14 December 2023
EMA/582593/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Fexinidazole Winthrop

International non-proprietary name: fexinidazole

Procedure No. EMEA/H/W/002320/II/0016

Note

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

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List of abbreviations

AE: Adverse event

AEs: Adverse events

AESI: Adverse event of special interest

AIDS: Acquired immunodeficiency syndrome

ALT: Alanine aminotransferase

API: Active pharmaceutical ingredient

A.R.: Analytical reagent

AST: Aspartate aminotransferase

ATC: Anatomical Therapeutic Chemical

AUC: Area under the curve

$AUC_{0-\infty}$: Area under the curve from time zero to infinity

b.i.d: Twice daily

BBB: Blood-brain barrier

BLOQ: Below limit of quantification

BP: Blood pressure

CD: Chagas Disease

CHMP: Committee for Medicinal Products for Human Use

CI: Confidence interval

CL/F: Apparent clearance

CLM1: Apparent clearance of M1

CLM2: Apparent clearance of M2

C_{max}: Maximal concentration

CNS: Central nervous system

Conc.: Concentration

COVID-19: Coronavirus disease 2019

CRF: Case report form

CS: Clinically significant

CS: Cockayne Syndrome

CSF: Cerebrospinal fluid

CSR: Clinical study report

CV %: Coefficient of variation

CYP: Cytochrome

CYP: Cytochrome P450

D1: Duration of absorption

DALA: Drug abuse liability assessment

DBS: Dried blood spot

DNA: Deoxyribonucleic acid

DNDi: Drugs for Neglected Diseases initiative

DRC: Democratic Republic of the Congo

DSMB: Data safety monitoring board

DSUR: Development safety update report

ECG: Electrocardiogram

EEG: Electroencephalogram

EMA: European Medicines Agency

EML: Essential Medicines List

EOH/EoH: End of hospitalisation

EOS: End of study

EOT/EoT: End of treatment

EP: Evaluable patients (population)

EU-M4all: European Union Medicines for all

FDA: Food and Drug Administration

G6PD: Glucose-6-phosphate dehydrogenase

GCP Good Clinical Practice

g-HAT: Gambiense human African trypanosomiasis or human African trypanosomiasis due to *Trypanosoma brucei gambiense*

GLP: Good Laboratory Practice

HAT: Human African Trypanosomiasis

HCPs: Health care professionals

HIV: Human immunodeficiency virus

HPLC: high performance liquid chromatography

HR: Heart rate

I.D.: Internal diameter

IC50: Concentration to reach 50% of inhibitory growth

ICF: Informed consent form

ICH: International Council for Harmonisation of Technical Requirements for

ID: Identification

IMP: Investigational medicinal product

IMPAMEL: Improved application of melarsoprol (clinical program)

ITT: Intention to treat

IV: Intravenous

LAMP: Loop-mediated isothermal amplification

k12: Micro rate constant from compartment 1 to compartment 2

k23: Micro rate constant from compartment 2 to compartment 3

M1: Metabolite 1, Fexinidazole sulfoxide (fexinidazole metabolite)

M2: Metabolite 2, Fexinidazole sulfone (fexinidazole metabolite)

mAECT: Mini-anion exchange centrifugation technique

mAECT-BC: Mini-anion exchange centrifugation technique on buffy coat

MedDRA: Medical Dictionary for Regulatory Activities terminology

MHCT: Microhaematocrit centrifugation technique

MIC: Minimal inhibitory concentration to completely inhibit parasite growth

min: minute

mITT: Modified intention to treat

MoA: Mode of action

MS: Missing sample

MSF: Médecines Sans Frontières

n: Number of samples

NA/NAP: Not applicable

NDA: National Drug Authority

NECT: nifurtimox-eflornithine combination therapy

NHSRC: National Health Science Research Committee

NR: Not reportable

NSSCP: National sleeping sickness control programs

PASS: Post-authorisation safety study

PBRER: Periodic benefit-risk evaluation report

PC: Poor chromatography

PCR: polymerase chain reaction

PD: Pharmacodynamic

pdeath: Proportion of deaths

PL: Package leaflet

PK: Pharmacokinetic / Pharmacokinetics

population PK / popPK: Population pharmacokinetic(s)

POS: Powder for oral suspension

PT: Preferred term

PTRE: Post-treatment reactive encephalopathy

qPCR: Quantitative polymerase chain reaction

QTc: QT interval on electrocardiogram corrected

QTcF: QT interval on electrocardiogram corrected according to the Fridericia's formula

r-HAT: Human African trypanosomiasis due to *T. b. rhodesiense* or Rhodesiense human African trypanosomiasis

RMP: Risk management plan

RNA: Ribonucleic acid

RT: Reverse transcription

RT-qPCR: Reverse transcription-quantitative polymerase chain reaction

SAE: Serious adverse event

SAP: Statistical analysis plan

SBP: Systolic blood pressure

SD: Standard deviation

SmPC: Summary of product characteristics

SNR: Sample not received

SOC: System organ class

SOH: Scientific opinion holder

T. b. / *T. brucei*: *Trypanosoma brucei*

t.i.d: Three times per day

$t_{1/2}$: terminal elimination half-life

TC: Treatment completer(s)

TEAE / TEAEs: Treatment-related adverse event / Treatment emergent adverse events

TPP: Target product profile

USA: United States of America

v/v: Volume per volume

V1/F: Apparent volume of distribution

VL: Visceral leishmaniosis

WBC: White blood cells

WHO: World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Sanofi Winthrop Industrie submitted to the EMA on 30 May 2023 an application for a variation[1] to the CHMP Scientific Opinion.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of both first stage (haemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei rhodesiense for FEXINIDAZOLE WINTHROP based final results from study DNDI-FEX-07-HAT - Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to Trypanosoma brucei rhodesiense: a multicentre, open-label clinical trial; this is a phase-II/III, multicenter, open-label, non-randomized, single-arm clinical trial to assess the efficacy and safety of fexinidazole in patients with r-HAT. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet, and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity.

Not applicable

Scientific advice

The SOH received Scientific Advice from the CHMP on the 16 December 2021 (EMADOC-360526170-923213) and a follow up Scientific Advice on the 23 February 2023 (EMADOC-360526170-1354001). The initial Scientific advice pertained to clinical development aspects regarding the acceptability of the study DNDi-FEX-07-HAT to support the extension of indication including the sample size as well as to the regulatory submission strategy. On the follow up Scientific Advice the SOH requested advice on the duration of the follow up in study DNDiFEX007 and on the proposal to review the available efficacy and safety data about melarsoprol in r-HAT patients to contextualise results from single arm fexinidazole study (DNDiFEX007).

[1] Which corresponds, by analogy, to a Type II variation pursuant to Commission Regulation (EC) 1234/2008

1.2. Steps taken for the assessment.

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

Rapporteur: Fátima Ventura Co-Rapporteur: N/A

Timetable	Actual dates
Submission date	30 May 2023
Start of procedure	17 June 2023
CHMP Rapporteur Assessment Report	11 August 2023
PRAC Rapporteur Assessment Report	16 August 2023
PRAC Outcome	31 August 2023
CHMP members comments	4 September 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 September 2023
Request for supplementary information (RSI)	14 September 2023
CHMP Rapporteur Assessment Report	14 November 2023
PRAC Rapporteur Assessment Report	30 October 2023
PRAC members comments	22 November 2023
Updated PRAC Rapporteur Assessment Report	24 November 2023
PRAC Outcome	30 November 2023
CHMP members comments	4 December 2023
Updated CHMP Rapporteur Assessment Report	7 December 2013
CHMP Scientific Opinion	14 December 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Rhodesiense human African trypanosomiasis (r-HAT) is a rare disease qualified as “the neglected among the neglected diseases” that contributes to a small proportion of HAT cases (<2% in 2012 and about 7% in 2021).

Rhodesiense-HAT is depicted as the acute and aggressive form of HAT, as the first symptoms appear within 1 to 3 weeks, and the progression from first to second stage occurs within 3 to 8 weeks.

It is noteworthy that r-HAT and Gambiense human African trypanosomiasis (g-HAT) diseases differ in most of their characteristics (see Table below). Rhodesiense trypanosomiasis is a zoonotic disease with humans being accidental hosts, unlike gambiense trypanosomiasis for which humans are the primary hosts. *T. b. rhodesiense* parasites are transmitted by tsetse flies of the *Glossina morsitans* group, living in drier and more open areas of woodlands and savannahs than the tsetse flies of the *Glossina palpalis* group living in

riverine and forest areas and which transmit g-HAT disease. Wildlife and domestic animals (mainly cattle) constitute the animal reservoirs of *T. b. rhodesiense* parasites, which technically prevents the eradication of r-HAT cases in humans. Wildlife animals may get infected by various species of trypanosomes and develop trypanotolerance including for r-HAT.

Table 1. Characteristics of Rhodesiense versus Gambiense trypanosomiasis

Parameters	Rhodesiense (r-HAT) disease	Gambiense (g-HAT) disease
Parasite	*T. b. rhodesiense*	*T. b. gambiense*
Transmission	Tsetse fly bite *Glossina morsitans group*	Tsetse fly bite *Glossina palpalis group*
Reservoir	Domestic animals (cattle), wild-life game animals **Zoonotic disease** leading to r-HAT **outbreaks**	Humans
Duration	Weeks to a few months **Acute**	2 to 3 years Chronic
Location	East and Southeastern Africa (Malawi, Uganda, Zambia, United Republic of Tanzania, Zimbabwe)	West Africa (DRC, Angola, CAR, Guinea, Congo, Gabon, Chad, Cameroon, South Sudan)
Epidemiology	Neglected tropical disease (NTD) Rare 86/6314 cases (2%) in 2013 55/802 cases (7%) in 2021	Neglected tropical disease (NTD) Decreasing prevalence 6228/6314 cases (98%) in 2013 747/802 cases (93%) in 2021
Disease stages	FIRST STAGE: blood and lymph ≤5 WBC/µL and no trypanosomes in CSF SECOND STAGE: CSF and central nervous tissues ↑ in WBC count in the CSF or presence of parasites in the CSF >5 WBC/µL and/or trypanosomes in CSF	
Time to first symptoms onset	**1 to 3 weeks**	First months: minimal, intermittent
Progression to stage 2	**Fast CNS invasion:** 3 to 8 weeks	Slow CNS invasion: ≥1 year
Clinical signs and symptoms often present	Red sore at bite site called "chancre" Fever (≥37.5°C), lymphadenopathy, headache, tremor, somnolence **Elevated blood parasitaemia (10.10^3 cells/mL)** Impairment of thyroid, neuroendocrine, adrenocortical, and cardiac functions Organ failure may lead to death	Chronic and intermittent fever, lymphadenopathy, headache, pruritus, insomnia Low blood parasitaemia (<100 cells/mL) Musculoskeletal pain and enlargement of the liver and spleen Cardiac involvement
	In general, similar clinical signs and symptoms in pediatric patients	
Outcome	Fatal if left untreated	
Screening tests	**None**	CATT
Oral therapy	**None**	Fexinidazole (for both stages)
First-line stage-1 therapy	Suramin, IV	Fexinidazole, PO[a]
First-line stage-2 therapy	Melarsoprol, IV Twice higher risk of ES in r-HAT than g-HAT Higher CFR due to melarsoprol- in r-HAT than in g-HAT patients	Fexinidazole, PO NECT (PO/IV) if severe disease (WBC-CSF ≥100 cells/µL)
Relapse	**Early** with acute symptoms including rapid death (within 2 weeks to 3 months)[b]	Late relapse (within 12 to 18 months after treatment)

Abbreviations: **CAR**, Central African Republic; **CATT**, card agglutination test for trypanosomiasis; **CFR**, case fatality rate; **CNS**, central nervous system; **CSF**, cerebrospinal fluid; **DRC**, Democratic Republic of the Congo; **ES**, encephalopathic syndrome; **g-HAT**, human African trypanosomiasis due to *T. b. gambiense*; **IM**, intramuscular; **IV**, intravenous; **NECT**, nifurtimox-eflornithine combined therapy; **PO**, per oral; **r-HAT**, human African trypanosomiasis due to *T. b. rhodesiense*; ***T. b.***, *Trypanosoma brucei*; **WBC**, white blood cells

Source: WHO reports (1, 7), WHO (6, 5), Checchi (15) Seixas (16)

a Pentamidine IV or IM as first-line therapy for children aged <6 years and weighing <20 kg (1)

b According to data reported in IMPAMEL III study (17) and WHO report (7)

Claimed therapeutic indication

This dossier submitted for this application proposed to extend the current approved indication for fexinidazole in the treatment of g-HAT to HAT due to *T. b. rhodesiense*:

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

Epidemiology and risk factors, screening tools/prevention

Uganda was recently validated for g-HAT elimination as a public health problem, and the number of r-HAT detected cases has steadily decreased over the past 10 years in Uganda. Cattle insecticide spraying and r-HAT case detection at cattle marketplaces are strongly recommended to progress towards r-HAT elimination.

People at high risk of r-HAT infection are workers with activities close to tsetse fly habitats such as riverine thickets. Depending on the type of occupation, women are at higher risk of r-HAT infection than men, i.e., when collecting water, mushrooms or firewood, whereas the reverse applies for men when herding cattle, fishing, hunting and honey collecting.

Because of the animal reservoirs of *T. b. rhodesiense*, the interactions between cattle with tsetse flies and their proximity with wildlife animals further increase the risk of disease transmission to humans. Families living at the periphery of villages and closer to animal reservoirs are at higher risk of disease transmission. When a family member gets sick, the rest of the family is at high risk of contracting the disease. The type of plants cultivated around homesteads also seems to impact the risk of r-HAT transmission (e.g., lower with bananas than cassava).

In the latest geographical report about HAT covering 2016 to 2020 about 69 000 km^2 were estimated to be at risk of *T. b. rhodesiense* infection, with no area at high or very high risk, and only 9403 km^2 at moderate risk. Zambia is the country with the largest area at risk (34 525 km^2), followed by Tanzania (12 519 km^2) and Malawi (8992 km^2). Over 2016 to 2020, 2.5 million subjects were estimated to be at risk of r-HAT, without any subject at very high or high risk, and 6% at moderate risk (141 000 persons) of which the majority (89%) was in Malawi (126 000 persons). Of note, the proportion of the at-risk population potentially covered by fixed health facilities is lower for r-HAT than for g-HAT.

In non-endemic countries, 35/49 (71%) cases diagnosed over 2011 to 2020 were r-HAT cases, mostly stage-1 r-HAT (91%). These “exported cases” were acquired by tourists visiting national parks and wildlife reserves and their incidence has increased over the past 10 years in contrast to the incidence of the disease in endemic countries. The data from non-endemic countries strongly suggest a problem of under-detection of endemic r-HAT cases.

Most r-HAT cases are diagnosed at late stages because of the absence of specific early clinical signs and symptoms, and the fast progression of the disease. Many cases of r-HAT are believed to remain under-reported because of the lack of screening tests and the low awareness of the disease by the population and health-care workers. Using a decision-tree model to evaluate under-detection during an epidemic outbreak in Uganda, it was estimated that up to 39% of cases and 92% of deaths had not been reported. The progression of rapid diagnostic tests for malaria has further reduced the detection of r-HAT parasites during microscopic blood examination. The coronavirus disease 2019 (COVID-19) pandemic has likely led to r-HAT under-detection and late diagnosis.

The longer the time before r-HAT diagnosis, the higher the risk of patient’s death either from the disease itself or the adverse reactions to the arsenic-based therapy, namely melarsoprol.

Among 13 r-HAT endemic countries, 6 reported cases over the past 10 years. Although the number of r-HAT cases had decreased sharply over 2012 to 2018, r-HAT evolves through outbreaks that can rapidly modify this trend (Table below).

Considering the epidemiology of Rhodesiense trypanosomiasis, DNDi focused on the 2 countries that had reported the highest numbers of cases over 2012 to 2018 (Malawi and Uganda) to set up the protocol of

Study DNDi-FEX-07-HAT, which was finalised in 2018 (Table below).

Table 2. Number of Rhodesiense trypanosomiasis cases by endemic country over 2012 to 2021

Country	2012	2013	2014	2015	2016	2017	2018 [b]	2019	2020	2021
Kenya	2	0	0	0	0	0	0	0	0	0
Malawi	**18**	**35**	**32**	**30**	**35**	**7**	**15**	**91**	**89**	**49**
Uganda	**71**	**43**	**70**	**28**	**10**	**13**	**4**	**5**	**2**	**2**
Tanzania [a]	4	1	1	2	4	3	0	3	1	1
Zambia	6	6	12	9	4	3	5	15	6	3
Zimbabwe	9	1	3	3	1	1	0	2	0	0
Total	**110**	**86**	**118**	**72**	**54**	**27**	**24**	**116**	**98**	**55**

Source: WHO Global Health Repository (5), last update 21 July 2022; Data presented in Table 2 includes updated data from Table 3

a United Republic of Tanzania

b The protocol of DNDi-FEX-07-HAT was finalized in November 2018

DNDi also used epidemiologic data reported by the WHO, such as the number of r-HAT patients who received treatment (suramin for stage 1 and melarsoprol for stage 2), and the overall number of patients who died during hospitalization (Table below). The case-fatality rate (CFR) (calculated by using the overall number of r-HAT cases as a denominator and not the overall number of stage-2 r-HAT patients, who are at higher risk of death either from disease or treatment) which remained high in Malawi in 2018 (13%), was likely due to late disease diagnosis and severe adverse drug reactions, however, the fatality rates presented are likely under-estimated because of case and death underreporting. Of note, these fatality rates were:

Table 3. Treated Rhodesiense cases and fatality rates over 2014 to 2018 in Malawi and Uganda

Country	Parameters	2014	2015	2016	2017	2018
Malawi (4 sites to treat patients)	Treated cases	36	25	35	11	15
	Stage 1	3	20[a]	2	1	5
	Stage 2	33	5[a]	33	10	10
	Deaths	7	3	2	1	2
	Fatality rates (%)	7/36 (19.4%)	3/25 (12%)	2/35 (5.7%)	1/11 (9.1%)	2/15 (13.3%)
Uganda (10 sites to treat patients)	Treated cases	69[b]	28	10	13	3[b]
	Stage 1	*14*	10	4	2	*2*
	Stage 2	*56*	18	6	11	*2*
	Deaths	1	2	0	0	0
	Fatality rates (%)	1/69 (1.4%)	2/28 (7%)	0/10 (0%)	0/13 (0%)	0/3 (0%)

Source: WHO third stakeholders meeting on r-HAT (30), 10-11 April 2019

a There was likely a permutation between stage 1 and stage 2 for treated cases as reported by Lemerani et al. (38)

b One of the reported cases was not treated, but the disease stage of this case was not specified in the report

Clinical presentation, diagnosis and stage/prognosis

Three forms of r-HAT disease have been described in the literature: asymptomatic, subacute as well as acute infections.

Overall, r-HAT disease is an acute disease in contrast with the chronic g-HAT disease. In a few weeks *T. b. rhodesiense* parasites reach high levels in the blood and lymph and colonize the CNS, thereby starting a lethal neuropathogenic process of infection. In endemic countries, this fast progression to a severe disease is exacerbated by the lack of disease awareness and its under-detection.

Both r-HAT and g-HAT diseases are defined by 2 main stages: a first stage with parasites located in the blood and lymph (hemo-lymphatic stage 1) showing mostly unspecific symptoms, then starts a characteristic disruption of the circadian rhythm of the sleep/wake cycle and a second stage with parasites that have crossed the blood-brain barrier (BBB) and colonized the CSF and central nervous tissues (meningo-encephalitic or stage 2), with resulting neurological symptoms which, if untreated, lead to somnolence, wasting, coma and death. These 2 stages are identified by the increase of the WBC count or the presence of parasites in the CSF. This stage distinction had been artificially set up to decide when the patient required a therapeutic drug able to cross the BBB.

Some initial clinical signs and symptoms are more frequent in r-HAT than g-HAT patients, such as fever (≥37.5°C), elevated blood parasitemia and the local skin reaction called “trypanosomal chancre” in stage-1 patients. Because of passive screening and acute evolution, r-HAT diagnosis is often done at late stages, with severe headaches, pruritus, metabolic abnormalities and sleep disturbances (leading to the name of “sleeping sickness”) dominating the clinical presentation. Moreover, impairment of thyroid, neuroendocrine, adrenocortical and cardiac function are more frequent in r-HAT than g-HAT patients.

Most clinical signs and symptoms of each HAT disease stage are seen at similar frequencies in children, including sleep disturbances. More infants are seen at the late stage, most likely because of a delayed diagnosis and the immaturity of the BBB.

If left untreated r-HAT patients generally suffer from central nervous system (CNS) impairment and usually die within 4 to 6 months from cardiac failure and arrest.

In contrast to g-HAT diagnosis, no serological tests are available for r-HAT diagnosis, which depends on the microscopic detection of parasites mainly in blood and CSF from clinical suspects. Both *T. b. rhodesiense* and *T. b. gambiense* trypanosomes can only be distinguished from each other by molecular biological tests that are not available in most African health facilities with HAT expertise. Trypanosome distinction therefore relies on the specific geographical distribution of each subspecies: *T. b. rhodesiense* in East and South-Eastern Africa (e.g., Malawi, Uganda, United Republic of Tanzania, Zambia, Zimbabwe) and *T. b. gambiense* in West and Central Africa (e.g., DRC, Angola, Central African Republic, Guinea, Congo, Gabon, Chad, Cameroon, South Sudan, Equatorial Guinea, Ivory Coast).

Management

To treat stage-2 r-HAT patients, the drug needs to cross the BBB, which implies to identify the stage of the disease for treatment decision making. This is performed via an invasive lumbar puncture to collect CSF samples in which WBC and parasite levels are evaluated:

- first stage: WBC count ≤5 cells/µL and no trypanosomes in CSF
- second stage: WBC count >5 cells/µL and/or trypanosomes in CSF

Despite their potential toxicity, 2 drugs are recommended by the WHO as first-line therapies to treat r-HAT patients as they are currently the only available therapies (7): suramin for stage-1 and melarsoprol for stage-2 r-HAT adult and pediatric patients.

- Suramin is derived from the trypan blue dye and has been used to treat HAT since 1922 (39). It is highly bound to plasma proteins (about 99.7%), has a long half-life (about 36 to 60 days) (37)

and is mainly eliminated by renal excretion (40). Suramin is associated with several side effects (e.g., nephrotoxicity, hemolytic anemia, peripheral neuropathy, bone marrow toxicity), but severe adverse reactions are rare and associated with the overall health status of the patient (e.g., concomitant disease, nutritional status). Although deaths have been reported in patients on suramin, it used to be considered as the safest drugs for stage-1 r-HAT.

- Melarsoprol is an organo-arsenic compound (diluted in propylene glycol) that has been used to treat HAT since 1949. It is rapidly metabolized into active metabolites that reach in the CSF 3% of their plasma levels and are eliminated mainly via the urine and the bile. Melarsoprol is frequently associated with severe complications as the encephalopathic syndrome or post-treatment reactive encephalopathy (PTRE) occurs in up to 10% of melarsoprol-treated patients (regardless of HAT type) and may result in a “cytokine storm” leading to death in 10% to 50% of the cases .Other common adverse reactions observed with melarsoprol include skin (pruritus, rashes and exfoliative dermatitis <1%), gastrointestinal (nausea, vomiting, abdominal pain, diarrhea), neurological (headache) and cardiac disorders (chest pain, tachycardia, failure). Occasional adverse reactions are peripheral motor or sensorial neuropathy, renal dysfunction and hepatotoxicity. Intravenous injections of melarsoprol are painful and often cause thrombophlebitis and vein fibrosis.

  Melarsoprol regimens have been set up empirically and vary between countries (e.g., 3 or 4 series of 3 days separated by 1-week intervals for up to 1-month hospitalization). The 10-day schedule of melarsoprol was implemented of the “Improved application of melarsoprol” (IMPAMEL) clinical program in g-HAT (IMPAMEL I and II) patients and (IMPAMEL III) in r-HAT patients. In the IMPAMEL III clinical trial, all cases of melarsoprol therapy failures in r-HAT patients at discharge corresponded to death cases related to drug or disease (9/107, failure rate of 8.4% at discharge), whereas 1 relapse case and 3 death cases were reported at the 12-month visit (13/107, failure rate of 12.1% at 12 months). Moreover, cases of melarsoprol resistance have been described, further emphasizing the need of a new therapy for stage-2 r-HAT patients.

Table 4. Treatments for Rhodesiense trypanosomiasis in adult and pediatric patients living in endemic countries at the time of fexinidazole clinical development program

r-HAT stage	Drug name (marketing date)	Route, dose[a]	Comments
Stage 1	Suramin (1922) (Germanin®, Bayer)	Test dose (4 to 5 mg/kg) then weekly slow IV injections (20 mg/kg not >1 g) on Days 3, 10, 17, 24 and 31	Need skilled health-care workers Potential moderate toxicity Long therapy (5 weeks) Remains first-line therapy in stage-1 r-HAT
Stage 2	Melarsoprol (1949) (Arsobal®, Sanofi)	2.2 mg/kg/day slow bolus IV injection for 10 days	Need skilled health-care workers Severe adverse reactions Painful injections Potential parasite resistance Remains the only drug effective in stage-2 r-HAT

Abbreviations: **IV**, intravenous; **r-HAT**, human African trypanosomiasis due to *T. b. rhodesiense*

a The WHO (7) and MSF (48, 49) recommend the same dosages in adult and pediatric patients (no specific age or bodyweight), but for suramin the Centers for Disease Control and Prevention (CDC) (50) recommends: test dose 2 mg/kg (maximum 100 mg), and treatment dose: 10–15 mg/kg (maximum 1 g) for pediatric r-HAT patients.

Source: WHO (7), MSF (48, 49) and CDC (50)

While only IV and potentially toxic drugs are available and recommended to treat r-HAT patients, g-HAT patients (aged ≥6 years and weighing ≥20 kg) benefit from fexinidazole as an oral treatment for both the first and second stages of the disease (in patients with WBC count in CSF <100 cells/µL) since 2020.

Furthermore, stage-2 r-HAT patients are at high risk of death not only resulting from the disease itself, but also from melarsoprol, which remains the only indicated treatment. Of note, r-HAT patients treated with melarsoprol face a twice higher risk of encephalopathic syndrome than g-HAT patients (median risk: 10.6% versus 5.6%), which illustrates again the higher severity of r-HAT disease (see Table below).

Table 5. Summary of the incidence rates of encephalopathic syndrome and death in HAT patients

Parameters	r-HAT	g-HAT
	Numbers	
Total number of HAT patients	2934	11 665
Melarsoprol treated patients	1715	8152
Number of ES cases	149	384
	Average, median [minimum to maximum]	
Incidence risk of ES	10.6%, 10.6% [1.5% to 28.0%]	4.3%, 5.6% [1.5% to 23.5%]
HAT mortality	11.6%, 11.5% [5.2% to 19.0%]	9.4%, 6.3% [2.7% to 34%]
Death due to ES	42.2%, 46.0% [6.6% to 100.0%]	46.4%, 44.4% [13.7% to 100%]
Case Fatality Rate of ES	57.3%, 52.6% [21.4% to 100.0%]	43.8%, 50% [33% to 100%]

Abbreviations: **ES**, encephalopathic syndrome; **HAT**, human African trypanosomiasis due to *T. b. rhodesiense* (**r-HAT**) or *T. b. gambiense* (**g-HAT**) parasites

Source: J. Seixas PhD thesis (16)

Because of the animal reservoir for *T. b. rhodesiense* parasites, r-HAT evolves by outbreaks which would be faster controlled by an oral therapy, with the potential to be administered in the field, thereby increasing access to therapy, and reducing the interval between diagnosis and treatment initiation.

The limitations associated with the first-line current therapies for r-HAT include:

- The absence of a well-tolerated life-saving treatment, in particular for stage-2 patients;
- The absence of a common treatment for both r-HAT stages, which would negate the necessity of disease staging via lumbar puncture;
- The mandatory hospitalization for IV injections for suramin or melarsoprol therapies;
- The elevated direct and indirect costs of invasive IV therapies;
- The increased risk of infections resulting both from lumbar punctures and repeated IV injections of suramin or melarsoprol therapies;
- The reported cases of resistance to melarsoprol; and
- The limited access to treatment for patients living in remote areas

At the WHO network meeting for HAT elimination about the “oral treatment for rhodesiense HAT. Perspectives for a trial on fexinidazole”, HAT stakeholders and endemic countries requested the development of new drugs and defined a Target Product Profile (TPP) for r-HAT:

- An oral 10-day treatment to be used for both stages in adult (including pregnant women) and pediatric patients;
- A better safety profile (acceptable <1% drug-related mortality) than that of melarsoprol; and
- An acceptable efficacy outcome for the oral treatment (acceptable >88% at 12 months as for the standard IV treatment).

The HAT experts and endemic countries also agreed on the proposed study design in r-HAT patients:

- Multi-country, multicentre, prospective, one-arm trial;
- Second-stage cohort as the urgency is to replace melarsoprol (if no treatment related-death in 10 stage-2 patients at end of hospitalization [EOH]), then a first-stage cohort could be analyzed in futility analysis;
- The threshold of unacceptable failure rate (death or presence of trypanosomes) at end of treatment could be set at 9%.
- The effectiveness endpoints at 6 and 12 months should be planned with higher thresholds up to 12% at one-year follow-up (failure: r-HAT related death-according to data safety monitoring board [DSMB] opinion -or relapse);
- General good health status during follow up is considered as treatment success.

Because melarsoprol iatrogenic deaths in the latest clinical trial (IMPAMEL III) corresponded to most deaths of r-HAT patients during treatment (8/9, 89%), the SOH considers that fexinidazole represented a well-tolerated therapeutic option to fulfil the unmet needs in the treatment of r-HAT patients and participate in the maintenance of the elimination of r-HAT as a public health problem by 2030.

In addition to these drugs, pentamidine can be also noted. However, pentamidine is not recommended as first-line in r-HAT in endemic countries because of reported therapy failure cases. However, it has been used occasionally to treat stage-1 r-HAT patients with success in non-endemic countries, where pentamidine is available as it may be used for other indications. Pentamidine has not been recently tested in r-HAT patients because it barely crosses the BBB and the urgent need for a new treatment for r-HAT was identified for stage-2 patients.

At the 2nd WHO stakeholder meeting about r-HAT in 2017, in addition to better surveillance systems, screening and diagnostic tools, there was a “strong demand from endemic countries to extend the clinical trials of fexinidazole as a treatment for r-HAT”. In contrast with fexinidazole, NECT is presumed not to be effective against r-HAT because eflornithine had only a weak activity against *T. b. rhodesiense* in vitro.

The ultimate objective of the fexinidazole development program for r-HAT is to provide an alternative therapy to available r-HAT treatments with a short course, oral, stage-independent (i.e., crossing the BBB), well-tolerated and effective therapeutic option.

2.1.2. About the product

On 15 November 2018, fexinidazole was granted a positive opinion under Article 58 of Regulation (EC) No. 726/2004 (now named European Union Medicines for all or “EU-M4all”) by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) to be used outside the European Union for both stages of g-HAT in adult and paediatric patients (aged ≥6 years and weighing ≥20 kg).

Fexinidazole was subsequently registered for this indication by two endemic countries, the Democratic Republic of the Congo (DRC) on 24 December 2018 and Uganda on 05 October 2021, and by the United States on 16 July 2021.

In addition, fexinidazole is currently distributed by the World Health Organization (WHO) in the remaining g-HAT endemic countries (Angola, Burkina Faso, Cameroon, Congo, Central African Republic, Chad, Equatorial Guinea, Gabon, Guinea and South Soudan).

In 2019, the WHO generated interim guidelines for the treatment of g-HAT and recommended to use fexinidazole as a first-line treatment in patients aged ≥6 years and weighing ≥20 kg and in first-stage or non-severe second-stage (i.e., white blood cell [WBC] count in the cerebrospinal fluid [CSF] <100 cells/µL). The WHO also added fexinidazole to the WHO Essential Medicines List (EML) for adults and for children (EMLc) for this same indication.

Fexinidazole is a member of the 5-nitroimidazole group which belongs to the antiparasitic class. As indicated in the current approved SmPC for fexinidazole, no specific studies have been performed to assess the mode of action (MoA) of fexinidazole and its 2 metabolites, fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The fexinidazole HAT clinical development program includes data from r-HAT and g-HAT patients (see original application dossier for g-HAT patients).

On 5 March 2021, Sanofi and DNDi presented to the WHO the potential early submission to the EMA of fexinidazole extension of indications in r-HAT (type-II variation) to optimize the early fexinidazole access as in the context of r-HAT outbreaks even more patients could benefit of a well-tolerated oral treatment. The WHO supported the strategy of the accelerated proposal based on an initial report containing the data of about 70% of the patients having completed the 12-month follow up and the availability of the remaining follow-up data during the evaluation by the EMA under the EU-M4all procedure considering the urgent need for an alternative well-tolerated treatment to melarsoprol. The WHO specified that the guidelines about r-HAT treatment will be updated on the basis of the final results of the fexinidazole study and once a positive opinion would have been issued by the EMA.

A phase-II/III efficacy and safety study was conducted in adult and paediatric patients with r-HAT (both stages) in Malawi and Uganda (DNDi-FEX-07-HAT). This application dossier relies on this clinical trial.

The ultimate objective of Study DNDi-FEX-07-HAT was to find an alternative treatment to both melarsoprol for stage-2 r-HAT patients and suramin for stage-1 r-HAT patients.

The same fexinidazole regimens as in g-HAT patients (see Section 4.2 of the SmPC) were used in r-HAT patients in Study DNDi FEX-07-HAT. Fexinidazole was administered in fed conditions as recommended, as food was found to increase the relative bioavailability of fexinidazole.

At the data cut-off date for the initial CSR for Study DNDi-FEX-07-HAT on 25 January 2022 the datasets were complete up to Week 9 (all evaluable patients had completed their 9-Week visit), but the datasets were still incomplete at Month 6 (6 patients ongoing) and at Month 12 at that time.

On 19 July 2021, Sanofi requested scientific advice, pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council, for the open-label design with a limited sample size to support the extension of indication, and for an early submission for a fexinidazole extension of indication (type-II variation) in r-HAT patients on the basis of the treatment phase results of all included patients and the 1-year post-treatment phase results of 2/3 of included patients.

On 16 December 2021, the CHMP acknowledged the hurdles with performing a randomized non-inferiority study considering the low sample size and mentioned the limitation to draw formal conclusions on fexinidazole efficacy relative to melarsoprol in the absence of a melarsoprol control arm.

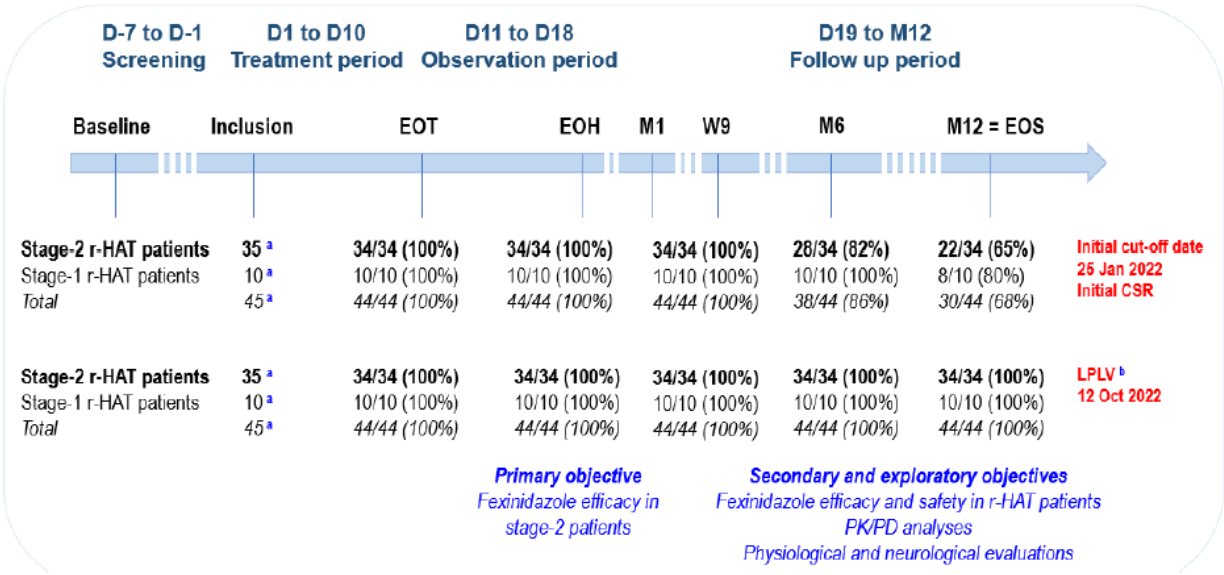
The CHMP agreed that the SOH might submit data from all subjects regarding treatment efficacy and at least 2/3 of subjects with complete 12 months follow up at the time of submission of the variation procedure in the understanding that the 12-months follow-up data of the remaining patients will be added during the procedure. The CHMP agreed to receive an early application as a type-II variation, provided a 24-month patient follow-up is reviewed as post-approval commitment. This sequential submission procedure, which should allow an earlier access to oral treatment for r-HAT.

On 05 December 2022, Sanofi requested a follow up for the initial scientific advice of the 16 December 2021 and provided additional information in particular about the differences between g-HAT and r-HAT diseases and the duration of follow up for r-HAT patients.

On 23 February 2023, the CHMP acknowledged that both evidence and time were lacking to prolong the duration of the 12-month follow up in r-HAT patients. The CHMP mentioned that after full review of the data they may be able to conclude that the completed 12-month follow-up period was sufficient.

Figure 2. Schedule of Study DNDi-FEX-07-HAT

Figure 2 - Schedule of Study DNDi-FEX-07-HAT

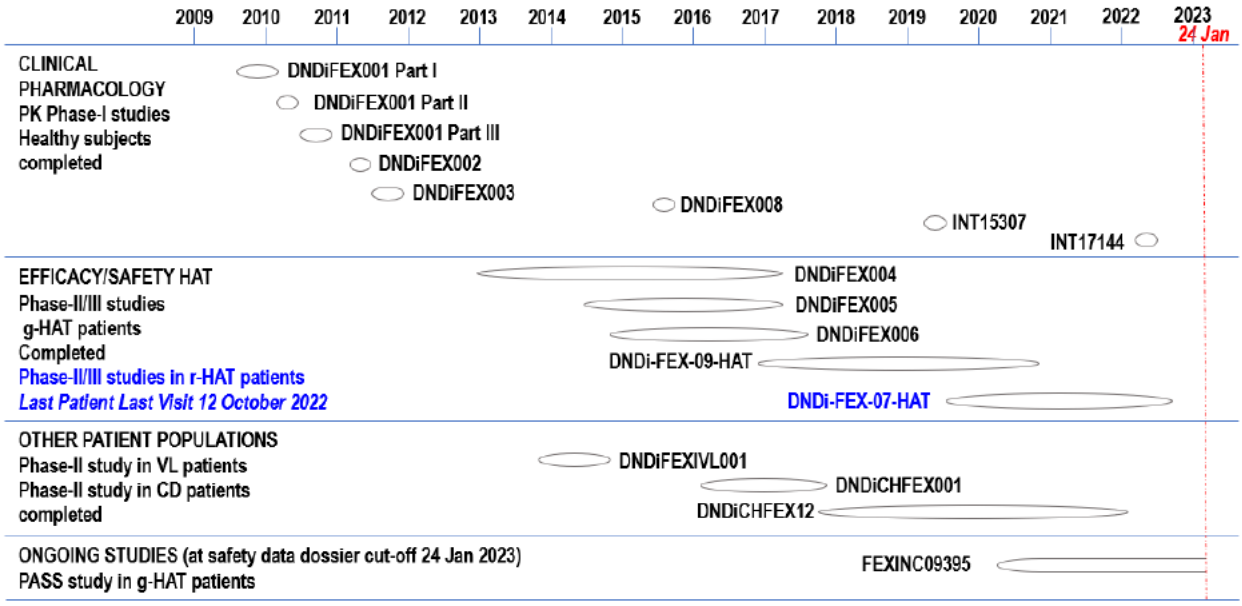


Abbreviations: **CSR**, clinical study report; **D**, day; **EOH**, end of hospitalization; **EOS**, end of study; **EOT**, end of treatment; **LPLV**, last patient last visit; **M**, month; **PD**, pharmacodynamics; **PK**, pharmacokinetics; **r-HAT**, human African trypanosomiasis due to *T.b. rhodesiense*; **W**, week

a One patient was excluded from the evaluable patient population. Patient No. 1035 died on Day 8 following an event of acute renal failure which was considered as unrelated to study drug or disease by the Investigator, the Sponsor and the independent DSMB (see Section 5.5).

b The complete datasets of patient follow up at Month 6 and Month 12 will be presented in the final CSR which will be submitted during the regulatory procedure of the type-II variation

Figure 3. Fexinidazole clinical development program



Abbreviations: **CD**, Chagas disease; **DDI**, drug-drug interactions; **g-HAT**, human African trypanosomiasis due to *T. b. gambiense*; **Jan**, January; **r-HAT**, human African trypanosomiasis due to *T. b rhodesiense*; **PK**, pharmacokinetic; **VL**, Visceral Leishmaniasis

The CHMP considered that all the concerns expressed in the previous advice regarding basing a new indication on an uncontrolled trial remain valid. The primary objective of Study DNDi-FEX-07-HAT is related to a safety parameter; to show that the fatality rate (r-HAT or treatment related death) at EOH in stage-2 patients treated with fexinidazole is smaller than a threshold of unacceptable rate of 8.5%. This threshold

has been set up according to the mortality rate obtained in stage-2 r-HAT patients treated with melarsoprol at EoH in the IMPAMEL III study and which had been rounded up to 8.5%. CHMP noted that while IMPAMEL III set out to investigate a specific melarsoprol 10-day schedule, the regimens used and still in use in different regions have not been standardised, and it is not known either if the general management of patients improved during more than one decade that elapsed between studies, which could affect the comparison.

The CHMP agreed to review a meta-analysis of data for melarsoprol collected from the literature despite the anticipation of many potential confounding factors applicable to cross-study comparisons. They specified that the relative efficacy of fexinidazole versus melarsoprol cannot be established from such an exercise.

2.1.4. General comments on compliance with GLP and GCP

- GLP

As per the Bioanalysis Project Leader Statement, the analytical work was conducted in compliance with the current Good Clinical Practice standards (ICH E6) and the EMA GCP Inspectors Working Group reflection paper, the analytical protocol (approved on 29 July 2020), the amendment no. 1 (approved on 23 December 2021) and following the Standard Operating Procedures currently in use in the Bioanalysis Department at SGS Life Sciences.

The study was conducted in a GLP certified facility. There was no significant deviation that affected the quality or integrity of the study.

- GCP

The DNDi-FEX-07-HAT – fexinidazole study Sponsor was the organisation Drugs for Neglected Diseases initiative (DNDi), 15 chemin Camille-Vidart, 1202 Geneva, Switzerland.

According to the clinical study report, the study was performed in compliance with the ethics principles of the Directive 2001/20/EC derived from international ethics guidelines, including the Declaration of Helsinki, the ICH E6 Guideline for Good Clinical Practice, all applicable national laws, rules, and regulations. The studies also meet with the requirements of the standard operating procedures for clinical investigations and documentation of the Sponsor.

This multicentre study was conducted in 2 centres in Malawi (Rumphi District Hospital) and Uganda (Lwala Hospital). Eligible patients with human African trypanosomiasis (HAT) from other hospitals and centres were to be referred for treatment to Lwala or Rumphi Hospital.

As a Clinical trial carried outside European Union, it complied with the ethical requirements of Directive 2001/20/EC.

The study constituted an independent Data Safety Monitoring Board (DSMB).

