 18 months (-7.9%; 95% CI [-12.5 to -3.4]), remained within the predefined limit of 13%. The increase is mainly due to 3 deaths that are clearly unrelated to the drug and 2 patients in success at month 18 who did not attend the 24-month visit.

Table 30: New failures at 24 months and patients with a classification switch between 18 and 24 months (mITT population) – DNDiFEX follow-up CSR

Patient	Primary CSR		Follow-up CSR		Comments
	18 months	24 months	18 months	24 months	
New failures at 24 months					
Fexinidazole group					
1[a]	Success	Ongoing	Success	Failure (lost to follow-up)	Did not do the 24M visit
NECT group					
2	Failure (no data after 12M)	Ongoing	Failure (lost to follow-up)	Failure (lost to follow-up)	Did not do the 18M and 24M visits
Patients with a classification switch between 18 and 24 months					
Fexinidazole group					
3	Success	Failure (CSF WBC >20)	Success	Failure	WBC from 6 at 18M to 27 cells/µL at 24M
4	Success	Failure (Died after 18M)	Success	Failure	Ameloblastoma
5	Success	Failure (Died after 18M)	Success	Failure	Alcohol poisoning
6	Success	Failure (CSF WBC>20)	Success	Failure	WBC from 1 at 18M to 80 cells/µL at 24M
1[a]	Success	Ongoing	Success	Failure (lost to follow-up)	Did not do the 24M visit
7	Success	Failure (Died after 18M)	Success	Failure	Inguinal hernia strangulated
8	Success	Failure (lost to follow-up)	Success	Failure	Did not do the 24M visit
9	Failure (Trypanosomes in blood)	Success	Failure	Success	No trypanosomes and CSF WBC ≤20 cells/µL at 24M
10	Failure (CSF WBC >20)	Success	Failure	Success	No trypanosomes and CSF WBC ≤20 cells/µL at 24M
11	Failure (CSF WBC >20)	Success	Failure	Success	No trypanosomes and CSF WBC ≤20 cells/µL at 24M
NECT group					
No patient had a classification switch					

CSF = cerebrospinal fluid; ID = identification; M = month; NECT = Nifurtimox-Eflornithine Combination Therapy; WBC = white blood cell.

a Of the 10 patients with a classification switch between 18 and 24 months, Patient 1 is the only patient who was considered "ongoing" in the primary CSR. This patient appears twice in the table because it is also a new failure at 24 months.

Analysing at individual patient's classification, there were 7 failures between 18 and 24 months and 3 more successes in the fexinidazole group, and no change in the NECT group. The 7 failures that occurred between 18 and 24 months in the fexinidazole group were due to 3 deaths, 2 patients being lost to follow-up and 2 patients with a CSF WBC above the limit of 20 cells/µL. For 6/7 failures, patient's status at 24 months was already known and described in the primary CSR. A probable relapse between 18 and 24 months was observed for 2 of the 7 failures, ie, the 2 patients presenting with a CSF WBC above the 20 cells/µL at 24 months. These late probable relapses represent 0.8% of the 237 patients in the mITT population who received fexinidazole and completed the 24-month visit.

The timing of relapse was previously investigated in a large cohort of mostly-adult patients treated with eflornithine (2). In this study, follow-up data at 24 months obtained in approximately half the sample (533 patients) showed 16 relapses (3.0%) between 18 and 24 months. In contrast with our study, most relapses and disease-related deaths occurred after 12 months in this study (2).

The number of proven relapses (rescue medication, or presence of trypanosomes, or WBC in CSF larger than the limit) was 3 at M6, 7 at M12, 3 at M18 (but possibly only 2 due to a doubtful and not sustained presence of trypanosomes in 1 patient) and 2 at M24 (Table 23). The conservative cumulated relapse rate was therefore 4.92% at M18 and 5.68% at M24. The difference in cumulated relapse rate between fexinidazole and NECT was significant at M12 (p = 0.035, exact test, 2-sided), at M18 (p = 0.006, exact test, 2-sided) and at M24 (p = 0.003, exact test, 2-sided).

Table 31: Relapse rate (rescue medication, or presence of trypanosomes, or WBC in CSF larger than the limit) in the ITT population in DNDiFEX004 study

ITT set of patients	Fexinidazole N (%)	NECT N (%)	Cumulated relapses fexinidazole N (%)	Cumulated relapses NECT N (%)	Excess relapse rates
Randomized	264	130	0	0	
Relapse at M3	0	0 (0%)	0	0	0%
Relapse at M6	3 (1.14%)	0 (0%)	3 (1.14%)	0 (0%)	1.14%
Relapse at M12	7 (2.65%)	0 (0%)	10 (3.79%)	0 (0%)	3.79%
Relapse at M18	3 (1.14%)	0 (0%)	13 (4.92%)	0 (0%)	4.92%
Relapse at M24	2 (0.76%)	0 (0%)	15 (5.68%)	0 (0%)	5.68%

Abbreviations: **CSF**, cerebrospinal fluid; **ITT**, intention-to-treat; **LTFU**, lost-to-follow-up; **M**, month; **NECT**, nifurtimox-eflornithine combination therapy; **WBC**, white blood cells

The applicant further clarified that the time of relapse, identified as either the initiation of rescue treatment or a high value of WBC or the presence of trypanosomes, was based on the visit timeframe (the time of the visit allowed a window of a few months). In a few cases rescue treatment was initiated after the first suspicion of relapse, but the time of relapse was based on the time of "worsening".

Table 32 reflects the total number of cases considered as relapse after the final analysis of all data with complete follow-up for all patients at 24 months. The data presented in this table have been adjusted to reflect the time of the initiation of the rescue treatment which can be considered as a confirmation of relapse.

Table 32: Relapse rates of fexinidazole and NECT (final analysis with complete follow-up)

		Number of relapses			
	Set of patients	by12 months (D365)	12 to 18 months (D548)	>18months (D549+)	Total at end of follow-up
Fexinidazole	262	3 (1.15%)	6 (2.29%)	5 (1,9%)	14* (5.3%)
NECT	127	0	0	0	0

*A total of 17 patients treated with fexinidazole were initially considered as relapse but 3 were not confirmed at Month 24

Regarding the overall death rate in the ITT population over time, Table 24 shows an excess rate of deaths at M24 of 1.87% and the relative risk of death at M24 of 2.21 (3.41/1.54). The excess rate of deaths and relative risk of death at M24 with fexinidazole is not statistically significant.

Three out of 7 failures between M18 and M24 are due to death unrelated to treatment according to the Investigator (strangulated hernia, ameloblastema and acute alcohol intoxication) and the small death rate (1.54%) in NECT at M24 was probably due to chance as the overall death rate for NECT in other clinical studies was estimated at 4.6%, which is about 3 times more than in the DNDiFEX004 pivotal study.

The time of relapse, identified as either the initiation of rescue treatment or a high value of WBC or the presence of trypanosomes, was based on the visit timeframe; in the study, the time of the visit allowed a window of a few months (as described below) so that a relapse occurring for example at D371 was reported as M12:

Table 33: Death occurrence over time in the ITT population in DNDiFEX004 study

Deaths in ITT set	Fexinidazole N (%)	NECT N (%)	Cumulated failure fexinidazole N (%)	Cumulated failure NECT N (%)	Excess death rates
Randomized	264	130	0	0	
Death EOH	2 (0.76)	0 (0)	2 (0.76)	0 (0)	0.76%
Death M3	3 (1.14)	1 (0.77)	5 (1.89)	1 (0.77)	1.12%
Death at M6	0 (0)	0 (0)	5 (1.89)	1 (0.77)	1.12%
Death at M12	1 (0.38)	1 (0.77)	6 (2.27)	2 (1.54)	0.73%
Death at M18	0 (0)	0 (0)	6 (2.27)	2 (1.54)	0.73%
Death at M24	3 (1.14)	0 (0)	9 (3.41)	2 (1.54)	1.87%

Abbreviations: **EOH**, end of hospitalization; **ITT**, intention-to-treat; **M**, month; **NECT**, nifurtimox-eflornithine combination therapy

Although cumulative failure rate and death rate were higher at all relevant time points for fexinidazole, with a 24- month death rate exceeding 1%, differences were not statistically significant. It is interesting to note that in this study the confirmed cases of failure in fexinidazole (relapse with WBC or trypanosomes in CSF and/or start of rescue medication) was around 6% (excluding the unrelated deaths and lost to follow up) and this was 0% for NECT, which is around the expected margin of difference between Fexinidazole and NECT at the start of the study. It is also acknowledged that additional non-relapse failures at month 24 were losses to FU and deaths were generally not related to either the study drug or to HAT. The higher relapse rate is considered significant to the risk: benefit assessment. Of note, most of the relapses responded adequately to rescue treatment with NECT. Following the recommendations at the Expert (SAG) meeting the applicant agreed to span the follow-up

up to 24 months, in order to capture late relapses with fexinidazole therapy, and related information was included in the updated PI.

Summary of pivotal study

The following table summarise the efficacy results from the main study DNDIFEX004 supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 34: Summary of efficacy for trial DNDIFEX004

Title: Efficacy and safety of fexinidazole compared to nifurtimox-eflornithine combination therapy (NECT) in patients with late-stage human African trypanosomiasis (HAT) due to T. b. gambiense : a pivotal, non-inferiority, randomised, open-label, multicentre study (DNDiFEX004)			
Study identifier	DNDIFEX004 (Clinical Trials Database NCT01685827)		
Design	Randomized (2:1), active comparator, open-label, multicenter, phase II/III study		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		18 months (primary efficacy endpoint) with further analysis at 25 months not applicable not applicable
Hypothesis	Non-inferiority admitted if the lower bound of the 95% CI for the observed difference in the primary efficacy variable between fexinidazole and the comparator treatment did not exceed 13%.		
Treatments groups	Experimental treatment		Fexinidazole Formulation: 600-mg tablets Route(s) of administration: oral (with food) Dose regimen: 1800 mg (3 x 600 mg tablets) administered orally, once daily for 4 days (Days 1 through 4), followed by 1200 mg (2 x 600 mg tablets) administered orally, once daily for 6 days (Days 5 through 10) Patients randomized and treated: 264
	Reference treatment		Nifurtimox Eflornithine Combination Therapy (NECT) Formulation: Combination of α-difluoromethylornithine (DFMO, injectable solution 20 g/100 mL) and nifurtimox (120-mg tablets) Route(s) of administration: intravenous injection route for DFMO, oral route for nifurtimox Dose regimen: DFMO administered as a 2-hour intravenous infusion at a dose of 400 mg/kg/day, in 2 divided doses (ie, administered twice daily), for 7 days (Days 1 through 7); nifurtimox administered at a dose of 15 mg/kg/day, in 3 divided doses (ie, administered three times daily) for 10 days (Days 1 through 10) Number randomized and treated: 130
Endpoints and definitions	Primary endpoint	<label>	Outcome (either success or failure) of treatment as assessed at the Test-of-Cure (TOC) visit, 18 months after EOT, based on the adapted WHO criteria (death considered a failure, regardless of the cause)

	Secondary endpoint	<label>	Outcome (either success or failure) of treatment as assessed at Day 11 (24 hours after EOT), and 3, 6, 12, and 24 months, after the EOT
Database lock	<date>		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	mITT: all ITT patients, except those who fled an area of armed conflict and with no post-treatment data.		
Descriptive statistics and estimate variability	Treatment group	Fexinidazole	NECT
	Number of subject	239/262	124/127
	Success rate	91.22%	97.64%
	Difference (FEX-NECT) (97.06CI)	-6.42 [-11.22; -1.61]	
	Primary (sensitivity): Outcome at 18 months using the algorithm of classification (mITT)	237/262	124/127
		90.46%	97.64%
		-7.18 [-12.10; -2.26]	
		P-value: 0.0100	
	Success rate at 18 months using the second imputation method and experts' adjudication (mITT)	226/262	119/127
		86.26 %	93.70%
		-7.44 (-14.04; -0.85)	
		P-value: <0.01	

- Study DNDIFEX005:

Efficacy and safety of fexinidazole in patients with stage 1 or early stage 2 HAT due to *T. b. gambiense*: a prospective, multicentre, open-label, cohort study, plug-in to the pivotal study

Methods

Study Participants

Study DNDIFEX005 was conducted in patients, aged 15 years and older, with stage 1 or early stage 2 HAT due to *T. b. gambiense*, with mandatory confirmed evidence of parasite in the blood or lymph and absence of parasite in the CSF. Otherwise, essentially the same inclusion and exclusion criteria used for study DNDIFEX004 were applied.

Patients were to be predominantly classified as Stage 1 (haemo-lymphatic), which would imply the direct and indirect exclusion of CNS involvement. However, the evidence of slight pleocytosis of WBC 6 - 20 cells/ µL was considered acceptable and classified by the applicant as Early stage 2 (see above). For the purposes of the study, patients were stratified by WBC count in CSF into two strata:

- Patients with stage 1 HAT: CSF-WBC, ≤5 cells/µL.
- Patients with early stage 2 HAT: CSF-WBC, 6 - 20 cells/µL.

Treatments

For study DNDIFEX005, the chosen standard adult dose regimen of fexinidazole, as described above was used in all patients.

Objectives

For study DNDIFEX005, which initiated recruitment circa 2 years after study DNDIFEX004, thus benefiting from the efficacy and safety data collected so far in patients with Stage 2 disease, the overall objective was to complement efficacy data from adult patients with stage 2 disease, collected in study DNDIFEX004, with efficacy data in patients with Stage 1 disease. By this mean evidence was expected to be gathered to support the effectiveness of fexinidazole through the whole clinical spectrum of the disease, as requested in the proposed indication.

The objective was to demonstrate that the success rate with fexinidazole at 12 months after the end of treatment (EOT) was greater than 80% in stage 1 or early stage 2 HAT patients. A success rate of ≤ 80% was considered unacceptable. This limit was calculated by subtracting the margin of 13% (pivotal study) to the success rate expected with the reference treatments at 12 months (93%), which was estimated by combining the historical success rates of NECT in stage 2 patients and pentamidine in stage 1 patients. While subject to discussion, this very conservative reference value of 80% did not have a significant impact on the definition of the sample size, which was ultimately the result of convenience. Besides, the success rates proved to be far higher than this reference value.

The primary efficacy endpoint was the outcome (either success or failure) of treatment as assessed at the TOC visit, 12 months after the EOT, based on adapted WHO criteria, which are essentially the ones described for study DNDIFEX004 for assessment of either failure or success.

If the patient was not a definitive failure at 12 months and if a lumbar puncture was performed at 18 months but not 12 months, then the outcome at 18 months was carried backward. Patients who did not have a lumbar puncture at 12 months but had not yet reached 18 months, were considered as failures in the primary efficacy analysis at 12 months.

The secondary efficacy endpoints were the outcome (either success or failure) of treatment as assessed at 24 hours, and 6 and 18 months after the EOT.

Blood, lymph, and CSF samples were subjected to similar procedures as described for DNDIFEX004 and processed in at the time points specified in the chart below for efficacy assessments. Samples were tested by the local laboratory at each investigational site for the presence of trypanosomes, as follows:

Table 35: Schedule of study procedures

Procedures	Pre-screening and screening	Baseline	Treatment period										EOT visit[a] until EOH visit[b]		Follow-up period[c]	
Time point	D-15 to D-1	D-4 to D-1	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D11-D18	Week 9[d]	6, 12, 18 months[e]
Blood and/or lymph sampling for detection of trypanosomes	X												X			X
CSF sampling (lumbar puncture) for detection of trypanosomes and WBC count	X															X

The methods of handling missing values were similar to the ones used for study DNDIFEX004.

For study DNDIFEX005, based on the preliminary data from DNDIFEX004 (an expected 89% success rate at 18 months in Stage 2 patients) and considering that the disease is less severe in patient with stage 1 and early stage 2 HAT than in patients with late stage 2 HAT, a 91% success rate was expected for the population with Stage 1 disease.

An exact test with a success rate of 91%, an exact power of 91.7% and a type I error of 0.025 required a sample size of 113 patients, which corresponded to the minimal sample size to include.

It was planned to enrol all stage 1 and early stage 2 patients who were diagnosed during the recruitment and follow-up period of the main pivotal study (DNDiFEX004) and who consented to participate in this plug-in study DNDiFEX005. The enrolment ran until the last patient of the pivotal study had completed the 6-month visit to allow for maximum safety information and to complete the follow-up of both studies at the same time.

The population was stratified in 2 subpopulations: patients with CSF WBC ≤5 cells/µL(stage 1) and patients with CSF WBC between 6 and 20 cells/µL(early stage 2). The strata were self-weighted, i.e., the number of patients in each stratum depended solely on the number of patients who gave consent to participate in the study.

Because the success rate could significantly depend on the stage, it was planned to include a sufficiently large number of patients at stage 1 to have, with the same expected success rate at 12 months (91%), a statistical power of at least 85%. To achieve this power, it was necessary to include at least 101 stage 1 patients. However, considering the slow pace of enrolment it was decided that the objective of enrolling 101 patients would only apply to stage 1 patients, not early stage 2 patients (per Protocol Amendment 2, release date 25 August 2015).

Therefore, ultimately, the difficulties in enrolment have driven the sample size for both studies (the pivotal and DNDiFEX005 study).

Results

Recruitment

A total of 238 patients were pre-selected (i.e. screened) for the study and signed the informed consent: 195 patients and 43 patients with stage 1 and early stage 2 HAT, respectively. Of these 238 screened patients, 8 patients (3.4%) were not included in the study: 6 patients with stage 1 HAT and 2 patients with early stage 2 HAT. Reasons for non-inclusion were meeting exclusion criteria (5 patients: positive pregnancy test (n=2), abnormalities on ECG (n=2), diabetes mellitus discovered (n=1), withdrawal of consent (2 patients) and other reasons (1 patient whose baseline biochemistry analysis was unavailable due to technical issues)).

Therefore, a total of 230 patients were included in the study: 189 patients (82.2%) and 41 patients (17.8%) with stage 1 and early stage 2 HAT, respectively. Each of the 8 study sites included between 15 and 47 patients in the study, all included in the ITT population.

In the ITT population, 4 patients (1.7%) were prematurely withdrawn from the study, 3 patients with stage 1 HAT and 1 patient with early stage 2 HAT. All 4 premature study withdrawals were the result of patient death. Premature withdrawal occurred before the completion of the 12-month visit in 3 out of the 4 patients who withdrawn (75%).

The four deaths were reviewed by 3 independent experts and were considered unrelated to treatment or to HAT as follows:

- One with early stage 2 HAT died due to anaemia, pulmonary sepsis and nephropathy between 12 and 18-months follow-up
- One with stage 1 HAT died due to meningeal syndrome and encephalitis between EOH and 6 months follow-up
- One with stage 1 HAT died due to shock between 6 and 12 months follow-up
- One with stage 1 HAT died due to Crohn's disease and peritonitis between 6 and 12 months follow-up

The four who died were the only patients who did not attend all visits up to and including month 12.

At the time of database lock (31 March 2017) a total of 227/230 patients (98.7%) had reached the primary time point at 12 months. Three patients (1.3%), all with stage 1 HAT died before the 12-month visit. A total of 157/230 patients (68.3%) had reached the additional 18-month time point: 132/189 patients (69.8%) with stage 1 HAT and 25/41 patients (61.0%) with early stage 2 HAT. At the time of database lock, for 69/230 patients (30.0%), the study was still ongoing: 54/189 patients (28.6%) with stage 1 HAT and 15/41 patients (36.6%) with early stage 2 HAT. The remaining 4/230 patients (1.7%) died before the 18-month visit, including 1 patient (Patient 501_025) who died between the 12- and 18-month visits.

A total of 166 patients had not reached the Week 9 time point (9 weeks after Day 1) by mid-December 2014 and were therefore scheduled to attend the Week 9 visit (as per Protocol Amendment 2); all 166 patients attended this visit.

All 230 included patients (189 patients and 41 patients with stage 1 and early stage 2 HAT, respectively) completed treatment. In addition, there were no cases of temporary treatment discontinuations.

Conduct of the study

In study DNDIFEX005, all patients received the correct dose of treatment. Protocol amendments are not expected to affect the efficacy results and there were no significant protocol deviations.

Baseline data

The demographic characteristics of the population included are well described and do not reveal notable findings.

The most commonly reported medical histories in the ITT population were from the Investigations SOC, reported in 76 patients (33.0%) overall.

Other common medical or surgical conditions were also reported but did not seem relevant for the efficacy assessment. Malaria was reported in 5 patients (2.65%) in the early stage 1, and 1 patient (2.44%) in early stage 2 [overall 6 (2.61%)].

The clinical signs and symptoms of HAT reported in patients at the inclusion visit were more commonly experienced intermittently rather than continuously, and had a variable time to onset, appearing from <1 week to >6 months before screening, with the following overall prevalence:

- >20% of overall patients: headache (67.0%), weight loss (36.2%), amenorrhoea (23.7%), fever (25.2%), asthenia (23.1%) and pruritus (22.2%)
- 3-20% of overall patients: insomnia (17.8%), impotence (15.9%), anorexia (13.5%), other symptoms (12.6%), nausea (10.4%), drowsiness (9.6%), tremor (5.7%) and diarrhoea (3.5%)
- <3% of overall patients: convulsion (1.3%), gait disturbance (1.3%) and behavioural disorders (0.9%).

Weight loss was reported in 2.8% to 72.0% of patients depending on which site was considered. For other signs and symptoms reported in >20% of overall patients (excluding amenorrhoea), the prevalence between sites ranged from 47.2% to 93.1% for headache, from 6.7% to 60.0% for fever, from 0.0% to 46.4% for asthenia and from 6.7% to 37.9% for pruritus.

Similar clinical signs and symptoms of HAT were observed in the EP population.

The entry test in the diagnosis algorithm of HAT was CATT, which is a serological test. All patients tested positive, except 12 patients tested by the mobile team: 5 were negative, 5 did not do the test and 2 had missing data but all 12 patients complied with the criteria for stage 1 HAT by presenting with trypanosomes in blood or lymph. The tests performed to confirm the presence of trypanosomes revealed that parasites were detected in the lymph in 23.5% of patients (of 230 patients), and in the blood in 14.4% to 38.3% of patients depending on the method used, i.e., CTC (WOO), mAECT or mAECT-BC.

The absence of trypanosomes in the CSF was confirmed in all other patients.

The median CSF WBC count considering all patients was 3.0 cells/µL.

Almost all patients were in good health (97.0% and 99.6% at screening and baseline, respectively), with an altered general health recorded in 7 patients (3.0%) and 1 patient (0.4%) at screening and baseline, respectively.

Generally, similar results for vital signs, Karnofsky score and general health were observed in the ITT population and the EP population, regardless of HAT stage.

Cervical adenomegaly was found in 63/230 patients (27.5%): 49/189 patients (26.1%) with stage 1 HAT and 14/41 patients (34.1%) with early stage 2 HAT and was most frequently observed in the lateral cervical region.

The majority of patients had normal results for each of the items of the neurological and psychiatric examination.

Just like in the pivotal study, in the DNDiFEX005 study, as the treatments were always administered in hospital environment, the reported compliance with treatment is very high. Similarly, concomitant medication was rare and mainly represented by paracetamol. Patients with recent or concomitant treatments for HAT were rare and excluded from the analysis.

In general, it should be considered that the selection of the patients was correct and the adequate to the proposed objectives. The compliance with diagnostic procedures at baseline and outcome assessment was very good as was the compliance with treatment.

Numbers analysed

The numbers analysed in this study per analysis population are shown in the table below:

Table 36: Data sets analysed (including population)

	Disease Stage		
Analysis datasets	**Stage 1 (N=189)**	**Early Stage 2 (N=41)**	**Total (N=230)**
ITT Population - N (%)			
Yes	189 (100.0%)	41 (100.0%)	230 (100.0%)
Total	189	41	230
PP Population - N (%)			
Yes	189 (100.0%)	41 (100.0%)	230 (100.0%)
Total	189	41	230
TC Population - N (%)			
Yes	189 (100.0%)	41 (100.0%)	230 (100.0%)
Total	189	41	230
EP Population - N (%)			
Yes	186 (98.4%)	40 (97.6%)	226 (98.3%)
No	3 (1.6%)	1 (2.4%)	4 (1.7%)
Total	189	41	230

Percentages are based on the number of patients in the included population.
EP = evaluable patients; ITT = intention-to-treat; PP = per protocol; TC = treatment completers.
Source: Table 15.1.6.

Outcomes and estimation

Table 37

DNDiFEX005		FEX		Difference [97.06% CI
Primary analysis: success rate at 12 months using the primary imputation method (ITT)	230	227 (98.7%)	NA	[96.2%; 99.7%]

The success rate at 12 months was calculated based on the primary imputation method (algorithm of classification at 12 months). The overall success rate at 12 months was 98.7%, 95% CI [96.2; 99.7], which was significantly higher than the expected 91%. As the lower bound of the 95% CI for the overall success rate was greater than 80%, the pre-defined primary study endpoint was met. For stage 1 patients the success rate was 98.4%, 95% CI [95.4; 99.7], with 3 patients (1.6%, 95% CI [0.3; 4.6]) considered as failures. For early stage 2 patients, the success rate was 100.0%, 95% CI [91.4; 100.0].

Table 38: Success rate at 12 months according to HAT stage using the primary imputation method (ITT population)

	Disease Stage		
	Stage 1 (N=189)	Early Stage 2 (N=41)	Total (N=230)
Outcome at 12 months (Primary imputation method)			
N	189	41	230
Success	186 (98.4%) [95.4%;99.7%]	41 (100.0%) [91.4%;100.0%]	227 (98.7%) [96.2%;99.7%]
Failure	3 (1.6%) [0.3%;4.6%]	0 (0.0%) [0.0%;8.6%]	3 (1.3%) [0.3%;3.8%]

Data regarding success and failure are provided as N (%) [95% CI] (binomial law).
CI = confidence interval; HAT = Human African Trypanosomiasis; ITT = intention-to-treat.
Source: Table 15.2.10.

In the CSR of DNDiFEX005 study (table below) patients were considered failures at 12 months using the primary imputation method (algorithm classification). Among the 3 patients counted as failures at month 12 because of death, two of them were already considered failures at 6 months due to missing lumbar puncture. Then, both died between 6 and 12 months of follow-up (Day 202 and Day 345, respectively, according to the CRFs) and were thus confirmed as failures at 12 months.

Table 39: Patients who were failures at 12 months using the primary imputation method (including patients) – Study DNDiFEX005

Patient ID	HAT stage	Patient included (x) in				Classification for failure
		ITT	PP	TC	EP	
503_006	Stage 1	x	x	x	No	Death (due to meningeal disorder and encephalitis) on Day 54 (between EOH and 6 months of follow-up)
509_011	Stage 1	x	x	x	No	Death (due to shock) on Day 202 (between 6 and 12 months of follow-up)
510_006	Stage 1	x	x	x	No	Death (due to Crohn's disease and peritonitis) on Day 345 (between 6 and 12 months of follow-up)

Note: 6 other patients (Patient 509_004, Patient 509_012, Patient 509_013, Patient 509_017, Patient 509_018 and Patient 509_019) were considered failures at 6 months only due to missing lumbar puncture. These patients were considered as successes at 12 months.
Day 1 was the first day of treatment.
EP = evaluable patients; ID = identification; ITT = intention-to-treat; PP = per protocol; TC = treatment completers.
Source: data review meeting (16-1-9-support), Listing 16.2.6.2.

The second imputation method consisted of imputing a failure in the absence of a lumbar puncture at 12 months. The overall success rate at 12 months in the ITT population was 96.5%, 95% CI [93.3; 98.5], with 8 patients (3.5%, 95% CI [1.5; 6.7]) considered as failures: 3 of them had died and 5 did not have lumbar puncture at 12 months.

The third imputation method consisted of the absence of imputation of missing data, except for definitive failure, which was carried forward. If there were missing values (e.g. CSF WBC count) at the 12-month visit, followed by a success or failure at the additional 18-month visit, the status (success or failure) at the 18-month visit prevailed at the 12-month visit. The overall success rate at 12 months in the ITT was 98.7%, 95% CI [96.2; 99.7], with 3 patients (1.3%, 95% CI [0.3; 3.8]) considered as failures. The overall success rate was the same to that obtained using the primary imputation method.

The ITT population was identical to the PP population and the TC population, and therefore the success rates were the same. The relationship between success rate and WBC count in CSF at screening was not statistically significant (OR 2.692; 95% CI [0.661; 10.971]; p=0.1662).

Also, with regard to clinical signs and symptoms, a general improvement was observed. The number patients included with early stage 2 is insufficient to allow for any conclusion regarding potential differences between groups.

The efficacy data from study DNDIFEX005, is compatible with a high success rate at 12 months in patients with Stage 1 HAT. The observed success rate is comparable to the historical success rate of pentamidine and suramin (efficacy rate of 75-95 reported for Stage 1 HAT due to *T. B gambiense* (Neujean, 1950; Neujean and Evens, 1958), which must both be administered parenterally.

Ancillary analyses

In the final analysis at 12 months (primary CSR), 3 patients (1.3%) were considered as failures due to death in the ITT population. All 3 patients died from causes that were not considered related to the treatment or to the disease (meningeal syndrome and encephalitis in one case, shock in another case, Crohn's disease and peritonitis in the last case). In the follow-up analysis with complete 18-month data, there were no new failures at 12 months. Therefore, the additional 18-month data did not change the analyses of the primary efficacy endpoint. All sensitivity analyses confirmed the primary findings. One of these sensitivity analyses (third method of imputation) was updated in the follow-up analysis due to additional 18-month data for 1 patient, with no impact on success rate; there was 1 additional success but also 1 additional patient included in the analysis (227 successes out of 230 patients, versus 226 successes out of 229 patients originally), giving a success rate of 98.7%, 95% CI [96.2 to 99.7]. There were no changes to the other sensitivity analyses.

At 18 months, 5 patients were considered as failures (no change from the initial analysis described in the primary CSR) resulting in an overall failure rate of 2.2%. All 69 of the patients who had not reached the 18-month time point at final database lock completed the study and were considered as successes at 18 months. There were 2 more failures at 18 than at 12 months because 2 patients had a classification switch: 2 successes became failures (1 death from anemia, pulmonary sepsis and nephropathy, and 1 patient who had a CSF WBC > 20 cells/µL at 18 months).

