EU-RISK MANAGEMENT PLAN FOR ACOZIBOROLE WINTHROP® (ACOZIBOROLE)

Risk Management Plan (RMP) Version number	Version 1.0
Data Lock Point (DLP)	25-FEB-2025
Date of final sign-off	02-MAR-2026

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	Updated in line with the Pharmacovigilance Risk Assessment Committee (PRAC) Rapporteur's request and the summary of product characteristics (SmPC) revisions proposed by the Committee for Medicinal Products for Human Use (CHMP) Rapporteur (procedure EMEA/H/W/006686/0000).
Summary of significant changes in this RMP	Significant changes: • Pharmacovigilance plan: removal of standard Follow-Up (FU) form description. • Others: changes to align with revised European Union (EU)-SmPC. The following modules and annexes have been updated: Cover page, Part I, Part II Module SI, Part II Module SVII, Part III, Part VI and Part VII. Annex 8.

CHMP: Committee for Medicinal Products for Human Use; EMEA: European Medicines Agency; EU: European Union; FU: Follow-Up; PRAC: Pharmacovigilance Risk Assessment Committee; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	-	-

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	Not applicable
Approved with procedure	Not applicable
Date of approval (opinion date)	Not applicable

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

Qualified Person Responsible for Pharmacovigilance (QPPV) name	[redacted][a], [redacted]
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV of Sanofi.
QPPV: Qualified Person Responsible for Pharmacovigilance.

TABLE OF CONTENT

TABLE OF CONTENT **3**

LIST OF TABLES **5**

LIST OF FIGURES **7**

ABBREVIATIONS **8**

PART I: PRODUCT (S) OVERVIEW **10**

PART II: SAFETY SPECIFICATION **12**

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) **12**

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION **19**

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE **22**

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS **26**

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME 26

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES 27

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES 27

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE **30**

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION **31**

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES 31

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS **32**

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION 32

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP 32

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP 35

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP 37

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION 38

SVII.3.1. Presentation of important identified risks and important potential risks 38

SVII.3.2. Presentation of the missing information 41

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS 43

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES) 44

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES 44

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES 44

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES 45

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES 47

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES) 48

V.1 ROUTINE RISK MINIMIZATION MEASURES 48

V.2 ADDITIONAL RISK MINIMIZATION MEASURES 49

V.3 SUMMARY OF RISK MINIMIZATION MEASURES 50

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 52

I. THE MEDICINE AND WHAT IT IS USED FOR 52

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS 52

II.A List of important risks and missing information 53

II.B Summary of important risks 53

II.C Post-authorization development plan 55

II.C.1 Studies which are conditions of the marketing authorization 55

II.C.2 Other studies in post-authorization development plan 55

REFERENCES 57

PART VII: ANNEXES 60

LIST OF TABLES

Table 1 - RMP version to be assessed as part of this application 2
Table 2 - Other RMP versions under evaluation 2
Table 3 - Details of the currently approved RMP 2
Table 4 - QPPV name and signature 2
Table 5 - Product Overview 10
Table 6 - Epidemiology of Human African Trypanosomiasis 12
Table 7 - Key safety findings from non-clinical studies and relevance to human usage 20
Table 8 - Overall exposure to acoziborole in Human African trypanosomiasis due to *T. b. gambiense* by age and sex - Treated set (DNDi-OXA-02-HAT) 23
Table 9 - Correspondence for staging terminology between pivotal study for acoziborole and new WHO guidelines for the treatment of g-HAT 24
Table 10 - Overall exposure to acoziborole in Human African trypanosomiasis due to *T. b. gambiense* by g-HAT stage - Treated set (DNDi-OXA-02-HAT) 24
Table 11 - Overall exposure to acoziborole in Seropositive to Human African trypanosomiasis due to *T. b. gambiense* by age and sex - Safety set (DNDi-OXA-04-HAT) 25
Table 12 - Important exclusion criteria in pivotal studies in the development programme (OXA002) 26
Table 13 - Exposure of special populations included or not in clinical trial development programmes 27
Table 14 - Important identified risk considered for inclusion in the list of safety concerns: Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction) 35
Table 15 - Important potential risk considered for inclusion in the list of safety concerns: Arrhythmia caused by shortening of QT interval) 36
Table 16 - Missing information considered for inclusion in the list of safety concerns: Use during pregnancy 36
Table 17 - Missing information considered for inclusion in the list of safety concerns: Use during breastfeeding 37
Table 18 - Important identified risk: Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction) 38
Table 19 - Important potential risk: Arrhythmia caused by shortening of QT interval 40
Table 20 - Missing information: Use during pregnancy 41
Table 21 - Missing information: Use during breastfeeding 42
Table 22 - Summary of the safety concerns 43
Table 23 - Additional pharmacovigilance activities (category 1 to 3) summary 44
Table 24 - Ongoing and planned additional pharmacovigilance activities 45
Table 25 - Description of routine risk minimization measures by safety concern 48
Table 26 - Additional risk minimization measures 50
Table 27 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern 50
Table 28 - List of important risks and missing information 53

Table 29 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction) 53

Table 30 - Important potential risk with corresponding risk minimization activities: Arrhythmia caused by shortening of QT interval 54

Table 31 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during pregnancy 54

Table 32 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during breastfeeding 55

Table 33 - Other studies in post-authorization development plan 55

LIST OF FIGURES

Figure 1 - Geographical distribution of HAT, 2021-2022 12
Figure 2 - Number of new reported HAT cases from 2000 to 2022.....13
Figure 3 - Algorithm of WHO recommendations on the management of persons with g-HAT (15)....16

ABBREVIATIONS

AE:	Adverse Event
aRMM:	Additional Risk Minimization Measure
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under the Curve
AUC_{last}:	Area Under the Curve From 0 to the Last Quantifiable Concentration
BCRP:	Breast Cancer Resistance Protein
BMI:	Body Mass Index
CATT:	Card Agglutination Test for Trypanosomiasis
CHMP:	Committee for Medicinal Products for Human Use
CI:	Confidence Interval
C_{max}:	Maximum Plasma Concentration
CNS:	Central Nervous System
CPSF3:	Cleavage and Polyadenylation Specificity Factor 3
CSF:	Cerebrospinal Fluid
CYP:	Cytochrome P450
DALA:	Drug Abuse Liability Assessment
DDI:	Drug-Drug Interaction
DLP:	Data Lock Point
DOT:	Directly Observed Treatment
DRC:	Democratic Republic of the Congo
ECG:	Electrocardiogram
e-CTD:	Electronic Common Technical Document
EEA:	European Economic Area
EMEA:	European Medicines Agency
EPAR:	European Public Assessment Report
ER:	Experimental event Rate
EU:	European Union
EU-M4all:	European Union-Medicines For All
FU:	Follow-Up
g-HAT:	*Gambiense* Human African Trypanosomiasis
GLP:	Good Laboratory Practice
HAT:	Human African Trypanosomiasis
HCP:	Healthcare Professional
hERG:	human Ether-a-go-go-Related Gene
HIV:	Human Immunodeficiency Virus
I^2:	Level of Heterogeneity
ICH:	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
INN:	International Nonproprietary Name
LMP:	Last Menstrual Period
LP:	Lumbar Puncture
MAH:	Marketing Authorization Holder
mRNA:	Messenger Ribonucleic Acid
MSF:	Medecins Sans Frontieres/Doctors Without Borders

n:	Number of Patients
N:	Total Number of Patients
NECT:	Nifurtimox-Eflornithine Combination Therapy
NOAEL:	No-Observed-Adverse-Effect Level
NSSCP:	National Sleeping Sickness Control Programme
OATP1B1:	Organic Anion Transporting Polypeptide 1B1
OATP1B3:	Organic Anion Transporting Polypeptide 1B3
PASS:	Post Authorization Safety Study
PBPK:	Physiological Based Pharmacokinetic
PD:	Pharmacodynamic
P-gp:	P-glycoprotein
pH:	Potential of Hydrogen
PK:	Pharmacokinetic
PL:	Package Leaflet
PRAC:	Pharmacovigilance Risk Assessment Committee
Q:	Quarter
QPPV:	Qualified Person Responsible for Pharmacovigilance
QTc:	Corrected QT Interval
QTcF:	Corrected QT Interval by Fridericia's Formula
r-HAT:	Rhodesiense Human African Trypanosomiasis
RMM:	Risk Minimization Measure
RMP:	Risk Management Plan
SAE:	Serious Adverse Event
SAR:	Serious Adverse Reaction
SmPC:	Summary of Product Characteristics
SUSAR:	Suspected Unexpected Serious Adverse Reaction
T+:	Trypanosomiasis Confirmed Parasitologically
TEAE:	Treatment Emergent Adverse Event
T_{NC}:	Trypanosomiasis Not Confirmed Parasitologically
UGT:	Uridine Diphosphate-Glucuronosyltransferase
WBC:	White Blood Cell
WHO:	World Health Organization

PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance (International Nonproprietary Name [INN] or common name)	Acoziborole
Pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Code)	ATC Code to be confirmed
Scientific Opinion Holder	Sanofi Winthrop Industrie
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Acoziborole Winthrop
Marketing authorization procedure	EU-M4all procedure
Brief description of the product	Chemical class: Benzoxaborole.
	Summary of mode of action: Acoziborole binds and blocks the active site of cleavage and polyadenylation specificity factor 3 (CPSF3), a metallo-β-lactamase that processes messenger ribonucleic acid (mRNA) and facilitates gene expression. This action results in inhibition of maturation of mRNA of the parasite and not the host CPSF3.
	Important information about its composition: Not applicable
Hyperlink to the product information	Refer to electronic Common Technical Document (e-CTD) Module 1.3.1 English proposed Product Information.
Indication in the EEA	*Current:* *Acoziborole Winthrop is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic), including severe second-stage with ≥100 White Blood Cell (WBC)/µL with or without trypanosomes in cerebrospinal fluid (CSF), human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense (g-HAT) in adolescents ≥12 years old with body weight ≥40 kg, and in adults.* *Acoziborole should be used in line with official recommendations (see section 4.4).*
	Proposed: Not applicable
Dosage in the EEA	Current: *Single dose of 960 mg (in 3 tablets) for adolescents ≥12 years old with body weight ≥40 kg, and for adults.*
	Proposed: Not applicable

Pharmaceutical form and strength	Current: *Tablets 320 mg.*
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	Not applicable as EU-M4all procedure.

ATC: Anatomical Therapeutic Chemical; CPSF3: Cleavage and Polyadenylation Specificity Factor 3; CSF: Cerebrospinal Fluid; e-CTD: Electronic Common Technical Document; EEA: European Economic Area; EU: European Union; EU-M4all: European Union-Medicines For All; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; INN: International Nonproprietary Name; mRNA: Messenger Ribonucleic Acid; RMP: Risk Management Plan; WBC: White Blood Cell.

PART II: SAFETY SPECIFICATION

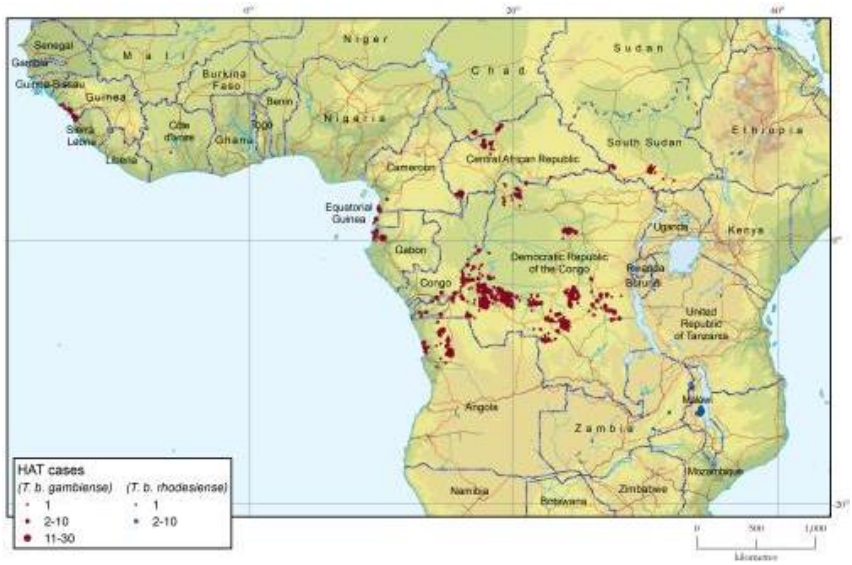
PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Acoziborole Winthrop is indicated for the treatment of both first-stage (hemo-lymphatic) and second-stage (meningo-encephalitic), including severe second-stage with ≥100 White Blood Cell (WBC)/µL with or without trypanosomes in cerebrospinal fluid (CSF), human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense (g-HAT) in adolescents ≥12 years old with body weight ≥40 kg, and in adults.

Acoziborole should be used in line with official recommendations (see section 4.4).

The epidemiology of the disease is summarized in the following table.

Table 6 - Epidemiology of Human African Trypanosomiasis

Indication	Human African trypanosomiasis due to *T. b. gambiense*
New cases, incidence and prevalence	Human African trypanosomiasis caused by *T. b. gambiense* (*Gambiense*-Human African trypanosomiasis [g-HAT]) is predominantly found in 24 countries across West and Central Africa. (1) Cases of g-HAT represent the highest disease burden of HAT. **Figure 1 - Geographical distribution of HAT, 2021-2022**  **Reported new cases:** Geographically, the number of reported new cases varies significantly by country and region. In the past decade, more than 70% of reported cases occurred solely in the Democratic Republic of the Congo (DRC). (2)(3) In 2023, the World Health Organization (WHO) received reports of 675 new cases of g-HAT, from only 10 countries with varying distributions across affected countries. **Table 6a - Number of New *T. b. gambiense* Cases Reported from 2019 to 2023; Data extracted from the WHO Global Health Observatory. (3) Last Updated 28-Nov-2024. Number of reported cases of Human African Trypanosomiasis (*T. b. gambiense*) (who.int)** **Country** | **Year**

Indication	Human African trypanosomiasis due to *T. b. gambiense*

	2019	2020	2021	2022	2023
All	876	565	747	799	675
DRC	613	395	425	516	394
Central African Republic	86	39	44	110	104
Guinea	69	36	28	30	24
Angola	30	33	174	44	52
Chad	16	17	15	18	7
South Sudan	11	15	10	30	50
Congo	17	15	18	10	14
Gabon	8	11	18	21	12
Cameroon	20	2	11	7	11
Equatorial Guinea	3	1	3	13	7
Other	3	3	1	1	0

DRC: Democratic Republic of the Congo; *T. b: Trypanosoma brucei*; WHO: World Health Organization.