Data management and statistical analysis of data was conducted by Epicentre (Paris, France).

Both sites were initiated before starting the study to develop a common understanding of the clinical study protocol, CRF, and study procedures, in compliance with GCP (from 10 to 11 April 2019 in Malawi and from 05 to 07 November 2019 in Uganda). Due to the late study start at the Uganda site, a site initiation visit refresh was held from 07 to 09 September 2020. The Sponsor conducted Investigator meetings with the Principal Investigator and Coordinating Investigators and training sessions (from 19 to 21 February 2019 in Malawi and from 25 to 27 June 2019 in Uganda) for the study staff and clinical research associates at each site.

An inspection was held at the Lwala site, in Uganda, conducted by the National Drug Authority (NDA) in Uganda on 19-21 August 2019 (pre-authorisation inspection) and the Sponsor audited Epicentre on 24 and 25 September 2019. There were no other site audits due to the COVID-19 pandemic.

Reports were provided and the CHMP concluded that the DNDi-FEX-07-HAT – fexinidazole study had been conducted in compliance with GCP.

2.2. Non-clinical aspects

2.2.1. Introduction

No new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP. No or low risk preclinical safety issues were identified for fexinidazole. Please refer to Section 5.3 of the SmPC.

Some details on non-clinical pharmacology and pharmacokinetics were provided as part of the dossier:

- The trypanocidal effect of fexinidazole and of its 2 metabolites on *T. b. rhodesiense* parasites has been validated in vitro, in parallel with other T. b. subspecies: *T. b. gambiense* and *T. b. brucei* .
- The concentrations of fexinidazole, M1 and M2 that enabled to reach 50% of inhibitory growth (IC_{50}) for the *T. b. rhodesiense* strain appeared higher than those obtained for the T*. b. gambiense* strain, but they remained lower than those obtained for the *T. b. brucei* strain .The latter is an animal infective sub-species which is considered as a reliable surrogate of the human infective sub-species *T. b. rhodesiense* and *T. b. gambiense*. This *T. b. brucei* strain was used to establish the minimal concentrations that completely inhibit visible parasite growth (MIC): 5.0, 4.74 and 2.20 µg/mL for fexinidazole, M1, and M2, respectively.
- In vitro time-kill assays using *T. b. brucei* strain showed that 3-fold MIC levels for M1 and M2 had to be maintained for at least 48 to 72 hours in the blood of HAT patients (g-HAT or r-HAT) to reach trypanocidal efficacy.As M2 is the most abundant metabolite in human plasma/blood, a target blood concentration was set for M2 (3 x 2.2 = 6.6 µg/mL) and rounded up to >10 µg/mL**.** Of note, g-HAT patients, who were cured, had M2 blood concentrations >10 µg/mL over 3 days at the end of the maintenance-dose phase indicating that such M2 blood concentrations were effective against *T. b. gambiense* parasites in blood and in CSF (see original application dossier).
- The trypanocidal activity of fexinidazole on *T. b. rhodesiense* parasites was also validated in vivo using acute mouse models of HAT infections. Complete cure of acute infection was reached in mice administered an oral 4-day 100 mg/kg/d fexinidazole dose regimen which corresponded to a twice-lower daily dose of fexinidazole (100 versus 200 mg/kg/d) and a shorter regimen (4 versus 5 days) than the dose regimen used in the chronic mouse model of HAT.

From these in vitro and in vivo non-clinical experiments fexinidazole was expected to be at least as efficacious in patients with r-HAT as in patients with g-HAT.

2.2.2. Ecotoxicity/environmental risk assessment

As stated in the Questions & Answers on “Guideline on the environmental risk assessment of medicinal products for human use” document (EMA/CHMP/SWP/44609/2010 Rev. 1, 2016 - question 2), the submission of a new Environmental Risk Assessment (ERA) is required for a type II variation or a line extension if an increase in environmental exposure is expected. And the increase in environmental exposure should be assessed on a case-by-case basis.

The ERA provided for this application consists of an adequate justification for the absence of specific study data. Due to the limited number of patients to be treated, the small batch size and the specific supervision of the product distribution, the justification has been accepted, as per the EMA procedural advice for medicinal products intended exclusively for markets outside the European Union under Article 58 of Regulation (EC) No 726/2004 in the context of co-operation with the World Health Organisation (WHO). ERA omission was accepted considering:

1. The medicinal product will be used to treat patients with Human African Trypanosomiasis, a rare tropical disease (<3000 cases per year). According to the WHO, the number of new HAT cases reported annually continuously decreased since 2009. The number of gambiense HAT (g-HAT) cases per year has drastically decreased. The WHO reported 953 cases in 2018, 876 in 2019, 565 cases in 2020 and 774 cases in 2021. The new proposed indication, rhodesiense HAT (r-HAT) concerns a very limited number of cases (98 cases in 2021 and 55 cases in 2022 according to the WHO Global Health Repository.

2. Moreover, fexinidazole will be distributed through the WHO Neglected Tropical Diseases (NTD) department to National Sleeping Sickness Control Programs (NSSCPs) and from there to the treatment centres, where the product will be given to patients after confirmed diagnosis of HAT. (NTD medicine donations by diseases and pharmaceutical donors' commitment (last updated November 2022 https://cdn.who.int/media/docs/default-source/ntds/neglected-tropical-diseases-non-disease-specific/ntd-medicine-donation.pdf?sfvrsn=24d10542_20).

3. The product will not be available through pharmacies or out of a predefined distribution system.

4. Fexinidazole it is not intended to be marketed in the European Economic Area (EEA) but intended exclusively for markets outside the Community, in countries where HAT occurs, i.e. in Sub-Saharan Africa and therefore, the applicant is recommended to liaise with the local authorities where the medicinal product is intended to be authorised in order to discuss any potential environmental impact and any specific arrangements to limit this impact if needed.

5. Besides, 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.

6. The precautionary and safety measures taken in order to reduce any risk to the environment and enhance environmental protection, by including the general statement on the SmPC and PL have been applied according to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMEA/CHMP/SWP/4447/00 corr 2, 2006.

Therefore, the proposed modification to the therapeutic indication will not cause an increase in the environment. Thus, no significant increase in active substance usage or increase in environmental exposure from the introduction of would be expected.

In short, no environmental risk is expected with the approval of fexinidazole 600 mg tablet in this extension of indications.

2.2.3. Discussion on non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable. No or low risk preclinical safety issues were identified for fexinidazole (see Section 5.3 of the SmPC).

The SOH provided a justification to not perform an Environmental Risk Assessment (ERA) that is acceptable according to the Questions & Answers document on "Guideline on the Environmental Risk Assessment of medicinal products for human use", EMA/CHMP/SWP/44609/2010. Rev.1, 2016 and EMA procedural advice for medicinal products intended exclusively for markets outside the European Union under Article 58 of Regulation (EC) No 726/2004 in the context of co-operation with the World Health Organisation (WHO)

The approval of fexinidazole 600 mg tablet will not lead to increase of environmental exposure. There are no objections from an environmental risk assessment point of view.

2.2.4. Conclusion on non-clinical aspects

Based on the updated data submitted in this application, the extended indication does not lead to a significant increase in environmental exposure further to the use of fexinidazole.

Considering the above data, fexinidazole is not expected to pose a risk to the environment.

The applicant is recommended to liaise with the local authorities where the medicinal product is intended to be authorised in order to discuss any potential environmental impact and any specific arrangements to limit this impact if needed.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the SOH.

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

- Tabular overview of clinical studies

TABULAR OVERVIEW OF CLINICAL STUDIES

Type of study	- Study identifier - Location of study report - Coordinating Investigator (and center) - Number of centers	- Objective(s) of study - Study design and type of control	Test product(s): - Formulation - Dosage regimen - Route of administration	Reference therapy: - Formulation - Dosage regimen - Route of administration	Number of study participants - Total[a, b, c] - Gender[b] (M/F) - Age[b] mean ± SD (range) - Treatment group[b]	Healthy study participants or diagnosis of study participants	Duration of treatment	Study status Type of report
Efficacy/Safety	DNDi-FEX-07-HAT 2 active centers	To assess the efficacy and safety of fexinidazole in adults and children with human African trypanosomiasis due to trypanosoma brucei rhodesiense at any stage of the disease Multicentre, open-label, nonrandomized study	- 600 mg tablets - Adult patients and children with body weight ≥35 kg: 1800 mg (3 tablets) for 4 days (Day 1 to Day 4), followed by 1200 mg (2 tablets) for 6 days (Day 5 to Day 10). - Children with body weight ≥20 kg and <35 kg: 1200 mg (2 tablets) for 4 days (Day 1 to Day 4), followed by 600 mg (1 tablet) for 6 days (Day 5 to Day 10). - Oral	- Not applicable	- 45/45/44 - 31/14 - 27.0 ± 16.1 (7-69) years - Fexinidazole group: 45	Study participants with human African trypanosomiasis due to trypanosoma brucei rhodesiense at any stage of the disease	10 days	Complete Initial report with the results of the primary efficacy endpoints

a Enrolled
b Treated
c Completed treatment period
M: male, F: female, SD: standard deviation.

2.3.2. Pharmacokinetics

Study DNDi-FEX-07-HAT

Study DNDi-FEX-07-HAT is a multicentre, Phase II/III, open-label, non-randomised study aiming to assess the efficacy and safety of fexinidazole in patients with r-HAT. This study was designed as a single arm study

treating patients with fexinidazole only, with a benchmark study design comparing the observed fatality rate to an unacceptable rate.

Study was conducted in 2 centres in Malawi (Rumphi District Hospital) and Uganda (Lwala Hospital). Eligible patients with human African trypanosomiasis (HAT) from other hospitals and centres were to be referred for treatment to Lwala or Rumphi Hospitals.

As exploratory objectives, the study intended to assess the pharmacokinetics of fexinidazole and its main metabolites in the blood.

The study planned to enrol 34 evaluable patients, aged ≥6 years old, with confirmed stage 2 r-HAT by evidence of *T. brucei rhodesiense* infection in CSF. Patients with stage 1 r-HAT were also recruited in parallel, without any predefined targeted sample size.

All patients received fexinidazole. Fexinidazole was administered as 600 mg tablets, to be taken orally, once daily, with the dosage regimen depending on the body weight:

- Body weight ≥35 kg:
  - ✓ 1800 mg (3 tablets) for 4 days (Day 1 to Day 4), followed by
  - ✓ 1200 mg (2 tablets) for 6 days (Day 5 to Day 10)
- Body weight ≥20 and <35 kg:
  - ✓ 1200 mg (2 tablets) for 4 days (Day 1 to Day 4), followed by
  - ✓ 600 mg (1 tablet) for 6 days (Day 5 to Day 10).

Fexinidazole was administered within 30 minutes of the main meal and the total duration of treatment was 10 days. Food was found to increase the relative bioavailability of fexinidazole and to reduce the overall variability of pharmacokinetic parameters, as assessed during the initial approval of the drug product. Furthermore, concomitant food appeared necessary to reach potential M2 therapeutic levels and therefore the SmPC for fexinidazole (Section 4.2) recommends administering fexinidazole tablets with food each day at about the same time of the day in g-HAT patients. This recommendation was applied to r-HAT patients in Study DNDi-FEX-07-HAT.

The study population included 9 patients aged <12 years (20.0%) and a higher proportion of male than female patients (68.9% versus 31.1%). The median age was 24.0 years, and the youngest patient was 7.0 years old (i.e., ≥6 years old, as per inclusion criteria). The oldest patient was 69.0 years old. There was 1 pregnant woman (2.2%) and no breastfeeding women.

Pharmacokinetics Assessment

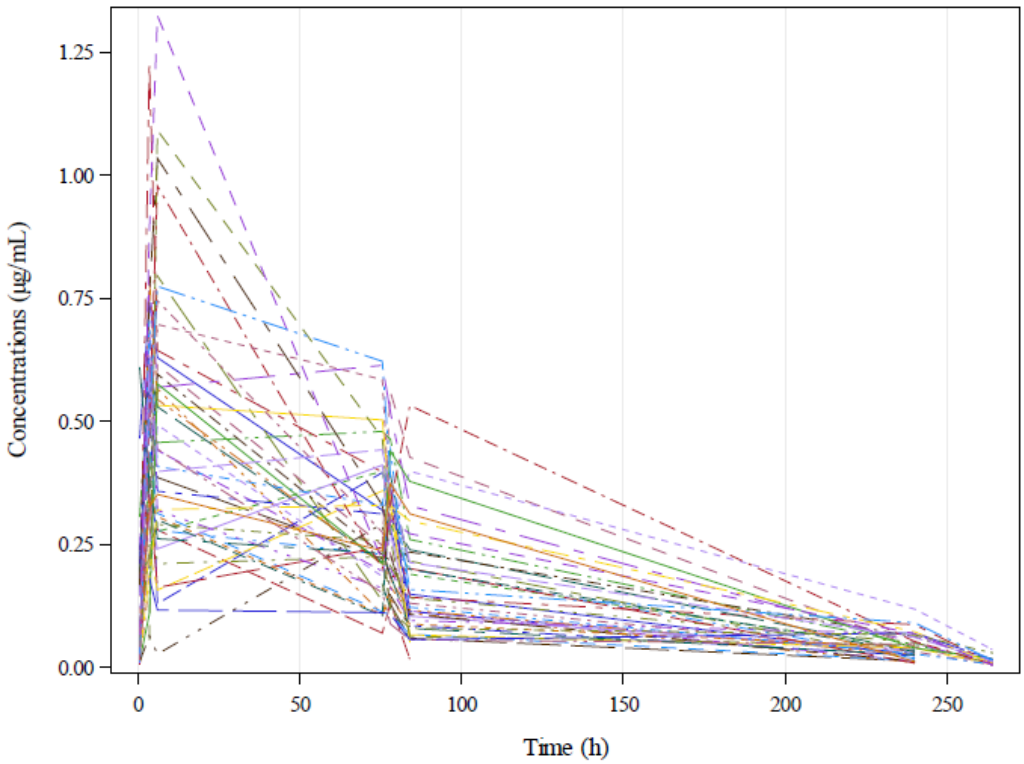
Fexinidazole and its two metabolites (M1: fexinidazole sulfoxide and M2: fexinidazole sulfone) concentration levels were determined in whole blood from a DBS sample, using a validated analytical method.

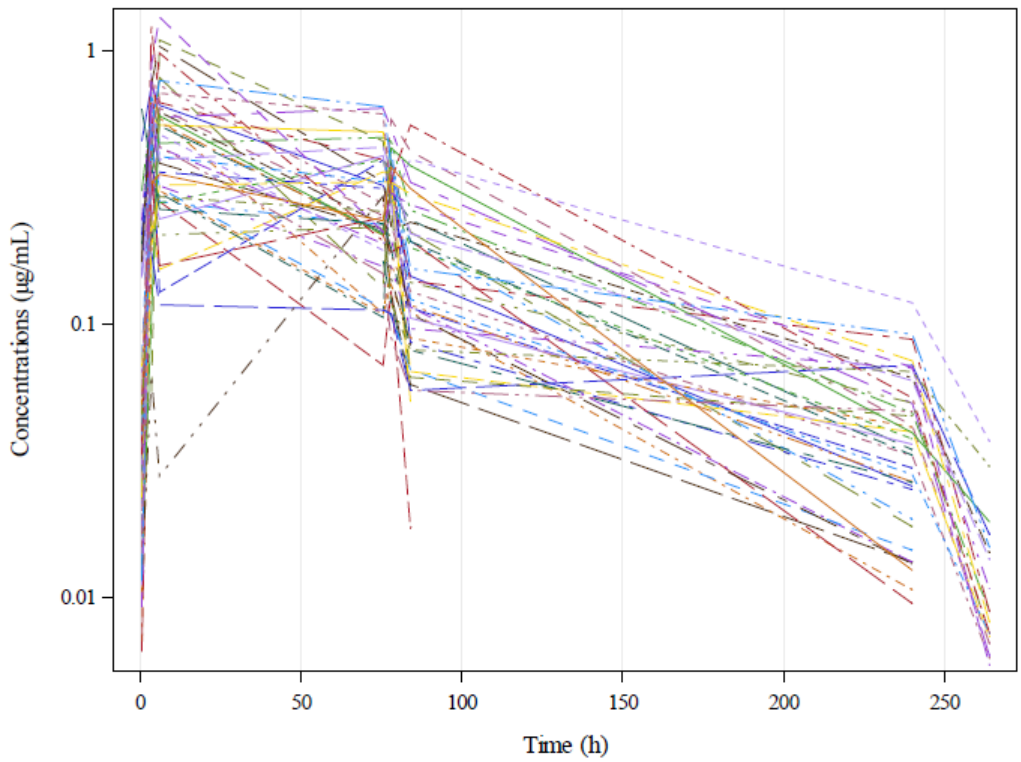
Blood sampling for PK analysis, approximately 2 mL each time, were collected at the following time points: Day 1 (0.5, 3.5, and 6 hours post dosing), Day 4 (3.5, 6, and 12 hours post dosing), and Day 10 (24 and 48 hours post dosing, which corresponds to Day 11 and Day 12, respectively). A small amount of blood was placed on a Drop Blood Sample (DBS) card and shipped to the Central Laboratory for analyses.

The PK analysis was performed on the patients who received fexinidazole, regardless of the quantity, and for whom at least one blood sample for PK was available (PK population). The PK population included 45 patients: 11 children with body weight <35 kg, 6 children with body weight ≥35 kg, and 28 adults.

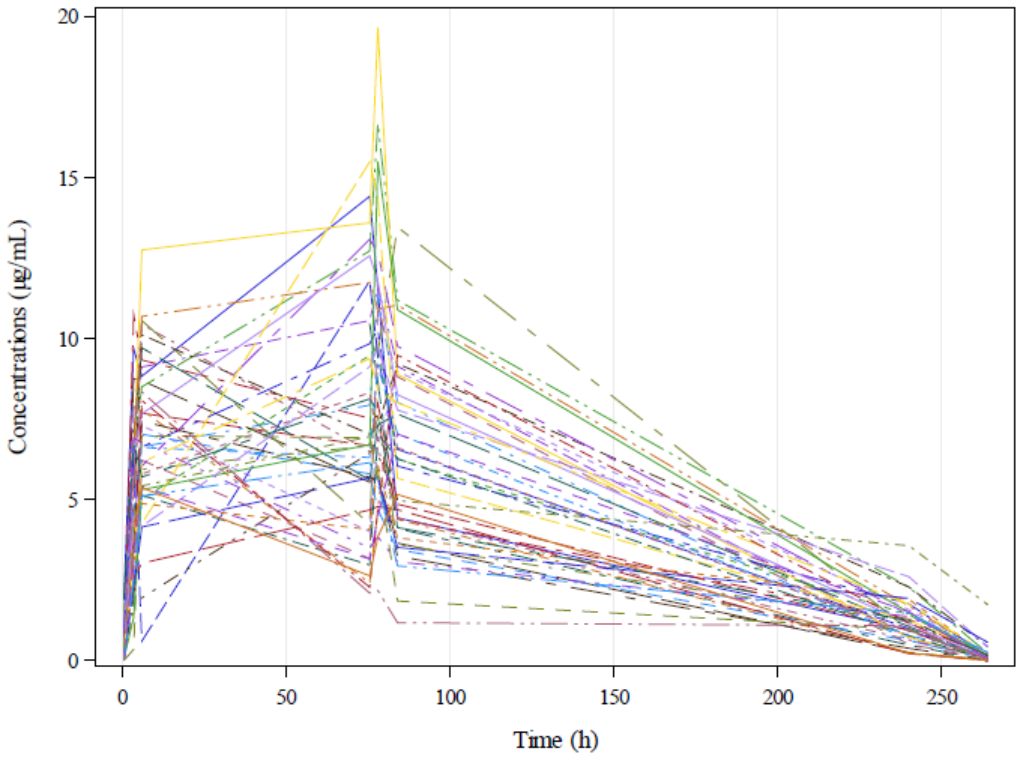
These blood concentration data were then used in a population PK analysis for adult and paediatric r-HAT patients (DNDi-FEX-07-HAT) to apply, and to adapt if required, the same population PK model as the one developed for fexinidazole in adult and paediatric g-HAT patients (DNDiFEX004, DNDiFEX006).

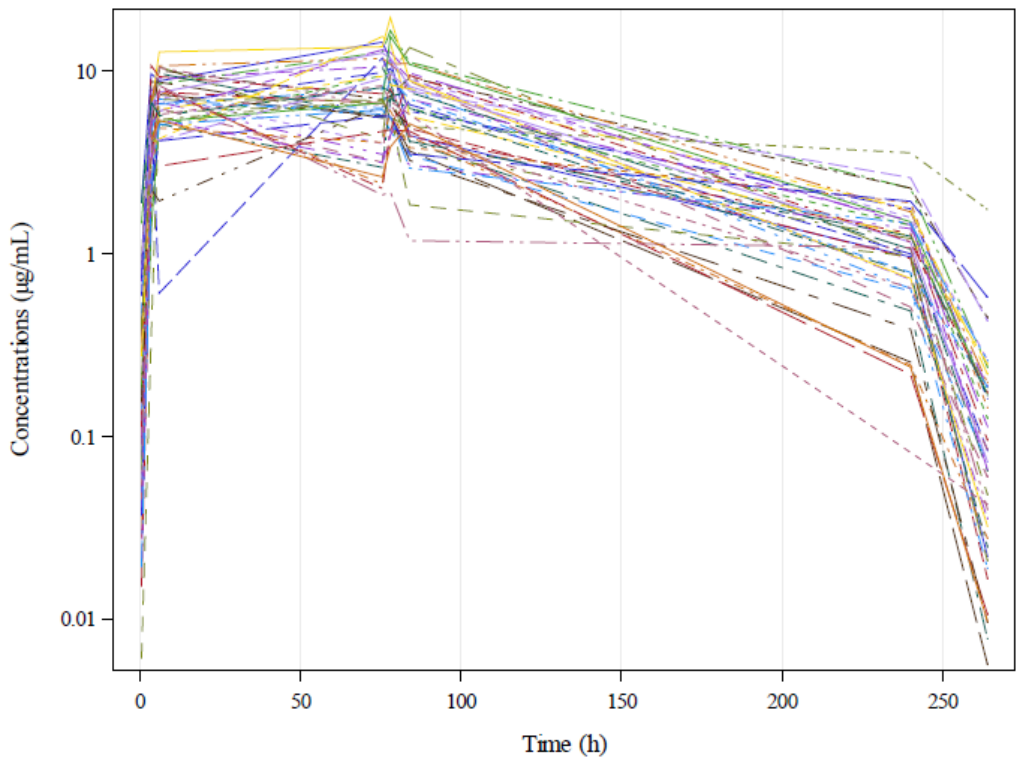
In the figures below are the spaghetti plots for fexinidazole observed in study DNDi-FEX-07-HAT, in linear and semi-logarithmic scales:



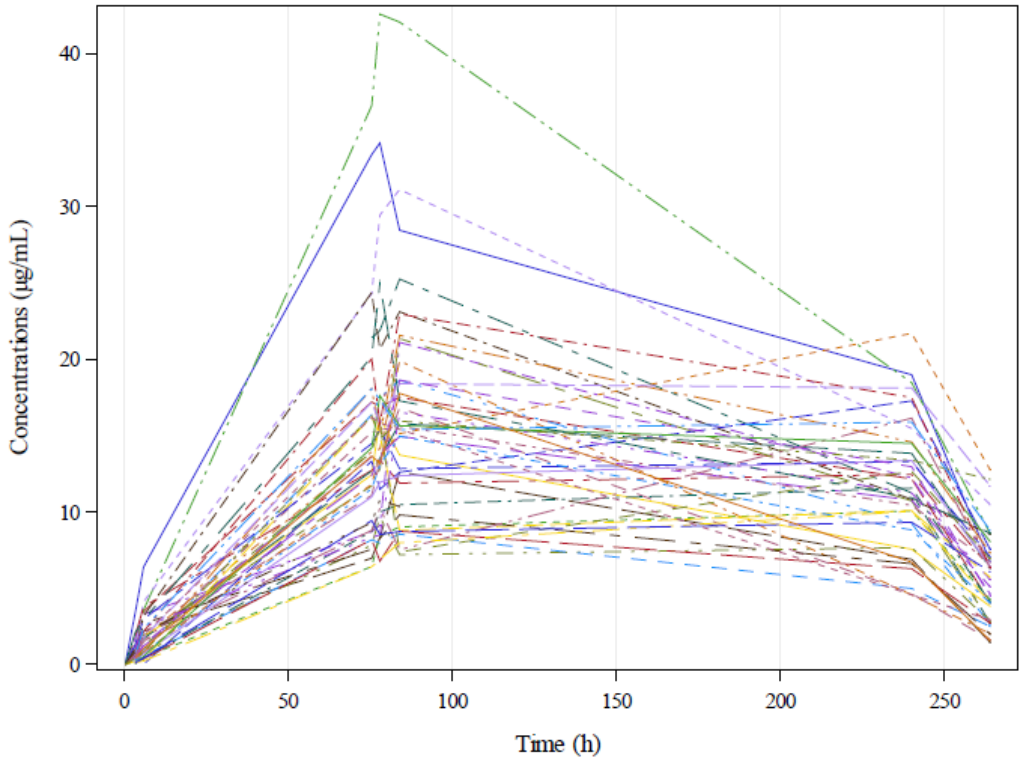


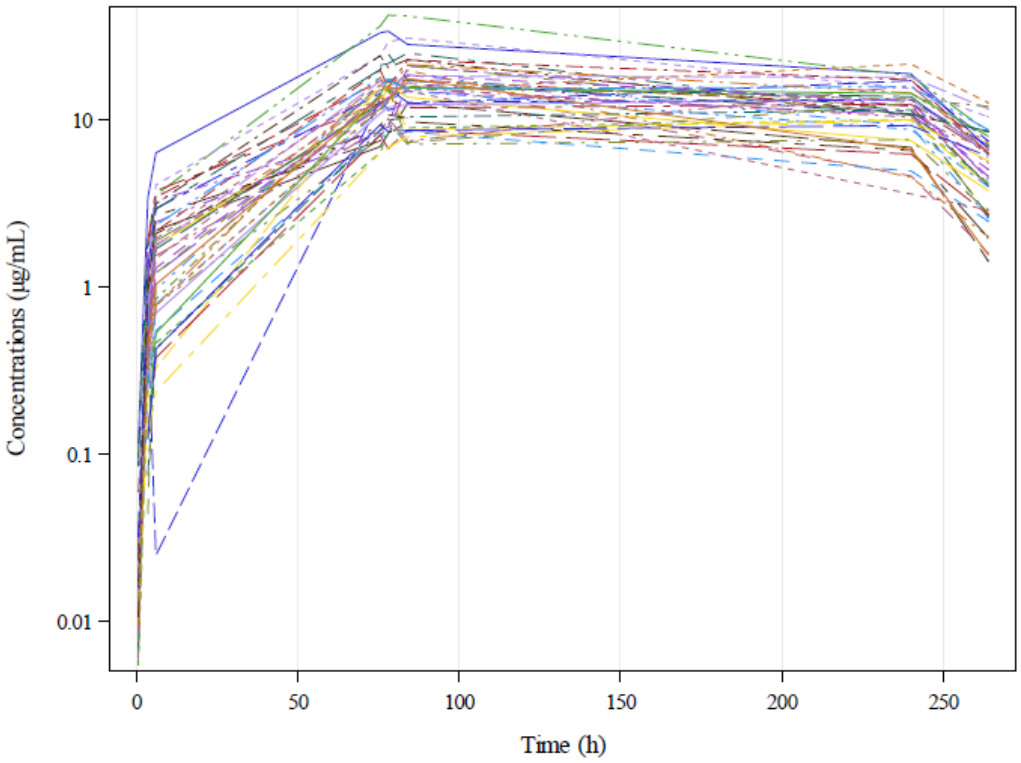
In the figures below, the spaghetti plots for fexinidazole metabolite M1 observed in study DNDi-FEX-07-HAT, in linear and semi-logarithmic scales are presented:



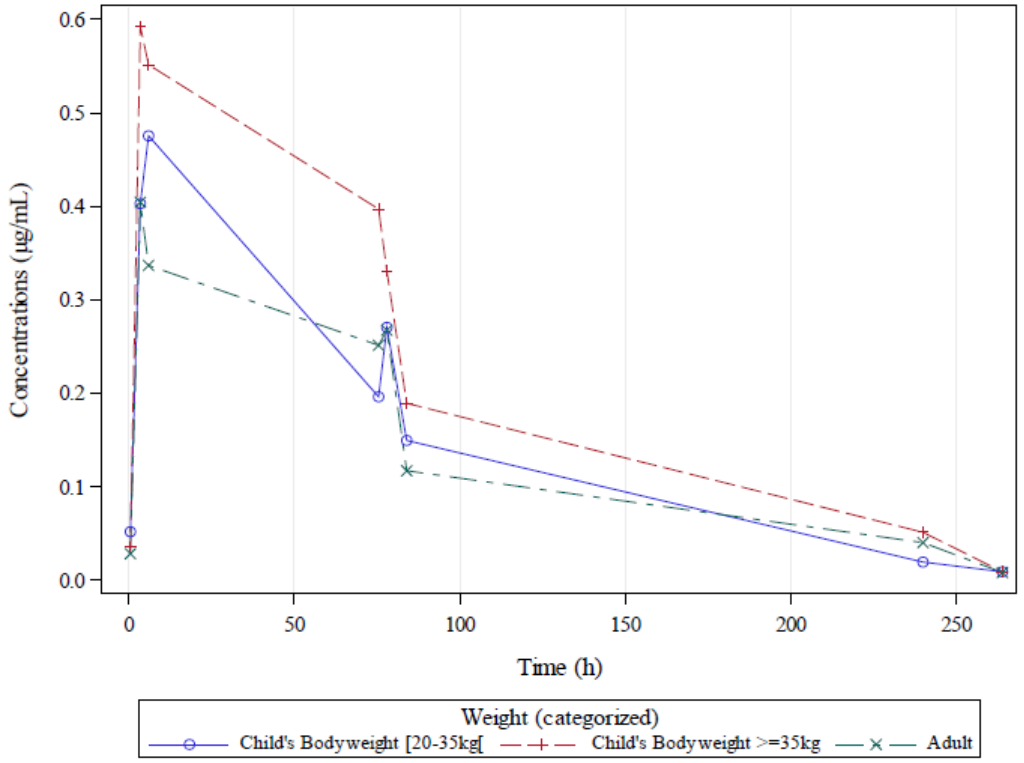


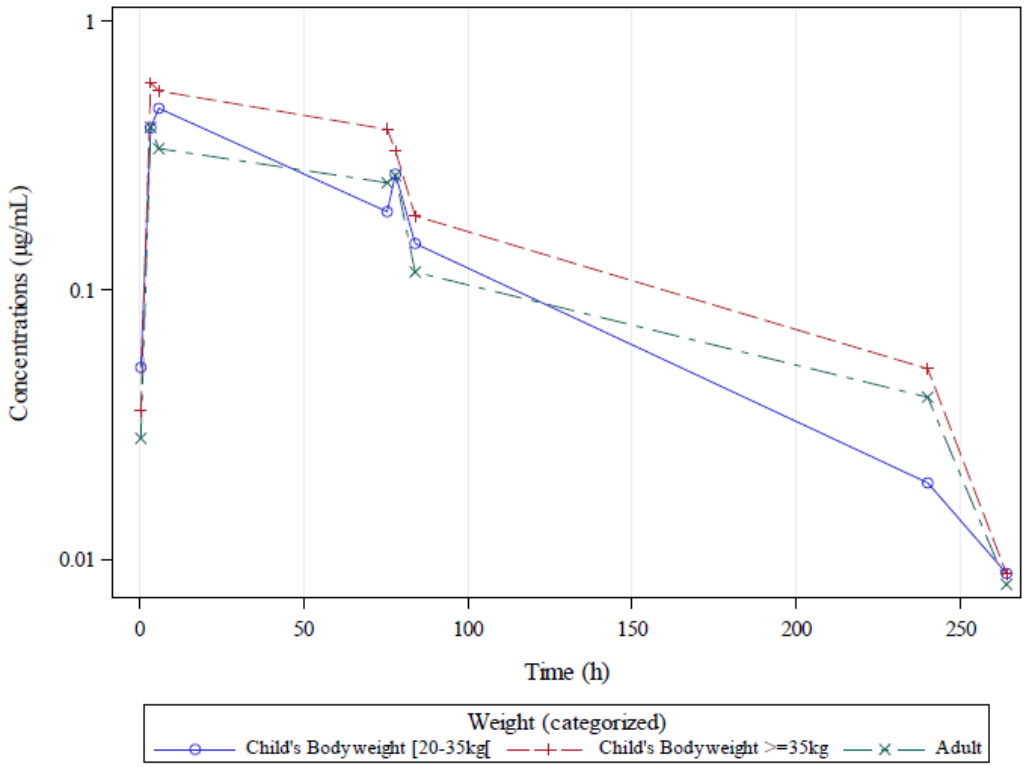
In the figures below, the spaghetti plots for fexinidazole metabolite M2 observed in study DNDi-FEX-07-HAT, in linear and semi-logarithmic scales are presented:



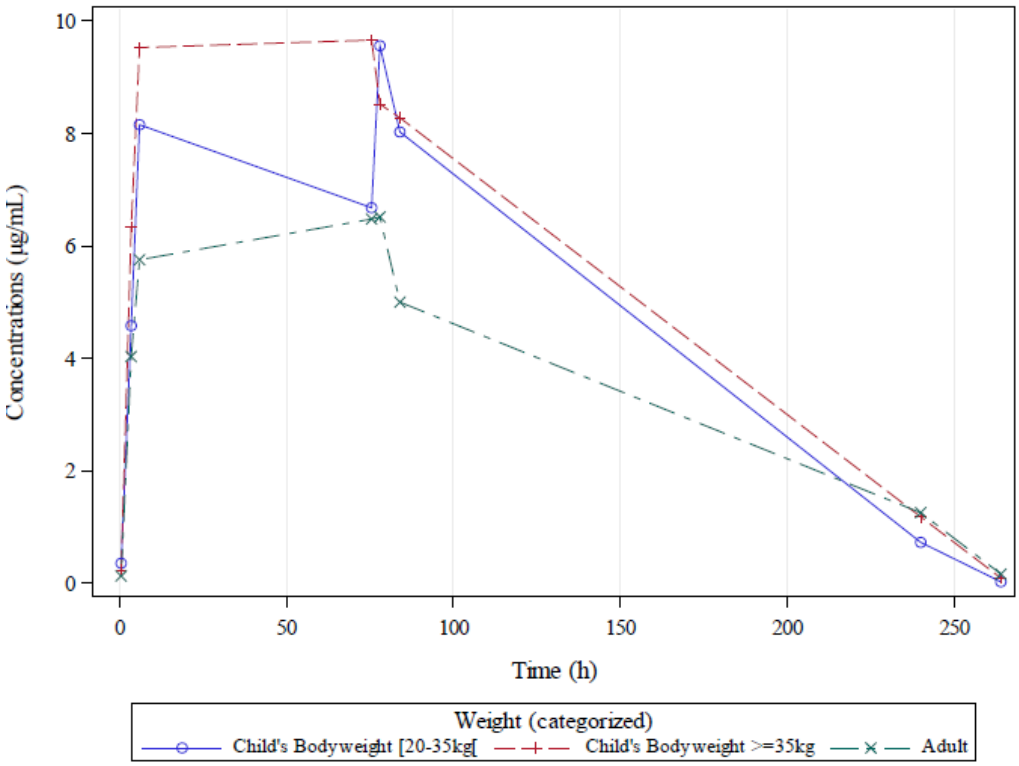


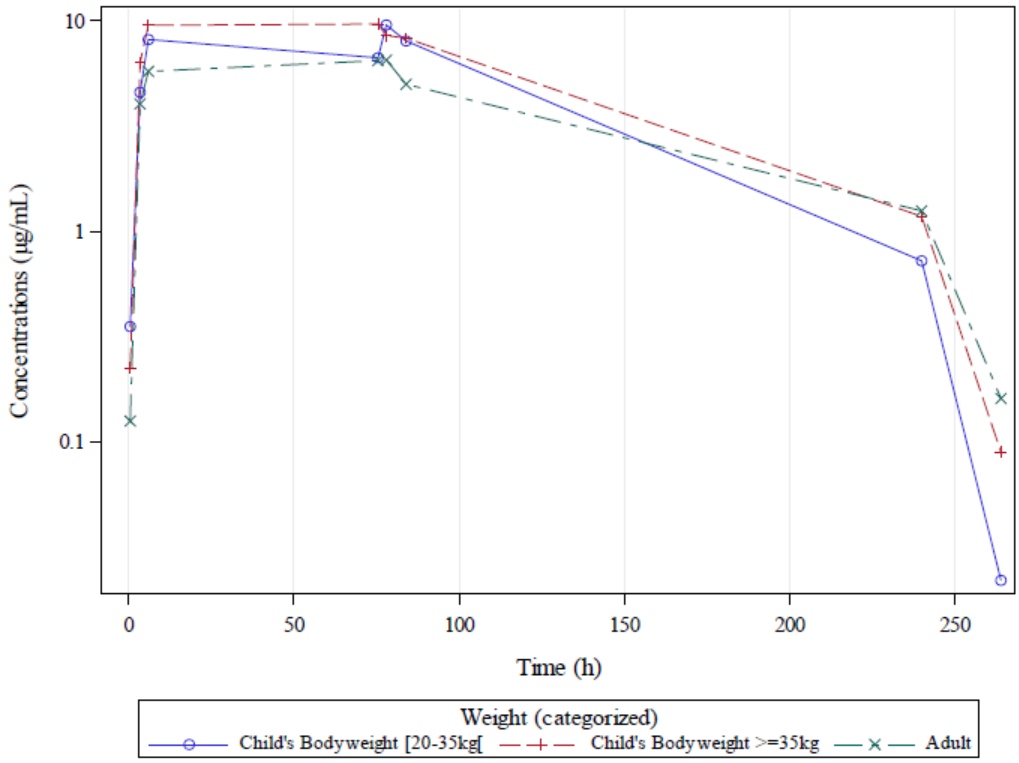
In the figures below, the median pharmacokinetic profiles for fexinidazole observed in study DNDi-FEX-07-HAT, by body weight, in linear and semi-logarithmic scales are presented:



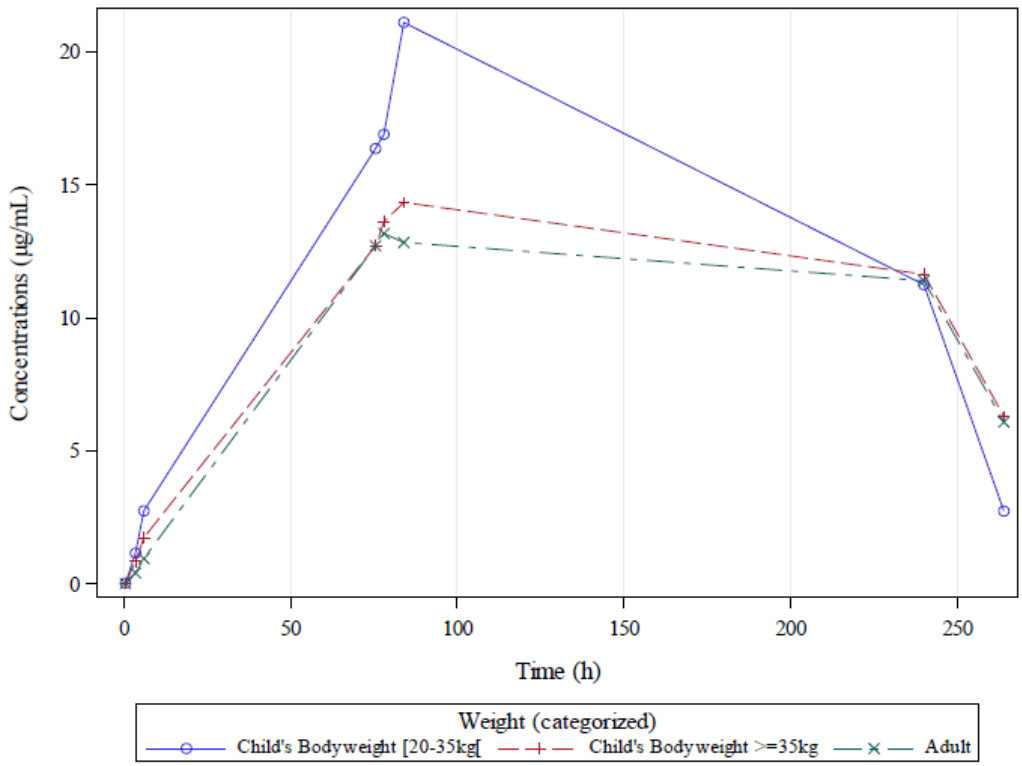


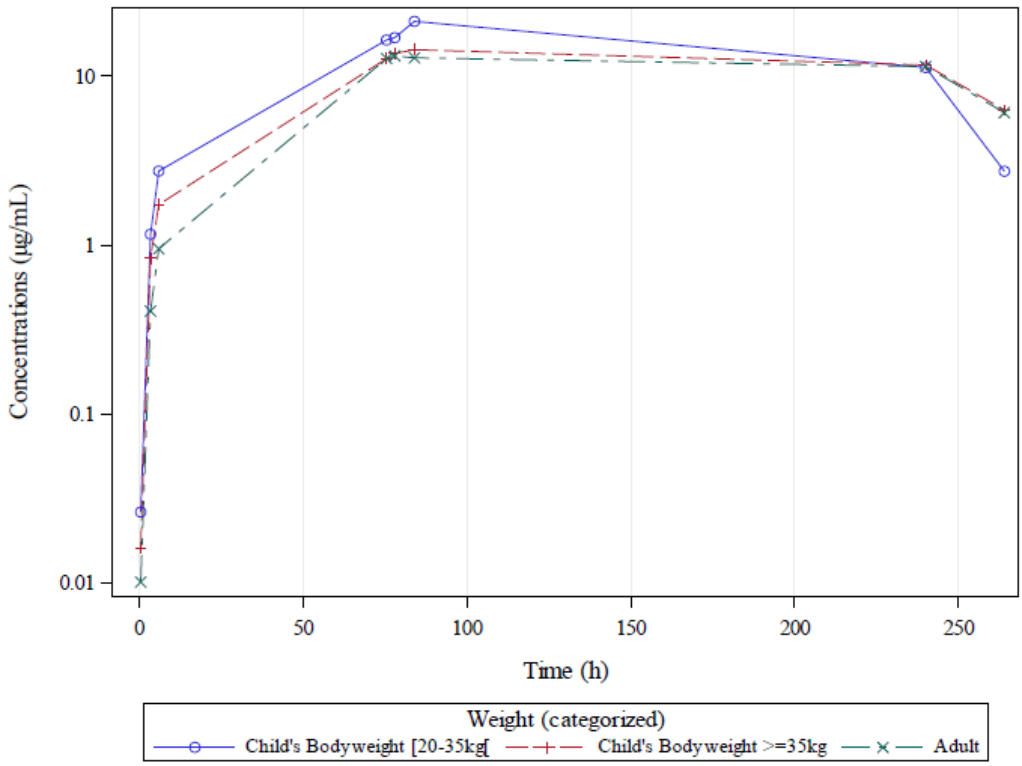
In the figures below, the median pharmacokinetic profiles for fexinidazole metabolite M1 observed in study DNDi-FEX-07-HAT, by body weight, in linear and semi-logarithmic scales are presented:



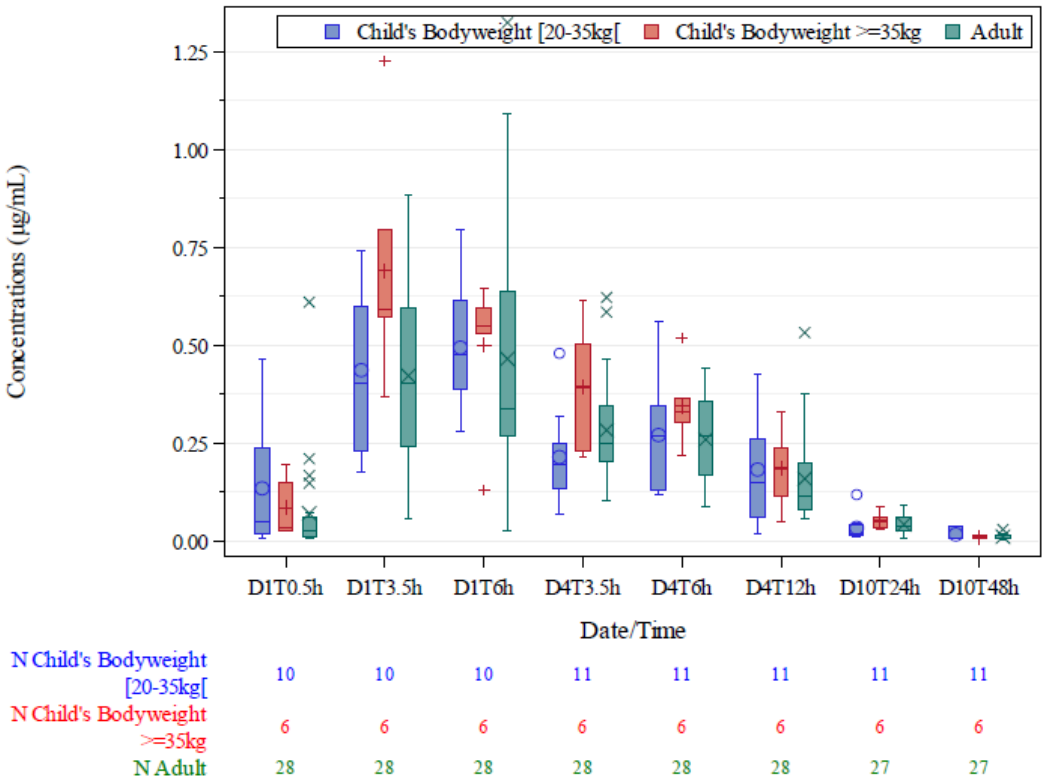


In the figures below, the median pharmacokinetic profiles for fexinidazole metabolite M2 observed in study DNDi-FEX-07-HAT, by body weight, in linear and semi-logarithmic scales are presented:

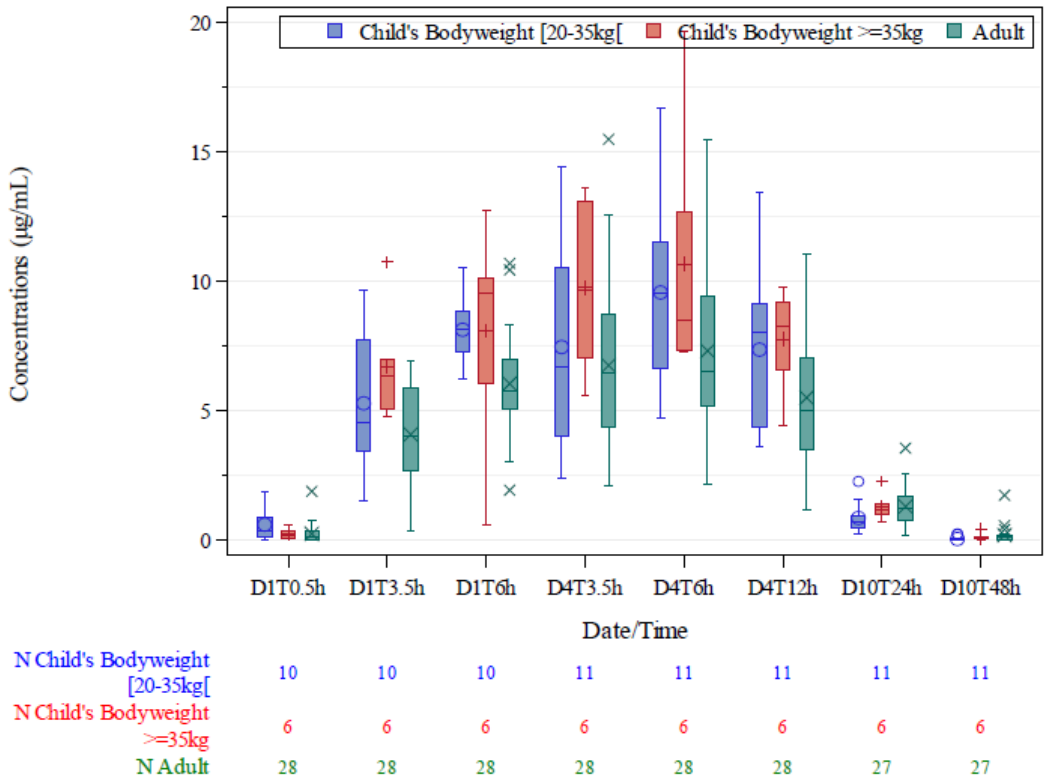




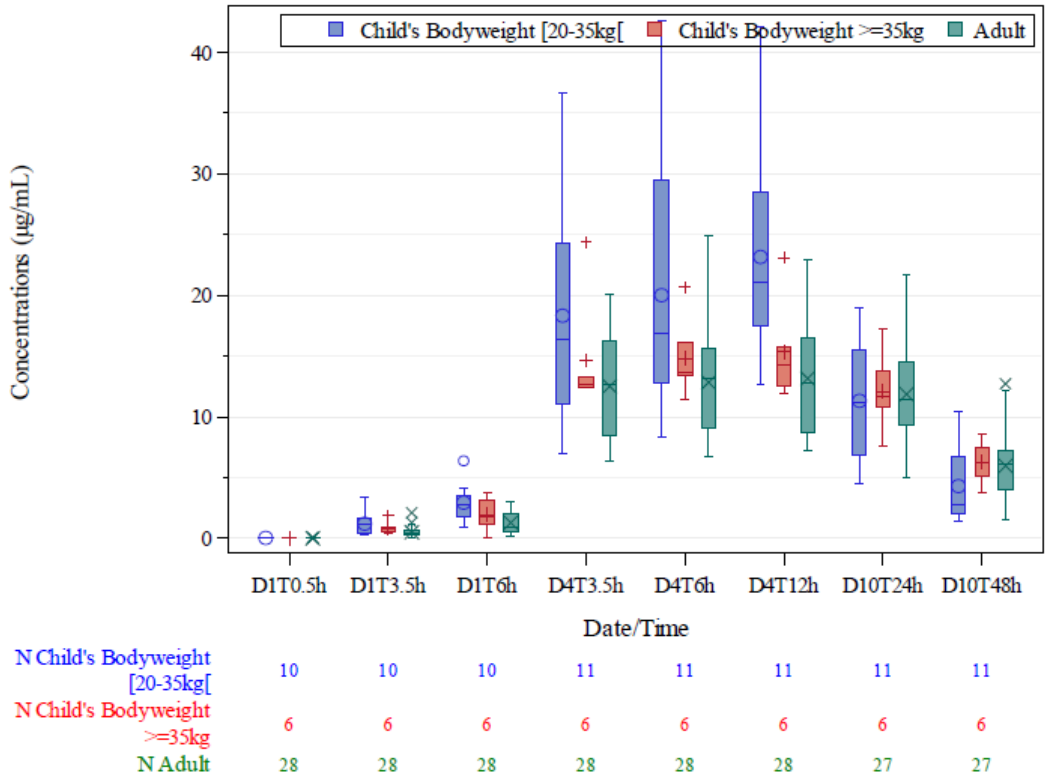
In the figure below, the distribution of fexinidazole concentration (µg/mL) by visit and bodyweight observed in study DNDi-FEX-07-HAT is presented:



In the figure below, the distribution of fexinidazole metabolite M1 concentration (µg/mL) by visit and bodyweight observed in study DNDi-FEX-07-HAT is presented:



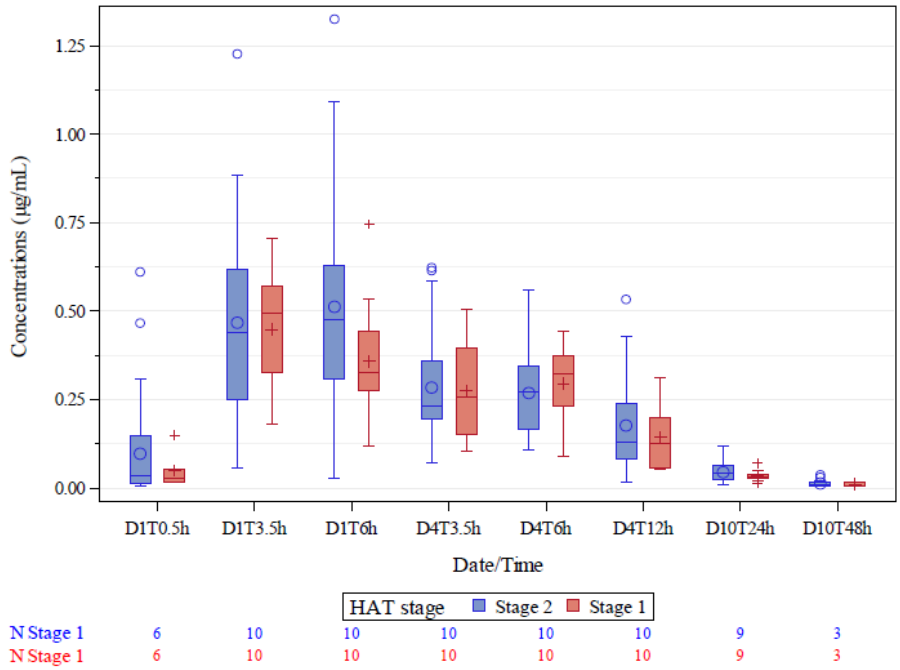
In the figure below, the distribution of fexinidazole metabolite M2 concentration (µg/mL) by visit and bodyweight observed in study DNDi-FEX-07-HAT is presented:



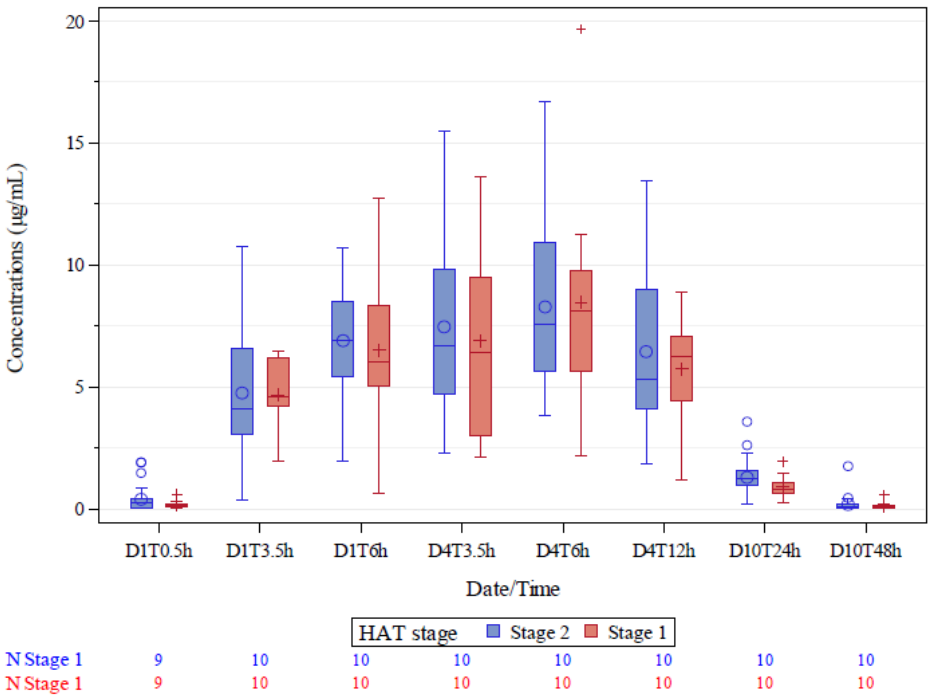
From the pharmacokinetic profiles it is shown that fexinidazole concentrations measured in children with BW<35 kg are in line with those measured in adults but for children with BW ≥35 kg, their concentrations are slightly higher. For M1, the three subgroups seemed comparable, and for M2 children with BW<35 kg had a higher concentration than the other 2 groups. However, when exploring more closely M2 data, there are only 4 children out of 11 with high concentrations and the others are in line with the two other subgroups.

A target of 10 µg/mL was fixed for M2 from previous studies. The percentage of patients with observed M2 levels in DBS higher than 10 µg/mL, at 24 h after the last administration on Day 10, was high for both children and adults, i.e., 63.6 % for children with BW < 35 kg, 83.3% for children with BW >= 35kg and 70.4% for adults.

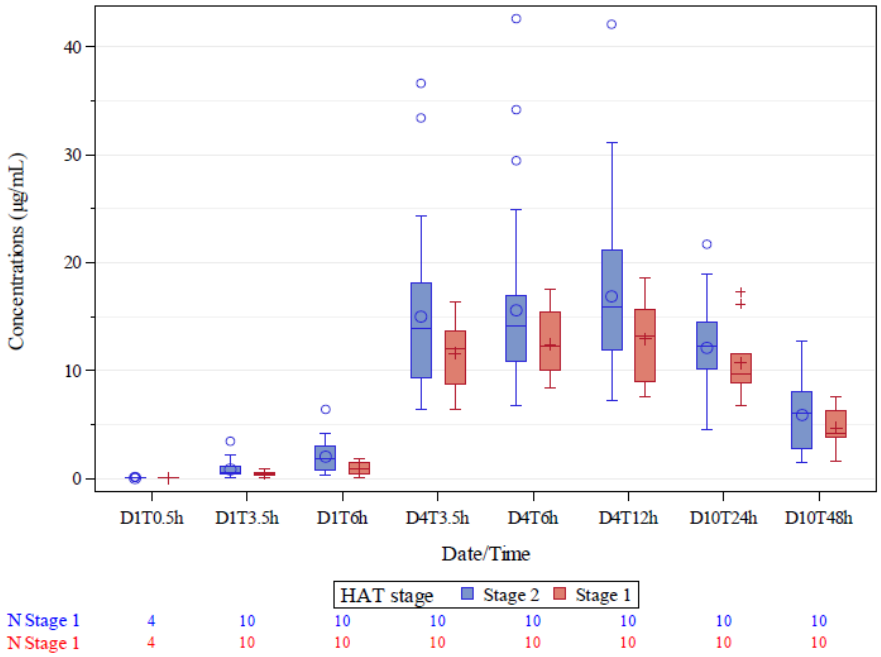
In the figure below, it is presented the distribution of fexinidazole concentration (µg/mL) by visit and HAT stage, observed in study DNDi-FEX-07-HAT:



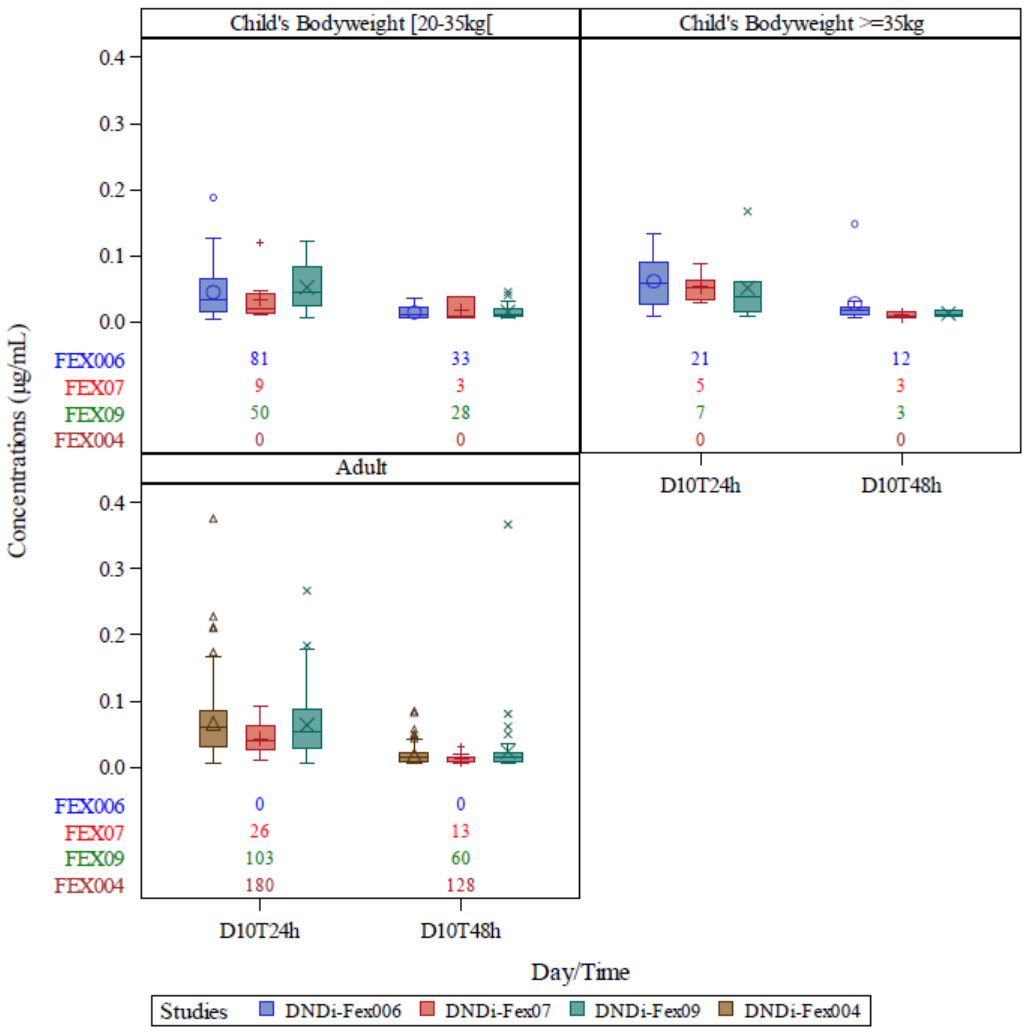
In the figure below, the distribution of fexinidazole metabolite M1 concentration (µg/mL) by visit and HAT stage, observed in study DNDi-FEX-07-HAT is presented:



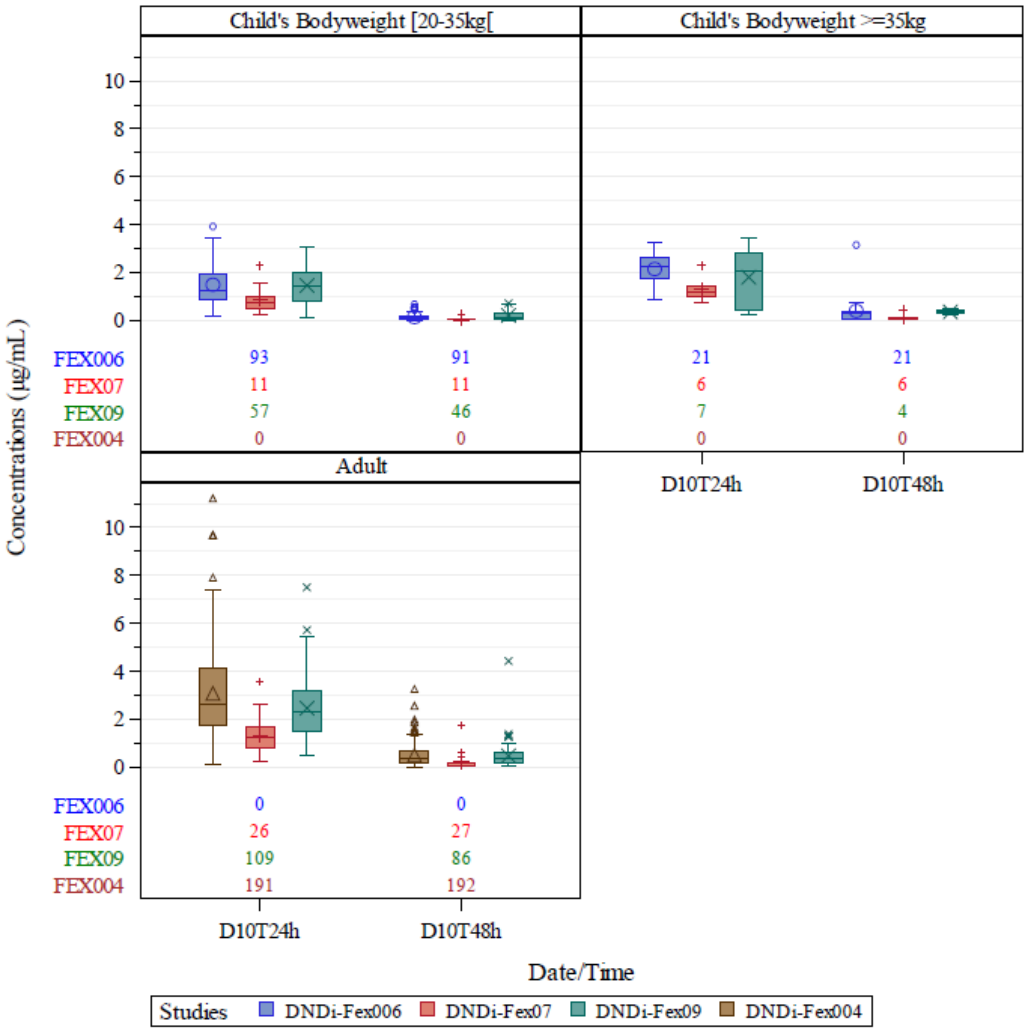
In the figure below, the distribution of fexinidazole metabolite M2 concentration (µg/mL) by visit and HAT stage, observed in study DNDi-FEX-07-HAT is presented:



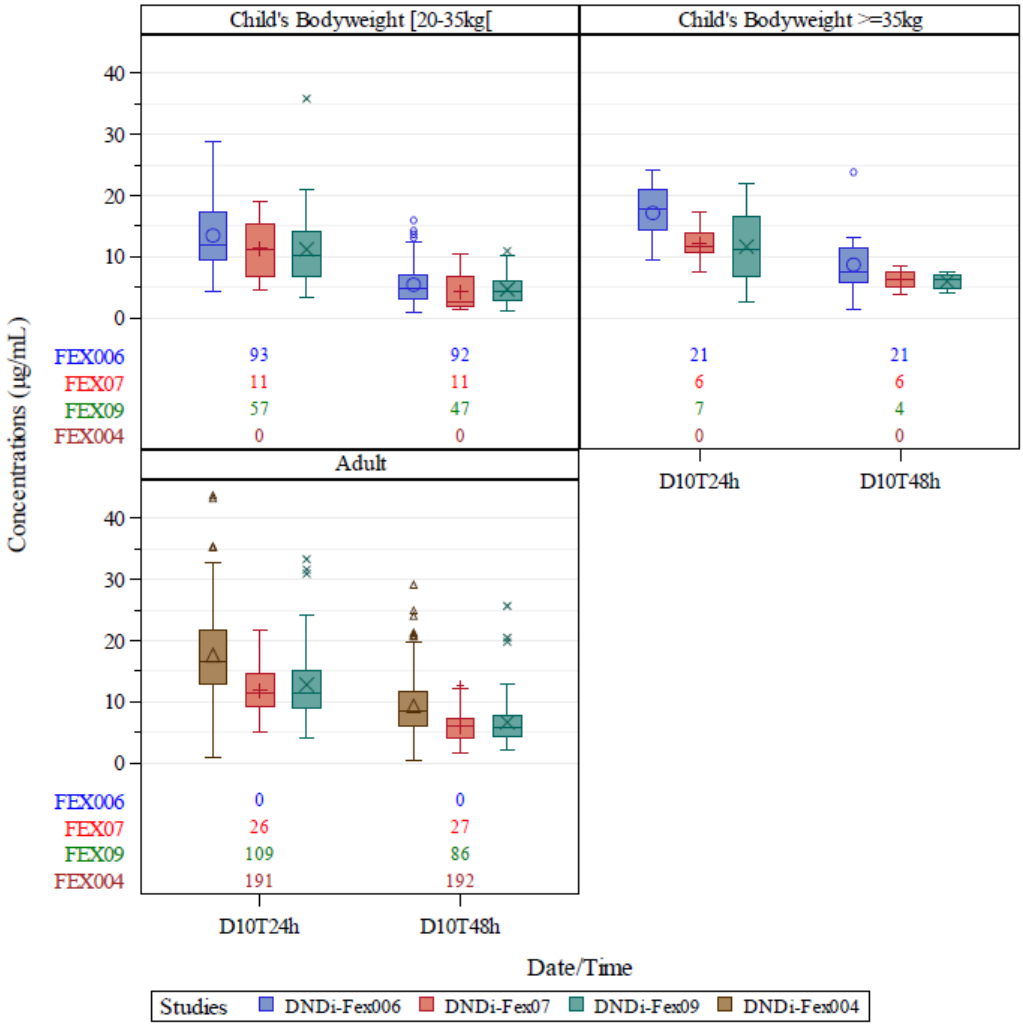
In the figure below, the distribution of fexinidazole concentration (µg/mL) by visit and study, as observed in studies FEX-06, FEX-07, FEX-09 and FEX-04 is presented.



In the figure below, the distribution of fexinidazole metabolite M1 concentration (µg/mL) by visit and study, as observed in studies FEX-06, FEX-07, FEX-09 and FEX-04 is presented.



In the figure below, the distribution of fexinidazole metabolite M2 concentration (µg/mL) by visit and study, as observed in studies FEX-06, FEX-07, FEX-09 and FEX-04 is presented.



The CHMP noted that distribution of fexinidazole, M1 and M2 DBS concentrations by HAT stage by sex (figures not shown in this assessment report) showed that, there is no difference between male and female nor by HAT stage in fexinidazole, M1 and M2 exposure.

According to popPK report, only one patient confirmed a HAT relapse. This patient received fexinidazole as planned in the protocol, and blood concentrations for fexinidazole and metabolites M1 and M2 were similar to those of other patients.

A comparison of fexinidazole, M1 and M2 concentrations between studies DNDiFEX004, DNDiHATFEX006 DNDi-FEX-09-HAT and DNDi-FEX-07-HAT was performed at Day 10 at 24 h and 48 h (common time points) and showed that the distribution of fexinidazole is quite comparable between studies and body weight category. M1 exposure was slightly lower in study DNDI-FEX-07-HAT for the three-body weight category, and M2 concentrations was similar between DNDi-FEX-09-HAT and DNDi-FEX-07-HAT and considered quite lower than DNDiFEX004 and DNDiHATFEX006 studies. However, in all cases, median M2 concentrations were above the efficacy target of 10 µg/mL.

It should also be noted that compared to other studies, the number of subjects in DNDi-FEX-07-HAT was lower, which could affect the results, especially for the subgroups of children.

Population Pharmacokinetics model

The popPK model was built on the population of r-HAT patients from study DNDi-FEX-07-HAT, treated with fexinidazole with available PK samplings. A total of 45 patients were included in the analysis (28 adults and

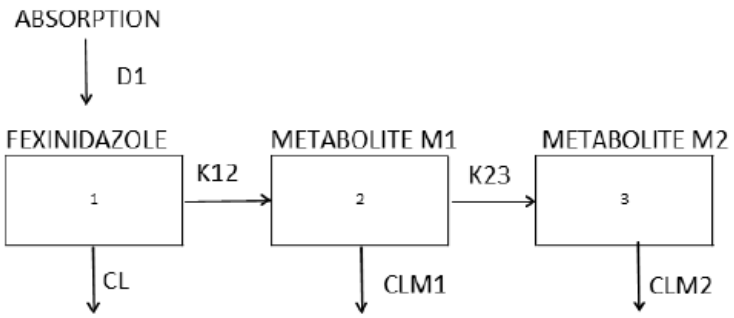
17 children). A total of 44 patients fully completed the study. One patient died during the hospitalisation period due to causes unrelated to r-HAT and/or fexinidazole.

The number of concentrations included in the analysis was 320 for fexinidazole, 352 for M1 and 332 for M2. A total of 52 concentrations were excluded from the analysis because they were below the limit of quantification (BLQ) which corresponded to less than 5% of the overall concentration.

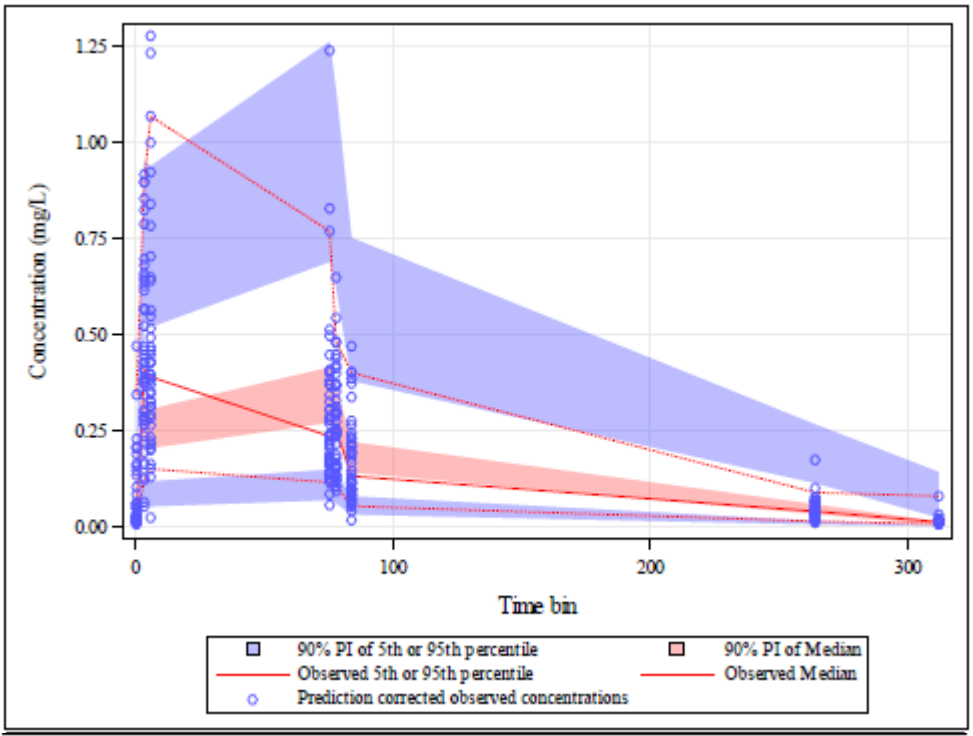
PopPK Modelling

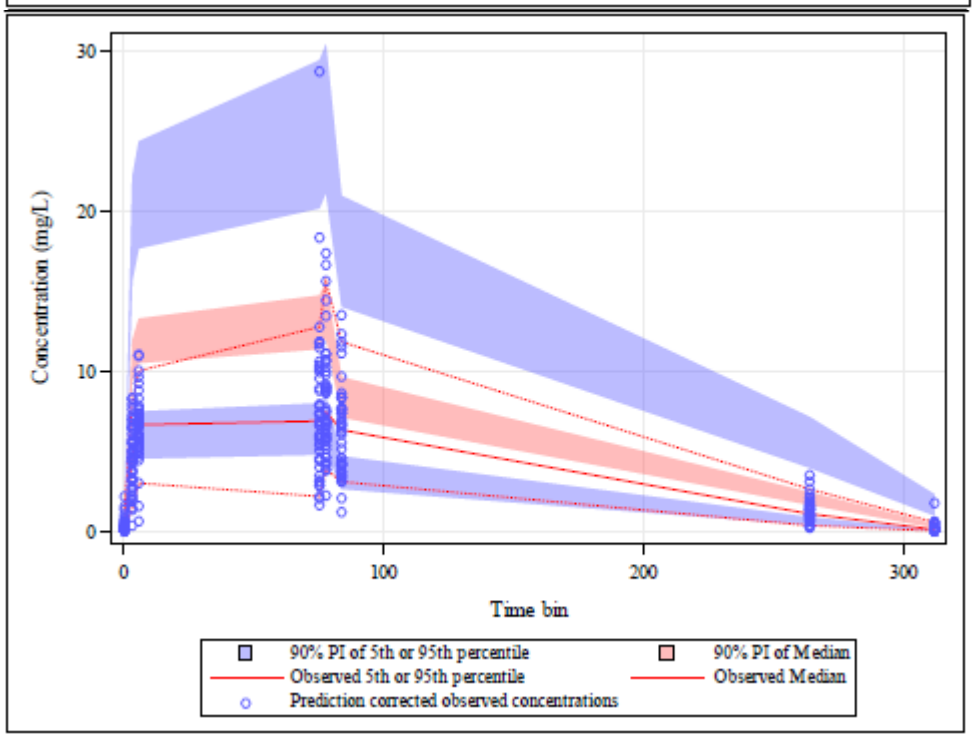
The initial popPK model was developed using data from g-HAT patients from studies DNDiFEX004, DNDiHATFEX006. This model was assessed during the initial submission and approval of Fexinidazole Winthrop.

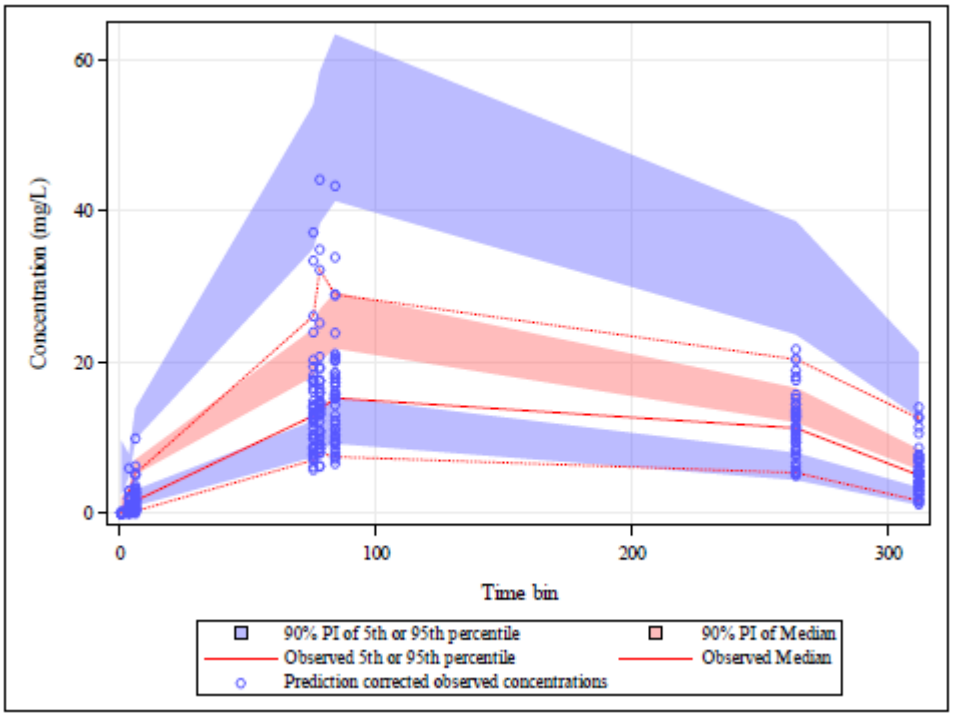
The structural popPK model was one-compartment model with zero order absorption and elimination for fexinidazole and a one-compartment model with rate of formation and elimination for each metabolite. The model was parameterized in terms of fexinidazole CL/F, apparent volume of distribution of fexinidazole (V1/F), duration of absorption (D)1, apparent clearance of M1 (CLM1), apparent clearance of M2 (CLM2), micro rate constant from compartment 1 (fexinidazole) to compartment 2 (M1) (k12) and micro rate constant from compartment 2 (M2) to compartment 3 (M3) (k23). The figure below represents the developed model:



The validated popPK model was fitted into DNDi-FEX-07-HAT data and DNDi FEX-09-HAT data. Below are the visual predicted figures for fexinidazole and its metabolites in DNDi-FEX-07-HAT study.


FEXINIDAZOLE
Concentration (mg/L)
1.25
1.00
0.75
0.50
0.25
0.00
0
100
200
300
Time bin
90% PI of 5th or 95th percentile
90% PI of Median
Observed 5th or 95th percentile
Observed Median
Prediction corrected observed concentrations


M1
Concentration (mg/L)
30
20
10
0
0
100
200
300
Time bin
90% PI of 5th or 95th percentile
90% PI of Median
Observed 5th or 95th percentile
Observed Median
Prediction corrected observed concentrations



From VPCs it is observed a bias at the loading dose phase in DNDi-FEX-07-HAT study, as fexinidazole decreased between Day 1 and Day 4 and this impacted M1 and M2 concentrations. However, the terminal phase was correctly predicted. Therefore, it was considered to pool all data from the 4 studies (DNDiFEX004, DNDiHATFEX006, DNDiHATFEX007 and DNDiHATFEX009), challenging the model and not only refined.

PopPK Final Model

Several models were tested during model development: saturable absorption, mixture of linear and nonlinear fexinidazole elimination, saturable biotransformation from fexinidazole and M1, time-varying bioavailability, time-varying fexinidazole elimination. None of these models were estimable considering the lack of data at Day 1 and Day 4 compared to the maintenance phase (unbalanced data between DNDiFEX07 and previous studies). Thus, the same model was kept, and the effect of dose as structural covariate was tested in several parameters to capture the nonlinearity. This effect was found significant on k_{12} and CLM1/F (M1 PK parameters) as k_{12} and CLM1/F decreased by increasing doses.

The addition of dose effect did not improve however the fitting at the loading dose phase for fexinidazole (also confirmed with the residuals plots at higher concentrations of fexinidazole) but allowed to better capture the kinetics of M1 and M2 of DNDi-FEX-07-HAT data.

The population PK parameters for the structural model, according to a median bodyweight of r-HAT children and adult patients, are presented in the table below. It is observed that estimates for clearance, volume of distribution and k_{23} increased by bodyweight.

		Children		Adults
	Typical value	Child's Bodyweight [20-35kg[	Child's Bodyweight >=35kg	Adult
	median weight 70 kg	median weight 25 kg	median weight 41 kg	median weight 52 kg
CL/F (L/h)	497	229	332	397
V_1/F (L)	6775	3129	4536	5421
D_1(h)*	1.11	1.11	1.11	1.11
k_{12} (h^{-1}) for dose 1200 mg	0.004	0.004	0.004	0.004
CL_{M1}/F (L/h) for dose 1200 mg	0.561	0.259	0.375	0.448
k_{23} (h-1)	0.141	0.065	0.094	0.112
CL_{M2}/F (L/h)	0.059	0.027	0.039	0.047

** D_1 was not scaled to a bodyweight*

After selection of potential covariates by univariate analysis, a full model including all significant covariates was estimated and a statistical model was obtained by backward deletion. Finally, V_1/F and CLM2/F were found to be statistically different by HAT type. Overall, the improvement of final model compared to base model was characterized by a decrease of 70 points in the objective function.

Parameter	Estimate (%RSE)	95%CI	IIV CV	Shrinkage
Fexinidazole model parameters				
$CL/F=q_1*(Weight/70)^{0.75}*EXP(h_1)$				
q_1: CL/F typical value	502 (3.23%)	(470; 534)		
h_1 (IIV CL/F)	0.372 (6.42%)	(0.325; 0.418)	CV= 61%	3.69%
$V_1/F=q_2*(Weight/70)^{0.75}*EXP(h_2) \times(1+q_{10}\times gHAT)$				
q_2: V_1/F typical value for r-HAT	5577 (4.78%)	(5055; 6100)		
h_2: (IIV V_1/F)	0.304 (6.8%)	(0.264; 0.345)	CV= 55.2%	6.07%
q_{10}: Effect of HAT V_1/F	0.231 (21.9%)	(0.132; 0.331)		
Covariance between omega CL/F and V_1/F	0.303 (6.93%)	(0.261; 0.344)	R= 0.9	
$D1=q_3$				
q_3: D_1 typical value	0.304 (6.8%)	(0.264; 0.345)		
M1 model parameters				
$k_{12}=q_4*EXP(h_3)*(Dose/1200)^{q_9}$				
q_4: k_{12} typical value for 1200 mg	0.014 (6.22%)	(0.012; 0.015)		
h_3: (IIV k_{12})	0.091 (7.23%)	(0.078; 0.104)	CV= 30.2%	11.83%
q_9: Dose exponent k_{12}	-1.796 (6.06%)	(-2.01; -1.58)		
$CL_{M1}/F=q_5*(Weight/70)^{0.75}*(Dose/1200)^{q_{11}}$				
q_5: CL_{M1}/F typical value for 1200 mg	2.14 (5.54%)	(1.91; 2.38)		
q_{11}: Dose exponent CL_{M1}/F	-1.502 (7.25%)	(-1.72; -1.29)		
M2 model parameters				
$k_{23}=q_6*(Weight/70)^{q_8}$				
q_6: k_{23} typical value	0.137 (2.74%)	(0.130; 0.145)		
q_8: allometric exponent k_{23}	0.372 (10.2%)	(0.298; 0.447)		
$CL_{M2}/F=q_7*(Weight/70)^{0.75}*EXP(h_4) \times(1+q_{12}\times gHAT)$				
q_7: CL_{M2}/F typical value for r-HAT	0.049 (5.41%)	(0.044; 0.054)		
h_4: (IIV CL_{M2}/F)	0.076 (9.1%)	(0.062; 0.090)	CV= 27.6%	9.29%
q_{12}: Effect of HAT CL_{M2}/F	0.185 (33.9%)	(0.062; 0.307)		
Residual error				
ε_1: fexinidazole proportional component	0.149 (3.82%)	(0.137; 0.160)	CV= 38.5%	
ε_2: M1 proportional component	0.096 (3.33%)	(0.090; 0.102)	CV= 31%	
ε_3: M2 proportional component	0.019 (4.27%)	(0.018; 0.021)	CV= 13.9%	
ε_4: M2 additive component	1.45 (8.14%)	(1.22; 1.68)	SD= 1.20 µg/mL.	

* All typical population parameters except D_1 and k_{12} were normalized for a 70 kg patient
RSE = Root Square error calculated as percent relative standard error
CL/F in L/h, V_1/F in L, D_1 in h, k_{12} in h^{-1}, CL_{M1}/F in L/h, k_{23} in h^{-1} and CL_{M2}/F in L/h.

The precision of fixed effects parameters did not change significantly, in comparison to the base model (RSE still lower than 10%, except for effect of HAT on V_1/F and CLM2/F at 22% and 34%, respectively). The residual error was unchanged.

The final statistical model exhibited the same characteristics as the base model, with residuals homogeneously distributed around zero when plotted against concentrations, predictions or time with the same bias for fexinidazole and M1.

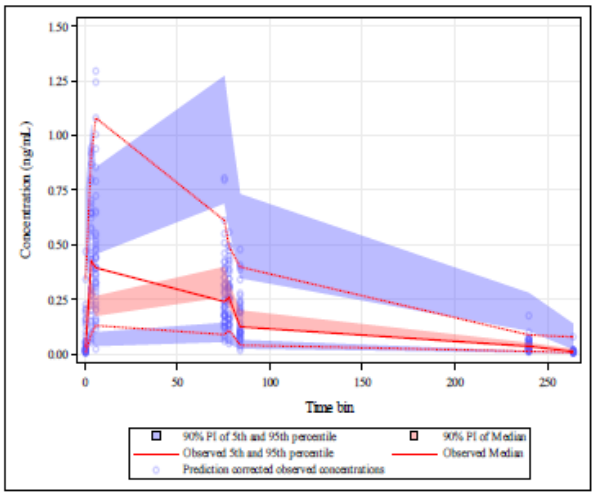
Compared to the base model, the final statistical model accounted for difference in apparent volume of distribution V_1/F and CLM2/F according to HAT type. The relationship was captured by proportional model, as shown in the following table with the difference between HAT groups.