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 to 99.3]) versus 96.9% (95% CI [92.9 to 99.0]) in the initial analysis.

The other secondary analyses regarding the time course of failure all confirmed the analyses presented in the primary CSR.

The follow-up analysis of the 18-month data did not change the findings presented in the primary CSR of the DNDiFEX005 study. Fexinidazole, as an oral drug, showed high efficacy in the stage-1 and early stage-2 patients (CSF WBC ≤20 cells/µL). No new safety issues were raised and the benefit-risk balance of fexinidazole for treating adult patients with stage-1 or early stage-2 HAT due to *T. b. gambiense*, regardless of disease stage, appears positive. The overall success rate was slightly lower at 18 months (97.8%, 95% CI [95.0 to 99.3]) than at 12 months (98.7%, 95% CI [96.2 to 99.7]). This observation does not raise concerns regarding the existence of a clinically or epidemiologically relevant relapse rate in patients with stage 1 and early stage-2 HAT treated with the proposed 10-day oral regimen of fexinidazole.

Clinical studies in special populations

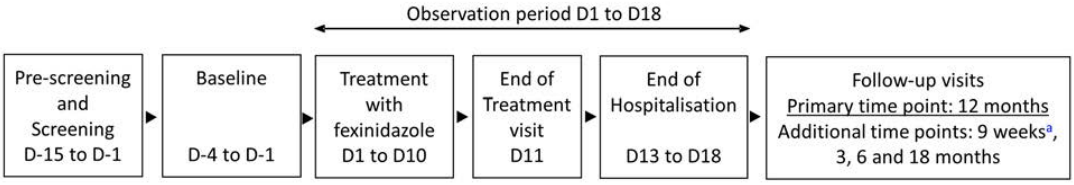
- Study DNDIFEX006:

Efficacy and safety of fexinidazole in children at least 6 years old and weighting over 20 kg with HAT due to *T. b. gambiense*: a prospective, multicentre, open study, plug-in to the pivotal study

Supportive data for efficacy also may be derived from study DNDIFEX006, the paediatric study which has been conducted in children aged 6 years to 15 years, or weighing more than 20 kg, and able to swallow the tablets (as no specific formulation intended for paediatric use was developed). The study was to include patients regardless of the HAT stage, so that essentially the same methodologic criteria applied as for studies DNDIFEX004 and DNDIFEX005.

The need for compliance with parasitologic and cytologic criteria, both at baseline and at TOC visit, at 12 months, was required, as for the two studies in adults. However, the need for a lumbar puncture at the 12-month time point was not mandatory for the assessment of a patient as a success as it could be replaced by either a lumbar puncture at the late 19-month visit or a lumbar puncture at the 6-month time point PLUS additional evidence of favourable evaluation.

The study procedures are summarized as follows:



The 12 months after the EOT time point for assessment of the efficacy endpoint, was set because the relapse rate between 12 and 18 months is very low and highly consistent across the various treatments administered to patients with stage 2 HAT.

The planned sample size for the present study was 125 or 126 patients. With a sample size of 125 patients, the probability of rejecting H0A (H0A: success rate ≤80%) was 97.5% if the true success rate is 92% with a one-sided type I error of 0.025. The probability of rejecting H0B (H0B: success rate ≥92%) was also 97.5% if the true success rate was 80% with a one-sided type I error of 0.025.

No reflections regarding the possibility of stratification by any criterion (age, weight, disease stage, disease stratum, dose regimen) were considered for the determination of sample size.

The only stratification was for the purpose of the study and used WBC count in CSF into three strata:

- Children with stage 1 HAT: evidence of trypanosomes in the blood or lymph, no trypanosomes in the CSF, and CSF WBC ≤5 cells/µL
- Children with early stage 2 HAT: evidence of trypanosomes in the blood or lymph, no trypanosomes in the CSF, and CSF WBC 6 to 20 cells/µL
- Children with late stage 2 HAT: evidence of trypanosomes in the blood or lymph, and either CSF WBC >20 cells/µL or trypanosomes in the CSF (adapted from WHO for clinical studies on HAT).

The definition of analysis populations was generally similar to the one used in studies DNDIFEX004/005.

All children received fexinidazole for 10 days with food while resident as follows:

- Body weight ≥20 kg and <35 kg - 1200 mg (2 x 600-mg tablets) once daily for 4 days and 600 mg (1 tablet) once daily for 6 days
- Body weight ≥35 kg - same as in adults in DNDiFEX004

In addition to the difference in age and weight criteria for inclusion, children were to have a Z-score for BMI that was <2 standard deviations below the norm according to the WHO 2007 growth reference data.

Statistical analysis of the primary efficacy endpoint consisted in computing the success rate at 12 months with its two-sided 95% confidence interval (CI) using the Clopper-Pearson method. Two sets of statistical hypotheses (A and B) were then tested simultaneously:

- H_{0A}: the true success rate was ≤80% (ie, the unacceptable rate)

  H_{1A}: the true success rate was >80%
- H_{0B}: the true success rate was ≥92% (ie, the targeted or expected rate for fexinidazole)

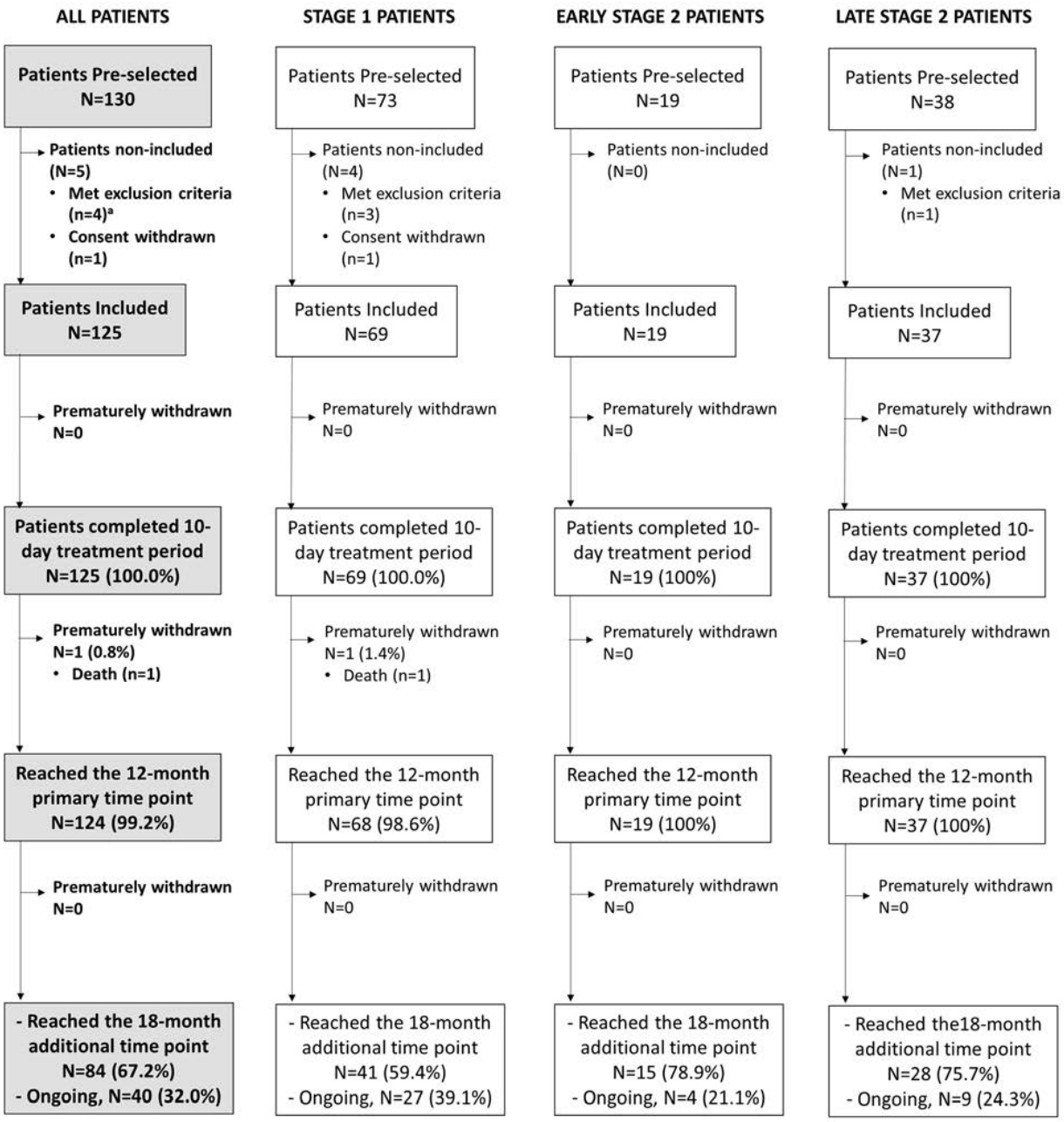
  H_{1B}: the true success rate was <92%.

If H_{0A} was rejected, then the success rate was significantly larger than 80% and the estimate was compatible with 92%. In that case, H_{0B} was automatically accepted but not necessarily true. If H_{0B} was rejected, then the success rate was significantly smaller than the target of 92% and the estimate was compatible with the unacceptable rate of 80%. In that case, H_{0A} was automatically accepted but not necessarily true.

The ITT population was used to perform the primary efficacy analysis. Apart from the primary efficacy analysis (12 months, ITT), a set of sensitivity and secondary analyses was predefined, rather similar to the ones defined for study DNDIFEX005, and will be presented along with the efficacy results.

No potentially significant changes were made to the study conduct or statistical analyses.

A total of 125 patients were included in the study: 69 patients (55.2%) with stage 1 HAT, 19 patients (15.2%) with early stage 2 HAT and 37 patients (29.6%) with late stage 2 HAT.



Premature withdrawals were very rare. In the ITT population, 1 patient with stage 1 HAT died after completion of the 10-day treatment period and before the 12-month primary follow-up visit. At the time of database lock, no patients had been withdrawn between the primary time point (12 months) and the additional time point (18 months).

All 125 included patients (69 patients with stage 1 HAT, 19 patients with early stage 2 HAT and 37 patients with late stage 2 HAT) completed treatment. There was one case of temporary treatment discontinuation due to vomiting after treatment re-administration.

Major protocol deviations were reported in 2 patients (1.6%), both were excluded from the PP population, while kept in the ITT. Median values for age (11.0 y), weight (27.0 kg), height (130.0 cm) and BMI (16.1) were comparable across the three clinically-defined strata.

With regard to baseline clinical data, the most commonly reported medical histories were from the Investigations SOC, reported in 41 patients (32.8%) overall. There were no marked differences between disease stages regarding the prevalence of medical histories. The only preferred term of those described above, which was reported at a >10-point difference between stages was blood albumin decreased in 10.1% of patients with stage 1 HAT, 26.3% with early stage 2 HAT and 27.0% with late stage 2 HAT.

Overall, as expected, the majority of clinical signs and symptoms of HAT were reported at a higher incidence for late stage 2 patients, than stage 1 or early stage 2 patients, e.g. drowsiness (70.3%, 18.8% and 15.8%, respectively), asthenia (56.8%, 23.2% and 10.5%), pruritus (35.1%, 15.9% and 15.8%), gait disturbances (18.9%, 1.4% and 0.0%), behavioural disorders (35.1%, 4.3% and 5.3%) and insomnia (18.9%, 2.9% and 5.3%). In addition, tremor and language disorders were only reported for late stage 2 patients (32.4% and 16.2%, respectively).

A very high variation in the frequency of HAT symptoms and signs was observed across the different sites (for instance, asthenia varied from 0 to 92%).

Diagnosis of HAT and HAT staging

The diagnosis of HAT was established by the presence of trypanosomes in blood or lymph. All patients presented with trypanosomes in either the blood or lymph as per protocol.

Regarding CATT, 9 patients tested negative. However, all 9 patients complied with the criteria for stage 1 HAT (at least) by presenting with trypanosomes in blood or lymph.

The tests performed to confirm the presence of trypanosomes revealed that parasites were detected in the lymph in 42 of 56 patients (75.0%), and in the blood in 43.9% to 86.7% of patients tested depending on the method used, i.e., CTC (WOO), mAECT or mAECT-BC (number of patients tested varying from 21 to 82).

The CSF was examined in all patients. Trypanosomes in the CSF were found in 25 patients (20.0%), who were all classified as late stage 2 HAT patients despite 2 of them having a CSF WBC count lower than 21 cells/µL.

The median CSF WBC count was the following:

- All patients regardless of stage: 5.0 cells/µL
- Patients with stage 1 HAT: 3.0 cells/µL overall (maximum value was 5 cells/µL as per protocol)
- Patients with early stage 2 HAT: 9.0 cells/µL overall (minimum value was 6 cells/µL and maximum value was 20 cells/µL)
- Patients with late stage 2 HAT: 193.0 cells/µL overall (minimum value was 5.0 cells/µL and maximum value was 857.0 cells/µL).

The majority of patients were in good health (81.6% and 88.8% at screening and baseline, respectively), as assessed through the analysis of baseline vital signs and Karnofsky score, with an altered general health recorded in 23 patients (18.4%) and 14 patients (11.2%) at screening and baseline, respectively. The proportion of patients with an altered general health was higher at screening and baseline for late stage 2 patients (46.0% and 32.4%) than stage 1 (7.3% and 2.9%) or early stage 2 (5.3% and 0%) patients.

Lateral cervical adenomegaly was the most frequently reported abnormality found in 56 patients (44.8%) overall. This abnormality was more prevalent in patients with late stage 2 HAT (64.9%) than those with stage 1 (36.2%) or early stage 2 HAT (36.8%).

Other abnormalities reported in >5% of patients overall included abnormal sound (cardiac auscultation) in 8 overall patients (6.5%), and skin abnormalities (abnormality other than scratching lesion), in 12.8% of overall patients.

The majority of patients, regardless of HAT stage, had normal results for each of the neurological/psychiatric items at inclusion. Abnormalities, when reported were generally present at a higher incidence in patients with late stage 2 HAT than those with stage 1 or early stage 2 HAT.

Mean hematology values at screening were within reference range for all parameters except for basophils (mean 0.01%; reference range: 0.4-2.5%) and monocytes (mean 2.73%; reference range: 4.5-13.1%), which were both low. However, this could be explained by the difficulties in performing a visual count of these specific cells on the slide. As per protocol, none of the patients had severe leukopenia (WBC <2000 cells/µL).

The most frequently reported concomitant medications were paracetamol in 28 patients overall (22.4%), and metoclopramide (in 20 patients (16.0%)).

In the ITT population, all 125 patients completed treatment on Day 10 or Day 11. All patients received the treatment as planned in the protocol except 8 patients (6.4%).

Efficacy results

Primary efficacy endpoint

The overall success rate at 12 months was 97.6%, 95% CI [93.1; 99.5], which was significantly higher than the expected/targeted 92%. The lower bound of the 95% CI for the overall success rate (93.1%) was greater than 80% (the unacceptable success rate).

The primary study endpoint was met.

There were 3 failures at 12 months (failure rate 2.4%, 95% CI [0.5; 6.9]) in the ITT population:1 patient died before the 12-month time point after traumatic aggression and the patient was excluded from the EP population; and 2 patients had CSF WBC count >20 cells/µL at 12 months.

As expectable, no notable differences were observed across sites in terms of the result of the main efficacy variable. In addition, the sensitivity analyses did not change the favorable assessment for the primary efficacy variable.

The second imputation method consisted of imputing a failure in the absence of a lumbar puncture at 12 months. The overall success rate at 12 months was 96.0%, 95% CI [90.9; 98.7], with 5 patients (4.0%, 95% CI [1.3; 9.1]) considered as failures.

Secondary analyses

Success rate at 12 months according to HAT stage using the primary imputation method was analyzed and did not reveal notable differences. It should be noted that the rather small number of patients may explain the small differences observed.

Table 40: Success rate at 12 months according to HAT stage using the primary imputation method (ITT population)

	Disease Stage				
	Stage 1 (N=69)	Early Stage 2 (N=19)	Late Stage 2 (N=37)	Stage 2 Early or Late (N=56)	Total (N=125)
Outcome at 12 months (First imputation Method)					
Missing	0	0	0	0	0
Success	68 (98.6%) [92.2%; 99.9%]	18 (94.7%) [74.0%; 99.9%]	36 (97.3%) [85.8%; 99.9%]	54 (96.4%) [87.7%; 99.6%]	122 (97.6%) [93.1%; 99.5%]
Failure	1 (1.4%) [0.0%; 7.8%]	1 (5.3%) [0.1%; 26.0%]	1 (2.7%) [0.1%; 14.2%]	2 (3.6%) [0.4%; 12.3%]	3 (2.4%) [0.5%; 6.9%]
Total	69	19	37	56	125

Data regarding success and failure are provided as N (%) [95% CI] (binomial law).
The upper limit (95% CI) of the success rate in stage 1 patients was 100.0% in the source table, instead of 99.9%, due to rounding. The table above provides the exact value rounded down when there is at least one observed failure.
Success rate was compared between stage 1, early stage 2 and late stage 2 HAT patients using a Fisher exact test (p=0.562).
CI = confidence interval; HAT = Human African Trypanosomiasis; ITT = intention-to-treat.
Source: Table 15.2.10.

The relationship between the success rate at 12 months and the WBC count in CSF at screening was estimated through a logistic regression, with WBC count set as a quantitative covariate. No statistically significant relationship was observed between success rate and WBC count in CSF at screening (odds ratio (OR), 1.000, 95% CI [0.992; 1.008], p=0.9872).

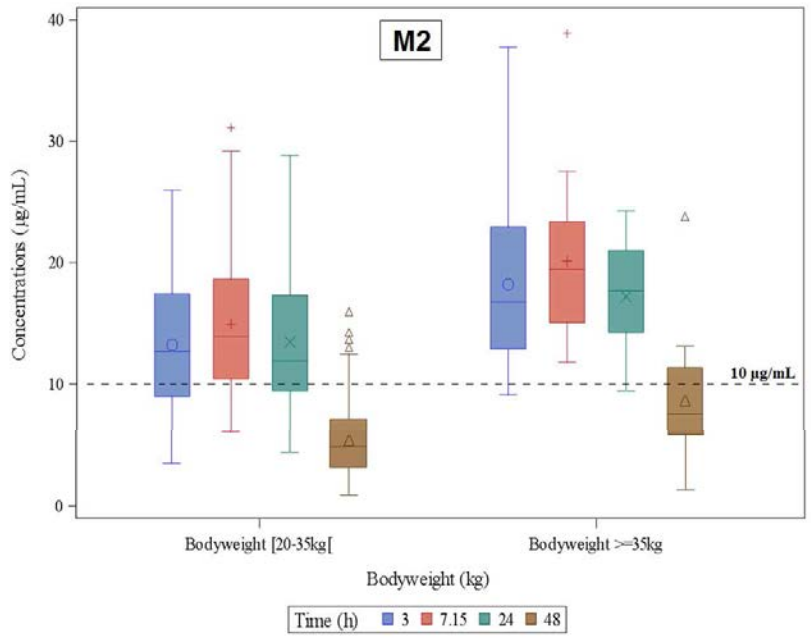
The evaluation of the success rate at 18 months was based on criteria that were similar to those used in the primary analysis. A total of 85 patients were considered in this analysis: 84 patients who reached the 18-month time point and one patient who was prematurely withdrawn due to death. The overall success rate at 18 months was 97.6% (95% CI [91.8; 99.7]) with 2 patients (2.4%, 95% CI [0.3; 8.2]) considered as failures, 1 in stage 1 and 1 in late stage 2. There was 1 less failure than at 12 months because 1 patient (early stage 2) had a CSF WBC count of 36 cells/µL at 12 months, but <20 cells/µL at 6 and 18 months without receiving any rescue treatment. Consequently, this patient was a success at 18 months.

Other statistical analyses were performed, which also do not change the overall favorable efficacy assessment.

The PK in plasma and CSF were evaluated in a subset of patients in this study. Following the 10-day oral regimen, the concentrations of fexinidazole, M1 and M2 in the blood were lower for patients in the ≥20 to <35 kg weight group than for those in the ≥35 kg weight group at all-time points. When considering only the 24-hour interval on Day 10, mean concentrations were 10 to 30% lower in patients in the ≥ 20 to <35 kg weight group.

A target of 10 µL /mL for M2 in plasma was previously established for adult patients, which was compatible with effective levels. In this study, 85/114 overall patients (75%) had M2 levels higher than 10 μg/mL at 24 hours after the last administration on Day 10 (65/93 patients [70%] in the ≥20 to <35 kg weight group and 20/21 patients [95%] in the ≥35 kg weight group). Among these patients, 20/114 patients (17%) had levels higher than 20 μg/mL (14% and 33% in the ≥20 to <35 kg and ≥35 kg weight groups, respectively). At 48 hours after last administration on Day 10, there were still 15% of patients with M2 levels higher than 10 μg/mL (11% in the ≥20 to <35 kg weight group and 33% in the ≥35 kg weight group).

Distribution of M2 concentration (µg/mL) measured on Day 10, following multiple administrations of fexinidazole



M2 = fexinidazole sulfone.

Source: population PK analysis report, Figure 1.

Figure 15

Samples of CSF were available for 27 patients (24 in the ≥20 to <35 kg weight group and 3 in the ≥35 kg weight group). The analysis confirmed that high M2 levels were reached in the CSF. All 27 patients (100%) had M2 CSF concentrations higher than the half-maximal effective concentration (IC_{50} = 0.270 µg/mL) 24 hours after the last administration on Day 10. The ratio of CSF to DBS concentration was quite comparable between patients and was about 0.5 for M2 and M1 with a coefficient of variation (CV) of about 15%.

In summary, the data from paediatric patients aged 6 to 15 years indicates a success rate after 12 months of treatment of around 95%. The numbers included were small and do not allow for an adequate comparison between the two stages of disease. The results for patients in early stage 2 showed a wide 95% CI. Analysis regarding the result by age and by weight is not presented. In addition, a correlation between weight and efficacy was not made.

These findings are in support of the efficacy of fexinidazole for the treatment of Stage 1 disease, but also indicate that the compound and the proposed regimen show a considerable therapeutic effect in patients with stage 2.

Analysis performed across trials

Rescue treatment with NECT

Fourteen patients in all HAT studies were reported as having received a rescue treatment with NECT. Data on the outcome were not recorded in the CRF but collected after unblinding. Among these patients 7 were lost to follow-up, 5 were considered cured and 2 had uncertain evolution as there was no post 6 months data. As part

of updated guidelines, patients treated with NECT are not requested to come back for verification, only in case of symptoms. It can therefore be argued that the lost to follow-up patients could be inferred as potentially without symptoms, so that a total of 12/14 patients treated with NECT seems to have resulted in a positive outcome after fexinidazole failure.

Table 41: Outcome of NECT therapy in HAT patients with fexinidazole treatment failure

Clinical study	Patient	Full fexinidazole dose received	Timing	Outcome after NECT treatment
Treatment failure - rescue treatment (NECT) before 18 months				
DNDiFEX004	1	yes	At 18 months (Day 554)	LFU
	2	yes	Between 12 and 18 months (Day 406)	cured
	3	yes	Between 6 and 12 months (Day 299)	cured
	4	yes	At 12 months (Day 371)	cured
	5	yes	At 12 months (Day 368)	Uncertain evolution: 39 cells in CSF at 6-month follow-up
	6	yes	At 18 months (Day 535)	LFU
	7	yes	At 6 months (Day 193)	Uncertain evolution: 21 cells in CSF at 6-month follow-up
	8	yes	Between 6 and 12 months (Day 283)	LFU
	9	yes	At 18 months (Day 551)	cured
	10	yes	At 12 months (Day 443)	LFU
	11	yes	At 18 months (Day 637)	LFU
	12	yes	At 12 months (Day 402)	LFU
Treatment failure - due to CSF>20 cells/µL				
DNDiFEX004	13	yes	24 months	LFU
DNDiFEX006	14	yes	18 months	cured

Abbreviations: **CSF**, cerebrospinal fluid;; **HAT**, human African Trypanosomiasis; **HIV**, human immunodeficiency virus; **LFU**, lost to follow up;; **NECT**, nifurtimox-eflornithine combination therapy

It is significant that 12/14 patients with relapse were assessed as cured after rescue treatment with NECT. These data are relevant to the risk: benefit ratio assessment.

Analysis of potential predictors of response

The applicant conducted an analysis of potential predictors of response that could be related to the observed difference in response rates between fexinidazole and NECT, extending the analysis to DNDiFEX004, DNDiFEX005 and DNDiFEX006 studies with fexinidazole.

Four predictors of failure were investigated:

1. The presence of trypanosomes in CSF at entry.

In patients with late stage 2 HAT with detected trypanosomes at baseline, the failure rate in mITT was substantially higher for fexinidazole (11.6% vs 2.3% with NECT), while the failure rates were similar in patients without trypanosome detection in CSF at baseline (3.4% and 2.6%, respectively), thus indicating that this was a good predictor of failure of fexinidazole treatment. As estimated by the applicant, with all due restrictions due to a wide difference in failure rates, the negative predictive value for each treatment was similar:

Table 42: Evaluation of the predictor properties of the presence of trypanosomes in CSF in late stage-2 adults HAT patients (DNDiFEX004)

Late stage-2 adults	With tryps in CSF			No tryps in CSF		
mITT (n = 388)		67.3%			32.7%	
	Fexi	NECT	Delta[a]	Fexi	NECT	Delta[a]
Failure rate %	11.56	2.27	9.29	3.41	2.56	0.85
(n/N)	(20/173)	(2/88)	p = 0.011[b]	(3/88)	(1/39)	p = 0.554[b]
Sn (% of detected failures)	86.96	66.66				
Correct prediction of failure (%)[c]	11.56	2.27				
Sp (% of detected successes)	35.71	30.64				
Correct prediction of success (%)	96.59	97.44				
Expected Sn is not predictive[d]	67.3					
ITT (n = 393)		67.4%			32.6%	
	Fexi	NECT	Delta[a]	Fexi	NECT	Delta[a]
Failure rate %	12.57	4.44	8.13	3.41	5.00	-1.59
(n/N)	(22/175)	(4/90)	p = 0.038[b]	(3/88)	(2/40)	p = 0.506[b]
Sn (% of detected failures)	88.00	66.66				
Correct prediction of failure (%)[c]	12.57	4.44				
Sp (% of detected successes)	35.71	30.65				
Correct prediction of success (%)	96.59	95.00				
EP (n = 382)		67.8%			32.2%	
	Fexi	NECT	Delta[a]	Fexi	NECT	Delta[a]
Failure rate %	11.05	1.15	9.89	3.53	0.00	3.53
(n/N)	(19/172)	(1/87)	p = 0.004[b]	(3/85)	(0/38)	p = 0.337[b]
Sn (% of detected failures)	86.36	100				
Correct prediction of failure (%)[c]	11.05	11.49				
Sp (% of detected successes)	34.89	30.64				
Correct prediction of success (%)	96.47	100				

Abbreviations: EP, evaluable population; Fexi, fexinidazole; ITT, intention-to-treat; mITT, modified intention-to-treat, NECT, nifurtimox-eflornithine combination therapy; p, p-value; Sn, sensitivity; Sp, specificity.

a A negative delta is in favor of fexinidazole

b One-sided exact test for p-value of the failure rate : Fexinidazole versus NECT

c The percentage of correct prediction of failures (PPV) is equal to the failure rate in the subgroup meeting the criterion

d If the criterion is not predictive the expected sensitivity is equal to the percentage of patients meeting the criterion within the studied population.

Therefore, the presence of trypanosomes in CSF was a useful discriminator for treatment success in patients with late sage 2 HAT, supporting the benefit of choosing NECT as a preferential treatment and also the usefulness of performing a LP which would significantly improve the chance for cure (9.3%).