Trend of new reported cases:

The number of reported new cases has varied significantly over time. Between 2000 and 2022, the reported number of new cases decreased by 97%, from 25 841 to 799 as illustrated in Figure 2. (4)(5) Although there has been a consistent decline, the trend reached a symbolic threshold of fewer than 1000 cases in 2018, which has been maintained since then. (6)

Figure 2 - Number of new reported HAT cases from 2000 to 2022

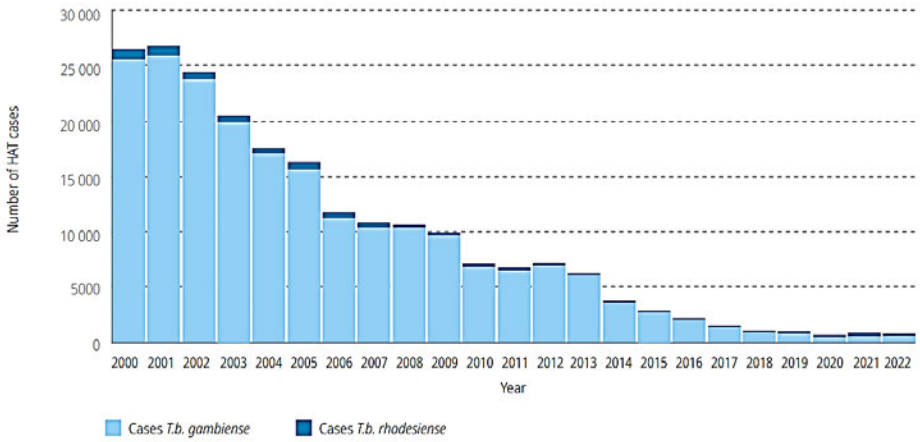


Figure obtained from WHO Guidelines for the treatment of HAT 2024.

HAT: Human African Trypanosomiasis; *T. b.: Trypanosoma brucei*; WHO: World Health Organization.

Prevalence

While the count of reported cases to the WHO Global Health Observatory remains the best measure available to track the burden of disease, some studies have attempted to provide estimates of prevalence despite the epidemiological challenges.

Prevalence varies significantly by region and over time, influenced by various factors and the fact that the capacity of the health systems in HAT endemic countries remains poor. Several epidemics have affected prevalence, including those between 1896 and 1906 in Uganda and the Congo Basin, in the 1920s in several countries, and from 1970 to the late 1990s. The activation of elimination programs following the slow increase of disease by the end of the 20th century led to a substantial reduction in the number of cases. An uncertain number of cases remain undetected, although when we see the reduction of 95% in the last 25 years, we can be

Indication	Human African trypanosomiasis due to *T. b. gambiense*
	confident that control activities are effective. The sustainable elimination of the disease, including the interruption of g-HAT transmission, is targeted for 2030 for at least 65% of all endemic countries. According to the 2023 annual report from the National Sleeping Sickness Control Programme (NSSCP) of the DRC, the seroprevalence estimated with the card agglutination test for trypanosomiasis (CATT) method was estimated at 0.30% via active screening and at 0.46% via passive screening. When using rapid diagnostic testing, the estimates were slightly higher at 0.81% and 1.09% for the active and passive screening approaches, respectively, partly due to their lower specificity. (7) A recent cross-sectional study conducted in four districts in the Republic of Congo estimated the prevalence of HAT infection between Jun-2020 and Jan-2021 to be 0.3 in the study population (n = 8556) with predominance of patients at stage 1 of the disease (84%), adults, and in two out of the four districts surveyed. (8)
Demographics of the population in the authorized or proposed indication	**The population at risk:** The population at risk as a percentage of each country's total population varies. Franco et al. 2024 (9) provided data on the population at risk of contracting *T. b. gambiense* for each country from 2018 to 2020, as shown in Table 6b. The at-risk population includes three categories including very high and high, moderate, low and very low risk. Among these, low and very low risk categories fall under the concept of elimination as a public health problem. In brief, the total population of endemic countries was 686.8 million people (very high and high risk: 9000; moderate risk: 1.2 million; low and very low risk: 37.6 million). A total of 38.9 million people, or 5.7% of the population, are at risk of g-HAT (See Table 6b for the details).

Table 6b - Population at risk of contracting *T. b. gambiense* (number of people x 10^3. Period 2018-2020 adopted from Franco et al., 2024. (9)

Country	Total country population 2022[a]	Population at risk 2018-2022				
		Very High and High	Moderate	Low and Very Low	Total at risk	% of total country population
Angola	34 689	0	111	2328	2439	7.0
Burkina Faso	21 948	0	0	0	0	0
Cameroon	29 337	0	44	158	202	0.7
Central African Republic	5434	5	128	455	587	10.8
Chad	17 996	0	27	483	509	2.8
Congo	5526	0	17	711	728	13.2
Côte d'Ivoire	28 571	0	0	395	395	1.4
DRC	108 384	0	758	28 747	29 505	27.2
Equatorial Guinea	1670	0	33	36	69	4.1
Gabon	2305	4	14	54	72	3.1
Guinea	12 915	0	95	2390	2485	19.2
Sierra Leone	8560	0	0	247	247	2.9
South Sudan	11 575	0	11	1201	1212	10.5

Indication	Human African trypanosomiasis due to *T. b. gambiense*

Uganda	46 289	0	0	437	437	0.9
Other Endemic Countries[b]	351 637	0	0	0	0	0
Total	686 835	9	1239	37 641	38 889	5.7

a As per Landscan.
b Countries at marginal risk: Benin, Gambia, Ghana, Guinea-Bissau, Liberia, Mali, Niger, Nigeria, Senegal and Togo.
DRC: Democratic Republic of the Congo; *T. b.: Trypanosoma brucei*.

Age

Although g-HAT predominantly affects adults, children typically experience lower infection rates due to reduced exposure to tsetse flies during daily activities. (10) In a study by Médecins Sans Frontières on HAT control projects, 120 (17.5%) out of 684 treated second-stage patients were children under 15. Prevalence rates peak in the young-to-mid adult range in most case-finding surveys. Infants are more commonly encountered within the second-stage of the disease, likely due to delayed diagnosis and the immature blood-brain barrier. (11) There have been a few documented cases of congenital g-HAT transmission diagnosed within five days of birth, as well as three cases in children born to infected mothers who had left the endemic area before delivery. (12)

Sex

Sex distribution varies depending on behavior and activities within specific epidemiological settings. In areas where high-risk activities include mining, hunting, and fishing, males tend to have a higher infection prevalence than females. However, in transitional vegetation zones between forest and woodland, where infection is linked to cultivation and activities near water sources, prevalence is similar between males and females in case detection surveys. (10) Additionally, domestic activities such as washing clothes (13) and walking long distances daily (14) are known risk factors that may influence the sex distribution of infection. (10)

Race/ethnic origin

- Human African trypanosomiasis caused by *T. b. gambiense* is endemic in 24 West and Central African countries. The tsetse fly's habitat and the possibility of human-fly contact due to the occupations of the people at risk dictates the geographical distribution of HAT; human racial or ethnic factors have no impact.
- Tsetse infestation areas are regions within 24 African countries where tsetse flies, the vectors for *Trypanosoma brucei* (the parasite causing HAT), are found. These areas are critical for understanding the distribution and risk of g-HAT. Mapping these regions is essential for controlling and eventually eliminating the disease, as they are the primary zones for transmission.
- Travelers to these tsetse infested countries can be at risk of contracting HAT through the bite of an infected tsetse fly.

Main existing treatment options	**Treatment for *T. b. gambiense*** All anti-trypanosomal treatments are donated to WHO by the manufacturers and distributed by WHO to endemic countries. The treatment choice depends on the disease form and the disease stage. The earlier the disease is treated, the better the prospect of complete cure without sequelae. The most recent WHO treatment guidelines for g-HAT were issued in Jun-2024.

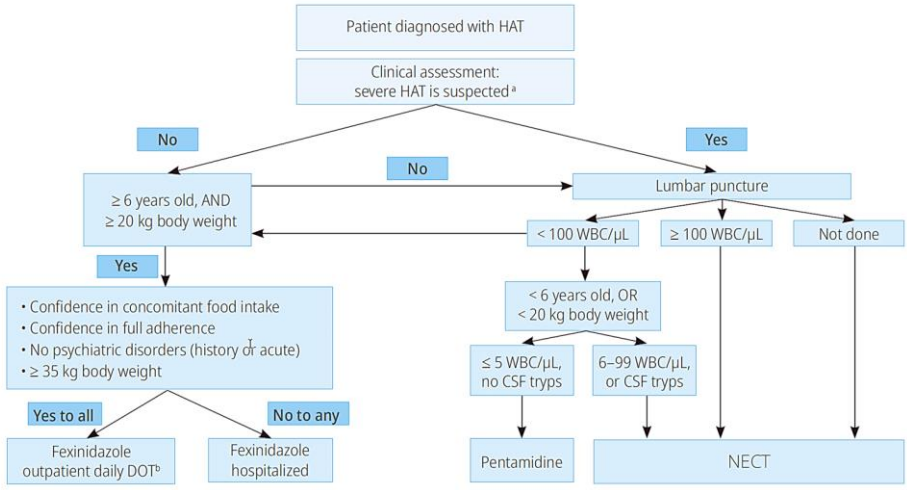
Indication	Human African trypanosomiasis due to *T. b. gambiense*

Table 6c - Summary of treatment choices for patients with g-HAT (WHO treatment guidelines 2024)

Age, body weight	Clinical examination	CSF findings	Treatment		
			1st choice	2nd choice	Rescue[a]
< 6 years or < 20 kg		≤ 5 WBC/µL, no trypanosomes	pentamidine	–	NECT
		> 5 WBC/µL, or trypanosomes	NECT	eflornithine	NECT-long or melarsoprol
≥ 6 years and ≥ 20 kg	No suspicion of severe HAT	LP not needed	fexinidazole	– LP needed – pentamidine (first-stage) or NECT (second-stage)	NECT or NECT long
	Suspicion of severe HAT	< 100 WBC/µL	fexinidazole	pentamidine (first-stage) or NECT (second-stage)	NECT or NECT long
		≥ 100 WBC/µL or failed LP	NECT	fexinidazole	NECT-long or melarsoprol

CSF: Cerebrospinal Fluid; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis LP: Lumbar Puncture; NECT: Nifurtimox-Eflornithine Combination Therapy; WBC: White Blood Cells; WHO: World Health Organization.

Figure 3 - Algorithm of WHO recommendations on the management of persons with g-HAT (15)



CSF, cerebrospinal fluid; DOT, directly observed treatment; NECT, nifurtimox–eflornithine combination therapy; WBC, white blood cell
[a] Presence of symptoms and signs consistent with severe second-stage HAT, as detailed in Box in section 2.1.3.
[b] If the health facility has capacity for supervised administration as an outpatient.

CSF: Cerebrospinal Fluid; DOT: Directly Observed Treatment; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis NECT: Nifurtimox-Eflornithine Combination Therapy; WBC: White Blood Cells; WHO: World Health Organization.

Natural history of the indicated condition in the untreated population including mortality and morbidity

Human African trypanosomiasis poses a significant threat to public health in affected regions and is usually fatal if left untreated. (16) HAT is classified into two types depending on the subspecies of the infecting *T. b.* parasite: *rhodesiense* HAT (r-HAT) and *gambiense* HAT (g-HAT).

- *Rhodesiense* HAT (r-HAT), caused by *T. b. rhodesiense* infection, typically manifests as an acute illness, progressing to the second stage within a few weeks and often leading to death within six months, usually due to damage to multiple organs and systems, including the central nervous system (CNS). (17) It is mainly found in eastern and southern Africa.
- *Gambiense* HAT (g-HAT), caused by *T. b. gambiense* infection, is characterized by a chronic, progressive course that can last for several years. Without treatment, it commonly

Indication	Human African trypanosomiasis due to *T. b. gambiense*
	results in cachexia, lethargy, coma, and eventual death. (10) It is mainly found in western and central Africa. Following a tsetse fly bite, patients infected with *T. b. gambiense* rarely experience an immediate local reaction (less than 5%), which is less frequent than in those infected by *T. b. rhodesiense* (5-26%). (10)(17) The incubation period for g-HAT ranges from a few days to several years, while for r-HAT, it is typically shorter (less than three weeks). The signs and symptoms of sleeping sickness are typically nonspecific and influenced by various factors, including the parasite species, the disease stage, characteristics of the individual host, and specific disease foci. While clinical manifestations of r-HAT and g-HAT may exhibit similarities, they can vary in frequency, severity, and onset kinetics. **The clinical presentation of HAT has been categorized classically in two stages**: (15) • The first, known as the haemo-lymphatic stage, involves the dissemination of parasites in the lymph and blood, which entails bouts of fever, headache, enlarged lymph nodes, joint pains and itching. • Later, the second stage, termed the meningo-encephalitic stage, involves the invasion of the CNS, leading to neurological signs and symptoms, including disturbances in sleep patterns, behavior changes, confusion and poor coordination. • Many symptoms overlap between the two stages, making clinical differentiation challenging and necessitating cerebrospinal fluid analysis for accurate diagnosis to determine the best adapted treatment. • Following the introduction of fexinidazole, a new classification based on White Blood Cell (WBC) count has been proposed: - Haemo-lymphatic stage (first-stage): $\leq$5 WBC/μL and no trypanosomes in Cerebrospinal Fluid (CSF). - Meningo-encephalitic stage (second-stage): >5 WBC/μL or trypanosomes in CSF. - Severe meningo-encephalitic stage (severe second-stage): $\geq$100 WBC/μL with or without trypanosomes in CSF. **Diagnosis involves 3 steps:** • Screening for potential infection using serological tests (only available for *T. b. gambiense*) and clinical examination including cervical lymph node palpation; • Confirmation by observing microscopically the parasite in body fluids; and • Staging the disease progression via clinical examination and analysis of cerebrospinal fluid obtained by lumbar puncture, if needed. Early diagnosis is important to avoid progressing to the neurological stage with more complex and risky treatment. The long, relatively asymptomatic first stage of g-HAT is one of the reasons why active screening of exposed populations is done, to detect cases at an early stage and remove them as reservoir. Exhaustive screening requires a major investment in human and material resources. In Africa such resources are often scarce, particularly in remote areas. Hence, some infected individuals may die before they can ever be diagnosed and treated.
Important co-morbidities	Human African trypanosomiasis mainly affects populations in remote rural areas with limited health services, leading to underreporting. Factors such as war, displacement, and poverty favor transmission. Patients with HAT often experience comorbidities such as malnutrition, other parasitic infections including malaria, and increased susceptibility to viral and bacterial infections, including tuberculosis. The primary co-morbidity reported in HAT patients is co-infection with malaria. A retrospective study at Kenya's National Sleeping Sickness Referral Hospital identified 31 r-HAT patients between 2000 and 2009. The study found the most common co-infections among these patients were malaria (100%), helminthiasis (64.5%), typhoid (22.5%), urinary tract infections (16.1%), Human immunodeficiency virus (HIV) (12.9%), and tuberculosis (3.2%). (18)