PK parameters	HAT Type	
	g-HAT	r-HAT
V_1/F (L)	6865	5577
CL_{M2}/F (L/h)	0.060	0.049

Prediction-corrected performance visual checks (pcVPC) performed for the base and final model are compared in the figures below for fexinidazole and its metabolites:

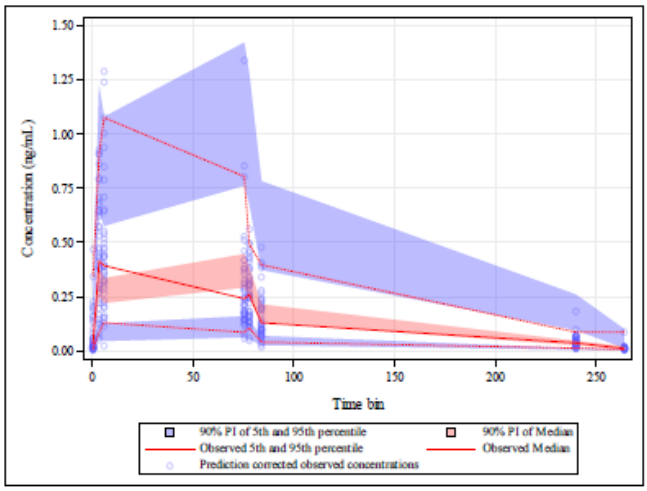
Base

Fexinidazole

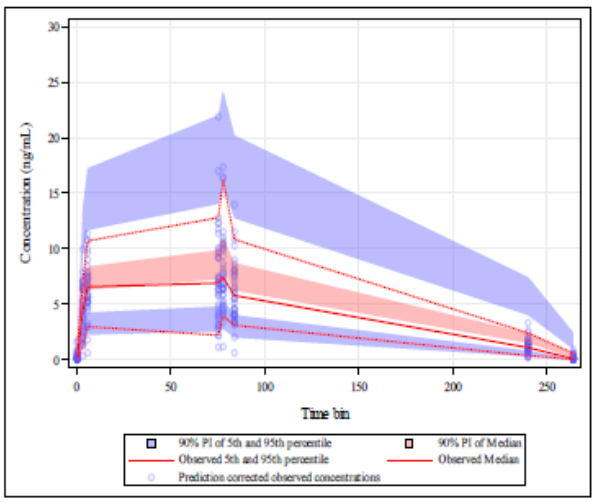


Final

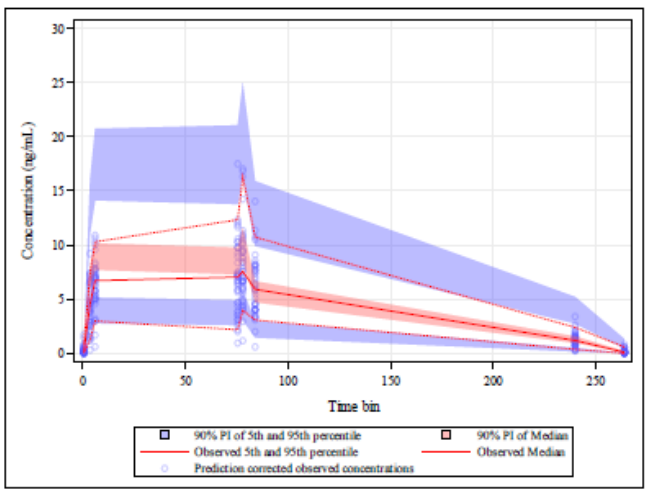
Fexinidazole

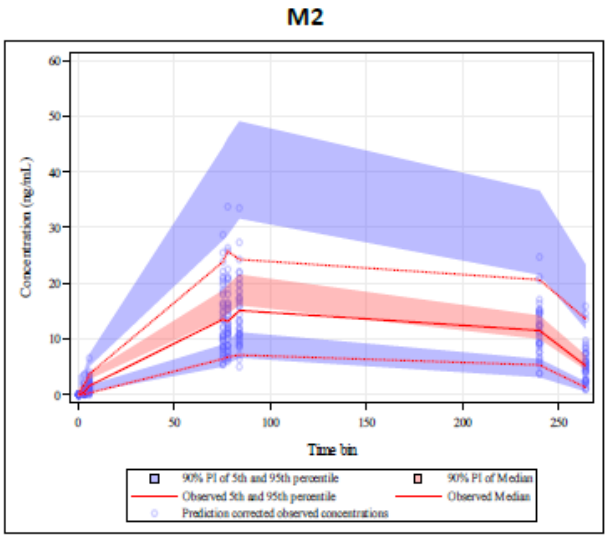


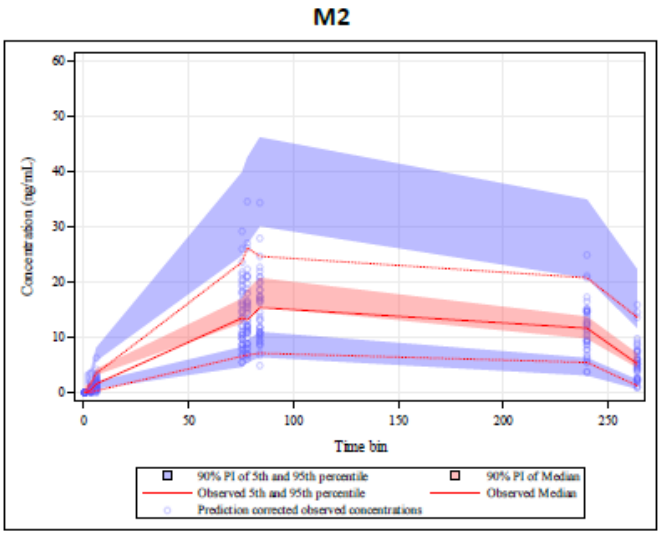
M1



M1







The general pattern for all compounds best capture was obtained with the final model compared to the base model for M1 and M2. However, based on the VPCs for the final model, the PopPK model is not able to describe appropriately the observed PK data *vs* time for fexinidazole (under-predictions on Day 1 and over-predictions on Day 4), for M1 (over-prediction on Days 1+4) and for M2 (over-prediction on Days 1+4). Overall, the model tended to overestimate the concentrations at 95th percentile (outlier patients), especially for M2.

Individual model-derived AUC_{0-24} on Day 4 and Day 10 by HAT type (g-HAT vs. r-HAT) and weight category are summarized in the tables below for fexinidazole, and its metabolites M1 and M2.

g-HAT

g-HAT - Fexinidazole

Weight (categorized)	Statistics	AUC0-24 (µg*h/mL) - Day 4	AUC0-24 (µg*h/mL) - Day 10
Child's Bodyweight [20-35kg[	N/Nmiss	150/0	150/0
	Mean (SD)	7.55 (3.90)	3.81 (2.00)
	GM (CV%)	6.64 (51.65)	3.34 (52.36)
	Min/Median/Max	0.7/6.89/22.5	0.4/3.45/11.3
Child's Bodyweight >=35kg	N/Nmiss	28/0	28/0
	Mean (SD)	6.32 (2.52)	4.21 (1.74)
	GM (CV%)	5.87 (39.87)	3.88 (41.35)
	Min/Median/Max	2.8/5.63/11.7	1.9/3.76/7.9
Adult	N/Nmiss	313/0	300/13
	Mean (SD)	4.90 (2.32)	3.26 (1.58)
	GM (CV%)	4.37 (47.36)	2.89 (48.49)
	Min/Median/Max	0.7/4.63/16.0	0.5/3.06/10.7

g-HAT - Fexinidazole metabolite M1

Weight (categorized)	Statistics	AUC0-24 (µg*h/mL) - Day 4	AUC0-24 (µg*h/mL) - Day 10
Child's Bodyweight [20-35kg[	N/Nmiss	150/0	150/0
	Mean (SD)	294.33 (89.12)	149.06 (50.58)
	GM (CV%)	278.33 (30.28)	140.11 (33.94)
	Min/Median/Max	95.2/297.29/528.5	47.6/148.70/422.8
Child's Bodyweight >=35kg	N/Nmiss	28/0	28/0
	Mean (SD)	446.69 (127.14)	296.86 (91.44)
	GM (CV%)	431.36 (28.46)	285.37 (30.80)
	Min/Median/Max	229.4/426.25/916.4	152.9/284.30/645.5
Adult	N/Nmiss	313/0	300/13
	Mean (SD)	431.15 (110.43)	288.18 (79.33)
	GM (CV%)	416.85 (25.61)	277.75 (27.53)
	Min/Median/Max	151.2/436.20/1030.9	101.0/288.90/833.2

g-HAT - Fexinidazole metabolite M2

Weight (categorized)	Statistics	AUC0-24 (µg*h/mL) - Day 4	AUC0-24 (µg*h/mL) - Day 10
Child's Bodyweight [20-35kg[	N/Nmiss	150/0	150/0
	Mean (SD)	776.90 (222.80)	444.06 (137.43)
	GM (CV%)	745.05 (28.68)	424.48 (30.95)
	Min/Median/Max	382.7/757.40/1483.3	220.5/428.40/895.5
Child's Bodyweight >=35kg	N/Nmiss	28/0	28/0
	Mean (SD)	1206.48 (364.77)	892.71 (338.11)
	GM (CV%)	1158.90 (30.23)	844.01 (37.87)
	Min/Median/Max	545.3/1145.40/2515.2	375.8/840.25/2224.0
Adult	N/Nmiss	313/0	300/13
	Mean (SD)	1171.76 (293.73)	897.24 (271.42)
	GM (CV%)	1135.95 (25.07)	859.70 (30.25)
	Min/Median/Max	487.0/1139.60/2056.7	383.8/853.65/1882.0

r-HAT

r-HAT - Fexinidazole

Weight (categorized)	Statistics	AUC0-24 (µg*h/mL) - Day 4	AUC0-24 (µg*h/mL) - Day 10
	N/Nmiss	11/0	11/0
Child's Bodyweight [20-35kg[	Mean (SD)	6.39 (2.30)	3.20 (1.15)
	GM (CV%)	5.99 (36.05)	3.00 (36.08)
	Min/Median/Max	3.0/5.62/9.8	1.5/2.81/4.9
Child's Bodyweight >=35kg	N/Nmiss	6/0	6/0
	Mean (SD)	8.15 (3.58)	4.75 (1.02)
	GM (CV%)	7.66 (43.94)	4.66 (21.37)
	Min/Median/Max	5.8/6.73/15.2	3.8/4.49/6.3
Adult	N/Nmiss	28/0	27/1
	Mean (SD)	6.32 (2.83)	4.18 (1.91)
	GM (CV%)	5.88 (44.81)	3.89 (45.79)
	Min/Median/Max	3.7/5.63/16.7	2.4/3.77/11.7

r-HAT - Fexinidazole metabolite M1

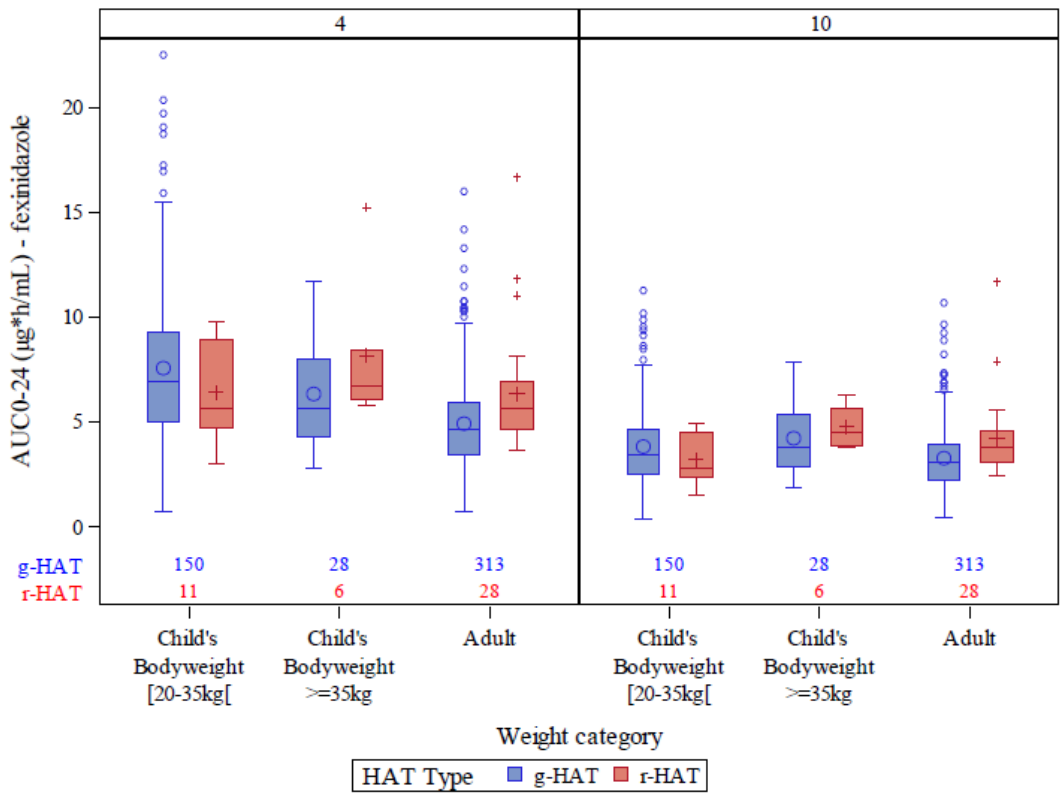
Weight (categorized)	Statistics	AUC0-24 (µg*h/mL) - Day 4	AUC0-24 (µg*h/mL) - Day 10
Child's Bodyweight [20-35kg[	N/Nmiss	11/0	11/0
	Mean (SD)	271.42 (91.42)	135.79 (45.84)
	GM (CV%)	258.42 (33.68)	129.27 (33.76)
	Min/Median/Max	149.2/265.94/454.4	74.7/133.00/227.9
Child's Bodyweight >=35kg	N/Nmiss	6/0	6/0
	Mean (SD)	459.06 (250.26)	264.53 (88.99)
	GM (CV%)	415.93 (54.52)	253.21 (33.64)
	Min/Median/Max	282.6/345.63/930.7	188.4/222.00/388.2
Adult	N/Nmiss	28/0	27/1
	Mean (SD)	432.19 (222.21)	269.54 (120.25)
	GM (CV%)	395.01 (51.42)	251.54 (44.61)
	Min/Median/Max	198.0/382.25/1321.4	132.0/252.20/748.4

r-HAT - Fexinidazole metabolite M2

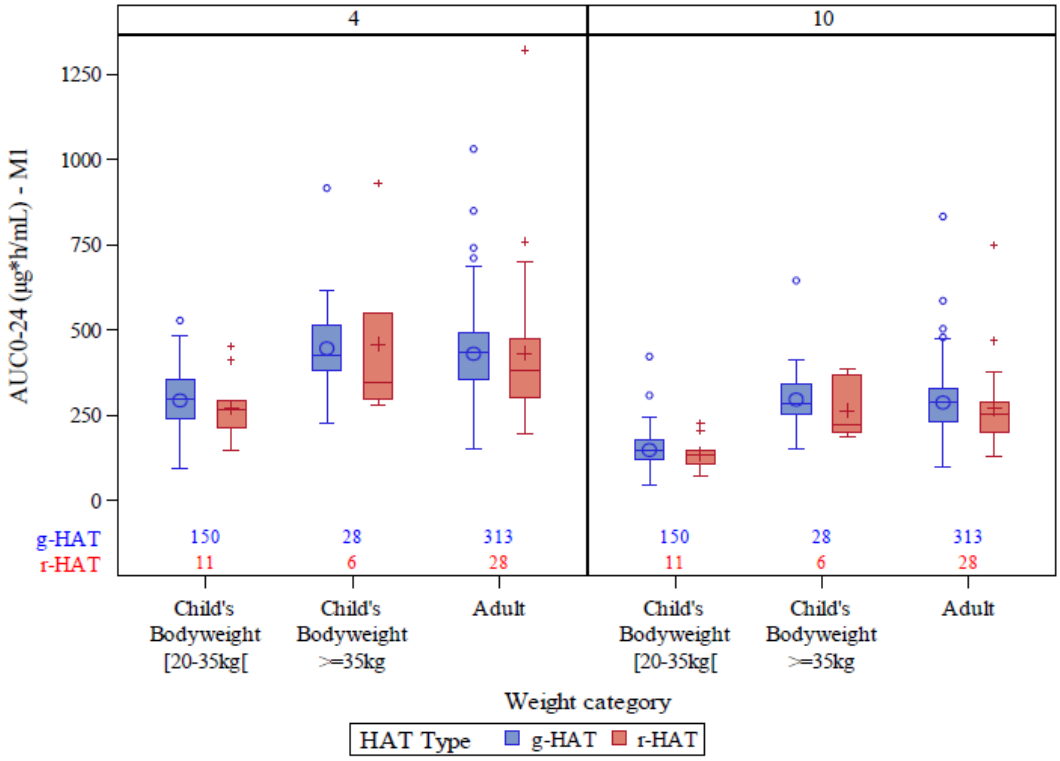
Weight (categorized)	Statistics	AUC0-24 (µg*h/mL) - Day 4	AUC0-24 (µg*h/mL) - Day 10
Child's Bodyweight [20-35kg[	N/Nmiss	11/0	11/0
	Mean (SD)	784.76 (312.66)	445.22 (203.68)
	GM (CV%)	736.94 (39.84)	412.65 (45.75)
	Min/Median/Max	417.6/749.60/1503.6	220.5/408.90/973.4
Child's Bodyweight >=35kg	N/Nmiss	6/0	6/0
	Mean (SD)	1182.78 (325.76)	792.18 (192.43)
	GM (CV%)	1140.98 (27.54)	770.80 (24.29)
	Min/Median/Max	692.6/1232.60/1482.8	479.8/792.75/1080.0
Adult	N/Nmiss	28/0	27/1
	Mean (SD)	1205.79 (422.04)	896.96 (349.00)
	GM (CV%)	1134.15 (35.00)	835.33 (38.91)
	Min/Median/Max	551.9/1144.90/2000.6	435.1/842.50/1682.0

Individual model-derived AUC_{0-24} on Day 4 and Day 10 by HAT type (g-HAT vs. r-HAT) and weight category are summarized in the figures below for fexinidazole, and its metabolites M1 and M2.

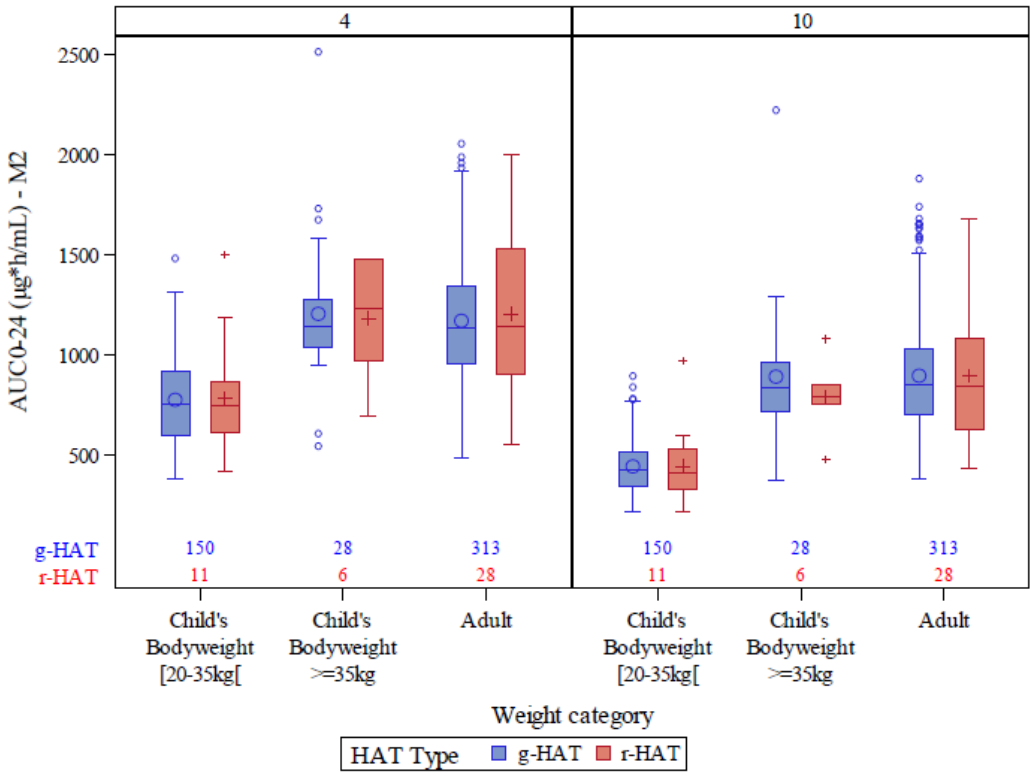
Fexinidazole



Fexinidazole metabolite M1



Fexinidazole metabolite M2



The figures above show that despite the difference in the volume of distribution (V_1/F) of fexinidazole and clearance (CLM2/F) of M2 between HAT type was statistically significant in the popPK model, their impact

on derived exposure of fexinidazole, M1 and M2 could not be clearly identified. The distribution of derived AUC_{0-24} at Day 4 and Day 10 were similar between the two HAT forms, for each group.

A full model including all previous fexinidazole studies in HAT patients was performed in the current analysis. According to PopPK report, nonlinearity of fexinidazole and M1 was observed but could not be properly captured by modelling as only a few data were available at Day 1 and Day 4 compared to the previous studies in DNDiFEX004, DNDiHATFEX006 and DNDi-FEX-09-HAT, for which only data at steady state of fexinidazole were collected. Inclusion of dose effect on k_{12} and CLM1/F allowed to better predict M1 and M2 concentrations. Moreover, a difference was highlighted by HAT type in volume of distribution (V_1/F) of fexinidazole and elimination of M2.

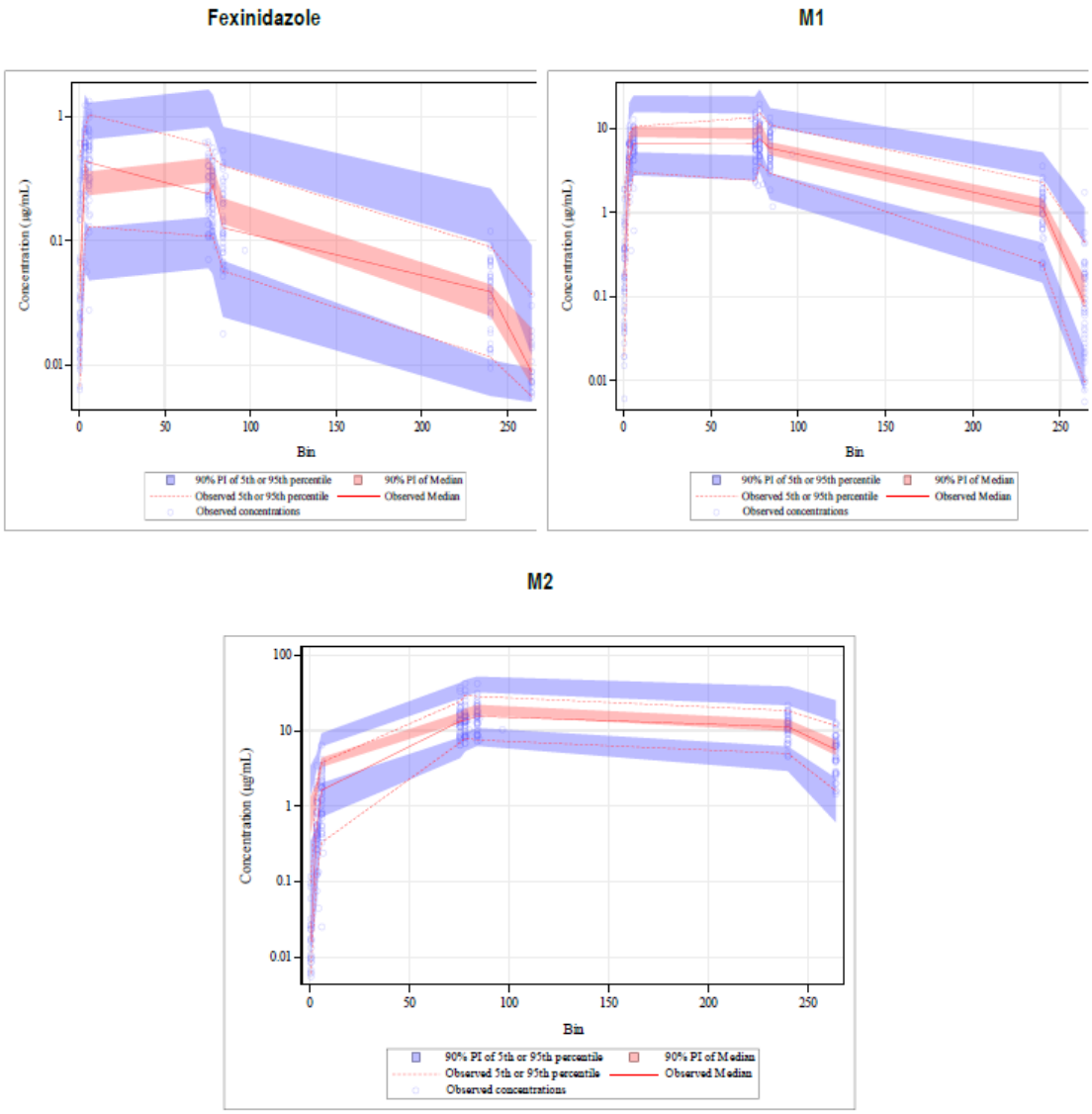
Generally, the CHMP considered that the final popPK model showed some evident misspecification during the loading dose phase: based on the VPCs for the final model, the PopPK model was not able to describe the observed PK data *vs* time for fexinidazole (under-predictions on Day 1, over-predictions on Day 4), for M1 (over-prediction on Days 1+4) and for M2 (over-prediction on Days 1+4). Nevertheless, during PopPK model development, the SOH has tested several models (saturable absorption, mixture of linear and non-linear fexinidazole elimination, saturable biotransformation of fexinidazole and M1, time-varying bioavailability, time-varying fexinidazole elimination) to improve the model fit to the loading dose, without success. An attempt to improve model fit by re-estimating model parameters by only including data from r-HAT patients was also tested. However, an overparameterized model (condition number exceeded 1000) was obtained with the M1 PK parameters (micro rate constant from compartment 1 to compartment 2 [k12] and apparent clearance of M1 [CLM1]) not precisely estimated (relative standard error [RSE] > 50%). This means that with the DNDi-FEX-07-HAT data alone, even a simple popPK model combining fexinidazole and its 2 metabolites did not allow a correct estimation of the parameters, so elaborating a more complex model to improve the fit between Day 4 and Day 1 would not been possible. Therefore, a standalone model using only data from DNDi-FEX-07-HAT was not an option.

Of note, all the development of therapeutic dose finding was based mainly on M2, which is the major circulating and pharmacologically active moiety, thus a popPK model including parent and metabolites was targeted.

Based on the above, the SOH decided to use the developed final PopPK model with pooled data for predictions of the maintenance phase, despite model misspecification for loading dose phase. For the maintenance phase it is considered that the final model well captures the pharmacokinetic profile of the 3 analytes (fexinidazole, M1 and M2). Therefore, the proposed SmPC was revised to include the following sentence in section 5.2 (Pharmacokinetic properties – Absorption):

« The exposures of fexinidazole and its metabolites M1 and M2 were comparable between g-HAT and r-HAT patients at the end of the maintenance dose (Day 10).»

Prediction-corrected Visual Predictive Check (pcVPC) for fexinidazole and its 2 metabolites (M1 and M2) concentrations (µg/mL) over time bins according to final model- DNDi-FEX-07-HAT data (log scale)



Abbreviations: M1, fexinidazole sulfoxide; M2, fexinidazole sulfone; pcVPC, prediction-corrected Visual Predictive Check

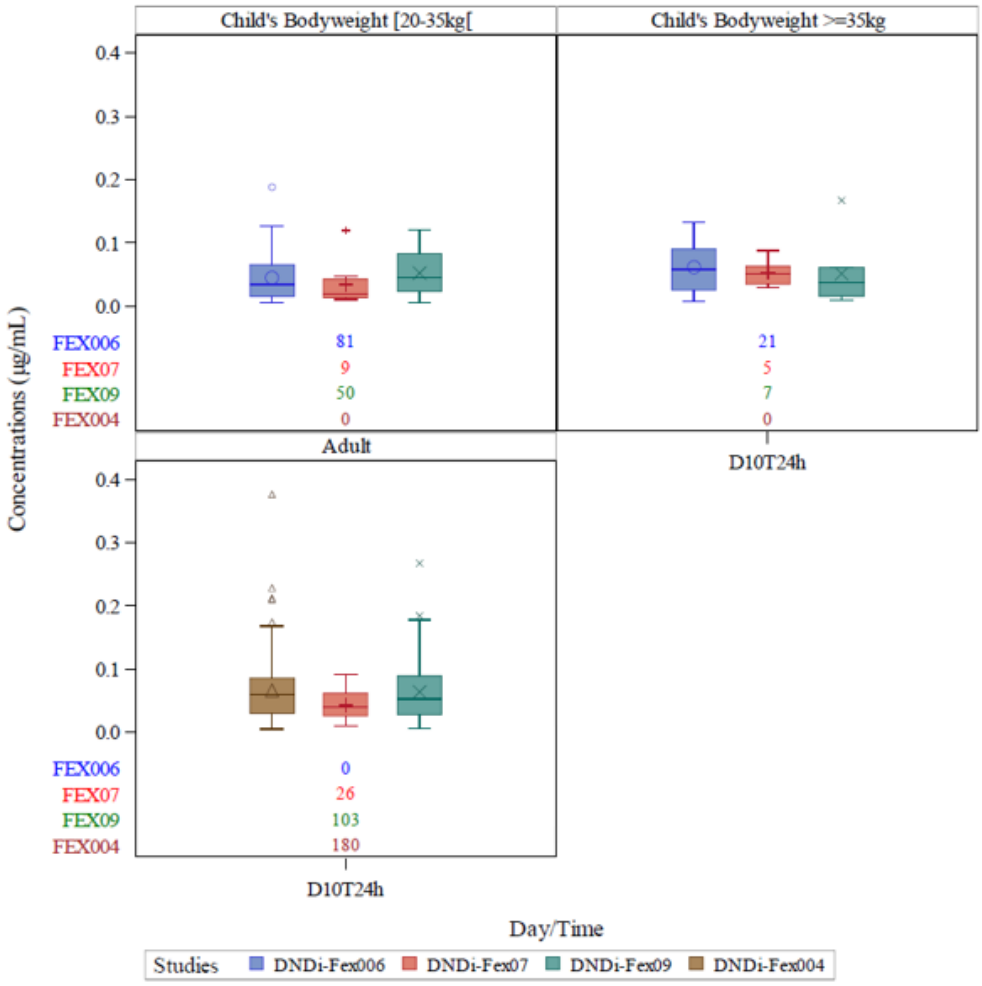
At the request of the CHMP, a by-time-point comparison of actual observed blood concentrations of fexinidazole, M1 and M2 between r-HAT and g-HAT has been provided in a tabular format. Comparative results (summary statistics) have been provided for fexinidazole, M1 and M2 measured from human dried blood spot (DBS) samples on Day 10, 24 hours after the last administration, in studies DNDi-FEX-07-HAT, DNDiFEX004, DNDiFEX006 and DNDi-FEX-09-HAT. Day 10 – 24h is considered as the most relevant timepoint given that it corresponds to the expected metabolite M2 t_{max}. Similar geometric mean values and variability was observed between studies for M2, for each group.

Descriptive statistics of observed fexinidazole concentrations (µg/mL) by body weight category and study – Day 10, 24 hours after the last administration

Visit	Body weight group	Statistics	DNDiFEX004	DNDiFEX006	DNDi-FEX-09-HAT	DNDi-FEX-07-HAT
			Fexinidazole			
D10T24h	Child's body weight [20-35 kg[	N/Nmiss		81/12	50/7	9/2
		Mean (SD)		0.045 (0.036)	0.052 (0.034)	0.034 (0.034)
		GM (CV%)		0.031 (81.098)	0.040 (64.477)	0.025 (100.144)
		Min/Median/Max		0.01/0.034/0.19	0.01/0.045/0.12	0.01/0.019/0.12
	Child's body weight ≥35 kg	N/Nmiss		21/0	7/0	5/1
		Mean (SD)		0.061 (0.042)	0.051 (0.054)	0.053 (0.023)
		GM (CV%)		0.046 (67.703)	0.034 (105.827)	0.049 (44.020)
		Min/Median/Max		0.01/0.058/0.13	0.01/0.037/0.17	0.03/0.051/0.09
	Adult	N/Nmiss	180/11		103/7	26/1
		Mean (SD)	0.066 (0.049)		0.064 (0.047)	0.043 (0.022)
		GM (CV%)	0.050 (74.436)		0.047 (74.033)	0.037 (50.211)
		Min/Median/Max	0.01/0.059/0.38		0.01/0.053/0.27	0.01/0.040/0.09

Abbreviations: **CV**, coefficient of variation; **D**, day; **GM**, geometric means; **h**, hour; **SD**, standard deviation

Distribution of fexinidazole concentrations (µg/mL) by study and body weight category – Day 10, 24 hours after the last administration

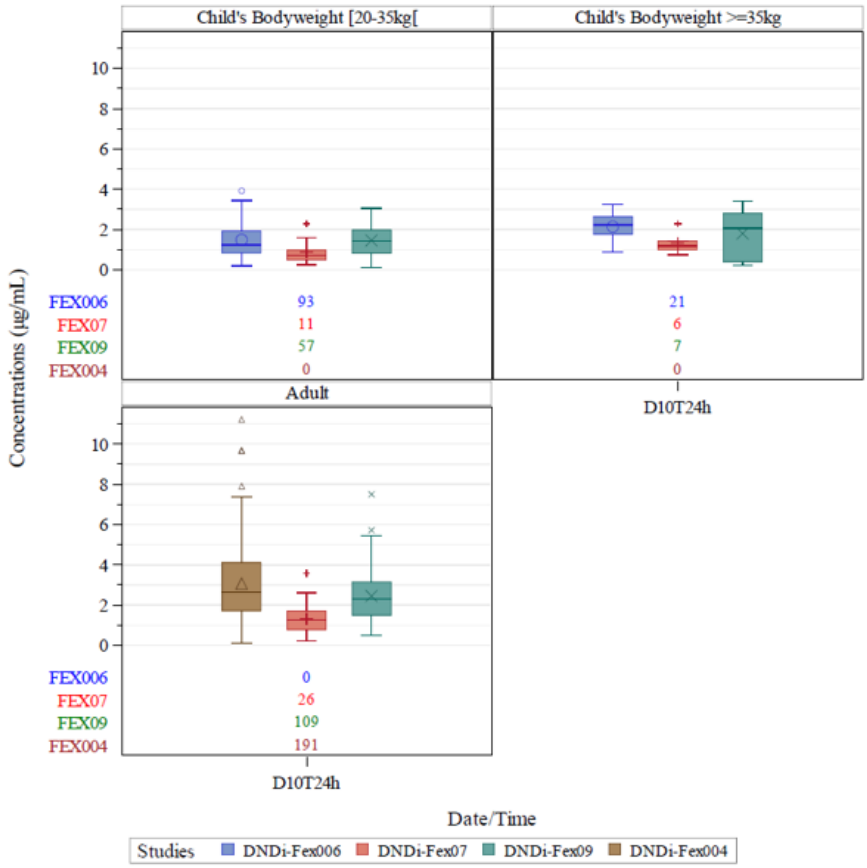


Descriptive statistics of observed fexinidazole sulfoxide (M1) concentrations (µg/mL) by body weight category and study – Day 10, 24 hours after the last administration

Visit	Body weight group	Statistics	DNDiFEX004	DNDiFEX006	DNDi-FEX-09-HAT	DNDi-FEX-07-HAT
			Fexinidazole sulfoxide (M1)			
D10T24h	Child's body weight [20-35 kg[	N/Nmiss		93/0	57/0	11/0
		Mean (SD)		1.484 (0.821)	1.454 (0.740)	0.873 (0.603)
		GM (CV%)		1.273 (55.302)	1.192 (50.911)	0.710 (69.113)
		Min/Median/Max		0.19/1.231/3.92	0.11/1.443/3.05	0.25/0.724/2.28
	Child's body weight ≥35 kg	N/Nmiss		21/0	7/0	6/0
		Mean (SD)		2.140 (0.674)	1.802 (1.209)	1.303 (0.542)
		GM (CV%)		2.014 (31.522)	1.268 (67.090)	1.221 (41.624)
		Min/Median/Max		0.87/2.230/3.23	0.21/2.050/3.42	0.73/1.177/2.29
	Adult	N/Nmiss	191/0		109/1	26/1
		Mean (SD)	3.072 (1.825)		2.452 (1.241)	1.321 (0.724)
		GM (CV%)	2.521 (59.390)		2.130 (50.602)	1.114 (54.819)
		Min/Median/Max	0.12/2.645/11.22		0.49/2.297/7.50	0.22/1.251/3.57

Abbreviations: **CV**, coefficient of variation; **D**, day; **GM**, geometric means; **h**, hour; **M1**, fexinidazole sulfoxide; **SD**, standard deviation

Distribution of fexinidazole sulfoxide (M1) concentrations (µg/mL) by study and body weight category – Day 10, 24 hours after the last administration

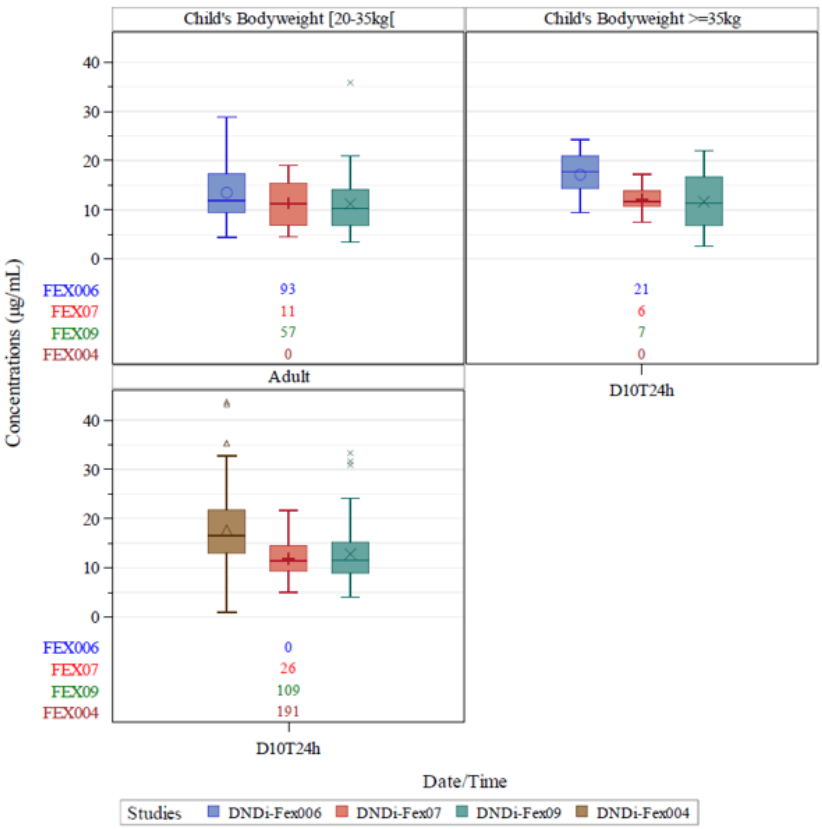


Descriptive statistics of observed fexinidazole sulfone (M2) concentrations (μg/mL) by body weight category and study – Day 10, 24 hours after the last administration

Visit	Body weight group	Statistics	DNDiFEX004	DNDiFEX006	DNDi-FEX-09-HAT	DNDi-FEX-07-HAT
			Fexinidazole sulfone (M2)			
D10T24h	Child's body weight [20-35 kg[	N/Nmiss		93/0	57/0	11/0
		Mean (SD)		13.489 (5.568)	11.220 (5.721)	11.327 (4.928)
		GM (CV%)		12.365 (41.277)	9.971 (50.991)	10.250 (43.507)
		Min/Median/Max		4.45/11.870/28.91	3.43/10.238/35.86	4.56/11.242/18.98
	Child's body weight ≥35 kg	N/Nmiss		21/0	7/0	6/0
		Mean (SD)		17.168 (4.517)	11.658 (6.770)	12.114 (3.284)
		GM (CV%)		16.553 (26.312)	9.623 (58.074)	11.738 (27.106)
		Min/Median/Max		9.43/17.702/24.23	2.55/11.314/21.99	7.55/11.632/17.27
	Adult	N/Nmiss	191/0		109/1	26/1
		Mean (SD)	17.619 (6.947)		12.806 (5.701)	11.873 (4.019)
		GM (CV%)	16.122 (39.428)		11.699 (44.516)	11.199 (33.849)
		Min/Median/Max	0.91/16.551/43.72		4.10/11.509/33.30	4.98/11.392/21.69

Abbreviations: **CV**, coefficient of variation; **D**, day; **GM**, geometric means; **h**, hour; **M2**, fexinidazole sulfone; **SD**, standard deviation

Distribution of fexinidazole sulfoxide (M2) concentrations (μg/mL) by study and body weight category – Day 10, 24 hours after the last administration



Geometric means (GM) and coefficient of variation (CV%) of observed fexinidazole, M1 and M2 concentrations (μg/mL) by body weight category compared to predicted concentrations by the population PK model – Day 10, 24 hours after the last administration

Visit	Body weight group	Statistics	Predicted concentration (DNDi-FEX-07-HAT)	Observed concentration (DNDi-FEX-07-HAT)
		Fexinidazole		
D10T24h	Child's body weight [20-35kg[	N/Nmiss	11/0	9/2
		GM (CV%)	0.021 (89.617)	0.025 (100.144)
	Child's body weight ≥35kg	N/Nmiss	6/0	5/1
		GM (CV%)	0.055 (73.827)	0.049 (44.020)
	Adult	N/Nmiss	27/0	26/1
		GM (CV%)	0.047 (47.604)	0.037 (50.211)
		Fexinidazole sulfoxide (M1)		
D10T24h	Child's body weight [20-35 kg[	N/Nmiss	11/0	11/0
		GM (CV%)	0.755 (72.800)	0.710 (69.113)
	Child's body weight ≥35 kg	N/Nmiss	6/0	6/0
		GM (CV%)	1.330 (63.977)	1.221 (41.624)
	Adult	N/Nmiss	27/0	26/1
		GM (CV%)	1.078 (59.655)	1.114 (54.819)
		Fexinidazole sulfone (M2)		
D10T24h	Child's body weight [20-35 kg[	N/Nmiss	11/0	11/0
		GM (CV%)	10.917 (45.161)	10.250 (43.507)
	Child's body weight ≥35 kg	N/Nmiss	6/0	6/0
		GM (CV%)	11.259 (21.560)	11.738 (27.106)
	Adult	N/Nmiss	27/0	26/1
		GM (CV%)	10.040 (33.301)	11.199 (33.849)

Abbreviations: **CV**, coefficient of variation; **D**, day; **GM**, geometric means; **h**, hour; **M1**, fexinidazole sulfoxide; **M2**, fexinidazole sulfone

For g-HAT, when AUC_{0-24h} was derived by the model, based on the geometric means ratio, it was observed a 50% higher exposure of fexinidazole for the (20-35) kg group when compared to adults at Day 4 and a similar exposure at Day 10. For metabolites M1 and M2, it was observed a lower exposure (a decrease of approximately 30%) for the (20-35) kg group when compared to adults at Day 4 and a lower exposure (a decrease of approximately 50%) at Day 10.