2. Presence of > 100 WBC in CSF

The failure rate for fexinidazole in patients with late stage 2 HAT with > 100 WBC in CSF (13.1%) was also significantly higher than for NECT (1.3%), with a similar estimate for the negative predictive value for both treatments for this variable:

Table 43: Treatment success at 18 months according to baseline CSF-WBC count (late stage 2 HAT)

Treatment	WBC count	N	Treatment failure n (%)	Treatment success n (%)
fexinidazole	≤100	102	2 (2.0)	100 (98.0)
	>100	160	21 (13.1)	139 (86.9)
NECT	≤100	49	2 (4.1)	47 (95.9)
	>100	78	1 (1.3)	77 (98.7)

Abbreviations: WBC: White blood cell; CSF: Cerebrospinal fluid; NECT: nifurtimox-eflornithine combination therapy

Also, the presence of > 100 WBC in CSF would indicate an 11.8% higher chance of being cured with NECT, thus supporting the usefulness of performing a LP. This was also evident in the overall population (all stages)

Table 44: Evaluation of the predictor properties of the presence of >100 WBC in CSF in all HAT stages treated with fexinidazole (adults and children)

All HAT stages	WBC >100	WBC ≤100
mITT (n = 617)	30.30%	69.70%
	Fexi	Fexi
Failure rate %	11.76	1.86[a]
(n/N)	(22/187)	(8/430)
Sn (% of detected failures)	73.33	
Correct prediction of failure (%)[b]	11.76	
Sp (% of detected successes)	71.89	
Correct prediction of success (%)	98.14	
EP (n = 608)	30.26%	69.74%
	Fexi	Fexi
Failure rate %	11.41	0.71[a]
(n/N)	(21/184)	(3/424)
Sn (% of detected failures)	87.50	
Correct prediction of failure (%)[b]	11.41	
Sp (% of detected successes)	72.08	
Correct prediction of success (%)	99.29	

Abbreviations: EP, evaluable population; Fexi, fexinidazole; Sn, sensitivity; Sp, specificity; mITT, modified intention-to-treat.

a Two-sided exact test: p = 0.000 for mITT and EP

b The percentage of correct prediction of failures (PPV) is equal to the failure rate in the subgroup meeting the criterion

¶

3. Presence of > 400 WBC in CSF at baseline

In patients with late stage 2 HAT, the 400 WBC cut-off value was even more discriminatory for the failure rate with fexinidazole (16.5% failures and 2.9% failures with NECT), with the estimate for the negative predictive value being similar for both treatments:

Table 44: Evaluation of the predictor properties of the presence of >400 WBC in CSF in late stage-2 adults HAT patients (DNDiFEX004)

Late stage-2 adults	WBC >400			WBC ≤400		
mITT (n = 389)		30.15%			69.85%	
	Fexi	NECT	Delta[a]	Fexi	NECT	Delta[a]
Failure rate % (n/N)	16.46 (13/79)	2.94 (1/34)	13.52 p = 0.037[b]	5.46 (10/183)	2.15 (2/93)	3.31 p = 0.168[b]
Sn (% of detected failures)	56.52	33.33				
Correct prediction of failure (%)[c]	16.46	2.94				
Sp (% of detected successes)	72.38	73.39				
Correct prediction of success (%)	94.54	97.85				
ITT (n = 394)		29.92%			70.08%	
	Fexi	NECT	Delta[a]	Fexi	NECT	Delta[a]
Failure rate % (n/N)	16.46 (13/79)	2.94 (1/34)	13.52 p = 0.037[b]	6.49 (12/185)	5.21 (5/96)	1.28 p = 0.446[b]
Sn (% of detected failures)	52.00	16.66				
Correct prediction of failure (%)[c]	16.46	2.94				
Sp (% of detected successes)	72.38	73.39				
Correct prediction of success (%)	93.51	94.79				
EP (n = 383)		30.23%			69.77%	
	Fexi	NECT	Delta[a]	Fexi	NECT	Delta[a]
Failure rate % (n/N)	15.38 (12/78)	0.00 (0/33)	15.38 p = 0.011[b]	5.56 (10/180)	1.09 (1/92)	4.47 p = 0.067[b]
Sn (% of detected failures)	54.54	0.00				
Correct prediction of failure (%)[c]	15.38	0.00				
Sp (% of detected successes)	72.03	73.39				
Correct prediction of success (%)	94.44	98.91				

Abbreviations: EP, evaluable population; Fexi, fexinidazole; ITT, intention-to-treat; mITT, modified intention-to-treat, NECT, nifurtimox-eflornithine combination therapy; p, p-value; Sn, sensitivity; Sp, specificity.

a A negative delta is in favor of fexinidazole

b One-sided exact test for p-value of the failure rate : Fexinidazole versus NECT

c The percentage of correct prediction of failures (PPV) is equal to the failure rate in the subgroup meeting the criterion

Therefore, in patients with late stage 2 and > 400 WBC in CSF, treatment with NECT was associated with, at least, a 13.5% better chance for success.

4. Clinical signs and symptoms score

The clinical signs and symptoms score at entry used several severity thresholds from 12 to 7. Only the thresholds ≥12 and ≥10 were presented because other thresholds showed no clear advantages. The clinical signs and symptoms used are based on the standard list of HAT "warning symptoms". The weighing of 5 significant signs and symptoms (Sleepiness, Pruritus, Tremor, Asthenia and Recurrent headache) has been extremely simplified with respectively 5, 4, 3, 2 and 1 points according to the rank of their discriminating power.

A "formal" statistical approach (multivariate logistic regression on the evaluable set of HAT patients) led to the selection of sleepiness, because once sleepiness is in the model, no additional symptoms improved significantly the explanation of the response (failure rate). However, the score uses additional information to base the evaluation on a symptom profile instead of the presence of a single symptom (too much weight).

Due to the 2:1 allocation ratio in DNDiFEX004 study, the delayed recruitment in DNDiFEX005 and DNDiFEX006 studies, as well as the premature closure of centre 06 (for war reasons) and late addition of 3 centres (sites 07, 09 and 10), the success and failure rates of the overall population were estimated using a correction based on the duration of recruitment at the level of each centre for each segment of the population and another estimation without any weighting.

The classical approach for predictor assessment was used and based on the following Table:

Table 45: Model of table used for the predictive assessment of a criterion

Prediction through the rule	Actual outcome		Total number
	Failure	Success	
Prediction of Failure	A: number of true failures	B: number of false failures	A + B (number of predicted failure)
Prediction of Success	C: number of false successes	D: number of true successes	C + D (number of predicted success)
Total number	A + C (number of observed failures)	B + D (number of observed successes)	N: Sample size

The following properties were assessed for each predictor:

1. Convenience or burden: based on the need to perform a lumbar puncture at entry.

2. Sensitivity (Sn) is the proportion of observed failures at 18 months and detected at baseline through the use of the predictor: Sn = A/(A + C). If Sn = 100%, all treatment failures were detected at baseline. (1 – Sn) is the proportion of treatment failures that were not detected at baseline.

3. Positive Predictive Value (PPV) is the estimation of the probability that a predicted failure is a real treatment failure, or the proportion of correctly predicted failures: PPV = A/(A + B)

4. Specificity (Sp) is the proportion of observed successes at 18 months that were detected at baseline using the predictor: Sp = D/(B + D). (1 –Sp) is the proportion of false failures or undetected successes at baseline. These patients may have to endure the burden of the procedure such as performance of LP, long traveling, hospitalization, despite they will be successful with an oral treatment and local administration.

5. Negative Predictive Value (NPV) is the estimation of the probability that a predicted success is a real treatment success, or the proportion of predicted successes that are true: NPV = D/(C + D).

6. Proportion of predicted failures: proportion of patients in the retained population for whom a failure was predicted (A + B)/N. This information is also the expected proportion of patients for whom a failure was predicted due to pure randomness (H0). Indeed, if the predictor does not predict failures then the following proportions will be equal on average (expectation):

A/(A + C) = B/(B + D) = (A + B)/N.

If Sn >(A + B)/N, the predictor performs better than pure randomness or independence of predictor and treatment outcome. If Sn is similar to (A + B)/N, the predictor is a poor predictor even if the proportion of observed failures that were predicted as failures (Sn) is large.

Robustness is the variability of results according to:

- the set of patients: ITT, mITT and EP.

- the populations: all HAT stages, all stage-2 in children and adults or late stage-2 in adults (DNDiFEX004 study). It is expected that the properties depend upon the population. As a matter of fact, Sn and Sp will not be the same in the subgroup of late stage-2 than in the overall HAT population (all stages confounded). The Sn or Sp in a subpopulation can be different than that in the overall population.

Moreover, the magnitude of treatment effect was measured by the excess rate of failure between fexinidazole and NECT group. Such difference in failure rates was estimated only in the randomized DNDiFEX004 study.

In summary, using a threshold of 10 in the signs and symptoms score, corresponding to sleepiness (5 points), and the combination of at least 2 of the followings, pruritus (4 points), tremor (3 points), asthenia (2 points) or recurrent headache (1 point), the analyses using either the scores of 12 or 10 as cut-off values (≥ 12 or ≥ 10) led to the following conclusions:

Conclusion on the signs and symptoms score 12:

For late stage-2 HAT patients, the threshold of 12 had a sensitivity of 61% for mitt and 64% for EP and a specificity of 68% in all sets of patients (Table 47).

Table 46: Evaluation of the predictor properties of the signs and symptoms score

Table 2 - Evaluation of the predictor properties of the signs and symptoms score ≥12 in late stage-2 adults HAT patients (DNDiFEX004)

Late stage-2 adults	Symptoms score ≥12			Symptoms score <12		
mITT (n = 389)		34.35%			65.65%	
	Fexi	NECT	Delta	Fexi	NECT	Delta
Failure rate %	15.55	0	15.55	5.23	3.61	1.62
(n/N)	(14/90)	(0/44)	p = 0.003[a]	(9/172)	(3/83)	p = 0.156[a]
Sn (% of detected failures)	60.87	0.00				
Correct prediction of failure (%)[b]	15.55	0.00				
Sp (% of detected successes)	68.20	64.52				
Correct prediction of success (%)	94.77	96.39				
ITT (n = 394)		34.47%			65.53%	
	Fexi	NECT	Delta	Fexi	NECT	Delta
Failure rate %	16.48	2.22	14.26	5.78	5.88	-0.10
(n/N)	(15/91)	(1/45)	p = 0.021[a]	(10/173)	(5/85)	p = 0.587[a]
Sn (% of detected failures)	60.00	16.66				
Correct prediction of failure (%)[b]	16.48	2.22				
Sp (% of detected successes)	68.20	64.51				
Correct prediction of success (%)	94.21	94.12				
EP (n = 383)		34.88%			65.12%	
	Fexi	NECT	Delta	Fexi	NECT	Delta
Failure rate %	15.56	0.00	15.55	4.76	1.23	3.53
(n/N)	(14/90)	(0/44)	p = 0.003[a]	(8/168)	(1/81)	p = 0.150[a]
Sn (% of detected failures)	63.64	0.00				
Correct prediction of failure (%)[b]	15.56	0.00				
Sp (% of detected successes)	67.80	64.51				
Correct prediction of success (%)	95.24	98.77				

Abbreviations: EP, evaluable population; Fexi, fexinidazole; ITT, intention-to-treat; mITT, modified intention-to-treat, NECT, nifurtimox-eflornithine combination therapy; p, p-value; Sn, sensitivity; Sp, specificity.

a One-sided exact test for p-value of the failure rate : Fexinidazole versus NECT

b The percentage of correct prediction of failures (PPV) is equal to the failure rate in the subgroup meeting the criterion

It is poorer than the 87% for trypanosomes in CSF but signs and symptoms score increases the detection of failures with respect to pure randomness of 79% with the excess rate of observed sensitivity from pure randomness of 27% (61%-34.4%), while the presence of trypanosomes increased the prediction of true failures with respect to pure randomness by only 30% (excess rate from pure randomness of 20%, 87%-67%). The sensitivity with respect to pure randomness is consequently better with this criterion than trypanosomes or WBC >100. Because the potential consequence of a false failure (undetected success) is a less important issue than the potential consequence of an undetected failure (false success), it is preferable to get a better sensitivity than specificity in the most at risk population (late stage-2 HAT).

Moreover, because of the gap between sensitivity and specificity, the sensitivity can be increased and specificity decreased through the threshold decrease of the signs and symptoms score.

Conclusion on the signs and symptoms score 10:

Table 47: Evaluation of the predictor properties of the signs and symptoms score ≥ in late stage-2 adults HAT patients (DNDiFEX004)

Late stage-2 adults	Symptoms score ≥10			Symptoms score <10		
mITT (n = 389)		42.4%			57.6%	
	Fexi	NECT	Delta	Fexi	NECT	Delta
Failure rate %	16.21	1.79	14.42	3.31	2.82	0.49
(n/N)	(18/111)	(1/56)	p = 0.000[a]	(5/151)	(2/71)	p = 0.602[a]
Sn (% of detected failures)	78.26	33.33				
Correct prediction of failure (%)[b]	16.21	1.79				
Sp (% of detected successes)	61.08	55.64				
Correct prediction of success (%)	96.68	97.18				
ITT (n = 394)		42.4%			57.6%	
	Fexi	NECT	Delta	Fexi	NECT	Delta
Failure rate %	16.96	5.17	11.74	3.95	4.17	-0.22
(n/N)	(19/112)	(3/58)	p = 0.022[a]	(6/152)	(3/72)	p = 0.596[a]
Sn (% of detected failures)	76.00	50.00				
Correct prediction of failure (%)[b]	16.96	5.17				
Sp (% of detected successes)	61.08	55.65				
Correct prediction of success (%)	96.05	95.83				
EP (n = 383)		42.63%			57.37%	
	Fexi	NECT	Delta	Fexi	NECT	Delta
Failure rate %	15.45	1.79	13.66	3.38	0.00	3.38
(n/N)	(17/110)	(1/56)	p = 0.004[a]	(5/148)	(0/69)	p = 0.144[a]
Sn (% of detected failures)	77.27	100.00				
Correct prediction of failure (%)[b]	15.45	1.79				
Sp (% of detected successes)	60.59	55.65				
Correct prediction of success (%)	95.24	100.00				

Abbreviations: EP, evaluable population; Fexi, fexinidazole; ITT, intention-to-treat; mITT, modified intention-to-treat, NECT, nifurtimox-eflornithine combination therapy; p, p-value; Sn, sensitivity; Sp, specificity.

a One-sided exact test for p-value of the failure rate : Fexinidazole versus NECT

b The percentage of correct prediction of failures (PPV) is equal to the failure rate in the subgroup meeting the criterion

- 78% of the overall population with a score <10 and an overall success rate of 98.5% with fexinidazole (considering the EP set), that could be treated with fexinidazole without LP at entry. In the mITT population, this rate was of 97.5% considering any cause of failures (lost to follow-up at M 18, death regardless the cause).

- 22% of the population with a score ≥10 and a failure rate of 13.2% (mITT) in the overall population and of 16.2% in late stage-2 patients (mITT), which are greater than those with NECT and pentamidine (2.4% and 9.5%, respectively). Since patients with a score >10 present a larger risk of failure, they should be managed with more caution.

Based on all these assumptions, the applicant considered that the oral availability of fexinidazole and its efficacy for both stages of the disease allow categorizing the HAT patients for treatment solely based on their symptomatology. It was argued that this approach would not only allow improving early access to treatment but also eliminate the need of painful and potentially hazardous LP, considered as one major barrier to accept treatment.

This clinical approach to categorize patients was evaluated following a multivariate logistic regression analysis on the pooled dataset from the DNDiFEX004, DNDiFEX005 and DNDiFEX006 studies, which showed that elevated WBC count and trypanosomes in the CSF were correlated to the signs and symptoms score based on the presence of a combination of sleepiness, pruritus, tremor, asthenia and recurrent headache. Higher score seemed predictive of a lower success rate with fexinidazole and a higher difference of failure rates as compared to NECT.

Considering the lower success rate of fexinidazole in an identifiable subgroup of (stage-2) HAT patients, the applicant proposed the following management scheme for patients with a higher risk of failure based on the simple symptomatology, and for the most appropriate setting for treatment with fexinidazole (Figure 1):

- any person who has either been screened as positive (via CATT or RDT) or suspected of HAT in the peripheral health structures will be referred to the closest health structure where he/she can be diagnosed for HAT, i.e. where specific analysis in blood/lymph nodes to search for trypanosomes will be done.

- any person could also spontaneously present to a health structure able to diagnose for HAT.

Once diagnosed, the applicant proposed 2 different case management options:

1. the patient presenting with any sign or symptom predictive of higher risk of relapse, i.e. sleepiness, and a combination of at least 2 of the following signs and symptoms, pruritus, tremor, asthenia or recurrent headache (as defined in the score), or children with a weight between 20 and 35 kg, will be considered as category H (hospitalized) and he/she must be referred to a centre to be hospitalized for Directly Observed Treatment (DOT) administration with fexinidazole. Any circumstance that could alert the prescriber on a risk of non-adherence and / or non-compliance of “at home “treatment, would also be an indication for hospitalisation to implement DOT. If NECT is available in the healthcare centre, the treatment option may be decided upon the physician’s choice.

2. the patient weighing more than 35 kg, who does not present any combination of signs or symptoms predictive of higher risk of relapse or any risk factor for lack of compliance, will be considered as category A (ambulatory), and he/she will be eligible to receive fexinidazole treatment as ambulatory or at home with the proposed recommendation for use or supervision as per national guidelines. Patients will be contacted post-treatment and asked for compliance and adverse drug reactions (ADRs).

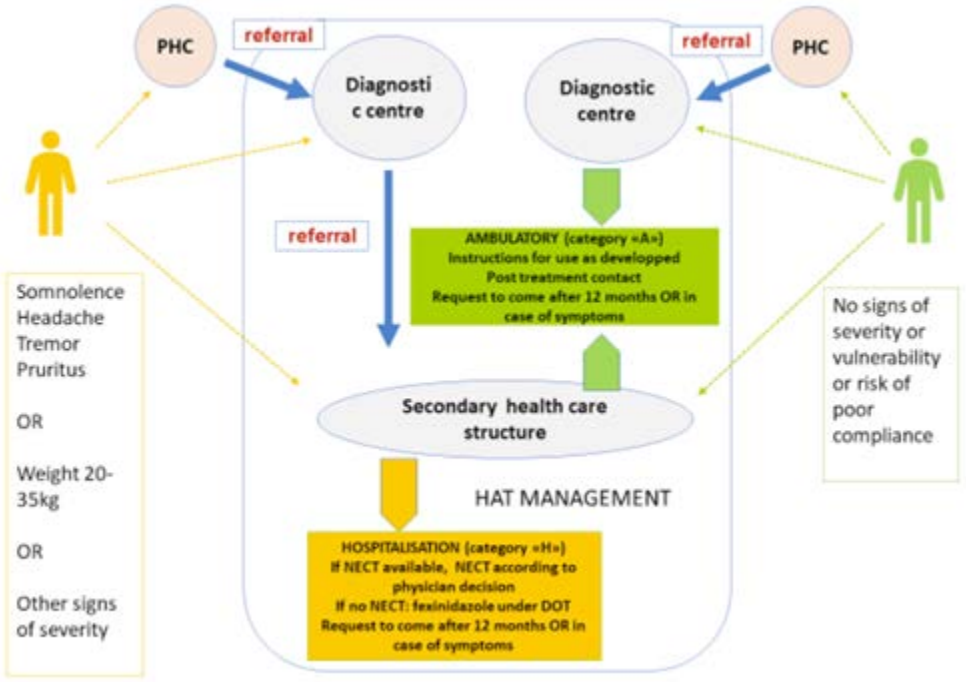


Figure 16: Schematic representation of the proposed management of HAT patients in the field

Additionally, for the first years of introduction of fexinidazole and to ensure that relapses are not missed, the applicant proposed that patients should be systematically requested to present at 12 months after the treatment for clinical assessment. Suspicion of relapse would be managed as per national guidelines. In case of not spontaneous attendance at 12 months, active information search on the health status would be recommended.

Resistance potential

Regarding patients who may fail on fexinidazole, the applicant has discussed the impact of pre-treatment with fexinidazole on subsequent chance of poor success with NECT. It is agreed that the risk of developing resistance to fexinidazole is low, given the low number of late stage-2 HAT cases. Furthermore, rescue treatment with NECT was provided to a small number of fexinidazole failed patients (n=14). Five of these patients were considered cured, 7 were lost to follow-up and 2 had uncertain evolution as there was no data was available post-6 months of the treatment. However, this has to be interpreted in the context of current follow-up guidance where patients are requested to return for verification only in case of symptoms. Under these circumstances, it is reassuring, there is currently no evidence for any adverse impact on success of NECT due to prior treatment with fexinidazole.

Additional data from ongoing studies

DNDiFEX009 commenced recruitment during 2017. Available data from open-label study DNDiFEX09 has been duly provided. A significant rate of vomiting (33%) was reported and, although considered mild, the potential impact on adequate completion of treatment in outpatients may be of concern. This is consistent with the results of the pivotal study. A recommendation has been included in the SmPC on how to proceed in case vomiting occurs during fexinidazole treatment. The applicant confirmed that DNDiFEX09 study aims to complete recruitment by August 2019 and follow-up by March 2021 and that the final CSR will thus be available on

Q3-2021. As the study is open-label, the applicant states that it may be able to provide ongoing information upon request.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical development was intended to support a broad indication across stages 1 and 2 HAT, i.e. for treatment of both first-stage [haemo-lymphatic] and second-stage [meningo-encephalitic] HAT due to *Trypanosoma brucei gambiense* in adults and children ≥ 6 years old and weighing ≥ 20 kg.

The focus was to demonstrate that fexinidazole was similarly efficacious to the standard recommended treatment NECT for late stage 2 HAT. The assumption was made that if fexinidazole at the selected dose regimen performed well in patients who already had evidence of CNS invasion by *T. b. gambiense*, it would also elicit high cure rates in earlier stages of the disease. With a lower age limit of 15 years in the pivotal comparative study, it was assumed that efficacy in late stage 2 HAT could be extrapolated to younger subjects if they achieved comparable blood and CSF levels of metabolite M2.

Staging of patients to qualify for the pivotal study in late stage 2 HAT due to *T. b. gambiense* was based on confirmed evidence of parasite in the CSF (regardless of WBC count) or, if no parasites were detected in CSF, the CSF WBC had to exceed 20 cells/µL. This definition of late stage 2, which was applied in all three of the applicant's studies, would equate to a slightly different terminology used by WHO and in HAT guidance, as shown below. Similarly, the applicant's definition of early stage 2 would have different terminology in WHO's classification. Nevertheless, the programme does cover patients across the stages, regardless of the terminology, and the wording of the indication does not refer to "early" and "late". Therefore, the differences between the applicant's definitions and the other terminologies, does not affect the conclusions and, for simplicity, this discussion will use the applicant's classification.

Table 48: HAT staging criteria at inclusion (clinical efficacy studies in HAT)

FEX (004-005-006) criteria	WHO criteria	HAT stage guidance	Trypanosomes in blood or lymph	Trypanosomes in CSF	WBC in CSF
Stage 1	Stage 1	Stage 1	Positive	Negative	≤5 cells/ µL
Early stage 2	Intermediate stage 2	Early stage 2	Positive	Negative	[6 to 20] cells/ µL
Late stage 2	Intermediate stage 1	Early stage 2	Positive	Positive	≤5 cells/ µL
Late stage 2	Intermediate stage 2	Late stage 2	Positive	Positive	[6 to 20] cells/ µL
Late stage 2	Second stage	Late stage 2	Positive	Negative or positive	>20 cells/ µL

The fact that the supplementary studies in subjects from 15 years with stage 1 and early stage 2 HAT and in subjects from 6 - <15 years of age with stage 1 or 2 HAT were uncontrolled can be accepted in this case due to the difficulties in conducting GCP-compliant studies at multiple sites in remote regions.

The overall approach and the provision of one pivotal and two supplementary studies is deemed acceptable.

The choice of the comparators, either active or historical, is well justified and adequately documented with supportive literature. NECT, used in the pivotal study, is currently the recommended treatment option for Stage 2 disease.

Study DNDiFEX004

The clinical data presented for the assessment of efficacy is essentially based on one randomised, open-label study in which the proposed dose regimen of 10 day oral treatment of fexinidazole (1800 mg OD in the first 4 days followed by 1200 mg OD for the next 6 days) is compared with the reference combination treatment of parenteral eflornithine and oral nifurtimox (NECT) in patients with documented Stage 2 HAT, developed to demonstrate that an all oral treatment regimen could be used in the advanced meningo-encephalitic stage.

A primary endpoint at 18 months in the pivotal study was accepted, subject to follow-up to 24 months in total.

The dose regimen was that proposed for the SmPC for adults, adolescents and children from 6 years with body weight from 35 kg but the formulation used was not the same as the commercial tablet. As shown in the bioequivalence study, plasma exposures met the usual criteria for bioequivalence but were numerically lower for the commercial formulation vs. the Phase 3 formulation. At the same time, M1 and M2 levels in DBS from patients appeared to be higher than plasma levels in healthy volunteers similarly dosed.

Many, but not all patients, had symptoms that would raise some suspicion of the diagnosis. Testing for trypanosomes was variable across the study sites. However, all patients presented with trypanosomes in the CSF (in about 67%) or had CSF WBC count >20 cells/µL. Parasites were detected in the lymph in 35.6% and in the blood in 13.5% to 25.2% depending on the method used. Sites 9 and 10, and to a lesser extent site 7, were unusual in that less than half of patients had trypanosomes in CSF. Whilst these patients must have had the requisite CSF WBC count to be eligible, it seems that evidence of trypanosomal infection in these patients was mainly based on blood tests. These sites also seemed to have lower median CSF WBC vs. all other sites except for site 5. The applicant confirmed that the inclusion of patients based on WBC count > 20 with or without trypanosomes in CSF is in line with the recommended WHO criteria for a clinical trial in stage-2 HAT. The reason for the higher number of cases without trypanosomes and lower median CSF WBC in sites 7,9 and 10 is explained by a temporal difference in the trial initiation at these sites which occurred more than a year later and resulted in less severe/advanced stage-2 HAT patients being recruited. Consequently, a higher number of patients had to be screened before fewer patients were found to be eligible.

In the ITT population, 128/394 (32.48%) patients had no trypanosomes in the CSF at baseline (88 in fexinidazole and 40 in NECT arm), and among those, 34 (8.62%) (18 in fexinidazole and 16 in NECT arm) had concomitant malaria that was always treated with Coartem (artemether- lumefantrine) prior to starting the study treatment. Further, it is confirmed that CSF WBC counts were measured prior to malaria treatment and therefore any confounding of the results due to erroneous diagnosis of stage-2 HAT in these patients is likely to bias the results in favour of NECT. Therefore, this is not likely to adversely affect the robustness of the results.

The applicant's pre-defined non-inferiority margin was -13%, which derived from pre-trial consultation with experts and was deemed as being "acceptable" when considering the advantages of an oral-only treatment that might be used regardless of disease stage.

The Blackwelder test was used in the primary analysis. This test is simply the standard normal approximation to the binomial test for comparing two proportions, but testing the shifted null hypothesis of whether the inferiority of fexinidazole to NECT equals the margin of acceptable difference (13%) instead of zero as would be used in superiority testing. This is achieved by adding 13% to the observed difference and then performing the usual test. The confidence intervals provided are the standard confidence intervals from the normal approximation.

The result of the Blackwelder test will be statistically significant (p< 0.0294) if the 97.06% confidence interval is entirely above -13%. This is an acceptable approach for a non-inferiority analysis. Note that the p-values must be strictly interpreted as a test of non-inferiority and not as a test of whether there is a statistically significant difference between the treatments.

In pivotal study DNDIFEX004 , an accumulation of methodologic limitations (mostly unblinded design, mostly convenience-determined sample size due to constraints in recruitment, choice of a limit for the difference in response that is subject to discussion, post-hoc definition of a mITT population for the primary efficacy analysis excluding patients that would be considered losses to follow-up, rescue of patients that would be considered as failures by the pre-defined algorithm by an unblinded expert advisory board) contribute to a decreased quality of the evidence produced through the sole comparative study in patients with second stage HAT. Also, it should be noted that the pharmacologic data produced previous to the conduction of the Phase II/III efficacy development programme is insufficient to provide evidence that the proposed dose regimen is associated with adequate CSF/CNS concentrations of fexinidazole in a sufficient proportion of patients. The PK data produced from the PK activities of study DNDIFEX004 was also not useful to fully clarify these uncertainties. Additionally, other dose regimens that could provide different and potentially more adequate time-kill profiles were not explored.

Study DNDiFEX005

The plug-in rationale for the open-label study DNDIFEX005 is the provision of supporting evidence that the same oral dose regimen of fexinidazole was acceptable treatment for adults with less advanced stages of HAT disease. In this light, even though open-label study DNDiFEX005 could be considered a supportive study, there is a rationale for considering the two studies as main studies, since they encompass the full HAT natural history, which is the scope of the application.

Study DNDiFEX006

Study DNDIFEX006 included only paediatric patients (6 to 15 years) with either Stage 1 or Stage 2 disease and is considered as both a supportive study and a study in special populations.

Of the 125 patients aged 6-14 years included in the study, ~55% were stage 1, ~15% had early stage 2 and ~30% had late stage 2 HAT (2/3 of these had trypanosomes in CSF). The 6-month and 12-month follow-up visits were each attended by all except one patient who had died before the 6-month visit.

Efficacy data and additional analyses

Study DNDiFEX004

In the primary analysis, the failure rates were 8.8% for fexinidazole and 2.4% for NECT, with a lower bound of the 97% CI of -11.22% and an upper bound that was below zero (-1.6%). Furthermore, in all the sensitivity analyses conducted, fexinidazole was consistently somewhat less effective than NECT. The results paint a clear picture that fexinidazole is statistically significantly worse than NECT but the difference is unlikely to be larger than 13%. For example, in each analysis population except for the ITT the upper bound of the CI around the difference between treatments was below zero and in the ITT population the bounds were [-10.5, 0.8%].

Using the primary imputation method, which applied to the primary analysis, a cure (as opposed to a probable cure) required that the patient was alive at 18 months, with no evidence of trypanosomes in any body fluid and CSF WBC $\leq$20 cells/ μ L. However, patients were counted as a (probable) success if lumbar puncture was refused at 18 months but they had no signs or symptoms of HAT at 18 months, did not report any sign of relapse later and had a favourable evolution at the last available assessment. When all patients with missing LP results at

month 18 were instead counted as failures the totals increased by 13 in the fexinidazole group (36 instead of 23) and 5 in the NECT group (8 instead 3). In this analysis the 97% CI around the treatment difference were (-14, -0.9%), missing the applicant's pre-defined margin. However, it is stated that 16 of the 18 additional failures due to missing lumbar puncture at 18 months were successes at 24 months.

There is no justification for removing site 06 beyond it being the site where the results most favoured NECT. It is not surprising that the results look better for fexinidazole once this site is removed but this analysis is not considered to be appropriate based as it is on a post hoc data-driven exclusion of certain patients, and should be disregarded.

Leaving site 06 aside, the two highest enrolling sites had the lowest success rates for fexinidazole (86.4% and 88.3%, respectively) while the success rates for NECT were 95.5% and 96.7%, respectively. The three lowest enrolling sites (2 with 21 patients each and one with 9 patients) had 100% success rates for fexinidazole.

The applicant recognizes the difficulty in explaining the success rate of individual sites due to their relatively small sample size. No relationship was found between the size of sites and the success rate (R^2 = 0.0678, p = 0.4672). However, when excluding site 06(clearly an outlier, there is a significant relationship between the size of sites and success rates per site (R^2 = 0.543, p = 0.0234). Sites with the largest recruitment were those with the smallest success rate and vice versa.

It was therefore next verified whether the size of sites was related to the severity of patients as measured by the number of WBC in CSF and as this was found to be associated with a higher risk of failure in a pooled analysis. A significant positive linear relationship was observed (R^2 = 0.641, p = 0.0095), suggesting that the largest sites, not only started the study at least one year earlier, but tended to have more severe patients (higher number of WBC) than sites with a small recruitment and therefore a larger the proportion of patients at risk of failure, patients explaining the differences in fexinidazole success rates between sites. This analysis further supports the concerns with the efficacy of the proposed 10-day oral regimen in patients with late stage-2 HAT.