Indication	Human African trypanosomiasis due to *T. b. gambiense*
	According to a recent systematic review and meta-analysis, several studies have provided estimates of the prevalence of malaria among HAT patients, varying from 23% to 88%, with an estimated pooled prevalence at 50% (95% confidence interval [CI]: 28% to 78%, level of heterogeneity [I^2] = 98.1%, based on five studies). (19) Co-infections with HIV have been reported, but studies indicate that concurrent HIV infection does not increase the risk of contracting HAT and does not appear to influence the clinical presentation of r-HAT. (20) There is some evidence suggesting cardiac involvement in HAT. (21) In a prospective study examining cardiac involvement in 60 patients with g-HAT in the DRC, major electrocardiogram (ECG) alterations were observed in 71% of HAT patients, compared to 18% in healthy controls. (22) Moreover, symptoms such as exertional dyspnea (19% versus 1.7%) and palpitations (18% versus 5%) were more frequent in patients with HAT as well, although there were no reports of heart failure. Across multiple clinical trials investigating various HAT therapies, the frequency of palpitation/arrhythmia ranged from 4% to 22%. (23)(24)(25) It is also expected that the prevalence of chronic non-infectious diseases commonly observed in the general population, such as hypertension and diabetes, also apply to the HAT population. According to the DRC Demographic and Health Survey 2023-2024, 7.7% of women and 13.3% of men residing in rural areas reported hypertension. The corresponding figures for diabetes were 2.3% and 2.5%. (26)

CATT: Card Agglutination Test for Trypanosomiasis; CI: Confidence Interval; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; DRC: Democratic Republic of the Congo; DOT: Directly Observed Treatment; ECG: Electrocardiogram; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; HIV: Human Immunodeficiency Virus; I^2: Level of Heterogeneity; LP: Lumbar Puncture; n: Number of Patients; NECT: Nifurtimox-Eflornithine Combination Therapy; NSSCP: National Sleeping Sickness Control Programme; r-HAT: Rhodesiense Human African Trypanosomiasis; *T. b.: Trypanosoma brucei*; WBC: White Blood Cell; WHO: World Health Organization.

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Acoziborole was evaluated for its potential safety using a comprehensive set of preclinical studies conducted throughout its development.

The preclinical studies performed to support the clinical development of acoziborole were conducted as per the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines and consists in nonclinical safety pharmacology studies, general toxicity studies spanning from single dose to repeated dose toxicity studies up to 13-weeks duration, in vitro and in vivo genotoxicity studies and reproductive and developmental toxicity studies.

The safety pharmacology studies were conducted to assess the potential effects of acoziborole on cardiovascular physiological functions by human Ether-a-go-go-Related Gene (hERG) in vitro assay and by in vivo telemetry study in dogs, respiratory effects by plethysmography in rats, CNS effects by conducting functional observation battery in rats, and gastrointestinal transit in rats.

The general toxicity studies were conducted following single oral administration in rats to assess the maximum tolerable dose levels, followed by 7-days repeated oral administration in rats and dogs to assess the systemic effects and to select the dose levels for the pivotal repeated dose toxicity studies. The Good Laboratory Practice (GLP) compliant 28-days repeated dose oral toxicity was conducted to support the first-in-human Phase I clinical trial. Following the long elimination half-life of acoziborole observed in the Phase I clinical trial, 13-weeks oral repeated dose toxicity studies in rats and dogs were conducted to cover the exposure period in humans. The 28-day and 13-week oral repeated dose toxicity studies in rats and dogs were used to identify and evaluate the potential target organs and key risks.

The potential genotoxicity effects of acoziborole were evaluated in a standard battery of genotoxicity studies as per ICH S2 (R1) guidelines two in vitro studies namely bacterial reverse mutation assay and mammalian chromosomal aberration study followed by an in vivo micronucleus test in rats.

The reproductive and developmental effects of acoziborole were assessed for all stages through a comprehensive set of studies as per the ICH guidelines. Accordingly, the reproductive studies conducted were a male/female fertility study in rats, embryo-fetal developmental toxicity study in rats and rabbits, pre- and post-natal developmental toxicity study in rats.

The toxicokinetic analysis was included in the single and repeated dose toxicity, in vivo genotoxicity and reproductive toxicity studies, to document plasma exposures of acoziborole at the doses tested and enable comparison to human exposure.

Carcinogenicity studies were not conducted as acoziborole is indicated as single oral dose regimen and not intended for repeated administration in humans.

The key non-clinical findings are presented in the following table.

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity	
• **Key issues identified from single or repeated dose toxicity studies:**	
- This gastro-intestinal toxicity was observed in Wistar rats at 400 mg/kg with the lethal dose at 800 mg/kg bodyweight. The maximum tolerated oral dose level was 200 mg/kg following two single oral toxicity studies in rats.	Cause of death is considered due to the gastrointestinal lesions such as stomach ulcers, mucosal erosions who led to reduced food consumption in the rats. Dose levels showing single dose toxicity were beyond the intended clinical doses.
- Reduced bodyweight gain and food consumption were observed at top dose levels throughout the repeated-dose toxicity studies in rats and dogs. The finding was observed as reversible during treatment free period.	Bodyweight loss and food consumption have not been identified as a limiting effect of acoziborole in the context of clinical trials. These changes were considered secondary to the repeated compound-related overt toxicity at top dose levels in animals. Potential central effects on food consumption and satiety cannot be excluded.
- Vacuolations of cortical cells in adrenal (male rats and both sexes in dogs) and pancreas glands (both sexes in rats) were observed. The pancreas finding was reversible and the adrenal vacuolations at reduced severity were observed at the end of the 6-week recovery period. At above the no-observed-adverse-effect level (NOAEL) dose levels in 28 day repeated dose toxicity studies (cumulative area under the curve [AUC] at least >3-fold compared to clinical exposure), reversible changes in liver (hepatocellular hypertrophy, hepatocyte/sinusoidal single cell necrosis) were observed in rats and dogs. No hepatic changes in 13-week toxicity study in both rats and dogs.	The change is considered adaptive/reversible changes in animals, not relevant to humans. In addition, these effects should be mitigated by the single dose administration in human. No hepatotoxicity observed in Acoziborole exposed participants.
- Unilateral sperm granulomas in epididymis were observed only in rats (not observed in dogs) at top dose levels in 13-week toxicity study and this finding had not reverted at the end of 6-weeks recovery period.	Sperm granulomas correlated with adrenal cortical vacuolation in rats but were absent in dogs despite of higher exposure. In the DNDi-OXA-07-HAT clinical trial conducted in healthy participants, there was no evidence of acoziborole effect on the levels of testosterone or adrenal hormones.
• **Reproductive/developmental toxicity studies:**	
- Acoziborole did not show any effect on fertility parameters, reproductive capacity, early embryonic development, pregnancy, no direct effect on the prenatal development or post-natal development through weaning and lactation. There was minimal to moderate maternal toxicity at the top dose level of 25 mg/kg in rats and at ≥15 mg/kg in rabbits which led to reduced fetal or pup body weight and placental weight. The NOAEL for fertility and reproductive performance in rats was 25 mg/kg, maternal/fetal NOAEL in embryofetal toxicity and pre- and post-natal development study in	This finding is potentially relevant to humans, although limited to high dose levels (minimal reduced fetal and placenta weight). In rats and rabbits, acoziborole was not found to induce related cases of malformations. The reduced fetal weight and growth retardation in pups are considered as key non-clinical safety findings. Effects observed in animals at high dose levels while acoziborole was found to cross the placenta and to be excreted in milk of rats. Exposure through milk is considered possible in breast-fed children. Therefore, “Use during pregnancy” and “Use during breastfeeding” are considered “missing information”.

Key Safety Findings	Relevance to human usage
rats was 15 mg/kg while in rabbits, the maternal NOAEL was 5 mg/kg and fetal NOAEL is <5 mg/kg. Acoziborole was found to cross the placenta and to be excreted through milk in rats.	
• **Genotoxicity** - Acoziborole was non-mutagenic in Ames test and was found positive in one of the testing conditions in in vitro mammalian chromosomal aberration study - at the highest tested concentration of 210 µg/mL for 3 hours in the absence of metabolic activation, with a NOAEL of 66 µg/mL (ie, at least 3 times the mean maximum plasma concentration [C_{max}]) in the human single ascending dose study at the highest tested dose of 1200 mg. However, in the in vivo rat micronucleus test, acoziborole did not indicate any potential for genetic toxicity.	No risk of mutagenicity/aneugenicity following single oral dose in humans.
• **Carcinogenicity** - In accordance with ICH guideline S1A, no carcinogenicity studies are conducted for acoziborole. Carcinogenicity studies are only required for pharmaceuticals that will be continuously administered for at least 6-months. There were no other causes for concern regarding potential carcinogenicity of acoziborole.	Acoziborole is administered as a single dose regimen in humans (960 mg) and is characterized by a long half-life of around 296 hours (12.3 days) in patients with g-HAT. Considering single dosing and no cause of concern for genotoxicity, the residual exposure due to long half-life to induce carcinogenicity is considered low.
Safety pharmacology • There were no key safety findings in CNS, respiratory, cardiovascular or gastrointestinal transit testing with acoziborole.	Overall, no effect of acoziborole seen on the main vital functions.
Other toxicity-related information or data • Phototoxicity: Acoziborole was demonstrated as non-binding with melanin in rats, and non-phototoxic in the 3T3 Neutral Red Uptake Assay. • Immunotoxicity: The clinical pathology, organ weights and histopathology readouts in the toxicology studies did not show any relevant changes suggestive of immunotoxicity concern requiring further toxicological qualification.	No evidence of phototoxicity, or concerns for immunotoxic effects related to acoziborole administration in humans.

AUC: Area Under the Curve; C_{max}: Maximum Plasma Concentration; CNS: Central Nervous System; g-HAT: *Gambiense* Human African Trypanosomiasis; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; NOAEL: No-Observed-Adverse-Effect Level.

Conclusion from the key safety findings:

On the basis of these non-clinical findings, the use of acoziborole during pregnancy/breastfeeding is considered as “missing information” (see [Part II Module SVII]).

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Overview of the clinical development program:

The safety analysis on acoziborole (cut-off date of 25 February 2025) was conducted on participants enrolled in 5 completed studies and 2 ongoing studies.

Five completed studies:

- DNDi-OXA-02-HAT - **pivotal study**: a Phase II/III, multicenter, open-label, non-randomized, single-arm, efficacy and safety of a 960 mg single oral dose acoziborole in patients aged ≥15 years with early-, intermediate- or late-stage human African trypanosomiasis due to *T. b. gambiense* (g-HAT) **confirmed** parasitologically.
- DNDi-OXA-04-HAT - supportive safety study: a Phase II/III, randomized, multicenter, double-blind, placebo-controlled, parallel-arm study to assess the safety and tolerability of a 960 mg single oral dose of acoziborole compared with placebo in adolescent and adult subjects seropositive to g-HAT, **not confirmed** parasitologically.
- Clinical pharmacology studies conducted in **healthy** male participants:
  - DNDiOXA001: a Phase I, randomized, double-blind, placebo-controlled sequential study (3 parts) to assess the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of acoziborole after single oral ascending doses in healthy male participants of sub-Saharan African origin.
  - DNDi-OXA-03-HAT: a Phase I, open-label, single-dose, single-period study to assess the mass balance recovery, metabolite profile and metabolite identification of a single oral dose of [^{14}C]-acoziborole containing a small amount or radioactivity (30.64 kBq) in healthy Caucasian male participants.
  - DNDi-OXA-07-HAT: a Phase I, single center, open-label, non-randomized, three-treatment, two-period, pharmacokinetic drug interaction study to assess the effect of a 960 mg single oral dose of acoziborole on the PK of midazolam (cytochrome P450 [CYP3A4] sensitive substrate) and dextromethorphan (CYP2D6 sensitive substrate) in healthy Malay male participants.

Two ongoing studies:

- DNDi-OXA-05-HAT: a phase II/III, open-label, single-arm clinical study to assess the efficacy and safety of single-dose acoziborole in children (1-14 years old) diagnosed with g-HAT and **confirmed** parasitologically.
- StrogHAT: a phase IIIb epidemiological and safety study with acoziborole administered to adolescent and adult participants seropositive for g-HAT **not confirmed** parasitologically.

From these two studies, only serious adverse reaction (SAR) and suspected unexpected serious adverse reaction (SUSAR) up to the data cut-off were provided, if any reported.

- The safety database was thus limited to a small number of participants (aged ≥15 years) (N = 208) with the targeted indication ie, g-HAT confirmed parasitologically (T+), because of the low incidence of this rare disease. Therefore, it was supplemented by data collected from 906 participants seropositive for g-HAT (906 on acoziborole and 300 on placebo)

(aged ≥15 years) and not confirmed parasitologically (T_{NC}) enrolled in a double-blind placebo-controlled safety study. As participants with T+ or T_{NC} g-HAT do not share the same health status, their data were not pooled for safety analyses on acoziborole.

Overall Clinical trial exposure:

DNDi-OXA-02-HAT

In the pivotal study DNDi-OXA-02-HAT, all 208 (100%) patients with g-HAT (T+), received a single oral dose of acoziborole (960 mg = 3 x 320 mg tablets) on Day 1.

Exposure by age and sex in DNDi-OXA-02-HAT is summarized in Table 8. Most patients treated with acoziborole are between 18 and 64 years of age (96.6% in male, 91.2% in female).