For r-HAT, when AUC_{0-24h} was derived by the model, based on the geometric means ratio, it was observed a similar exposure of fexinidazole for the (20-35) kg group when compared to adults at Day 4 and a lower exposure at Day 10 (a decrease of approximately 20%). For metabolites M1 and M2, it was observed a lower exposure for the (20-35) kg group when compared to adults at Day 4 and at Day 10, with decreases of approximately 35% and 50%, respectively.

The table below summarizes the calculations for the geometric means ratios for (20-35) kg / Adult.

			Geometric means for *AUC0-24 (µg*h/mL)*				Ratio
Type	Analyte	Day	[20-35[kg	>=35 kg	Adult		[20-35[kg / Adult
g-HAT	Fexinidazole	4	6.64	5.87	4.37		1.52
g-HAT	Fexinidazole	10	3.34	3.88	2.89		1.16
g-HAT	M1	4	278.33	431.36	416.85		0.67
g-HAT	M1	10	140.11	285.37	277.75		0.50
g-HAT	M2	4	745.05	1158.9	1135.95		0.66
g-HAT	M2	10	424.48	844.01	859.7		0.49
r-HAT	Fexinidazole	4	5.99	7.66	5.88		1.02
r-HAT	Fexinidazole	10	3	4.66	3.89		0.77
r-HAT	M1	4	258.42	415.93	395.01		0.65
r-HAT	M1	10	129.27	253.21	251.54		0.51
r-HAT	M2	4	736.94	1140.98	1134.15		0.65
r-HAT	M2	10	412.65	770.8	835.33		0.49

As the model clearly showed misspecification due to the nonlinearity observed and not supported by the model, the comparison of model-derived PK exposure between g-HAT and r-HAT patients on Day 4 should not be taken into account. However, the model well predicted the observed data of all compounds at the maintenance phase and on Day 10. Therefore, the SOH proposed to summarize in the SmPC the comparison of the PK exposures based on predicted AUC_{0-24} between g-HAT and r-HAT patients and in paediatric g-HAT and r-HAT patients based only on Day 10 calculated exposures.

Despite considering that the AUC_{0-24} (µg.h/mL) data on Day10 calculated by the POP PK model and Bayesian analysis using not only the concentration at 24 h but also at 48 h after the last dose, are reliable estimate of the overall exposures at Day 10, the SOH agreed with the CHMP to report in the SmPC the comparison of fexinidazole, M1 and M2 exposure between g-HAT and r-HAT based on the C_{24h} (or corresponding C_{trough}) on Day 10. Therefore, the SOH has summarized the geometric means of the C_{24h} at Day 10, calculated by the POP PK model and Bayesian analysis together with their ratio in the pediatric populations versus the adult population (Table below). As previously shown with the AUC_{0-24} (µg.h/mL), there is a good consistency between the C_{24h}, Day 10 calculated by the model and the observed C_{24h}, Day 10. Using the calculated C_{24h}, Day 10 allows to have mean estimates, across the different clinical studies and by g-HAT or r-HAT population and pediatric populations of adult population.

Geometric mean fexinidazole, M1 and M2 C_{24h} (µg/mL) on Day 10 and corresponding ratios

		Pediatrics C_{24} (µg/mL)		Adults C_{24} (µg/mL)	Ratio	
		[20-35kg[	>=35kg	Adult	[20-35kg[/adult	>=35kg/adult
g-HAT	Fexinidazole	0.03	0.05	0.05	0.60	1.00
	M1	1.22	1.94	2.21	0.55	0.88
	M2	11.3	15.5	14.5	0.78	1.07
r-HAT	Fexinidazole	0.02	0.06	0.05	0.40	1.20
	M1	0.76	1.33	1.08	0.70	1.23
	M2	10.9	11.3	10.0	1.09	1.12

In paediatric patients with g-HAT or r-HAT weighing ≥ 35 kg and receiving the standard dosing regimen, fexinidazole, M1 and M2 exposures (based on concentrations 24 h post-dose on Day 10) were comparable to adult patients exposures, at the end of the maintenance dose (Day 10).

In children with g-HAT or r-HAT weighing [20-35[kg receiving the adjusted dosing regimen, as compared to adult patients receiving the standard dosing regimen, fexinidazole and M1 exposures (based on concentrations 24 h post-dose on Day 10) were 30 to 60 % lower, and M2 exposures were comparable, at the end of the maintenance dose (Day 10, based on concentrations at 24 h post-dose). This had no impact on clinical efficacy (see section 4.4 hospitalisation of patients).

Based on results from study DNDiFEX007, the wording of SmPC section 5.2 regarding r-HAT patients was updated in the proposed SmPC, for “Absorption” and Paediatric population”.

2.3.3. Pharmacodynamics

No new clinical pharmacodynamics data have been submitted in this application, which is considered acceptable. However, some details were provided on the PD of fexinidazole in the treatment of r-HAT patients.

- The presence of trypanosomes was detected at baseline for disease staging and monitored at various time points in the blood and in the CSF of patients using various techniques.No trypanosomes were detected in the blood of evaluable r-HAT patients on fexinidazole at Day 5 (45/45) or Day 10 (44/44)
- No trypanosomes were detected in the CSF of evaluable r-HAT (44/44) patients on fexinidazole at Day 10

These data supported the trypanocidal activity of fexinidazole against *T. b. rhodesiense* parasites in the blood and CSF of r-HAT patients.

Mechanism of action

Fexinidazole is a member of the 5-nitroimidazole group which belongs to the antiparasitic class. As indicated in the current approved SmPC for fexinidazole, no specific studies have been performed to assess the mode of action (MoA) of fexinidazole and its 2 metabolites, fexinidazole sulfoxide (M1) and fexinidazole sulfone (M2).

Pharmacokinetic/Pharmacodynamic relationships

The measured concentrations of M2 in the blood of r-HAT patients at Day 4 (12 hours) and at Day 10 (24 hours, i.e., Day 11) were at least above 3-fold MIC levels for M2 in almost all patients, and were compatible as already mentioned above with an effective trypanocidal activity of fexinidazole as no trypanosomes were detected in the blood (Day 5 or Day 10) or CSF (Day 10) of all evaluable patients (45 patients at Day 5 and 44 patients at Day 10).

Trypanocidal concentrations of M2 in patient blood at Day 4 (12 hours) and Day 11

M2 blood concentrations levels	Number of patients (%)	
	Day 4 (12 hours)	Day 10 (24 hours, Day 11)
>3-fold MIC for M2 = 6.6 µg/mL	44/44[a] (100%)	39/43[b] (91%)
> targeted M2 concentration 10 µg/mL	34/44[a] (77%)	31/43[b] (72%)

Abbreviations: **M2**, fexinidazole sulfone metabolite; **MIC**, minimal concentration to completely inhibit parasite growth

a PK data for 44 patients on Day 4 because 1 value was missing due to a non valid spot (Patient No. 2001)

b PK data for 43 patients on Day 11 because 2 values were missing due to a non valid spot (Patient No. 2001) and no sample received (Patient No. 1035 died on Day 8)

2.3.4. Discussion on clinical pharmacology

Regarding pharmacokinetics, a full PopPK model including all previous fexinidazole studies in HAT patients was performed in the current analysis. During PopPK model development, several models have been tested to improve the model fit to the loading dose, but without success. The final model shows an evident misspecification during the loading dose phase. However, for the maintenance phase it is considered that the final model well captures the pharmacokinetic profile of the 3 analytes (fexinidazole, M1 and M2). Therefore, the proposed SmPC was revised to include this information in section 5.2 - Pharmacokinetic properties – Absorption.

Despite considering that the AUC_{0-24} (µg.h/mL) data on Day10 calculated by the POP PK model and Bayesian analysis using not only the concentration at 24 h but also at 48 h after the last dose, are reliable estimate of the overall exposures at Day 10, the SOH agreed with the CHMP to report in the SmPC the comparison of fexinidazole, M1 and M2 exposure between g-HAT and r-HAT based on the C_{24h} (or corresponding C_{trough}) on Day 10.

In paediatric patients with g-HAT or r-HAT weighing ≥ 35 kg and receiving the standard dosing regimen, fexinidazole, M1 and M2 exposures (based on concentrations 24 h post-dose on Day 10) were comparable to adult patients exposures, at the end of the maintenance dose (Day 10).

In children with g-HAT or r-HAT weighing [20-35[kg receiving the adjusted dosing regimen, as compared to adult patients receiving the standard dosing regimen, fexinidazole and M1 exposures (based on concentrations 24 h post-dose on Day 10) were 30 to 60 % lower, and M2 exposures were comparable, at the end of the maintenance dose (Day 10, based on concentrations at 24 h post-dose). This had no impact on clinical efficacy (see section 4.4 hospitalisation of patients). Therefore, the proposed SmPC was revised to include this information in section 5.2 - Pharmacokinetic properties –Paediatric population.

2.3.5. Conclusions on clinical pharmacology

The SOH concluded that as *no trypanosomes were detected either in blood from Day 5 onwards or in CSF at EOT in any r-HAT patients* and *the therapeutic blood levels for M2 were reached in most if not all patients from Day 4 to 24 hours after the last dose of fexinidazole*, *these data support the use of the fexinidazole dose regimen which is recommended in the current approved SmPC for fexinidazole in g-HAT patients in r-HAT patients:*

Fexinidazole tablets (600 mg) to be taken per oral in fed conditions at about the same time of the day each day:

- *Body weight ≥20 kg and <35 kg (1200/600 mg):*

  - Loading dose phase (Day 1 to Day 4): 1200 mg/d (2 tablets) for 4 days

  - Maintenance dose phase (Day 5 to Day 10): 600 mg/d (1 tablet) for 6 days

- Body weight ≥35 kg (1800/1200 mg):

  - Loading dose phase (Day 1 to Day 4): 1800 mg/d (3 tablets) for 4 days

  - Maintenance dose phase (Day 5 to Day 10): 1200 mg/d (2 tablets) for 6 days

Based on the data provided this conclusion was endorsed by the CHMP. The proposed SmPC wording in section 5.2 for r-HAT patients was updated appropriately.

2.4. Clinical efficacy

This application for extension of the indications to include treatment of both first stage (haemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*, in patients aged ≥6 years old and with body weight ≥20 Kg, for Fexinidazole Winthrop relies on a one clinical trial (DNDi-FEX-07-HAT) which was conducted in adult and pediatric stage-2 and stage-1 r-HAT patients in Malawi and Uganda. DNDi-FEX-07-HAT - Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*.

Proposed indication

Fexinidazole Winthrop is indicated for the treatment of both first-stage (haemo-lymphatic) and second-stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense *(g-HAT) and* Trypanosoma brucei rhodesiense *(r-HAT) in adults and children ≥6 years old and weighing ≥ 20 kg. Fexinidazole should be used in line with official recommendations.*

Fexinidazole Winthrop is recommended to be administered as 600 mg tablets, taken orally, once daily, with food, with the dosage regimen depending on the body weight:

Body weight ≥35 kg (Total administered dose: 14400 mg):

- 1800 mg (3 tablets) for 4 days (Day 1 to Day 4), followed by
- 1200 mg (2 tablets) for 6 days (Day 5 to Day 10)

Body weight ≥20 and <35 kg (Total administered dose: 8400 mg):

- 1200 mg (2 tablets) for 4 days (Day 1 to Day 4), followed by
- 600 mg (1 tablet) for 6 days (Day 5 to Day 10).

The CHMP noted that the SOH submitted one single trial in support of the proposed indication. Hence, the primary evidence of the effect of fexinidazole on r-HAT is based on one single study, the DNDi-FEX-07-HAT study.

The efficacy results of DNDi-FEX-07-HAT are reported in an initial clinical study report (CSR). At the data cut-off date for this initial CSR on 25 January 2022, all patients (N = 44) had reached Week 9 and datasets were complete, but they were incomplete at Month 6 (6 patients ongoing) and at Month 12 (14 patients ongoing), which corresponds to the end of study (EoS). The final results of the primary

efficacy endpoint at end of hospitalization (EoH) and the final results for the secondary efficacy endpoints at EoH and Week 9 were presented in this initial CSR, while SOH stated that the final results at Month 6 and at Month 12 (or EoS) would be reported in the final CSR that would need to be submitted as part of this variation procedure.

In the initial Scientific Advice requested by the SOH to guide on the submission of this extension of the indications, the CHMP agreed that the SOH could submit data from all subjects regarding treatment efficacy and at least 2/3 of subjects with complete 12 months follow up at the time of approval in the understanding that the 12-months follow-up data of the remaining patients would be added during the procedure.

As the last enrolled patient occurred on 17/11/2021 and study follow-up ends when 12 months is completed for the last enrolled patient (11/2022), all patients had already reached the end of study. The full data and final CSR of the DNDi-FEX-07-HAT study were therefore requested. The final CSR of the DNDi-FEX-07-HAT study was submitted. All the visits missing in the initial CSR (6 patients at the 6-month visit and 14 patients at the 12-month visit) were completed and presented in the final report. No relevant efficacy or safety new information was reported in the two visit times missing (no other death or relapse cases were identified) which allowed to state that the efficacy and acceptable safety profiles of fexinidazole in r-HAT patients described in the initial CSR were confirmed based on the full data in the final CSR for Study DNDi-FEX-07-HAT.

2.4.1. Dose response study

No dose response studies were performed in subjects with r-HAT.

The dose and the dosing regimen of fexinidazole depend on body weight.

The choice of the dose for the DNDi-FEX-07-HAT study was based on the results of the analysis of PK and pharmacodynamic data from adults (healthy volunteers and patients) and on the minimum inhibitory concentration.

The dosing schedule in adults used in Phase II/III studies in stage 2 g-HAT patients (DNDiFEX004 and DNDiHATFEX005) consisted in a 4-day period where a loading dose (1800 mg per day) was administered to reach effective drug (fexinidazole and active metabolites) levels in the blood and CSF in a reduced amount of time, followed by a 6-day period where lower fexinidazole doses (1200 mg per day) are delivered to ensure the maintenance of effective drug levels in the blood and CSF. The 10-day regimen was well tolerated and allowed to reach the CSF concentrations of the pharmacologically active metabolites that are expected to be effective in late stage 2 g-HAT.

The DNDiFEX003 (NCT0148370) study showed that the dosing regimen for g-HAT patients with body weight ≥35 kg (as described above) was optimal to rapidly reach exposure levels in the brain at least twice as high as the minimal inhibitory concentration for the sulfone metabolite M2. The total dose for the 10-day treatment was 14400 mg. The use of a loading dose also leads to a shorter duration of treatment, which in turn avoids fexinidazole related increases in liver enzyme levels. The optimal dosing regimen should also include concomitant intake of food to maximise exposure over a short period of time and to reduce the dose administered (DNDiFEX001 Part 2, DNDiFEX002).

The progression of g-HAT is identical in adults and children, and a comparable schedule (i.e., 4-day loading dose and a 6-day maintenance dose) was applied to children (DNDiHATFEX006). The choice of the fexinidazole doses to be delivered in children was based on the objective to give comparable amount of fexinidazole by unit of body weight. Safety data showed similar outcome to that described in the adult

population and the benefit-risk balance of fexinidazole for treating children with g-HAT, regardless of the disease stage, appeared positive.

Given the fixed general dosing schedule and the available formulation (i.e., 600-mg tablets), the dosing regimen for children weighing ≥20 to <35 kg was 1200 mg daily for 4 days, followed by 600 mg daily for 6 days, for a total dose administered of 8400 mg.

Using this dosing regimen, a child weighing 20 kg would receive:

• Dose from Day 1 to Day 4: 60 mg/kg (1200 mg/day), which was slightly higher than the maximum dose administered at Day 1 in the 35 kg children or adults (51.4 mg/kg – 1800 mg/day)

• Total administered dose: 420 mg/kg (8400/20), which was close to the dose administered in children or adults ≥35 kg of weight (411.4 mg/kg for a 35 kg weight individual – 14400/35).

The doses and the dosing regimens of fexinidazole used in DNDi-FEX-07-HAT study were those approved for the treatment of g-HAT.

The CHMP noted that no dose response studies were performed for the r-HAT proposed indication and the same dose used for g-HAT was proposed.

This was considered acceptable, taking into account the low number of r-HAT cases, the difficult access to the remote areas where the disease is more prevalent and the COVID-19 pandemic during the conduct of the DNDi-FEX-07-HAT study.

2.4.2. Main study

DNDi-FEX-07-HAT study

DNDi-FEX-07-HAT study, is a phase-II/III, multicenter, open-label, non-randomized, single-arm clinical trial to assess the efficacy and safety of fexinidazole in patients with r-HAT.

The Sponsor for this study was the organisation Drugs for Neglected Diseases initiative (DNDi). The study was conducted at 2 centres, in Malawi and Uganda. Eligible patients with human African trypanosomiasis (HAT) from other hospitals and centres were to be referred for treatment to Lwala or Rumphi Hospital. The study constituted an independent Data Safety Monitoring Board (DSMB). Data management and statistical analysis of data was conducted by Epicentre (France).

Overview of the efficacy and safety clinical trial conducted in r-HAT patients – Study DNDi-FEX-07-HAT

Study	Indication	Design	Duration and schedule	Study drug and dose	Primary objective
DNDi-FEX-07-HAT *ongoing at the time of the data cut-off date for the initial CSR*[a]	Human African trypanosomiasis due to *T. b. rhodesiense* (r-HAT)	Phase II/III, multicenter, open-label, non-randomized, single-arm, efficacy and safety of fexinidazole Study conducted in Malawi and Uganda	The participation of each patient lasted approximately 12 months and included: Screening/baseline: 7 days (Day -7 to Day -1) Treatment period: 10 days (Day 1 to Day 10) End of treatment (EOT): Day 11 End of hospitalization (EOH): Day 12 to Day 18 Follow-up visits: Month 1, Week 9, Month 6 and Month 12 Time to end of study (EOS)[a]: 12 months after Day 1	Clinical fexinidazole tablets (600 mg) PO in fed conditions[c] Body weight ≥35 kg (1800/1200 mg) *loading dose Day 1-Day 4* 1800 mg/d (3 tablets) for 4 days *maintenance dose Day 5-Day 10* 1200 mg/d (2 tablets) for 6 days Body weight ≥20 kg and <35 kg (1200/600 mg) *loading dose Day 1-Day 4* 1200 mg/d (2 tablets) for 4 days *maintenance dose Day 5-Day 10* 600 mg/d (1 tablet) for 6 days	To show that the fatality rate (r-HAT or treatment related death) at EOH in stage-2 patients[d] treated with fexinidazole is smaller than a threshold of unacceptable rate of 8.5%

Abbreviations: **CSR**, clinical study report; **d**, day; **DSMB**, data safety monitoring board; **EOH**, end of hospitalization; **EOS**, end of study; **EOT**, end of treatment; **PO**, per oral; **r-HAT**, human African trypanosomiasis due to *T. b. rhodesiense*; ***T. b.***, *Trypanosoma brucei*

Source: DNDi-FEX-07-HAT CSR

a At the time of the initial data cut-off date – 25 January 2022, the datasets was complete up to Week 9 (N = 44), except 1 patient who died prematurely at Day 8 for reason unrelated to study drug or disease according to the Sponsor, the Investigator and the independent evaluation by the DSMB. The datasets were incomplete at Month 6 (*6 patients were ongoing*) and at Month 12 (*14 patients were ongoing*). Please note that the last patient last visit was on 12 October 2022

b Month-1 visit consisted of a home visit to the patient by the Investigator. In case of clinical concerns, the Investigator could request a parasitological test

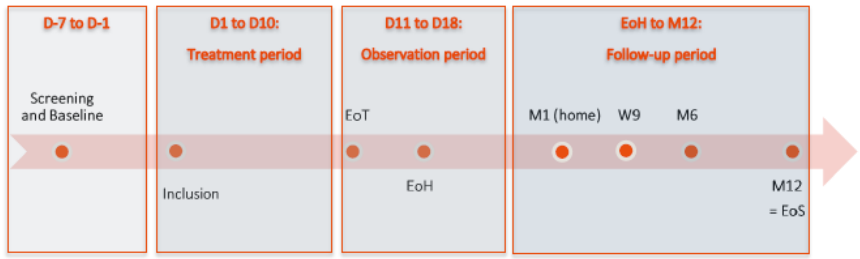
c Patients were given fexinidazole with 1 complete meal (or 1 Plumpy'Nut® sachet) per day at about the same time of the day each day

d It was planned to recruit 34 evaluable patients with stage 2 r-HAT and any number of patients with stage 1 r-HAT; 45 patients were included and treated (35 patients with stage-2 r-HAT and 10 patients with stage-1 r-HAT: *safety population*); 44 patients were evaluable for efficacy (including 34 evaluable patients with stage 2 r-HAT for the primary endpoint)

The participation of each patient was supposed to last approximately 12 months and include:

- Screening/baseline: 7 days (Day -7 to Day -1)
- Treatment period: 10 days (Day 1 to Day 10)
- End of treatment (EoT): Day 11
- End of hospitalization (EoH): Day 12 to Day 18
- Follow-up visits: Month 1, Week 9, Month 6 and Month 12
- Time to end of study (EoS): 12 months after Day 1

Figure 1 – Study design



D = day; EoH = end of hospitalisation; EoS = end of study; EoT = end of treatment; M = month; W = week.
Source: Clinical study protocol in 16-1-1-amendment-3.

Methods

Study participants

According to the standard medical procedures for HAT, patients presenting at the study site underwent the following tests within 7 days before Informed Consent Form (ICF) signature:

- Blood: parasite detection was performed by using microscopic examination of capillary or venous blood samples for parasite detection – blood samples had to be processed according to the mini-anion exchange centrifugation technique (mAECT). If mAECT was not available, the microhaematocrit centrifugation technique (MHCT or Woo test) or the thick or thin blood smear could be used for initial diagnosis.
- Lymph node aspirates: if any enlarged cervical lymph node was detected, aspirate sampling and microscopic examination for parasite detection was to be done, if routinely performed at the centre.
- CSF: a lumbar puncture was performed to collect CSF on patients with trypanosomes in blood and/or lymph, followed by WBC count, modified single centrifugation and microscopic examination for parasite detection to evaluate the disease stage.

Note: If the patient was parasite-negative in the blood and/or lymph node aspirate and lumbar puncture had not been performed, the patient was not proposed to enter the study. If signs strongly suggestive of HAT were present, a lumbar puncture could be performed at the Investigator's discretion; if trypanosomes were then detected in the CSF, the patient could be proposed to enter the study if all inclusion and exclusion criteria were met.

Parasite-positive patients were informed about the study and offered to sign the Informed consent form (ICF) before undergoing any further testing. Using CSF and/or blood samples which were taken as part of

standard of care, microscopic videos of the trypanosomes in the CSF and in the blood could be taken but were transmitted to the Sponsor only after the patient signed the ICF.

A patient's stage of r-HAT was classified as:

- Stage 1, defined as the presence of trypanosomes in blood and/or lymph, no trypanosomes in the CSF, and CSF WBC ≤5 cells/µL of CSF;
- Stage 2, defined as the presence of trypanosomes in the CSF and/or evidence of trypanosomes in blood, lymph, with CSF WBC >5 cells/µL.

Inclusion criteria

Patients had to meet all the following inclusion criteria to be eligible for enrolment into the study:

- Signed ICF (plus assent for children)
- ≥6 years old
- ≥20 kg body weight
- Ability to ingest at least one complete meal per day (or at least one Plumpy'Nut® sachet)
- Karnofsky index ≥40
- Parasitological confirmed of *T. brucei rhodesiense* infection.
- Having a permanent address or being traceable by others and willing and able to comply with follow-up visit schedule.
- Agreement to be hospitalised for a minimum of 13 days and to receive the study treatment.

Exclusion criteria

The presence of any of the following excluded a patient from study enrolment:

- Active clinically relevant medical conditions other than HAT that could jeopardise patient's safety or, at the Investigator's discretion, could interfere with participation in the study (e.g., patients at risk of QT prolongation)
- Compromised general health or severely deteriorated general condition, such as severe malnutrition, cardiovascular shock, respiratory distress, or terminal illness.
- Patients with severe hepatic impairment (e.g., clinical signs of cirrhosis or jaundice)
- Known hypersensitivity to fexinidazole, to any nitroimidazole drugs (e.g., metronidazole, tinidazole), or to any of the excipients.
- Patients previously enrolled in the study or having already received fexinidazole.

The CHMP endorsed the inclusion and exclusion criteria to be eligible for enrolment into the study.

Treatments

As an open-label, non-randomized, single-arm clinical trial, all patients were assigned to treatment with fexinidazole.

Fexinidazole was administered (dose and dosing regimen) as described above, as 600 mg tablets, to be taken orally in a single intake within 30 minutes of a meal under direct observation of an authorised staff member at the daily dose of (regardless of the stage of the r-HAT). The tablets had not to be broken or crushed.

Fexinidazole was administered over 10 days, preferably at the same time every day, and only during hospitalisation. A study nurse oversaw the patient's food intake to make sure that the patient had eaten sufficiently (if the patient could not eat enough, the patient was to be provided with a bag of Plumpy'Nut).

Patients who vomited shortly after dosing (within 2 hours of study treatment administration) received the daily dose of fexinidazole again. If vomiting occurred more than 2 hours after study treatment administration, fexinidazole was not re-administered, as study treatment absorption was likely to have been complete.

The CHMP considered acceptable that no dose response studies were performed for the r-HAT proposed indication and the same dose and the dosing regimen used for g-HAT were proposed, taking into account the low number of r-HAT cases, the difficult access to the remote areas where the disease is more prevalent and the COVID-19 pandemic during the conduct of the DNDi-FEX-07-HAT study.

Objectives

Outcomes/endpoints

- Primary endpoint

<u>The primary objective was:</u>

- To show that the failure rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5% (derived from the on-treatment mortality rate observed in stage-2 r-HAT patients on 10-day melarsoprol at EOH (IMPAMEL III study)).

  Rationale: The major issue with melarsoprol was not the cure rate if the patient survives at EoH, but the fatality rate due to neurotoxicity during the treatment period.

To design study DNDi-FEX-07-HAT, DNDi took advantage of the design and results obtained in the IMPAMEL III study.

The IMPAMEL III trial (2005–2009) enrolled 54 r-HAT patients in a missionary hospital in Tanzania and 53 patients in a district hospital in Uganda. This pooled group of 107 patients was evaluated at EoH and at 12 months, to compare the 12-month efficacy and safety of a 10-day melarsoprol schedule with historical clinical data about a 23-day (or more) melarsoprol schedule (3 or 4 series of 3 days separated by 1 week) in stage-2 r-HAT patients (excluding children aged <6 years, pregnant women and unconscious or moribund patients).

Historical controls were therefore obtained from patient files, which had been collected over 2 years in Uganda (N = 147) and in Tanzania (N = 153) before study initiation and were used for the comparative arm. As similar safety and efficacy results were obtained between the 10- and the 23-day melarsoprol schedule, endemic countries started thereafter to modify their guidelines in favour of the shorter melarsoprol schedule.

More specifically, in stage-2 r-HAT patients (N = 107) treated with 10-day melarsoprol, the proportion of encephalopathic syndrome (ES) cases (12/107) was of 11.2% (95% CI: 5.1% to 17.3%), whereas the proportion of deaths (9/107) was of 8.4% (95% CI: 3% to 13.8%) at EoH and it increased to 11.2% (12/107) at 12 months. Of note, most deaths at EoH were related to melarsoprol-triggered ES (8/9 [89%]), whereas one death case (1/9 [11%]) was related to an acute form of r-HAT disease. During the follow-up, three other patients died; 2 were unrelated deaths and one patient from Uganda died 2 months after discharge of unknown reasons.

The analysis of historical files of patients treated with a long melarsoprol regimen indicated that the proportion of ES cases (39/300) was of 13.0% (95% CI: 9.2% to 16.8%) and the proportion of deaths (28/300) was of 9.3% (95% CI: 6.0% to 12.6%) at EoH.

In addition, the clinical cure rates for the 10-day melarsoprol regimen were 91.6% (98/107) at EoH and 89.5% (94/105) at 12 months (considering evaluable patients and excluding 2 unrelated deaths which occurred during follow up and led to a total of 105 evaluable r-HAT patients) (one patient from Uganda experienced a relapse 2 weeks after hospital discharge (trypanosomes in blood) and was reported at the 12-month visit and one died from unknown reasons).

The overall calculated failure rates (including death cases and relapses) were thus of 8.4% (9/107) at EoH and of 12.1% (13/107) at 12 months. As no relapse was reported at EoH, the failure rate corresponds to the fatality rate at EoH.

The fatality rate of 8.4% at EoH was rounded at 8.5% to set the unacceptable limit of fatality rate at EoH for the primary objective in Study DNDi-FEX-07-HAT and the failure rate of 8.4% at EoH was rounded up to 9% to set the unacceptable limit of failure in evaluable stage-2 r-HAT patients in Study DNDi-FEX-07-HAT (the secondary, short-term objective).

It is noteworthy that ES cannot be prevent. ES is a badly defined complication involving a complex host-drug-parasite interaction. Probably, a genetically determined individual susceptibility exists that produces a peculiar type of immune response in the central nervous system that, in combination with the presence of trypanosomes and melarsoprol, results in a catastrophic condition. ES may occur at any time-point after the first melarsoprol administration and up to 30 days after the last one, with a median and peak occurrence around day nine of treatment.

The concomitant use of steroids during melarsoprol therapy proved to reduce the incidence oI ES in *T. b. gambiense* patients but this could not be shown in *T. b. rhodesiense* and also no benefit could be attributed to the suramin pre-treatment.

In the absence of a direct comparison with melarsoprol in study DNDi-FEX-07-HAT, the unacceptable fatality rate at EoH needs to be supported by additional data and analyses.

Analyses of the IMPAMEL III study, systematic review of other published studies, and of WHO epidemiological data, including meta-analyses and meta-regressions, have been conducted to estimate the fatality rate at EoH in stage 2 r-HAT patients treated with melarsoprol and to provide some insights of the context of the DNDi-FEX-07-HAT study.

Studies from literature included a total of 5365 stage 2 r-HAT patients treated with melarsoprol and epidemiological data from 2012 to 2021 reported 492 stage 2 r-HAT patients treated with melarsoprol.

Overall, all analyses conducted supported the unacceptable fatality rate at EoH of 8.5% and some showed an estimated fatality rate at EoH significantly higher than 8.5%. These results are based on one study with a moderate risk of bias, 25 studies with a serious risk of bias, and epidemiological data from six endemic countries over a period of 10 years. Fatality rate at EoH estimates were consistent within and across studies as well as across data sets. A significant effect of country was identified in both the data set of studies from

literature and the WHO epidemiological data. The fatality rate at EoH estimates for Malawi were significantly higher than the unacceptable fatality rate at EoH and were replicated across data sources.

In conclusion, the estimations of fatality rate at EoH from IMPAMEL III data and from the meta-analysis based on all countries are close to each other and consequently consistent. Estimations are more often larger than 8.5% suggesting that 8.5% reflects conservatively the fatality rate for all countries.

There is a clear country effect mainly due to Malawi in which the fatality rate is approximately 2-fold of the overall estimate. Fatality rate for WHO data is larger than other estimates except in Malawi for which all estimates converge around the double of risk. It cannot be discarded that mortality regardless the cause and absence of entry criteria concerning moribund and comatose patients in WHO data may partly explains a higher fatality rate.

The established threshold of unacceptable fatality rate (8.5%) is clearly not an overestimate of what can be observed in patients treated with melarsoprol especially in Malawi.

Table 6. Summary of fatality rate at EOH in the various analyses performed

Dataset	Analysis	Patient Population/Group of Studies/Adjustment Factors	Fatality rate at EOH estimate
IMPAMEL III	*Patient-level analysis – Prospective trials*		
		Patients without suramin pre-treatment	8.4%
		All patients treated with melarsoprol	10.2%
	Patient-level analysis – Prospective and retrospective trials		
		All treated patients	9.6%
	Study-level analysis		
		All studies	9.4%
		Prospective studies	10.2%
		Retrospective studies	9.1%
Published studies	*Patient-level analysis*		
		All treated patients	8.4%
		Treated patients recruited in Malawi	17.0%
	Study-level – meta-analyses		
		All studies	8.9%
		Studies in Malawi	16.5%
		Studies reporting r-HAT- and treatment-related deaths	9.7%
		Clinical trials only	12.8%
	Study-level – meta-regressions		
		Adjustment for Malawi	16.6%
		Adjustment for r-HAT- and treatment-related deaths	9.6%
		Adjustment for clinical trials	12.9%
		Adjustment for Malawi, clinical trials, and r-HAT- and treatment-related deaths	21.4%
WHO epidemiological data (2012-2021)	*Patient-level analysis*		
		Patients treated in endemic countries	12.4%
		Patients treated in Malawi	16.0%

The CHMP noted that the primary objective of the DNDi-FEX-07-HAT study was to show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5%, which was derived from the on-treatment mortality rate observed in stage-2 r-HAT patients on 10-day melarsoprol at EOH (IMPAMEL III study). To design study DNDi-FEX-07-HAT, DNDi took advantage of the design and results obtained in the IMPAMEL III study.

The overall calculated failure rates (including death cases and relapses) in the IMPAMEL III study were of 8.4% (9/107) at EoH and of 12.1% (13/107) at 12 months. As no relapse was reported at EoH, the failure rate corresponds to the fatality rate at EoH. The fatality rate of 8.4% at EoH was rounded at 8.5% to set the unacceptable limit of fatality rate at EoH for the primary objective in Study DNDi-FEX-07-HAT and the failure rate of 8.4% at EoH was rounded up to 9% to set the unacceptable limit of failure in evaluable stage 2 r-HAT patients in Study DNDi-FEX-07-HAT (the secondary, short-term objective).

Since by the design of the study, a direct comparison with treatment with melarsoprol was not feasible to evaluate the efficacy, and safety concerns are associated with the treatment with melarsoprol, namely its neurotoxicity, the primary objective primary in Study DNDi-FEX-07-HAT seems to be valid and mortality is considered a robust endpoint.

Analyses of the IMPAMEL III study, systematic review of other published studies, and of WHO epidemiological data, including meta-analyses and meta-regressions (although with potential confounding factors applicable to cross-study comparisons and serious risk of bias for all studies but moderate for IMPAMEL III) showed that the estimations of fatality rate at EoH are close to each other and consequently consistent. The established threshold of unacceptable fatality rate (8.5%) is clearly not an overestimate of what can be observed in patients treated with melarsoprol especially in Malawi – it should be noted that most of the patients included in the DNDi-FEX-07-HAT study (43/45 – 95.6%) were from the Malawi site.

The primary endpoint selected for the DNDi-FEX-07-HAT study was acknowledged by the CHMP which nevertheless considered that being a single arm trial its outcome should not be reported in the SmPC in comparison with historical point estimate for fatal cases (<8.5%) in patients treated with melarsoprol in the IMPAMEL III study but should instead be displayed as stand-alone data and using the ITT principle and 95% CI.

Secondary endpoints

The secondary objectives were:

- To show that the failure rate (r-HAT or treatment-related death according to DSMB or presence of trypanosomes) at the EoH in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of an unacceptable rate of 9% (the secondary, short-term objective).

  Rationale: A new compound could show low mortality rate but still be not efficacious.

- To show that the proven failure rate (r-HAT or treatment-related death according to DSMB or relapse) at 12 months (or before) in patients with stage 2 r-HAT treated with fexinidazole was below an unacceptable rate of 12%.

  Rationale: A new compound could be nontoxic and initially efficacious (trypanosomes no longer observed at EoH), but the durability of effect could be poor (i.e., no complete elimination of trypanosomes or persistence of high WBC in CSF during follow-up).

Failure at EoH was assessed by the presence of trypanosomes in blood or CSF at EoT, death related to r-HAT or study treatment at EoH according to DSMB, or absence of clinical improvement leading to the use of rescue medication.

As stated before, in IMPAMEL III study, the clinical cure rates for the 10-day melarsoprol regimen were 91.6% (98/107) at EoH and 89.5% (94/105) at 12 months (considering evaluable patients and excluding 2 unrelated deaths which occurred during follow up and led to a total of 105 evaluable r-HAT patients) (one patient from Uganda experienced a relapse 2 weeks after hospital discharge (trypanosomes in blood) and was reported at the 12-month visit and one died from unknown reasons).

The overall calculated failure rates (including death cases and relapses) were thus of 8.4% (9/107) at EoH and of 12.1% (13/107) at 12 months. As no relapse was reported at EoH, the failure rate corresponds to the fatality rate at EoH.

The failure rate of 8.4% at EoH was rounded up to 9% to set the unacceptable limit of failure in evaluable stage-2 r-HAT patients in Study DNDi-FEX-07-HAT (the secondary, short-term objective).

The 12-month follow up takes into account the acuteness of r-HAT disease and differs from the 24-month follow up that was used in g-HAT pivotal study (DNDiFEX004). While most g-HAT relapses are diagnosed around or before 12 months, r-HAT relapses are considered to occur earlier as the disease progresses fast, involves more severe general symptoms and a higher number of trypanosomes in the blood of r-HAT patients. The natural history of r-HAT may suggest that any true relapses would likely occur early and later onset cases may represent new infections. This 12-month follow-up duration was discussed with the CHMP during the follow up scientific advice and CHMP specified that a conclusion on whether at 12 months follow up period is sufficient would only be possible after full review of the data, including details of any recurrences reported during the full follow-up period.

This 12-month follow up was used in the IMPAMEL III study (N = 107). In this study, all cases of melarsoprol therapy failure in r-HAT patients at EoH corresponded to death cases (9/107 - failure rate of 8.4% at discharge). Among 3 additional deaths reported during follow up, 2 were considered as unrelated to r-HAT and one was of unknown reason. At 12 months, Kuepfer et al. reported that one patient from Uganda experienced a relapse 2 weeks after hospital discharge (trypanosomes in blood), and the relapse rate at 12 months was thus of 0.9% (1/107) in r-HAT patients treated with the 10-day melarsoprol schedule. In conclusion, the failure rates (including death cases and relapses) in the IMPAMEL III study were of 8.4% (9/107) at EoH and of 12.1% (13/107) at 12 months.

The CHMP noted that one of the secondary endpoints selected for the DNDi-FEX-07-HAT study was to show that the proven failure rate (r-HAT or treatment-related death according to DSMB or relapse) at 12 months (or before) in patients with stage 2 r-HAT treated with fexinidazole was below an unacceptable rate of 12%. A follow-up period of 12 months selected for the DNDi-FEX-07-HAT study is considered adequate and thus, accepted for the demonstration of the persistence of efficacy in r-HAT patients who suffer from an acute disease.

The other secondary endpoint was to show that the failure rate (r-HAT or treatment-related death according to DSMB or presence of trypanosomes) at the EoH in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of an unacceptable rate of 9% (the secondary, short-term objective).

Based on the rationale provided by the SOH, these two second endpoints selected for the DNDi-FEX-07-HAT study were endorsed by the Committee.

In addition, the other long-term secondary endpoints were:

- To estimate the failure rate at EoH and at 12 months in patients with stage 1 r-HAT treated with fexinidazole and to verify whether the estimates were smaller than that of suramin.
- To estimate the fatality rate and success rate at 12 months in the overall population (patients with stage 1 and stage 2 r-HAT) treated with fexinidazole.

  Rationale: (1) It was the same parasite; the same population of patients and the ultimate objective was to yield one treatment regardless of the stage of advancement of the disease. (2) Patients with stage 1 r-HAT were rare hence the estimates for stage 1 alone were not very informative and it must be only descriptive.

- To evaluate the safety profile of fexinidazole in patients with stage 1 and stage 2 r-HAT and to compare it to melarsoprol and suramin as reported in the literature.

These second endpoints were also endorsed. Because r-HAT patients progress rapidly from stage 1 to stage 2 and because stage-2 r-HAT patients are in a much worse health status than stage-1 patients, it was hypothesized and believed that if a treatment could be efficacious and well tolerated for stage-2 patients, it should also be efficacious and well tolerated for stage-1 patients. This rationale was supported by the CHMP.

The exploratory objectives were:

- To estimate the time course of relapse of fexinidazole from end of treatment (EoT) to end of study (EoS, i.e., at 12 months)
- To assess the PK of fexinidazole and its main metabolites in the blood
- To assess the reduction in the number of trypanosomes in the blood until EoS (at 12 months).

The CHMP endorsed the exploratory objectives selected for the DNDi-FEX-07-HAT study.

Sample size

DNDi explored various clinical trial design options with fexinidazole, which had shown a low fatality rate in stage-2 g-HAT patients (<1% at EoH):

A randomized controlled trial with a power of 80% would have required 124 patients per group if the primary endpoint was based either on the fatality rate or the failure rate at EoH. However, such a high number of patients could not be reached because r-HAT is a rare disease.

In the hypothesis of 20 patients per group for a randomized controlled trial, a failure rate of 9% and a fatality rate of 1% in the fexinidazole group (see below), implied an exact power of α = 2.39%. In this case, a frequentist statistical test could not be used to validate the working hypothesis of a smaller fatality rate in the fexinidazole group.

A non-inferiority trial involved a non-inferiority margin, which would have consisted of a possible difference in fatality rate in favor of the positive control, i.e., the melarsoprol group, but the goal of the trial would have been to verify whether fexinidazole could decrease the mortality rate at EoH compared with melarsoprol.

This design involved to recruit a high and therefore unreachable number of patients for an acceptable margin, although there was no acceptable margin with death as an endpoint.

The study design had to be adapted to the constraints of the disease, r-HAT is a rare and a neglected tropical disease (NTD) for which the transmission is limited to few East African countries. The incidence of r-HAT had decreased by nearly 5-fold over the 6 years before study design and reached 24 reported cases per year in 2018 throughout all endemic countries. Such low numbers of patients hindered any randomized controlled trial designs.

DNDi thus, adopted an open-label, non-randomized, single-arm, clinical trial in r-HAT patients treated only with fexinidazole. Such a design had already been chosen for the same reason in the IMPAMEL III study. While this IMPAMEL III study used historical patient files as controls, for fexinidazole clinical trial, DNDi used the results of the IMPAMEL III study to set up a threshold of an unacceptable fatality rate of 8.5% at EoH and a threshold of an unacceptable failure rate of 9% at EoH (as already explained above).

The constraints were discussed and understood by the CHMP at the initial scientific advice meeting for fexinidazole in r-HAT patients. CHMP acknowledged the hurdles with performing a randomized non-inferiority study considering the low sample size and mentioned the limitation to draw formal conclusions on fexinidazole efficacy relative to melarsoprol in the absence of a melarsoprol control arm.

For Study DNDi-FEX-07-HAT, the primary endpoint was not related to the failure rate but to the fatality rate. A sample size of 34 evaluable stage-2 patients allowed a reasonable statistical power of 71.1% for an expected fatality rate of 1% and of 84.3% for an expected fatality rate of 0.5%. This number of 34 evaluable stage-2 r-HAT patients was the minimal sample size allowing to get that reasonable statistical power.

DNDi thus set up a sample size of 34 evaluable stage-2 r-HAT patients and estimated that a final number of 50 patients including stage-1 r-HAT patients could be reached over 2 years, which would give the opportunity to collect data about stage-1 patients who are less affected by the disease.

The sample size was determined based on the primary analysis of the primary endpoint, i.e., the rate of deaths possibly related to r-HAT or treatment at EoH in patients with stage 2 r-HAT. The primary analysis was the comparison of the proportion of deaths (pdeath) to the threshold of 8.5%, with H0 being pdeath ≥8.5%.