The timing of failure has implications for the validity of a primary endpoint at month 18. In the primary efficacy analysis 16/23 failures (69.6%) in the fexinidazole group occurred within 12 months after EOT, including relapse in 15 (65.2%), death in 6 (26.1%), LTFU in one and consent withdrawal in one (4.3%). Two of 3 failures in the NECT group also occurred within 12 months after EOT, including death in 2 patients and no LP at 18 and 24 months in one patient. For all randomised patients who were considered a failure at 18 months using the primary imputation method 18/27 and 5/6 occurred within 12 months after EOT. However, available data at month 24 indicate additional failures in the fexinidazole group, suggesting that late relapse may be a problem for this treatment. The higher relapse rate is considered significant to the risk: benefit assessment. For this reason, PI includes now the need to follow-up patients after treatment up to 24 months. Of note, as reported below, most of the relapses responded adequately to rescue treatment with NECT.

Numerous sensitivity and ancillary analyses have been performed looking at the outcome at 18 months. They lend support to the finding from the primary analysis that fexinidazole is statistically significantly worse than NECT but the difference is unlikely to be larger than 13%. It is agreed that the analysis of month 18 outcomes using the second imputation method is probably overly conservative given that most of these patients, who were imputed as failures, are known to be successes at month 24. This analysis of outcomes at 18 months using the primary imputation method but with exact 95% CI rather than 97.06% confidence intervals cannot be compared with the other analyses. It will appear more favourable than the other analyses as 95% CI are narrower than 97.06% CIs.

Also, results show that a sub-group of patients with more severe CNS involvement (late stage 2 HAT) are at higher risk of failing if they are treated with fexinidazole compared with NECT. This subgroup, as defined by a

value of WBC >100 cells/µL of CSF, is indicative of a higher risk of failure in the fexinidazole studies vs NECT with a difference in efficacy of 86.9% in the fexinidazole arm versus 98.7% in the NECT arm (i.e. – 11.8%), and therefore the risk of failure seems to be higher with fexinidazole in this subgroup.

Study DNDiFEX005

Whilst there was no control group, the month 12 success rate (based on 227/230 patients who had reached this visit or previously died) in this stage 1 and early stage 2 HAT population aged at least 15 years was higher (98.7%; 95% CI [96.2; 99.7]) than that observed at month 18 with the same regimen in late stage 2 patients in the pivotal study. For 157 patients who had reached the 18-month visit with 4 prematurely withdrawn, the success rate at month 18 was 96.9% (95% CI [92.9; 99.0]), which is also higher than that at month 18 in the pivotal study.

When an outcome of failure was imputed in the absence of LP at 12 months, the overall success rate at 12 months was 96.5% (95% CI [93.3; 98.5]). When no imputation was made except for carrying forward definitive failure and using month 18 data to determine outcome at month 12, the success rate at 12 months was the same as in the primary analysis.

The large majority (82%) of the 230 patients in this study were stage 1 HAT. For stage 1 patients (n=135) the success rate at month 18 was 97.0% (95% CI [92.6; 99.2]), with 4 failures. For early stage 2 patients (n=26), the success rate was 96.2% (95% CI [80.4; 99.9]).

In the CSR of DNDiFEX005 study, patients were considered failures at 12 months using the primary imputation method (algorithm classification). Among the three patients counted as failures at month 12 because of death, two of them were already considered failures at 6 months due to missing lumbar puncture. Then, both died between 6 and 12 months of follow-up (Day 202 and Day 345, respectively, according to the CRFs) and were thus confirmed as failures at 12 months.

Considering the results of the pivotal study, which suggests that late relapses may be more likely to occur after fexinidazole vs. NECT, the applicant provided the full month 18 outcome data together with a detailed discussion of all failures. There was virtually no change in efficacy rate between 12 and 18 months. This observation does not raise concerns regarding the existence of a clinically or epidemiologically relevant relapse rate in patients with stage 1 and early stage-2 HAT treated with the proposed 10-day oral regimen of fexinidazole.

Study DNDiFEX006

Across this mixed population 3/122 patients failed at month 12, giving a high cure rate of 97.6% (95% CI [93.1; 99.5]). One of the failures had died of non-HAT causes but the other two (one early and one late stage 2 at study entry) were relapses with CSF WBC counts >20 cells/µL. With imputation of failure in the absence of LP at 12 months there were 5 failures but the overall success rate was 96.0% (95% CI [90.9; 98.7]). Thus, in this mixed age and HAT population, the success rate at month 12 was higher than that observed at month 18 in late stage 2 HAT patients in the pivotal study.

For 85 patients who had reached month 18, the success rate was also higher than at month 18 in the pivotal study (97.6%; 95% CI [91.8; 99.7]). Two patients were considered as failures (one stage 1 and one late stage 2). The third patient counted as a failure at month 12 (early stage 2 HAT with CSF WBC count of 36 cells/µL at 12 months) was counted as a success at month 18 because the CSF WBC was <20 cells/µL without rescue treatment. The full dataset at month 18 reported from this study including analyses regarding age, weight and dose to fully assess the risk of late relapses did not reveal any significant or notable trend. These results give further consistence to the use of the proposed doses of fexinidazole in paediatric patients (6-15 years).

Analysis across trials

Regarding the three analysed potential predictors of failure, the data submitted by the applicant indicates that the presence of trypanosomes in CSF, >100 WBC in CSF and > 400 WBC in CSF at baseline are discriminatory for a significantly better chance of treatment success with NECT. Although combined analyses of these three variables are not provided, the difference in response rate may go as high as 13.5% in favour of NECT in patients with > 400 WBC in CSF at baseline.

A clinical score, corresponding to somnolence/sleepiness (5 points), and the combination of at least 2 of the following symptoms, pruritus (4 points), tremor (3 points), asthenia (2 points) or recurrent headache (1 point), is used, although it is noted that somnolence/sleepiness is largely the most significant finding. The applicant further justified why sleepiness was not used as the main and single predictor knowing this criterion has a better sensitivity than the composite symptom score.

After analysing different score values as the cut-off for discrimination, the clinical score of ≥10 was proposed to be the most useful for clinical use with an optimal balance for sensitivity and specificity for late stage-2 HAT.

However, amongst limitations to this post-hoc analysis, the following is considered:

1. Data on clinical features are subject to the sensitivity and skills of the clinicians examining patients (interviewer bias) and to the method of collection, among other factors (observation bias). For this particular dataset obtained in GCP clinical trials, the data collection followed specialized training and used detailed case report forms. Other authors have analyzed larger cohorts of field data, finding different frequencies of clinical features and different associations of clinical features with high CSF WBC counts, with disease severity, and with treatment failure.

2. A classic analysis of the performance of Score >=10 to predict failure, taking the pooled data and the EP population (as most pertinent for this analysis), shows that the sensitivity of this predictor lies between 48.9% and 87.4%, lacking robustness.

The applicant's proposal was further discussed by the experts at the Scientific Advisory Group meeting.

Additional expert consultation

A Scientific Advisory Group (SAG) meeting was organised to address the following concerns:

1. ***Appropriateness and feasibility of identifying at peripheral health facilities in endemic areas the following patients reliably using clinical signs/symptoms based approach and without the aid of lumbar puncture results***

- ***a. patients with late stage-2 HAT who have a relatively lesser efficacy as compared to NECT and***
- ***b. patients who may have higher chances of cure with fexinidazole***

If this is considered appropriate & feasible, the acceptability of the proposed clinical criteria (somnolence and pruritus, tremor, asthenia or recurrent headache) should be commented upon.

The experts were united in their view that assessment of disease severity should best proceed via performance of a lumbar puncture (LP) , as to ascertain the CSF WBC count, as predictor of treatment success/failure with fexinidazole (FEX). The clinical assessment tool as proposed by the applicant, with the intention to obviate the need for LP, cannot be regarded as a reliable alternative modality. The experts' opinion is based on the fact that the proposed clinical score is derived from a post-hoc analysis across the applicant's trial programme, without

validation by other independent data and due to limited numbers analyzed, provides a poor sensitivity presenting a wide confidence interval around the values reported (sensitivity of the predictor reported to be lying between 48.9% and 87.4%, and therefore lacking robustness).

On the contrary, WBC count in CSF is regarded as the best indicator of severity and predictor of treatment failure; in the presented dataset the following is remarked:

CSF-WBC count > 100 / µL provided a 11.8 % increased favorable outcome for NECT than FEX

CSF-WBC count > 400 / µL provided a 13.5 % increased favorable outcome for NECT than FEX

As such, experts were united to view CSF-WBC > 100 / µL as cut-off, critical in defining a high risk group of patients with late stage g-HAT at increased risk for treatment failure if treated with fexinidazole. These patients should essentially preferentially be treated with other adequate treatment (NECT). In case NECT is unavailable or in a situation of intolerance with NECT, patients can only receive fexinidazole 10 days oral course, in a hospital or peripheral health facilities under supervision to ascertain compliance (e.g. daily food intake and tablets intake).

Thus, LP requirement prior to initiation of therapy should be the standard of care, unless conditions would make it impossible to perform a LP (exceptional) or the patient refuses the procedure (a rare event). For such situations, and in order to discriminate high vs. low risk patients, clinical assessment could be relied upon as an alternative, and based on local experience and available literature. The set of clinical criteria proposed by the applicant were however not deemed as satisfactory to be taken into account in making such decisions.

2. Acceptability of the ambulatory (treatment administered at home) use of fexinidazole except in the identified high-risk situations of anticipated poor compliance, children < 35kg and patients who are clinically severe at presentation but cannot receive NECT, taking into account that vomiting and nausea are frequent adverse effects of fexinidazole.

Oral fexinidazole should be administered to all eligible patients under strict supervision by trained health staff who fully understands the need for an effective treatment course, who needs to confirm that the patient is in fed condition and who directly observes each drug intake. This can be done in hospitals or peripheral health facilities, and in particular situations, at home, on condition that the above protocol is respected. The word “ambulatory” should be avoided to prevent misinterpretations by policymakers and by treatment prescribers.

3. Adequacy of the follow-up monitoring at recurrence of symptoms at 12 months and 24 months after treatment.

The experts concluded that ideally, the time of follow-up should span up to 24 months, in order to capture late relapses with fexinidazole therapy. Patients and health care professionals should be made aware to this risk of late relapse following therapy with fexinidazole and a most appropriate local arrangement should be in place to provide the optimum achievable follow-up.

Assessment of paediatric data on clinical efficacy

The data from paediatric patients aged 6 to 15 years indicates a success rate after 12 months of treatment of around 95%. However, the numbers included were small and do not allow for an adequate comparison between the two stages of disease. The results for patients in early stage 2 showed a wide 95% CI. Further efficacy analyses from study DNDiFEX006, namely by weight, dose-regimen and the effect of age did not reveal any significant or notable trend. These results give further consistence to the use of the proposed doses of fexinidazole in this age group.

These findings are in support of the efficacy of fexinidazole for the treatment of Stage 1 disease, but also indicate that the compound and the proposed regimen show a considerable therapeutic effect in patients with stage 2.

Data analysis lead to the conclusion that for children with a body weight lower than 35 kg, there is no suggestion of a lesser efficacy as compared to NECT. Nevertheless, as per SAG expert opinion, administration of fexinidazole in these patients should be done in a hospitalized setting during the whole course of the treatment.

2.5.4. Conclusions on the clinical efficacy

The primary and sensitivity analyses of the pivotal study DNDiFEX004 showed a consistent numerical inferiority for fexinidazole vs. current standard of care (NECT) for the treatment of patients with late stage 2 HAT. Although the pre-defined non-inferiority margin was -13% and the actual lower bound of the 97.06% CI around the treatment difference was -11.22%, the results show that a sub-group of patients with more severe CNS involvement are at higher risk of failing if they are treated with fexinidazole compared with NECT. This subgroup can be defined by a value of WBC >100 cells/µL of CSF which is indicative of a higher risk of failure in the fexinidazole studies vs NECT with a difference in efficacy of 86.9% in the fexinidazole arm versus 98.7% in the NECT arm (i.e. – 11.8%), and therefore the risk of failure seems to be higher with fexinidazole in this subgroup. Although fexinidazole shows good efficacy, also in those with severe CNS involvement, in the current clinical context the relative lower efficacy in that subgroup warrants a limitation of its use only in circumstances where other adequate treatment was not feasible. Hence, it was considered appropriate that this should be a warning in SmPC section 4.4 particularly as it is supported by the statement introduced in section 4.1.

The issue of whether an approach based on clinical signs and symptoms could replace the usual recommended performance of a lumbar puncture (LP), in order to identify those patients that should preferably be treated with other adequate treatment (NECT), was discussed by the applicant. It must be noted that LP is a useful and generally low risk approach that is generally recommended for correct staging (and thus choice of therapy). The applicant has reviewed the data with the intention to identify 'predictors of failure' and found that presence of trypanosomes in CSF, number of WBCs in CSF (>100 WBC in CSF and > 400 WBC in CSF at baseline) and that clinical signs and symptoms (number and severity) could be used to identify a sub-group of patients where 'treatment failure' was higher compared to NECT. In order to estimate true and false events of success or failure, it would be expected that a reference diagnostic method was used for the presence/absence of trypanosomes in CSF and WBC in CSF. A more adequate description of the reference method used for the determination of these two was provided. The methodology for the microscopic examination of CSF samples was described and expected to have been adopted with the control methodology that was also submitted. The possibility of unacceptable variations in local practice has already been discussed in light of the potential clinical consequences and incorporated in the final decision and SmPC recommendations.

A clinical score, corresponding to somnolence/sleepiness (5 points), and the combination of at least 2 of the following symptoms, pruritus (4 points), tremor (3 points), asthenia (2 points) or recurrent headache (1 point), was proposed, although it is noted that somnolence/sleepiness is largely the most significant finding. After analyzing different score values as the cut-off for discrimination, the score of ≥10 was proposed as most useful for clinical use with an optimal balance for sensitivity and specificity for late stage-2 HAT. However, the choice of sub-group based on the sensitivity/specificity calculations should ideally be validated in another independent data set which is a weakness of this approach in this instance. Nevertheless, it can be agreed based on the submitted analysis that in general, patients with worse/clinically more severe signs and symptoms are the ones more likely to relapse on fexinidazole as compared to NECT. The comparison between the discriminatory power of the clinical score approach, namely using the ≥ 10 value, as compared to the laboratory approach requiring the performance of a LP, seems to be adequate and allow for the acceptable identification of the population with

more severe disease stages at risk for failure and benefiting from being excluded from first-line treatment with fexinidazole. Based on the results, it is agreed that these patients are optimally treated after hospitalisation, LP and first-line treatment with NECT. Fexinidazole has a significantly worse performance at patients with high score levels, thus questioning the adequacy of its use in this subset of patients in situations where NECT is an available option. This wide difference is now adequately reflected in PI in order to ensure that the best practice is recommended. The number of patients that had lower score values at either cut-off and were considered failures is worth of consideration, as it shows that patients may present with lower clinical scores and still have difficult to treat disease. As such, the decision regarding the best treatment approach for patients with stage 2 HAT is a complex one and should most probably still rely on a conjunction of clinical and laboratory elements which should still include CSF data, when these are available. A value of CSF-WBC >100 has been retained as indicative of a higher risk of failure in the fexinidazole studies, with the cut-off shown to reach a very good sensitivity (87.5%) at the expense of specificity (72.8%) and as a result, allowing to detect most of observed failures.

As the pivotal study results show the possibility for late relapse after fexinidazole treatment as compared to NECT, the PI now includes the warning that patients should have a follow-up monitoring at recurrence of symptoms suggestive of HAT, at 12 months and 24 months after treatment completion with fexinidazole and that patients should be made aware of the risk of relapse after therapy and instructed to contact healthcare staff in case of signs of relapse.

Separately, the data from study DNDIFEX005, open label, non-comparative, in adult patients (> 15 years, N=230) with Stage 1 disease indicates that a 10 day oral regimen of fexinidazole obtains a good success rate at 12 months (≥95%), which is comparable favourably to the rate observed with currently recommended regimens, pentamidine and suramine, also considering that the latter compounds cannot be administered by the oral route. The results from study DNDIFEX006, an open-label study conducted in children aged 6 to 15 years with both stage 1 and stage 2 HAT disease indicates t a good overall response rate of around 95%, for a 10 day oral regimen of fexinidazole, as adjusted by body weight in two basic dose levels. Although the results tended to be less favourable for patient with Stage 2 (early and late combined), the numbers were too small to allow for reliable inferences.

The applicant agreed that in children with ≤35 kg, for patients at higher risk of failure with fexinidazole, those with higher disease severity, those with lower potential of compliance, and in patients with psychiatric disorders, administration of fexinidazole should be made in hospital setting or peripheral health facilities, for supervision of full compliance. Administration of fexinidazole to all eligible patients should only be done under the strict supervision of trained health staff, required to confirm that the patient is in a fed condition and directly observing the intake of each fexinidazole tablet.

2.6. Clinical safety

Patient exposure

Table 49 - Study designs and treatment regimens in clinical studies

DNDi Study Study status	Design	Purpose	Treatment/Study duration	Cohorts planned	Patients included#			Fexinidazole formulation	Study drug and dose
					F	P/N	T		
DNDiFEX004 complete to Month 18	Phase II/III, pivotal, multicentre, non-inferiority, randomised, open-label study in patients ≥ 15 years	Efficacy and safety of fexinidazole compared to NECT therapy	10 days / 25 months	2 cohorts (randomised 2:1 to receive fexinidazole)	264	130	394	oral tablet (600 mg)	fed conditions: fexinidazole: 1800 mg (3 tablets) once a day D1-4 + 1200 mg (2 tablets) once a day D5-10 or NECT: nifurtimox (15 mg/kg/day) 3 times a day for D1-10 + DFMO (400 mg/kg/day) twice a day for D1-7
DNDiFEX005 complete to Month 12	Phase II/III, multicentre, open-label, cohort study in patients ≥ 15 years	Efficacy of treatment at 1-year follow-up in stage 1 or early stage 2 HAT patients	10 days / 19 months	Single group of patients	230	0	230	oral tablet (600 mg)	fed conditions: 1800 mg (3 tablets) once a day D1-4 + 1200 mg (2 tablets) once a day D5-10
DNDiFEX006 complete to Month 12	Phase II/III, multicentre, open-label, cohort study in patients between 6 and 15 years	Efficacy and safety of 10 days treatment in HAT at stage 1 or 2 in children ≥ 6 years and weighing ≥ 20 kg	10 days / 19 months	Single group of patients – treatment administered by body weight	125	0	125	oral tablet (600 mg)	fed conditions: Body weight ≥ 20 kg and <35 kg: 1200 mg (2 tablets) once a day D1-4 +600 mg (1 tablet) once a day D5-10 Body weight: ≥ 35 kg (same as adults): 1800 mg (3 tablets) once a day D1-4 +1200 mg (2 tablets) once a day D5-10
DNDiFEX001 Part I Complete		Single ascending dose safety tolerability and PK data	single dose	9 cohorts of 8 subjects Per cohort: 6 subjects active treatment; 2 subjects placebo	54	18	72	oral suspension	fasting conditions, single dose: 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, 1800 mg, 2400 mg, 3000 mg, 3600 mg

DNDiFEX001 Part II complete	Phase I, randomised, double-blind, placebo-controlled in subjects 18 to 45 years	Bioavailability of tables versus oral suspension and assessment of food effect	3 single doses	1 cohort	-	-	13	oral suspension versus tablet	3-way cross-over; 3 single doses: A: 1200 mg fasting condition oral suspension; B: 1200 mg fasting condition oral tablets; C: 1200 mg fed condition, oral tablets 14 day washout period between doses
DNDiFEX001 Part III complete		Multiple ascending doses	14 days	3 cohorts of 8 subjects Per cohort: 6 subjects active treatment; 2 subjects placebo	21	6	27	oral tablet	multiple ascending doses from Day 1-14: 1200 mg, 2400 mg, 3600 mg fasting conditions
Overall DNDiFEX001	-	-	-		88	24	112		
DNDiFEX002 complete	Phase I, randomised, open-label in subjects 18 to 45 years	Impact of food on relative bioavailability	3 single dose	1 cohort	12	0	12	oral tablet	3-way cross-over; 1200 mg in 3 conditions: A: fasting; B: fed (meal type 1) C: fed (meal type 2) 14 day washout period between doses
DNDiFEX003 complete	Phase I, double-blind, placebo-controlled, randomised in subjects 18 to 45 years	PK of oral fexinidazole	10 days	2 cohorts of 18 subjects Per cohort: 12 subjects fexinidazole; 6 subjects placebo	22	8	30	oral tablet	multiple ascending dose: Cohort 1: 1800 mg D1-4 + 1200 mg D5-10 Cohort 2: 2400 mg D1-4 + 1200 mg D5-10 fed conditions
DNDiHATFEX008 complete	Phase I, open-label, randomised, replicate design in subjects 18 to 45 years	Bioequivalence of reference versus proposed marked formulation of fexinidazole	4 single doses (2 test/ 2 reference)	2 cohorts/sequences: TRTR or RTRT	30	-	30	oral tablet	2-treatment, 2-sequence, 4-period Reference: 1200 mg Test: 1200 mg fed conditions 14 day wash out period between doses
Ongoing studies at the safety data cut-off (15 August 2017; no CSRs available)									
DNDiFEX009 ongoing	Phase IIIb, open-label, multicentre, cohort study in patients 6 years and over[b]	Efficacy and safety of 10 days treatment in HAT in any stage	10 days	Single group of patients – treatment administered by body weight	174 planned; 28 patients treated by 15 August 2017			oral tablet (600 mg)	Body weight ≥ 20 kg and <35 kg: 1200 mg (2 tablets) once a day D1-4 600 mg (1 tablet)

		patients ≥ 6 years					once a day D5-10 Body weight: ≥ 35 kg (same as adults): 1800 mg (3 tablets) once a day D1-4 1200 mg (2 tablets) once a day D5-10 fed conditions

a The duration of treatment was initially of 8 weeks. However, from 17 October 2014 all patients that had received greater than 2 weeks had treatment immediately interrupted. All other patients who had initiated treatment were instructed to complete a 2-week treatment course
b Patients could be treated as in- or out-patients in this study
F=Fexinidazole; P=Placebo; T=Total; N=NECT

DFMO=α-difluoromethylornithine; HAT= human African trypanosomiasis; HD=high dose; LD=low dose; NECT= combination therapy with eflornithine and nifurtimox; PK= pharmacokinetic; QD=quaque die (once a day); F=Fexinidazole; P=Placebo; T=Total; N=NECT
R=reference; T=test; VL= visceral leishmaniasis

Clinical studies in the development programme that contribute to the safety evaluation of fexinidazole (at the safety data cut-off date of 15 August 2017) are summarised as follows:

- Three (3) Phase II/III clinical studies in the HAT indication clinically complete to the primary endpoint: DNDiFEX004, DNDiFEX005 and DNDiFEX006. Safety data are reported to the database lock (DBL) date for each individual study. Follow-up safety data from PV reports are included as ongoing data in this submission. The complete safety data from patients in these 3 studies will be available upon request after submission. All 3 studies are included in a pooled safety analysis.
- Two (2) completed studies assessed safety in different patient populations: DNDIFEXIVL001 in primary VL patients, and DNDiCHFEXI001 in indeterminate CD patients (Table 51)
- Four (4) completed Phase I clinical pharmacology studies (DNDiFEX001 Parts I-III; DNDiFEX002; DNDiFEX003; DNDIHATFEX008) in healthy volunteers (Table 51)
- One (1) ongoing study: Study DNDiFEX009 in HAT patients (Table 51)

Three (3) studies in the HAT indication have been initiated to document the efficacy and safety of fexinidazole in different populations, all using the same based dosing regimen (except for children below 35 kg). Of the 10 study sites from which patients were enrolled into the pivotal study, 8 sites were also used for patient recruitment into the cohort plug-in studies. These 3 studies expose increasing numbers of patients to fexinidazole, and therefore provide better insight on fexinidazole efficacy and safety profile.

The pivotal reference study DNDiFEX004 included late stage 2 HAT adult male and female patients, and evaluated the efficacy and safety of fexinidazole compared to the reference treatment NECT in an unbalanced randomisation ratio of 2:1.

The study DNDiFEX005 was initiated as an open-label study to include early stages (stage 1 and early stage 2) HAT adult male and female patients.

The study DNDiFEX006 aimed to include paediatric HAT patients of all stages between 6 and 15 years old weighing ≥20 kg. The same regimen of treatment (i.e., 10 days fexinidazole treatment in a once a day dosing with food, including a loading dose over the first 4 days) was used. The dose depended upon the weight of children (<35 kg or ≥35 kg).

These HAT patient studies have been completed to the primary endpoint and any follow-up PV data have been captured up to the safety data cut-off (15 August 2017). No new safety signals emerged from the 18 months follow up data from DNDiFEX004, DNDiFEX005 and DNDiFEX006 studies.

Table 50: Database lock dates for all clinical efficacy and safety studies in HAT

Study	DBL date	Randomised / Treated population	Patients withdrawn at time of data lock	Patients completed to primary endpoint	Patients completed to final study visit (additional timepoint)	Patients ongoing at time of CSR DBL	Patients ongoing at time of submission cut-off (15 Aug 17)
DNDiFEX004	05 January 2017	394	31[a]	371	319	44	0
DNDiFEX005	31 March 2017	230	4[b]	227	157	69	0
DNDiFEX006	31 March 2017	125	1[c]	124	84	40	0
DNDiFEX009	NA	28	0	0	0	NA	28

DBL=database lock; HAT=human African trypanosomiasis; NA=not applicable

a In DNDiFEX004, 23 patients withdrew (including 8 deaths) before completion of the 18-month follow-up visit (primary endpoint); a further 8 patients withdrew (including 3 deaths) after the 18-month follow-up visit.

b In DNDiFEX005, 3 patients died before completion of the 12-month follow-up visit (primary endpoint); a further 1 patient died after the 12-month follow-up visit

c In DNDiFEX006, 1 patient died before completion of the 12-month follow-up (primary endpoint); there were no other patient withdrawals

Source: 5.3.5.1 Study DNDiFEX004, 5.3.5.2 Study DNDiFEX005, 5.3.5.2 Study DNDiFEX006

Two studies in other patient populations administering fexinidazole have been conducted. Study DNDiFEXIVL001 was an open, single arm, proof-of-concept study conducted in VL adult patients to document safety and efficacy treated with the same dosing regimen as the HAT studies. Study DNDiCHFEXI001 was a-double-blind placebo-controlled study conducted in CD patients using different dosing regimen (1200 mg daily or 1800 mg daily for either 2, 4 or 8 weeks); 40 patients treated with fexinidazole were evaluated for safety (7 patients received placebo).

The Phase I clinical pharmacology programme (DNDiFEX001 Parts I to III, DNDiFEX002 and DNDiFEX003) in view of the patient population affected (HAT which is endemic exclusively in sub-Saharan African countries), was carried out in volunteers of sub-Saharan African origin. To date, 184 healthy subjects have been enrolled in human pharmacology studies (Phase I) with fexinidazole and received either single doses of up to 3600 mg under fasting condition, once-daily multiple-doses of up to 3600 mg for 14 days under fasting condition, once-daily multiple-doses of 1800 mg or 2400 mg for 4 days followed by 1200 mg for 6 days under fed condition or placebo.

In children between 6 years and 15 years weighting at least 20Kg there is an ongoing study (DNDiFEX006) with 125 patients enrolled and completed to month 12.

Table 51: Exposure by study and treatment and studies in the pooled analysis (ITT population)

		DNDiFEX004		DNDiFEX005	DNDiFEX006	All
Description	**Statistics**	**NECT (N=130)**	**Fexinidazole (N=264)**	**Fexinidazole (N=230)**	**Fexinidazole (N=125)**	**Fexinidazole (N=619)**
Treatment duration (days)	N	130	264	230	125	619
	Mean	10.05	9.97	10.00	10.01	9.99
	SD	0.21	0.36	0.00	0.09	0.24
	Median	10.00	10.00	10.00	10.00	10.00
	Q1, Q3	10.00, 10.00	10.00, 10.00	10.00, 10.00	10.00, 10.00	10.00, 10.00
	Min, Max	10.0, 11.0	5.0, 10.0	10.0, 10.0	10.0, 11.0	5.0, 11.0
		Eflornithine (mg/kg)	**Nifurtimox (mg/kg)**		**Fexinidazole (mg)**	
Cumulative dose (sum of all doses)	N	130	130	264	230	125	619
	Mean	2826.81	150.20	14363.64	14400.00	9456.00	13386.11
	SD	79.24	4.57	429.92	0.00	2245.51	2237.25
	Median	2800.00	150.00	14400.00	14400.00	8400.00	14400.00
	Q1, Q3	2800.00,2859.57	147.06, 152.94	14400.00, 14400.00	14400.00, 14400.00	8400.00, 8400.00	14400.00, 14400.00
	Min, Max	2643.1, 3094.7	138.6, 165.8	8400.0, 14400.0	14400.0,14400.0	8400.0, 14400.0	8400.0, 14400.0

NECT=Nifurtimox-Eflornithine Combination Therapy; Q=quartile; SD=standard deviation

Data source: 5.3.5.3 Pooled analysis (Table 14.1.10.a Extent of exposure by Treatment Group ITT population)

Across the fexinidazole clinical programme, 853 patients or subjects have been exposed to fexinidazole in 10 studies. Although this was not the number intended initially due to difficult access in terms of patients and their location, the numbers presented seem acceptable. Almost all of 619 HAT patients exposed to fexinidazole completed a 10-day treatment period as shown below. There were 516 HAT patients exposed to the proposed regimen for adults and children from 35 kg and 103 received the regimen proposed for children with body weight 20-34 kg.

The 18 months follow up safety data from patients in studies DNDiFEX004, DNDiFEX005 and DNDiFEX006, namely the available data in children weighting at least 20 kg and older than 6 years were provided with no new safety signals being emerged.

Additionally, there were 184 healthy subjects enrolled in human pharmacology studies (Phase I), some of whom received only placebo. DNDiFEXIVL001 was conducted with the HAT regimen in 14 adults with visceral leishmaniasis (VL) while DNDiCHFEXI001 evaluated daily dosing for 2-8 weeks in 47 patients with Chagas Disease (CD).