Table 8 - Overall exposure to acoziborole in Human African trypanosomiasis due to *T. b. gambiense* by age and sex - Treated set (DNDi-OXA-02-HAT)

	Patients (N = 208)	
	Female (N = 91)	Male (N = 117)
Age group		
15 - 17 years	5 (5.5)	4 (3.4)
18 - 64 years	83 (91.2)	113 (96.6)
≥65 years	3 (3.3)	0

Study included DNDI-OXA-02-HAT
PGM=PRODOPS/SCYX7158/OXA002/CSR/REPORT/PGM/rmp_age_gender_s_t.sas
OUT=REPORT/OUTPUT/rmp_age_gender_s_t_i.rtf (02JUL2024 9:35)
N: Total Number of Patients; *T. b.: Trypanosoma brucei*.

In DNDi-OXA-02-HAT, staging of g-HAT disease was done according to the following definitions:

- **Early stage**: No trypanosomes in the CSF, trypanosomes in blood/lymph, and CSF WBC ≤5 cells/µL of CSF;
- **Intermediate stage**: No trypanosomes in the CSF, trypanosomes in blood/lymph, WBC between 6 and 20 cells/µL of CSF;
- **Late stage**: Trypanosomes in the CSF and/or evidence of trypanosomes in blood/lymph, and CSF WBC >20 cells/µL of CSF.

The g-HAT staging terminology used in the pivotal study is different from the one used in the 2024 WHO guidelines (see Table 9 for terminology correspondence).

Table 9 - Correspondence for staging terminology between pivotal study for acoziborole and new WHO guidelines for the treatment of g-HAT

Disease stage			Criteria for treatment choice		
			Blood/lymph node sampling	Lumbar puncture	
WHO HAT treatment guidelines (2024)	DNDi-OXA-02-HAT	Clinical description	Trypanosomes in blood/lymph	Trypanosomes in CSF	WBC in CSF (cells/µL)
First stage	Early stage	First stage	+	-	≤5
Non-severe second stage	Intermediate	Hemo-lymphatic stage	+	-	6 to 20
	Not specified	Second-stage	+	+ or -	>5
	Late stage	Meningo-encephalitic stage	+	-	>20
		(if trypanosomes in CSF)	+ or -	+	
Severe second stage			+	+ or -	≥100

(+) = trypanosomes observed; (-) = trypanosomes not observed.
CSF: Cerebrospinal Fluid; g-HAT: *Gambiense* Human African Trypanosomiasis; HAT: Human African Trypanosomiasis; WBC: White Blood Cells; WHO: World Health Organization.

Table 10 below summarizes exposure to acoziborole by g-HAT stage in DNDi-OXA-02-HAT. 167 patients (80.3%) have late-stage g-HAT.

Table 10 - Overall exposure to acoziborole in Human African trypanosomiasis due to *T. b. gambiense* by g-HAT stage - Treated set (DNDi-OXA-02-HAT)

	Patients (N = 208)
g-HAT stage	
Early and Intermediate Stage	41 (19.7)
Late Stage	167 (80.3)

Study included DNDI-OXA-02-HAT
PGM = PRODOPS/SCYX7158/OXA002/CSR/REPORT/PGM/rmp_ghat_s_t.sas OUT=REPORT/OUTPUT/rmp_ghat_s_t_i.rtf (20DEC2024 11:34)
g-HAT: *Gambiense* Human African Trypanosomiasis; N: Total Number of Patients; *T. b.*: *Trypanosoma brucei*.

The elimination half-life of acoziborole is about 296 hours (12.3 days) in patients with g-HAT at the single oral therapeutic dose of 960 mg. Clinically a drug is essentially eliminated from the body after five half-lives, corresponding to 62 days for acoziborole treatment. A fetus was considered exposed to acoziborole in utero if the pregnancy start date (calculated from the first day of the last menstrual period [LMP]) was estimated to be up to 62 days after acoziborole intake.

In the study DNDi-OXA-02-HAT, there were 7 pregnancies reported within 6 months after dosing. Among these 7 pregnancies, the fetus was considered exposed to acoziborole in utero in 4 cases.

DNDi-OXA-04-HAT

In DNDI-OXA-04-HAT, all 906 (100%) seropositive participants (T_{NC}) in the acoziborole arm in the safety set received a single oral dose of acoziborole (960 mg = 3 x 320 mg tablets).

Exposure by age and sex in DNDi-OXA-04-HAT is summarized in Table 11. Most participants treated with acoziborole are between 18 and 64 years of age (80.9% in male, 81.9% in female).

Table 11 - Overall exposure to acoziborole in Seropositive to Human African trypanosomiasis due to *T. b. gambiense* by age and sex - Safety set (DNDi-OXA-04-HAT)

	Patients (N = 906)	
	Female (N = 476)	Male (N = 430)
Age group		
15 - 17 years	55 (11.6)	46 (10.7)
18 - 64 years	390 (81.9)	348 (80.9)
≥65 years	31 (6.5)	36 (8.4)

Study included DNDI-OXA-04-HAT
PGM = PRODOPS/SCYX7158/OXA004/CSR/REPORT/PGM/rmp_age_gender_04_s_t.sas
OUT = REPORT/OUTPUT/rmp_age_gender_04_s_t_i.rtf (24OCT2024 11:55)
N: Total Number of Patients; *T. b.: Trypanosoma brucei*.

In DNDi-OXA-04-HAT, there were 8 pregnancies reported in the acoziborole group within 4 months after dosing. Among these 8 pregnancies, the fetus was considered exposed to acoziborole in utero in 5 cases (pregnancy start date from the first day of LMP) estimated to be up to 62 days after acoziborole intake as explained above.

Clinical pharmacology studies

In the 3 clinical pharmacology studies, healthy participants aged from 18 to 64 years old were exposed to acoziborole. In DNDiOXA001, 102 subjects received one dose of acoziborole from 20 mg to 1200 mg. In DNDi-OXA-03-HAT, 6 subjects received 960 mg single oral dose of radiolabeled acoziborole and in DNDi-OXA07-HAT, 19 subjects received single dose of 960 mg of acoziborole.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 12 - Important exclusion criteria in pivotal studies in the development programme (OXA002)

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Pregnancy or breastfeeding women.	To avoid potential harm to an unborn fetus through exposure of drug or a newborn through exposure of drug from breast milk.	Yes	Not applicable
Patient has a medical condition of serious inter-current illness including significant cardiovascular or liver disease, suspected or proven active infection, CNS trauma or seizure disorder, coma or consciousness disturbances. Severely deteriorated health status, eg, due to cardiovascular shock, respiratory distress syndrome or end-stage disease.	Possibility that these medical conditions of serious inter-current illness could jeopardize the patient's safety or significantly interfere with study compliance including all prescribed evaluations and follow-up activity, and measurement of safety and efficacy endpoints.	No	Acoziborole did not affect the CNS, liver or respiratory functions in non-clinical studies (Part II Module SII). Acoziborole exposure in patients having active infection, CNS trauma or seizure disorder, consciousness disturbances does not constitute a safety concern. Acoziborole is not recommended in patients with severe hepatic impairment. Due to its oral administration as full or crushed tablets, acoziborole cannot be given to patients in coma.
Patient has a severe malnourishment (defined as Body Mass Index [BMI] <16).	Exclusion to get data in patients with normal BMI.	No	No acoziborole dose adjustment to the weight for patients ≥40 kg is considered, based on PK and safety data. (Part II Module SII).
Patient was previously treated for HAT (except prior treatment with pentamidine).	Efficacy assessments of acoziborole could be altered by the previous treatment.	No	Acoziborole was not studied in patients treated previously for HAT as the efficacy results may have been impacted in this population, but no specific safety issues are foreseen.
Patient is not treated appropriately for malaria or for soil-transmitted helminthiasis prior administration of acoziborole.	To avoid bias in efficacy and safety assessment.	No	Treatment with Acoziborole in patients having these comorbidities does not constitute a risk factor.

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Patient has clinically significant abnormal laboratory values including severe leukopenia at less than 2000/mm^3; Potassium below 3.5 mmol/L.	Safety assessments of acoziborole could be impaired by these clinically abnormal laboratory values.	No	No specific risk expected with acoziborole based on the laboratory parameters.

BMI: Body Mass Index; CNS: Central Nervous System; HAT: Human African Trypanosomiasis; PK: Pharmacokinetic.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

The clinical development program can detect uncommon adverse drug reactions (ADRs) (≥1/1000 to <1/100) or more frequent. The pivotal Phase II/III trial with 208 g-HAT patients has a 65% probability of detecting at least one occurrence of an ADR in the acoziborole group if this event truly occurs in at least 0.5% of the population. This is significantly improved by including a supportive Phase II/III study of 906 seropositive but parasitologically not confirmed participants, increasing the detection probability to 99% for ADRs with a 0.5% occurrence rate.

Cumulative effects in g-HAT treated patients are not anticipated because of the unique administration of acoziborole (single dose administration of a 960 mg dose).

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 13 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	The elimination half-life of acoziborole is about 296 hours (12.3 days) in patients with g-HAT at the single oral therapeutic dose of 960 mg. Clinically a drug is essentially eliminated from the body after five half-lives, corresponding to 62 days for acoziborole. A fetus was considered exposed to acoziborole in utero if the pregnancy start date (calculated from the first day of LMP) was estimated to be before or up to 62 days after acoziborole intake. Maternal exposure to acoziborole in DNDi-OXA-02-HAT (g-HAT): Among the 7 cases of pregnancy reported in the study within 6 months of dosing, the fetus was considered exposed to acoziborole in utero in 4 cases. Maternal exposure to acoziborole in DNDi-OXA-04-HAT (seropositive but unconfirmed parasitologically): Among the 8 cases of pregnancy reported in the study within 4 months of dosing, the fetus was considered exposed to acoziborole in utero in 5 cases.

Type of special population	Exposure
Breastfeeding women	Breastfeeding women were not included in the clinical development programme. No case of exposure during breastfeeding was reported.
Patients with relevant comorbidities	Patients with relevant comorbidities, severe hepatic impairment, renal impairment, cardiovascular diseases and immunocompromised were not included in the clinical development programme.
Populations with relevant different ethnic origin	The distribution of patients with different ethnic origin is the following: sub-Saharan African patients (n = 310) from DNDi-OXA-02-HAT pivotal study (n = 208) and DNDiOXA001 study (dose ascending study in Healthy participants [n = 102]); Malay (n = 20) from DNDi-OXA-07-HAT study; Caucasian Healthy participants (n = 6) from the DNDI-OXA-03-HAT Mass balance study. In addition, the DNDi-OXA-04-HAT study included only participants with sub-Saharan African ethnic origin (n = 906).
Adolescent population (15 to 17 years)	Overall, 9 patients out of 208 (4.3%) were adolescents (15 to 17 years old) in the pivotal study DNDi-OXA-02-HAT. In addition, the DNDi-OXA-04-HAT study included 101 out of 906 (11.1%) adolescent participants (15 to 17 years old).
Elderly population (65 years and older)	Overall, 3 elderly patients (≥65 years old) out of 208 (1.4%) were included in the pivotal study DNDi-OXA-02-HAT. In addition, the DNDi-OXA-04-HAT study included 67 out of 906 (7.4%) elderly (≥65 years old).
Subpopulations carrying known and relevant genetic polymorphisms	Not applicable
Other	Not relevant.

g-HAT: *Gambiense* Human African Trypanosomiasis; LMP: Last Menstrual Period; n: Number of Patients.

The use of acoziborole has not been studied in pregnant or breastfeeding women. There is limited data in pregnant women and no data in breastfeeding women. Non-clinical studies showed that acoziborole crosses the placenta and is excreted in maternal milk but do not indicate direct or indirect harmful effects with respect to maintenance of pregnancy or embryo-fetal development (see RMP [Part II Module SII]). However, assuming the targeted population of the indication could include women of childbearing potential and considering the risk of accumulation of Acoziborole in breastfeed children, the “Use during pregnancy” and “Use during breastfeeding” are considered as “missing information” (Part II Module SVII).

Acoziborole exhibits low systemic clearance with elimination occurring mainly through hepato-biliary clearance coupled with slow metabolism. Its terminal half-life is long (296 hours in patients with g-HAT). The effect of hepatic impairment on acoziborole PK profile was not investigated. Patients with “significant liver disease” were excluded in all Phase II/III studies. In the population PK analysis using data from participants with g-HAT (DNDi-OXA-02-HAT), liver function variables at baseline (including albumin) were not identified as significant covariates affecting the PK of acoziborole. Based on the totality of data, use in patients with severe hepatic impairment and/or with clinical signs of jaundice or ascites, is not recommended in the labeling. In DNDi-OXA-03-HAT, renal elimination of unchanged acoziborole was found to be very limited (0.6% of the dose) and there was not a single metabolite accounting for the radioactivity excreted in urine but numerous ones representing each less than 2.1% of the dose. In addition, acoziborole is administered as a single dose regimen. Therefore, renal function impairment is not expected to significantly modify the PK of acoziborole. No adjustment in dosing of acoziborole is required in

patients with renal impairment. Overall, the use of acoziborole in this population is not considered as a safety concern.

To date, there is no information to suggest that patients of specific racial or ethnic origins are adversely affected by acoziborole. The pivotal study (DNDi-OXA-02-HAT) as well as the study in g-HAT seropositive individuals (DNDi-OXA-04-HAT) included participants from sub-Saharan African countries where HAT due to *T. b. gambiense* is endemic. Clinical pharmacology studies in African, Caucasian and Malay healthy males did not raise specific safety concerns.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

Because this is the initial submission of the RMP for acoziborole and the drug is not yet registered in any market worldwide, this module is “not applicable”.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

Following the review of all the data available on acoziborole and related compounds, the Applicant considers the risk of dependence and abuse for acoziborole nil to very low. The drug substance has no similarity to known scheduled substances, and there is no information on the potential of drug dependence and abuse for products of the same pharmaceutical class.

The drug showed no specific activity on CNS targets, and there were no CNS-related clinical signs in animals or humans following oral administration of acoziborole that could support any potential for drug dependence and abuse with this drug [Part II Module SII].

Moreover, the controlled distribution system of the drug product excluding availability in pharmacies, the single-dose treatment pack and supervised administration of the treatment by trained healthcare professionals (HCPs) will prevent any potential risk of product diversion for misuse or off-label use. The risk of overdose or medication errors is also considered extremely low. Therefore, no subsequent risks for public health are anticipated with acoziborole and no drug scheduling is requested (Drug abuse liability assessment [DALA]).

Overall, based on these elements, no other specific risk minimization measures (RMMs) related to abuse, misuse, and overdose will be implemented for acoziborole as part of the RMP. No specific postmarketing DALA-related monitoring is planned at this time outside of routine pharmacovigilance safety monitoring.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

Refer to e-CTD sequence 0000, Module 2.7.4 Summary of Clinical Safety.