If the sample size was too small, the null hypothesis was not rejected even if no deaths were observed (whatever the observed death rate, H0 was not rejected). The minimal sample size to get a possible rejection of H0 (fatality rate at EoH = 8.5% or more) in favour of H1 (fatality rate <8.5%) was 34 evaluable patients with stage 2 r-HAT for α = 0.05 one-sided. In that case if no patients died during treatment the exact one-sided test became significant (p=0.0488).

Consequently, the sample size was not set according to a minimal power of 80%, but according to the possible rejection of the null hypothesis. The second consequence of such an approach was: as soon as one death possibly related to r-HAT or study treatment was observed at EoH, the study could be stopped for futility and failure (inconclusive result). To accept one failure and get a rejection of the null hypothesis once one failure was observed, the minimal sample size became 53 patients (p=0.0496, for 1/53 deaths). A sample size of 42 patients without any death would reject the null hypothesis at a two-sided significance α-level of 0.05. Because these sample sizes could not be reached within 2 years, the study would have been unfeasible if these rules were applied.

The recruitment could therefore stop once 34 evaluable patients with stage 2 r-HAT were involved.

The reachable and proposed sample size justifies the statistical model used and could thus be endorsed by the Committee.

Randomisation

Not applicable. Study DNDi-FEX-07-HAT is a non-randomized study.

Blinding (masking)

Not applicable. Study DNDi-FEX-07-HAT is an open-label study.

Study DNDi-FEX-07-HAT is a phase-II/III, multicenter, open-label, non-randomized, single-arm clinical trial to assess the efficacy and safety of fexinidazole in patients with r-HAT which was conducted in adult and pediatric (≥6 years old), stage-2 and stage-1 r-HAT patients, in Malawi and Uganda.

The CHMP acknowledged the constraints to raise other clinical designs options are understood. However, noted that the lack of a direct comparison with melarsoprol in clinical study DNDi-FEX-07-HAT hampers the assessment of efficacy as compared to melarsoprol.

Statistical methods

A Statistical Analysis Plan was provided by the SOH.

Analysis efficacy variables were:

- Primary efficacy variable:
    - Death possibly related to r-HAT or to Fexinidazole (according to DSMB), up to the end of hospitalisation in stage 2 r-HAT patients.
- Secondary efficacy variables:
    - The success and failure at the end of hospitalisation in stage 1 and stage 2 r-HAT patients;
    - The success and failure at the M12 visit.
    - Unsatisfactory clinical and parasitological response during the observation period and at the EoT visit.

Failure was defined as: presence of trypanosomes in any body fluid at EoT; or Death possibly related to r-HAT or treatment, according to DSMB, at EoH; or Absence of clinical improvement leading to the use of rescue medication.

Unsatisfactory clinical and parasitological response was defined as: the compound analysis of the evolution of signs and symptoms of r-HAT, as well as laboratory tests and parasitological tests during the observation period (or during follow-up). This unsatisfactory response was evaluated through: Persistence at EoH (or during follow-up) of signs and symptoms reported at baseline (with the same grade), or occurrence at EoH (or during follow-up) of new signs of r-HAT; Persistence at EoH (or during follow-up) of abnormal laboratory test results reported at baseline or occurrence at EoH (or during follow-up) of new abnormalities; or Persistence at EoT of positive result(s) of parasitological tests reported at baseline.

- Exploratory efficacy variables to assess the efficacy were:
    - The earliest time to detect a relapse
    - The quantification of trypanosomes in blood at all visits
    - Trypanosome nucleic acids detection until the end of study

Analysis efficacy populations were:

- Intention to treat (ITT)
- Evaluable patients (EP)
- Modified intention to treat (mITT)
- Treatment completers (TC)

The definition of analysis population of patients and the type of analysis conducted for each are presented in the “used for” column:

Population	Definition	Used for
Intention to treat (ITT)	All recruited patients (stage 1 and stage 2), who signed the ICF and were eligible for treatment according to the Investigator	Description of the disposition of patients.
Evaluable patients (EP)	Patients who took at least one dose of fexinidazole, excluding: those whose death during hospitalization was documented and clearly attributable to other causes than r-HAT or treatment according to the DSMB, those who left the hospital without being medically discharged by the site Investigator before the planned EOH period (Day 12-18), and whose status on the primary outcome could not be retrieved	Primary population used in the primary efficacy analysis The choice of this population as the primary one was justified by the fact that the study would be inconclusive if only one death related to study drug occurred
Modified intention to treat (ITT)	All patients from the ITT population who took at least one dose of the study treatment, regardless of study deviations/violations and stage of r-HAT	Sensitivity analysis Safety population
Treatment completers (TC)	All patients who completed the 10 days of treatment with fexinidazole	Sensitivity analysis

Abbreviations: DSMB, data safety monitoring board; EOH, end of hospitalization; EP, evaluable patients; ICF, informed consent form; ITT, intention to treat; r-HAT, human African trypanosomiasis due to *Trypanosoma brucei rhodesiense;* TC, treatment completers

Source: DNDi-FEX-07-HAT CSR, Section 8.7.3.1

The modified intent to treat (mITT) population was used for sensitivity analyses. This set was also the safety population.

The primary population for efficacy analyses was the population of evaluable patients.

Another population for efficacy is composed of patients from the mITT who completed the treatment with fexinidazole, either in 10 days or in 11 days if one dose of fexinidazole is missed.

Analysis of the Primary endpoint

The primary analysis of the primary endpoint was the comparison of the proportion (pdeath) of deaths possibly related to r-HAT or to Fexinidazole at the end of the hospitalization to the threshold of 8.5%.

The hypothesis of test was under H0: $pdeath \geq 8.5\%$ vs H1 $pdeath < 8.5\%$. The hypothesis was tested using a one-sided exact test for proportions, at the 0.05 significance level.

This comparison was performed on the stage 2 patients from the evaluable population which must was composed of at least 34 patients.

Sensitivity analyses would be performed by repeated this comparison on stage-2 patients from the mITT and completers if those populations contain at least 34 patients.

Analysis of the Secondary endpoints

The proportion of failure at the end of hospitalisation was compared to the thresholds of 9% on stage 2 patients from the mITT and completer populations.

The fatality rate at EoH, failure rate at EoH and failure rate at 12 months were estimated.

Because the sample size was very small, no null hypotheses was testable.

The estimate of fatality rate at EoH, failure rate at EoH and failure rate at 12 months for stage-1 and stage-2 combined were calculated and tested against the unacceptable limit of 8.5%, 9% and 12%, respectively.

The failure rate at the M12 visit was compared to the threshold of 12% on the stage-2 r-HAT patients from the mITT and treatment completer populations, using a one-sided test if the observed rate if below 12%.

The fatality rate at EoH, failure rate at EoH and failure rate at 12 months was estimated and presented with a 95% CI, on the stage-2 r-HAT patients from the mITT and treatment completer populations. No comparison to pre-specified thresholds was performed.

The fatality rate at EoH, failure rate at EoT, and failure rate at the month 12 visit was then estimated in the entire (stage-1 and stage 2-patients) evaluable population and compared respectively to the pre-specified threshold of 8.5%, 9% and 12%. The comparisons were repeated on the mITT and completers.

All comparisons were done using a one-sided exact test for proportions, at the 0.05 significance level (one sided).

Time to failure (as defined previously) and time to reduction in the number of trypanosomes in the blood were estimated using survival analysis.

A Data Safety Monitoring Board (DSMB) was implemented and conducted review of data following the developed charter in use for the study.

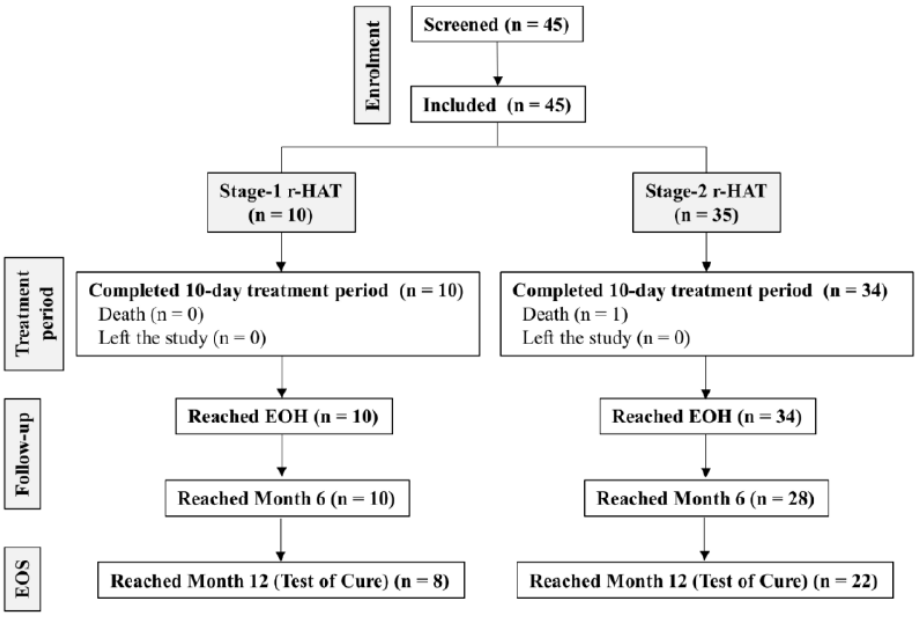
All analyses were performed using STATA version 15.0 or higher for the final analysis.

The Statistical Analysis Plan was endorsed by CHMP.

Results

Participant flow

Flow diagram - Study DNDi-FEX-07-HAT:



At the data cut-off date for this initial CSR on 25 January 2022, all patients (N = 44) had reached Week 9 and datasets were complete, but they were incomplete at Month 6 (38 patients reached and 6 patients were ongoing) and at Month 12 (30 patients reached and 14 patients were ongoing) (EoS).

Recruitment

The study was conducted in 2 sites: 1 in Malawi and 1 in Uganda. Overall, 45 patients were included in the study, 35/45 (78%) stage-2 and 10/45 (22%) stage-1 r-HAT patients; 43 patients in Malawi and 2 in Uganda. All received fexinidazole treatment in fed conditions and according to body weight (either from 20 to <35 kg or ≥35 kg) as recommended by the current approved SmPC for fexinidazole.

Conduct of the study

Protocol amendments

The study approvals were obtained on Protocol v2.0 (dated on 16 November 2018). There were 3 protocol amendments that were submitted during the study (dated on 23 January 2020, 27 August 2021 and 19 August 2022).

Table 4 – Summary of protocol amendments

Amendment number	Protocol version	Date	Purpose of amendment
NA	2.0	16-Nov-2018	NA
1 (not submitted)	3.0	04-Sep-2019	• Amendment 1 had been prepared and finalised internally. However, this amendment was never submitted and the changes were reported into Amendment 2 (see below)
2	4.0	23-Jan-2020	• Following the update of the IB, the protocol was aligned with the IB content, notably with updates of the concomitant treatments prohibited
3	5.0	27-Aug-2021	• Positive opinion from EMA for the treatment of HAT due to *T. brucei gambiense* added • Clarification about contraception for women of childbearing potential added • Removal of the exclusion criterion for women in the first trimester of pregnancy • Sponsor's address updated • Monitor's back-up removed • Change of Project Manager • Addition of a safety information regarding the study treatment fexinidazole
4	6.0	19-Aug-2022	• Due to a high turnover in the Study Monitors, it was decided to remove the paragraph presenting the names, titles, addresses and phone numbers of the monitors (in the section 'Contact Details' of the protocol)

EMA = European Medicines Agency; IB = Investigator's Brochure; NA = not applicable.

Other changes in the conduct of the study

The study was actively recruiting at the time of the onset of the COVID-19 pandemic, which led to a delayed study start in Uganda, delayed shipment of investigational medicinal product (IMP) kits to Uganda and Malawi, and slower recruitment in the second year. The slower recruitment was also due to the expiration of the NHSRC approval in Malawi, a shortage in study staff during holiday season, and the difficulty to find cases in the area around study sites. A summary of the impact of the COVID-19 pandemic was provided. Importantly, all follow-up visits took place as per protocol, and within the planned time windows, despite the pandemic.

Four visit types were planned: pre-study visit, initiation visit, monitoring visits during the study, and close-out visit. Monitoring visits to the study site were planned to be conducted periodically by the Sponsor representatives or designated clinical monitor to ensure that GCP and all aspects of the protocol were followed. Any misconduct or serious GCP non-compliance information was to be documented in all relevant sections of the CSR. During these visits, source documents were reviewed for verification of consistency with data on CRFs and SAE/AESI/pregnancy/child surveillance forms.

The coronavirus disease (COVID-19) pandemic impacted the on-site monitoring visits. A process for remote monitoring visits was put in place during 2020 and 2021 and the monitoring plan was updated accordingly.

Protocol deviations

One patient (who died before the EoH visit for reasons considered as unrelated to r-HAT disease or treatment) had a major deviation:

- Fexinidazole was crushed and administered through nasogastric tube (from Day 5 to Day 7), whereas the protocol specified not to crush the tablets. This patient received fexinidazole by nasogastric tube due to a diminution of his consciousness. As per protocol, no pharmacokinetic samples were collected on these days, which did not allow to assess the blood concentrations of fexinidazole and its metabolites. Of note, the absence of trypanosomes in blood at Day 5 and in post-mortem CSF suggested that he was exposed to therapeutic concentrations of M2 during the loading-dose phase (Day 1 to Day 4).

Patients who vomited shortly after dosing (within 2 hours of study treatment administration) received the daily dose of fexinidazole again. If vomiting occurred more than 2 hours after study treatment administration, fexinidazole was not re-administered, as study treatment absorption was likely to have been complete. A total of 7 patients had at least one re-administration due to vomiting. During the loading-dose phase (Day 1 to Day 4), 6 patients experienced vomiting within 2 hours after study treatment administration; treatment was readministered in all 6 patients. During the maintenance-dose phase, only one patient experienced vomiting within 2 hours after administration on Day 10 and was readministered. However, these re-administrations were anticipated in the protocol and therefore do not represent protocol deviations per se.

Minor protocol deviations were reported at the time of initial cut-off date. The most frequently reported minor deviations were deviations regarding the planned procedures of parasitological tests (23 patients), ECGs or neurological examination (17 patients each).

Baseline data

The countries of study conduct, Malawi and Uganda, were in line with the areas at highest risk and their unmet needs of an oral and potentially better tolerated treatment for Rhodesiense human African trypanosomiasis (r-HAT).

The demographics and baseline characteristics of the r-HAT study population analyzed for fexinidazole covered the target population.

The median age of r-HAT patients was 24 years. They were 17 pediatric patients aged 7 to 16 years, including 11 children aged 7 to 12 years (9 aged <12 years and 2 aged 12 years), 6 adolescents aged 13 to 16 years and 28 adult patients aged 18 to 69 years. Two patients were aged of at least 65 years (one stage-1 male and one stage-2 female patient,).

More male than female patients participated in the study (31/45 [69%] versus 14/45 [31%]), including 1/45 (2%) pregnant woman. There were no breastfeeding women in the study population. While the same number of male and female stage-2 r-HAT children participated in the study (N = 5, each), there were twice more male than female adolescent and adult stage-2 r-HAT patients (17 versus 8). This is in line with the IMPAMEL III study and other studies conducted in stage-2 r-HAT patients, and likely reflects the activities of men which put them at higher risk of contact with tsetse flies (e.g., herding cattle, fishing, hunting and honey collecting).

Baseline characteristics were also consistent with poor nutritional state and depressed anabolism in this patient population.

Forty-six patients were screened, and 45 patients were included in the study: 35/45 (78%) patients with stage-2 r-HAT and 10/45 (22%) patients with stage-1 r-HAT.

Table 10 - Baseline demographic characteristics - mITT population - Study DNDi-FEX-07-HAT

Characteristics	Statistics, categories	DNDi-FEX-07-HAT (N = 45)
Sex	Total males, n (%)	31 (68.9%)
	<12 years, n (%)[a]	5 (11.1%)[a]
	≥12 years, n (%)	26 (57.8%)
	Total females, n (%)	14 (31.1%)
	<12 years, n (%)[a]	4 (8.9%)[a]
	≥12 years, n (%)	9 (20.0%)
Age (years)	Mean (SD)	27.0 (16.1)
	Median (Q1, Q3)	24.0 (13.0, 38.0)
	Min; Max	7.0; 69.0
Body weight (kg)	Mean (SD)	48.1 (15.0)
	Median (Q1, Q3)	51.8 (37.0, 60.0)
	Min; Max	23.0; 72.6
Height (cm)	Mean (SD)	157.0 (16.5)
	Median (Q1, Q3)	160.0 (147.0, 167.0)
	Min; Max	124.0; 191.0
BMI (kg/m²)	Mean (SD)	19.0 (3.6)
	Median (Q1, Q3)	18.7 (16.0, 21.6)
	Min; Max	12.8; 29.5

Abbreviations: **BMI**, body mass index; **Max**, maximum; **Min**, minimum; **mITT**, modified intention to treat; **SD**, standard deviation; **Q**, quartile

Source: DNDi-FEX-07-HAT CSR, Table 7

a In this table, the age cut off was at 12 years because the reproductive potential was taken into account. However, 2 children were aged 12 years and had a body weight <35 kg which implied that all children (N = 11) aged 7 to 12 years received the 1200/600 mg fexinidazole regimen

Infections and Infestations were the most frequent medical history, being reported in 5 patients (11.1%), with a similar prevalence of all PTs in this SOC: malaria was reported in 2 patients (4.4%) while acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV) infection, and tinea infection were each reported in 1 patient (2.2%).

Table 8 – Medical history by SOC and PT – mITT population

SOC PT	Total (N=45) Number of patients (%) with any event
Infections and infestations	**5 (11.1)**
Malaria	2 (4.4)
Acquired immunodeficiency syndrome	1 (2.2)
HIV infection	1 (2.2)
Tinea infection	1 (2.2)
Blood and lymphatic system disorders	**2 (4.4)**
Leucocytosis	1 (2.2)
Thrombocytopenia	1 (2.2)
Investigations	**2 (4.4)**
Hepatic enzyme increased	2 (4.4)
Nervous system disorders	**2 (4.4)**
Epilepsy	1 (2.2)
Mutism	1 (2.2)
Metabolism and nutrition disorders	**2 (4.4)**
Diabetes mellitus	1 (2.2)
Oedema	1 (2.2)
Cardiac disorders	**1 (2.2)**
Bundle branch block right	1 (2.2)
Pregnancy, puerperium and perinatal conditions	**1 (2.2)**
Pregnancy	1 (2.2)
Skin and subcutaneous tissue disorders	**1 (2.2)**
Wound	1 (2.2)

HIV = human immunodeficiency virus; mITT = modified Intention-to treat; N = number of patients in the population; PT = preferred term; SOC = system organ class.

Source: Table 16.2.4.1.4.

A total of 4 patients (8.9%) had a history of r-HAT, with 1 patient (2.2%) with stage 1 r-HAT and treated with suramin and 3 patients (6.7%) with stage 2 r-HAT and treated with melarsoprol.

Table 9 – History of r-HAT – mITT population

	Total (N=45)	Treatment received	Time since previous treatment (days)[a]
History of r-HAT, n (%)	4 (8.9)		
Stage 1, n (%)	1 (2.2)	Suramin	223
Stage 2, n (%)	3 (6.7)	Melarsoprol	215, 379, 238

a Time since end of previous treatment for r-HAT to date of screening in study DNDi-FEX-07-HAT

mITT = modified intention-to treat; N = number of patients in the population; n = number of patients with at least one adverse event in the category; r-HAT = rhodesiense human African trypanosomiasis.

Source: Table 16.2.4.1.3, Listing 16.2.1.2.3, and Listing 16.2.4.2.3.

The clinical signs and symptoms of r-HAT that were reported by the patients at the inclusion visit had the following frequencies:

- >85% of patients: fever (97.8%), headache (95.6%), drowsiness (86.7%)
- >30% to ≤60% of patients: insomnia (55.6%), asthenia (40.0%), pruritus (33.3%), slimming or weight loss (31.1%)
- >4% to ≤25% of patients: impotence (23.1% of men ≥12 years old), anorexia (15.6%), gait disorders (13.3%), nausea (13.3%), behavioural disorders (8.9%), speech disorders (6.7%), convulsion (4.4%), diarrhoea (4.4%), tremor (4.4%)
- No patients presented amenorrhoea.

Time of onset was variable for all these frequently reported signs and symptoms (in >30% of patients). Frequently reported signs and symptoms appeared mostly up to 1 month before baseline in the majority of patients. The first signs and symptoms to appear (>6 months before baseline) were fever (in 2.3% of patients with the symptom), headache (2.3%), drowsiness (2.6%), and pruritus (6.7%), and followed (from >3 months to ≤6 months before baseline) by insomnia (8.0%) and asthenia (5.6%). Slimming or weight loss (92.8%) appeared <3 months before baseline.

Regarding the characteristics of the most frequently reported signs and symptoms of r-HAT, there were more patients experiencing them intermittently than continuously, more specifically the ones present in >32% of patients.

Signs and symptoms were mostly mild or moderate in severity in the majority of patients. The number of patients with severe signs and symptoms was generally low (provided with the incidence relative to the total number of patients with that sign and symptom): headache (6 patients, 14.0%), fever (5 patients, 11.4%), asthenia (3 patients, 16.7%), drowsiness (2 patients, 5.1%), gait disorders (1 patient, 16.7%), and pruritus (1 patient, 6.7%).

Baseline clinical signs and symptoms of r-HAT and time from symptoms at baseline – mITT population

Presence of sign or symptom, n (%)		Presence of sign or symptom depending on its duration from baseline					
		<1 wk	1 to 4 wk	1 to 3 mo	3 to 6 mo	>6 mo	Unknown
Total with any sign/symptom	**45 (100.0)**	**26 (57.8)**	**41 (91.1)**	**9 (20.0)**	**2 (4.4)**	**1 (2.2)**	**2 (4.4)**
Fever	44 (97.8)	2 (4.5)	34 (77.3)	5 (11.4)	1 (2.3)	1 (2.3)	1 (2.3)
Headaches	43 (95.6)	5 (11.6)	30 (69.8)	5 (11.6)	1 (2.3)	1 (2.3)	1 (2.3)
Drowsiness	39 (86.7)	13 (33.3)	19 (48.7)	4 (10.3)	1 (2.6)	1 (2.6)	1 (2.6)
Insomnia	25 (55.6)	12 (48.0)	8 (32.0)	2 (8.0)	2 (8.0)	0 (0.0)	1 (4.0)
Asthenia	18 (40.0)	3 (16.7)	11 (61.1)	3 (16.7)	1 (5.6)	0 (0.0)	0 (0.0)
Pruritus	15 (33.3)	5 (33.3)	8 (53.3)	1 (6.7)	0 (0.0)	1 (6.7)	0 (0.0)
Slimming/ weight loss	14 (31.1)	3 (21.4)	7 (50.0)	3 (21.4)	0 (0.0)	0 (0.0)	1 (7.1)
Anorexia	7 (15.6)	3 (42.9)	4 (57.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gait disorders	6 (13.3)	2 (33.3)	3 (50.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	6 (13.3)	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Impotence[a]	6 (23.1)	3 (50.0)	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Behavioural disorders	4 (8.9)	1 (25.0)	2 (50.0)	1 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Speech disorders	3 (6.7)	1 (33.3)	2 (66.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Convulsion	2 (4.4)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tremor	2 (4.4)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	2 (4.4)	2 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Amenorrhoea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

a In men ≥12 years old, n=26

HAT = human African trypanosomiasis; mITT = modified intention-to treat; mo = month(s); N = number of patients in the population; n = number of patients with the symptoms and/or signs; wk = week(s).

Note: the percentages of patients with the sign/symptom depending on time from baseline are calculated relative to the total number of patients with that sign or symptom.

Source: Table 16.2.4.1.8.

All patients presented with trypanosomes in the blood by using the mAECT except one patient who was positive only for thick or thin blood smear. Parasites were detected in the blood in 91% (thick or thin blood smear) to 98% (mAECT) of patients depending on the method used; the mini-anion exchange centrifugation technique on buffy coat (mAECT-BC) was performed in 6 patients (5 patients were positive) and MHCT (Woo test) was performed in one patient (who was positive). Four patients were positive only for mAECT but negative for the thick or thin blood smear the mAECT-BC and the MHCT (Woo test) were not done for these patients. Lymph node aspirate was not performed in any patient.

Overall, 34/45 (76%) patients had trypanosomes in the CSF when using the modified single centrifugation technique, and one patient was trypanosome-negative but had a CSF-WBC count of 12 cells/µL and was thus identified with stage 2. The levels of WBC in the CSF varied widely (from 0 to 363 cells/ µL). Most patients (27/45 [60%]) had CSF-WBC levels >5 cells/µL, including 10/45 (22%) stage-2 r-HAT patients with CSF-WBC levels >100 cells/µL. The 4 patients with positive mAECT and negative thick/thin blood smear presented trypanosomes in the CSF (with CSF-WBC levels varying from 20 to 113 cells/µL). A patient who was negative for mAECT and mAECT-BC, but positive in blood with the thick/thin blood smear also presented trypanosomes in the CSF (WBC level of 182 cells/µL).

Disease diagnosis and staging at baseline – mITT population – Study DNDi-FEX-07-HAT

Characteristics	Statistics, categories	DNDi-FEX-07-HAT (N = 45)
Blood tests		
mAECT, n (%)	Positive	44 (97.8%)
	Negative	1 (2.2%)
Number of trypanosomes observed in blood, n (%)	1 to 5	5 (11.4%)
	6 to 20	4 (9.1%)
	20 to 50	5 (11.4%)
	>50	29 (65.9%)
	Missing	1 (2.3%)
mAECT-BC, n (%)	Positive	5 (11.1%)
	Negative	1 (2.2%)
	Not done	39 (86.%7)
Thick or thin blood smear, n (%)	Positive	41 (91.1%)
	Negative	4 (8.9%)
CSF tests		
Trypanosome, n (%)	Positive	34 (75.6%)
	Negative	11 (24.4%)
	Method: Modified single Centrifugation	45 (100.0%)
WBC (/mm3)	Mean (SD)	62.1 (96.4%)
	Median (Q1, Q3)	8.0 (3.0, 61.0)
	Min; Max	0.0; 363.0
	WBC>5, n (%)	27 (60.0%)
	of which WBC>100, n (%)	10 (22.2%)
r-HAT stage n (%)	Stage 1	10 (22.2%)
	Stage 2	35 (77.8%)

Abbreviations: **Max**; maximum; **Min**, Minimum; **mAECT**, mini-anion exchange centrifugation technique; **mAECT-BC**, mini-anion exchange centrifugations technique on buffy coat; **mITT**, modified intention-to treat; **Q**, quartile; **r-HAT**, rhodesiense human African trypanosomiasis; **SD**, standard deviation; **WBC**, white blood cells

Source: DNDi-FEX-07-HAT CSR, Table 11, Appendix 16.2.6 Efficacy data, Listing 16.2.6.2.2

As per protocol, all patients were tested for malaria before starting the study treatment. A total of 35 patients (77.8%) were negative. The rapid detection test was positive in 10 patients (22.2%), 3 (6.7%) of whom were also positive for the thick blood smear test.

Of the 10 patients who were positive for malaria at baseline, 1 patient was not treated before receiving study treatment (the patient had a TEAE of malaria on Day 3 and started treatment during the study period - from Day 5 to Day 7), 8 patients were treated with the artemisinin-based combination of artemether and lumefantrine starting before study treatment, and 1 patient was treated with artesunate before starting treatment with fexinidazole and continued with the combination of artemether and lumefantrine from Day 1 to Day 4.

Numbers analysed

The first patient was included on 29/9/2019 and the last patient included was on 17/11/2021.

At the time of initial cut-off date (25/1/2022):

- Up to W9, the dataset was complete for all visits: all patients completed all visits from baseline to W9 (n=44), except 1 patient who died prematurely;
- After W9, the dataset was incomplete: 38 patients completed up to the M6 visit and 30 patients completed up to the M12 visit (which represents 84.4% and 66.7% of the 45 enrolled patients, respectively);
- A total of 14 patients were still being followed up.

Thus, the SOH submitted at the beginning with this extension of indication an initial CSR. The final results of the primary efficacy endpoint at end of hospitalization (EoH) and the final results for the secondary efficacy endpoints at EoH and Week 9 were presented hereafter, while the final results at Month 6 and at Month 12 (or EoS) were reported in the final CSR submitted later during this variation procedure.

Patient disposition and reasons for premature study discontinuation -Study DNDi-FEX-07-HAT

Parameter	Primary timepoint EOH	Additional timepoints			
		Month 1 (M1)	Week 9 (W9)	Month 6 (M6)	Month 12 (M12) EOS Test of cure
Stage-2 patients					
Reached	34/35 (97%)	34/35 (97%)	34/35 (97%)	34/35 (97%)	34/35 (97%)
Reached EP	34/34 (100%)	34/34 (100%)	34/34 (100%)	34/34 (100%)	34/34 (100%)
Reason for premature withdrawal					
Death	1/35 (3%)	1/35 (3%)	1/35 (3%)	*1/28*	*1/35*
Treatment failure	0/35 (0%)	0/35 (0%)	1/35 (3%)	*1/28*	*1/35*
Stage-1 patients					
Reached	10/10 (100%)	10/10 (100%)	10/10 (100%)	10/10 (100%)	10/10 (100%)
Reason for premature withdrawal					
Death	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	*0/10*
Treatment failure	0/10 (0%)	0/10 (0%)	0/10 (0%)	0/10 (0%)	*0/10*
Total patients (both stages)					
Reached	44/45 (98%)	44/45 (98%)	44/45 (98%)	38/45 (84%)	44/45 (98%)
Reached EP	44/44 (100%)	44/44 (100%)	44/44 (100%)	38/44 (86%)	44/44 (100%)

Abbreviations: EOH, end of hospitalization; EOS, end of study; EP, evaluable patient
Source: DNDi-FEX-07-HAT CSR, Table 5 and Figure 3

a Patient (stage-2 r-HAT) died during hospitalization and was excluded from the evaluable patient (EP) population.
b Patient (stage 2 r-HAT) was trypanosome-positive at Week 9 (modified single centrifugation of CSF test) and received rescue medication (melarsoprol) on the next day
c Proportions not calculated as some patients had not yet reached this timepoint at the initial data cut-off date

All (98%) but one patient completed the 10-day treatment. One stage-2 r-HAT patient died during hospitalization from acute kidney injury considered as unrelated to r-HAT disease or treatment by the Investigator and the Sponsor, and as evaluated by the independent DSMB. This patient was excluded from the EP population, which consisted of 34 stage-2 patients for the analysis of the primary endpoint.

All patients in ITT population received at least one dose of study drug, meaning that ITT and modified ITT (mITT) were identical (N = 45).

The stage-2 r-HAT evaluable patient (EP) population consisted of 34 patients for the primary efficacy endpoint.

Datasets analyzed - Study DNDi-FEX-07-HAT

Data sets analyzed	r-HAT patients at primary endpoint (EOH)		
	Stage-2	Stage-1	Total

Data sets analyzed	r-HAT patients at primary endpoint (EOH)		
ITT Population	35	10	45
mITT Population	35	10	45
TC Population	34[a]	10	44
EP Population	34[a]	10	44

Abbreviations: EP, evaluable patients; ITT, intention-to-treat; mITT, modified intention-to-treat; r-HAT, human African trypanosomiasis due to *T. b. gambiense*; TC, treatment completers

Source: DNDi-FEX-07-HAT CSR, Table 6

a Death of a patient (acute kidney injury) occurred at Day 8 and was considered as unrelated to r-HAT or treatment

Outcomes and estimation

All efficacy endpoints assessed up to EoH (including the primary endpoint) were analysed based on the complete dataset.

44 patients at EoH, M1 and W9 (1 patient died before EoH)

38 patients at M6

30 patients at M12.

Primary endpoint

The primary objective was:

- To show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5%.

One stage-2 r-HAT patient died during hospitalization before EoH, from acute kidney injury. The Investigator assessed the SAE of “acute renal failure” as not related to fexinidazole and DSMB reviewed this case and concluded that the death was not related to fexinidazole or r-HAT.

For the primary efficacy endpoint, the fatality rate at EoH (Day 12 to Day 18), considering only deaths possibly related to r-HAT or fexinidazole, as assessed by an independent DSMB, was calculated in stage-2 r-HAT patients and compared to the unacceptable fatality rate set at 8.5%. This analysis was conducted using the evaluable patient population (N = 34), from which the patient who died on Day 8 for reason considered as unrelated to study treatment or disease was excluded as per protocol.

The fatality rate at EoH (defined as the rate of r-HAT or treatment-related deaths at EoH - Day 12 to Day 18) in patients with stage 2 r-HAT included in the EP population was 0% (90% CI 0.00, 8.43) with an upper limit of the 90% CI <8.5%, thereby excluding the threshold of unacceptable rate and rejecting the null hypothesis of a rate ≥8.5% (p = 0.0488, one-sided exact test).

Efficacy outcome at the primary endpoint

Fatality outcome at EOH. Study DNDi FEX-007-rHAT

Analysis	Fatality rate at EOH[d] (Study DNDi-FEX-007-HAT)
Primary (endpoint) analysis (stage 2)	
Attributable fatality rate, EP pop, N = 34, n(%) [90%CI][a]	0 (0.0%) [0.00%; 8.43%] p = 0.0488[b]
Sensitivity analyses (stage 2)	
Attributable fatality rate, ITT pop, n = 35, [90%CI][a]	0 (0.0%) [0.00%; 8.35%] p = 0.0446[b]
Attributable fatality rate, TC pop, n = 34 [90%CI][a]	0 (0.0%) [0.00%; 8.43%] p = 0.0488[b]
All cause fatality rate, ITT pop, n = 35 [95%CI][a,e]	1 (2.9%) [0.07%; 14.92%]
Secondary analyses (stage 1 and 2[c])	
Attributable fatality rate, EP pop, n = 44, [90%CI][a]	0 (0.0%) [0.0%; 6.58%] p = 0.0201[b]
All cause fatality rate, ITT, n = 45, [95%CI][a, e]	1 (2.22%) [0.06; 11.77%]

Abbreviations: CI Confidence Interval, EOH End of Hospitalisation, EP Evaluable patient, mITT modified intent to treat = ITT, r-HAT Human African trypanosomiasis due to T.b.rhodesiense, TC Treatment completers, TRT treatment
Source: Study DNDi-FEX-007 HAT CSR Tables 17, 18 and 19 and additional post-hoc analyses for all cause fatality rates
a: Clopper Pearson Confidence interval
b: comparison to the pre-specified threshold (8.5%) (1-sided exact test).
c: Total population includes stage 2 (n = 35 for ITT and n = 34 for EP) and stage 1 (n = 10 for EP and ITT) patients
d: Fatality rate at EOH and month 12 are the same (no deaths during follow-up).
e Post hoc analysis (no p value)

Efficacy outcome at Month 12. Study DNDi FEX-007-rHAT. Failure rate includes relapse and death.

Analysis	Failure rate at Month 12[d] (Study DNDi-FEX-007-HAT)
Planned secondary analysis (stage 2)	
Failure rate (attributable to treatment or r-HAT), EP pop, N = 34, n(%) [90%CI][a]	1 (2.9%) [0.15%; 13.2%] p = 0.0730[b]
Sensitivity analyses (stage 2)	
Failure rate (attributable to trt or r-HAT), ITT pop, n = 35, [90%CI][a]	1 (2.85%) [0.15%; 12.85%] p = 0.0479[b]
Failure rate (attributable to trt or r-HAT), TC pop, n = 34 [90%CI][a]	1 (2.9%) [0.15%; 13.2%] p = 0.0730[b]
Failure rate (any cause), ITT pop, n = 35 [95%CI][a,e]	2 (5.7%) [0.70%; 19.16%]
Secondary analyses (stage 1 and 2[c])	
Failure rate (attributable to trt or r-HAT), EP pop, n = 44, [90%CI][a]	1 (2.27%) [0.12%; 10.33%] p = 0.0235[b]
Failure rate (any cause), ITT, n = 45, [95%CI][a,e]	2 (4.44%) [0.54; 15.15%]

Abbreviations: CI Confidence Interval, EOH End of Hospitalisation, EP Evaluable patient, mITT modified intent to treat = ITT, r-HAT Human African trypanosomiasis due to T.b.rhodesiense, TC Treatment completers, TRT treatment
Source: Study DNDi-FEX-007 HAT CSR Tables 17 and additional post-hoc analyses for failure rate for any cause.
a: Clopper Pearson Confidence interval
b: comparison to the pre-specified threshold (12%) (1-sided exact test).
c: Total population includes stage 2 (n = 35 for ITT and n = 34 for EP) and stage 1 (n = 10 for EP and ITT) patients
d: No failure (attributable to trt or disease) in EP population at EOH and one failure for any cause at EOH in ITT
e Post hoc analysis (no p value)

The attributable fatality rate at EoH was also of 0% when calculated for the mITT population (N = 35), the TC population (N = 34), as the death which occurred before EoH, and was considered as unrelated to r-HAT and study treatment, was not counted as per protocol. In addition, the attributable fatality rate at EoH was also of 0% when using the total population of evaluable r-HAT patients (N = 44) in a supplementary analysis. The results of these sensitivity and supplementary efficacy analyses were therefore consistent with the primary efficacy analysis.

In spite of the approach taken by the SOH in presenting the outcome of the primary endpoint based on the data gathered for EP, the CHMP was not in agreement that the data should be presented as such in the SmPC, considering the DNDi-FEX-07-HAT was a single arm trial. In addition, CHMP did not find appropriate to reflect in the SmPC, the study comparison of the upper bound of the 90% CI of fatal cases (8.5%) between the EOH in patients treated with fexinidazole vs the historical point estimate for fatal cases in patients treated with melarsoprol.

As such, the CHMP requested the presentation of the pivotal data as stand-alone using the ITT population principle (i.e., including all patients and not excluding the fatal cases) instead with a 95% CI around the point estimate and considering all-cause mortality and failure.

As requested, the 95% CI were produced on the intention-to-treat (ITT) population for the following endpoints:

• The death rate for a cause possibly related to the treatment or disease at EOH and at Month 12 in the ITT population of stage-2 r-HAT patients was of 0% (0/35) (95% CI: 0.00% to 10.00%).

• The death rate for any cause in stage-2 r-HAT up to EOH and at Month 12 in the ITT population of stage-2 r-HAT patients are of 2.86% (1/35) (95% CI: 0.07% to 14.92%).

• The failure rate at EOH in stage-2 patients (N = 35) in the ITT population was of 2.86% (1/35) (95% CI: 0.07% to 14.92%). In stage-1 patients (N = 10), the failure rate at EOH was of 0%.

• At test of cure (Month 12), the failure rate in the ITT population of stage-2 r-HAT patients (N = 35) was of 5.7% (2/35) (95% CI: 0.70% to 19.16%).

The upper limit of the 95% CI of fatality and failure rates are beyond their pre-planned unacceptable limits due the study design and sample size calculation. Nevertheless, the SOH noted that the fatality rate for all-causes (2.86%) in Study DNDi-FEX-07-HAT is comparable to what was observed in g-HAT patients in DNDiFEX004 study.

Post-hoc analysis of treatment failure including all-cause mortality in intention-to-treat-population.

	End of hospitalisation	12 months
Stage 2	2.9% (1/35) (95% CI: 0.07% to 14.9%)	5.7% (2/35) (95% CI: 0.70% to 19.2%)
Stage 1	0% (0/10)	0% (0/10)
Overall (stage 1 and 2)	2.2% (1/45) (95% CI: 0.06% to 11.8%)	4.4% (2/45) (95% CI: 0.5% to 15.2%)

The SmPC section 5.1 referring to Rhodesiense HAT – DNDiFEX007 was updated accordingly.

The demographics and baseline characteristics of the r-HAT study population analyzed for fexinidazole covered the target population and the countries included in the study, Malawi and Uganda, were in line with the areas at highest risk. Since in DNDI-FEX-07-HAT, 97% of patients with stage 2 r-HAT were from Malawi, the SOH additionally presented an out-of-protocol analysis comparing the results of that study with data in the literature regarding mortality rates from Malawi (significantly different from those of other countries) considering it to be a signal in favour of fexinidazole.

Secondary endpoints

The secondary short-term objective was:

- To show that the failure rate (r-HAT or treatment-related death according to DSMB or presence of trypanosomes) at the EoH in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of an unacceptable rate of 9% (the secondary, short-term objective).

The secondary, efficacy long-term endpoints were:

- To show that the proven failure rate (r-HAT or treatment-related death according to DSMB or relapse) at 12 months (or before) in patients with stage 2 r-HAT treated with fexinidazole was below an unacceptable rate of 12%.
- To estimate the failure rate at EoH and at 12 months in patients with stage 1 r-HAT treated with fexinidazole and to verify whether the estimates were smaller than that of suramin.
- To estimate the fatality rate and success rate at 12 months in the overall population (patients with stage 1 and stage 2 r-HAT) treated with fexinidazole.

Based on data provided, there was only one case out of 30 evaluable patients at M12, of relapse reported. The patient, who had stage 2 r-HAT (having 60 cells/ul in CSF at baseline), had an early relapse at W9, a timepoint that had been reached by the whole population of evaluable patients (Trypanosomes were only detected in the CSF) and received rescue medication (melarsoprol) on the next day.

The analysis of dried blood spot (DBS) concentrations for fexinidazole, M1 and M2 (performed at D1, D4 and D11) in this r-HAT patient showed that similar concentrations to those obtained in other r-HAT patients were obtained for each compound. Furthermore, the blood levels for M2 were >10 µg/mL from Day 4 onwards to Day 11, suggesting that effective M2 concentrations had been reached and maintained throughout fexinidazole treatment in this patient.

However, this patient was diagnosed with malaria at baseline and was not treated before receiving study treatment (the patient had a treatment-related adverse event of malaria on Day 3 and started treatment with artemether/lumefantrine during the study period - from Day 5 to Day 7). It is noteworthy that DBS were only performed at D1, D2 and D11.

On the other hand, 20% of patients in DNDi-FEX-07-HAT study took artemether/lumefantrine at screening and the exposure of these patients was compared with patients without artemether/lumefantrine administration, the data suggesting that administration of artemether/lumefantrine at screening do not impact fexinidazole, M1 and M2 exposure.

No other patients relapsed among those who had completed the study at the cut-off date for this initial CSR.

The comparison with the unacceptable failure rate at M12 (12%) for patients with stage 2 r-HAT and for all patients regardless of r-HAT stage will be performed once the dataset is complete at all time points and presented in the final CSR (secondary, long-term objective).

Patient with relapse by stage EP population- Study DNDi-FEX-07-HAT

Relapse in r-HAT EP (N = 44) up to Month 12 (EOS) n (%) [90% CI]		
Stage 2 (N = 34)	**Stage 1 (N = 10)**	**Total (N = 44)**
1 (2.94) [0.15%, 13.21%]	0 (0.00%) [0.00%, 25.89%]	1 (2.27%) [0.12%, 10.33%]

Abbreviations: **CI**, confidence interval; **EP**, evaluable patients; **r-HAT,** human African trypanosomiasis due to *T.b. rhodesiense*
Source: DNDi-FEX-07-HAT Final CSR, Table 23

Regarding stage-1 HAT, the failure and fatality rate were of 0% at EOH and at EOS, as no relapse or death cases were reported in stage-1 r-HAT patients up to Month 12.

All 10 patients with stage 1 r-HAT were alive at EoH and none had a relapse up to EoH. None of these 10 patients showed any *T. brucei rhodesiense* at EoT in the mAECT or the modified single centrifugation of CSF test; the mAECT-BC was also performed for 4 patients with stage 1 and all patients were negative.