Table 52: Extent of Exposure by HAT Stage and by Dose Regimen Categorised in the Pooled Analysis (ITT Population)

Description	Statistics	By HAT Stage		By Dose Regimen		All
		Stage 1 Fexinidazole (N=258)	Stage 2 Fexinidazole (N=361)	Fexinidazole 1800/1200 mg (N=516)	Fexinidazole 1200/600 mg (N=103)	Fexinidazole (N=619)
Treatment duration (days)	N	258	361	516	103	619
	Mean	10.00	9.98	9.98	10.01	9.99
	SD	0.00	0.31	0.26	0.10	0.24
	Median	10.00	10.00	10.00	10.00	10.00
	Q1, Q3	10.00, 10.00	10.00, 10.00	10.00, 10.00	10.00, 10.00	10.00, 10.00
	Min, Max	10.0, 10.0	5.0, 11.0	5.0, 10.0	10.0, 11.0	5.0, 11.0
Fexinidazole – cumulative dose (sum of all doses in mg)	N	258	361	516	103	619
	Mean	13137.21	13563.99	14374.42	8434.95	13386.11
	SD	2435.97	2068.85	345.80	164.32	2237.25
	Median	14400.00	14400.00	14400.00	8400.00	14400.00
	Q1, Q3	14400.00, 14400.00	14400.00, 14400.00	14400.00, 14400.00	8400.00, 8400.00	14400.00, 14400.00
	Min, Max	8400.0, 14400.0	8400.0, 14400.0	8400.0, 14400.0	8400.0, 9600.0	8400.0, 14400.0

a One patient from Study DNDiFEX006 who should have received the lower dosing regimen (equivalent to a total dose of 8400 mg) actually received the higher dosing regimen (equivalent to a total dose of 10800 mg). This patient has been summarised in the dosing regimen group for the actual dose taken (ie, the higher dosing regimen).

HAT=human African trypanosomiasis; ITT = intent-to-treat; Q = quartile; SD = standard deviation

Data source(s): 5.3.5.3 pooled analysis (Table 14.1.10.b and Table 14.1.10.a Extent of exposure by Dose Regimen Class ITT population)

Of note:

1-Exclusion criteria in pivotal clinical studies within the development programme:

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hypersensitivity to fexinidazole and/or to any nitroimidazole drugs	Hypersensitivity may be potentially severe/ serious and might interfere with the evaluation of study medication.	No	The use of fexinidazole is contraindicated in case of hypersensitivity to fexinidazole and/or to any nitroimidazole drugs.
Children <6 years old or weighing less than 20 kg	Clinical program limited to adults and children above 6 years old, due to the size of the tablet.	Yes	
Children < 6 years old weighing 20 kg or more	Population not included in CT clinical program limited to adults and children above 6 years old, due to the size of the tablet.	No	No reason to anticipate any safety issue as metabolism would not be different from a 6 years old - probability of a HAT child of <6 years with weight ≥25 is low based on existing data from excluded patients in DNDiFEX006.
Patients with severe hepatic impairment	Might interfere with the evaluation of study medication.	Yes	The use of fexinidazole is contraindicated in case of severe hepatic impairment.
○ Laboratory abnormalities, clinically significant such as AST and ALT ≥2 ULN ○ Total Bilirubin >1.5 ULN ○ Severe Leucopenia (<2000/mm³)	Might interfere with the evaluation of study medication.	No	Transaminase increase considered as an important potential risk. Neutrophil count decrease considered as an important potential risk. .
Pregnancy/Lactation	Absence of safety data in these populations.	Yes	
QTcF ≥450 msec	Might interfere with the evaluation of study medication.	No	QTcF prolongation considered as important identified risk.

HAT: Human African Trypanosomiasis; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ULN: Upper Limit Of Normal.

2-Limitations to detect adverse reactions in clinical trial development programmes:

The clinical development programme can detect adverse drug reactions (ADRs) that are uncommon (≥1/1000 to <1/100) or more frequent. Indeed, with approximately 619 HAT patients exposed in the Phase 2/3 clinical program, the probability to observe at least one occurrence of an adverse event in the fexinidazole group is 95%, if this event truly occurs in at least 0.48% of the population. Cumulative effects are not anticipated due to the short half-life of fexinidazole, extensive metabolism and lack of accumulation shown on repeat dosing studies. In addition, no cumulative effects are expected from the metabolites, M1 and M2, as their C_{max} showed no increase on repeat dosing studies following dose reduction (to maintenance dose) under the clinical dosing scheme, and they showed no affinity for any specific tissues e.g., melanin containing tissues. Furthermore, due to a short half-life, the M1 metabolite showed little potential for accumulation over time.

3- Limitations in respect to populations typically under-represented in clinical trial development programmes: Pregnant and breastfeeding women.

The table below shows overall similar safety profiles for fexinidazole and NECT in the HAT studies.

Table 53: Overview of adverse events in patients with HAT (ITT population, HAT pooled analysis

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
AEs	121 (93%) [608]	247 (94%) [1525]	214 (93%) [1277]	116 (93%) [584]	577 (93%) [3386]
TEAEs	121 (93%) [607]	247 (94%) [1525]	214 (93%) [1258]	116 (93%) [583]	577 (93%) [3366]
TEAEs: BL to EOH	121 (93%) [586]	246 (93%) [1483]	214 (93%) [1226]	115 (92%) [569]	575 (93%) [3278]
TEAEs: Post-EOH	11 (8%) [21]	25 (9%) [42]	20 (9%) [32]	10 (8%) [14]	55 (9%) [88]
Serious TEAEs	13 (10%) [22]	31 (12%) [51]	20 (9%) [32]	10 (8%) [14]	61 (10%) [97]
TEAEs Leading to Death[a]	2 (2%) [2]	9 (3%) [11]	4 (2%) [8]	1 (<1%) [2]	14 (2%) [21]
Relatedness of TEAEs to study treatment:					
Unrelated	88 (68%) [262]	202 (77%) [602]	131 (57%) [399]	86 (69%) [230]	419 (68%) [1231]
Possibly Related	103 (79%) [345]	215 (81%) [923]	195 (85%) [859]	103 (82%) [353]	513 (83%) [2135]
TEAEs leading to discontinuation of study treatment:					
Temporary or Permanent	3 (2%) [3]	2 (<1%) [2]	0	1 (<1%) [1]	3 (<1%) [3]
Permanent	0	2 (<1%) [2]	0	0	2 (<1%) [2]
Serious TEAEs leading to discontinuation of study treatment:					
Temporary or Permanent	1 (<1%) [1]	2 (<1%) [2]	0	0	2 (<1%) [2]
Permanent	0	2 (<1%) [2]	0	0	2 (<1%) [2]

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
TEAEs related to event/SOC of interest:					
Haematological event	4 (3%) [4]	1 (<1%) [1]	6 (3%) [6]	5 (4%) [5]	12 (2%) [12]
Hepatotoxicity	5 (4%) [5]	23 (9%) [24]	2 (<1%) [2]	1 (<1%) [1]	26 (4%) [27]
QT Prolongation	1 (<1%) [1][b]	0	0	0	0
Neuropsychiatric	11 (8%) [13]	33 (13%) [38]	22 (10%) [33]	10 (8%) [10]	65 (11%) [81]

Note: Format is number of subjects (percent of subjects) [number of events]

a TEAEs with an outcome of death (note that 4 SAEs that had an outcome of death were evaluated as severe; see Section 3.1.2.1). Deaths are included that were captured prior to the database lock point for each individual CSR. One further patient died in Study DNDiFEX005 after the reporting period and details are included in ongoing deaths.

b This was 1 event of cardio-respiratory arrest from the SMQ: Torsade de pointes/QT prolongation.

The dictionary versions used were MedDRA version 16.0 for the DNDiFEX004 study and MedDRA version 16.1 for the DNDiFEX005/DNDiFEX006 studies. An impact analysis for the dictionary version change has been conducted and to ensure the homogeneity of the coding some terms have been re-coded using the MedDRA version 16.1.

In the DNDiFEX004 study, 1 AE with partial start date (Patient 404_003 AE: WEIGHT GAIN) in the fexinidazole arm should have been considered as a TEAE.

AE=adverse event; BL=baseline; EOH=end of hospitalisation; HAT=human African trypanosomiasis; ITT=intent-to-treat; NECT=nifurtimox-eflornithine combination therapy; TEAEs=treatment-emergent adverse event.

Source: 5.3.5.3 Pooled analysis (Table 14.3.1.1.a)

The pooled analysis in HAT patients does not include data from DNDiFEX009 as the study is ongoing and very few patients will have reached month 18 when the pooled analysis has been performed.

The other patient populations (VL and CD) have not been included in the pooled analysis, as well, as the indications and regional populations, are considered too variable to the pool of patients with HAT. Study DNDiCHFEXI001 is of particular interest following premature study interruption due to safety concerns after the inclusion of 47 patients.

Comparison of fexinidazole *versus* NECT in adult patients with late Stage 2 HAT (**DNDiFEX004**)

In Study DNDiFEX004, there were no major differences between fexinidazole and NECT treatments regarding the percentage of patients reporting at least 1 TEAE (93.6%2 and 92.3%, respectively), patients reporting TEAE(s) that started during the 10-day treatment period (89.0% and 88.5%, respectively), patients reporting TEAE(s) that were considered by the Investigator as possibly related to treatment (81.4% and 78.5%, respectively), patients reporting TEAE(s) of severe intensity (22.7% and 21.5%, respectively), and patients reporting SAE(s) (11.7% versus 10.0%, respectively). Mild or moderate TEAEs were reported for 245/264 (92.8%) patients receiving fexinidazole and 116/130 (89.2%) patients receiving NECT.

From the clinical database for DNDiFEX004, AEs resulting in death were reported for 11 patients in the safety population: 9/264 (3.4%) patients who received fexinidazole and 2/130 (1.5%) patients who received NECT. Although the number of deaths was higher in the fexinidazole group, the difference was not statistically significant; from the data presented no trend seems to be present in neither group (fenixidazole vs NECT). Additional PV cases not captured in the clinical database include a death of completed suicide pre-inclusion and a foetal death of spina bifida in the NECT group after DBL.

Clear differences by >5% in TEAE incidence between groups were as follows:

- Higher incidence with fexinidazole than NECT: insomnia (28.0% versus 11.5%), tremor (22.0% versus 10.8%), headache (34.8% versus 23.8%), asthenia (22.7% versus 13.8%), nausea (25.8% versus 19.2%), dizziness (18.9% versus 13.1%), hypocalcaemia (13.6% versus 2.3%; the PT blood calcium decrease was also reported in 0.4% of patients who received fexinidazole), feeling hot (9.5% versus 2.3%), hypalbuminaemia (8.7% versus 3.1%), abdominal pain upper (10.2% versus 4.6%; however PTs of abdominal pain and abdominal pain lower were reported less frequently with fexinidazole than NECT), chest pain (8.7% versus 3.1%), and dyspepsia (12.9% versus 7.7%).
- Lower incidence with fexinidazole than NECT: pyrexia (8.7% versus 18.5%) and chills (1.5% versus 9.2%), hyperkalaemia (10.2% versus 19.2%), convulsion (1.9% versus 7.7%).

Fexinidazole in a cohort of adult patients with Stage 1 and early Stage 2 HAT (**DNDiFEX005**)

In Study DNDiFEX005, TEAEs were reported by 214/230 (93.0%) patients during the study: 176/189 (93.1%) patients with stage 1 HAT and 38/41 (92.7%) patients with stage 2 HAT. Of the overall patients who experienced TEAEs, 212/230 (92.2%) patients had TEAEs which started during the 10-day treatment period; 61/230 (26.5%) patients reported post-treatment period TEAEs. Possibly related TEAEs were reported in 195/230 (84.8%) patients. Mild or moderate TEAEs were reported in 214/230 (93.0%; 1216 events) patients and severe TEAEs in 27/230 (11.7%; 41 events) patients.

From the clinical database for DNDiFEX005, there were 4 deaths in the safety population (3 patients with stage 1 HAT and 1 patient with early stage 2 HAT); none of the events leading to death were considered possibly related to treatment. At least 1 SAE was reported in 20/230 (8.7%) patients: 31/32 SAEs in 19/230 (8.3%) patients started post-treatment period and 2 non-fatal SAEs in 2/230 (0.9%) patients of psychotic disorder and hyponatremia (asymptomatic) were considered possibly related to treatment. No TEAEs led to temporary or permanent study drug discontinuation. Additional PV cases not captured in the clinical database include the death of 1 patient due to SAEs of cardiogenic and hypovolemic shock and a foetal death due to foetal distress syndrome 551 days after the EOT. The SAEs of cardiogenic shock, hypovolaemic shock and foetal distress are deemed as unrelated to fexinidazole.

By PT, the most frequently reported TEAEs in >5% patients were: nausea (43.0% patients), vomiting (42.2% patients), headache (40.4% patients), asthenia (30.4% patients), dizziness (25.2% patients), insomnia (24.8%

patients), tremor (22.6% patients), dyspepsia (20.0% patients), decreased appetite (19.1% patients), feeling hot (16.5% patients), abdominal pain upper (9.6%), gastritis (7.4%), abdominal pain (7.4%), back pain (7.4%), blood sodium increased (7.4%), salivary hypersecretion (7.0%), neck pain (6.5%), palpitations (6.1%), hallucination (5.2%), and hot flush (5.2%).

Fexinidazole in a cohort of paediatric patients with any stage HAT (**DNDiFEX006**)

During Study DNDiFEX006, TEAEs were reported by 116/125 (92.8%) patients. Of the reported TEAEs, 113/125 (90.4%) patients had TEAEs which started during the 10 day treatment period. Possibly related TEAEs were reported in 103/125 (82.4%) patients. Mild or moderate TEAEs were reported for 115/125 (92.0%; 553 events) patients and severe TEAEs were reported in 25/125 (20.0%; 30 events) patients.

From the clinical database for DNDiFEX006, there was 1 death in the safety population (stage 1 HAT), following SAEs of dyspnoea and injury (dyspnoea following traumatic aggression that led to death) which occurred before the 6-month visit (171 days after EOT) and was not considered treatment-related by the Investigator or the Sponsor. A total of 14 SAEs were reported in 10/125 (8.0%) patients. All 14 SAEs started after the treatment period and before the study DBL; 1 patient (1/125; 0.8%) experienced a single non-fatal SAE of hyperkalaemia (asymptomatic) that was considered possibly related to treatment. No TEAEs led to permanent study drug discontinuation; 1 TEAE in 1/125 (0.8%) patient led to temporary treatment discontinuation. Three further related SAEs (PV cases) in 1 patient of malaria, anaemia and typhoid fever (severe malaria with tolerated anaemia and typhoid fever) were reported prior to the dossier cut-off date (15 August 2017) and were not included in the clinical database (started >400 days after last dose of fexinidazole). All 3 SAEs (malaria, anaemia, typhoid fever) are considered as unrelated to fexinidazole.

In line with observations from the individual study analyses, data from the pooled analyses of AEs from HAT studies DNDiFEX004, DNDiFEX005 and DNDiFEX006 showed that the most frequently reported TEAEs (≥10% patients) by SOC were: gastrointestinal disorders (70% of fexinidazole patients vs. 49% NECT), nervous system disorders (58% vs. 49%), general disorders and site conditions (43% vs. 39%), metabolism and nutrition disorders (33% vs. 49%), psychiatric disorders (32% vs. 18%), musculoskeletal and connective tissue disorders (18% vs. 16%), investigations (11% vs. 8%) and blood and lymphatic system disorders (10% vs. 14%) (Table 55).

By PT, the most frequently reported TEAEs in >5% patients were vomiting (68.8% patients), nausea (37.6% patients), headache (32.8% patients), asthenia (31.2% patients), decreased appetite (19.2% patients), tremor (19.2% patients), salivary hypersecretion (14.4%), abdominal pain (12.0%), anaemia (11.2%), insomnia (9.6%), back pain (8.0%), dizziness (8.8%), pyrexia (8.8%), malaria (7.2%), blood potassium increased (7.2%), and dyspepsia (5.6%).

Table 54

Table 55 - Adverse events occurring in ≥1% patients by SOC and PT (ITT population, HAT pooled analysis)

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Any TEAE	**121 (93%) [607]**	**247 (94%) [1525]**	**214 (93%) [1258]**	**116 (93%) [583]**	**577 (93%) [3366]**
Gastrointestinal disorders	**64 (49%) [130]**	**157 (59%) [353]**	**179 (78%) [428]**	**98 (78%) [257]**	**434 (70%) [1038]**
Vomiting	37 (28%) [46]	75 (28%) [101]	97 (42%) [114]	86 (69%) [134]	258 (42%) [349]
Nausea	26 (20%) [27]	68 (26%) [73]	99 (43%) [125]	47 (38%) [59]	214 (35%) [257]
Dyspepsia	10 (8%) [11]	34 (13%) [43]	46 (20%) [52]	7 (6%) [8]	87 (14%) [103]
Abdominal pain	16 (12%) [17]	25 (9%) [29]	17 (7%) [19]	15 (12%) [17]	57 (9%) [65]
Abdominal pain upper	6 (5%) [8]	27 (10%) [32]	22 (10%) [27]	2 (2%) [2]	51 (8%) [61]
Salivary hypersecretion	3 (2%) [3]	16 (6%) [17]	16 (7%) [20]	18 (14%) [20]	50 (8%) [57]
Gastritis	2 (2%) [3]	8 (3%) [13]	17 (7%) [24]	6 (5%) [6]	31 (5%) [43]
Constipation	2 (2%) [2]	13 (5%) [14]	5 (2%) [5]	0	18 (3%) [19]
Diarrhoea	5 (4%) [5]	8 (3%) [8]	2 (<1%) [2]	2 (2%) [2]	12 (2%) [12]
Abdominal distension	0	8 (3%) [8]	3 (1%) [3]	0	11 (2%) [11]
Dry mouth	1 (<1%) [1]	1 (<1%) [1]	8 (3%) [8]	1 (<1%) [1]	10 (2%) [10]
Dysphagia	1 (<1%) [1]	1 (<1%) [1]	1 (<1%) [1]	6 (5%) [7]	8 (1%) [9]
Inguinal hernia	1 (<1%) [1]	3 (1%) [3]	5 (2%) [9]	0	8 (1%) [12]
Abdominal pain lower	3 (2%) [4]	1 (<1%) [1]	4 (2%) [6]	0	5 (<1%) [7]
Nervous system disorders	**64 (49%) [117]**	**158 (60%) [308]**	**142 (62%) [283]**	**61 (49%) [96]**	**361 (58%) [687]**
Headache	32 (25%) [46]	92 (35%) [134]	93 (40%) [134]	41 (33%) [50]	226 (37%) [318]
Tremor	15 (12%) [16]	58 (22%) [68]	52 (23%) [61]	24 (19%) [26]	134 (22%) [155]
Dizziness	18 (14%) [23]	50 (19%) [56]	58 (25%) [74]	11 (9%) [12]	119 (19%) [142]
Extrapyramidal disorder	2 (2%) [2]	9 (3%) [9]	0	1 (<1%) [1]	10 (2%) [10]
Paraesthesia	0	6 (2%) [6]	4 (2%) [4]	0	10 (2%) [10]
Convulsion	10 (8%) [14]	5 (2%) [5]	1 (<1%) [1]	1 (<1%) [1]	7 (1%) [7]
Head discomfort	0	3 (1%) [4]	3 (1%) [3]	0	6 (<1%) [7]
Dysgeusia	0	3 (1%) [3]	2 (<1%) [2]	0	5 (<1%) [5]
Movement disorder	2 (2%) [2]	1 (<1%) [1]	0	2 (2%) [2]	3 (<1%) [3]
Palmomental reflex	0	3 (1%) [3]	0	0	3 (<1%) [3]
Psychomotor hyperactivity	2 (2%) [2]	2 (<1%) [3]	0	1 (<1%) [1]	3 (<1%) [4]
Cerebellar syndrome	2 (2%) [2]	1 (<1%) [1]	0	1 (<1%) [1]	2 (<1%) [2]
General disorders and administration site conditions	**51 (39%) [85]**	**122 (46%) [184]**	**94 (41%) [151]**	**51 (41%) [65]**	**267 (43%) [400]**
Asthenia	19 (15%) [23]	60 (23%) [73]	70 (30%) [86]	39 (31%) [44]	169 (27%) [203]
Feeling hot	3 (2%) [4]	25 (9%) [29]	38 (17%) [48]	1 (<1%) [1]	64 (10%) [78]
Pyrexia	24 (18%) [27]	23 (9%) [27]	3 (1%) [4]	11 (9%) [13]	37 (6%) [44]
Chest pain	5 (4%) [5]	23 (9%) [25]	4 (2%) [4]	2 (2%) [2]	29 (5%) [31]
Gait disturbance	2 (2%) [2]	12 (5%) [13]	0	0	12 (2%) [13]
Chills	12 (9%) [12]	4 (2%) [4]	6 (3%) [6]	1 (<1%) [1]	11 (2%) [11]
Fatigue	1 (<1%) [1]	2 (<1%) [2]	0	2 (2%) [3]	4 (<1%) [5]
Catheter site pain	2 (2%) [2]	0	0	0	0

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Extravasation	3 (2%) [3]	0	0	0	0
Injection site reaction	3 (2%) [3]	0	0	0	0
Metabolism and nutrition disorders	**64 (49%) [95]**	**131 (50%) [190]**	**47 (20%) [56]**	**24 (19%) [25]**	**202 (33%) [271]**
Decreased appetite	24 (18%) [29]	56 (21%) [58]	44 (19%) [52]	24 (19%) [24]	124 (20%) [134]
Hypocalcaemia	3 (2%) [3]	36 (14%) [37]	0	0	36 (6%) [37]
Hyperkalaemia	25 (19%) [26]	27 (10%) [29]	0	0	27 (4%) [29]
Hypoalbuminaemia	4 (3%) [4]	23 (9%) [24]	0	0	23 (4%) [24]
Hyponatraemia	15 (12%) [18]	20 (8%) [21]	0	0	20 (3%) [21]
Hyperglycaemia	9 (7%) [9]	9 (3%) [9]	0	0	9 (1%) [9]
Dehydration	2 (2%) [2]	1 (<1%) [1]	3 (1%) [3]	1 (<1%) [1]	5 (<1%) [5]
Hypoglycaemia	2 (2%) [3]	4 (2%) [5]	0	0	4 (<1%) [5]
Hypokalaemia	0	3 (1%) [3]	0	0	3 (<1%) [3]
Psychiatric disorders	**23 (18%) [31]**	**103 (39%) [159]**	**73 (32%) [110]**	**19 (15%) [27]**	**195 (32%) [296]**
Insomnia	15 (12%) [17]	74 (28%) [83]	57 (25%) [69]	12 (10%) [14]	143 (23%) [166]
Agitation	1 (<1%) [1]	10 (4%) [14]	7 (3%) [7]	2 (2%) [2]	19 (3%) [23]
Hallucination	0	3 (1%) [3]	12 (5%) [14]	2 (2%) [2]	17 (3%) [19]
Logorrhoea	3 (2%) [3]	6 (2%) [6]	7 (3%) [8]	2 (2%) [2]	15 (2%) [16]
Anxiety	0	10 (4%) [10]	1 (<1%) [1]	2 (2%) [2]	13 (2%) [13]
Psychotic disorder	4 (3%) [5]	7 (3%) [7]	3 (1%) [3]	3 (2%) [3]	13 (2%) [13]
Abnormal behaviour	1 (<1%) [1]	7 (3%) [7]	4 (2%) [6]	1 (<1%) [1]	12 (2%) [14]
Depression	0	4 (2%) [4]	0	0	4 (<1%) [4]
Nightmare	1 (<1%) [1]	4 (2%) [5]	0	0	4 (<1%) [5]
Depressed mood	1 (<1%) [1]	3 (1%) [3]	0	0	3 (<1%) [3]
Personality change	0	3 (1%) [5]	0	0	3 (<1%) [5]
Musculoskeletal and connective tissue disorders	**21 (16%) [29]**	**58 (22%) [92]**	**38 (17%) [53]**	**13 (10%) [15]**	**109 (18%) [160]**
Back pain	12 (9%) [15]	30 (11%) [36]	17 (7%) [21]	10 (8%) [12]	57 (9%) [69]
Neck pain	7 (5%) [8]	23 (9%) [27]	15 (7%) [18]	3 (2%) [3]	41 (7%) [48]
Muscle spasms	1 (<1%) [1]	7 (3%) [8]	0	0	7 (1%) [8]
Myalgia	0	4 (2%) [4]	2 (<1%) [4]	0	6 (<1%) [8]
Arthralgia	1 (<1%) [1]	1 (<1%) [1]	3 (1%) [3]	0	4 (<1%) [4]
Musculoskeletal pain	0	4 (2%) [5]	0	0	4 (<1%) [5]
Musculoskeletal stiffness	2 (2%) [2]	1 (<1%) [1]	0	0	1 (<1%) [1]
Investigations	**10 (8%) [10]**	**7 (3%) [8]**	**42 (18%) [51]**	**21 (17%) [27]**	**70 (11%) [86]**
Blood potassium increased	0	0	11 (5%) [11]	9 (7%) [10]	20 (3%) [21]
Blood sodium decreased	0	1 (<1%) [1]	17 (7%) [18]	1 (<1%) [1]	19 (3%) [20]
Romberg test positive	2 (2%) [2]	3 (1%) [3]	3 (1%) [3]	3 (2%) [3]	9 (1%) [9]
Blood albumin decreased	0	0	7 (3%) [7]	1 (<1%) [1]	8 (1%) [8]
Blood potassium decreased	0	0	1 (<1%) [1]	5 (4%) [5]	6 (<1%) [6]
Blood calcium decreased	0	1 (<1%) [1]	1 (<1%) [1]	3 (2%) [3]	5 (<1%) [5]
Blood glucose increased	1 (<1%) [1]	0	4 (2%) [5]	1 (<1%) [1]	5 (<1%) [6]

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Heart sounds abnormal	2 (2%) [2]	1 (<1%) [1]	1 (<1%) [2]	0	2 (<1%) [3]
Blood alkaline phosphatase decreased	2 (2%) [2]	0	0	0	0
Blood and lymphatic system disorders	**18 (14%) [19]**	**29 (11%) [33]**	**13 (6%) [14]**	**20 (16%) [21]**	**62 (10%) [68]**
Anaemia	14 (11%) [14]	24 (9%) [25]	7 (3%) [7]	14 (11%) [15]	45 (7%) [47]
Neutropenia	2 (2%) [2]	1 (<1%) [1]	6 (3%) [6]	5 (4%) [5]	12 (2%) [12]
Leukopenia	2 (2%) [2]	0	0	0	0
Infections and infestations	**8 (6%) [10]**	**22 (8%) [33]**	**13 (6%) [14]**	**12 (10%) [14]**	**47 (8%) [61]**
Malaria	1 (<1%) [1]	5 (2%) [5]	1 (<1%) [1]	9 (7%) [10]	15 (2%) [16]
Appendicitis	1 (<1%) [1]	1 (<1%) [1]	3 (1%) [3]	0	4 (<1%) [4]
Gastroenteritis	1 (<1%) [1]	3 (1%) [3]	1 (<1%) [1]	0	4 (<1%) [4]
Nasopharyngitis	1 (<1%) [1]	3 (1%) [3]	0	1 (<1%) [1]	4 (<1%) [4]
Influenza	0	3 (1%) [3]	0	0	3 (<1%) [3]
Urinary tract infection	2 (2%) [2]	1 (<1%) [1]	2 (<1%) [2]	0	3 (<1%) [3]
Fungal infection	0	0	0	2 (2%) [2]	2 (<1%) [2]
Respiratory, thoracic and mediastinal disorders	**11 (8%) [18]**	**32 (12%) [34]**	**9 (4%) [12]**	**6 (5%) [8]**	**47 (8%) [54]**
Cough	6 (5%) [6]	16 (6%) [16]	4 (2%) [4]	3 (2%) [3]	23 (4%) [23]
Dyspnoea	1 (<1%) [2]	6 (2%) [6]	2 (<1%) [4]	1 (<1%) [3]	9 (1%) [13]
Rhinorrhoea	2 (2%) [2]	0	2 (<1%) [2]	1 (<1%) [1]	3 (<1%) [3]
Hiccups	3 (2%) [6]	2 (<1%) [2]	0	0	2 (<1%) [2]
Vascular disorders	**9 (7%) [10]**	**24 (9%) [26]**	**18 (8%) [20]**	**1 (<1%) [1]**	**43 (7%) [47]**
Hot flush	4 (3%) [4]	13 (5%) [13]	12 (5%) [13]	1 (<1%) [1]	26 (4%) [27]
Hypertension	1 (<1%) [2]	12 (5%) [12]	3 (1%) [4]	0	15 (2%) [16]
Phlebitis	2 (2%) [2]	0	0	0	0
Skin and subcutaneous tissue disorders	**8 (6%) [9]**	**22 (8%) [23]**	**13 (6%) [15]**	**7 (6%) [8]**	**42 (7%) [46]**
Hyperhidrosis	2 (2%) [2]	7 (3%) [7]	10 (4%) [12]	1 (<1%) [1]	18 (3%) [20]
Pruritus	4 (3%) [5]	10 (4%) [11]	2 (<1%) [2]	5 (4%) [5]	17 (3%) [18]
Pruritus generalised	1 (<1%) [1]	4 (2%) [4]	0	1 (<1%) [1]	5 (<1%) [5]
Eye disorders	**3 (2%) [3]**	**15 (6%) [18]**	**16 (7%) [17]**	**10 (8%) [10]**	**41 (7%) [45]**
Eye pain	1 (<1%) [1]	3 (1%) [4]	10 (4%) [10]	2 (2%) [2]	15 (2%) [16]
Photophobia	0	6 (2%) [6]	3 (1%) [3]	2 (2%) [2]	11 (2%) [11]
Vision blurred	1 (<1%) [1]	2 (<1%) [2]	3 (1%) [3]	0	5 (<1%) [5]
Conjunctivitis	0	1 (<1%) [2]	0	3 (2%) [3]	4 (<1%) [5]
Eyelid oedema	0	0	0	2 (2%) [2]	2 (<1%) [2]
Cardiac disorders	**7 (5%) [10]**	**18 (7%) [21]**	**17 (7%) [18]**	**4 (3%) [5]**	**39 (6%) [44]**
Palpitations	5 (4%) [5]	13 (5%) [16]	14 (6%) [15]	3 (2%) [4]	30 (5%) [35]
Tachycardia	1 (<1%) [2]	3 (1%) [3]	1 (<1%) [1]	0	4 (<1%) [4]

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Renal and urinary disorders	**7 (5%) [8]**	**13 (5%) [16]**	**6 (3%) [6]**	**0**	**19 (3%) [22]**
Leukocyturia	1 (<1%) [1]	3 (1%) [3]	0	0	3 (<1%) [3]
Urinary incontinence	2 (2%) [3]	3 (1%) [3]	0	0	3 (<1%) [3]
Proteinuria	2 (2%) [2]	1 (<1%) [1]	0	0	1 (<1%) [1]
Injury, poisoning and procedural complications	**14 (11%) [20]**	**15 (6%) [18]**	**0**	**2 (2%) [2]**	**17 (3%) [20]**
Procedural pain	9 (7%) [9]	7 (3%) [7]	0	1 (<1%) [1]	8 (1%) [8]
Forearm fracture	3 (2%) [3]	0	0	0	0
Reproductive system and breast disorders	**1 (<1%) [1]**	**5 (2%) [5]**	**5 (2%) [6]**	**0**	**10 (2%) [11]**

Note: Format is number of subjects (percent of subjects) [number of events]

The dictionary versions used were MedDRA version 16.0 for the DNDiFEX004 study and MedDRA version 16.1 for the DNDiFEX005/DNDiFEX006 studies. An impact analysis for the dictionary version change has been conducted and to ensure the homogeneity of the coding some terms have been re-coded using the MedDRA version 16.1

In the DNDiFEX004 study, 1 AE with partial start date (Patient 404_003 AE: WEIGHT GAIN) in the fexinidazole arm should have been considered as a TEAE.