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

The following safety topics are not considered important for inclusion in the list of safety concerns in the RMP and will be discussed in Section SVII.1.1:

- Potential harm from overdose
- Potential for risks resulting from medication errors
- Potential for off-label use
- Pharmacological class effect common to other members of the pharmacological class
- Effect on fertility
- Impact of other drugs on acoziborole pharmacokinetics
- Risk with minimal clinical impact on individuals
- Non-important potential risks of effect of acoziborole on drugs mainly metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or uridine diphosphate-glucuronosyltransferase (UGT)1A1; on Breast Cancer Resistance Protein (BCRP) substrates and on P-glycoprotein (P-gp) substrates.
- Potential for transmission of infectious agents
- Risks associated with the disposal of the used product
- Risks related to the administration procedure
- Use in patients with severe hepatic impairment

The following safety topics are considered important for inclusion in the list of safety concerns in the RMP and will be discussed in Section SVII.1.2:

- Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)
- Arrhythmia caused by shortening of QT interval
- Use during pregnancy
- Use during breastfeeding

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP

- **Risk not applicable considering the controlled distribution and access programs scheme for acoziborole**
  - Potential harm from overdose: To date, no case of overdose has been reported during the clinical development programme of acoziborole. Healthy male subjects were exposed to dose up to 1200 mg. Moreover, the safety profile of healthy male participants who received a single dose of acoziborole up to 1200 mg in study DNDiOXA001 did not raise any specific issues at the highest doses tested. No dose response effects were observed. There is no antidote for acoziborole and in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate. In addition, the Controlled Access Program scheme and the product presentation in a single dose pack (3 tablets of 320 mg acoziborole packaged in aluminium blister), make this risk of overdose very low.
  - Potential for risks resulting from medication errors: Due to the Controlled Access Program scheme and the oral administration of three tablets of 320 mg once (packaging of three tablets), this risk is very low.
  - Potential for off label use: The risk of using acoziborole in children below 12 years old or with body weight below 40 kg, or in other parasitic disease is considered low as the diagnosis of g-HAT is to be confirmed before administration. In addition, the modalities for the distribution of acoziborole to the endemic countries ie, Controlled Access Program and controlled distribution system supervised by the NSSCPs in collaboration with WHO make the diversion of the drug unlikely (See [RMP Part V]).
- **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)**
  - Pharmacological class effect common to other members of the pharmacological class not thought to be an important identified or potential risk with acoziborole: Acoziborole belongs to the benzoxaborole class compounds. Two marketed products of this class have been identified (Crisaborole and Tavaborole), but they are administered by topical route. No important clinical risks have been reported with these products that could be relevant for acoziborole, which is administered orally. Acoziborole is the first oxaborole-based entity to be developed as an oral drug and is intended to be a single-dose treatment for g-HAT.
  - Effect on fertility: Non-clinical studies showed that acoziborole crosses the placenta but has no effect on fertility as well as fetal or post-natal development in rats (see [Part II Module SII]).
  - Impact of other drugs on acoziborole PK: Acoziborole has a low intrinsic metabolic clearance in vitro and is weakly and slowly metabolized in vivo in humans. No single CYP is expected to contribute significantly to the total elimination of acoziborole.
  - Given the low solubility of acoziborole regardless of the potential of hydrogen (pH) tested, its low metabolic clearance, and the absence of major transporter involvement in its disposition (organic anion transporting polypeptide 1 B1 [OATP1B1], organic anion transporting polypeptide 1 B3 [OATP1B3], P-gp, BCRP), other drugs are unlikely to affect the PK of acoziborole.

- Risk with minimal clinical impact on individuals: Non-important identified risk of headache was found following treatment emergent adverse events (TEAEs) analysis. In the pivotal clinical study (DNDi-OXA-02-HAT), headache was reported in 24.5% patients with g-HAT and assessed as related to acoziborole in 1% patients. From data in seropositive participants but parasitologically unconfirmed (DNDi-OXA-04-HAT), headache was reported with statistically higher occurrence in the acoziborole arm: 5.8% of the participants in the acoziborole group and 2.7% of the participants in the placebo group (experimental event rate [ER]: +3.2, 95% CI: 0.3; 5.3). In the acoziborole arm, more headaches were reported as related compared to the placebo arm (3.1% vs 1.7%). Overall, episodes of headache were mainly of mild or moderate intensity, non-serious and observed mainly during the hospitalization period. Therefore, risk of headache is assessed as not important.
- Non-important potential risks of effect of acoziborole on drugs mainly metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or UGT1A1; on BCRP substrates and P-gp substrates: Based on in vitro interaction studies (studies CYP2139 R2 for CYP induction, IHH0111 for UGT induction and CYP2139 R2E for transporter inhibition) and static approach predictions, there is a risk of induction of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and UGT1A1 and inhibition of BCRP transporter by acoziborole in vivo. The physiological based pharmacokinetic (PBPK) predictions showed that acoziborole may produce a
    - Weak decrease in the AUC of a CYP1A2 (27%) or CYP2B6 (43%) sensitive substrate.
    - Moderate decrease in the AUC of a CYP2C8 (55% to 66%), CYP2C9 (51%), CYP2C19 (67%) or UGT1A1 (52%) sensitive substrate.
    - Weak increase in the AUC of a BCRP transporter sensitive substrate (1.25-fold).

  No clinical evidence of lack of efficacy in participants treated with drugs mainly metabolized by CYP2C9, CYP2C19 and CYP2B6 (diazepam, omeprazole, gliclazide, glibenclamide, and ketamine) was observed in the clinical studies.

  Since acoziborole is a strong inducer of CYP3A4 in vivo, P-gp may also be induced because it is regulated by the Pregnane X receptor (PXR) pathway.

  Overall, the risk was assessed as not important (weak to moderate interactions predicted) but cannot be excluded based on limited clinical data available.

- **Risk not applicable considering the oral route of administration and the composition of acoziborole**
    - Potential for transmission of infectious agents: None of the excipients of acoziborole formulation are from animal origin. Acoziborole is administered by oral route.
    - Risks associated with the disposal of the used product: Being a single oral dose treatment, the volume of the disposed product will be small such as the volume of patients considering the epidemiology of the disease.
    - Risks related to the administration procedure: Acoziborole is administered by oral route via a single administration and under the supervision of a health care practitioner (controlled programs).

- **Missing information where there is no reasonable expectation that current or future pharmacovigilance activities will characterize the safety profile further, and for which current labeling is considered sufficient to mitigation.**

  - Use in patients with severe hepatic impairment:

    Patients with clinically significant liver disease were excluded from all Phase II/III clinical studies. Acoziborole is excreted slowly by the hepatobiliary route and by metabolism. The effect of hepatic impairment on acoziborole PK profile was not investigated. In the absence of data use in patients with severe hepatic impairment and/or clinical signs of jaundice or ascites is not recommended.

    There is no plan to further characterize the safety profile in these patients and labeling statements are considered adequate to mitigate risk in patients with severe hepatic impairment.

    Therefore "Use in patients with severe hepatic impairment" is not retained as part of the RMP list of safety concern.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Table 14 - Important identified risk considered for inclusion in the list of safety concerns: Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)

Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)	
Scientific evidence that has led to the inclusion	**In vitro data** In vitro interaction study (study CYP2139 R2 induction and study CYP2139 R2I CYP inhibition) has shown that acoziborole can inhibit CYP2D6 and induce CYP3A4, leading to risk of drug-drug interaction (DDI). **Clinical data** The DNDi-OXA-07-HAT clinical PK DDI study showed that acoziborole is: • A strong inhibitor of CYP2D6, as shown by the13.0- and 35.3-fold increase of C_{max} and area under the curve from 0 to the last quantifiable concentration (AUC_{last}), respectively, of the sensitive CYP2D6 probe dextromethorphan, when co-administered with acoziborole. • A strong inducer of CYP3A4, as shown by the 85% and 92% decrease of C_{max} and AUC_{last}, respectively, of the sensitive CYP3A4 probe midazolam, when co-administered with acoziborole.
Risk-benefit impact	• Strong CYP2D6 inhibition by acoziborole may increase the exposure of the concomitant drugs metabolized by CYP2D6 and have an impact on their safety profile with an increased risk of ADR (such as tramadol and paroxetine). Overall, the benefit-risk profile remains favorable considering minimization measures (see Summary of Product Characteristics [SmPC], educational material) and the severity of the disease. Of note, in case of prodrugs, the impact will be on the efficacy profile and risk of therapeutic failure caused by decreased exposure(s) of the active metabolite(s). • Strong CYP3A4 induction by acoziborole may decrease the exposure of the concomitant drugs metabolized by CYP3A4 (such as lopinavir, ritonavir, atazanavir, darunavir, cabotegravir, fostemsavir, lenacapavir, daclatasvir, delamanid, praziquantel, nifedipine, fentanyl, quinine, and artemether and

Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)	
	lumefantrine combination therapy) and have an impact on their efficacy with a risk of therapeutic failure. Overall, the benefit-risk profile remains favorable considering minimization measures (see SmPC, educational material) and the severity of the disease. Of note, in case of prodrugs, the impact will be on the safety profile and increased risk of ADR associated with increased exposure(s) of the active metabolite(s).

ADR: Adverse Drug Reaction; AUC_{last}: Area Under the Curve From 0 to the Last Quantifiable Concentration; C_{max}: Maximum Plasma Concentration; CYP: Cytochrome P450; DDI: Drug-Drug Interaction; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

Table 15 - Important potential risk considered for inclusion in the list of safety concerns: Arrhythmia caused by shortening of QT interval)

Arrhythmia caused by shortening of QT interval	
Scientific evidence that has led to the inclusion	**Clinical data** Shortening of corrected QT interval by Fridericia's formula (QTcF) was observed in healthy volunteers, seropositive participants and participants with early and late forms of g-HAT exposed to acoziborole. **Non-clinical data** Three studies related to cardiovascular function were conducted with acoziborole: hERG in vitro assay, secondary pharmacology by assessing interaction with various enzymes or channels, and a cardiovascular function assessment in the conscious telemetered dog. Non-clinical development of acoziborole did not evidence any QT shortening in animals.
Risk-benefit impact	Shortening of QTcF was observed in healthy volunteers, seropositive participants and participants with early and late forms of g-HAT exposed to acoziborole. As of the DLP, the clinical significance of QTcF shortening remains unclear. Nevertheless, no cardiac TEAEs were associated with shortening of QT interval in participants exposed to acoziborole.

DLP: Data Lock Point; g-HAT: *Gambiense* Human African Trypanosomiasis; hERG: human Ether-a-go-go-Related Gene; QTcF: Corrected QT Interval by Fridericia's Formula; TEAE: Treatment Emergent Adverse Event.

Table 16 - Missing information considered for inclusion in the list of safety concerns: Use during pregnancy

Use during pregnancy	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	**Non-clinical data** Non-clinical studies showed that acoziborole crosses the placenta in rats but has no effect on fertility, fetal or post-natal development in rats; in rabbits, fetal development effects were observed at ≥15 mg/kg (RMP [Part II Module SII]). **Clinical data** The elimination half-life of acoziborole is about 12.3 days in patients with g-HAT at the single oral therapeutic dose of 960 mg. Clinically a drug is essentially eliminated from the body after five half-lives, corresponding to 62 days for acoziborole. A fetus was considered exposed to acoziborole in utero if the pregnancy start date (first day of LMP) was estimated to be before or up to 62 days after acoziborole intake. This time

Use during pregnancy	
	frame is slightly different from that initially used in CSRs (within 83 days), which was based on healthy participants. Maternal exposure to acoziborole in DNDi-OXA-02-HAT (g-HAT) and DNDi-OXA-04-HAT (seropositive but not confirmed parasitologically): Pregnancy was an exclusion criterion in both clinical trials; however, a total of 15 pregnancies were reported after acoziborole dosing. Among these 15 cases of pregnancy, the fetus was considered exposed to acoziborole in utero in 9 cases (4 cases in DNDi-OXA-02-HAT and 5 cases in DNDi-OXA-04-HAT).
Risk-benefit impact	In animal, acoziborole crosses the placenta. Limited data are available in pregnant women from clinical studies. None of the serious adverse events (SAEs) reported in the mothers (participants) or the newborns (some with fatal outcome) were assessed as related to acoziborole (see Table 20). As the targeted population of the indication should include women of childbearing potential, the use of acoziborole in pregnant women is considered as missing information.

CSR: Clinical Study Report; g-HAT: *Gambiense* Human African Trypanosomiasis; LMP: Last Menstrual Period; RMP: Risk Management Plan; SAE: Serious Adverse Event.

Table 17 - Missing information considered for inclusion in the list of safety concerns: Use during breastfeeding

Use during breastfeeding	
Scientific rationale for anticipating a different safety profile in the particular subpopulation/use that has led to the inclusion	**Non-clinical data** In non-clinical studies, acoziborole was excreted in maternal milk and offspring was exposed through breastfeeding, suggesting that exposure during breastfeeding is likely to occur in humans (RMP [Part II Module SII]). Overall, after single oral dosing of [^{14}C] acoziborole to dam albino rats, radiolabeled drug-related material was excreted into maternal milk and the systemic exposure and half-life values of total radioactivity were similar in plasma and milk (module 2.6.4, section 7.3). Effects on suckling rat pups were limited to transient growth retardation at high dose level (25 mg/kg) only. **Clinical data** There are no data from the use of acoziborole in breastfeeding women.
Risk-benefit impact	Acoziborole is excreted in maternal milk. Effects on suckling rat pups were limited to transient growth retardation at high dose level only. However, due to the long elimination half-life of acoziborole and its possible passage in milk in humans, there is a risk of acoziborole accumulation in breastfed babies. (RMP [Part II Module SIV]). As eligible patients to acoziborole treatment may include lactating women, the use of acoziborole in breastfeeding women is considered as missing information.