The long-term secondary objective, i.e. to show that the failure rate (r-HAT or treatment-related death according to DSMB or relapse) at 12 months (or before) in patients with stage 2 r-HAT treated with fexinidazole was below an unacceptable rate of 12%, was not achieved. One relapse case occurred in a stage-2 patient at Week 9 (trypanosome-positive in the CSF and CSF-WBC count of 12 cells/µL) which was successfully retreated with melarsoprol. No other relapse case was reported in the complete set of stage-2 r-HAT patients who had reached EOS (N = 34). Based on this, the failure rate at Month 12 in stage-2 r-HAT EP was 2.94% (1/34) (90% CI: 0.15% to 13.21%) with an upper limit >12%, which was higher than initially forecasted in the protocol. The failure of this secondary objective is mainly due to the small sample size which necessarily resulted in a large confidence interval. Furthermore, this retained threshold of unacceptable failure rate at 12 months of 12.0% was found to be similar to the 12-month failure rates that could be observed a study analysis of IMPAMEL III. Secondary efficacy analyses related to failure rate in stage-1 patients at EOH could only be descriptive considering the small sample size of 10 patients. The failure rate was of 0% at EOH and at EOS, as no relapse or death cases were reported in stage-1 r-HAT patients up to Month 12.

In the total population of r-HAT EP (stage-1 + stage-2), the failure rate at Month 12 (EOS) was 2.27% (90% CI: 0.12% to 10.34%) with an upper limit of the 90% CI below the rate of 12% ($p < 0.05$).

The success rate at Month 12 (EOS) in the total population of r-HAT EP was 97.73% (90% CI: 89.61% to 99.88%).

The 4 patients who had been treated for r-HAT before the study either with melarsoprol (N = 3) or suramin (N = 1) and the 2 patients who had AIDS/ HIV infection at baseline were all cured at test of cure.

The relapse observed (at W9) occurred in a patient with the diagnosis of malaria at baseline but who took artemether/lumefantrine only between D5 and D7 of fexinidazole (DBS were performed only at D1, D4 and D11). The SOH provided an adequate rational sustained by bibliography, supporting the absence of malaria interference on r-HAT and the absence of PK interaction of artemether/lumefantrine on fexinidazole and its active metabolites which argue against an explanation for the relapsing patient. Also, the SOH summarizes the current data about fexinidazole resistance which also argue against a case of resistance of *Trypanosoma brucei (T. b.) rhodesiense* to fexinidazole in the relapsing patient. Although the case of the relapsing patient remains without a plausible justification, the explanation provided is acceptable.

Table 14 - Secondary efficacy endpoints: Failure rates at Month 12 (EOS) –Study DNDi-FEX-07-HAT

Analyzed population (EP)	Secondary endpoints: Failure rates at test of cure at M12 n (%) [90% CI][a], comparison with unacceptable rate at EOS (12%)[b]
Stage-2 r-HAT EP at M12 N = 34	1[c] (2.94%) [0.15%; 13.21%], p = 0.073015
Stage-1 r-HAT EP at M12 N = 10	0 (0.0%) NA[d]
Total population EP at M12 N = 44	1[c] (2.27%) [0.12%; 10.34%], p = 0.025254

Abbreviations: **CI**, confidence interval; **CSF**, cerebrospinal fluid; **EP,** evaluable patients; **M12,** month 12**; NA,** not applicable**; r-HAT**, human African trypanosomiasis due to *T. b. rhodesiense;* **WBC**, white blood cells
Source: DNDi-FEX-07-HAT Final CSR, Section 10.2.2

a Clopper-Pearson 90% CI, if applicable

b The comparison to the pre-specified threshold was done using a one-sided exact test at the 0.05 significance level

c One patient (Patient No. 1027, stage-2 r-HAT) was considered as a failure at test of cure. Trypanosomes were detected in the CSF at Week 9 (modified single centrifugation of CSF test) and the CSF-WBC count was of 12 cells/µL (baseline 60 cells/µL). This patient was successfully retreated with melarsoprol

d The comparison with unacceptable rate was not performed because of the small number of patients with stage 1 r-HAT

Unsatisfactory clinical and parasitological responses at M12 were very rare: 1 patient with stage 2 r-HAT had persistent abdominal pain and was trypanosome-positive at W9 (the relapse described above) and 1 patient with stage 2 r-HAT had persistent splenomegaly, which was intermittent during follow-up but did not worsen over time (3 cm at baseline versus 2 cm at M12).

Efficacy of fexinidazole in patients with cerebrospinal fluid white blood cells count (CSF-WBC) **>100/µL**

Based on the SmPC for *T. b. gambiense* there was some lack of efficacy for patients with cerebrospinal fluid white blood cells count (CSF-WBC) >100/µL and these patients should only be treated with fexinidazole if no other adequate treatment (e.g. NECT) is available or tolerated (efficacy of 86.9% in the fexinidazole arm versus 98.7%% in the NECT arm). As stated by CHMP in the initial Scientific Advice provide to the SOH as support for the extension of indication, this phenomenon should be also investigated for r-HAT and at the time of the submission of the extension of indication data for CSF-WBC should be available for these patients.

Considering the EP population, the proportion of patients with CSF-WBC ≤5 cells/µL doubled from baseline to Week 9 (41% to 80%), whereas the proportion of patients with CSF-WBC >20 cells/µL (39%) and >50 cells/µL (32%) steadily decreased from baseline to Week 9 down to 2% or 0%. It is noteworthy that none of the 10 patients who had high CSF-WBC levels at baseline ≥100 cells/µL, presented such WBC levels in the CSF from EoT onwards. Furthermore, all patients with high CSF-WBC levels ≥100 cells/µL had a 3- to up to 37-fold reduction between baseline and EoT which was further maintained up to Week 9 down to 2% or 0%, and down to 0% at Month 12. Five patients (5/43 [12%]) had CSF-WBC levels >5 and <20 cells/µL at Month 12. It is noteworthy that none of the 10 patients who had high CSF-WBC levels at baseline ≥100 cells/µL, presented such WBC levels in the CSF from EOT onwards. Furthermore, all patients with high CSF-WBC levels ≥100 cells/µL had a 3- to up to 37-fold reduction between baseline and EOT which was further maintained up to Month 12.

Table 15 - Levels of white blood cells in the cerebrospinal fluid of r-HAT evaluable patients over time - Study DNDi-FEX-07-HAT

Time point	Baseline	Day 11 EOT	Week 9	Month 6	Month 12 EOS
EP	**N = 44**	**N = 44**	**N = 44**	**N = 44**	**N = 43[c]**
Levels of WBC (cells/µL) in the CSF of r-HAT EP population					
Median (Q1, Q3)	8.0 (3.0, 65.0)	7.5 (3.0, 28.5)	1.0 (0.0, 4.5)	0.0 (0.0, 2.0)	1.0 (0.0, 3.0)
Min-max	0.0; 363.0	0.0; 88.0	0.0; 25.0[a]	0.0; 169.0	0.0; 14.0
Number of r-HAT evaluable patients					
WBC ≤5 cells/µL	18/44 (41%)	20/44 (45%)	35/44 (80%)	38/44 (86%)	38/43[d] (88%)
WBC>20 cells/µL	17/44 (39%)	14/44 (32%)	1/44[a] (2%)	2[b]/44 (4%)	0/43 (0%)
WBC>50 cells/µL	14/44 (32%)	7/44 (16%)	0/44 (0%)	1[b]/44 (2%)	0/43 (0%)
WBC≥100 cells/µL	10/44 (23%)	0/44 (0%)	0/44 (0%)	0/44 (0%)	0/43 (0%)

Abbreviations: **CSF**, cerebrospinal fluid; **CSR**, clinical study report; **EOS**, end of study; **EOT**, end of treatment; **EP,** evaluable patients; **Max,** maximum; **Min,** minimum; **Q,** quartile; **r-HAT**, human African trypanosomiasis due to *T. b. rhodesiense;* **SD**, standard deviation; **WBC**, white blood cells

Source: DNDi-FEX-07-HAT Final CSR, Table 22 and Appendix 16.2.6 Efficacy data, Listing 16.2.6.1.18

a One patient (Patient No. 1039, stage-2 r-HAT) had CSF-WBC count >20 cells/µL at Week 9. The patient was not considered as a failure because his CSF-WBC count gradually decreased from baseline to Week 9 (278 cells/µL at baseline, 88 cells/µL at EOT, and 25 cells/µL at Week 9, see Table 23) and was in a satisfactory clinical condition. Note that the patient did not receive any rescue medication at Week 9. His CSF-WBC levels kept decreasing at Month 6 (3 cells/µL) and the patient was considered as cured at test of cure (0 cell//µL).

b One patient (Patient No. 1004, stage-2 r-HAT) had WBC >50 cells/µL in CSF at Month 6 (169 cells/µL). The patient was not considered as a failure because the patient was HIV-positive, with poor compliance to HIV treatment. The patient was trypanosome-negative and had CSF WBC count <20 cells/µL at Month 12 (12 cells/µL). Two patients (Patient No. 1002 and Patient No. 1030) had a transient increase in CSF WBC count at Month 6 to 27 cells/µL that had decrease to 0 and 3 cells/µL, respectively, at Month 12, likely due to random variation as their clinical profile was "silent" (see Table 23)

c One patient (Patient No. 1006) refused the lumbar puncture at Month 12 but was in good clinical condition (see Table 23)

d Five patients (Patients Nos. 1004, 1009, 1036, 1040 and 2001) had CSF-WBC count of 14, 7, 6, 11 and 6 cells/µL, respectively, at Month 12

In Study DNDi-FEX-07-HAT, besides 3 cases of transient CSF-WBC level increase at Month 6, all patients experienced decreased CSF-WBC levels from EoT onwards, even those who had a CSF-WBC ≥100 cells/µL at baseline. These data support the activity of fexinidazole regardless of the baseline CSF-WBC levels of r-HAT patients.

The CHMP agreed on the fact that based on the data so far provided and contrary to what occurs for g-HAT, fexinidazole seems to be efficacious in patients with cerebrospinal fluid white blood cells count (CSF-WBC) >100/µL at baseline.

Efficacy of fexinidazole in pediatric r-HAT patients

Pediatric patients received different fexinidazole doses according to their body weight:

- 11 children (7 to 12 years old) weighing from 20 to <35 kg received the 1200/600 mg dose and 6 adolescents (13 to 16 years old) weighing ≥35 kg received the 1800/1200 mg dose. There were 10 children and 4 adolescents with stage-2 r-HAT and 1 child and 2 adolescents with stage-1 r-HAT.

Observed concentrations of fexinidazole measured in children with BW<35 kg were in line with those measured in adults but for children with BW>=35 kg their concentrations are slightly higher. For M1, the three subgroups seemed comparable, and for M2 children with BW<35 kg had a higher concentration than the other two groups. When exploring more closely M2 data there were only 4 children out of 11 with high concentrations and other were in line with the two other subgroups.

At data cut-off date for initial CSR, 3 pediatric patients were ongoing at Month 6 and 6 were ongoing at Month 12. All stage-1 pediatric patients (N = 3) had reached Month 12.

None of the 17 pediatric patients experienced death or relapse at EOH and up to Month 12. These data suggested that fexinidazole was efficacious in r-HAT pediatric patients aged 7 to 16 years. Of note, all pediatric patients had CSF-WBC levels ≥100 cells/µL (range: 113 to 363 cells/µL) at baseline.

Ancillary analyses

The following exploratory efficacy endpoints were planned:

- Earliest time to detect a relapse from EoT to M12 (EoS)
    - Presence of trypanosomes in any body fluid, or
    - The date of death, if attributable to r-HAT or treatment administration, according to the DSMB, or
    - The administration of rescue medication.
- Time to reduction in the number of trypanosomes in the blood

  The semi-quantification of trypanosomes in blood was to be assessed by mAECT and the detection of trypanosome nucleic acids until EoS was to be assessed by RT-qPCR.

The time to failure (earliest time to detect a relapse) and the time to reduction in the number of trypanosomes in the blood will be estimated with survival analysis in the final CSR. Descriptive data regarding the earliest time to detect a relapse are presented in the initial CSR.

Exploratory analyses investigated the activity of fexinidazole against trypanosomes in blood and CSF during treatment and the efficacy of treatment up to test of cure at Month 12 (EOS), by using microscopic and molecular techniques. Fexinidazole fast activity at killing parasites was observed both in blood (Day 4) and CSF (EOT), in line with the primary and secondary efficacy endpoints at EOH and the decrease in clinical signs and symptoms of the disease as early as Day 5. Furthermore, these exploratory analyses confirm the maintenance of parasite clearance in both in blood and CSF from EOT to Month 12 in all but one patient. The detection of the relapse case by using LAMP PCR on genomic DNA extracted from DBS sample at Week 9 confirms the high sensitivity of LAMP PCR as trypanosomes were not detected in blood by using microscopic techniques.

Overall, these results confirmed the fast activity of fexinidazole at killing parasites in blood and the persistence of parasite clearance up to Month 12.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 7. Summary of Efficacy for trial DNDi-FEX-07-HAT

Title: Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial		
Study identifier	DNDi-FEX-07-HAT	
Design	Multicentre, open-label, nonrandomised, clinical trial on efficacy/tolerability of fexinidazole in patients with r-HAT due to *Trypanosoma brucei rhodesiense*	
	Duration of main phase:	Treatment period: D1-D10 (EoT); Observation period: D11-D18 (EoH); and Follow up until Month 12 (EoS)
	Duration of Run-in phase:	Not applicable
	Duration of Extension phase:	Not applicable
Hypothesis	H0: Proportion of deaths (pdeath) ≥8.5% at EoH	
Treatments groups	Fexinidazole	Fexinidazole according to body weight, 10 days of treatment, 45 patients
Endpoints and definitions	Primary endpoint: Pdeath < 8.5% at EoH	Fatality rate (death possibly related to r-HAT or treatment) at EoH in stage-2 patients treated was below the unacceptable rate of 8.5%
	Secondary endpoints: Failure rate at EoH and comparison to prespecified threshold of 9%	Failure rate at EoH in stage-2 patients treated (r-HAT or treatment-related death according to DSMB or presence of trypanosomes) and comparison to prespecified threshold of 9%
	Failure rate at EoS and comparison to prespecified threshold of 12%	Failure rate at EoS (or before) in stage-2 patients treated (r-HAT or treatment-related death according to DSMB or relapse) and comparison to prespecified threshold of 12%
	Failure rate at EoH and at EoS in patients with stage 1 r-HAT	Failure rate at EoH and at EoS in patients with stage 1 r-HAT treated with fexinidazole and to verify whether the estimates were smaller than that of suramin
	Fatality rate and success rate at EoS in the overall population (patients with stage 1 and stage 2 r-HAT)	Failure rate at EoS in patients with stage 1 and stage 2 r-HAT treated with fexinidazole

<table>
<tr><td colspan="5">Title: Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to Trypanosoma brucei rhodesiense: a multicentre, open-label clinical trial</td></tr>
<tr><td></td><td colspan="2">Safety profile of fexinidazole in patients with stage 1 and stage 2 r-HAT and to compare it to melarsoprol and suramin as reported in the literature.</td><td colspan="2"></td></tr>
<tr><td colspan="5">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Fatality rate (death possibly related to r-HAT or treatment) at EoH in stage-2 patients treated was below the unacceptable rate of 8.5%</td></tr>
<tr><td rowspan="4">escriptive statistics and estimate variability</td><td>Treatment group</td><td colspan="3">Fexinidazole</td></tr>
<tr><td>Number of subjects</td><td colspan="3">45 (35 stage 2 r-HAT and 10 stage 1 r-HAT patients)</td></tr>
<tr><td rowspan="2">EoH
Frequencies and percentage per item</td><td colspan="3">Fatality rate (death possibly related to r-HAT or treatment) at EoH in stage-2 patients treated was below the unacceptable rate of 8.5%</td></tr>
<tr><td>Primary analysis
EP population</td><td colspan="2"></td></tr>
</table>

Title: Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial			
		Sensitivity analysis N (%) of death possibly related to r-HAT or to Fexinidazole up to the end of hospitalisation – stage 1, stage 2 and stage 1+2 r-HAT patients mITT population	Stage 1 (N=10): 0 (0.00%) Stage 2: All cause fatality rate, ITT, pop: ((N=35, (95 %IC)): 1 (2.86%) [0.07%; 14.92%]. Post hoc analysis (no p value) Attributable fatality rate: ITT pop, (N = 35, (90%CI)): 0 (0.0%) [0.00%; 8.35%] p = 0.0446* TC pop, (N = 34, (90%CI)): 0 (0.0%) [0.00%; 8.43%] p = 0.0488* *(one sided exact test with a benchmark of 0.085 for fatality on stage 2 patients) Stage 1 and 2 All cause of fatality rate, ITT, (N=45), (95% IC): 1 (2.22%), [0.06 – 11.77]. Post hoc analysis (no p value) Attributable fatality rate, EP pop, (N=44) (90% IC): 0 (0.0%), [0.00 – 6.58], p= 0. 02001* * (one sided exact test with a benchmark of 0.085 for fatality on all patients) All cause fatality rate, ITT, N=45, (95% IC): 1 (2.22%) [0.06; 11.77%] Post hoc analysis (no p value)

Title: Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial			
Effect estimate per comparison	Secondary endpoint Failure rate at EOH – stage 1, stage 2 and stage 1+2 r-HAT patients mITT population (N=45)	Stage 1 r-HAT	(N=10) 0 (0.0%
		Stage 2 r-HAT one-sided exact test with a benchmark of 0.09 for failure on stage 2 patients Clopper-Pearson 90% CI P-value	(N=35) 0 (0.00%) 0.00; 8.20 p= 0.036851
		Stage 1 + Stage 2 r-HAT one-sided exact test with a benchmark of 0.09 for failure on stage 1 + stage 2 patients Clopper-Pearson 90% CI P-value	(N=45) 0 (0.0%) 0.00; 6.44 p= 0.01435
	Secondary endpoint Failure at EOH – stage 1, stage 2 and stage 1+2 r-HAT patients EP population & TC population (N=44)	Stage 1 r-HAT	(N=10) 0 (0.0%)
		Stage 2 r-HAT one-sided exact test with a benchmark of 0.09 for failure on stage 2 patients Clopper-Pearson 90% CI P-value	(N=34) 0 (0.00%) 0.00; 8.43 p= 0.040496

Title: Efficacy and safety of fexinidazole in patients with Human African Trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicentre, open-label clinical trial			
		Stage 1 + Stage 2 r-HAT one-sided exact test with a benchmark of 0.09 for failure on stage 1 + stage 2 patients Clopper-Pearson 90% CI P-value	(N=44) 0 (0.00%) 0.00; 6.58 p= 0.015770
	Secondary endpoint N (%) of patients with a relapse - stage 1 and stage 2 r-HAT patients EP population (N=44)	Stage 1 r-HAT	(N=10) 0 (0.00%)
		Stage 2 r-HAT	(N=34) 1 (2.94%), [0.15 - 13.21]
		Stage 1 + Stage 2 r-HAT	(N=44) E pop, (90% IC) 1 (2.27%), [0.12 - 10.33] p= 0.0235* * comparison to the pre-specified threshold (12%) (1-sided exact test). (N=45), Failure rate (any cause), IIT, (95%IC): 2 (4.44%), (0.54;15.15%) Post hoc analysis (no p value)

2.4.3. Discussion on clinical efficacy

Fexinidazole is a 2-substituted 5-nitroimidazole, formulated for oral administration, with *in vitro* and *in vivo* activity against both *T. brucei rhodesiense* and *T. brucei gambiense* parasites. Fexinidazole acts primarily as a biologically active prodrug, with the sulfoxide and sulfone metabolites (later referred to as M1 and M2, respectively) providing most of the trypanocidal activity.

Fexinidazole efficacy and safety have been tested in 3 clinical trials during which fexinidazole was administered as a 10-day treatment to adults and children with g-HAT at all stages (DNDiFEX004, DNDiHATFEX005, DNDiHATFEX006). Pooled efficacy data from these studies indicate a success rate of 95.1% (confidence interval [CI] 93.1% – 96.7%) among patients having received at least one dose of fexinidazole and followed up to 18 months. In the same analysis population, however, the success rate decreased to 88.2% (CI 82.7% – 92.5%) when CSF WBC count at baseline was above 100 cells/µL.

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

Fexinidazole for the use in HAT due to *T. brucei gambiense* (g-HAT) received a positive opinion from the European Medicines Agency (EMA) on 15 November 2018 and was registered in the Democratic Republic of the Congo (DRC) on 24 December 2018 and in Uganda on 3 October 2021. On 16 July 2021, the Food and Drug Administration (FDA) approved fexinidazole as the first all-oral treatment for both stages of g-HAT.

Human African trypanosomiasis due to *Trypanosoma brucei (T. brucei) rhodesiense* (r-HAT) is the zoonotic, acute form of sleeping sickness in Eastern Africa. The disease can be rapidly lethal if untreated and has caused large epidemics in the past century.

Over the past 15 years, efforts by the national HAT control programs in all HAT endemic countries and key stakeholders have brought down the patient number to less than 120 per year. Despite these encouraging numbers, approximately 77,000 people were living in areas still with moderate to high risk of contracting r-HAT (data between 2014 and 2018). East Africa is affected by sleeping sickness in separated foci, which, over time, tend to remain spatially stable but fluctuate in transmission intensity. To date, Malawi and Uganda reported the highest number of cases worldwide. Latest World Health Organization (WHO) available data between 2015 and 2021 showed 316 cases in Malawi (71% of all) and 64 in Uganda (14%).

To date, only melarsoprol, an arsenic-based drug, is available for late stage (meningo-encephalitic stage) r-HAT. Its use is associated with severe adverse drug reactions, the most important being an encephalopathic syndrome, which occurs in an average of 10.6% of patients with r-HAT, with a case fatality rate of 57.3% (5). Patients treated with melarsoprol need to be hospitalised.

Suramin, a sulphated naphthylamide, remains the treatment of choice for early haemolymphatic stage r-HAT as it does not penetrate the CSF. Suramin's relapse levels were between 6.9% to 31% of patients with stage 1 r-HAT, increasing up to 64% in patients with borderline CSF anomalies (white blood cells [WBC] count between 7 to 10 cells/µL).

In a declaration for the elimination of r-HAT, WHO stakeholders urged for a safe, effective, and preferably oral treatment. DNDi in charge of the clinical development, and Sanofi, responsible for the regulatory and industrial steps, have co-developed an oral formulation of fexinidazole for the treatment of HAT.

The ultimate objective of the present study DNDi-FEX-07-HAT was to show that fexinidazole offered an alternative to melarsoprol in patients with stage 2 r-HAT and to suramin in patients with stage 1 r-HAT.

Design and conduct of clinical studies

DNDi-FEX-07-HAT study was a multicentre, Phase II/III, open-label, non-randomised study aiming to assess the efficacy and safety of fexinidazole in patients with r-HAT. This study was designed as a single arm study treating patients with fexinidazole only, with a benchmark study design comparing the observed fatality rate to an unacceptable rate. The unacceptable rate was that of melarsoprol in the recent years, based on the discussion of the WHO network for HAT elimination and as reported in the clinical trial IMPAMEL III.

The constraints to raise other clinical designs options are understood. However, the lack of a direct comparison with melarsoprol in clinical study DNDi-FEX-07-HAT will hamper assessment of efficacy as compared to melarsoprol.

The present study planned to enroll 34 evaluable patients, aged ≥6 years old, with confirmed stage 2 r-HAT by evidence of T*. brucei rhodesiense* infection in CSF. Patients with stage 1 r-HAT were also recruited in parallel, without any predefined targeted sample size.

The doses and the dosing regimens of fexinidazole used in DNDi-FEX-07-HAT study are those approved for the treatment of g-HAT.

Patients underwent screening within Day -7 to Day -1. Baseline assessments were performed within Day -4 to Day -1. The treatment period was Day 1 to Day 10, and there was an EoT assessment at Day 11 (EoT visit). Patients were hospitalised from the time of their arrival at the investigational site until the EoH visit at Day 12 to Day 18. They were permitted to leave the hospital from Day 12 up to Day 18 if their clinical status was considered satisfactory.

The follow-up visits took place at 1 month (M1 visit), 9 weeks (W9 visit), 6 months (M6 visit), and 12 months (M12 visit) after Day 1. The EoS was at M12. Unscheduled visits could occur at any time.

The primary endpoint was to show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5% (derived from the on-treatment mortality rate observed in stage-2 r-HAT patients on 10-day melarsoprol at EOH (IMPAMEL III study)) and the short-term secondary endpoint was to show that the failure rate (r-HAT or treatment-related death according to DSMB or presence of trypanosomes) at the EoH in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of an unacceptable rate of 9%.

Other secondary endpoints were long-term endpoints - success, failure and fatality rates at M12 – stage 1, stage 2 and stage 1+2 r-HAT patients.

Overall, the conduct of the study was considered acceptable.

Efficacy data and additional analyses

Despite the proposed clinical trial design being a single arm study, associated with important methodological limitations as well as the small sample size due to the rarity of the disease, the increased uncertainty due to the 90% CI and eventually the no completion of the assessment of the full data from DNDi-FEX-07-HAT (only an initial CSR was provided) the efficacy results provided show a single death in 35 patients at end of hospitalisation (EOH; regardless causality) in the stage 2 group and none in 10 patients in the stage 1 group. In addition, among the 35 patients with stage 2 only 1 relapsed at week nine while no relapse was observed so far among the 10 stage 1 patients and no additional relapses were reported in the 22/34 and 8/10 subjects in the respective stage groups that had reached Month 12/end of study at the initial data cut-off. As such, despite limited the data clearly shows a benefit of fexinidazole in the therapeutic management of the r-HAT versus melarsoprol in the treatment of stage 2 r-HAT and stage 1 r-HAT.

Since limited clinical data will become available, the SOH is highly encouraged to conduct post-licensure studies on efficacy and safety of fexinidazole in *T. b. rhodesiense* HAT (e.g. cohort studies describing long term efficacy in all patients treated for *T. b. rhodesiense HAT*).

The demographics and baseline characteristics of the r-HAT study population analyzed for fexinidazole covered the target population and the countries of study conduct, Malawi and Uganda, and were in line with the areas at highest risk.

Overall, 34/45 (76%) patients had trypanosomes in the CSF when using the modified single centrifugation technique, and one patient was trypanosome-negative but had a CSF-WBC count of 12 cells/µL and was thus identified with stage 2. The levels of WBC in the CSF varied widely (from 0 to 363 cells/ µL). Most patients (27/45 [60%]) had CSF-WBC levels >5 cells/µL, including 10/45 (22%) stage-2 r-HAT patients with CSF-WBC levels >100 cells/µL.

The stage-2 r-HAT evaluable patient (EP) population consisted of 34 patients for the primary efficacy endpoint.

One stage-2 r-HAT patient, who died during hospitalization from acute kidney injury which was considered as unrelated to r-HAT disease or treatment by the Investigator and the Sponsor, and by the independent DSMB, was excluded from the EP population for the analysis of the primary endpoint.

So far, one case of early relapse was reported in a stage-2 patient at Week 9 follow up, a timepoint that had been reached by the whole population of evaluable patients. Trypanosomes were only detected in the CSF in this patient who was successfully retreated with melarsoprol. No other relapse case was reported at Month 12.

The primary endpoint which was to show that the failure rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5%, was met.

The secondary, short-term objective (also at EoH) was also met: the failure rate at EoH (defined as r-HAT or treatment-related death, presence of trypanosomes at EoT, or absence of clinical improvement leading to the use of rescue medication) in patients with stage 2 r-HAT was smaller than the unacceptable rate of 9%.

44/ 45 patients with stage 2 r-HAT completed 12 months and with stage 1 r-HAT 10/10. As the last enrolled patient occurred on 17/11/2021 and study follow-up ends when 12 months is completed for the last enrolled patient (11/2022), all patients had already reached the end of study.

Assessment of paediatric data on clinical efficacy

Paediatric patients received different fexinidazole doses according to their body weight.

None of the 17 paediatric patients experienced death or relapse at EOH and up to Week 9 for the complete set of paediatric patients and up to Month 12 for the incomplete set of patients (6 ongoing). These data suggested that fexinidazole was efficacious in r-HAT paediatric patients aged 7 to 16 years weighing ≥ 20 kg.

2.4.4. Conclusions on the clinical efficacy

The efficacy of fexinidazole in treating r-HAT infection was investigated in efficacy analyses at EoH and at additional timepoints, i.e. Week 9, Month 6 and Month 12.

Fexinidazole seems to be efficacious in treating Rhodesiense infection in adult and pediatric stage-1 and stage-2 evaluable patients up to 12 months. Furthermore, all patients with high CSF-WBC levels ≥100 cells/µL had a 3- to up to 37-fold reduction between baseline and EoT which was further maintained up 12 months.

2.5. Clinical safety

Introduction

Products of similar class to fexinidazole, such as metronidazole and tinidazole have been associated with side effects including nephrotoxicity, metallic taste, dry mouth, facial/drug eruption, skin rash, and even Stevens Johnson syndrome. Cutaneous reactions including rash have also been observed with benznidazole.

In Chagas disease (CD) study, skin hyperpigmentation was reported in 10 patients (25%) and were considered related to study drug. None of these effects were classified as serious and no other signs of phototoxicity occurred frequently in CD patients.

Less than 1% of drug related pruritus were observed in the HAT clinical program. Hyperpigmentation and signs of phototoxicity were not detected in HAT or visceral leishmaniosis (VL) studies.

Overall, 3 nitroimidazole class effects are included in the list of safety concerns for fexinidazole either as an important identified risk for “psychiatric events” or as an important potential risk for “vomiting” and “hepatotoxicity including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)” (RMP v3.0, SVII.3.1). The latter was recently added to the latest version (22 December 2022) of the current approved SmPC for fexinidazole in g-HAT indication.

Safety discussion on the approved indication (g-HAT):

Across all studies in the fexinidazole clinical program, a total of 853 patients or subjects have been exposed to fexinidazole in 10 studies, both in HAT and additional indications.

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 (already in line with a known class effect)
- Haematological and neutropenia-related disorders (see comment on study DNDiFEXICH001)
- Neuropsychiatric disorders (including DALA) (already in line with a known class effect)
- Gastrointestinal disorders

Specificities of safety assessment in r-HAT patients

It is noteworthy that r-HAT is an acute and more severe disease than g-HAT as it may lead to death within 6 months. Patients enrolled had several signs and symptoms of the disease but patients with severely deteriorated general condition, such as severe malnutrition, cardiovascular shock, respiratory distress, or terminal illness were excluded to match with the inclusion/exclusion criteria of the IMPAMEL III study, and also because patients needed to be able to swallow fexinidazole tablets.

Pregnant women, preferably after the first trimester of pregnancy, and breastfeeding women could be included in Study DNDi-FEX-07-HAT but not in IMPAMEL III study, as melarsoprol is contra-indicated in pregnant women. No breastfeeding women were included in any study population for r-HAT, and one pregnant woman (third trimester) was included in Study DNDi-FEX-07-HAT.

Paediatric and adult patients were evaluated with the same physiological and clinical scales, despite the absence of paediatric adaptation for some of them (e.g., Karnofsky score).

All patients received treatment for helminthiasis (albendazole) and for malaria (artemether/lumefantrine, or artesunate) if tested positive before starting fexinidazole therapy.

As the Investigators at each study site were not accustomed to the routine assessment of electroencephalograms (ECG), their recordings were sent to a specific provider (in France) for centralized reading.

Although adverse events (AEs) were assessed by the Investigators, the Sponsor also assessed the relatedness of deaths and SAEs. Furthermore, an independent DSMB was constituted to ensure that harm was minimized and benefits maximized to the patients enrolled in the study, which included to evaluate the relationship to drug or disease of potential death cases.

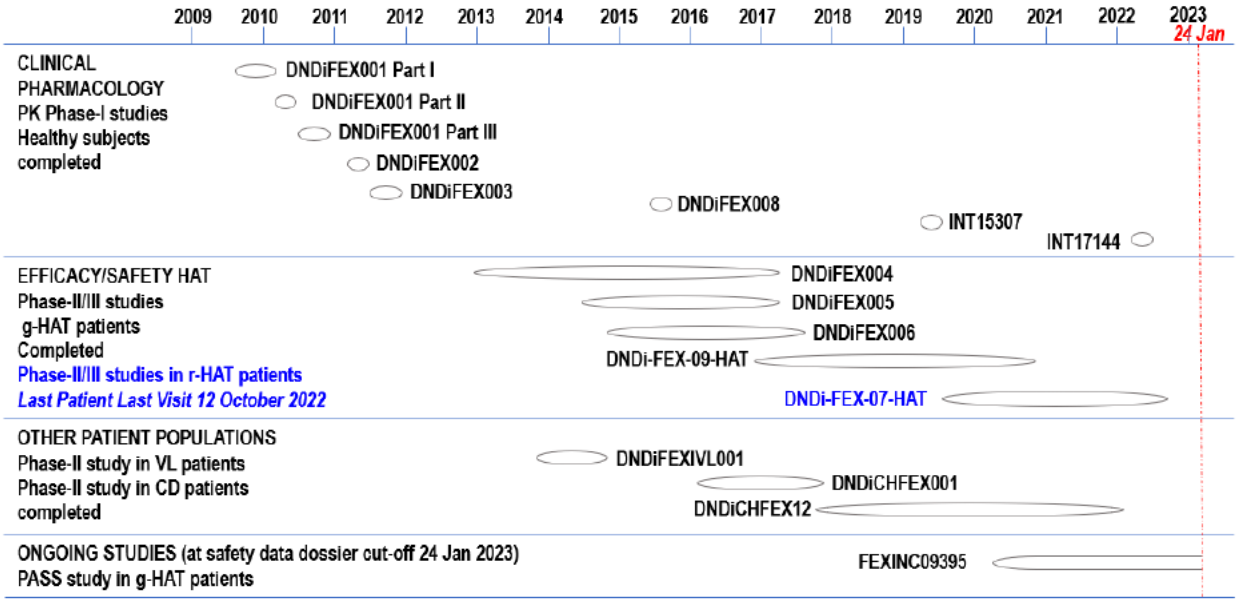
Treatment-emergent adverse events (TEAEs) in r-HAT patients were defined as any AE that had a start date on or after the date of first study treatment administration. They were classified according to whether they occurred during the hospitalization period (from Day 1 until the EOH visit at Day 12 to Day 18), or during the follow-up period (starting from Month 1 visit onwards).

After the EOH visit (Day 12 to Day 18), only SAEs, AESIs, or AEs considered as possibly related to fexinidazole were collected up to Month 12, as patients were not exposed to fexinidazole anymore due to its terminal half-life of 14 hours and that of its M1 (15 hours) and M2 (23 hours) metabolites.

Patient exposure

Up to safety data-cut-off date of 24 January 2023, 1281 healthy subjects, g-HAT and r-HAT patients were enrolled in 16 completed clinical studies (Figure below), and 362 patients with g-HAT were exposed to fexinidazole in endemic countries (CAR, Chad, DRC, Equatorial Guinea, Gabon, Guinea).

Figure 3 - Fexinidazole clinical development program



Abbreviations: **CD**, Chagas disease; **DDI**, drug-drug interactions; **g-HAT**, human African trypanosomiasis due to *T. b. gambiense*; **Jan**, January; **r-HAT**, human African trypanosomiasis due to *T. b rhodesiense*; **PK**, pharmacokinetic; **VL**, Visceral Leishmaniasis

Fexinidazole has been administered in paediatric and adult patients with r-HAT only in the context of the clinical efficacy and safety trial sponsored by DNDi (Study DNDi-FEX-07-HAT).

Of the 45 screened patients who signed the informed consent, all were included in the study (see Table below) which was conducted in 2 sites: one in Malawi and one in Uganda. As all patients in the ITT population received at least one dose of study treatment, both ITT and modified intention-to-treat (mITT) populations were the same population.

Table 1 - Study evaluated in the Summary of Clinical Safety and study status

Study	Summary of key study information	Study duration	Number of study participants evaluated for safety
Study participants with human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*			
DNDi-FEX-07-HAT[a] *Complete*	Efficacy and safety of fexinidazole in patients with human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*: a multicenter, open-label clinical trial	12 months	45 *35 stage 2* *10 stage 1*

a Please note that the last patient last visit was completed on 12 October 2022. Data were reported in 2 CSRs: Initial CSR (dated 21 April 2023) Initial cut-off date for data analysis was on 25 January 2022 and database lock on 06 September 2022. Final CSR (dated 12 June 2023) database lock was on 12 May 2023

As of 25 January 2022, data cut-off date of the initial CSR for Study DNDi-FEX-07-HAT, a total of 45 r-HAT patients had been screened and included in the study:

- 35/45 (78%) patients with stage-2 r-HAT
- 10/45 (22%) patients with stage-1 r-HAT

The safety population included 17 paediatric (11 children and 6 adolescents) and 28 adult patients with r-HAT

Overall, 44/45 patients reached EOH and Week 9, because one patient died on Day 8, while 38/45 (84%) patients reached Month 6 and 30/45 (67%) patients reached Month 12.

These data were updated during the procedure with the submission of the final CSR:

As of 12 October 2022, last patient last visit of Study DNDi-FEX-07-HAT, all r-HAT patients of the mITT population had completed the study up to Month 12. One out of 45 patients (2%) died before EOT due to an SAE of acute kidney injury, which was considered as unrelated to study drug or disease by the Investigator and Sponsor and according to the independent DSMB and was considered as premature treatment discontinuation. Consequently, there were 44 treatment completers (TC).

All but one r-HAT patient (44/45) completed their fexinidazole 10-day regimen according to their body weight. Patients with body weight ≥35 kg (6 adolescents and 28 adults) received the 1800/1200 mg fexinidazole dose regimen (total dose: 14 400 mg and 10 800 mg for one patient), whereas patients with body weight ≥20 kg and <35 kg (11 children) received the 1200/600 mg fexinidazole dose regimen (total dose: 8400 mg).

Expected levels of steady-state fexinidazole exposure in blood were reached as measured in the PK analysis.

Overall, 7/45 (16%) patients (5 stage-2 and 2 stage-1 r-HAT patients) vomited within 2 hours after study treatment administration and all were re-administered a fexinidazole dose.

- 6 patients (including 1 child and 2 adolescents) vomited during the loading-dose phase (Day 1 to Day 4),
- 1 adult patient vomited on the last day of the maintenance-dose phase (Day 5 to Day 10).

Table 5 - Exposure in r-HAT patients - Safety population

Parameter	DNDi-FEX-07-HAT					
	Fexinidazole 1800/1200 mg/d (N = 34)	Fexinidazole 1200/600 mg/d (N = 11)	Stage 2 (N = 35)	Stage 1 (N = 10)	Male (N = 31)	Female (N = 14)
Patients who completed treatment (n/N, %)[a]	33/34 (97%)	11/11[b] (100%)	34/35 (97.1%)	10/10 (100%)	30/31 (96.8%)	14/14 (100%)
Patients aged 7 to 12 years BW (≥20 to <35 kg) (n/N, %)[a, b] N = 11	0/34 • (0%)	11/11[b] (100%)	10/35[b] (29%)	1/10[b] (10%)	6/31[b] (19%)	5/14[b] (36%)
Patients aged >12 years BW≥35 kg (n/N, %)[a, c] N = 34	33/34 (97%)	0/11 (0%)	25/35 (71%)	9/10 (90%)	25/31 (81%)	10/14 (71%)
Fexinidazole total dose						
In TC	14 400 mg	8400 mg	-	-	-	-
In patient with TD	10 800 mg	-	-	-	-	-
Doses administered without a meal	0	0	0	0	0	0
Vomiting						
Patients aged 7 to 12 years[a, b] BW (≥20 to <35 kg)	-	1/11[b] (9%) Day 1	1/10[b] (10%)	-	-	1/14[b] (7%)
Patients aged >12 years[a, c] BW≥35 kg	1/28, Day 1 1/6, Day 3 2/28, Day 4 1/6, Day 4 *1/28[d], Day 10* 6/34 (18%)	-	4/35 (11%)	2/10 (20%)	4/31 (13%)	1/14 (7%)

Abbreviations: **BW**, body weight; **TC**, treatment completers; **TD**, treatment discontinuation
Source: DNDi-FEX-07-HAT Final CSR Appendix 16.2.4, Listings 16.2.4.2, Appendix 16.2.5.2 PK report
a Proportions calculated using data in listings
b Age range include 2 children aged 12 years because their body weight was <35 kg and they received 1200/600 mg fexinidazole regimen. In contrast, in Table 6, the age cut off was at 12 years because the reproductive potential was taken into account
c Six adolescent and 28 adult patients with body weight ≥35 kg received 1800/1200 mg fexinidazole regimen
d Only one patient vomited during the maintenance dose phase

Adverse events

During hospitalization (data at 25 January 2022), 37 TEAEs were reported in 20/45 (44%) r-HAT patients:

- 7 treatment-related TEAEs were reported in 5 patients and were deemed mild-to-moderate in intensity and non-serious. These TEAEs belonged to the system organ class (SOC) investigations (9%) and included TEAEs of electrocardiogram U-wave abnormality, electrocardiogram QT prolonged (QTcF <500 ms), and blood pressure increased, and to the SOC gastrointestinal disorders (4%) and included TEAEs of gastritis and vomiting.

Of note, the event of vomiting was considered as related by the Investigator, but not by the Sponsor because vomiting occurred <2 hours after the first dose of fexinidazole which was re-administered

without vomiting without any corrective antiemetic treatment. None of these TEAEs justified a change in the current approved SmPC for fexinidazole.

- 29 AEs were reported in 16 patients and belonged to the SOC of gastrointestinal disorders (22%) and investigations (20%),and included respectively events of vomiting (13%) and electrocardiogram U-wave abnormality (7%). All events were considered as non-serious and patients recovered completely.
- 1 SAE of acute renal injury, which as considered as non-related to treatment or disease by the Investigator, the Sponsor and the DSMB, led to permanent treatment discontinuation after 7 doses and to patient's death on Day 8.

During the follow-up period (starting from the Month-1 visit), only events (AEs, AESIs, TEAEs) which were considered as possibly related to study treatment, and all SAEs, were to be reported.

In addition, 2 other SAEs considered as not related to study treatment (or disease) were reported in2 patients.

Overall, no AESIs, defined as neuropsychiatric signs and symptoms (excluding headaches and insomnia, which were reported as AEs) requiring specialized therapeutic intervention, were reported in Study DNDi-FEX-07-HAT.

Three new TEAEs were reported in the final CSR:

- 2 TEAEs of hypertension
- 1 TEAE of hypothermia

All 3 TEAEs started on Day 10, were of mild intensity, and were considered as unrelated to study treatment. All 3 patients completely recovered within a day. During follow up, no new TEAEs (AESIs, SAEs or AEs possibly related to fexinidazole, i.e., the only TEAEs to be reported during follow up as per protocol) were reported in the final CSR. During the whole study, a total of 42 TEAEs were reported in 22/45 (49%) patients.