HAT=human African trypanosomiasis; ITT=intent to treat; NECT=nifurtimox-eflornithine combination therapy; SOC=system organ class

Source: 5.3.5.3 Pooled analysis (Table 14.3.1.2.a)

Similarly, the most frequently reported TEAEs by PT (≥5% patients) in the pooled analysis were generally consistent with observations from the individual study analyses as follows: vomiting (42%), headache (37%), nausea (35%), asthenia (27%), insomnia (23%), tremor (22%), decreased appetite (20%), dizziness (19%), dyspepsia (14%), feeling hot (10%), abdominal pain (9%), back pain (9%), abdominal pain upper (8%), salivary hypersecretion (8%), anaemia (7%), neck pain (7%), hypocalcaemia (6%), pyrexia (6%), chest pain (5%), gastritis (5%), and palpitations (5%).

Patients treated with the higher fexinidazole dose had a higher incidence of AEs in the SOCs nervous system disorders (60% vs. 49%), metabolism and nutrition disorders (35% vs. 19%), psychiatric disorders (34% vs. 17%), musculoskeletal and connective tissue disorders (19% vs. 11%), vascular disorders (8% vs. <1%) and cardiac disorders (7% vs. 2%).

Kaplan-Meier analyses showed that there was a rapid onset after first exposure to fexinidazole for vomiting, nausea, headache, asthenia, insomnia (high dose regimen), tremor, decreased appetite, dizziness (high dose regimen), dyspepsia (high dose regimen), feeling hot (high dose regimen), abdominal pain, abdominal pain upper (high dose regimen), salivary hypersecretion and anaemia.

The incidence of vomiting and nausea are higher in stage 1 patients than Stage 2 patients and the incidence of insomnia, pyrexia and hypocalcaemia are higher in stage 2 patients than stage 1 patients. The applicant explored the potential explanations for the apparent higher frequency of vomiting in adults with stage 1 and early stage 2 HAT vs. late stage 2 HAT: a specific concomitant illness/events that could have increased vomiting in stage 1 and early stage 2 HAT adults compared with stage-2 adults, which is nevertheless not confirmed in literature; or early-stage patients might be more susceptible to this AE than late-stage patients due to the central origin of vomiting induced by fexinidazole, which may be supported by a study in rodents. However, in DNDiFEX004 vomiting frequency was relatively low and similar in both Fexinidazole and NECT treatment arms, whereas in the study of Priotto et al. evaluating NECT and eflornithine safety in confirmed stage-2 HAT adults, the rate of vomiting/nausea was much higher in NECT arm and closer to that observed in DNDiFEX005 which evaluated fexinidazole in early-stage HAT. The incidence of vomiting and salivary hypersecretion was higher in the lower dose regimen group exclusively given to children weighing ≥20 kg to <35 kg in Study DNDiFEX006 compared to the high dose regimen group. There are verbal reports from investigators, which suggest that some children may have had problems swallowing the fexinidazole tablets causing them to vomit. Other causes than the size of the pill cannot be ruled out as causing the vomit. The incidence of insomnia, dizziness, dyspepsia, feeling hot, abdominal pain upper, and hypocalcaemia was higher in the high dose regimen group.

AEs considered possibly drug-related were reported between start of treatment and EOT in 506/619 (82%) fexinidazole vs. 78% NECT patients. The most commonly reported with fexinidazole were vomiting (37% vs. 25% NECT), nausea (33% vs. 19%), asthenia (19% vs. 11%), decreased appetite (17% vs. 13%), headache (16% vs. 6%), insomnia (15% vs. 7%), tremor (14% vs. 6%), dizziness (14% vs. 10%) and dyspepsia (12% vs. 6%). Severe AEs were reported between baseline and EOH in 11% fexinidazole and 16% NECT patients. Grade 4 TEAEs were observed in 12 (2%) fexinidazole and 4 (3%) NECT patients, of which 8 and 3 in respective groups occurred between baseline and EOH.

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.

Cardiac AEs and AEs related to QT interval prolongation

Overall, 39/619 (6%) HAT patients treated with fexinidazole experienced 44 cardiac disorder AEs, most of which (27/39 patients; 31/44 AEs) were considered possibly related to fexinidazole and were coded to the PTs palpitations (22 patients; 26 AEs), tachycardia (4; 4) and sinus tachycardia (1; 1). None was severe in intensity.

In Study DNDiFEX004, more patients in the fexinidazole group had abnormal QTc values 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%) in NECT patients. Three (3) 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 of 60 ms. No QTcF values >480 ms were measured.

Based on studies in healthy volunteers and HAT patients, a C-R model was built that appears for M2 more consistent than those built for fexinidazole and M1, especially because it addressed the cumulative effect on ΔQTcF after multiple dosing, which was consistent with M2 accumulation, and show dissipation of effects on ΔQTcF 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 ΔQTcF 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 ΔQTcF 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. No consistent effects on PR interval and QRS duration were observed in HAT patients.

- - QT monitoring was performed in healthy subjects in Phase I studies. In healthy subjects, there was no clinically relevant out of range QT prolongation observed. Based on these results, QT was closely monitored in HAT patients (Studies DNDiFEX004 and DNDiFEX006). QT prolongation with imidazole derivatives metronidazole and delamanid is documented in the literature. Data from the clinical studies suggest that fexinidazole treatment can also be associated with this class effect. However, it appears not to exhibit such a higher risk profile compared to other nitroimidazoles as QTcF does not approach or exceed values associated with adverse clinical sequelae. Additionally, the data do not indicate the existence of a cumulative effect with the concomitant medications used in the HAT clinical trials. No consistent effects of the 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 reported during the development programme suggesting a life-threatening ventricular arrhythmia reported during the development programme, but it seems to exist a relation between patients with hypokalemia and prolongation of QTc.

When comparing the fexinidazole dose regimen groups to placebo in CD patients, 13/40 (33%) patients in the fexinidazole groups had abnormal QTcF values during the study *versus* none in the placebo group. In the

fexinidazole group, 40% patients had a change from baseline in QTcF between 30 and 60 ms compared to 29% of placebo patients. None of the patients in the study had a recorded change from baseline in QTcF >60 ms and none had values for this variable exceeding 500 ms. The exposure response analysis in CD patients indicated that the active metabolite M2 of fexinidazole appeared to increase QTcF rather than the parent compound or metabolite M1. Expert opinion obtained by the Applicant based on the ECG data suggests that no ECG recording is needed before, during or after a treatment with fexinidazole for HAT. However, to minimise the risk of life threatening arrhythmias, the Applicant recommends that caution should be exercised in at risk patients, i.e., those:

- with congenital prolongation of QTc interval, hypokalaemia, cardiac arrhythmia, heart failure, family history of sudden death, etc.
- treated concomitantly with other drugs that can block potassium channels, such as antiarrhythmics, neuroleptics, certain antimicrobial agents and non-sedating antihistamines, cisapride, domperidone or methadone.
- treated concomitantly with other drugs that can induce bradycardia, such as betablockers.
- treated with medicinal products with long elimination $t_{1/2}$ and known to prolong the QTc interval that may still be circulating at the time fexinidazole treatment course is commenced, such as anti-malarials.

If patients are, or need to be, treated with drugs known to prolong QTcF interval or to induce bradycardia, 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 is eliminated from the body (allow a washout period of 7 days).

Because documented cases of TdP are relatively rare, even for drugs that prolong the QT/QTc, they are often not reported until large populations of patients have received the agent in post-marketing settings. A commitment has been made that once commercialized the available post-marketing adverse event data will be examined for evidence of QT/QTc interval prolongation and TdP and for adverse events possibly related to QT/QTc interval prolongation, such as cardiac arrest, sudden cardiac death and ventricular arrhythmias (e.g., ventricular tachycardia and ventricular fibrillation). A well characterized episode of TdP has a high probability of being related to drug use, whereas the other events that are reported more commonly would be of particular concern if reported in a population at low risk for them (e.g., young men experiencing sudden death).

The applicant has adopted a conservative attitude to manage the risk of prolonged QTc. The conditions which are associated with increased risk of prolonged QTc are now contraindicated. In addition any concomitant drugs that may cause an increased risk of prolonged QTc are also contraindicated except for anitpsychotics which can be used with caution under close monitoring. This is acceptable despite only limited experience with concomitant use as the total treatment duration is short. In addition, the risk of prolonged QTc has been clearly communicated in section 4.4 and 4.8 of the SmPC. These measures are considered appropriate and adequate.

Hepatotoxicity disorders

Generally, any increases seen in 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). One of 619 fexinidazole patients had one case of transient ALT increased between 3x and 5x ULN in Study DNDiFEX004 in the fexinidazole group *versus* none in the NECT group between EOT and EOH considered possibly drug-related. 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. Review of the three HAT studies showed that the reported abnormalities were limited to mild asymptomatic increases of liver enzymes below the definition of acute liver injury. One of 619 fexinidazole patients had ALT between 3 and 5xULN between EOT and EOH considered possibly drug-related. There were no such increases in the NECT group, no patient in the study had values >5xULN and no patient met Hy's Law criteria. In product information Fexinidazole is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild to moderate underlying hepatic injury or liver function test abnormalities. The applicant acknowledges that the risk of hepatic injury is low as evidenced by the low number of reported events on raised liver enzymes. Nevertheless, the applicant considers it appropriate to reflect the lack of experience in patients with hepatic impairment and contradict its use in patients with cirrhosis or jaundice. This is accepted.

Although hepatotoxicity seems related to the use of fexinidazole, none of the values observed was >5xs ULN for ALT. There were also some cases of hypoalbuminemia that seem to be related to malnutrition rather that to acute liver failure. It is agreed that the hepatotoxicity should continue to be monitored and patients must avoid hepatotoxic drugs whilst using fexinidazole.

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.

VL patients who received the same fexinidazole dose regimen as adult HAT patients also experienced neutropenia, with 2 patients suffering grade 4 events, although from a baseline of grade 3 neutropenia. These were not classifed as serious and resolved spontaneously.

In the CD study DNDiFEXICH001, there were 8 events (in 8 patients; 4 high-dose and 4 low-dose), of treatment-related, asymptomatic and transient neutropenia considered SAEs, amongst neutropenia reports in 13 patients, which led to study closure. 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.

With a 10-day treatment period in HAT studies 12/619 fexinidazole patients (2%) experienced neutropenia, with no apparent difference in frequency based on HAT stage and no infectious complications. Four cases (one severe) had transient non-serious neutropenia that occurred during treatment and was considered possibly related to fexinidazole.

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, it is concluded 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, it is recommended that fexinidazole should be used with caution in patients with evidence or history of blood dyscrasias. In addition, patients are advised to return to the clinic if after discharge, they develop a fever within 3 months.

Neuropsychiatric disorders (including DALA)

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 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, e.g., 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. Four (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%) in line 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 - psychomotor hyperactivity - occurred in fexinidazole treated patients that was considered resolved at the time of DBL.

In CD, 14 (35.0%) patients treated with fexinidazole experienced sensory peripheral neuropathy. This signal was not detected in the much larger HAT population and is considered to be in line with the peripheral neuropathy reported with prolonged and intense courses of metronidazole. These peripheral neuropathies resolved after the treatment is stopped or doses are reduced.

The above mentioned results suggest that psychiatric symptoms, mostly insomnia in adults, occur commonly during treatment with fexinidazole. Most of these AEs were classifed as mild or moderate. A small number of psychiatric SAEs occurred during treatment with fexinidazole that 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. As a precaution, the Applicant placed a warning in the SmPC for use of fexinidazole in patients with history of acute psychiatric symptoms and recommends that such patients should be hospitalised during the entire treatment period with fexinidazole.

Concerning Neuropsychiatric disorders (including DALA) it is difficult to interpret some of these AE due to the nature of HAT. Some of the events observed seem class related and were already seen with the use of metronidazole. Although these events must continue to be monitored at this stage, the applicant included these aspects in the SmPC.

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 minutes period after administration. In the CD study, where the daily dose was the same as administered for the HAT loading doses, although for longer durations, vomiting also very frequently occurred (50% fexinidazole-treated patients) and at similar rates to those seen in the loading dose phase of the HAT studies. Patients with VL also experienced vomiting, very commonly, mostly related to treatment during study DNDiFEXIVL001, although only 1 of the 14 patients experienced early vomiting.

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 27/125 patients (21.6%) in the first 2 hours after administration. There was a higher incidence of vomiting in children weighing ≥20 kg to < 35 kg but the applicant was not able to rule out other causes for the vomiting besides difficulty of swallowing the tablets.

In relation to the reported difficulty of children in swallowing the tablets it appears that the 600 mg tablets are not suitable for some children that would be included within the indication for use and it should be noted that (with no PIP) the applicant has no plan to develop an age-appropriate formulation. The applicant has clarified

that it is not appropriate to crush tablets as it can increase bioavailability, which can affect tolerability. An appropriate statement in the SmPC has been added to reflect this recommendation. Further, the development of a dispersible formulation for paediatrics is strongly encouraged.

In most fexinidazole patients, treatment was re-administered once after vomiting. The profile of vomiting during treatment with fexinidazole is in line 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. 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 will be 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.

Phototoxicity

In the pre-clinical stage of the development it was observed that both the M1 and M2 metabolites of fexinidazole carried a signal for phototoxicity in the 3T3 test at high concentrations (>500 µg/mL), indicating a potential for phototoxicity reactions in patients treated with fexinidazole and exposed to sunlight or artificial ultraviolet (UV)-A light. It is unclear to what extent reassurance on the lack of phototoxicity could be derived from the clinical experience gained given that HAT2 patients are most likely hospitalised, and healthy volunteers are expected to have been advised of using photoprotection. Healthy volunteers with “history of photosensitivity” were excluded from the initial studies. No cases were reported after search in the safety database with the high level term (HLT) “Photosensitivity and photodermatosis conditions” and the preferred term (PT) “Retinal phototoxicity”. Phototoxicity occurred in 25% of patients on DNDiCHFEXI001 study but apparently with none being severe.

Other adverse events

The applicant has conducted a systemic search of the database for hypersensitivity and confirms that there is no signal of this to date with fexinidazole in HAT.

Serious adverse event / deaths / other significant events

The serious advents are in line with the adverse events observed in the total of patients.

In Phase 1 studies 2 subjects who received daily doses of 2400 or 3600 mg under fasting conditions had SAEs of severe anxiety on day 9 considered unrelated and increased transaminases on day 16 considered possibly related (>30xULN but no elevation of bilirubin). The latter patient had stopped treatment on day 15 and on day 44 AST was 1.7xULN with ALT 3.7xULN. Full investigation for non-treatment-related causes of the transaminase increase was negative.

Table 55: Grade 4 (life-threatening) TEAEs between baseline and EOH by study (ITT population HAT pooled analysis)

	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazo (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Life threatening	**3 (2%) [3]**	**4 (2%) [6]**	**2 (<1%) [2]**	**2 (2%) [3]**	**8 (1%) [11]**
Metabolism and nutrition disorders	**3 (2%) [3]**	**2 (<1%) [3]**	**0**	**0**	**2 (<1%) [3]**
Hypocalcaemia	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Hyperkalaemia	3 (2%) [3]	1 (<1%) [1]	0	0	1 (<1%) [1]
Hyponatraemia	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Psychiatric disorders	**0**	**3 (1%) [3]**	**0**	**0**	**3 (<1%) [3]**
Personality change	0	2 (<1%) [2]	0	0	2 (<1%) [2]
Acute psychosis	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Investigations	**0**	**0**	**2 (<1%) [2]**	**2 (2%) [3]**	**4 (<1%) [5]**
Blood calcium decreased	0	0	0	1 (<1%) [1]	1 (<1%) [1]
Blood sodium decreased	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Blood potassium increased	0	0	0	1 (<1%) [1]	1 (<1%) [1]
Blood potassium decreased	0	0	0	1 (<1%) [1]	1 (<1%) [1]
Blood glucose increased	0	0	1 (<1%) [1]	0	1 (<1%) [1]

Note: Format is number of subjects (percent of subjects) [number of events]

The dictionary versions used were MedDRA version 16.0 for the DNDiFEX004 study and MedDRA version 16.1 for the DNDiFEX005/DNDiFEX006 studies. An impact analysis for the dictionary version change has been conducted and to ensure the homogeneity of the coding some terms have been re-coded using the MedDRA version 16.1

In the DNDiFEX004 study, 1 AE with partial start date (Patient 404_003 AE: WEIGHT GAIN) in the fexinidazole arm should have been considered as a TEAE

EOH=end of hospitalisation; HAT=human African trypanosomiasis; ITT=intent-to-treat; TEAEs = treatment-emergent adverse event.

Source: 5.3.5.3 Pooled analysis (Table 14.3.1.28.2.a)

In the HAT studies a total of 61 (10%) of 619 fexinidazole-treated patients experienced at least one SAE. The highest incidence of SAEs was in the SOCs of infections and infestations (27/619; 4%) and gastrointestinal disorders (15/619; 2%); however, all SAEs in these SOCs were considered by the Investigator as unrelated to study medication. Most of these occurred between EOH and the primary endpoint assessment visits. For all SAEs of infection, there was no associated evidence of neutropenia at the time of onset. Six patients had SAEs considered possibly drug-related, including personality change (2), psychotic disorder or acute psychosis (2), increased blood potassium and decreased blood sodium.

Fourteen (14) SAEs occurred between the start of treatment and EOH, the period in which fexinidazole and/or its metabolites, M1 and M2, could be considered still present in the blood. These events include poisoning, suicidal ideation, personality change, acute psychosis, psychotic disorder, aspiration pneumonia, hyponatraemia, AIDS, psychomotor hyperactivity, respiratory tract infection, increased blood glucose, blood potassium increased. Of these, between the investigators and the Sponsor, most of the neuropsychiatric and laboratory biochemistry abnormality SAEs were considered to be possibly related to fexinidazole, either in the absence of any reasonable explanation or due to temporal relationship.

Considering patients >15 years of age with late stage 2 disease only, 10 SAEs in 9 patients (3.4%) who received fexinidazole and 3 events in 3 patients (2.3%) who received NECT (hyperkalaemia, hyperglycaemia, concussion) occurred between the start of the treatment and EOH. Most of these were considered by the Investigator to be unrelated to study treatment.

Fourteen (14) patients experienced TEAEs that resulted in death, none of which were considered as possibly related to study treatment by investigators and 12 of which occurred well after patients were discharged from hospital; 2 TEAEs that resulted in death, poisoning and aspiration pneumonia in Study DNDiFEX004 occurred during the treatment period with fexinidazole.

Comparison of SAEs across fexinidazole dose groups does not show a difference in the incidence of events (10% patients in each dose group). However, the data do suggest that across disease stages patients with late stage 2 disease have a greater incidence of SAE's than those with earlier stage disease.

In the CD study, there were 15 fexinidazole (and no placebo) patients with 24 SAEs, including the patient who committed suicide and 8 with neutropenia. In addition, 2 SAEs of Grade 3 leukopenia were reported.

In ongoing studies, up to 15 August 2017, 6 SAEs were reported in 4 patients in DNDiFEX005 (malaria and genito-urinary infection, injury in right thigh, fatal hypovolaemic and cardiogenic shock and fatal foetal distress; see above re deaths). There were also 3 SAEs in one patient in DNDiFEX006 (malaria, anaemia and typhoid fever) and 3 SAEs in 3 patients in DNDiFEX009 (confusional state, anxiety, febrile gastroenteritis).

Deaths

Up to the safety cut-off date of 15 August 2017, 18 patients treated with fexinidazole experienced at least 1 TEAE with an outcome of death in the clinical programme, 14 of which occurred in the HAT patient population (see above) and 1 in the CD population. A further 3 fatal PV cases, not captured in the clinical study databases (i.e., occurred after DBL while the patient was still ongoing in the follow-up phase of the study or during the ongoing DNDiFEX009 HAT study), and associated with patients treated with fexinidazole, occurred before the safety data cut-off of 15 August 2017 (1 in the HAT population and 2 foetal deaths associated with parents with HAT; 1 to a mother treated with fexinidazole and 1 to a father treated with fexinidazole and mother treated with NECT).

Table 56: TEAEs leading to death by study (ITT population, HAT pooled analysis)

System Organ Class Preferred Term	DNDiFEX004 NECT (N=130)	DNDiFEX004 Fexinidazole (N=264)	DNDiFEX005 Fexinidazole (N=230)	DNDiFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Any	2 (2%) [2]	9 (3%) [11]	4 (2%) [8]	1 (<1%) [2]	14 (2%) [21]
Injury, poisoning and procedural complications	**0**	**3 (1%) [3]**	**0**	**1 (<1%) [1]**	**4 (<1%) [4]**
Poisoning	0	2 (<1%) [2]	0	0	2 (<1%) [2]
Alcohol poisoning	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Injury	0	0	0	1 (<1%) [1]	1 (<1%) [1]
Infections and infestations	**0**	**1 (<1%) [2]**	**2 (<1%) [2]**	**0**	**3 (<1%) [4]**
Influenza	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Peritonitis	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Pneumonia	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Pulmonary sepsis	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Gastrointestinal disorders	**0**	**1 (<1%) [1]**	**1 (<1%) [1]**	**0**	**2 (<1%) [2]**
Crohn's disease	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Inguinal hernia strangulated	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Respiratory, thoracic and mediastinal disorders	**0**	**1 (<1%) [1]**	**0**	**1 (<1%) [1]**	**2 (<1%) [2]**
Dyspnoea	0	0	0	1 (<1%) [1]	1 (<1%) [1]
Pneumonia aspiration	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Blood and lymphatic system disorders	**0**	**0**	**1 (<1%) [1]**	**0**	**1 (<1%) [1]**
Anaemia	0	0	1 (<1%) [1]	0	1 (<1%) [1]
General disorders and administration site conditions	**0**	**1 (<1%) [1]**	**0**	**0**	**1 (<1%) [1]**
Death	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**0**	**1 (<1%) [1]**	**0**	**0**	**1 (<1%) [1]**
Ameloblastoma	0	1 (<1%) [1]	0	0	1 (<1%) [1]
Nervous system disorders	**0**	**0**	**1 (<1%) [2]**	**0**	**1 (<1%) [2]**
Encephalitis	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Meningeal disorder	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Renal and urinary disorders	**0**	**0**	**1 (<1%) [1]**	**0**	**1 (<1%) [1]**
Nephropathy	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Vascular disorders	**0**	**0**	**1 (<1%) [1]**	**0**	**1 (<1%) [1]**
Shock	0	0	1 (<1%) [1]	0	1 (<1%) [1]
Cardiac disorders	**1 (<1%) [1]**	**0**	**0**	**0**	**0**
Cardio-respiratory arrest	1 (<1%) [1]	0	0	0	0
Metabolism and nutrition disorders	**1 (<1%) [1]**	**1 (<1%) [2]**	**0**	**0**	**1 (<1%) [1]**
Hypoglycaemia	1 (<1%) [1]	1 (<1%) [1]	0	0	1 (<1%) [1]
Starvation	0	1 (<1%) [1]	0	0	1 (<1%) [1]

Note: Format is number of subjects (percent of subjects) [number of events]

Adult patients with late stage 2 HAT– comparison with NECT (DNDiFEX004)

From the clinical database for Study DNDiFEX004 there were 11 deaths in the ITT population: 9 (3.4%) patients who received fexinidazole and 2 patients who received NECT (1.5%). A 12th patient died (suicide) before randomisation. None of the deaths were considered by the Investigator to be related to treatment. However, based on the definition of causality, the Sponsor could not exclude any relationship with the study drug and therefore considered that 4 deaths could at the very least, be possibly related, 3 in the fexinidazole group (poisoning in 2 patients and pneumonia in 1 patient) and 1 in the NECT group (hypoglycaemia). Two patients (0.8%) who received fexinidazole died during treatment (on Day 5, due to poisoning, and on Day 8 due to pneumonia aspiration). The AE of poisoning was considered unrelated by the Investigator but possibly related by the Sponsor (and pneumonia aspiration was considered unrelated).

Additional PV cases not captured in the clinical database at the time of database cut-off of 15 August 2017 include: a foetal death of spina bifida to a mother treated with NECT and father treated with fexinidazole (pregnancy started 4 months after EOT with NECT and 3 months after EOT with fexinidazole).

In study DNDiFEX004 there seems to exist a comparable number of AE between the two groups involved, although unexpectedly a higher number of deaths in the fexinidazole group is observed. Although the number of deaths was higher in the fexinidazole group, that difference was not statistically significant; from the data presented no trend seems to be present in neither group (fenixidazole vs NECT).

Adult patients with early stage 2 and stage 1 HAT (DNDiFEX005)

From the clinical database for Study DNDiFEX005, there were 4 deaths in the ITT population (1.7%) in 3 patients with stage 1 HAT and 1 patient with early stage 2 HAT. The events (SAEs) leading to death were meningeal disorder and encephalitis in 1 patient, Crohn's disease and peritonitis in 1 patient, shock in 1 patient and anaemia, pulmonary sepsis and nephropathy in 1 patient. None of the events leading to death were considered to be related to treatment and all were considered unexpected for the study medication, based on reference information. Additional fatal PV cases not captured in the clinical database at the time of database cut-off for the study that occurred before the safety data cut-off date of 15 August 2017 include: the death of 1 patient due to SAEs of cardiogenic shock and hypovolemic shock and a foetal death due to foetal distress syndrome, occurring during child birth. The mother had been treated with fexinidazole several months before this SAE leading to fatality. None of these cases were considered related to treatment.

Paediatric patients with any stage HAT (DNDiFEX006)

From the clinical database for Study DNDiFEX006, there was 1 death in the ITT population (0.8%): 1 patient (stage 1 HAT) had 2 SAEs (dyspnoea and injury, caused by a traumatic aggression) that led to death, which were considered as unrelated to treatment and unexpected for the study medication, based on reference safety information. There were no additional fatal PV cases not captured in the clinical database up to the safety data cut-off date of 15 August 2017.

Overdose

In the clinical pharmacology study DNDiFEX001, subjects received 3600 mg daily for 14 days in fasting conditions; 1 subject developed significant increases in hepatic transaminases at the end of the dosing period which returned to normal rapidly after the last dose without other treatment. In study DNDiFEX003, the second cohort was planned to be treated with 2400 mg fexinidazole for 4 days then 1800 mg for 5 days in fed conditions. The study was stopped following unacceptable tolerability after 6 subjects were entered into cohort 2.

A paediatric patient in DNDiFEX006 received the higher dosing regimen (1800/1200 mg) instead of the lower dosing regimen (1200/600 mg) as adjusted for their weight as per protocol. At inclusion the patient presented with HAT symptoms of headache, pruritus and weight loss; blood potassium and calcium were normal and albumin was just below normal levels. The patient experienced TEAEs of vomiting over the first 5 days of treatment and increased potassium and decreased calcium levels were observed from Day 11 to Week 9. The profile of TEAEs in this patient was therefore consistent with those observed in patients who received the higher dose of fexinidazole.

No further cases of overdose have been reported in HAT clinical trials. Due to the saturable dose response model, the E_{max} of about 30 ms calculated for QTcF is not expected to be increased in case of overdose, on average, at the population level. In cases of suspected overdosage symptomatic and supportive therapy should be given as appropriate. White blood cell counts and transaminases (AST and ALT) should be monitored.

Dependence or abuse potential

An analysis of DALA was undertaken across HAT studies which found that the potential for drug abuse is low and even less in the paediatric population <15 years of age. Euphoria TEAEs were mostly dizziness in NECT- and fexinidazole-treated patients (9% to 25%). Within the fexinidazole treatment arms, the incidence of dizziness was lowest in the paediatric study DNDiFEX006 (9%), than in the adult studies (14% in the NECT arm, 19% in the fexinidazole arm in DNDiFEX004 and 25% in DNDiFEX005). There was also a difference in the incidence of dizziness by dosing regimen with a higher incidence in patients receiving 1800/1200 mg compared to 1200/600 mg. There was no difference in the incidence of dizziness by HAT stage 1 or stage 2.

TEAEs related to impaired attention, cognition, mood and psychomotor events or dissociative/psychotic events were low in incidence (≤5%) in both NECT-treated and fexinidazole-treated patients; there were no differences between study treatment arms, by dose regimen or by HAT stage.

Given the planned controlled distribution system, it is not expected that overdose and/or misuse happen.

Laboratory findings

Biochemistry

Overall, in HAT patients administered fexinidazole, shifts in laboratory biochemistry parameters were balanced.

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.