RMP: Risk Management Plan.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable since this is the first RMP for acoziborole.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

The following risk(s) have been identified for acoziborole in the RMP:

- Important identified risk:
  - Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)
- Important potential risk:
  - Arrhythmia caused by shortening of QT interval
- Missing information:
  - Use during pregnancy
  - Use during breastfeeding

SVII.3.1. Presentation of important identified risks and important potential risks

Table 18 - Important identified risk: Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)

Important identified risk	**Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)**
Potential mechanism	Acoziborole has a strong induction effect on CYP3A4 and a strong inhibitory effect on CYP2D6. Acoziborole was shown to inhibit CYP2D6 in vitro (Study CYP2139 R2I CYP inhibition) and to induce CYP3A4 in vitro (Study CYP2139 R2 Induction). An in vivo clinical DDI study (DNDI-OXA-07-HAT) has shown that a single oral dose of 960 mg of acoziborole increased by around 35-fold the exposure of dextromethorphan (CYP2D6 probe) and decreased by around 92% the exposure of midazolam (CYP3A4 probe). Based on these data, it is predicted that in vivo, acoziborole could • Increase the exposure of medicinal products mainly metabolized by CYP2D6 such as tramadol and paroxetine. • Decrease the exposure of medicinal products highly metabolized by CYP3A4 such as lopinavir, ritonavir, atazanavir, darunavir, cabotegravir, fostemsavir, lenacapavir, daclatasvir, delamanid, praziquantel, nifedepine, fentanyl, quinine, and artemether and lumefantrine combination therapy. The effects on enzymes may persist for up to 3 months after treatment.
Evidence source(s) and strength of evidence	In vitro data: CYP2139 R2I CYP inhibition, CYP2139 R2 Induction Clinical data from OXA007 study Physiological based pharmacokinetic (PBPK) report (BMG43-A).
Characterization of the risk	Effect of acoziborole on drugs mainly metabolized by CYP3A4: Single administration of acoziborole 960 mg with a single dose of midazolam under fasting conditions reduced midazolam C_{max} by 85% and AUC_{last} by 92%. Risk of decreased exposure of concomitant drugs taken by patients and mainly metabolized by CYP3A4 could result in potential therapeutic failure of these drugs (or exaggerated side effects in case of prodrugs).

Important identified risk	**Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)**
	Effect of acoziborole on drugs mainly metabolized by CYP2D6: Single administration of acoziborole 960 mg with a single dose of dextromethorphan under fasting conditions increased dextromethorphan C_{max} by 13.0-fold and AUC_{last} by 35.3-fold. Risk of increased exposure of concomitant drugs taken by patients and mainly metabolized by CYP2D6 could result in exaggerated and/or prolonged main effects and also side effects of these drugs (or potential therapeutic failure in case of prodrugs).
Risk factors and risk groups	None
Preventability	Routine risk minimization measures (See RMP [Part V]) including: Contraindication with some antiretroviral drugs such as lopinavir, ritonavir, atazanavir, darunavir, cabotegravir, fostemsavir and lenacapavir, and with daclatasvir, delamanid, praziquantel,, nifedipine and artemether and lumefantrine combination therapy. Caution is advised when acoziborole is concomitantly used with drugs which are mainly metabolized by CYP2D6 or CYP3A4. A review of concomitant medicinal products should be conducted when initiating acoziborole treatment and during 3 months after acoziborole single-dose treatment based on the long half-life of acoziborole (12.3 days). The label recommendations may include the following for 3 months after acoziborole intake; • Dosage adjustment of concomitant drug(s). • Treatment schedule adjustment of concomitant drug(s) or acoziborole. • Switch to other drugs not impacted by interaction or to other drugs indicated in g-HAT. • To avoid using of herbal or traditional medicines for which impact of acoziborole cannot been established. • To use reliable method of barrier contraception in addition to hormonal contraceptives. Additional risk minimization measures (See RMP [Part V]) including: • Educational material to alert patients, HCP or medical about the risk of DDI. • National sleeping sickness controlled access program.
Impact on the risk-benefit balance of the product	Increased risk for adverse reactions associated with increased exposures of the drugs mainly metabolized by CYP2D6 due to acoziborole. Increased risk of treatment failure associated with decreased exposures of the drugs mainly metabolized by CYP3A4 due to acoziborole. The benefit-risk profile of acoziborole in adolescent and adult patients with g-HAT is considered favorable under appropriate recommendations for use and risk management activities.
Public health impact	No public health impact is expected.

AUC_{last}: Area Under the Curve From 0 to the Last Quantifiable Concentration; C_{max}: Maximum Plasma Concentration; CYP: Cytochrome P450; DDI: Drug-Drug Interaction; g-HAT: *Gambiense* Human African Trypanosomiasis; HCP: Healthcare Professional; PBPK: Physiological Based Pharmacokinetic; RMP: Risk Management Plan.

Table 19 - Important potential risk: Arrhythmia caused by shortening of QT interval

Important potential risk	Arrhythmia caused by shortening of QT interval
Potential mechanism	Mechanism unknown.
Evidence source(s) and strength of evidence	**Clinical data:** Systematic presence of a small, QTcF shortening in studies with humans.
Characterization of the risk	**Clinical trials:** • DNDiOXA001 Study in Healthy volunteers: Different doses of acoziborole (ranging from 160 mg to 1200 mg) were compared to a placebo (6 participants on acoziborole and 2 on placebo by dose). The changes in ECG parameters (like QTcF, heart rate, RR, PR, and QRS intervals) varied from baseline to Day 11 and from Visit 1 to 7 (approximately Day 18 to 60), regardless of the dose. The ECG Holter analysis showed slight changes in QTcF with different doses of acoziborole. However, measures were done at different time points depending on the dose (D-1 and D-4 for low doses and D-1 only for doses above 600 mg not covering the C_{max}). Replicate ECGs were done at later timepoints (D-8 and after). Maximum decrease was noted at D-11 -13.5 ms (-22.9; -4.1) for the 960 mg dose; -11.8 (-21.2; -2.4) at D-8 for the dose 1000 mg and -12.7 (-22.1; -3.3) for 1200 mg. No dose effect was detected. No conclusion could be drawn from PK-PD analysis since done by dose level with D-1 data only for doses ≥600 mg. • DNDi-OXA-07-HAT: Out of 19 participants who were exposed to acoziborole, 18 had a post-baseline decrease of the QTcF. None decreased below 360 ms (Day 9, 11, 22 and 31). The lowest post-baseline value was 367 ms. • DNDi-OXA-002-HAT study in participants with g-HAT: Post-baseline decreases of QTcF between 340 to 359 ms were recorded in 14.4% of participants and decreases between 320 to 339 ms in 2.9% of participants. The lowest post-baseline QTcF value was 326 ms. • The concentration-response analysis confirmed the acoziborole-induced decrease in QTcF. At the observed geometric mean blood C_{max} value (10.5 µg/mL), the estimated decrease from baseline QTcF was 9.28 ms (90% CI: 10.1 to 8.43 ms). • DNDi-OXA-04-HAT study (seropositive but not confirmed parasitologically participants): New onset shortening of QTcF was observed in a higher proportion of participants randomized to acoziborole compared to placebo (4.7% vs 1.5%). The ECG analysis set of a subset of ECG and PK data in study DNDi-OXA-04-HAT consisted of 283 treated participants, 215 with acoziborole and 68 with placebo. In line with central tendency, the concentration-response analysis confirmed the acoziborole-induced decrease of QTcF. At Day 5, the estimated decrease in QTcF was -10.9 ms [90% CI: -13.7-8.11]. No arrhythmia caused by shortening of QT interval was reported in any of the 1206 participants (906 on acoziborole, 300 on placebo) in study DNDi-OXA-04-HAT, nor in any other acoziborole study.
Risk factors and risk groups	The clinical significance of QT shortening is unclear. Potential risk factors may include congenital Short QT Syndrome and acquired shortening of the QT interval (eg, fever, hyperkalemia, hypercalcemia and thyroid disorders and concomitant drugs known to shorten the QT). (27) Clinical signs and symptoms may be absent, and the patient may present with sudden onset ventricular arrhythmia and cardiac arrest. (28) A family history of sudden death, in particular in infancy, and genetic testing are not considered useful predictors. (28)

Important potential risk	Arrhythmia caused by shortening of QT interval
	Prevalence of Short QT Syndrome in general population: between 0.01% to 0.5%. (29)(30) The prevalence of drug induced QT shortening is unknown and no data is available for the target population. Knowledge about other risk factors is limited and there are no specific signs or symptoms characteristic of shortening of the QT interval other than ventricular arrhythmia which is a life-threatening condition.
Preventability	There is no consensus on diagnostic criteria for shortening of QT and the lower limit of normal for corrected QT interval (QTc). (27)(31) Routine risk minimization measures with labelling statements (See RMP [Part V]) include: • Contraindication in patients with Familial Short-QT syndrome • Caution when prescribing acoziborole in combination with other medicinal products that are known to shorten the QT interval. Additional risk minimization measures (See RMP [Part V]) with the national sleeping sickness controlled treatment access program.
Impact on the risk-benefit balance of the product	The benefit-risk balance remains positive in the g-HAT population. Untreated g-HAT may cause QT prolongation (32) and dilated cardiomyopathy and ultimately death in almost all patients.
Public health impact	No public health impact is expected.

C_{max}: Maximum Plasma Concentration; ECG: Electrocardiogram; g-HAT: *Gambiense* Human African Trypanosomiasis; PD: Pharmacodynamics; PK: Pharmacokinetic; QTc: Corrected QT Interval; QTcF: Corrected QT Interval by Fridericia's Formula; RMP: Risk Management Plan.

SVII.3.2. Presentation of the missing information

Table 20 - Missing information: Use during pregnancy

Missing Information	Use during pregnancy
Evidence source(s) and strength of evidence	**Non-clinical data** Clinical data from DNDi-OXA-02-HAT (g-HAT patients) and DNDi-OXA-04-HAT (seropositive but parasitologically not confirmed participants).
Anticipated risk/consequence of the missing information **Or Population in need for further characterization**	Non-clinical studies showed that acoziborole crosses the placenta in rats but has no effect on fertility, fetal or post-natal development in rats and fetal development in rabbits (RMP [Part II Module SII]). Limited data are available in pregnant women exposed to acoziborole from DNDi-OXA-02-HAT (g-HAT) (N = 7) and DNDi-OXA-04-HAT (seropositive but parasitologically not confirmed) (N = 8) clinical studies. The elimination half-life of acoziborole was about 296 hours (12.3 days) in patients with g-HAT at the single oral therapeutic dose of 960 mg. Clinically a drug is essentially eliminated from the body after five half-lives, corresponding to 62 days for acoziborole. A fetus was considered exposed to acoziborole in utero if the pregnancy start date (first day of LMP) was estimated to be before or up to 62 days after acoziborole intake. The fetus was considered exposed to acoziborole in utero in 4 cases in DNDi-OXA-02-HAT (g-HAT) and in 5 cases in DNDi-OXA-04-HAT (seropositive but parasitologically not confirmed). Most pregnancies had a normal duration with no complications. There was one case of abortion (probably induced); 6 (out of 9) exposed newborns were in good general health at birth and were developing normally at the time of the last available follow-up (up to 2 years of age in 2 cases from DNDi-OXA-02-HAT). Death (stillbirth) occurred in 1 case due to fetal distress secondary to umbilical cord prolapse at delivery. One neonatal death was reported among pregnancies

Missing Information	Use during pregnancy
	considered exposed, at 2 days of age due to neonatal infection. Both cases of death and the case of abortion were assessed as not related to acoziborole. None of the SAEs reported at delivery in the mothers (participants) or the newborns were assessed as related to acoziborole. The target population of the indication should include women of childbearing potential. Caution in exposing women of childbearing potential and pregnant women are defined in the labeling section 4.6 of the SmPC. A post-authorization safety study (PASS) will collect outcomes in women and infants exposed to acoziborole during pregnancy, if any.

g-HAT: *Gambiense* Human African Trypanosomiasis; LMP: Last Menstrual Period; N: Total Number of Patients;
PASS: Post-Authorization Safety Study; RMP: Risk Management Plan; SAE: Serious Adverse Event; SmPC: Summary of Product Characteristics.

Table 21 - Missing information: Use during breastfeeding

Missing Information	Use during breastfeeding
Evidence source(s) and strength of evidence	Non-clinical data.
Anticipated risk/consequence of the missing information **Or Population in need for further characterization**	Available PK data in rats have shown that acoziborole is excreted into breast milk, suggesting that exposure through breastfeeding is likely to occur in humans. Effects on suckling rat pups were limited to transient growth retardation at high dose level only [Part II Module SII]. There are no data from the use of acoziborole in breastfeeding women. As there is a risk of accumulation of acoziborole in breastfed children, caution in exposing this subpopulation is defined in the labeling section 4.6 of the SmPC. A PASS will consider outcomes in women and infants exposed to acoziborole during breastfeeding although limited data is expected.

PASS: Post-Authorization Safety Study; PK: Pharmacokinetic; SmPC: Summary of Product Characteristics.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 22 - Summary of the safety concerns

Important identified risk	Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)
Important potential risk	Arrhythmia caused by shortening of QT interval
Missing information	Use during pregnancy
	Use during breastfeeding

CYP: Cytochrome P450.

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of acoziborole will continue to be further characterized in real life setting through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse events (AEs) and signal detection in periodic safety reports. The WHO will collect pharmacovigilance cases from the g-HAT centers with local support of NSSCPs.

The WHO will be in charge of distributing acoziborole to NSSCP centers locally and of the implementation of the dedicated routine pharmacovigilance system.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance activity includes the following planned study:

- A non-interventional Post-Authorization Safety Study of acoziborole for Human African Trypanosomiasis due to *Trypanosoma brucei gambiense*: Descriptive analysis of the safety and use of concomitant medicines in the Real-World using WHO Active Pharmacovigilance Data.

Table 23 - Additional pharmacovigilance activities (category 1 to 3) summary

EPM21869 - Acoziborole PASS (category 3)
Study short name and title Study short name: Acoziborole PASS. Title: Non-Interventional Post-Authorization Safety Study of Acoziborole for Human African Trypanosomiasis due to *Trypanosoma brucei gambiense*: Descriptive Analysis of the Safety and Use of Concomitant Medicines in the Real-World Using WHO Active Pharmacovigilance Data.
Rationale and study objectives Acoziborole is a new treatment for g-HAT with a favorable safety profile compared to existing treatments such as fexinidazole and NECT. The only currently important identified risks for acoziborole are potential drug interactions due to its effect on drugs mainly metabolized by CYP2D6 and CYP3A4. Furthermore, owing to its long half-life, acoziborole may cause drug interactions with other medicines up to 3 months after treatment. An additional risk minimization measure consisting of a patient card will be implemented and serve to inform/remind patients and HCPs about the key messages related to the risk of drug interactions due to potentially interacting medicines in the 3-month post-acoziborole period. Moreover, while the safety of acoziborole has been established in clinical trials so far, further assessment in real-world settings is also valuable, especially since it will often be used in resource-limited conditions in remote regions of sub-Saharan African countries. Also, due to exclusion in clinical trials, information about acoziborole exposure in pregnancy and breastfeeding remains limited or missing, although they may occur in real-world. In an attempt to address these knowledge gaps, this category 3 PASS is proposed with the overall aims to describe the real-world safety of acoziborole and the effectiveness of the patient card in minimizing the use of potentially interacting medicines in the 3-month post-treatment period. Safety in pregnant women and newborns exposed in utero and/or through breastfeeding will also be described, although limited data is expected. Primary objectives: • Evaluate the real-world safety of acoziborole treatment by describing the frequency of any AEs and use of any concomitant medicine in the 3-month period following acoziborole treatment. • Evaluate the effectiveness of the patient card by:

- describing the frequency of use of potentially interacting medicines in the 3-month period following acoziborole treatment;
- describing the frequency of AEs occurring after the use of potentially interacting medicines in the 3-month period following acoziborole treatment.