Table 9 - Overview of all adverse events by system organ class and preferred term by decreasing proportions in at least 1 patient - Safety population - Study DNDi-FEX-07-HAT

Safety parameter	DNDi-FEX-07-HAT (N = 45)
	Number of patients (%), *number of events*
Hospitalization period	
Gastrointestinal disorders	**10 (22.2%), *10***
Vomiting	6 (13.3%), *6*
Nausea	2 (4.4%), *2*
Dysphagia	1 (2.2%), *1*
Gastritis	1 (2.2%), *1*
Investigations	**9 (20.0%), *10***
Electrocardiogram U-wave abnormality	3 (6.7%), *4*
Electrocardiogram QT prolonged	2 (4.4%), *2*
Blood pressure increased	1 (2.2%), *1*
Hemoglobin decreased	1 (2.2%), *1*
Electrocardiogram T wave abnormal	1 (2.2%), *1*
Electrocardiogram T wave inversion	1 (2.2%), *1*
Metabolism and nutrition disorders	**4 (8.9), *4***
Hypoalbuminemia	3 (6.7%), *3*
Dehydration	1 (2.2%), *1*
Vascular disorders	**3 (6.7%), *3***
Hypertension	3 (6.7%), *3*
Infections and infestations	**3 (6.7%), *3***
Malaria	2 (4.4%), *2*
Bacteremia	1 (2.2%), *1*
Blood and lymphatic system disorders	**2 (4.4%), *2***
Anemia	1 (2.2%), *1*
Thrombocytopenia	1 (2.2%), *1*
Nervous system disorders	**2 (4.4%), *2***
Epilepsy	1 (2.2%), *1*
Extrapyramidal disorder	1 (2.2%), *1*
Renal and urinary disorders	**2 (4.4%), *2***
Acute kidney injury	1 (2.2%), *1*
Chromaturia	1 (2.2%), *1*
General disorders and administration site conditions	**2 (4.4%), *2***
Hypothermia	1 (2.2%), *1*
Inflammation	1 (2.2%), *1*

Safety parameter	DNDi-FEX-07-HAT (N = 45)
	Number of patients (%), *number of events*
Musculoskeletal and connective tissue disorders	1 (2.2%), *1*
Neck pain	1 (2.2%), *1*
Cardiac disorders	1 (2.2%), *1*
Sinus tachycardia	1 (2.2%), *1*
Follow-up period	
Infections and infestations	**2 (4.4%), 2**
Pneumonia	1 (2.2%), *1*
Urinary tract infection	1 (2.2%), *1*

Source: DNDi-FEX-07-HAT Final CSR, Table 27

Serious adverse event / deaths / other significant events

Serious Adverse Events

All treatment-emergent SAEs in r-HAT patients were single occurrences which were considered as not related to study treatment. In addition to the SAE of acute kidney injury (see below under deaths), the 2 other SAEs were:

- A moderate SAE of urinary tract infection at Day 18 for one pregnant patient who had been treated with fexinidazole for stage-2 r-HAT, was re-hospitalized. The patient was treated with IV ceftriaxone 2 g/d from for 5 days for urinary tract infection. The event resolved after 5 days.
- A severe SAE of pneumonia (verbatim: “severe community acquired pneumonia”) at Day 242 for one patient who had been treated with fexinidazole for stage-2 r-HAT (229 days post last treatment dose) , was re-hospitalized the same day the diagnosis was made. This event was considered as resolved 121 days after the hospital stay. The patient was treated with ceftriaxone 2 g/d IV during 9 days after hospitalisation, metronidazole 400 mg t.i.d orally at the same time during 5 days and paracetamol 1 g/d orally 3 days at the start of treatment. The patient was discharged after the end of treatment and followed as out-patient after that date. At a SAE follow-up visit 3 months later, all symptoms but a persistent dry cough had resolved, and a mild consolidation on the right upper lobe on the lateral aspect was observed by autoradiography. At EOS visit 20 days later, the chest X-ray showed a significant improvement, and the SAE was considered as clinically recovered.

Deaths

One r-HAT patient died during the hospitalization period.

The patient with a stage-2 r-HAT had a SAE of acute kidney injury for which the first symptoms started at Day 3, and which led to the patient's death at Day 8, after having received 7 days of study treatment.

Fexinidazole doses were administered by nasogastric tube together with food (0.6 L of milk) from Day 5 onwards, as the patient could not eat or swallow. The patient had no relevant medical history.

The first symptoms of the SAE started on Day 3. The patient was managed for dehydration with IV Ringer’s lactate 2 L as bolus (3 L/24 hours) and IV dextrose 5% (0.5 L) and gained some consciousness. On Day 4, the patient had a SAE of “acute renal injury due to dehydration”. Oxygen therapy (4 L/min) was started, and the patient received IV ceftriaxone 2 g twice daily (b.i.d) to treat an encephalitis (gram-positive rods found in the CSF culture, but considered as possible contaminant, not clinically significant), in addition to IV Ringer’s lactate (1 L), IV saline (0.5 L) and oral paracetamol (1 g b.i.d). On Day 5, the

patient received IV metronidazole 500 mg 3 times/d (t.i.d) for encephalitis, IV furosemide 40 mg b.i.d to avoid fluid overload, and a single dose of oral prednisolone 10 mg to reduce inflammation, in addition to its previous medications (IV ceftriaxone and paracetamol). On Day 6, the patient received dextrose 5% with furosemide to treat the metabolic acidosis and tap water by nasogastric tube. Although the patient should have also received IV calcium bicarbonate, only calcium bicarbonate tablets were available on site and the patient could not be treated because he could not swallow and could not be transferred to another hospital because he was unstable. On Day 7, the metabolic acidosis was ongoing and the patient was managed in the same way. On Day 8, the patient died due to acute renal failure, which was assessed as non-related to fexinidazole by the Investigator.

The hypernatremia and hyperchloremia of the patient were in favour of acute renal tubular affection rather than of concomitant infection. The patient had clear lungs at auscultation. He was negative for malaria at baseline, negative for HIV and serum cryptococcal antigen on Day 4, and negative for COVID-19 infection on Day 8. No trypanosomes were detected in the blood on Day 5 and in the post-mortem CSF on Day 8. In accordance with the DSMB meeting minutes dated Day 8 (death) and 10 days after, the independent DSMB concluded that the patient died from acute renal failure which was not related to fexinidazole or r-HAT. Of note, the Sponsor agreed with the Investigator and the DSMB.

AESI's

Safety events related to electrocardiograms

The variations in ECG were particularly investigated in r-HAT patients because fexinidazole was found to induce an average increase of 15 to 20 ms in the QTcF interval in g-HAT patients and 7% of adult g-HAT patients in the pivotal study had a QTcF interval duration >450 ms.

Among 9 ECG-related events, 4 were related to study treatment including 2 mild and moderate events of ECG QT prolonged (QTcF<500 ms) at Day 2 and Day 4, which resolved within <10 days, and 2 events of ECG U-wave abnormality associated with repolarization impairment at Day 4 and Day 11, and which resolved either on the same day or within <2 months.

Overall, the information about the potential pro-arrhythmic effect of fexinidazole which were collected in r-HAT patients did not impact on the potential risks previously identified in g-HAT patients and described in the current approved SmPC for fexinidazole.

Laboratory findings

Neutropenia was not identified in r-HAT patients, although "severe infection secondary to drug induced neutropenia" was an important potential risk in g-HAT patients (see introduction).

Clinical laboratory data obtained in r-HAT patients were in line with the fast improvement of the general health status as shown by the increase in glucose, potassium, calcium and albumin levels from baseline to Week 9.

As in g-HAT patients, no significant safety signals were raised in r-HAT patients for biochemical abnormalities.

Safety in special populations

No specific safety signals were identified in children with body weight <35 kg who had higher concentrations of M2 than paediatric patients with body weight ≥35 kg or than adults with body weight ≥35 kg.

Fexinidazole was well tolerated by children with r-HAT aged 7 to 12 years who received the 1200/600 mg fexinidazole regimen and by adolescents with r-HAT aged 13 to 16 years who received the 1800/1200 mg fexinidazole regimen.

Children with r-HAT reported 2 non-serious TEAEs in investigations and gastrointestinal disorders SOCs (electrocardiogram QT prolonged on Day 2 and vomiting on Day 1). Adolescents with r-HAT reported 3 non-serious TEAEs in investigations and gastrointestinal disorders SOCs (gastritis on Day 2, vomiting, and electrocardiogram T-wave abnormal).

As it was reported for g-HAT patients (see SmPC for fexinidazole, Section 4.8), a higher proportion of paediatric r-HAT patients experienced vomiting than adult patients during the loading-dose phase (3/17 [18%] versus 3/28 [11%]), or during the whole treatment phase (3/17 [18%] versus 4/28 [14%]).

Fexinidazole was well tolerated by paediatric r-HAT patients aged 7 to 16 years. No new safety signals were identified in paediatric r-HAT patients compared to the safety profile of paediatric g-HAT patients.

Safety related to drug-drug interactions and other interactions

No other potential impact on safety of drug-food or drug-drug interactions with fexinidazole than the ones previously described in g-HAT patients were identified in r-HAT patients.

Discontinuation due to adverse events

Except the stage-2 r-HAT patient who died on Day 8, no patient withdrew from fexinidazole treatment.

Post-marketing experience

Following the positive opinion from the EMA CHMP (EMA/791484/2018) for fexinidazole in g-HAT indication under Article 58 of Regulation (now “EU-M4all”) on 15 November 2018, fexinidazole was registered in the Democratic Republic of the Congo (DRC) on 24 December 2018 and in Uganda on 05 October 2021.

The distribution of fexinidazole started in DRC in January 2020 (first patient treated in DRC on 28 January 2020). In addition, fexinidazole is currently distributed by the WHO in the remaining g-HAT endemic countries (Angola, Burkina Faso, Cameroon, Congo, Central African Republic, Chad, Equatorial Guinea, Gabon, Guinea and South Soudan). Fexinidazole was also approved for use by the United States FDA on 16 July 2021, but no US patient has received fexinidazole so far.

Cumulative safety information from worldwide post-marketing experience of fexinidazole tablets (600 mg) and relevant safety literature covering the period from 16 May 2021 to 15 May 2022 were presented in the latest Development Safety Update Report (DSUR). As of 15 May 2022, a total of 3 DNDi sponsored clinical trials were still ongoing: studies DNDi-FEX-09-HAT, DNDi-FEX-12-CH and DNDi-FEX-07-HAT, the latter being the study presented for this application dossier.

In addition, as of 24 January 2023, data were reported on 362 patients with g-HAT who were treated with fexinidazole in endemic countries (Central African Republic, Chad, DRC, Equatorial Guinea, Gabon, Guinea), while participating in an ongoing PASS for which information is collected by NSSCP and the WHO, as part of NSSCP activity as per WHO interim guidelines. Serious AEs considered as unrelated to fexinidazole were reported during treatment (N = 3) and during follow up (N =3) in these g-HAT patients.

Patient exposure to fexinidazole during the reporting period of the latest DSUR was estimated at 1281 individuals during completed and ongoing clinical trials, thus including data collected from both g-HAT and r-HAT patients. No new safety signals were identified.

Since its first approval, the SmPC for fexinidazole has been updated to include “suicidal ideation” in Section 4.4 and Section 4.8, and the latest updated version on 22 December 2022 includes a warning for

patients with “Cockayne syndrome”, as the “irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome” was identified as an important potential risk.

The currently approved European RMP v2.1 (December 2021) has been updated with the two aforementioned risks which were recently identified and approved by the CHMP. Of note, an RMP v3.0 version was submitted in this application dossier.

Based on the evaluation of the cumulative safety data and the benefit-risk analysis included in the latest Periodic Benefit-Risk Evaluation Report (PBRER) (covering the period from 16 November 2020 to 15 May 2021), the benefit-risk balance for fexinidazole in the treatment of g-HAT remains positive in the current approved conditions of use when used in accordance with the instructions provided in the SmPC for fexinidazole.

2.5.1. Discussion on clinical safety

Very scarce data on safety related to the proposed new indication is available, mostly due limited number of patients included in Study DNDi-FEX-07-HAT (45 in total: 10 with stage-1 r-HAT; 35 with stage-2 r-HAT; 11 children, 6 adolescents and 28 adult patients).

All of the AEs reported in relation to the patients included in the Study DNDi-FEX-07-HAT study were already previously known from the treatment of g-HAT patients with fexinidazole namely the ECG alterations and gastrointestinal disorders (including vomiting). No psychiatric adverse drug reactions, with the exception of headaches and insomnia, requiring specialized therapeutic intervention, were reported.

No deaths related to fexinidazole were reported.

No new risks related to fexinidazole were observed in paediatric or adult r-HAT patients (both stages).

Precautionary measures related to pregnancy and breastfeeding are needed for r-HAT patients, in line with the actions already in place for treatment of g-HAT.

In conclusion, with the available data, fexinidazole oral treatment offers a well-tolerated alternative to IV treatments (suramin and melarsoprol) for the management of r-HAT patients (both stages) aged ≥6 years and weighing ≥20 kg.

Pharmacovigilance data will be collected in r-HAT patients who will receive fexinidazole through controlled accessed programs in endemic areas.

The limitation to this indication, related to safety, concerns the limited number of patients included in the study DNDi-FEX-07-HAT. Nevertheless, overall, fexinidazole appeared efficacious in both stage-2 and stage-1 r-HAT patients up to Month 12.

No new concerns related to safety were present that were not already previously described/present in the SmPC.

Assessment of paediatric data on clinical safety

No new data concerning safety in paediatric patients (children and adolescents) was available from Study DNDi-FEX-07-HAT. The concern related to vomiting is already addressed in the PI of Fexinidazole.

2.5.2. Conclusions on clinical safety

No new safety data arise from the data available from Study DNDi-FEX-07-HAT. Due to the nature of r-HAT, and the safety profile already known from the use of fexinidazole in g-HAT is not anticipated that new

safety issues arise, besides those already in place for fexinidazole. Due to the small number of patients included in the pivotal study, some other adverse effects may be mis/under represented.

2.5.3. PSUR cycle

The scientific opinion holder shall submit periodic safety update reports for this product every 3 years until otherwise agreed by the CHMP.

2.6. Risk management plan

The SOH submitted an updated RMP version 3.0 with this application, followed by an updated RMP version 3.1.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 3.1 is acceptable.

Safety concerns

Important identified risks	Psychiatric events[a]
	Vomiting
Important potential risks	Pro-arrhythmic effect
	Severe infection secondary to drug-induced neutropenia
	Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)
	Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[b]
	Development of resistance to fexinidazole (For *T.b. gambiense* and *T.b. rhodesiense* HAT indications), cross resistance between fexinidazole and nifurtimox (For *T.b. gambiense* HAT indication only)
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, suicidal ideation.

b Drugs metabolized by CYP1A2 (caffeine, duloxetine, melatonin, tacrine, tizanidine, theophylline), CYP3A4 (such as lovastatin, simvastatin or nisoldipine) and CYP2C19 (such as omeprazole, lansoprazole, S-mephenytoin, diazepam).

CS: Cockayne Syndrome; CYP: Cytochrome P450; HAT: Human African Trypanosomiasis.

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit risk)				
None				
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019 Planned Category 3	The primary objective of this PASS will be to assess the safety of fexinidazole in field conditions of use. The secondary objective will be to describe the effectiveness of fexinidazole, in real life use by evaluating occurrence of relapse at 12 and 24 months of follow-up.	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.	Database delivery by WHO Start of data analysis Final report of study results.	Q1 2025 Q2 2025 Q1 2026 No specific interim reports are planned but standard reporting based on PBRERs will be issued.

CYP: Cytochrome P450; FSI: First Subject In; g-HAT: *Gambiense* Human African trypanosomiasis; NSSCP: National Sleeping Sickness Control Program; PASS: Post-Authorization Safety Study; PBRER: Periodic Benefit-Risk Evaluation Report; Q: Quarter; WHO: World Health Organization.

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
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. • Controlled distribution.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** FEXINC09395 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Severe infection secondary to drug-induced neutropenia	**Routine risk minimization measures:** • SmPC: Labeled in sections 4.4 and 4.8 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 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome (CS)	**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 (for g-HAT): Post-authorization safety study of fexinidazole for human use: Analysis of real-life safety and effectiveness data on fexinidazole, collected by NSSCP and WHO as part of NSSCP activity as per WHO interim guidelines 2019.
Drug-drug interaction with concomitant drugs that are metabolized by CYP1A2, CYP3A4 and CYP2C19[b]	**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:** FEXINC09395 (for g-HAT): Post-authorization safety study of

2.6.1. Conclusion

The CHMP considers the risk management plan version 3.1 acceptable.

2.6.2. *Periodic Safety Update Reports submission requirements*

The scientific opinion holder shall submit periodic safety update reports for this product every 3 years until otherwise agreed.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

During the initial application the SOH has presented the results of a survey which was carried out in order to test the packaging of Fexinidazole Winthrop, with pictures, pictograms, colours and other information related with the key messages to be conveyed. This approach was considered acceptable within the context of an application under article 58. Taking into account the several constraints related to this particular application such as the therapeutic indication and where the disease occurs, the target population and other limitations, this was the most appropriate way of demonstrating that the target population and the healthcare professionals or other people involved in the distribution of Fexinidazole Winthrop are able to understand how the treatment is to be implemented, ensuring a high level of treatment compliance. The results of this survey were discussed during the initial application.

This type II variation concerns an extension of indication to include treatment of both first stage (haemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense*. The SOH simply proposes to update the appropriate sections of the current approved Package Leaflet and packaging (wallet) with the new information submitted within this procedure, which includes a few updates related to rhodesiense HAT.

The presented approach is considered acceptable since this variation does not introduce any relevant changes which affect the readability of the labelling and package leaflet. The important section “How to take Fexinidazole Winthrop” of the Package leaflet remains unchanged, since the posology and the crucial aspects are the same for both therapeutic indications.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Human African trypanosomiasis due to *Trypanosoma brucei (T. brucei) rhodesiense* (r-HAT) is the zoonotic, acute form of sleeping sickness in Eastern Africa.

Because of the animal reservoir for *T. b. rhodesiense* parasites, r-HAT evolves by outbreaks and has caused large epidemics in the past century.

Wildlife and domestic animals (mainly cattle) constitute the animal reservoirs of *T. b. rhodesiense* parasites, which technically prevents the eradication of r-HAT cases in humans. The encroachment to wildlife and the increasing density of livestock and humans are key parameters that sustain trypanosome transmission.

In contrast with the chronic g-HAT disease, r-HAT disease quickly progresses to an advanced stage.

Rhodesiense-HAT is depicted as the acute and aggressive form of HAT, as the first symptoms appear within 1 to 3 weeks, and the progression from first to second stage occurs within 3 to 8 weeks. In a few weeks *T. b. rhodesiense* parasites reach high levels in the blood and lymph and colonize the CNS, thereby starting a lethal neuropathogenic process of infection. If left untreated, r-HAT patients generally suffer from central nervous system (CNS) impairment and usually die within 4 to 6 months from cardiac failure and arrest. In endemic countries, this fast progression to a severe disease is exacerbated by the lack of disease awareness and its under-detection.

3.1.2. Available therapies and unmet medical need

Despite their potential toxicity and need of IV administration, 2 drugs are recommended by the WHO as first-line therapies to treat r-HAT patients as they are currently the only available therapies for this life-threatening disease: suramin for stage 1 or melarsoprol for stage 2 r-HAT.

Suramin, which does not penetrate the blood-brain barrier (BBB), is a long-lasting (5 weeks) therapy. Melarsoprol, which is an organoarsenic compound, is a 10-day therapy that may induce an encephalopathic syndrome (5% to 10%) that may lead to coma (10% to 50%).

The limitations associated with the first-line current therapies for r-HAT include:

- The absence of a well-tolerated life-saving treatment, in particular for stage-2 patients
- The absence of a common treatment for both r-HAT stages, which would negate the necessity of disease staging via lumbar puncture
- The mandatory hospitalization for IV injections for suramin or melarsoprol therapies
- The serious adverse events associated with suramin or melarsoprol therapies
- The elevated direct and indirect costs of invasive IV therapies
- The increased risk of infections resulting both from lumbar punctures, repeated IV injections or hospitalization of suramin or melarsoprol therapies
- The reported cases of resistance to melarsoprol
- The limited access to treatment for patients living in remote areas
- The contraindication of melarsoprol if G6PD is present.

3.1.3. Main clinical study

DNDi-FEX-07-HAT study, is a phase-II/III, multicenter, open-label, non-randomized, single-arm clinical trial to assess the efficacy and safety of fexinidazole in patients with stage-2 and stage-1 r-HAT, aged ≥6 years old and with body weight ≥20 Kg, which was conducted in Malawi and Uganda

3.2. Favourable effects

The primary endpoint which was to show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5%, was met: the fatality rate at EoH in evaluable patients (N=34) with stage 2 r-HAT was 0% (90% CI 0.00, 8.43) (p=0.0488) with an upper limit of the 90% CI which was below the rate of 8.5% (p <0.05, one-sided exact test). As per protocol, this population excluded one patient who died on Day 8 after 7 doses because of acute renal injury, which was evaluated as unrelated to study drug or disease by the Investigator and the Sponsor, and as assessed independently by the DSMB.

Sensitivity analysis of the primary efficacy endpoint at EOH was of 0.0% (90% CI: 0.00% to 35%) (p = 0.0446) in ITT (N = 35) and of 0.0% (90% CI: 0.00% to 8.43%) (p = 0. 0488) in TC populations (N = 34), thereby showing consistent results for the primary efficacy analyses.

Furthermore, supplementary analysis of the fatality rate in the total population of evaluable r-HAT patients (N = 44) was of 0.0% (90% CI: 0.00% to 6.58%) (p= 0.0201), thus supporting the efficacy of fexinidazole at EOH in both stages of r-HAT.

The secondary, short-term objective (also at EoH) which was to show that the failure rate at EoH (defined as r-HAT or treatment-related death, presence of trypanosomes at EoT, or absence of clinical improvement leading to the use of rescue medication) in patients with stage 2 r-HAT was smaller than the unacceptable rate of 9%, was met: the failure rate at EoH in patients with stage 2 r-HAT in EP population was 0% (90% CI: 0.00% to 8.43%)(p=0.0405).

None of the 34 evaluable patients with stage 2 r-HAT showed any *T. brucei rhodesiense* at EoT in blood or CSF from Day 5 onwards, which indicated a fast activity of fexinidazole against *T. b. rhodesiense* parasites and support the absence of therapy failure at EOH. Up to EoH, no patient had needed rescue medication.

In Study DNDi-FEX-07-HAT, besides 3 cases of transient CSF-WBC level increase at Month 6, all patients experienced decreased CSF-WBC levels from EOT onwards, even those who had a CSF-WBC ≥100 cells/μL at baseline. These data support the activity of fexinidazole regardless of the baseline CSF-WBC levels of r-HAT patients opposite to g-HAT for which no efficacy was demonstrated in case of CSF-WBC ≥100 cells/μL at baseline.

Because r-HAT patients progress rapidly from stage 1 to stage 2 and because stage-2 r-HAT patients are in a much worse health status than stage-1 patients, it was hypothesized and believed that if a treatment could be efficacious and well tolerated for stage-2 patients, it should also be efficacious and well tolerated for stage-1 patients. This rationale is supported by the data provided so far: no fatality or failure at EoH in stage 1 r-HAT patients was reported. All 10 patients with stage 1 r-HAT were alive at EoH and none had a relapse up to EoH. None of these 10 patients showed any *T. brucei rhodesiense* at EoT.

Fexinidazole induced a marked improvement in the general health status of r-HAT patients within 5 days, as shown by the median Karnofsky score from 70.0% at baseline to 100% at Day 5 and the >3-fold decrease in the proportion of patients having r-HAT clinical signs and symptoms at Day 5.

Despite the small-sample size due to the rare nature of the disease, the consistency of the results provided with the initial submission indicated that fexinidazole was efficacious in the survival of r-HAT patients and in treating r-HAT infection in blood and CSF at EOH.

The exploratory analyses confirm the maintenance of parasite clearance in both in blood and CSF from EOT to Month 12 in all but one patient. One case of early relapse was reported in a stage-2 patient at Week 9 follow up, a timepoint that had been reached by the whole population of evaluable patients. Trypanosomes

were only detected in the CSF in this patient who was successfully retreated with melarsoprol. No other relapse case was reported at 12 months.

3.3. Uncertainties and limitations about favourable effects

DNDi-FEX-07-HAT study was a multicentre, Phase II/III, open-label, non-randomised study aiming to assess the efficacy and safety of fexinidazole in patients with r-HAT. This study was designed as a single arm study treating patients with fexinidazole only, with a benchmark study design comparing the observed fatality rate to an unacceptable rate. The unacceptable rate was that of melarsoprol in the recent years, based on the discussion of the WHO network for HAT elimination and as reported in the clinical trial IMPAMEL III.

The constraints to raise other clinical designs options are understood. However, the lack of a direct comparison with melarsoprol in clinical study DNDi-FEX-07-HAT will hamper assessment of efficacy as compared to melarsoprol.

Rhodesiense HAT is endemic in east African countries with Malawi and Uganda showing the highest disease incidences at the time of study design. Most r-HAT patients (43/45 [96%]) in Study DNDi-FEX-07-HAT were from Malawi where an outbreak occurred since 2019. Of importance, heterogeneity in fatality rates was observed among endemic countries. A statistically significant country effect was also detected in both patient-level and study-level meta-analyses of the fatality rates in melarsoprol-treated patients (i.e., rate difference from the overall rate of 8.5% going from -3% to + 8.3%), and in the WHO epidemiological data (except in Uganda, all fatality rates were estimated >8.5% over 2012 to 2021). This country effect was particularly pronounced in Malawi for which the estimated fatality rate was consistently twice higher than the unacceptable margin (17% versus 8.5%). This indicated that the unacceptable fatality rate at EOH of 8.5% could be extrapolated to most r-HAT endemic countries and was particularly conservative for Malawi. Even so, this may be considered a limitation of the data and an uncertainty in case of treatment in other endemic countries.

The approach taken by the SOH in presenting the outcome of the primary endpoint based on the data gathered for EP excluding the death case as it was considered unrelated with the disease or the treatment as well as to do a study comparison of the upper bound of the 90% CI of fatal cases (8.5%) between the EOH in patients treated with fexinidazole vs the historical point estimate for fatal cases in patients treated with melasorpol was questioned by the CHMP. CHMP considered that the presentation in the SmPC of the pivotal data should be as stand-alone using the ITT population principle (i.e. including all patients and not excluding the fatal cases) with a 95% CI around the point estimate and considering all-cause mortality and failure. The request analysis revealed in the ITT population of stage-2 r-HAT patients a fatality rate for all-cause mortality and a failure rate in stage-2 r-HAT up to EOH and at Month 12 both of 2.86% (1/35) (95% CI: 0.07% to 14.92%). At test of cure (Month 12), the failure rate in the ITT population of stage-2 r-HAT patients (N = 35) was of 5.7% (2/35) (95% CI: 0.70% to 19.16%).

In stage-1 patients (N = 10), the failure rate at EOH was of 0%. The promising data regarding the use of Fexinidazole also for stage 1 r-HAT patients, with no fatalities or failures, has to be looked into with cautions due to the very limited number (N=10) of patients included in the study which has an already limited sample size (N=45).

The patient, who had stage 2 r-HAT (having 60 cells/ul in CSF at baseline) and that had an early relapse at Week 9 (trypanosomes were only detected in the CSF) and received rescue medication (melarsoprol) on the next day, had a diagnosis of malaria at baseline but took artemether/lumefantrine only between D5 and D7 of fexinidazole. The analysis of dried blood spot (DBS) concentrations for fexinidazole, M1 and M2

(performed at D1, D4 and D11) in this r-HAT patient showed that similar concentrations to those obtained in other r-HAT patients were obtained for each compound. Furthermore, the blood levels for M2 were >10 µg/mL from Day 4 onwards to Day 11, suggesting that effective M2 concentrations had been reached and maintained throughout fexinidazole treatment in this patient.

Also, 20% of patients in DNDi-FEX-07-HAT study took artemether/lumefantrine at screening and the exposure of these patients was compared with patients without artemether/lumefantrine administration, the data suggesting that administration of artemether/lumefantrine at screening do not impact fexinidazole, M1 and M2 exposure. However, this patient started treatment with artemether/lumefantrine from Day 5 to Day 7 (it is noteworthy that DBS were only performed at D1, D2 and D11). These data may suggest some interference of malaria or interaction with its medication in the outcome of r-HAT treated with fexinidazole. If this confirmed, it may be a cause for concern in areas where the two pathologies coexist. Whether the interaction with malaria or its treatment was not the problem, there is the possibility of facing a case of resistance of *T. b. rhodesiense* to fexinidazole. The SOH provided an adequate rational sustained by bibliography, supporting the absence of malaria interference on r-HAT and the absence of PK interaction of artemether/lumefantrine on fexinidazole and its active metabolites which argue against an explanation for the relapsing patient. Also, the SOH summarized the current data about fexinidazole resistance which also argue against a case of resistance of *Trypanosoma brucei (T. b.) rhodesiense* to fexinidazole in the relapsing patient. Although the case of the relapsing patient remains without a plausible justification, the explanation provided was considered acceptable.

Due to the reported relapse case at Week 9, the failure rate at Month 12 in stage-2 r-HAT EP was 2.94% (1/34) (90% CI: 0.15% to 13.21%) with an upper limit >12%, which was higher than initially forecasted in the protocol. As such, the long-term secondary objective, i.e. to show that the failure rate (r-HAT or treatment-related death according to DSMB or relapse) at 12 months (or before) in patients with stage 2 r-HAT treated with fexinidazole was below an unacceptable rate of 12%, was not achieved. The failure of this secondary objective is mainly due to the small sample size which necessarily resulted in a large confidence interval.

The current goal of elimination of HAT as a public health problem by 2020 may be undermined by the emergence and spread of resistance to current or new drugs.

The ease of taking a medication orally and the no-need for hospitalization to carry out the treatment of a pathology with the severity that is known to it, may lead to less vigilance on the part of doctors and consequently to: poor patient compliance, clinical errors in drug administration or drug resistance.

Since limited clinical data will become available, the SOH is highly encouraged to conduct post-licensure studies on efficacy and safety of fexinidazole in *T. b. rhodesiense* HAT (e.g. cohort studies describing long term efficacy in all patients treated for *T. b. rhodesiense HAT*).

3.4. Unfavourable effects

In Study DNDi-FEX-07-HAT, all AEs were collected in patients during fexinidazole exposure, while only AEs considered as possibly related to study drug (AEs, AESIs, TEAEs), and all SAEs were collected during follow up starting at Month 1.

The fexinidazole safety database benefits from other clinical studies and from the PASS in g-HAT patients in DRC (N = 362). Fexinidazole has an acceptable safety profile in paediatric and adult g-HAT patients (N = 619) as described in the current approved SmPC.

The safety profile of fexinidazole in r-HAT treatment was generally consistent with what was described for g-HAT patients and for other products of the nitroimidazole class.

As per the data for EOH and incomplete data for Month 6 and Month 12, no new safety events related to fexinidazole were observed in paediatric or adult r-HAT patients, which support the absence of any further precautions related to safety in the proposed SmPC for fexinidazole.

The risks for fexinidazole, which are reported in the RMP (v3.0 version) submitted with this application dossier, are psychiatric events for important identified risks, whereas important potential risks are vomiting, pro-arrhythmic effect, severe infection secondary to drug-induced neutropenia and hepatotoxicity, including irreversible hepatotoxicity/liver failure in patients with Cockayne Syndrome and drug-drug interaction with concomitant drugs that are metabolized by cytochrome P450 (CYP) 1A2, CYP3A4 and CYP2C19 (RMP v3.0 version).

However, no psychiatric adverse drug reactions, with the exception of headaches and insomnia, requiring specialized therapeutic intervention, were reported.

In addition, no new clinically relevant observations on ECG tracing alterations and gastrointestinal disorders (including vomiting) have been detected in r-HAT patients treated with fexinidazole when compared with the data available for g-HAT. In Study DNDi-FEX-07-HAT, clinical safety manifestations considered as related to fexinidazole were mostly mild and moderate and non-serious, and belonged either to the SOC of investigations (electrocardiogram U-wave abnormality, electrocardiogram QT prolonged - QTcF<500 ms, and blood pressure increased), or to the SOC of gastrointestinal disorders (gastritis and vomiting).

Contraindications and Warnings and Precautions to mitigate risks related to QT interval prolongation, and risk of vomiting within 2 hours of dosing are already described in the current approved SmPC for fexinidazole. Moreover, the information already included in the approved package leaflet (PL) and educational material are considered adequate for risk minimization measures.

One patient died during hospitalisation due to causes considered unrelated to r-HAT and/or fexinidazole by the Investigator, the DSMB, and the Sponsor. Therefore, this patient was considered non-evaluable for efficacy purposes. No deaths were reported during follow-up.

Of note, the diminution of consciousness in more severe cases could be a problem since the consequences in terms of serum and CSF levels of the drug and its metabolites are not known if tablets are crushed and administrated by nasogastric tube.

3.5. Uncertainties and limitations about unfavourable effects

Based on the data available at the initial cut-off date, there were no meaningful new safety signals emerging in the Study DNDi-FEX-07-HAT. However, very scarce data on safety related to the proposed new indication are available, mostly due limited number of patients included in this study (45 in total: 10 with stage-1 r-HAT; 35 with stage-2 r-HAT; 11 children, 6 adolescents and 28 adult patients).

In addition, more studies are needed to analyse the effects of administration of the drug by nasogastric tube.

The final CSR was submitted during the procedure, data were in line with the initial data submitted. However, due to the small number of patients included in the pivotal study, some other adverse effects may be mis/under-represented.

3.6. Effects Table

Table 10. Effects Table for Fexinidazole Winthrop, r-HAT

Effect	Short description	Unit	Treatment Fexinidazole	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Fatality rate at EOH in Stage 2 r-HAT patients	r-HAT or treatment-related death (EP population)	N (%)	0 (0.0%) N=34		90% CI: 0.00, 8.43 (p=0.0488)	CSR
Fatality rate at EOH in Stage 1 + Stage 2 r-HAT patients	r-HAT or treatment-related death (EP population)	N (%)	0 (0.0%) N=44		90% CI: 0.00, 8.43 (p= 0.020069)	CSR
Failure rate at EOH in Stage 2 r-HAT patients	r-HAT or treatment-related death according to DSMB or presence of trypanosomes (EP population)	N (%)	0 (0.00%) N=34		90% CI: 0.00, 8.43 (p=0.040496)	CSR
Relapse stage 1 and stage 2 r-HAT patients	Patients with a relapse - stage 1 and stage 2 r-HAT patients (EP population)	N (%)	Stage 1 – 0 (0.00%) N=10 Stage 2 – 1 (2.94%) at Week 9 follow-up (N=34) Stage 2 – 0 (0.0%) at EoS (N=22)		Only descriptive due to small sample size 0.15% - 13.21% (trypanosomes only detected in CSF, CSF-WBC levels of 12 cells/µL suggesting early relapse – rescue treatment with melarsoprol	CSR
All-cause mortality and failure in r-HAT patients	All recruited patients (stage 1 and stage 2), who signed the ICF and were eligible for treatment according to the Investigator (ITT population)	N (%)	Stage 1 – 0 (0%) (N=10) at EOH and 12 months Stage 2 – 1 (2.9%) at EOH (N=35) Stage 2 – 2 (5.7%) at 12 months (N=35) Stage 1+ Stage 2 – 1 (2.2%) at EOH (N=45) Stage 1+ Stage 2 – 2 (4.4%) at 12 months (N=45)		95% CI: 0.07%, 14.9% 95% CI: 0.70%, 19.2% 95% CI: 0.06%, 11.8% 95% CI: 0.5%, 15.2%	CSR
T. brucei rhodesiense at	Number of patients with	N	0 (N=34)		support the absence of	CSR

Effect	Short description	Unit	Treatment Fexinidazole	Control	Uncertainties / Strength of evidence	References
EoT in blood or CSF	Stage 2 showing parasites in blood or CSF from Day 5 onwards - activity of fexinidazole against *T. b. rhodesiense* parasites (EP population)				therapy failure at EOH	
Need for rescue medication at EOH	Number of patients need for rescue therapy	N	0 (N=34)		support the absence of therapy failure at EOH	CSR
Unfavourable Effects						
At EOH						
Death at EOH	SAE - Number of deaths	N	1		Considered not related with treatment by Investigator, the Sponsor and the DSMB	CSR
	SAE - Renal injury	N %	1 (2.2 % of N=45)			
Investigations	TEAEs - % patients with ECG U-wave abnormality, ECG QT prolonged (QTcF<500 ms) Increased blood pressure	%	9% (of N=45)			CSR
	AEs – ECG U-wave abnormality	%	6.7 % (of N=45)		considered as non-serious and patients recovered completely	CSR
	AEs – ECG QT prolonged	%	4.4 % (of N=45)			
Gastrointestinal disorders	TEAEs - Gastritis	%	4 % (of N=45)		as related by the Investigator, but not by the Sponsor	CSR
	TEAEs - Vomiting (mild to moderate)					
	AEs - Vomiting	%	13.3 % (of N=45)		considered as non-serious and patients recovered completely	CSR
	AEs – Nausea	%	4.4% (of N=45)			CSR
Metabolism and nutrition disorders	AEs – Hypoalbuminemia	%	6.7% (of N=45)			CSR
Infections and infestations	Malaria	%	4.4% (of N=45)			CSR
Blood and lymphatic system disorders	Anemia and Thrombocytopenia	%	4.4% (of N=45)			CSR

Effect	Short description	Unit	Treatment Fexinidazole	Control	Uncertainties / Strength of evidence	References
	Psychiatric events	N	0		No AESI of psychiatric events in r-HAT but sample size is limited Incidence in r-HAT less than in g-HAT	CSR and Clinical overview
During follow-up (>month 1) – only events (AEs, AESIs, TEAEs) considered as possibly related with Fexinidazole, and all SAEs reported						
Infections and infestations	Pneumonia + Urinary tract infection	%	4.4% (of N=45)			CSR

Notes: For unfavourable effects only listed above the ones reported for ≥2 patients in a total of 45 patients.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The primary endpoint in Study DNDi-FEX-07-HAT, which was to show that the fatality rate (r-HAT or treatment-related death) at the end of hospitalisation (EoH) in patients with stage 2 r-HAT treated with fexinidazole was smaller than a threshold of unacceptable rate of 8.5%, was met. This primary efficacy endpoint was set at EOH on the basis of the results obtained in IMPAMEL III study in patients treated with melarsoprol. The fatality rate in the IMPAMEL III study was of 8.4% (9/107). As melarsoprol-induced death at EOH (at least 10% to 50% of encephalopathic syndrome cases) was the main reason to find an alternative treatment to this IV therapy, the fatality rate at EOH in patients treated with fexinidazole was considered as a robust primary endpoint. The pertinence of this 8.5% threshold was recently confirmed in a meta-analysis of the estimations of fatality rates at EOH from IMPAMEL III data and from endemic countries either from other published data, and epidemiologic WHO data. Most estimated fatality rates were >8.5% which indicated that the established threshold of unacceptable fatality rate (8.5%) is not an overestimate of what can be observed in patients treated with melarsoprol.

Despite the limited number of participants in the DNDi-FEX-07-HAT (N = 45), all subpopulations were represented i.e., children (N = 11), adolescents (N = 6) and adults (N = 28) with stage-2 (N = 35) or stage-1 (N = 10) disease. Overall, the efficacy data provided so far support fexinidazole oral treatment as a well-tolerated alternative to IV treatments (suramin and melarsoprol) for the management of r-HAT patients (both stages) aged ≥6 years and weighing ≥20 kg (54).

Disease staging via lumbar puncture was required in Study DNDi-FEX-07-HAT to recruit enough evaluable stage-2 r-HAT patients as per protocol, however considering the activity of fexinidazole against trypanosomes in blood and in CSF, fexinidazole can be used both in stage-1 and stage-2 r-HAT patients r-HAT patients without any preliminary disease staging. This will favour compliance and prevent infections related with lumbar puncture procedure. Nonetheless, in case of therapy failure, disease staging will be required to decide on which rescue therapy to apply.

Fexinidazole will thus be an asset to rapidly control r-HAT outbreaks as soon as they are detected in the field, and even if r-HAT is a zoonotic disease, fexinidazole may participate in the reduction of r-HAT incidence.

Fexinidazole has an acceptable safety profile in paediatric and adult g-HAT patients (N = 619) as described in the current approved SmPC. In addition, the fexinidazole safety database benefits from other clinical studies and from the PASS in g-HAT patients in DRC (N = 362). Based on available data, no new safety signals were detected and the safety profile of fexinidazole in the treatment of r-HAT appears similar to the safety profile in g-HAT patients

Of particular importance due to the limited size of the population of the Study DNDi-FEX-07-HAT and the fact that r-HAT is a rare disease, is the risk minimization strategy proposed for the implementation of fexinidazole for r-HAT in the targeted endemic countries which includes:

- routine measures (SmPC and PL proposed in this dossier which have been updated to provide specific information for r-HAT)
- additional risk minimization measures including a controlled access program, controlled distribution and educational programs
- routine pharmacovigilance activities

In addition to these measures, several options for a 12-month follow up of r-HAT patients and reporting are stated to be investigated, considering the specificities of the disease, such as the limited number of patients, and the unpredictable outbreaks in remote areas. The follow up of r-HAT patients treated with fexinidazole following its implementation in endemic countries will ensure the further evaluation of the benefit-risk balance of fexinidazole in this new indication. This is endorsed.

Overall, the favourable effects associated with fexinidazole for r-HAT include:

- Well-tolerated life-saving treatment for both stages of the disease, in particular for stage-2 patients
- Apparently effective treatment even in cases where CSF WBC >100 cells/ µL
- The oral form of administration would negate the necessity of hospitalization and its increased risks associated
- Common treatment for both r-HAT stages, which would negate the necessity of disease staging via lumbar puncture, hospitalization. and its increased risks associated.
- Facilitate of access to treatment for patients living in remote areas
- Short treatment regimen
- Less fear on the part of patients to seek medical help since they will not need to perform lumbar puncture, nor IV treatment, nor to be hospitalized.

3.7.2. Balance of benefits and risks

The primary objective of this study was met: no r-HAT or treatment-related deaths were observed by the end of hospitalisation in patients with stage 2 r-HAT treated with fexinidazole.

In addition, no patients with stage 2 r-HAT showed at EOH any *T. brucei rhodesiense* in blood or CSF, and no patient needed rescue medication, giving a failure rate of 0% that was smaller than the unacceptable rate of 9% and therefore the short-term objective was also met.

A relapse case was observed at the 9-week visit, in a patient with stage 2 r-HAT who was successfully treated with melarsoprol as a rescue medication. Based on this, the failure rate at Month 12 in stage-2 r-HAT EP was 2.94% (1/34) (90% CI: 0.15% to 13.21%) with an upper limit >12%, which was higher than

initially forecasted in the protocol. As such, the long-term secondary objective, i.e. to show that the failure rate (r-HAT or treatment-related death according to DSMB or relapse) at 12 months (or before) in patients with stage 2 r-HAT treated with fexinidazole was below an unacceptable rate of 12%, was not achieved. However, the failure of this secondary objective should be viewed in the context of a small sample size which necessarily resulted in a large confidence interval.

Furthermore, no fatality or failure at EoH in stage 1 r-HAT patients was reported (all 10 patients with stage 1 r-HAT were alive and none had a relapse up to EoH) and none of these 10 patients showed any *T. brucei rhodesiense* at EoT.

Moreover, based on available data, no new safety signals were detected and the safety profile of fexinidazole in the treatment of r-HAT appears similar to the safety profile in g-HAT patients.

Based on the above, and even considering the limited number of r-HAT patients studied and the rarity of the r-HAT, the efficacy and safety data provided so far can lead to the conclusion of a positive benefit-risk balance at end of hospitalisation for the treatment of stage 1 and stage 2 of r-HAT with oral fexinidazole in paediatric and adult patients. This is even more relevant considering the critical toxicity of melarsoprol as the current standard of care as well as the oral formulation which eases the administration and favours the access to treatment in endemic areas.

3.7.3. Additional considerations on the benefit-risk balance

None

3.8. Conclusions

The overall benefit-risk of Fexinidazole Winthrop is positive,

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Scientific Opinion, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of both first stage (haemo-lymphatic) and second stage (meningo-encephalitic) of human African trypanosomiasis (HAT) due to *Trypanosoma brucei rhodesiense* for Fexinidazole Winthrop based on final results from study DNDI-FEX-07-HAT. As a consequence, sections 4.1, 4.4, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. A revised RMP version 3.1 has been approved.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan .

Amendments to the Scientific Opinion

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following CHMP Opinion for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion Fexinidazole Winthrop/H/W/002320/II/0016