The apparent anomalies, such as hypocalcaemia, hypokalaemia, hyponatraemia, hyperglycaemia and hypo-albuminaemia were observed only in the pivotal trial, which suggests that investigators may have changed the approach to reporting. The applicant has clarified that there was a different approach to reporting these laboratory abnormalities in the pivotal study (004) as adverse events of metabolism and nutritional disorders in contrast to other studies where it was correctly reported as lab abnormalities. Further, the applicant attributed the difference in reporting rates for some of these events to the disease which is plausible.

Liver function

Hepatotoxicity disorders are discussed above

Haematology

In an analysis of shifts in haematology parameters over time, a worsening in haemoglobin from normal to Grade 1 was reported for 14.1% treated with fexinidazole and a worsening in WBC from normal to high occurred in 15.5%. By HAT stage, a higher proportion of stage 2 HAT patients had a shift from normal to high WBC compared to stage 1 patients (18.8% vs. 10.9%). By dosing regimen, from baseline to EOT, a higher proportion of patients in the 1800/1200 mg dose group maintained normal haemoglobin and WBC compared to the 1200/600 mg group (Hb 71.5% vs. 56.3%; WBC 78.3% vs. 68.9%). A greater proportion of patients treated with 1200/600 mg had a shift from normal to high compared to 1800/1200 mg for WBC (21.4% vs. 14.3%) and platelets (9.7% vs. 3.9%).

Safety data from Study DNDiCHFEXI001 in CD patients showed alterations in haematological tests (delayed neutropenia) leading to early study termination. Additionally, it were reported specific treatment beyond supportive measures, inclusion of an additional follow-up visit (Week 9) in studies in HAT patients to monitor neutropenia and other standard biological values for potential delayed-onset abnormalities (please refer to section 4.3 - Haematological and neutropenia-related disorders)

Renal function

There is no information on dosing in patients with renal impairment. Fexinidazole and its metabolites have shown not to be eliminated by the kidney. No adjustment in dosing is required for patients with mild and moderate renal impairment, but caution should be exercised when treating those with severe renal impairment.

Safety in special populations

The sample sizes in several categories were not large enough to draw conclusions.

Intrinsic factors

An overview of the incidence of TEAEs by intrinsic subgroup category and study is presented in Table 45. Where intrinsic factor subgroup categories had sufficient sample sizes to draw comparisons, there were minimal differences in the overall incidence of TEAEs by age, gender, BMI or renal function. However, as noted above, rates for vomiting were higher in children (69% < 15 years, 35% 15-50 and 33% over 50 years), whereas children were less likely to have insomnia or dizziness. It should be noted that the sample sizes in several categories were not large enough to draw conclusions.

Table 57: Any TEAEs by age, gender, BMI and renal function and by study (ITT population, HAT pooled analysis)

Sub group	Category	DNDiFEX004 NECT		DNDiFEX004 Fexinidazole		DNDiFEX005 Fexinidazole		DNDiFEX006 Fexinidazole		All Fexinidazole	
		N	n (%) [event]	N	n (%) [event]	N	n (%) [event]	N	n (%) [event]	N	n (%) [event]
Any TEAE		**130**	**121 (93%) [607]**	**264**	**247 (94%) [1525]**	**230**	**214 (93%) [1258]**	**125**	**116 (93%) [583]**	**619**	**577 (93%) [3366]**
Age (years)	<15	0	0	0	0	0	0	123	114 (93%) [575]	123	114 (93%) [575]
	[15; 50 [	106	100 (94%) [512]	234	217 (93%) [1310]	187	175 (94%) [1020]	2	2 (100%) [8]	423	394 (93%) [2338]
	≥50	24	21 (88%) [95]	30	30 (100%) [215]	43	39 (91%) [238]	0	0	73	69 (95%) [453]
Gender	Female	50	47 (94%) [230]	130	97 (94%) [569]	115	107 (93%) [650]	58	54 (93%) [284]	276	258 (93%) [1503]
	Male	80	74 (93%) [377]	161	150 (93%) [956]	115	107 (93%) [608]	67	62 (93%) [299]	343	319 (93%) [1863]
BMI (kg/m^2)	<18.5	58	53 (91%) [275]	108	102 (94%) [629]	83	76 (92%) [414]	118	110 (93%) [553]	309	288 (93%) [1596]
	[18.5 ; 25]	68	64 (94%) [308]	152	142 (93%) [874]	142	134 (94%) [812]	7	6 (86%) [30]	301	282 (94%) [1716]
	>25	4	4 (100%) [24]	4	3 (75%) [22]	5	4 (80%) [32]	0	0	9	7 (78%) [54]
Renal function	Normal	84	81 (96%) [424]	162	150 (93%) [925]	151	139 (92%) [812]	105	96 (91%) [484]	418	385 (92%) [2221]
	Mild	39	33 (85%) [147]	92	87 (95%) [517]	66	62 (94%) [362]	17	17 (100%) [69]	175	166 (95%) [948]
	Moderate	6	6 (100%) [33]	10	10 (100%) [83]	13	13 (100%) [84]	1	1 (100%) [1]	24	24 (100%) [168]
	Severe renal insufficiency	1	1 (100%) [3]	0	0	0	0	2	2 (100%) [29]	2	2 (100%) [29]

Renal function categories: normal (≥80 mL/min); mild (≥50 to <80 mL/min); moderate (≥30 to <50 mL/min); severe renal insufficiency (<30 mL/min)
The dictionary versions used were MedDRA version 16.0 for the DNDiFEX004 study and MedDRA version 16.1 for the DNDiFEX005/DNDiFEX006 studies
An impact analysis for the dictionary version change has been conducted and to ensure the homogeneity of the coding some terms have been re-coded using the MedDRA version 16.1
In the DNDiFEX004 study, 1 AE with partial start date (Patient 404_003 AE: WEIGHT GAIN) in the fexinidazole arm should have been considered as a TEAE
BMI=body mass index; HAT=human African trypanosomiasis; ITT=intent to treat; NECT=nifurtimox-eflornithine combination therapy; TEAE=treatment-emergent adverse event
Source: 5.3.5.3 Pooled analysis (Table 14.3.1.50.a, Table 14.3.1.49.a, Table 14.3.1.51.a, and Table 14.3.1.53.a)

By state of the disease

At baseline, patients with stage 2 HAT had higher incidences of metabolism and nutrition disorders (51.0% vs. 0.8%), nervous system disorders (headache 22.2% vs. 8.9%) and blood and lymphatic system disorders (22.7% vs. 6.2%) compared to patients with stage 1 HAT. The incidence of AEs in the SOC of metabolism and nutrition disorders was 43% for stage 2 vs. 18% for stage 1 patients and rates for AEs in the SOC of psychiatric disorders were 37% vs. 24%, respectively. In contrast, there was no difference in rates of haematological

events and neutropenia by HAT stage. For AEs related to a pre-defined SMQ for hepatotoxicity, rates were 6% for stage 2 HAT and 1% for stage 1 HAT, mainly due to hypoalbuminaemia, which may reflect nutrition rather than hepatic dysfunction. There were no apparent differences in rates of impaired attention, cognition and mood based on HAT stage

Age

Where the sample sizes were sufficient to draw comparisons, review of data showed that the overall incidence of vomiting was highest in patients <15 years (69%) versus patients from 15 to 50 years (35%) versus patients ≥50 years (33%). Verbal reports from the Investigators suggest that patients in the paediatric study struggled to swallow the fexinidazole tablets which may have in part been the reason for the increased incidence of vomiting in these patients.

The incidence of vomiting and salivary hypersecretion is higher in children weighing ≥20 kg to <35 kg, are these AE related with difficulty swallowing. The applicant clarified that children weighting <35kg will be given treatment in hospital as part of a risk minimization measure. Other causes than the size of the pill cannot be ruled out as causing the vomit.

A table with the relation of AEs observed in the elderly population stratified by age groups was provided by the Applicant. Statements made after consideration of these data are meaningfully reflected in the product information.

Gender

Overall across all fexinidazole treated patients, there was no difference in the incidence in TEAEs by gender (93% patients in both groups), with similar results across all HAT studies.

Body mass index

Overall, the reported incidence of TEAEs across BMI categories was similar across all fexinidazole patients and compared to NECT treated patients.

Comorbid conditions and renal function

In the pooled HAT analysis, where the sample sizes were sufficient to draw comparisons by comorbid conditions and renal function, there were no clinically relevant findings in each study treatment arm or within the pooled data for fexinidazole and no clinically relevant differences between NECT and fexinidazole.

Fertility and use in pregnancy and lactation

The safety of fexinidazole for use in human pregnancy has not been established. There seems to exist no cases of exposure to fexinidazole during pregnancy, however there are some cases of pregnancies after taking the drug. To the extent of the information presented, it appears that no effect is observed in the children born from those pregnancies, nevertheless, the data is limited to draw any conclusion.

The rationale for a contraindication during the 1st trimester of pregnancy, i.e. out of precautionary principle, does not appear justified in absence of animal data directly or indirectly indicating harmful effects with respect to reproductive toxicity or teratogenicity at slightly below therapeutic doses. In animals, effects of fexinidazole on embryo-fetal development 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 (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Fexinidazole Winthrop® 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.

A study on fexinidazole concentrations in milk was conducted on lactating female albino rats after the administration of 800 mg eq/kg of [^{14}C]-fexinidazole. Based on these findings, the same extent of exposure can be expected in breastfed human newborns. Thus, for newborns with a mean weight of 3 kg who consume around 500 mL of breast milk per day, this corresponds to total exposure to M2 in the range of 9.0 to 15.5 mg/day, ie. 3.0 to 5.2 mg/kg.

The decision to allow exposure to pregnant (from 2nd trimester) and breastfeeding woman was supported by data from the full development and reproductive toxicology (DART) studies showing that there is no risk of toxicity on foetal or post-natal development with fexinidazole. The findings from preclinical studies show that fexinidazole and/or its metabolites do not induce any toxicity on reproductive function. 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.

Extrinsic Factors

As with other nitroimidazole class drugs, fexinidazole may cause disulfiram-like reaction (antabuse effect) characterised by flushing, rash, peripheral oedema, nausea, and headache. Patients should be advised not to take alcohol during fexinidazole therapy and for at least 48 hours afterwards.

Immunological events

No data was presented on immunological events. It appears that hypersensitivity reactions were not reported so far with fexinidazole and that pruritus rather than rashes had been reported in HAT patients (although a papular rash was reported in a CD patient). The applicant has conducted a systemic search of the database for hypersensitivity and confirmed that there is no signal of hypersensitivity to date with fexinidazole in HAT.

Safety related to drug-drug interactions and other interactions

Drug-food interactions

In study DNDiFEX001 Part II and in DNDiFEX002 the food and its metabolites appeared to have no impact on the overall safety and tolerability of fexinidazole.

It is recommended that Fexinidazole tablets should be taken orally once a day for 10 days with food (i.e., during or right after the main meal of the day and preferably at the same time each day) to ensure that efficacious concentrations are achieved.

Drug-drug interactions

Fexinidazole is metabolised and transformed in hepatocytes into M1 metabolite and M1 is in turn metabolised into M2 and M3. All metabolic reactions are nicotinamide adenine dinucleotide phosphate (NADPH)-dependent, thereby supporting the involvement of CYP enzymes in fexinidazole metabolism. Fexinidazole is also rapidly metabolised into M1 by flavin-containing monooxygenase-3 (FMO-3). In human hepatocytes, intrinsic clearance was fast and elevated in African American and Caucasian individuals (half-life=6.5 and 13.4 minutes, respectively) and moderate in paediatric individuals (half-life=33.2 to 60.6 minutes, respectively).

The applicant reviewed concomitant medications that are CYP substrates and were taken during treatment with fexinidazole but the numbers are very low. Numbers exposed to inhibitors or inducers of various CYP enzymes

are not provided due to the applicant's opinion on the risk of clinically significant interactions. 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 metabolized by CYP2B6 (buproprion, efavirenz) could result in a decreased exposure of those drugs and should therefore be avoided.

Table 58: Known CYP450 substrates, inhibitors and/or inducers taken in the period from first treatment to EOH (ITT population, HAT pooled analysis)

Description	DNDiFEX004 NECT (N=130)	DNDIFEX004 Fexinidazole (N=264)	DNDIFEX005 Fexinidazole (N=230)	DNDIFEX006 Fexinidazole (N=125)	All Fexinidazole (N=619)
Benzodiazepine Derivatives	**10 (7.7%) [12]**	**33 (12.5%) [51]**	**14 (6.1%) [19]**	**5 (4.0%) [8]**	**52 (8.4%) [78]**
Diazepam	10 (7.7%) [12]	33 (12.5%) [51]	14 (6.1%) [19]	5 (4.0%) [8]	52 (8.4%) [78]
H2-Receptor Antagonists	**1 (0.8%) [1]**	**1 (0.4%) [1]**	**13 (5.7%) [17]**	**1 (0.8%) [1]**	**15 (2.4%) [19]**
Cimetidine	1 (0.8%) [1]	1 (0.4%) [1]	13 (5.7%) [17]	1 (0.8%) [1]	15 (2.4%) [19]
Imidazole And Triazole Derivatives	**1 (0.8%) [1]**	**3 (1.1%) [3]**	**1 (0.4%) [1]**	**6 (4.8%) [6]**	**10 (1.6%) [10]**
Ketoconazole	0 (0.0%) [0]	1 (0.4%) [1]	0 (0.0%) [0]	4 (3.2%) [4]	5 (0.8%) [5]
Barbiturates And Derivatives	**3 (2.3%) [4]**	**2 (0.8%) [2]**	**2 (0.9%) [2]**	**2 (1.6%) [2]**	**6 (1.0%) [6]**
Phenobarbital	3 (2.3%) [4]	2 (0.8%) [2]	2 (0.9%) [2]	2 (1.6%) [2]	6 (1.0%) [6]
Artemisinin And Derivatives, Combinations	**0 (0.0%) [0]**	**1 (0.4%) [1]**	**0 (0.0%) [0]**	**4 (3.2%) [4]**	**5 (0.8%) [5]**
Artemether, Lumefantrine	0 (0.0%) [0]	1 (0.4%) [1]	0 (0.0%) [0]	4 (3.2%) [4]	5 (0.8%) [5]
Proton Pump Inhibitors	**1 (0.8%) [1]**	**3 (1.1%) [4]**	**1 (0.4%) [1]**	**0 (0.0%) [0]**	**4 (0.6%) [5]**
Omeprazole	1 (0.8%) [1]	3 (1.1%) [4]	1 (0.4%) [1]	0 (0.0%) [0]	4 (0.6%) [5]
Butyrophenone Derivatives	**0 (0.0%) [0]**	**1 (0.4%) [2]**	**1 (0.4%) [2]**	**0 (0.0%) [0]**	**2 (0.3%) [4]**
Haloperidol	0 (0.0%) [0]	1 (0.4%) [1]	1 (0.4%) [2]	0 (0.0%) [0]	2 (0.3%) [3]
Haloperidol Decanoate	0 (0.0%) [0]	1 (0.4%) [1]	0 (0.0%) [0]	0 (0.0%) [0]	1 (0.2%) [1]
Methanolquinolines	**0 (0.0%) [0]**	**1 (0.4%) [1]**	**1 (0.4%) [1]**	**0 (0.0%) [0]**	**2 (0.3%) [2]**
Quinine	0 (0.0%) [0]	1 (0.4%) [1]	1 (0.4%) [1]	0 (0.0%) [0]	2 (0.3%) [2]
Macrolides	**0 (0.0%) [0]**	**1 (0.4%) [1]**	**0 (0.0%) [0]**	**1 (0.8%) [1]**	**2 (0.3%) [2]**
Erythromycin	0 (0.0%) [0]	1 (0.4%) [1]	0 (0.0%) [0]	1 (0.8%) [1]	2 (0.3%) [2]
Fluoroquinolones	**2 (1.5%) [2]**	**1 (0.4%) [3]**	**1 (0.4%) [1]**	**0 (0.0%) [0]**	**2 (0.3%) [4]**

Note: Format is number of subjects (percent of subjects) [number of medications]
The dictionary versions used were WHO Drug December 2012, B2 format for the DNDiFEX004 study and WHO Drug September 2013, C format for the DNDiFEX005/DNDiFEX006 studies
A reconciliation between the 2 dictionary versions and formats has been performed to ensure the homogeneity of the coding
EOH=end of hospitalisation; HAT=human African trypanosomiasis; ITT=intent to treat; NECT=nifurtimox-eflornithine combination therapy
Source: 5.3.5.3 Pooled analysis (Table 14.3.3.12.a)

Drugs known to prolong the QT interval and/or induce bradycardia: in the development program, fexinidazole was seen to be associated with asymptomatic prolongation of the QTcF interval, with a few patients with QTcF values exceeding 450ms. Caution is therefore 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.

Discontinuation due to adverse events

The number of AE that lead to treatment discontinuation were in small number, with the exception of the ones observed in study DNDiCHFEXI001 in which dose and duration of treatment are different of the ones for HAT.

Table 59: Summary of AEs leading to treatment interruption or discontinuation reported in at least 5% of patients (Study DNDiCHFEXI001)

Parameter	High dose						Low dose						Fexinidazole Total	
Preferred Term	8 weeks (N=7) n (%)		4 weeks (N=6) n (%)		2 weeks (N=7) n (%)		8 weeks (N=7) n (%)		4 weeks (N=7) n (%)		2 weeks (N=6) n (%)		(N=40) n (%)	
Nausea	2	28.6%	3	50.0%	2	28.6%	0	0	3	42.9%	1	16.7%	11	27.5%
Depression	1	14.3%	2	33.3%	2	28.6%	2	28.6%	1	14.3%	1	16.7%	9	22.5%
Abdominal pain upper	2	28.6%	1	16.7%	1	14.3%	0	0	3	42.9%	1	16.7%	8	20.0%
Headache	1	14.3%	1	16.7%	2	28.6%	0	0	2	28.6%	1	16.7%	7	17.5%
Insomnia	0	0	1	16.7%	3	42.9%	0	0	2	28.6%	1	16.7%	7	17.5%
Anxiety	3	42.9%	1	16.7%	2	28.6%	0	0	0	0	0	0	6	15.0%
Decreased appetite	0	0	2	33.3%	1	14.3%	1	14.3%	1	14.3%	1	16.7%	6	15.0%
Vomiting	1	14.3%	1	16.7%	1	14.3%	0	0	1	14.3%	1	16.7%	5	12.5%
Electrocardiogram QT prolonged	0	0	1	16.7%	1	14.3%	2	28.6%	0	0	0	0	4	10.0%
Peripheral sensory neuropathy	2	28.6%	1	16.7%	0	0	1	14.3%	0	0	0	0	4	10.0%
Vertigo	0	0	0	0	1	14.3%	0	0	1	14.3%	1	16.7%	3	7.5%

n (%)=number and percentage of patients

Note: due to safety and tolerability issues identified during the study, from 17 October 2014 all patients that had received greater than 2 weeks of treatment had treatment immediately interrupted and all other patients who had initiated treatment were instructed to complete a 2-week treatment course. Thus, the duration of treatment and exposure to treatment were variable and the end of treatment was defined in accordance to the duration of the actual treatment regimen. All the 47 patients included in the safety populations received at least one dose of the study drug. There were 9 (19.1%) patients who completed the initially planned 8 weeks of treatment, 18 (38.3%) patients who received less than 2 weeks of treatment and 20 (42.6%) patients who received from 2 to less than 8 weeks of treatment. Therefore, the treatment groups presented here are as randomised and do not represent the actual duration of treatment received.

AE=adverse event; QT=QT interval

Source: 5.3.5.4 Erratum to DNDiCHFEXI001 (Table 17)

2.6.1. Discussion on clinical safety

Across all studies in the fexinidazole clinical programme, a total of 853 patients or subjects have been exposed to fexinidazole in 10 studies, both in HAT and additional indications.

In children between 6 years and 15 years, weighing at least 20 kg there is an ongoing study (DNDiFEX006) with 125 patients enrolled and complete to month 12.

The pooled safety analysis in HAT patients does not include data from DNDiFEX009 (ongoing) or data from patients with CD or VL. For the latter, dose and duration are different from those in the HAT studies. Of

note study DNDiCHFEXI001 is of particular interest following premature study interruption due to safety concerns (neutropenia) after the inclusion of 47 patients.

In line with observations from the individual study analyses, data from the pooled analyses of AEs from Studies DNDiFEX004, DNDiFEX005 and DNDiFEX006 showed that the most frequently reported TEAEs (≥10% patients) by SOC were: gastrointestinal disorders (70% patients), nervous system disorders (58% patients), general disorders and site conditions (43% patients), metabolism and nutrition disorders (33% patients), psychiatric disorders (32% patients), musculoskeletal and connective tissue disorders (18%), investigations (11% patients) and blood and lymphatic system disorders (10%).

Similarly, the most frequently reported TEAEs by PT (≥5% patients) in the pooled analysis were generally consistent with observations from the individual study analyses as follows: vomiting (42%), headache (37%), nausea (35%), asthenia (27%), insomnia (23%), tremor (22%), decreased appetite (20%), dizziness (19%), dyspepsia (14%), feeling hot (10%), abdominal pain (9%), back pain (9%), abdominal pain upper (8%), salivary hypersecretion (8%), anaemia (7%), neck pain (7%), hypocalcaemia (6%), pyrexia (6%), chest pain (5%), gastritis (5%), and palpitations (5%).

Of special interest were considered:

- Risk of QT prolongation: it cannot be established if it is a class effect as observed in metronidazole or an effect of hERG.
- Hepatotoxicity disorders
- Haematological and neutropenia-related disorders (see comment on study DNDiFEXICH001)
- Neuropsychiatric disorders (including DALA)
- Gastrointestinal disorders

No considerable differences related to gender, age (with the exception of the vomiting issue), or body mass index were noted. A disulfiram-like effect (probably drug class effect) though, is abundant.

Despite the overall picture for fexinidazole vs. NECT and for fexinidazole in different patient populations, there were some noted differences when comparing AEs at the PT level. For example, nausea and vomiting were reported more often in DNDiFEX005 and 006 compared to either treatment group in the pivotal trial. A problem in the children might be to some extent expected, and the applicant has commented on this finding. The applicant explored the potential explanations for the apparent higher frequency of vomiting in adults with stage 1 and early stage 2 HAT vs late stage 2 HAT. In the children there was a higher rate of vomiting with the lower dose but interpretation of this finding is complicated by the effect of age on the ability to take and tolerate oral dosing with tablets. Nevertheless, the applicant has clarified that it is not appropriate to crush tablets as it can increase bioavailability, and affect tolerability. The applicant has added an appropriate statement in the SmPC to reflect this recommendation.

Higher rate of asthenia and higher rate for some neuropsychiatric AEs with fexinidazole vs. NECT were observed. Furthermore, there are some apparent anomalies, such as the reporting of hypocalcaemia, hypokalaemia, hyponatraemia, hyperglycaemia and hypoalbuminaemia as AEs only in the pivotal trial. The applicant has clarified that there was a different approach to reporting these laboratory abnormalities in the pivotal study (004) as adverse events of “metabolism and nutritional disorders”, in contrast to other studies where it was correctly reported as lab abnormalities. Further on, the applicant attributed the difference in reporting rates for some of these events to the disease.

Patients treated with the higher dose had a higher incidence of AEs in the SOCs nervous system disorders (for example dizziness was reported in 22% who took 1800/1200 mg vs. 6% who took 1200/600 mg), metabolism and nutrition disorders, psychiatric disorders, musculoskeletal and connective tissue disorders, vascular disorders and cardiac disorders. Nevertheless, interpretation of these differences is potentially difficult because the effects of dose vs. age on the reporting rates cannot be distinguished.

Also, the risk of increased transaminase levels appeared to be related to the dose and duration of fexinidazole treatment. The observations in CD patients prompted the applicant to conduct a detailed analysis and seek expert opinion. At the recommended dose regimen for HAT the predicted and observed abnormalities in transaminases do not appear to be particularly alarming and the rates for elevated AST or ALT were similar for fexinidazole vs. NECT. Within DNDiFEX004, a detailed comparison of elevated transaminases between treatments did not suggest a higher risk with fexinidazole and none was Grade 2 or higher. There was a higher rate for elevated ALP with fexinidazole vs. NECT but it does not seem to have been any clinical consequences.

Whilst neutropenia was an issue that became known with prolonged exposure to fexinidazole in CD patients, there were 12 (2%) HAT patients treated with fexinidazole across the studies who had AEs of neutropenia and four cases were considered possibly drug-related. However, within DNDiFEX004 2 (1.5%) NECT patients and one fexinidazole patient (the CSR says none but the summary of safety shows 1) had AEs of neutropenia. In addition, in a subset of patients monitored for neutropenia the changes from baseline were comparable between treatments.

Given the fact, that there is no thorough QTc study, and the fact that the potential for drug-interactions have not been fully studied/understood, the applicant agreed to adopt a more conservative approach in terms of contra-indications and warnings to mitigate the risk of QTc prolongation. The effect on heart rate appears to be modest and there was no excess of AEs of tachycardia and palpitations with fexinidazole vs. NECT.

The applicant has conducted a systemic search of the database for hypersensitivity and confirms that there is no signal of this to date with fexinidazole in HAT.

The mortality rate has not been higher with fexinidazole vs. NECT and the listed causes do not suggest drug-related fatal AEs. In addition, although the difference in denominators means that caution is needed, there was no obvious increases risk of SAEs (overall or individual) with fexinidazole vs. NECT. There were effectively no HAT patients who permanently discontinued treatment due to AEs except for the two patients who died from non-HAT causes during treatment.

The limitations of the safety database are related with the disease itself (number of cases) and the difficulty to establish a clinical study in the location of interest. Therefore, taking account of the contextual use of this product and expected benefits, the identified limitations in terms of safety data are acceptable. Appropriate warnings have been added to the Product Information. It is further proposed that the presence of adverse side effects related to fexinidazole will be evaluated in a prospective, observational study (as outlined in the RMP).

Additional expert consultations

None

Assessment of paediatric data on clinical safety

The use in children>20 kg and >6 years is well documented in the SmPC, namely in section 4.2. The misuse in children below this age and weight and the higher event of vomiting in this special group population is addressed in the RMP.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

To the date and with the data presented by the applicant, fexinidazole appears to have an acceptable safety profile. There are no safety issues that would preclude endorsement of a proposed 10-day regimen for g-HAT.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Psychiatric events[a]
Important potential risks	Vomiting
	Pro-arrhythmic effect
	Severe infection secondary to drug-induced neutropenia
	Hepatotoxicity
	Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2 and CYP2C19[b]
	Development of resistance to fexinidazole, cross resistance between fexinidazole and nifurtimox
Missing information	Use in pregnancy/lactation
	Use in children <6 years old or less than 20 kg

a Psychiatric events: Insomnia, psychotic symptoms, depression, anxiety.
b Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
INT15307: An open-label, non-randomized, two-treatment, one-sequence crossover pharmacokinetic interaction study of 5-day repeated oral doses of fexinidazole on a single dose cocktail of caffeine and omeprazole used as probe substrates for CYP1A2 and CYP2C19 activities, respectively, in African sub-Saharan origin healthy subjects. Planned **Category 3**	To assess the effect of 5-day repeated oral doses of fexinidazole on the cytochrome P450 activity using a CYP probe cocktail (1A2 and 2C19)	Drug-drug interactions with concomitant drugs that are metabolized by CYP1A2 and CYP2C19	Clinical Study Report	30 September 2019

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
FEXINC09395: Prospective observational study of the safety of fexinidazole for human African trypanosomiasis Planned **Category 3**	To collect safety data and data on relapse occurrence within 12 months on fexinidazole	Presence of any adverse side effects related to fexinidazole: Any case of sudden death during treatment Delivery outcomes in women exposed to fexinidazole during pregnancy Two-year follow-up after delivery among children who received in utero exposure to fexinidazole	Clinical Study Report	30 September 2023

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Psychiatric events	**Routine risk minimization measures:** SmPC: Labeled in sections 4.4, 4.7 and 4.8 of the SmPC PL: Labeled in sections 2 and 4 of the PL **Additional risk minimization measures:** Guide for healthcare staff (visual aide) Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: None **Additional pharmacovigilance activities:** FEXINC09395**:** Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Important potential risks		
Vomiting	**Routine risk minimization measures:** SmPC: Labeled in sections 4.2 and 4.8 of the SmPC PL: Labeled in sections 3 and 4 of the PL **Additional risk minimization measures:** Guide for healthcare staff (visual aide) Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395: Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Pro-arrhythmic effect	**Routine risk minimization measures:** SmPC: Labeled in sections 4.3, 4.4, 4.5 and 4.8 of the SmPC PL: Labeled in sections 2 and 4 of the PL **Additional risk minimization measures:** Controlled access program	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395**:** Prospective

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Controlled distribution	observational study of the safety of fexinidazole for human African trypanosomiasis.
Severe infection secondary to drug-induced neutropenia	**Routine risk minimization measures:** SmPC: Labeled in section 4.4 of the SmPC PL: Labeled in section 4 of the PL **Additional risk minimization measures:** Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395**:** Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Hepatotoxicity	**Routine risk minimization measures:** SmPC: Labeled in sections 4.3, 4.4 and 5.1 of the SmPC PL: Labeled in sections 2 and 4 of the PL **Additional risk minimization measures:** Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395**:** Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2 and CYP2C19	**Routine risk minimization measures:** SmPC: Labeled in sections 4.5 and 5.2 of the SmPC PL: Labeled in section 2 of the PL **Additional risk minimization measures:** Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Study INT15307 FEXINC09395**:** Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Development of resistance to fexinidazole, cross resistance between fexinidazole and nifurtimox	**Routine risk minimization measures:** SmPC: Labeled in section 5.1 of the SmPC **Additional risk minimization measures:** Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395**:** Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Missing information		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use in pregnancy / lactation	**Routine risk minimization measures:** SmPC: Labeled in sections 4.6 and 5.3 of the SmPC PL: Labeled in section 2 of the PL **Additional risk minimization measures:** Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395**:** Prospective observational study of the safety of fexinidazole for human African trypanosomiasis.
Use in children <6 years old or less than 20 kg	**Routine risk minimization measures:** SmPC: Labeled in sections 4.1 and 4.2 of the SmPC PL: Labeled in section 2 of the PL **Additional risk minimization measures:** Controlled access program Controlled distribution	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The first periodic safety update report should cover the six-month period following the initial scientific opinion for this product on 15 November 2018.

Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed.

2.9. Product information

2.9.1. User consultation

A User testing of the Package Leaflet was not submitted by the applicant. This is not a mandatory requirement for a scientific opinion on a medicinal product under Article 58 of Regulation (EC) No 726/2004.

3. Benefit-Risk Balance

3.1. Therapeutic Context

The applicant proposes the use of a fixed 10-day regimen of oral fexinidazole for the treatment of 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.

3.1.1. Disease or condition

Human African trypanosomiasis (HAT), or sleeping sickness, is a life-threatening disease endemic to some restricted tropical regions in sub-Saharan Africa. Two subspecies of the protozoan parasite *Trypanosoma brucei (T. b.)* are pathogenic for humans: *T. b. gambiense*, responsible for the chronic form of the disease (average duration of approximately 2 years) and located in western and central Africa and *T. b. rhodesiense*, responsible for a more acute form of the disease (lasting from few weeks to 6 months) and located in eastern and southern Africa. The parasites are transmitted by the tsetse fly and it is generally accepted that humans constitute the epidemiologically important reservoir of the *T.b. gambiense*, parasite. With infection of a new human host, the parasites may enter the bloodstream and initiate a long process of systemic infection, which takes place initially in blood and lymph nodes but which may ultimately progress to involve the central nervous system and meningeal compartment. HAT is diagnosed from the presence of trypanosomes in blood or lymph nodes. The potential of the parasite to evade the successive host attempts to produce effective neutralizing antibodies leads to a protracted course of disease in *T. b. gambiense*, clinically manifested by irregularly repeated bouts of fever and a progression to severe consumptive neurologic disease over one to two years.

The disease is staged according to the presence or absence of trypanosomes in the CSF or, if none are detected in CSF, from the number of WBCs in the CSF. Two clinical stages are primarily defined: Stage 1 (haemolymphatic) HAT is characterised by mild and nonspecific symptoms including intermittent fever, headache, pruritus, and lymphadenopathy, with trypanosomes being present in the blood and lymphatic system. If not diagnosed and treated, the condition progresses to stage 2 (meningoencephalitic) HAT, in which parasites invade the central nervous system. Late stage 2 patients display neurological signs including mental confusion, worsening sleep disturbances and, eventually, coma, and death.

3.1.2. Available therapies and unmet medical need

Available therapies have been outlined in the introduction section of this report (Section 2.1.5).

The selection of the treatment for *T b. gambiense* HAT is based mainly on the disease stage, which currently requires the performance of a lumbar puncture and requires logistics for direct microscopy for parasitologic diagnosis (evidence of parasites in CSF and/or significant pleocytosis in the context of any other serology [generally card hemaglutination] or direct examination diagnostic test for trypanosomiasis).

Pentamidine is currently the drug of choice for the treatment of Stage 1 HAT caused by *T. b. gambiense*. It must be administered by the intramuscular route or, when possible, IV in saline over 2 hours, daily, for 7-10 days, at a dose of 4 mg/kg up to a maximum of 300 mg for both adult and children. Intramuscular injections of pentamidine are reported to be painful and may induce sterile abscesses. Pentamidine may not be as effective in intermediate stages and is not adequate for the treatment of the second stage of disease.

Few therapeutic options are available to treat meningo-encephalitic stage HAT. Until recently, available products were parenteral, toxic, painful, or difficult to manage. The introduction of eflornithine, or α -difluoromethylornithine (DFMO), initially as monotherapy and later in combination with nifurtimox (NECT), has improved the prognosis of treated patients and, since 2010, NECT has become the first-line therapy for stage 2 *T. b. gambiense* HAT. However, NECT treatment requires a minimum health infrastructure and personnel to administer 2 slow infusions every day for 7 days on top of an oral treatment every 8 hours for 10 days. NECT is associated with nausea and vomiting, which tends to appear at least 1 hour after simultaneous administration of both drugs. Melarsoprol, an organoarsenic drug, has been used for the rescue treatment of Stage 2 disease by *T. b. gambiense* in resource poor regions, being more affordable than eflornithine. An encephalopathic reaction to melarsoprol occurs in 5-10% of patients with a case-fatality rate of approximately 50% in such occurrence.

There is no exclusively oral treatment regimen for g-HAT. Availability of fexinidazole tablets would provide the means for sure an easier distribution and administration, potentially allowing quicker and wider access to treatment. Furthermore, the applicant argued that availability of an agent that could be used regardless of HAT staging would mean that a LP would not be prerequisite since the treatment would be uniform regardless of the result. Thus, it was proposed by the applicant that only those patients who fail initial treatment would require a staging LP. However, as per guidance provided during the evaluation by the advisory expert group, this proposal cannot be supported.

The disease course is essentially similar in adults and children, as are the current treatment options with proper dose adjustment. It is encouraged that any new treatment option should be also available for the paediatric population. The applicant has addressed this need in the development programme of fexinidazole.

3.1.3. Main clinical studies

The main objective of the clinical development programme was to demonstrate that a 10 day, oral regimen of fexinidazole would allow acceptable rates of cure for both Stage 1 and Stage 2 patients, thus avoiding the need for the mandatory pre-treatment definition of disease stage, based on the parasitological and cytological findings in CSF. The design and final version of the clinical development programme has been repeatedly discussed with technical consultants from both the scientific and regulatory areas prior to its implementation.

The applicant's definition of late stage 2 HAT deviated slightly from the terminology used by WHO and in HAT guidance. Similarly, the applicant's definition of early stage 2 would have different terminology in WHO's classification. Nevertheless, the programme covers patients across the stages, regardless of the terminology, and the wording of the indication does not refer to "early" and "late". Therefore, the noted difference between the applicant's and the other terminologies has no significantly impact on the conclusions.

The only comparative study (DNDiFEX004) was conducted in late stage 2 HAT against the standard of care comparator (NECT). This pivotal study aimed to demonstrate that fexinidazole was similarly efficacious to the standard recommended treatment NECT for late stage 2 HAT. The assumption was made that if fexinidazole at the selected dose regimen performed well in patients who already had evidence of CNS invasion by *T. b. gambiense*, it would also elicit high cure rates in earlier stages of the disease. With a lower age limit of 15 years in the pivotal comparative study, it was assumed that efficacy in late stage 2 HAT could be extrapolated to younger subjects if they achieved comparable blood and CSF levels of metabolite M2. Since NECT is given by IV and oral routes and use of dummy infusions plus double dummy oral treatment was perceived to be a difficult undertaking at study sites, an open label design was used. The study population, being the most difficult to treat, and overall design were agreed during a CHMP advice.

In addition, efficacy data are presented from 2 cohort uncontrolled 'plug-in' studies; these were initiated at the same study sites as the pivotal study (except 2 sites in Study DNDiFEX004) to increase the safety database and provide complementary data of efficacy for fexinidazole in adults with early stage 2 or stage 1 HAT (Study DNDiFEX005) and in children (of ≥6 years and 20 kg) with disease at any stage (Study DNDiFEX006), although most of these children were stage 1.

The patients included in all trials were representative of the target population, *as per* inclusion and exclusion criteria, and the criteria for the case definition of disease and diagnostic procedures were adequate and acceptably complied with. Completion of treatment as per protocol was almost universal.

3.2. Favourable effects

In the pivotal comparative study vs. NECT (DNDiFEX004) a primary endpoint of cure at 18 months post-treatment was accepted, subject to follow-up to 24 months.

The applicant's pre-defined non-inferiority margin was -13%, which was derived from pre-trial consultation with experts as being acceptable when considering the advantages of an oral-only treatment that might be used regardless of disease stage. In the primary analysis, 91.2 % success rate was observed with fexinidazole versus 97.6 % for NECT (–6·4%, 97·06% CI [–11·2 to –1·6]; p=0·0029). In this primary analysis, and in all the sensitivity analyses, fexinidazole was consistently less effective than NECT. However, the possible advantages of fexinidazole may outweigh the lower relative efficacy. These include: a single therapy as compared to combination treatment with NECT; an oral treatment for stage-1 and stage-2; no universal need for hospitalisation; and easier and more economic distribution. Some of the above advantages may possibly result in earlier and potentially wider access to treatment, closer to home.

In the uncontrolled DNDiFEX005 study, the month 12 success rate (based on 227/230 patients who had reached this visit or previously died) in this stage 1 and early stage 2 HAT population aged at least 15 years was 98.7% (95% CI [96.2; 99.7]). For 157 who had reached the 18-month visit and 4 prematurely withdrawn, the success rate was 96.9% (95% CI [92.9; 99.0]), which is higher than that observed at month 18 for late stage 2 HAT patients. Furthermore, in stage 1 patients (n=135) the success rate at month 18 was 97.0% (95% CI [92.6; 99.2]) while in early stage 2 patients (n=26) the success rate was 96.2% (95% CI [80.4; 99.9]).

The success rate observed in likewise uncontrolled study DNDIFEX006, conducted in 125 children aged between 6 and 14 years with either stage 1 (~55%), early stage 2 (~15%) or late stage 2 (~30%; 2/3 of these had trypanosomes in CSF; same proportion as in adults) the success rates were overall, 97.6% (95% CI [93.1; 99.5]), with only a slightly lower rate in patients with stage 2 disease (early and late stage 2, N=66). Across this mixed population 3/122 patients failed at month 12. For 85 patients who had reached month 18, the success rate was higher than at month 18 in the pivotal study (97.6%; 95% CI [91.8; 99.7]). Two patients were considered as failures (one stage 1, and one late stage 2 patient).

3.3. Uncertainties and limitations about favourable effects

The applicant assumed that the expectations were that fexinidazole should have an 'acceptable efficacy' and not 'non-inferior or equivalent efficacy'. Given the potential advantages of fexinidazole as an exclusively oral regimen, compared to NECT, the "acceptable margin" of 'a loss of efficacy of 5% (expectation) which should not reach 13% (threshold of unacceptable difference) may be reasonable, and as such the primary efficacy results were within the pre-set expectations.

There are two main uncertainties with respect to the use of fexinidazole in stage-2 HAT. The first one relates to the fact that the lower success rate with fexinidazole compared to NECT in the pivotal study. Whilst for the overall stage-2 HAT population, the magnitude of difference is judged as "acceptable", treatment outcome was shown to be worse in severe late stage 2 sub-group. The *post-hoc* data analysis identified that for patients presenting with somnolence and at least two (2) signs and symptoms - generally representing a more severe disease - the efficacy was 83.8% in the fexinidazole arm versus 98.2% on the NECT arm (Table 47). Separately, analysis showed that on LP, the presence of > 100 WBC in CSF would indicate an 11.8% higher chance of being cured with NECT (Table 43).

The second uncertainty relates to the fact that for the conducted studies, patients were hospitalised for treatment administration. The fact that compliance was virtually universal under the experimental conditions of the three trials with fexinidazole does not allow a conclusion on the success and potential consequences of failure of unsupervised treatment. Although the failures in the study were not associated with a lower exposure to fexinidazole, there is a rationale to expect a lower success rate if the treatment absorption or compliance is poor and the extent of loss in efficacy in the clinical practice is unknown. It should also be noted that the pharmacologic data produced before the conduction of the Phase II/III efficacy development programme is insufficient to provide evidence that the proposed dose regimen is associated with adequate CSF/CNS concentrations of fexinidazole in a sufficient proportion of patients. Other dose regimens that could provide different and potentially more adequate time-kill profiles were not explored. In this regard, there was also concern regarding the unexplained differences in exposures between healthy subjects and patients when dosed similarly and the derivation of the reduced dose for children of ≥20 to <35 kg, in whom the measured DBS levels of fexinidazole, M1 and M2 at 24 h after the last dose were 10% to 30% lower compared to the ≥35 kg group and lower compared to adults. Whilst there were only 3 failures in the paediatric population (n=127), these limited data cannot rule out an impact on clinical efficacy, especially in late stage 2 HAT. Compared to other children, potential underexposure for children of ≥20 to <35 kg remains a potential.

Some efficacy-related concerns are also raised by lack of understanding of the exact mechanism of action of fexinidazole, as well as lack of detailed insight on the risk of resistance. The applicant discussed the possibility of development of cross-resistance between nifurtimox and fexinidazole. Based on the current incidence of stage-2 HAT and *in vitro* studies investigating emergence of resistance, the risk of development of treatment resistance is estimated to be low. The exposure to trypanosomes and extent of fexinidazole usage will be limited and this greatly reduces the risk of propagation of resistant genes. In addition, *in vitro* studies on cross-resistance have shown that there is a difference in the level of resistance between fexinidazole and nifurtimox, which suggests that there are different mechanisms for resistance to these two medicines and consequently cross-resistance is unlikely to be a significant concern. Finally, even if there is resistance to both fexinidazole and nifurtimox, the trypanosomes will still be susceptible to eflornithine and this assertion is supported by the lack of resistance observed to eflornithine despite years of concomitant use of both eflornithine and nifurtimox.

3.4. Unfavourable effects

The summary of safety suggests no difference of importance between fexinidazole and NECT in subjects aged from 15 years with late stage 2 HAT but this comparison is limited by the fact that only 130 subjects were exposed to comparative therapy.

Cross-study comparisons, - noting that the uncontrolled studies were conducted at the same sites and with the same staff as the pivotal study -, suggest that HAT stage, age range and dose regimen also had no major impact on the overall safety profiles.

The most frequently reported TEAEs by preferred term (PT) (≥5% patients) in the pooled analysis were as follows: vomiting (42%), headache (37%), nausea (35%), asthenia (27%), insomnia (23%), tremor (22%), decreased appetite (20%), dizziness (19%), dyspepsia (14%), feeling hot (10%), abdominal pain (9%), back pain (9%), abdominal pain upper (8%), salivary hypersecretion (8%), anaemia (7%), neck pain (7%), hypocalcaemia (6%), pyrexia (6%), chest pain (5%), gastritis (5%), and palpitations (5%).

Of special interest were considered: risk of QT prolongation (confirmed as a class effect like the one observed in metronidazole); hepatotoxicity disorders; haematological and neutropenia-related disorders; neuropsychiatric disorders (including DALA); and gastrointestinal disorders.

Some differences were observed when comparing AEs at the PT level, such as nausea and vomiting were reported more often in DNDiFEX005 and 006 compared to either treatment group in the pivotal trial. Satisfactory explanations were provided by the applicant.

Underlining some of these observations is the difference between fexinidazole and NECT for ADRs. For example, rates for ADRs during treatment confirmed higher rates with fexinidazole vs. NECT for vomiting, nausea, asthenia, decreased appetite, headache, insomnia, tremor, dizziness and dyspepsia (among others). There is however no excess of severe or Grade 4 events reported in the fexinidazole group. Paediatric patients showed a similar safety profile to that of the adult population except for more frequent vomiting within 2 hours of administration. Vomiting within 30 minutes of fexinidazole administration occurred in 20% of paediatric population vs. 6.1% of adult patients, with a trend to a higher incidence of vomiting during the loading phase. Events of vomiting were mostly mild to moderate in intensity and did not result in permanent treatment discontinuation. A corresponding warning has been added to section 4.8 SmPC.

The risk of increased transaminase levels with fexinidazole appeared dose- and duration related. However, at the recommended dose regimen for HAT the rates for elevated AST or ALT were similar for fexinidazole vs. NECT. Whilst neutropenia was an issue that became known with prolonged exposure to fexinidazole in Chagas Diseases, no specific concerns were raised within the g-HAT programme. In a subset of patients monitored for neutropenia, the changes from baseline were comparable between treatments.

Importantly, and in contrast to NECT, fexinidazole has a clear effect on QTc. However, no thorough QT study has been conducted. The very clear QTc prolongation effect following oral dosing with fexinidazole was related to each of fexinidazole, M1 and M2 plasma levels but was only significantly correlated with the latter.

3.5. Uncertainties and limitations about unfavourable effects

The limitations of the safety database are related with the disease in itself (number of cases) and the difficulty to establish a clinical study at the location where the disease is prevalent (some countries are experiencing war in Africa, for instance); so given the importance that this medicine could achieve, the prevailing limitations can be accepted. In the proposed Product information, these limitations are accounted for.

Also, prolongation of QT seems to be related to the cumulatively exposure to the M2 plasma concentrations. Given the fact, that there is no thorough QTc study, and that the potential for drug-interactions have not been fully studied/understood, the applicant however agreed to adopt a more conservative approach to mitigate the risk due to prolongation of QTc in terms of appropriate contra-indications and warnings and justified the adequacy of the proposed approach*.* The SmPC considers the combined pharmacodynamic effects that may occur if fexinidazole is given with other agents that prolong QTc.

There are also several issues raised by the clinical pharmacology data with potential implications for safety that need to be addressed, such as lack of information on the fate of fexinidazole and the co-administration of fexinidazole with strong CYP inducers that could decrease fexinidazole exposure but would be expected to

increase M1 and M2 exposures. The applicant committed to perform additional *in vitro* studies with different *in vitro* systems/matrices to identify and/or confirm the enzymatic pathways involved in the metabolism of fexinidazole, the formation of fexinidazole sulfoxide (M1), the formation of fexinidazole sulfone (M2) and the potential metabolism of M2, however given the limited knowledge regarding the enantiomers of M1, these should be investigated as part of these studies. Moreover, the applicant has also agreed to perform a CYP induction study, for fexinidazole, M1 and M2, in accordance with the guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1). This study will also assess the potential of fexinidazole, M1 and M2 to induce CYP1A2, 2B6, and 3A using human hepatocytes.

Phototoxicity reactions observed in pre-clinical stage associated with both M1 and M2 metabolites (see section 5.3 SmPC); however phototoxicity signal was not confirmed during the clinical programme.

3.6. Effects Table

Table 60 - Effects Table for Fexinidazole Winthrop 600 mg tablets, both stages of human African trypanosomiasis (HAT) in adults and children ≥ 6 years old and weighing ≥ 20 kg (data cut-off: 15 August 2017)

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Success rate at 18 months (primary time point) after EOT, as per WHO criteria	Late Stage 2 HAT due to *T. b. gambiense,* in patients ≥ 15 years, male/female	% of patients	Fexinidazole 239/262 (91.2%; 89% expected)	NECT 124/127 (97.64%; 94% expected)	Acceptable difference set to ≤13% for non-inferiority Difference FEX vs NECT [97.06% CI]: -6.42 [-11.22; -1.61] -> despite larger than the -5% expected, remained within -13% -> primary endpoint met; Primary (sensitivity) analysis (18 months using algorithm class mITT): lower limit 97.06% CI -12.10 - > support primary analysis for non-inferiority of FEX vs. NECT	DNDIFEX004
Success rate at 24 months (additional time point) after EOT, as per WHO criteria	Late Stage 2 HAT due to *T. b. gambiense,* in patients ≥ 15 years, male/female	% of patients	Fexinidazole 207/264 (78.4%)	NECT 112/130 (86.2%)		DNDIFEX004

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Complement efficacy data Success rate at 12 months after EOT, as per WHO criteria	Stage 1 and early stage 2 HAT due to *T. b. gambiense*, patients ≥ 15 years (Stage 1 – 189 patients; early stage 2 – 41 patients)	% of patients	Fexinidazole	none	Acceptance of a success greater than 80% in stage 1 or early stage 2 HAT patients Success rate higher than expected: 7.7% Stage 1HTA - success rate 98.4%, 95% CI [95.4; 99.7] Early 2HTA - success rate - 100.0%, 95% CI [91.4; 100.0] Lower bound 95% CI > 80 -> endpoint met; Secondary analyses: lower limit 95%CI > 80% (93.3% and 96.2%) - > support primary analysis	DNDIFEX005
Success rate at 12 months after EOT, as per WHO criteria	HTA irrespective of stage (Stage 1 – 69 patients; early stage 2 – 19 patients; late stage 2 – 37 patients)	% of patients	Fexinidazole	none	Acceptance of a success greater than 80% Success rate higher than expected: 5.6% Stage 1 - Lower bound 95% CI > 80% (92.2%) -> endpoint met; But early stage 2 - Lower bound 95% CI < 80% (74%) -> endpoint not met; Late stage 2 - Lower bound 95% CI < 80% (85.5%) -> endpoint not met; 1 premature withdrawal – death – stage 1 (not treatment related) 2 patients had CSF WBC count >20 cells/µL at 12 months Second analysis: lower limit 95%CI > 80% (90.9%) -> endpoint met	DNDIFEX006
Success rate at 18 months additional time point after EOT, as per WHO criteria	HTA irrespective of stage Stage 1 – 41 patients; early stage 2 – 15 patients; late stage 2 – 28 patients	% of patients	Fexinidazole 84/125 (97.6%) [95% CI 91.8, 99.7]	none	Acceptance of a success greater than 80% Overall Lower bound 95% CI > 80% (91.8%) -> endpoint met; No premature withdrawals between 12 month and 18 month time points	DNDIFEX006

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
AEs (all) Serious TEAEs Lead to death TEAEs related to treatment			93% (all studies) 10% 2% 83%	93% 10% 2% 79%	=TEAEs No difference vs. NECT in AEs, TEAEs, TEAES leading to death More TEAEs related to treatment for FEX vs. NECT	
TEAE Gastrointestinal	All Vomiting Nausea Abdominal pain		70% 42% 35% 9%	49% 28% 20% 12%	Vomiting, esp. in children General higher TEAEs – GI for FEX vs. NECT	
TEAE CNS	All Headache Tremor Dizziness		58% 37% 22% 19%	49% 25% 12% 14%	General higher TEAEs – Neuro for FEX vs. NECT	
QTcF DNDIFEX004	>450 ms +30-60 ms +>60 ms >480 ms >500 ms	+ms 90% CI	7.2% 27.3% 3 patients 3 patients 2 patients	0% 6.9% 0 patients 0 patients	The QTc effect is noted; SmPC states adequate contraindications and precautions	
TEAE Blood	All Anaemia Neutropenia Leukopenia		10% 7% 2% 0%	14% 11% 2% 2%	General higher TEAEs – Blood for NECT vs. FEX	
TEAE Liver DNDIFEX004	ALT: 3-5x ULN		1 patient (transient)	0 patients	Similar proportion of patients in the fexinidazole and NECT arms had increases in LFTs above ULN	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The focus of the development programme was to demonstrate that fexinidazole was similarly efficacious to the standard recommended treatment NECT for late stage 2 HAT. The assumption was made that if fexinidazole at the selected dose regimen performed well in patients who already had evidence of CNS invasion by *T. b. gambiense*, it would also elicit high cure rates in earlier stages of the disease. With a lower age limit of 15 years in the pivotal comparative study, it was assumed that efficacy in late stage 2 HAT could be extrapolated to younger subjects if they achieved comparable blood and CSF levels of metabolite M2. Whereas the effectiveness on stage-1 and early stage 2 could probably be inferred from the effectiveness on late stage 2, the contrary would not apply, since the clearance of parasites in late stage 2 disease requires that adequate distribution into the CNS/CSF is attained and may provide an adequate time-kill profile to eradicate the parasite and prevent relapses.

The efficacy of the proposed dose regimen of fexinidazole for the treatment of stage 1 and early stage 2 disease in adults (study DNDIFEX005) and also in children (study DNDIFEX006), was adequately demonstrated. It must

be noted, that the efficacy rates for NECT achieved in controlled trials in late stage-2 disease were very high (94-95%), thus allowing for a high rate of clinical cure, associated with the possibility of improvement of established neurologic deficit, and also for a benefit for the epidemiologic control of the disease. However, the data obtained with the fexinidazole regimen for the treatment of adults with late stage 2 disease (study DNDIFEX004) were not fully reassuring in demonstrating that the difference in the observed success rate at 18 months after end of treatment is not unacceptably lower than the recognized high success rate for NECT. The applicant had established the limit of 13% for the acceptability of this difference in success rates. The final results for the main efficacy endpoint as evaluated at 18 months provided a lower efficacy estimate for fexinidazole (91·2% vs 97·6%; –6·4%, 97·06% CI [–11·2 to –1·6]; p=0·0029), albeit within the "acceptability margin". A sensitivity analysis in a more conservative subset of the study population yielded a lower 97.06 % CI of -12.10. It is presumed that the lower CI results reflect less than adequate fexinidazole levels achieved in the CNS with the proposed 10-day oral dose regimen, to eradicate the parasite load in the CNS in a significant proportion of patients. Some PK/PD data for the relationship between CSF levels of fexinidazole and treatment failure may be derived from the PK activities of study DNDIFEX004. Data from the pediatric study DNDIFEX006 also does not allow for full clarification on this issue. A dose regimen with lower fexinidazole dose levels (1200 mg/day for 4 days, followed by 600 mg/day for 6 days) with the objective of having similar exposure was derived, taking into account that non-clinical *in vitro* PK studies had shown that there were no major differences in the metabolism of fexinidazole and M1 and M2 metabolites between human, rat and dog hepatocytes from juveniles and adults. For trial DNDIFEX006, even though the overall rate of success in this population was very high and largely within acceptable limits, a trend was nonetheless observed towards a worse result in the few subjects with evidence of meningo-encephalitic involvement.

One uncertainty with respect to the use of fexinidazole in stage-2 HAT is the fact that whilst for the overall stage 2 HAT population, the acceptability of this lower efficacy is deemed as satisfactory (relative to NECT), a sub-group analysis revealed that in a sub-group of late stage-2 with more severe disease (defined as WBC >100 cells/ µL in CSF), the effect size is even lower. In the current clinical context, it is advised that fexinidazole should only be used in this subgroup if no other adequate (e.g. NECT) treatment is available or tolerated. A restriction of the indication (section 4.1 SmPC), excluding the severe late stage 2 is however <u>not advised</u>, taking account of the following: a) the clinical context may change; b) the definition of subgroup (of WBC >100 cells/ µL CSF) is not precise (as the value can vary between laboratories, specimens and timing of the CSF tap), c) the activity of fexinidazole is not likely to drop considerably at the "WBC >100 cells/ µL CSF" cut-off, but likely to gradually decrease with increasing severity, and d) even in the WBC >100 cells/ µL CSF" subgroup, fexinidazole shows considerable activity (> 80% success rate). The SmPC provides the relevant caution (section 4.4. SmPC) for the use of fexinidazole in patients with severe CNS involvement and emphasizes the need for hospitalization for these patients. More generally, the issue of compliance with treatment was considered in the light that for the trials, patients were hospitalized and thus findings do not allow for conclusions on the success and potential consequences of failure if treatment is unsupervised. As such, the applicant agreed to limit the administration of fexinidazole, in all cases, under the supervision of trained health staff, to ensure full compliance with the therapy (especially in view of the need to take tablets with food; and the higher propensity of nausea and vomiting noted in the trials). For patient at higher risk of failure with fexinidazole, with higher disease severity, with lower potential of compliance, in patients with psychiatric disorders, and in children with ≤35 kg, the administration of fexinidazole should occur in the hospital setting. Additionally, the follow-up monitoring is advised up to 24 months, to ensure the surveillance of potential relapses, as the pivotal study results indicated the possibility for such a late event.

As regards safety, potential risks include vomiting and pro-arrhythmic effects. For the latter, appropriate contra-indications and warnings have been introduced and a prospective, observational safety study with use of

fexinidazole will be conducted. In addition, a drug-drug interaction study with concomitant drugs that are metabolized by CYP1A2 and CYP2A19 is planned.

3.7.2. Balance of benefits and risks

The benefit -risk balance of fexinidazole administered as an oral dose regimen for adult and paediatric (aged 6 or more) patients with haemo-lymphatic (Stage 1 and early stage 2) human African trypanosomiasis 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 is considered as favourable. This treatment fulfils an unmet need in providing an oral alternative to the currently available treatment options, potentially allowing quicker and wider access to treatment. The Product Information has been updated to include a statement that fexinidazole therapy given in late stage 2 patients with higher severity (CSF-WBC > 100/µl) has shown an unacceptable lower efficacy in comparison to NECT and therefore its use in this sub-group should only be advised when no other adequate treatment is available or tolerated and for such cases, patients should be hospitalised for the whole treatment course. Additionally, with a recognised higher risk of relapse following 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. Patients and health care staff should be made aware to this risk of late relapse following therapy with fexinidazole and a most appropriate local arrangement should be in place to provide the optimum achievable follow-up. Fexinidazole should be administered to all eligible patients under strict supervision by trained health staff, fully understanding the need for an effective treatment course, and who need to confirm that the patient is in fed condition and also directly observe each tablet intake.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall benefit-risk balance of Fexinidazole Winthrop is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Fexinidazole Winthrop in 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 is favourable. This opinion is based upon the benefit-risk scenarios on the populations and conditions of use as documented with clinical data by the applicant.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the scientific opinion

- **Periodic Safety Update Reports**

The scientific opinion holder shall submit the first periodic safety update report for this product within 70 calendar days after the data lock point of 15/05/2019. Subsequently, the scientific opinion holder shall submit periodic safety update reports for this product every 6 months until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The scientific opinion holder shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the scientific opinion application and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Fexinidazole Winthrop in target countries, the scientific opinion holder must agree the content and format of the controlled access programme, the controlled distribution system, and the educational programme, including communication media and distribution modalities, with the National Competent Authority.

The controlled access programme, the controlled distribution system, and the educational programme are aimed at ensuring that patients are informed on the safe use of the medicine, and that they are supervised by trained health care staff.

The scientific opinion holder shall ensure that in each country where Fexinidazole Winthrop is marketed, all healthcare staff and patients/carers who will use Fexinidazole Winthrop have access to/are provided with the following educational package:

- Healthcare staff educational material
- Patient information pack

Healthcare staff educational material:

- The Summary of Product Characteristics
- Guide for healthcare staff (visual aide)

Key messages for the **Guide for healthcare staff**:

  - That the healthcare staff should instruct the patients/carers on how Fexinidazole Winthrop should be taken, and give guidance in case of adverse events;
  - That there is a risk of psychiatric events when using the medicine they need to be aware of;

- It should advise the healthcare staff how to continue the treatment after repeated events of patient vomiting;
- That the healthcare staff should convey to the patients/carers the importance of contacting them in the case of a second event of vomiting;
- That the healthcare staff should monitor the completion of the treatment.

The patient information pack:

- A patient/carer guide (visual aide)

Key messages for the **Patient/carer guide**:

- Mode of administration of Fexinidazole Winthrop;
- That the treatment will be initiated and supervised by a trained healthcare staff.