Secondary objective:

Describe the safety in pregnant women treated with acoziborole up to the end of delivery, and in offspring exposed in utero and/or through breastfeeding up to 24 months of age.

Study design

This will be a descriptive multinational real-world cohort study using secondary data collected from the active pharmacovigilance activities of NSSCPs and the WHO.

Study populations

All patients treated with acoziborole for g-HAT with data collected in the WHO acoziborole active pharmacovigilance database during a 3-year study period will be eligible.

Additionally, offspring of patients treated with acoziborole during pregnancy or while breastfeeding (ie, in utero and/or breastfeeding exposure) with data collected in the WHO acoziborole active pharmacovigilance database will be included.

Milestones

Protocol submission to PRAC: Estimated Quarter (Q)2 2026

Protocol endorsement by PRAC: Estimated Q4 2026

Data extraction (WHO database delivery to Marketing Authorization Holder [MAH]): Estimated Q1 2030

Start of data analysis: Estimated Q2 2030

Final report of study results: Estimated Q1 2031

AE: Adverse Event; CYP: Cytochrome P450; g-HAT: *Gambiense* Human African Trypanosomiasis; HCP: Healthcare Professional; MAH: Marketing Authorization Holder; NECT: Nifurtimox-Eflornithine Combination Therapy; NSSCP: National Sleeping Sickness Control Program; PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; WHO: World Health Organization.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 24 - Ongoing and planned additional pharmacovigilance activities

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				
Not applicable				
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				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
EPM21869 **Acoziborole PASS** Non-Interventional Post-Authorization Safety Study of Acoziborole for	Primary objectives: • Evaluate the real-world safety of acoziborole treatment by describing the frequency of any AEs and use of any concomitant	• Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by	Protocol submission to PRAC Protocol endorsement by PRAC	Estimated Q2 2026 Estimated Q4 2026

Study status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Human African Trypanosomiasis due to *Trypanosoma brucei gambiense*: Descriptive Analysis of the Safety and Use of Concomitant Medicines in the Real-World Using WHO Active Pharmacovigilance Data. Planned	medicine in the 3-month period following acoziborole treatment. • Evaluate the effectiveness of the patient card by: - describing the frequency of use of potentially interacting medicines in the 3-month period following acoziborole treatment; - describing the frequency of AEs occurring after the use of potentially interacting medicines in the 3-month period following acoziborole treatment. Secondary objective: Describe the safety in pregnant women treated with acoziborole up to the end of delivery, and in offspring exposed in utero and/or through breastfeeding up to 24 months of age.	CYP3A4 (strong induction) • Use during pregnancy • Use during breastfeeding	Data extraction (WHO database delivery to MAH) Start of data analysis Final report of study results	Estimated Q1 2030 Estimated Q2 2030 Estimated Q1 2031

AE: Adverse Event; CYP: Cytochrome P450; MAH: Marketing Authorization Holder; PASS: Post-Authorization Safety Study; PRAC: Pharmacovigilance Risk Assessment Committee; Q: Quarter; WHO: World Health Organization.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for acoziborole.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

The routine risk minimization measures include specific safety information into the labeling documents (both SmPC and package leaflet [PL]).

Table 25 - Description of routine risk minimization measures by safety concern

Safety concern	Routine risk minimization activities
Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)	**Routine risk communication:** • Labeled in section 4.3, section 4.4, section 4.5 of the SmPC. • Labeled in section 2 of the PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in sections 4.3, 4.4, and 4.5 of the SmPC. • Labeled in Section 2 of the PL. **Other routine risk minimization measures beyond the Product Information:** Not applicable
Arrhythmia caused by shortening of QT interval	**Routine risk communication:** • Labeled in section 4.3, section 4.4 of the SmPC. • Labeled in section 2 of the PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in section 4.3 and 4.4 of the SmPC. • Labeled in section 2 of the PL. **Other routine risk minimization measures beyond the Product Information:** Not applicable
Use during pregnancy	**Routine risk communication:** • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL. **Other routine risk minimization measures beyond the Product Information:** Not applicable
Use during breastfeeding	**Routine risk communication:** • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL. **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Labeled in section 4.6 of the SmPC. • Labeled in section 2 of the PL.

Safety concern	Routine risk minimization activities
	Other routine risk minimization measures beyond the Product Information: Not applicable

CYP: Cytochrome P450; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

The NSSCP is organized to minimize the public health and individual patient impact of sleeping sickness in endemic countries.

Acoziborole will only be available within this program as patient access is contingent on fulfilling specific requirements that will be defined by NSSCP in collaboration with WHO prior to being prescribed.

Acoziborole will be supplied within the NSSCP with additional risk minimization measures (aRMMs) in place, namely RMM control tools such as HCP qualification, traceability system, and one educational/safety advice tool (patient card).

HCP qualification: Given the severity of HAT disease, the endemic sub-Saharan African countries currently organize care of HAT patients from particularly remote rural endemic areas only in healthcare centers whose staff supervised by the NSSCPs will be identified, trained to administer and follow-up acoziborole treatment to HAT patients in line with the prescribing conditions described in the updated WHO HAT treatment guidelines. In these healthcare centers, patients will be treated with the currently available HAT treatments (ie, medication is taken by the patient directly at the HC center), and their safety will be supervised by HCPs formally trained for the treatment of HAT.

Traceability system: Conjointly with this program, distribution of acoziborole will be restricted to selected healthcare facilities, and its use reserved to HCPs trained by the NSCCPs in collaboration with WHO. Acoziborole will be distributed following the same procedure in place for the distribution of current HAT treatments (NECT, pentamidine, melarsoprol, suramin, fexinidazole), ie, through the WHO neglected tropical diseases department to NSSCPs and from there to the treatment centers. In more detail, the centers treating HAT patients (g-HAT and r-HAT) report the number of diagnosed cases and their need for products to the NSSCP for national consolidation; these data are then transferred to the WHO local office. Each national WHO office reports the data to the WHO headquarters (Geneva), where final consolidation takes place based on the number of cases reported and subsequent treatment needs. The WHO Geneva then holds regular forecasting meetings with drug manufacturers Sanofi for initiating manufacturing of the requested batches to finally supply the finished products to Médecins Sans Frontières/Doctors Without Borders (MSF) Logistique at Bordeaux, France. Under control and supervision by WHO Geneva, MSF-Logistique ships the products to each country, where the WHO local office receives the shipment and takes care of clearing customs. Once in the country, NSSCP takes over and distributes the products from national warehouses to each of the treatment centers, based on their previously declared needs. Products are stored at a secondary storage warehouse or directly at the treatment center and are only used under HCP supervision for HAT diagnosed patients. A traceability system is to be completed at dispatch of the medicinal product from the manufacturing site to each country where the medicinal product is provided.

The educational/safety advice tool consists of a Patient Card, with visuals and instructions to emphasize the communication of the key safety messages related the risk of DDI to the patients and other HCPs involved in the patient's care from whom additional drugs could be prescribed post acoziborole treatment (see [Annex 6]). Of note, the card should be developed by Sanofi and printed locally by the NSSCPs in sub-Saharan African countries where acoziborole is distributed.

Table 26 - Additional risk minimization measures

Patient Card	
Objectives	To remind "patients/caregivers" and to inform other HCPs or medical referents involved in patient's care for other conditions – ie, who are not distributing acoziborole in HAT centers, about the "Effects of Acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)" after Acoziborole single dose administration to minimize the impact of the DDI.
Rationale for the additional risk minimization activity	The card is considered necessary and complementary to the product information to provide information on the risk of DDI to patients and HCPs or medical referents involved in patient's care for other conditions, facilitate communication between them, and thus minimize the impact of DDI between Acoziborole and other drugs metabolized by CYP3A4 and CYP2D6 for up to 3 months after acoziborole intake.
Target audience and planned distribution path	**Target audience:** Patient diagnosed with HAT via trained HCP, additional HCP prescribing/distributing other drugs within 3 months after Acoziborole treatment. **Distribution paths**: Face to face through the treatment prescribers (if other channel, to be adapted at country level). **Periodicity of the distribution**: NSSCP takes over and distributes the products along with Patient Cards to each of the treating centers, based on their previously declared needs.
Plans to evaluate the effectiveness of the interventions and criteria for success	**Dissemination and knowledge outcomes**: Number of centers trained per country with total number of training certificates from WHO/NSSCP. **Health outcomes**: Description of AEs by frequency, severity, seriousness, relatedness reported during 3-months post-treatment period in the context of concomitant medicines mainly metabolized by CYP26 or CYP3A4. Analysis through final PASS report.

AE: Adverse Event; CYP: Cytochrome P450; DDI: Drug-Drug Interaction; HAT: Human African Trypanosomiasis HCP: Healthcare Professional; NSSCP: National Sleeping Sickness Control Programme; PASS; Post-Authorization Safety Study; WHO: World Health Organization.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Table 27 - Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)	**Routine risk minimization measures:** Labeled in section 4.3, section 4.4, section 4.5 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measures:** • Patient card.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Acoziborole PASS.

Safety concern	Risk minimization measures	Pharmacovigilance activities
	• Healthcare professional qualification and traceability system (via NSSCP).	
Arrhythmia caused by shortening of QT interval	**Routine risk minimization measures:** Labeled in section 4.3, section 4.4 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measures:** Healthcare professional qualification and traceability system (via NSSCP).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None
Use during pregnancy	**Routine risk minimization measures:** Labeled in section 4.6 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measures:** Healthcare professional qualification and traceability system (via NSSCP).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Acoziborole PASS.
Use during breastfeeding	**Routine risk minimization measures:** Labeled in section 4.6 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measures:** Healthcare professional qualification and traceability system (via NSSCP).	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** Acoziborole PASS.

CYP: Cytochrome P450; NSSCP: National Sleeping Sickness Control Programme; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Acoziborole Winthrop (Acoziborole)

This is a summary of the RMP for Acoziborole Winthrop. The RMP details important risks of Acoziborole Winthrop, how these risks can be minimized, and how more information will be obtained about Acoziborole Winthrop's risks and uncertainties (missing information).

Acoziborole Winthrop's SmPC and its PL give essential information to HCPs and patients on how Acoziborole Winthrop should be used.

This summary of the RMP for Acoziborole Winthrop should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Acoziborole Winthrop's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Acoziborole Winthrop is authorized for the treatment of both first-stage (hemo-lymphatic) and second stage (meningo-encephalitic), including severe second-stage with ≥100 White Blood Cell (WBC)/µL with or without trypanosomes in cerebrospinal fluid (CSF), human African trypanosomiasis (HAT) due to Trypanosoma brucei gambiense (g-HAT) in adolescents ≥12 years old with body weight ≥40 kg, and in adults (see SmPC for the full indication). It contains acoziborole as the active substance and it is given as tablets 320 mg.

Further information about the evaluation of Acoziborole Winthrop's benefits can be found in Acoziborole Winthrop's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

Link to the EPAR summary landing page.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Acoziborole Winthrop, together with measures to minimize such risks and the proposed studies for learning more about Acoziborole Winthrop's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and HCPs;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In the case of Acoziborole Winthrop, these measures are supplemented with *additional risk minimization* measures mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Acoziborole Winthrop is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Important risks of Acoziborole Winthrop are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Acoziborole Winthrop. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 28 - List of important risks and missing information

Important identified risk	Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)
Important potential risk	Arrhythmia caused by shortening of QT interval
Missing information	Use during pregnancy
	Use during breastfeeding

CYP: Cytochrome P450.

II.B Summary of important risks

Table 29 - Important identified risk with corresponding risk minimization activities and additional pharmacovigilance activities: Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)

Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)	
Evidence for linking the risk to the medicine	In vitro data: CYP2139 R2I CYP inhibition, CYP2139 R2 Induction Clinical data from OXA007 study Physiological based pharmacokinetic (PBPK) report (BMG43-A).
Risk factors and risk groups	None

Effect of acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction)	
Risk minimization measures	**Routine risk minimization measures** Labeled in section 4.3, section 4.4, section 4.5 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measures** • Patient card. • Healthcare professional qualification and traceability system (via NSSCP).
Additional pharmacovigilance activities	**Additional pharmacovigilance activities**: Acoziborole PASS. See Section II.C of this summary for an overview of the post-authorization development plan.

CYP: Cytochrome P450; NSSCP: National Sleeping Sickness Control Programme; PASS; Post-Authorization Safety Study; PBPK: Physiological Based Pharmacokinetic; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 30 - Important potential risk with corresponding risk minimization activities: Arrhythmia caused by shortening of QT interval

Arrhythmia caused by shortening of QT interval	
Evidence for linking the risk to the medicine	**Clinical data:** Systematic presence of a small, QTcF shortening in studies with humans.
Risk factors and risk groups	The clinical significance of QT shortening is unclear. Potential risk factors may include congenital Short QT Syndrome and acquired shortening of the QT interval (eg, fever, hyperkalemia, hypercalcemia and thyroid disorders and concomitant drugs known to shorten the QT). (27) Clinical signs and symptoms may be absent, and the patient may present with sudden onset ventricular arrhythmia and cardiac arrest. (28) A family history of sudden death, in particular in infancy, and genetic testing are not considered useful predictors. (28) Prevalence of Short QT Syndrome in general population: between 0.01% to 0.5%. (29)(30) The prevalence of drug induced QT shortening is unknown and no data is available for the target population. Knowledge about other risk factors is limited and there are no specific signs or symptoms characteristic of shortening of the QT interval other than ventricular arrhythmia which is a life-threatening condition.
Risk minimization measures	**Routine risk minimization measures** Labeled in section 4.3, section 4.4 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measures** Healthcare professional qualification and traceability system (via NSSCP).

NSSCP: National Sleeping Sickness Control Programme; PL: Package Leaflet; QTcF: Corrected QT Interval by Fridericia's Formula; SmPC: Summary of Product Characteristics.

Table 31 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during pregnancy

Use during pregnancy	
Risk minimization measures	**Routine risk minimization measures** Labeled in section 4.6 of the SmPC. Labeled in section 2 of the PL.

Use during pregnancy	
	Additional risk minimization measure Healthcare professional qualification and traceability system (via NSSCP).
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Acoziborole PASS. See Section II.C of this summary for an overview of the post-authorization development plan.

NSSCP: National Sleeping Sickness Control Programme; PASS; Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 32 - Missing information with corresponding risk minimization activities and additional pharmacovigilance activities: Use during breastfeeding

Use during breastfeeding	
Risk minimization measures	**Routine risk minimization measures** Labeled in section 4.6 of the SmPC. Labeled in section 2 of the PL. **Additional risk minimization measure** Healthcare professional qualification and traceability system (via NSSCP).
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Acoziborole PASS. See Section II.C of this summary for an overview of the post-authorization development plan.

NSSCP: National Sleeping Sickness Control Programme; PASS; Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Acoziborole Winthrop.

II.C.2 Other studies in post-authorization development plan

Table 33 - Other studies in post-authorization development plan

EPM21869 - Acoziborole PASS **Non-Interventional Post-Authorization Safety Study of Acoziborole for Human African Trypanosomiasis due to *Trypanosoma brucei gambiense*: Descriptive Analysis of the Safety and Use of Concomitant Medicines in the Real-World Using WHO Active Pharmacovigilance Data (Cat. 3)**
Purpose of the study: Acoziborole is a new treatment for g-HAT with a favorable safety profile compared to existing treatments such as fexinidazole and NECT. The only currently important identified risks for acoziborole are potential drug interactions due to its effect on drugs mainly metabolized by CYP2D6 and CYP3A4. Furthermore, owing to its long half-life, acoziborole may cause drug interactions with other medicines up to 3 months after treatment. An additional risk minimization measure

consisting of a patient card will be implemented and serve to inform/remind patients and HCPs about the key messages related to the risk of drug interactions due to potentially interacting medicines in the 3-month post-acoziborole period.

Moreover, while the safety of acoziborole has been established in clinical trials so far, further assessment in real-world settings is also valuable, especially since it will often be used in resource-limited conditions in remote regions of sub-Saharan African countries. Also, due to exclusion in clinical trials, information about acoziborole exposure in pregnancy and breastfeeding remains limited or missing, although they may occur in real-world. In an attempt to address these knowledge gaps, this category 3 PASS is proposed with the overall aims to describe the real-world safety of acoziborole and the effectiveness of the patient card in minimizing the use of potentially interacting medicines in the 3-month post-treatment period. Safety in pregnant women and newborns exposed in utero and/or through breastfeeding will also be described, although limited data is expected.

Primary objectives:

- Evaluate the real-world safety of acoziborole treatment by describing the frequency of any AEs and any concomitant medicine in the 3-month period following acoziborole treatment.
- Evaluate the effectiveness of the patient card by:
  - describing the frequency of use of potentially interacting medicines in the 3-month period following acoziborole treatment;
  - describing the frequency of AEs occurring after the use of potentially interacting medicines in the 3-month period following acoziborole treatment.

Secondary objective:

Describe the safety in pregnant women treated with acoziborole up to the end of delivery, and in offspring exposed in utero and/or through breastfeeding up to 24 months of age.

AE: Adverse Event; CYP: Cytochrome P450; g-HAT: *Gambiense* Human African Trypanosomiasis; NECT: Nifurtimox-Eflornithine Combination Therapy; PASS: Post-Authorization Safety Study; WHO: World Health Organization.

REFERENCES

1. Franco JR, Cecchi G, Priotto G, Paone M, Diarra A, Grout L, et al. Monitoring the elimination of human African trypanosomiasis at continental and country level: Update to 2018. PLoS Negl Trop Dis. 2020 May 21;14(5):e0008261.

2. World Health Organization, Key facts. Trypanosomiasis, human African (sleeping sickness) [Internet]. Geneva: World Health Organization; 2023 May 02 [cited 2024 May 17]. Available from: https://www.who.int/news-room/fact-sheets/detail/trypanosomiasis-human-african-(sleeping-sickness)

3. World Health Organization-Observatory. Global Health Observatory data repository of new reported cases (T.b. gambiense) Data by country [Internet]. Geneva: World Health Organization; 2024 [cited 2024 May 21]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/hat-tb-gambiense

4. World Health Organization-2023a. Human African Trypanosomiasis (sleeping sickness) [Internet]. Geneva: World Health Organization; 2024 [cited 2024 Feb 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/trypanosomiasishuman-african-(sleeping-sickness)

5. World Health Organization-2023b. Stakeholders meet in WHO to review progress towards elimination of human African trypanosomiasis [Internet]. Geneva: World Health Organization; 2023 Jun 08 [cited 2024 Arp 15]. Available from: https://www.who.int/news/item/08-06-2023-stakeholders-meet-in-who-to-review-progress-towards-elimination-of-human-african-trypanosomiasis

6. World Health Organization-Communication. Sleeping sickness elimination progresses in 2021 despite COVID-19 [Internet]. Geneva: World Health Organization; 2022 May 30 [cited 2024 May 03]. Available from: https://www.who.int/news/item/30-05-2022-sleeping-sickness-elimination-progresses-in-2021-despite-covid-19

7. National Sleeping Sickness Control Program - DRC [Programme National de Lutte contre la Trypanosomiase Humaine Africaine - RDC (PNLTHA-RDC)]. Annual report 2023. [Rapport annuel 2023]. Kinhasa, Democratic Republic of the Congo: National Sleeping Sickness Control Program - DRC [PNLTHA-RDC]; 2023.

8. Elenga VA, Lissom A, Elion DOA, Vouvoungui JC, Djontu JC, Boumpoutou RK, et al. Risk factors and prevalence of human African trypanosomiasis in individuals living in remote areas of the republic of Congo. BMC Public Health. 2022 Dec 12;22(1):2322.

9. Franco JR, Priotto G, Paone M, Cecchi G, Ebeja AK, Simarro PP, et al. The elimination of human African trypanosomiasis: Monitoring progress towards the 2021-2030 WHO road map targets. PLoS Negl Trop Dis. 2024 Apr 16;18(4):e0012111.

10. World Health Organization-Technical Report Series (no. 984). Control and surveillance of human African trypanosomiasis, Report of a WHO Expert Committee. [Internet]. Geneva: World Health Organization; 2013 [cited 2024 May 17]. Available from: https://iris.who.int/bitstream/handle/10665/95732/9789241209847_eng.pdf

11. Triolo N, Trova P, Fusco C, Le Bras J. Report on 17 years of studies of human African trypanosomiasis caused by T. gambiense in children 0-6 years of age. Med Trop (Mars). 1985 Jul-Sep;45(3):251-7.

12. Lindner AK, Priotto G. The unknown risk of vertical transmission in sleeping sickness-a literature review. PLoS Negl Trop Dis. 2010 Dec 21;4(12):e783.

13. Robays J, Ebeja Kadima A, Lutumba P, Miaka mia Bilenge C, Kande Betu Ku Mesu V, De Deken R, et al. Human African trypanosomiasis amongst urban residents in Kinshasa: a case-control study. Trop Med Int Health. 2004 Aug;9(8):869-75.

14. Courtin F, Jamonneau V, Camara M, Camara O, Coulibaly B, Diarra A, et al. A geographical approach to identify sleeping sickness risk factors in a mangrove ecosystem. Trop Med Int Health. 2010 Aug;15(8):881-9.

15. World Health Organization. Guidelines for the treatment of human African trypanosomiasis [Internet]. Geneva: World Health Organization; 2024 Jun 28 [cited 2024 Dec 09]. Available from: https://www.who.int/publications/i/item/9789240096035

16. Jamonneau V, Ilboudo H, Kabore J, Kaba D, Koffi M, Solano P, et al. Untreated human infections by Trypanosoma brucei gambiense are not 100% fatal. PLoS Negl Trop Dis. 2012;6(6):e1691.

17. MSF. MSF Clinical Guidelines - Diagnosis and treatment manual. Parasitic diseases. Chapter 6. 2022 Nov. p. 125-26.

18. Kagira JM, Maina N, Njenga J, Karanja SM, Karori SM, Ngotho JM. Prevalence and types of coinfections in sleeping sickness patients in kenya (2000/2009). J Trop Med. 2011;2011:248914.

19. Kotepui KU, Masangkay FR, De Jesus Milanez G, Kotepui M. Prevalence and outcomes of malaria as co-infection among patients with human African trypanosomiasis: a systematic review and meta-analysis. Sci Rep. 2021 Dec 10;11(1):23777.

20. Kuepfer I, Hhary EP, Allan M, Edielu A, Burri C, Blum JA. Clinical presentation of T.b. rhodesiense sleeping sickness in second stage patients from Tanzania and Uganda. PLoS Negl Trop Dis. 2011 Mar 1;5(3):e968.

21. Ortiz HIA, Farina JM, Saldarriaga C, Mendoza I, Sosa Liprandi A, Wyss F, et al. Human African trypanosomiasis & heart. Expert Rev Cardiovasc Ther. 2020 Dec;18(12):859-65.

22. Blum JA, Burri C, Hatz C, Kazumba L, Mangoni P, Zellweger MJ. Sleeping hearts: the role of the heart in sleeping sickness (human African trypanosomiasis). Trop Med Int Health. 2007 Dec;12(12):1422-32.

23. Priotto G, Kasparian S, Mutombo W, Ngouama D, Ghorashian S, Arnold U, et al. Nifurtimox-eflornithine combination therapy for second-stage African Trypanosoma brucei gambiense trypanosomiasis: a multicentre, randomised, phase III, non-inferiority trial. Lancet. 2009 Jul 4;374(9683):56-64.

24. Mesu VKBK, Kalonji WM, Bardonneau C, Mordt OV, Blesson S, Simon F, et al. Oral fexinidazole for late-stage African Trypanosoma brucei gambiense trypanosomiasis: a pivotal multicentre, randomised, non-inferiority trial. Lancet. 2018 Jan 13;391(10116):144-54.

25. Kuemmerle A, Schmid C, Kande V, Mutombo W, Ilunga M, Lumpungu I, et al. Prescription of concomitant medications in patients treated with Nifurtimox Eflornithine Combination Therapy (NECT) for T.b. gambiense second stage sleeping sickness in the Democratic Republic of the Congo. PLoS Negl Trop Dis. 2020 Jan 27;14(1):e0008028.

26. National Institute of Statistics, Kinhasa School of Public Health [Institut National de la Statistique, École de Santé Publique de Kinshasa]. Demographic and Health Survey 2023-2024 : Report on Key Indicators. [Enquête Démographique et de Santé 2023–24 : Rapport des indicateurs clés]. Rockville, Maryland, USA : ICF; 2024.

27. Shah RR. Drug-induced QT interval shortening: potential harbinger of proarrhythmia and regulatory perspectives. Br J Pharmacol. 2010 Jan;159(1):58-69.

28. Mazzanti A, Kanthan A, Monteforte N, Memmi M, Bloise R, Novelli V, et al. Novel insight into the natural history of short QT syndrome. J Am Coll Cardiol. 2014 Apr 8;63(13):1300-8.

29. Moriya M, Seto S, Yano K, Akahoshi M. Two cases of short QT interval. Pacing Clin Electrophysiol. 2007 Dec;30(12):1522-6.

30. Iribarren C, Round AD, Peng JA, Lu M, Klatsky AL, Zaroff JG, et al. Short QT in a cohort of 1.7 million persons: prevalence, correlates, and prognosis. Ann Noninvasive Electrocardiol. 2014 Sep;19(5):490-500.

31. Rudic B, Schimpf R, Borggrefe M. Short QT Syndrome - Review of Diagnosis and Treatment. Arrhythm Electrophysiol Rev. 2014 Aug;3(2):76-9.

32. Blum JA, Schmid C, Burri C, Hatz C, Olson C, Fungula B, et al. Cardiac alterations in human African trypanosomiasis (T.b. gambiense) with respect to the disease stage and antiparasitic treatment. PLoS Negl Trop Dis. 2009;3(2):e383.

PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

NOT APPLICABLE

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Key messages of the additional risk minimization measures

Prior to the launch of Acoziborole Winthrop in target countries, the applicant must agree with the National Competent Authority the modalities part of the National Sleeping Sickness Control Program (NSSCP) including Risk Minimization Measure (RMM) control tools , and the educational programme. Risk minimization tools are aimed at ensuring that patients are informed on the safe use of the medicine, that they are supervised by trained healthcare staff (healthcare professional [HCP] qualification), and at ensuring that the product is shipped according to the needs in endemic countries and distributed in NSSCP selected health care centers (traceability system) where HCP have been trained for safe use and administration of Acoziborole only to Human African Trypanosomiasis (HAT) diagnosed patients.

The educational programme is aimed at ensuring that patients and other healthcare professionals (HCPs or medical referents involved in patient's care for other conditions) are informed on the potential effect of Acoziborole on other drugs mainly metabolized by CYP2D6 (strong inhibition) or by CYP3A4 (strong induction) during the three-month period following acoziborole administration.

The applicant shall ensure that in countries where Acoziborole Winthrop is distributed, all HCPs, medical referents and "patients/caregivers exposed/receiving Acoziborole Winthrop" have access to/are provided with the following educational/safety advice tool:

- Patient Card for patients/caregivers but also for HCPs and other medical referents involved in patient's care for other conditions post acoziborole treatment.

1. <u>Physician educational/safety advice tool</u>:

- The Summary of Product Characteristics (SmPC).
- The Patient Card.

1.1 Patient Card:

The card includes:

- Treatment date, drug-drug interaction (DDI) end date, treatment center and patient contact details.
- Acoziborole indication.
- Information about DDI, reminder of contraindication and caution with some drugs mainly metabolized by CYP2D6 or CYP3A4, and to not use traditional medicines, for 3 months post-acoziborole treatment.
- Reminder for the HAT HCP to alert the patient about DDI and to give the Patient Card to the patient.

- Instructions for the patients to discuss DDI and/or to show the card to other HCPs or medical referents not trained in *Gambiense* Human African Trypanosomiasis (g-HAT), and to dispose of the Patient Card 3 months after Acoziborole treatment (through visuals).
- National or World Health Organization (WHO) Pharmacovigilance system contact details to report adverse events (AEs).

2. <u>Patient educational/safety advice tool</u>:

- The Patient Leaflet.
- The Patient Card - see description above.